Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Substituted Quinolinones, Part 12: Heterocyclization Reactions of 3-(3-Chromonyl)acryloylquinolinone with Some Bifunctional Nucleophiles

Mohamed Abass [a], Mohamed Abdel-Megid [a] & Mohamed Hassan [a]
[a] Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Heliopolis, Cairo, Egypt
Version of record first published: 25 Jul 2007.

To cite this article: Mohamed Abass , Mohamed Abdel-Megid & Mohamed Hassan (2007): Substituted Quinolinones, Part 12: Heterocyclization Reactions of 3-(3-Chromonyl)acryloylquinolinone with Some Bifunctional Nucleophiles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:2, 329-352

To link to this article: http://dx.doi.org/10.1080/00397910601033930

Synthetic Communications®, 37: 329–352, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601033930

Substituted Quinolinones, Part 12: Heterocyclization Reactions of 3-(3-Chromonyl)acryloylquinolinone with Some Bifunctional Nucleophiles

Mohamed Abass, Mohamed Abdel-Megid, and Mohamed Hassan
Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Heliopolis, Cairo, Egypt

Abstract: 4-Hydroxy-1-methyl-3-[*E*-3-(4-oxo-4*H*-chromen-3-yl)acryloyl]quinolin-2(1*H*)-one (**3**) was smoothly obtained via a one-pot aldol dehydration reaction of 3-acetyl-4-hydroxyquinolin-2(1*H*)-one with 3-formylchromone and was utilized to prepare miscellaneous triheterocyclic systems containing the quinolinone moiety. Both the α,β-unsaturated ketone side chain and the γ-pyrone ring in compound **3** were subjected to nucleophilic cyclization with certain 1,2- and 1,3-bifunctional *N*,*N*-, *N*,*O*-, *N*,*C*-, and *O*,*C*-nucleophiles under different reaction conditions. Many pyrazolinyl-, isoxazolinyl-, pyrimidinyl-, and pyridinylquinolinones bearing other six- or five-membered heterocyclic systems have been conveniently synthesized using more than one synthetic route.

Keywords: chromone, nucleophilic cycloaddition, quinolinone, α,β-unsaturated ketone

INTRODUCTION

Quinolinones are the effective moiety in a large number of natural and synthetic heterocyclic compounds that exhibit significant antibiotic activity

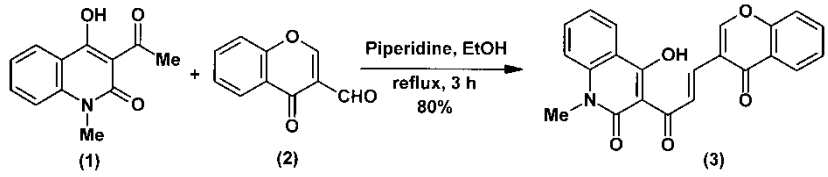
Received in the U.K. April 27, 2006
Dedicated to the memory of the late Professor Sayed Ibrahim El-Nagdi.
Address correspondence to Mohamed Abass, Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Heliopolis 11757, Cairo, Egypt. E-mail: m.abass@chemist.com

with very wide applications.[1–7] Our current program on chemistry of quinolinone is devoted to the synthesis of novel five- or six-membered substituted 3- or 4-hetarylquinolinone derivatives.[8–12] A special interest in this program is directed to the production of derivatives including pyrazoles and isoxazoles, which are known to exhibit significant antibiotic properties. Thus, pyrazoles showed important antimicrobial and antifungal activity,[13] cholesterol acyl-transferase inhibitory activity,[14] antidiabetic activity,[15] antidepressant activity,[16] and antianxiety activity.[17] Recently pyrazolines have received renewed attention with the registration of Indoxacarb, which has neuronal target action on insects.[18] On the other hand, isoxazoles and isoxazolines possess analgesic activity,[19] antiprotozoal activity,[20] anti-influenza virus activity,[21] antifungal activity,[22] antibacterial activity,[23] antidepressant,[24] anti-ischemic effects,[25] and anti-inflammatory activity.[26] Because of these interesting biological activities of quinolinones, pyrazoles, and isoxazoles, considerable attention has been directed at the synthesis of some new derivatives containing these moieties in one molecular frame.

Among the methods employed in the synthesis of 2-pyrazolines and isoxazolines, the condensation of α,β-unsaturated carbonyl compounds with hydrazines and hydroxylamine is commonly used.[27] Chromones are usually readily ring-opened via nucleophilic attack at the 2-position and when treated with a suitable binucleophile, ring opening can be effected, followed by ring closure leading to new ring systems (e.g., hydrazine and hydroxylamine give pyrazole and isoxazoles, respectively.[28–30] Recently we have disclosed that when both a γ-pyrone and an α,β-unsaturated carbonyl side chain are present in the same molecule, the reactivity of both moieties toward 1,2- and 1,3-binucleophiles is competitive, and the reaction mostly proceeds regioselectively, depending on the ambient reaction conditions and the used binucleophile reagent.[9] Building on this, our strategy to synthesize the target isolated triheterocyclic systems, which contain a quinolinone moiety, was obtain an easily accessible synthetic precursor that on modification can furnish the desired heterocycles. The key synthetic precursor should include an α,β-unsaturated carbonyl side chain connecting quinolinone and chromone moieties. These structural features are well assembled in the newly synthesized starting compound 3-[3-(chromon-3-yl) acryloyl]-quinolinone **3**.

RESULTS AND DISCUSSION

The desired precursor 4-hydroxy-1-methyl-3-[*E*-3-(4-oxo-4*H*-chromen-3-yl)-acryloyl]quinolin-2(1*H*)-one (**3**) was smoothly obtained via a one-pot aldol dehydration reaction of 3-acetyl-4-hydroxyl-1-methylquinolin-2(1*H*)-one (**1**)[31] with 3-formylchromone (**2**),[32] in 80% yield (Scheme 1). The ^{1}H NMR spectrum revealed that the olefinic α-proton is shifted downfield to the extent that it appears in the aromatic region ($\delta = 7.58$), and the

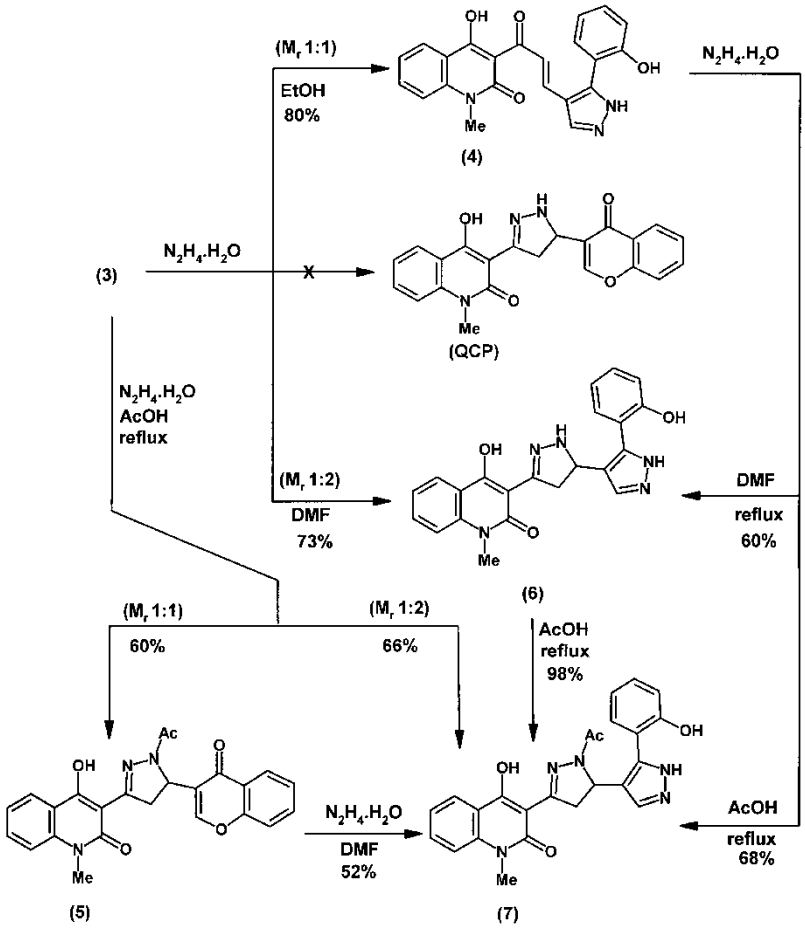


Scheme 1.

β-proton is considerably shifted to $\delta = 9.24$ as doublet ($J = 16$ Hz). The structure is assuming *E*-form, which suffers anisotropic effect due to the neighboring C═O of chromone system.

The reaction of compound **3** with an equimolar amount of hydrazine hydrate, in boiling ethanol, led to the opening of the pyrone ring. This was confirmed by the presence of an additional phenolic OH proton in its ^{1}H NMR spectrum. The data also revealed the enone side chain remains unaffected, and the product was characterized as 4-hydroxy-3-{*E*-3-[3-(2-hydroxyphenyl)-2*H*-pyrazol-4-yl]acryloyl}-1-methylquinoline-2(1*H*)-one (**4**), in 80% yield. Thus, under these conditions, the expected isomeric 3-quinolyl-5-chromonyl-2-pyrazoline (QCP) is completely ruled out. Fortunately, usage of glacial acetic acid as the solvent oriented the reaction away from the γ-pyrone nucleus and gave 3-[1-acetyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**), an *N*-acetylated derivative of the anticipated pyrazoline (QCP) (Scheme 2). Unfortunately, the ^{1}H NMR of the product cannot be measured because of its dimethyl sulphoxide (DMSO)-insolubility problem, but the integrated available data ensured enough routes to determine this structure. Thus, compound **5** does not give violet coloration with the phenolic OH ferric chloride test, indicating that γ-pyrone ring was not attacked, and also its IR spectrum shows characteristic bands due to chromone, quinolinone, and *N*-acetyl C═O groups at 1646, 1652, and 1666 cm^{-1}, respectively. The molecular ion peak obtained by mass spectrum of compound **5** (m/*z* 429) is the base peak (*I*%, 100). The fragmentation pattern showed a ($M-COCH_3$) peak at m/*z* 386. Furthermore, *C*, *H*, and *N* elemental analyses gave satisfactory results within $\pm 0.15\%$. In addition, this result is in accordance with the reported cyclization of α,β-unsaturated carbonyl compounds with hydrazine in glacial acetic acid.[9,29]

When compound **3** was reacted with 2 equivalent of hydrazine hydrate in boiling dimethyl formamide (DMF), nucleophilic attack occurs at both the chromone ring and the α,β-unsaturated ketone side chain, leading to the formation of 4-hydroxy-3-[3′-(2-hydroxyphenyl)-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazol-5-yl]-1-methylquinolin-2(1*H*)-one (**6**) in 73% yield. The ^{1}H NMR spectrum revealed typical peaks for the 2-pyrazoline nucleus as follows: two peaks appeared as multiplets at $\delta = 3.21-3.38$ due to 4-CH_2 and a peak at $\delta = 3.84$ due to 5-CH of pyrazoline. Further evidence for



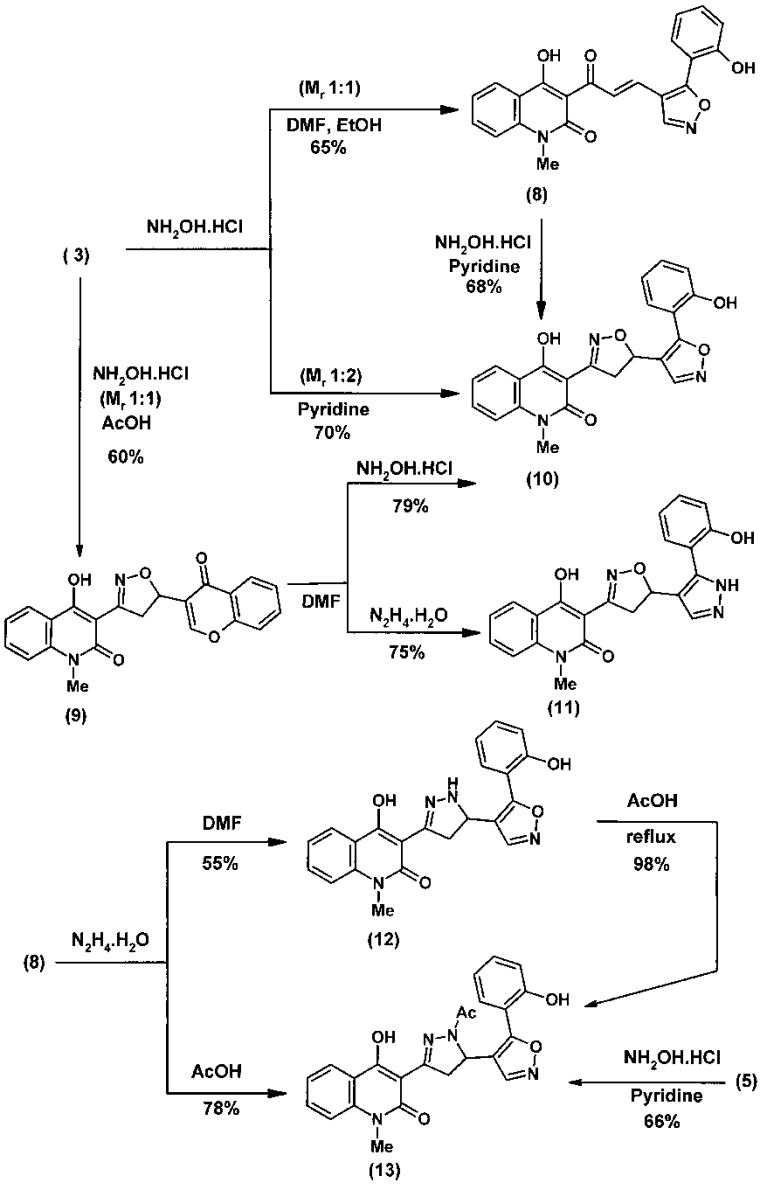
Scheme 2.

the structure of compound **6** was obtained when the same product was obtained by treating the pyrazolylacryloylquinolinone **4** with an excess amount of hydrazine hydrate in boiling DMF in 60% yield. Interestingly the reaction of compound **3** with 2 equivalent of hydrazine in acetic acid did not lead to either compound **5** or compound **6**. The spectral data of the product showed the presence of an acetyl group as indicated by a singlet peak at $\delta = 2.21$ beside clear evidence for pyrone ring-opening. Accordingly, it is believed that the product is an *N*-acetyl derivative of compound **6** and is formulated as 3-[2-acetyl-3′-(2-hydroxyphenyl)-3,4-dihydro-1*H*′,2*H*-3,4-bipyrazol-5-yl)-4-hydroxy-1-methylquinolin-2(1*H*)-one (**7**). Elucidative synthesis of compound **7** was achieved by treatment of compound **4** with hydrazine hydrate in glacial acetic acid and/or by treatment of compound **5** with hydrazine hydrate in boiling DMF (Scheme 2).

When the starting compound **3** was reacted with equimolar amount of hydroxylamine hydrochloride in a mixed solvent of ethanol–DMF (v/v 80:20), 4-hydroxy-3-{*E*-3-[5-(2-hydroxyphenyl)isoxazol-4-yl]acryloyl}-1-methylquinolin-2(1*H*)-one (**8**) was obtained in 65% yield. The refluxing of compound **3** with hydroxylamine hydrochloride at the same molar ratio (1:1) in glacial acetic acid proceeds in a completely different manner, and accordingly 4-hydroxy-1-methy1-3-[5-(4-oxo-4*H*-chromen-3-y1)-4,5-dihydroisoxazol-3-yl)quinolin-2(1*H*)-one (**9**) was characterized resulting from attack of the γ-pyrone nucleus. The reaction of both compounds **8** and **9** with hydroxylamine hydrochloride in boiling pyridine or DMF led smoothly to the formation of 4-hydroxy-3-[5-(2-hydroxypheny1)-4′,5′-dihydro-4,5′-biisoxazol-3′-y1]-1-methy1quinolin-2(1*H*)-one (**10**), which is obtainable directly from compound **3**, by using an excess of hydroxy1amine hydrochloride (1:2) in boiling pyridine (Scheme 3).

Interestingly, the chromeny1isoxazoliny1quinolinone **9** was treated with hydrazine hydrate in boiling DMF to give 4-hydroxy-3-{5-[3-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-4,5-dihydroisoxazol-3-y1}-1-methylquinoline-2(1*H*)-one (**11**), in 75% yield, whereas its isomer 4-hydroxy-3-{5-[5-(2-hydroxyphenyl) isoxazol-4-y1]-4,5-dihydro-1*H*-pyrazol-3-yl}-1-methy1quinolin-2(1*H*)-one (**12**) was afforded upon treating isoxazolylacryloy1quinolinone **8** with hydrazine hydrate in boiling DMF. Boiling compound **12** in glacial acetic acid led to acetylation, affording 3-{1-acetyl-5-[5-(2-hydroxypheny1) isoxazol-4-y1]-4,5-dihydro-1*H*-pyrazol-3-y1}-4-hydoxy-1-methyl-quinolin-2(1*H*)-one (**13**), a compound that was also obtained during heterocyclization of the acryloy1 derivative **8** by means of hydrazine hydrate in glacial acetic acid. In turn, treatment of *N*-acetylpyrazoline **5** with hydroxylamine hydrochloride furnished the same compound **13** (Scheme 3). However, the *N*-acetylpyrazolines are desirable since Chimenti et al. reported that the presence of the acetyl group on the *N*-1 of the pyrazoline nucleus is an important requisite and necessary for its antibacterial activity.[13]

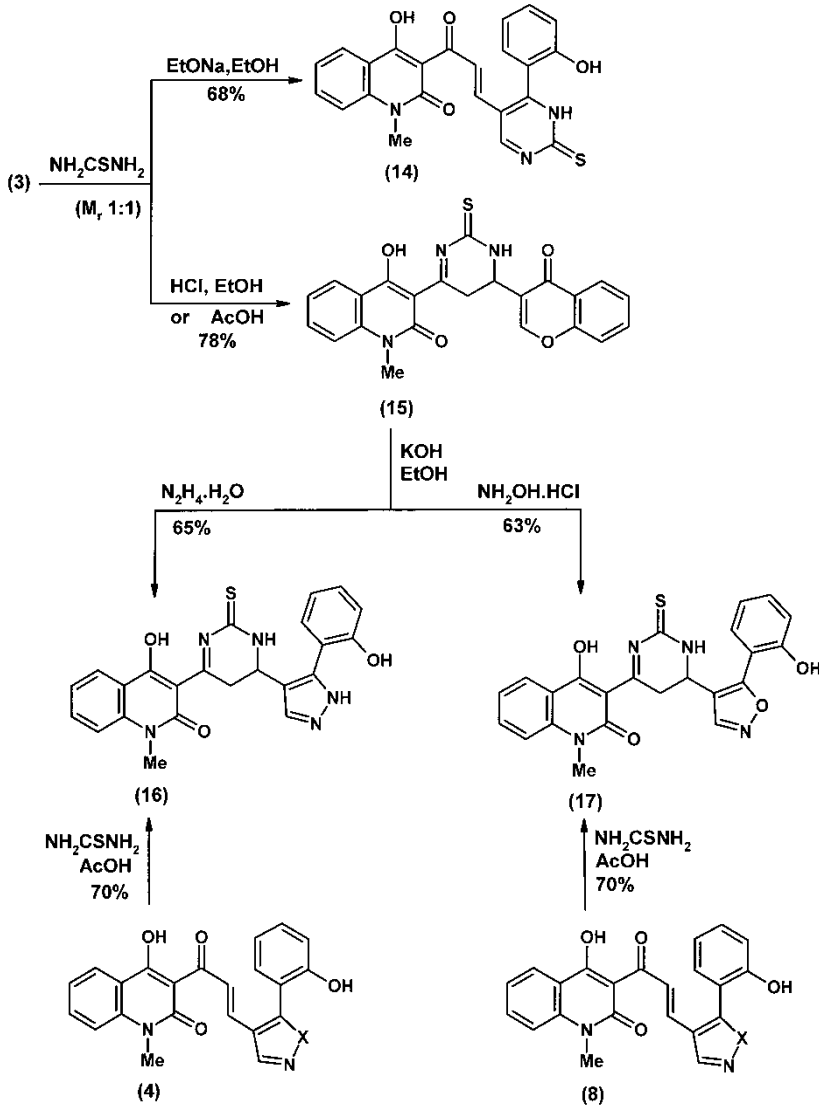
The reaction of compound **3** with thiourea, as a 1,3-binucleophile, was carried out under different reaction conditions. Thus, the reaction at molar ratio (1:1) in the presence of sodium ethoxide afforded 4-hydroxy-3-{*E*-3-[4-(2-hydroxypheny1)-2-thioxo-3*H*-pyrimidin-5-y1]acryloyl}-1-methylquinolin-2-(1*H*)-one (**14**), in 68% yield. It is known that the condensation of thiourea with 1,3-diketones can be either acid or base catalyzed. In the present case, the base is required to effect ring opening of the γ-pyrone (Scheme 4). In boiling ethanol containing a catalytic amount of hydrochloric acid or in boiling glacial acetic acid, the same reaction led to the formation of 4-hydroxy-1-methyl-3-[6-(4-oxo-4*H*-chromen-3-y1)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-y1]quinolin-2(1*H*)-one (**15**), in 78% yield. The mass spectrum of product **15** exhibited a base peak at $m/z = 171$ corresponding to the 3-vinylchromone radical cation. The ^{1}H NMR spectrum revealed characteristic chemical shifts of skeletal 5,6-dihydro-pyimidine-2(1*H*)-thione with two multiplets at $\delta = 3.42–3.54$ (5-CH_2) and 4.23 (6-CH), in



Scheme 3.

addition to an acidic proton at $\delta = 9.18$ (N-H) as a broad peak, revealing the existence of this ring system as the thione tautomer rather than the thiol tautomer.

The reaction of compound **15** with both hydrazine hydrate and hydroxylamine hydrochloride proceeded smoothly using ethanolic potassium



Scheme 4.

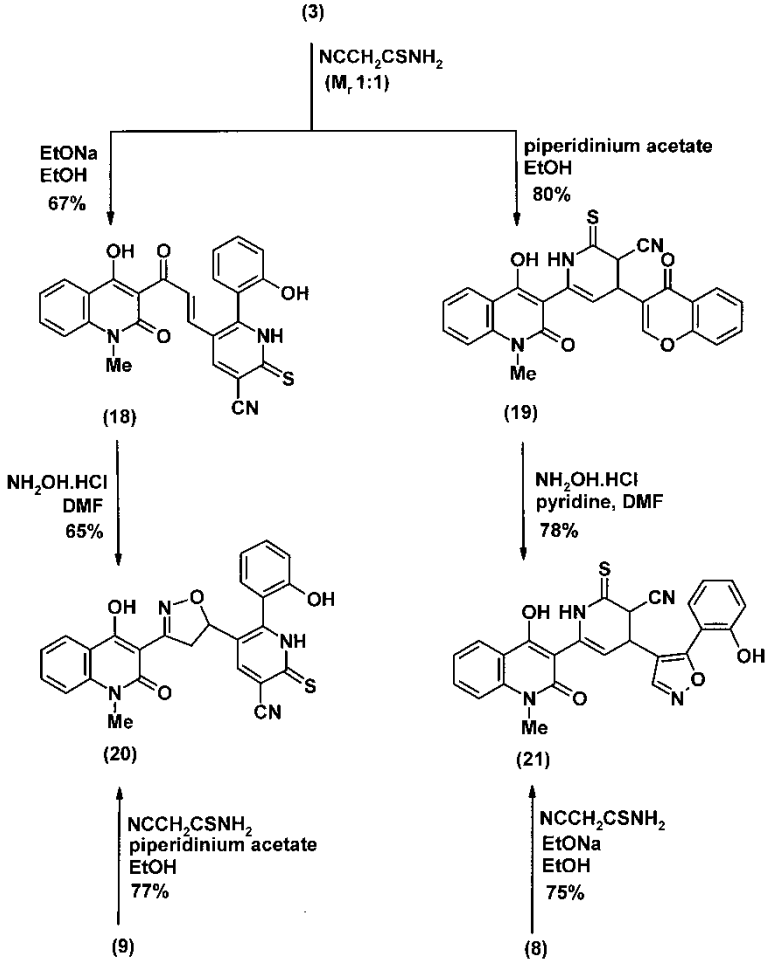
hydroxide to yield 4-hydroxy-3-{6-[5(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-2-thioxo-1,2,5,6-tetrahydro-pyrimidin-4-yl}-1-methylquinolin-2(1*H*)-ones (**16**) and its isoxazolyl analogue **17**, respectively (Scheme 4). The ^{1}H NMR spectrum of compound **16** showed the characteristic chemical shifts corresponding to the pyrimidinyl 5-CH_2 (H_AH_B), 4-CH_X system at $\delta = 3.47$, 3.53, and 5.51. Independent alternative synthesis of both compounds **16** and

17 was employed to confirm both structures. Thus, the reaction of compound **4** with thiourea in glacial acid led to compound **16**, whereas treatment of compound **8** with thiourea in acetic acid gave compound **17** (Scheme 4).

2-Thioxopyridine-3-carbonitriles are of increasing interest because of their use as intermediates for the synthesis of certain medicines. Thus, 5-[*E*-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxoprop-1-enyl]-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**18**) was prepared in the course of the reaction of an equimolar amount of cyanothioacetamide with compound **3**, using sodium ethoxide as a catalyst (Scheme 5). The ^{1}H NMR spectrum showed that the cyclization took place on the chromone and not on the enone side chain, where the chemical shifts at $\delta = 6.53$ and 8.16 ($J = 15.6$ Hz) (due to CO-CH═CH) confirmed the propensity for chromone ring opening in basic media. Evidence was provided by approaching another possible product accessible by a Michael route starting from compound **3** and cyanothioacetamide, at the same molar ratio (1:1), conducted in a relatively moderate basic medium using piperidinium acetate. Under these conditions, the γ-pyrone ring system is preserved, and the opportunity for Michael addition at the enone gives 6-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4-(4-oxo-4*H*-chromen-3-yl)-2-thioxo-1,2,3,4-tetahydropyridine-3-carbonitrile (**19**). ^{1}H NMR spectrum supported the structure **19** because the specific chemical shift due to the chromone C2-proton typically appeared at $\delta = 8.46$. In addition, the disappearance of the olefinic system, which was replaced with the characteristic chemical shifts of tetrahydropyridine nucleus, was evidently noticed.

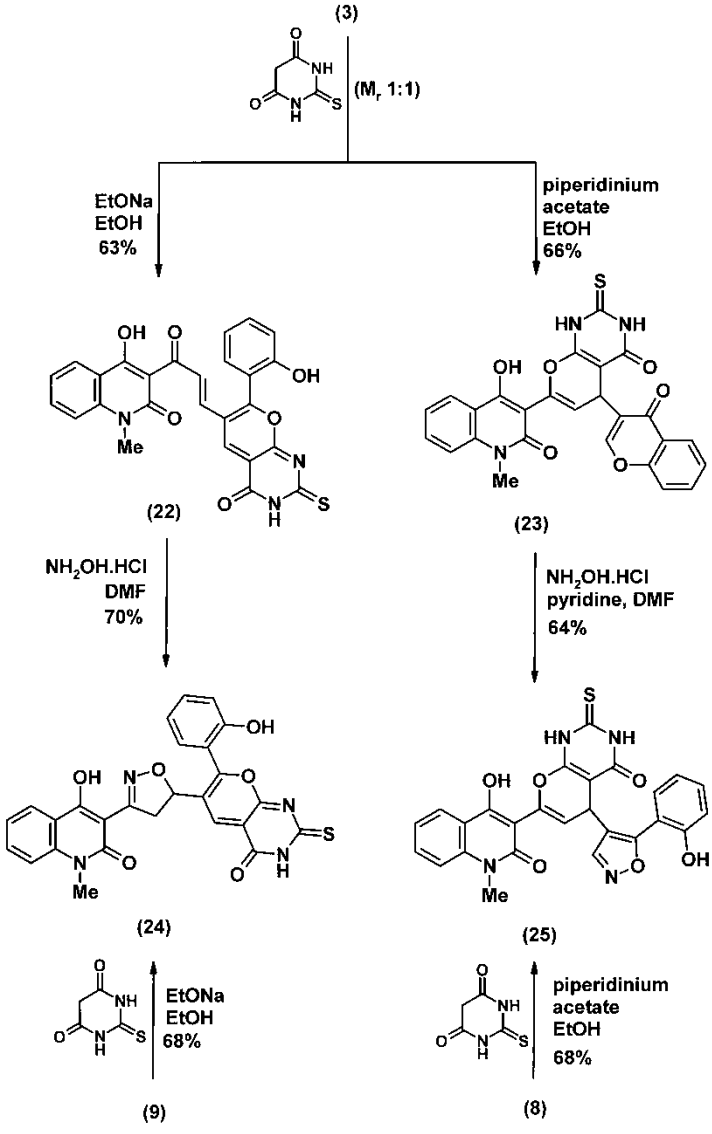
The heterocyclization reaction of both compounds **18** and **19** with hydroxylamine hydrochloride, in boiling DMF and/or pyridine, gave two interesting triheterocyclic systems: 5-[3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydro-isoxzol-5-yl]-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**20**) and 6-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4-[5-(2-hydroxyphenyl)-isoxazol-4-yl]-2-thioxo-1,2,3, 4-tetrahydro-pyridine-3-carbonitnile (**21**). However, the alternative preparation of the same two products, **20** and **21**, via treatment of compounds **9** and **8** with cyanothioacetamide in the presence of sodium ethoxide and/or piperidinium acetate, respectively, strongly supports their proposed structures (Scheme 5).

2-Thiobarbituric acid can be considered as a reactive cyclic methylene compound of the 1,3-dione type, which has been widely used to obtain pyranopyrimidines when cyclized with either enone systems or 1,3-dicarbonyl compound and recently with 3-substituted chromones.[9] Treatment of compound **3** with 2-thiobarbitunic acid at the molar ratio (1:1), in the presence of sodium ethoxide, afforded 6-[*E*-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropenyl]-7-(2-hydroxyphenyl)-2-thioxo-2,3-dihydropyrano[2,3-*d*]pyrimidin-4-one (**22**). When the same reaction was carried out in the presence of piperidinium acetate, a completely



Scheme 5.

different product was isolated and identified as 7-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-(4-oxo-4*H*-chromen-2-yl)-2-thioxo-1,2,3,5-tetrahydro pyrano[2,3-*d*]pyrimidin-4-one (**23**). Furthermore, both products **22** and **23** were reacted with hydroxylamine hydrochloride in boiling DMF to furnish the 6-[3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydroisoxazol-5-yl]-7-(2-hydroxyphenyl)-2-thioxo-2,3-dihydropyrano [2,3-*d*]-pyrimidin-4-one (**24**) and 7-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-[5-(2-hydroxyphenyl)isoxazol-4-yl]-2-thioxo-1,2,3,5-tetrahydro-pyrano[2,3-*d*]pyrimidin-4-one (**25**). Here again compounds **9** and **8** were utilized to synthesize the same products **24** and **25** by an alternate



Scheme 6.

route involving treatment with 2-thiobarbituric acid in the presence of the proper catalyst (Scheme 6).

In summary, an efficient flexible route to obtain a wide range of polyheterocyclic scaffolds, which have expected useful biological properties, has been developed. The presence of both enone and chromone in the precursor that bears a quinolinone moiety seems to be satisfying to large-scale

heterocyclizations depending on the nature of the used bifunctional nucleophiles, the molar ratios, and the ambient reaction conditions.

EXPERIMENTAL

Melting points were determined in open capillary tubes on Gallenkamp MFB-595 or Buchi digital melting-point apparatuses and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR 1650 spectrophotometer in KBr disks. ^{1}H NMR spectra were recorded on a Varian Gemini (200-MHz) instrument using DMSO-d_6 as solvent and TMS as an internal standard reference. Mass spectra were obtained on HP MS-5988 spectrometer by direct inlet (beam energy 70 eV). Elemental analyses were performed at Cairo University Micro-analytical Centre and Ain Shams University Analytical Unit. Silica-gel plates (Merck F254) were used to check purity. The compounds **1**[31] and **2**[32] were obtained according to the literature methods. Analytical and spectral data are listed in Tables 1 and 2, respectively.

4-Hydroxy-1-methyl-3-[*E*-3-(4-oxo-4*H*-chromen-3-yl) acryloyl]quinolin-2(1*H*)-one (3)

A mixture of acetylquinolinone **1** (2.17 g, 10 mmol), 3-formylchromone **2** (1.74 g, 10 mmol), and piperidine (0.2 mL) in ethanol (50 mL) was heated on a boiling water bath for 3 h. The reaction mixture was triturated with ethanol. The solid so obtained was filtered off, washed with diethyl ether, and crystallized to give compound **3**.

4-Hydroxy-3-{*E*-3-[3-(2-hydroxyphenyl)-2*H*-pyrazol-4-yl]acryloyl}-1-methyl-quinolin-2(1*H*)-one (4)

A mixture of **3** (1.87 g, 5 mmol) and hydrazine hydrate (0.25 mL, 5 mmol) in absolute ethanol (10 mL) was heated under reflux for 2 h and then poured into ice-cold water. The resulting solid was filtered and crystallized to give compound **4**.

3-[1-Acetyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (5)

A solution of start **3** (1.87 g, 5 mmol) and hydrazine hydrate (0.25 mL, 5 mmol) in glacial acetic acid (10 mL) was heated at reflux for 6 h. The reaction mixture was left to cool to room temperature. The crystalline product so obtained was filtered off and recrystallized to give compound **5**.

Table 1. Analytical data of the new compound

Compd. no.	Yield (%)*	Mp (°C)	Crystn. solvent	M. formula	M. wt	Microanalysis calcd. (found) (%)		
						C	H	N
3	80	226–228	AcOH	$C_{22}H_{15}NO_5$	373.73	70.77 (70.64)	4.05 (3.85)	3.75 (3.60)
4	80	228–230	EtOH/H_2O	$C_{22}H_{17}N_3O_4$	387.40	68.21 (68.15)	4.42 (4.22)	10.85 (10.69)
5	60	270–272	AcOH	$C_{24}H_{19}N_3O_5$	429.25	67.13 (67.08)	4.45 (4.30)	9.79 (9.65)
6	73,[a] 60[b]	245–246	DMF/H_2O	$C_{22}H_{19}N_5O_3$	401.43	65.83 (65.70)	4.77 (4.65)	17.45 (17.25)
7	66,[a] 68,[b] 52,[c] 98[d]	232–234	AcOH	$C_{24}H_{21}N_5O_4$	443.33	65.01 (64.88)	4.75 (4.60)	15.80 (15.68)
8	65	210–212	EtOH	$C_{22}H_{16}N_2O_5$	388.38	68.04 (67.85)	4.15 (4.03)	7.21 (7.10)
9	60	>300	AcOH	$C_{22}H_{16}N_2O_5$	388.38	68.04 (68.00)	4.15 (3.89)	7.21 (7.05)
10	70,[a] 68,[e] 79[f]	264–266	Dioxane	$C_{22}H_{17}N_3O_5$	403.40	65.50 (65.32)	4.25 (4.01)	10.42 (10.22)
11	75	240–242	DMF	$C_{22}H_{18}N_4O_4$	402.41	65.67 (65.44)	4.51 (4.31)	13.92 (13.75)
12	55	204–206	DMF	$C_{22}H_{18}N_4O_4$	402.41	65.67 (65.54)	4.51 (4.25)	13.92 (13.88)
13	66,[c] 78[e]	>300	Dioxane	$C_{24}H_{20}N_4O_5$	444.00	64.86 (64.77)	4.54 (4.21)	12.61 (12.39)
14	68	>300	DMF	$C_{23}H_{17}N_3O_4S$	431.47	64.03 (63.85)	3.97 (3.69)	9.74 (9.66)
15	78	185–187	DMF/H_2O	$C_{23}H_{17}N_3O_4S$	431.47	64.03 (63.80)	3.97 (3.65)	9.74 (9.68)
16	70,[b] 65[g]	238–240	Acetone	$C_{23}H_{19}N_5O_3S$	445.50	62.01 (61.85)	4.30 (4.08)	15.72 (15.68)
17	70,[e] 63[g]	277–278	EtOH	$C_{23}H_{18}N_4O_4S$	446.49	61.87 (61.58)	4.06 (3.89)	12.55 (12.41)
18	67	>300	DMF	$C_{25}H_{17}N_3O_4S$	455.50	65.92 (65.78)	3.76 (3.60)	9.23 (9.11)
19	80	234–236	Pyridine	$C_{25}H_{17}N_3O_4S$	455.50	65.92 (65.80)	3.76 (3.59)	9.23 (9.08)
20	77,[f] 68[h]	202–204	Acetone	$C_{25}H_{18}N_4O_4S$	470.51	63.82 (63.69)	3.86 (3.75)	11.91 (11.80)
21	75,[e] 78[i]	230–232	Pyridine	$C_{25}H_{18}N_4O_4S$	470.51	63.82 (63.66)	3.86 (3.74)	11.91 (11.59)
22	63	>300	DMF	$C_{26}H_{17}N_3O_6S$	499.51	62.52 (62.30)	3.43 (3.22)	8.41 (8.15)
23	66	190–192	DMF	$C_{26}H_{17}N_3O_6S$	499.51	62.52 (62.29)	3.43 (3.18)	8.41 (8.28)
24	68,[f] 70[j]	260–263	DMF	$C_{26}H_{18}N_4O_6S$	514.52	60.70 (60.59)	3.53 (3.38)	10.89 (10.66)
25	68,[e] 64[k]	240–243	DMF	$C_{26}H_{18}N_4O_6S$	514.52	60.70 (60.55)	3.53 (3.21)	10.89 (10.58)

*Yield starting from compounds: [a]**3**, [b]**4**, [c]**5**, [d]**6**, [e]**8**, [f]**9**, [g]**15**, [h]**18**, [i]**19**, [j]**22**, and [k]**23**

Table 2. Spectral data of the new compounds

Cpd. no.	IR (KBr), $\tilde{\nu}$ (cm^{-1})	^1H NMR (DMSO-d_6), δ	Mass, m/z (I %)
3	2923 (C–H_{aliph}), 2700 (br, H-bonded OH), 1654–1642 (C═O), 1600, 1590	3.65 (s, 3H, NCH_3), 7.37 (t, 1H, C6-H), 7.58–7.92 (m, 7H, H_{arom}+ CH_{α}═CH), 8.17 (d, J = 6.4 Hz, 1H, C8-H), 8.21 (d, 1H, C8′-H), 9.02 (s, 1H, C2′-H), 9.24 (d, J = 16 Hz, 1H, CH═CH_{β})	373 (38.65) ($M^{+\cdot}$), 228 (8.90), 202 (11.29), 171 (100), 145 (1.46), 104 (12.34), 77 (25.02)
4	3323–2680 (H-bonded OH and NH), 2900 (CH_{aliph}), 1640 (C═O), 1620, 1612	3.58 (s, 3H, NCH_3), 6.84–6.92 (m, 3H, H_{arom}+ $H_{pyrazole}$), 7.22–7.75 (m, 6H, H_{arom}+ H_{olefin}), 8.02 (d, J = 7 Hz, 1H, C5-H), 8.15 (d, 1H, J = 13 Hz, H_{olefin})	387 (23.13) ($M^{+\cdot}$), 371 (9.24), 228 (6.17), 202 (9.09), 171 (39.43), 104 (14.25), 73 (100)
5	2955 (C–H_{aliph}), 1666 (C═O), 1652 (C═O), 1646 (C═O), 1622, 1610, 1585		429 (100) ($M^{+\cdot}$), 386 (57.48), 277 (20.96), 202 (20.23), 170 (22.47), 105 (14.91), 73 (88.27)
6	3322–2715 (br, H-bonded NH and OH), 1644 (C═O), 1620, 1600	3.21–3.38 (m, 2H, 4-$CH_{pyrazoline}$), 3.57 (s, 3H, NCH_3), 3.84 (m, 1H, 5-$CH_{pyrazoline}$), 4.97 (br, 1H, $NH_{pyrazoline}$), 6.82–6.98 (m, 3H, H_{arom}), 7.18–7.31 (m, 3H, H_{arom}), 7.40 (br, 1H, N-$H_{pyrazole}$), 7.47 (d, J = 7 Hz, 1H, H_{arom}), 7.64 (t, 1H, H_{arom}), 8.02 (d, J = 6.6 Hz, 1H, 5-$CH_{quinolone}$)	401 (11.96) ($M^{+\cdot}$), 241 (26.46), 202 (30.98), 175 (37.94), 104 (20.92), 73 (100)
7	3350–2800 (br, H-bonded OH and NH), 1656 (C═O), 1644 (C═O), 1620, 1605	2.21 (s, 3H, $NCOCH_3$), 3.24 (d, 1H, 4-$CH_{pyrazoline}$), 3.43 (d, 1H, 4-$CH_{pyrazoline}$), 3.58 (s, 3H, NCH_3), 3.97 (m, 1H, C3-$H_{pyrazoline}$), 6.81 (m, 3H, H_{arom}), 7.22–7.78 (m, 6H, H_{arom} + N-$H_{pyrazole}$), 8.10 (d, J = 6.8 Hz, 1H, C5-$H_{quinolone}$)	443 (21.06) ($M^{+\cdot}$), 242 (81.93), 171 (41.55), 104 (17.16), 77 (100)

(*continued*)

Table 2. Continued

Cpd. no.	IR (KBr), $\tilde{\nu}$ (cm^{-1})	^{1}H NMR (DMSO-d_6), δ	Mass, m/z (I %)
8	2900 (C–H_{aliph}), 2679 (br, H-bonded OH), 1644 (C=O), 1620, 1607	3.64 (s, 3H, NCH_3), 6.87–7.44 (m. 5H, H_{arom}), 7.59–7.88 (m, 2H, H_{arom}+ CH_{β}=CH), 7.97 (s, 1H, 3-$CH_{isoxazole}$), 8.05 (dd, J = 7.8 & 1.2 Hz, 1H, 5-$CH_{quinolone}$), 8.20 (d, J = 16 Hz, 1H, CH_{α}=CH), 11.20 (br, 1H, OH), 11.67 (br, 1H, OH)	388 (9.90) ($M^{+\cdot}$), 341 (74.17), 228 (10.79), 201 (9.99), 171 (100), 104 (52.91), 77 (89.45)
9	2678 (br, H-bonded OH), 2950 (C–H_{aliph}), 1650–1643 (C=O), 1600, 1584		388 (42.08) ($M^{+\cdot}$), 341 (100), 228 (2.47), 202 (3.22), 171 (18.21), 104 (49.83), 77 (79.48)
10	2850 (br, H-bonded OH), 2900 (C–H_{aliph}), 1650 (C=O), 1600, 1574	3.30–3.45 (m, 2H, 4-$CH_{isoxazoline}$), 3.56 (s, 3H, NCH_3), 4.25 (m, 1H, 5-$CH_{isoxazoline}$), 6.93–7.70 (m, 7H, H_{arom}), 8.02 (d, J = 6.7 Hz, 1H, 5-$CH_{quinolone}$), 8.19 (s, 1H, 3-$CH_{isoxazole}$), 10.67 (br, 1H, OH), 12.32 (br, 1H, OH)	403 (18.81) ($M^{+\cdot}$), 228 (19.40), 175 (7.17), 104 (39.19), 57 (100)
11	3409–2689 (br, H-bonded NH and OH), 1635 (C=O), 1618 (C=N), 1583	3.32–3.57 (m, 2H, 4-$CH_{isoxazoline}$), 3.68 (s, 3H, NCH_3), 4.26 (m, 1H, 3-CH $_{isoxazoline}$), 6.86–7.65 (m, 7H, H_{arom}), 8.02 (d, J = 6.7 Hz, 1H, 5-$CH_{quinolone}$), 8.19 (s, 1H, 3-CH $_{isoxazole}$), 11.89 (br, 1H, OH) 12.54 (br, 1H, OH)	402 (2.59) ($M^{+\cdot}$), 216 (32.53), 201 (25.66), 184 (100), 171 (43.80), 104 (35.80), 77 (63.20)
12	3220–2770 (br, H-bonded OH and NH), 1647 (C=O), 1622 (C=N), 1585	3.25–347 (m, 2H, 4-$CH_{2pyrazoline}$), 3.58 (s, 3H, NCH_3), 4.05 (m, 1H, 5-$H_{pyrazoline}$), 5.22 (br, 1H, $NH_{pyrazoline}$), 6.85–7.78 (m, 7H, H_{arom}), 7.98 (d, J = 6.8 Hz, 1H, 5-$H_{quinolone}$), 8.10 (s, 1H, 3-$H_{pyrazole}$)	402 (13.68) ($M^{+\cdot}$), 216 (55.08), 201 (23.29), 171 (51.88), 104 (39.23), 77 (55.08), 60 (100)

13	2943 (C–H_{aliph}), 2677 (br, H-bonded OH), 1650 (C═O), 1660 (C═O_{acetyl}), 1620 (C═N), 1587	2.41 (s, 3H, $COCH_3$), 3.01, 3.14 (dd, 2H, 4-$CH_{2pyrazolin}$), 3.67 (s, 3H, NCH_3) 5.59 (m, 1H, 5-$H_{pyrazoline}$), 6.79–7.46 (m, 7H, H_{arom}), 8.06 (d, $J = 6.6$ Hz, 1H, 5-$H_{quinolone}$), 8.15 (s, 1H, 3-$H_{isoxazole}$), 10.74 (br, 1H, OH), 12.55 (br, 1H, OH)	
14	3350–2700 (br H-bonded OH, NH), 1655–1640 (C═O), 1622, 1605, 1220 (C═S)	3.64 (s, 3H, NCH_3), 6.80–7.92 (m, 10H, H_{arom}+ H_{olefin} + 6-$H_{pyrimidine}$), 8.02 (d, $J = 6.7$ Hz, 1H, 5-$H_{quinolone}$), 10.08 (br, 1H, $NH_{pyrimidins}$), 12.54 (br, 1H, OH)	
15	3355–2740 (br, H-bonded NH and OH), 1654–1644 (C═O), 1618-1590, 1337–1223 (NH-C═S)	3.42–3.54 (m, 2H, 5-CH_2 $_{pyrimidine}$), 3.67 (s, 3H, N-CH_3), 4.23 (m, 1H, 6-H $_{pyrimidine}$), 6.96–7.82 (m, 7H, H_{arom}), 8.18 (dd, $J = 6.9$ & 1.1 Hz, 1H, 5-$H_{quinolone}$), 8.42 (s, 1H, C2-$H_{chromone}$), 9.18 (br, 1H, $NH_{pyrimidine}$), 12.52 (br, 1H, OH)	431 (4.88) ($M^{+\cdot}$), 228 (3.25), 202 (10.09), 171 (100), 104 (12.00), 73 (9.38)
16	3300–2660 (br, H-bonded NH and OH), 1644 (C═O), 1621, 1585, 1215 (NH-C═S)	3.47–3.53 (m, 2H, 5-$CH_{pyrimidine}$), 3.67 (s, 3H, NCH_3), 5.51–5.57 (br, 1H, 4-$CH_{pyrimidine}$), 6.76 (br, 1H, N-$H_{pyrimidine}$), 6.80–7.63 (m, 7H, H_{arom}), 8.08 (dd, $J = 7$ & 1.3 Hz, 1H, 5-$H_{quinolone}$), 8.21 (s, 1H, 3-$H_{pyrazole}$), 8.42 (br, 1H, $NH_{pyrazole}$), 12.44 (br, 1H, OH), 12.68 (br, 1H, OH)	445 (24.84) ($M^{+\cdot}$), 227 (33.60), 171 (21.38), 105 (18.15)
17	3340–2730 (br, H-bonded NH and OH), 1648 (C═O), 1624–1590, 1240 (NH-C═S).	3.46–3.56 (m, 2H, 5-CH_2 $_{pyrimidine}$), 3.72 (s, 3H, NCH_3), 5.63–5.68 (m, 1H, 4-$H_{pyrimidine}$), 7.01 (br, 1H, N-$H_{pyrimidine}$), 7.12–7.62 (m, 7H, H_{arom}), 7.98 (d, $J = 6.5$ Hz, 1H 5-H $_{quinolone}$), 8.66 (s, 1H, 3-$H_{isoxazole}$), 11.88 (br, 1H, OH), 12.76 (br, 1H, OH)	446 (20.01) ($M^{+\cdot}$), 73 (100)

(*continued*)

Table 2. Continued

Cpd. no.	IR (KBr), $\tilde{\nu}$ (cm^{-1})	^{1}H NMR (DMSO-d_6), δ	Mass, m/z (I %)
18	3322–2647 (br, H-bonded NH and OH), 2222 (C≡N), 1660–1646 (C=O), 1622, 1608, 1321, 1274 (NH-C=S)	3.66 (s, 3H, N-CH_3), 6.53 (d, J = 15.6 Hz, 1H, COCH=CH), 7.22–7.85 (m, 7H, H_{arom}), 8.05 (dd, J = 7.1 & 1.3 Hz, 1H, C5-H), 8.16 (d, J = 15.6 Hz, 1H, COCH=CH), 8.70 (s, 1H, 4-$H_{pyridine}$), 11.40 (br, 1H, N-$H_{pyridine}$), 12.43–12.52 (br, 2H, 2 × OH)	
19	3430–2650 (br, H-bonded NH and OH), 2226 (C≡N), 1655–1643 (C=O), 1621 (C=N), 1595, 1338, 1208 (NH-C=S)	3.65 (s, 3H, N-CH_3), 3.80 (m, 1H, 4-$H_{pyridine}$), 4.17 (d, J = 2.3 Hz, 1H, 3-$H_{pyridime}$), 6.12 (d, J = 5.3 Hz, 1H, 5-$H_{pyriidine}$), 7.20–7.66 (m, 7H, H_{arom}), 8.07 (dd, J = 6.8 & 1.2 Hz, 1H, 5-$H_{quinolone}$), 8.46 (s, 1H, 2-$H_{chromone}$), 9.91 (br, 1H, NH)	
20	3244–2779 (br, H-bonded NH and OH), 2212 (C≡N), 1645 (C=O), 1221 (C=S)	3.16–3.33 (m, 2H, 4-$H_{2isoxazoline}$), 3.67 (s, 3H, N-CH_3), 5.56 (m, 1H, 5-H $_{isoxazoline}$), 7.22–7.73 (m, 7H, H_{arom}), 7.99 (dd, J = 6.9 & 1.2 Hz, 1H, 5-$H_{quinolone}$), 8.92 (s, 1H, 4-$H_{pyridine}$), 11.47 (br, 1H, $NH_{pyridine}$), 12.43–12.39 (br, 2H, 2 × OH)	470 (3.49) ($M^{+\cdot}$), 401 (3.08), 256 (1.76), 105 (1.40), 73 (100)
21	3430–2650 (br, H-bonded NH and OH), 2215 (C≡N), 1643 (C=O), 1619 (C=N), 1210 (NH-C=S)	3.65 (s, 3H, N-CH_3) 4.43–4.74 (m, 2H, 3-H and 4-$H_{pyridine}$), 6.32 (d, J = 13.2, 1H, 5-$H_{pyridine}$,), 7.20–7.82 (m, 7H, H_{arom}), 7.96 (s, 1H, 3-$H_{isoxazole}$), 8.09 (d, J = 6.8 Hz, 1H, 5-$H_{quinolone}$), 9.62 (br, 1H, $NH_{pyridine}$), 12.45–12.39 (br, 2H, 2 × OH)	

22	3300–2650 (br, H-bonded NH and OH), 1648–1658 (C═O), 1618–1610, 1240 (NH-C═S)	3.64 (s, 3H, NCH_3), 6.85 (d, 1H, $J = 15.8$ Hz, COCH═CH), 7.18–7.71 (m, 7H, H_{arom}), 8.00 (d, 1H, $J = 15.7$ Hz, COCH═CH), 8.13 (dd, $J = 6.5$, 1.1 Hz, 1H, 5-$H_{quinolone}$), 8.24 (s, 1H, 4-H_{pyran}), 9.54 (br, 1H, NH), 12.49–12.72 (br, 1H, 2 × OH)	
23	3330–3150 (br, H-bonded NH and OH), 1650–1643 (C═O), 1618 (C═N), 1590, 1210 (NH-C═S)	3.63 (s, 3H, NCH_3), 4.44 (d, $J = 5.2$ Hz, 1H, 4-H_{pyran}), 5.26 (d, $J = 5.1$ Hz, 1H, 3-H_{pyran}), 6.83–7.54 (m, 7H, H_{arom}), 8.08 (d, $J = 6.2$ Hz, 1H, 5-$H_{quinolone}$), 8.42 (s, 1H, 2-$H_{chromone}$), 10.44 (br, 1H, NH), 11.32 (br, 1H, NH), 12.58 (br, 1H, OH)	499 (4.12) ($M^{+\cdot}$), 439 (3.31), 330 (2.69), 210 (1.99), 73 (100)
24	3240–3090 (br, H-bonded NH and OH), 1644 (C═O), 1595, 1200 (NH-C═S)	3.24 (m, 2H, 4-$H_{2\ isozazoline}$), 3.67–3.51 (s, 3H, NCH_3), 6.20, (t, 1H, 5-$H_{isoxazaline}$), 7.22–7.80 (m, 7H, H_{arom}), 8.11 (d, $J = 5.8$ Hz, 1H, 5-$H_{quinolone}$), 8.20 (s, 1H, 4-H_{pyran}), 9.54 (br, 1H, $NH_{pyrimidine}$), 12.49–12.53 (br, 2H, 2 × OH)	514 (3.27) ($M^{+\cdot}$), 202 (1.70), 189 (2.04), 175 (1.13), 105 (3.14), 73 (100)
25	3210–3000 (br, H-bonded NH and OH), 1643 (C═O), 1590, 1210 (NH-C═S)	3.64 (s, 3H, NCH_3), 4.07 (d, $J = 2.6$ Hz, 1H, 4-H_{pyran}), 5.63 (d, $J = 6.6$ Hz, 1H, 3-H_{pyran}), 7.18–7.78 (m, 7H, H_{arom}), 8.06 (d, $J = 6.8$ Hz,1H, 5-H), 8.15 (s, 1H, 3-H), 10.46 (br, 1H, $NH_{pyrimidine}$), 11.87 (br, 1H, $NH_{pyrimidine}$), 12.54 (br, 1H, OH)	

4-Hydroxy-3-[3′-(2-hydroxyphenyl)-3,4-dihydro-1′*H*,2*H*-3,4′-bipyrazol-5-yl]-1-methylquinolin-2(1*H*)-one (6)

A mixture of either **3** (1.87 g, 5 mmol) or compound **4** (1.94 g, 5 mmol) and hydrazine hydrate (0.5 mL, 10 mmol) in DMF (20 mL) was heated under reflux for 4 h and then poured into ice-cold water. The resulting solid was filtered and crystallized to give bipyrazole **6**.

3-[2-Acetyl-3′-(2-hydroxyphenyl)-3,4-dihydro-1′*H*,2*H*-3,4-bipyrazol-5-yl)-4-hydroxy-1-methylquinolin-2(1*H*)-one (7)

Procedure A

Compound **5** (2.15 g, 5 mmol) and hydrazine hydrate (0.25 mL, 5 mmol) in DMF (10 mL) were heated under reflux for 4 h. After cooling, the precipitate was filtered and crystallized to give compound **7**.

Procedure B

A mixture of either **3** (1.87 g, 5 mmol) or compound **4** (1.94 g, 5 mmol) and hydrazine hydrate (0.5 mL, 10 mmol) in glacial acetic acid (20 mL) was heated under reflux for 3 h and then poured into ice-cold water. The resulting solid was filtered and crystallized to give compound **7**.

Procedure C

A solution of compound **6** (1.2 g, 3 mmol) in glacial acetic acid (10 mL) was boiled for 3 h. The reaction solution was left overnight to give a crystalline product, which was filtered off and recrystallized to give compound **7**.

4-Hydroxy-3-{*E*-3-[5-(2-hydroxyphenyl)isoxazol-4-yl]acryloyl}-1-methylquinolin-2(1*H*)-one (8)

A mixture of **3** (1.87 g, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol) in ethanol (20 mL) and DMF (5 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature and diluted with water (25 mL). The solid was collected by filtration and crystallized to give compound **8**.

4-Hydroxy-1-methy1-3-[5-(4-oxo-4*H*-chromen-3-y1)-4, 5-dihydroisoxazol-3-yl)-quinolin-2(1*H*)-one (9)

A mixture of **3** (1.87 g, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol) in glacial acetic acid (10 mL) was refluxed for 6 h. On cooling the reaction mixture to room temperature, a solid crystalline product was afforded, which was filtered off and recrystallized to give isoxazole **9**.

4-Hydroxy-3-[5-(2-hydroxypheny1)-4′,5′-dihydro-4, 5′-biisoxazol-3′-y1]-1-methy1-quinolin-2(1*H*)-one (10)

A solution of **3** (1.87 g, 5 mmol) or compound **8** (1.94 g, 5 mmol) in pyridine (10 mL) or **9** (1.94 g, 5 mmol) in DMF (15 mL) was treated with hydroxylamine hydrochloride (0.35 g, 5 mmol) and heated under reflux for 4 h. The reaction mixture was left to cool and acidified with dilute HCl (25 mL, 6 M). The solid was collected by filtration and crystallized to give bisoxazole **10**.

4-Hydroxy-3-{5-[3-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-4, 5-dihydroisoxazol-3-y1}-1-methylquinoline-2(1*H*)-one (11)

To a suspension of compound **9** (1.94 g, 5 mmol) in DMF (10 mL), hydrazine hydrate (0.4 mL, 8 mmol) was added, and the reaction mixture was refluxed for 4 h. The precipitate so formed after cooling was filtered and crystallized to give compound **11**.

4-Hydroxy-3-{5-[5-(2-hydroxyphenyl)isoxazol-4-y1]-4,5-dihydro-1*H*-pyrazol-3-yl}-1-methy1quinolin-2(1*H*)-one (12)

A mixture of compound **8** (1.94 g, 5 mmol) and hydrazine hydrate (0.4 mL, 8 mmol) in DMF (10 mL) was refluxed for 2 h. The solid that deposited on cooling to room temperature was filtered off and crystallized to give compound **12**.

3-{1-Acetyl-5-[5-(2-hydroxypheny1)isoxazol-4-y1]-4,5-dihydro-1*H*-pyrazol-3-y1}-4-hydoxy-1-methylquinolin-2(1*H*)-one (13)

Procedure A

A solution of compound **5** (2.15 g, 5 mmol) and hydrazine hydrate (0.4 mL, 8 mmol) in pyridine (10 mL) was refluxed for 4 h. Then the reaction

mixture was poured onto acidified ice-cold dilute HCl (25 mL, 6 M), and the resulting deposits were filtered and crystallized to give compound **13**.

Procedure B

A mixture of compound **8** (1.94 g, 5 mmol) and hydrazine hydrate (0.5 mL, 10 mmol) in glacial acetic acid (20 mL) was heated under reflux for 3 h and then poured into ice-cold water. The resulting solid was filtered and crystallized to give compound **13**.

Procedure C

A solution of compound **12** (1.2 g, 3 mmol) in glacial acetic acid (10 mL) was heated under reflux for 3 h. The reaction solution was left overnight to give crystalline product **13**.

4-Hydroxy-3-{*E*-3-[4-(2-hydroxypheny1)-2-thioxo-3*H*-pyrimidin-5-y1] acryloyl}-1-methylquinolin-2(1*H*)-one (14)

A mixture of **3** (3.73 g, 10 mmol), thiourea (0.77 g, 10 mmol), and sodium ethoxide (0.23 g of sodium in 5 mL of ethanol; 10 mmol) in ethanol (20 mL) was refluxed for 6 h. The reaction mixture was then cooled, poured onto water (50 mL), and acidified with dilute HCl (50 mL, 6 M) to give a solid precipitate, which was filtered off and crystallized to give pyrimidine **14**.

4-Hydroxy-1-methyl-3-[6-(4-oxo-4*H*-chromen-3-y1)-2-thioxo-1,2,5,6-tetrahydro-pyrimidin-4-y1]quinolin-2(1*H*)-one (15)

A mixture of **3** (1.87 g, 5 mmol) and thiourea (0.39 g, 5 mmol) in ethanol (10 mL) containing hydrochloric acid (0.5 mL, 36%) was heated under reflux for 3 h. Then the reaction mixture was poured into ice-cold water. The resulting precipitate was filtered and crystallized to give compound **15**.

4-Hydroxy-3-{6-[5(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-2-thioxo-1,2,5,6-tetrahydro-pyrimidin-4-yl}-1-methylquinolin-2(1*H*)-ones (16) and 4-Hydroxy-3-{6-[5-(2-hydroxyphenyl)-1*H*-isoxazol-4-yl]-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl}-1-methylquinolin-2(1*H*)-ones (17)

Procedure A

A mixture of compound **15** (2.16 g, 5 mmol) and the appropriate reagent [hydrazine hydrate (0.25 mL, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol)] in ethanol (25 mL, 95%) was treated with finely powdered potassium hydroxide (0.56 g, 10 mmol) and then refluxed for 3 h. Afterward it was left to cool and acidified with dilute HCl (6 M) until complete precipitation. The obtained yellow precipitate was filtered, dried, and crystallized to give pyrazole **16** and isoxazole **17**, respectively.

Procedure B

A mixture of either compound **4** or **8** (1.94 g, 5 mmol) and thiourea (0.39 g) in glacial acetic acid (20 mL) was heated at reflux for 4 h and then poured into ice-cold water. The resulting solid was filtered and crystallized to afford pyrazole **16** and isoxazole **17**, respectively.

5-[*E*-3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxoprop-1-enyl]-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (18)

Sodium ethoxide (0.23 g of sodium in 5 mL of ethanol; 10 mmol) was added to a mixture of **3** (1.87 g, 5 mmol) and cyanothioacetamide (0.5 g, 5 mmol) in ethanol (20 mL). The mixture was heated under reflux on a boiling water bath for 4 h. Then the reaction mixture was left to cool and acidified with dilute HCl (50 mL, 6 M). The solid was filtered and crystallized to afford pyridine **18**.

6-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4-(4-oxo-4*H*-chromen-3-yl)-2-thioxo-1,2,3,4-tetahydropyridine-3-carbonitrile (19)

Piperidinium acetate (0.44 g, 3 mmol) was added to a mixture of **3** (1.87 g, 5 mmol) and cyanothioacetamide (0.5 g, 5 mmol) in ethanol (20 mL). The mixture was heated under reflux on a boiling water bath for 4 h. The solid was filtered, washed with water, and crystallized to afford pyridine **19**.

5-[(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydroisoxazol-5-yl]-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (20) and 6-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4-[5-(2-hydroxyphenyl)-isoxazol-4-yl]-2-thioxo-1,2,3,4-tetrahydropyridine-3-carbonitnile (21)

Procedure A

A mixture of compound **18** or **19** (2.28 g, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol), in pyridine (5 mL) and/or DMF (20 mL), was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and acidified with dilute HCl (20 mL, 6 M). The solid was collected by filtration and crystallized to give compounds **20** and **21**, respectively.

Procedure B

Cyanothioacetamide (0.5 g, 5 mmol) was added to either a mixture of compound **9** and piperidinium acetate (0.44 g, 3 mmol) or compound **8** (1.94 g, 5 mmol) and sodium ethoxide (0.23 g sodium in 5 mL ethanol; 10 mmol), in absolute ethanol (30 mL). The mixture was refluxed for 4 h, on a boiling water bath, then cooled and acidified with dilute HCl (20 mL, 6 M). The solid that obtained was filtered off and crystallized to give compounds **20** and **21**, respectively.

6-[*E*-3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropenyl]-7-(2-hydroxyphenyl)-2-thioxo-2,3-dihydropyrano[2,3-*d*]pyrimidin-4-one (22)

Sodium ethoxide (0.23 g of sodium in 5 mL of ethanol; 10 mmol) was added to a mixture of **3** (1.87 g, 5 mmol) and 2-thiobarbituric acid (0.72 g, 5 mmol), in ethanol (20 mL). The reaction mixture was heated under reflux on a boiling water bath for 4 h, left to cool, and acidified with dilute HCl (25 mL, 6 M). The solid so obtained was filtered and crystallized to give pyrimidine **22**.

7-(4-Hyroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-(4-oxo-4*H*-chromen-2-yl)-2-thioxo-1,2,3,5-tetrahydropynano[2,3-*d*] pyrimidin-4-one (23)

Piperidinium acetate (0.44 g, 3 mmol) was added to a mixture of **3** (1.87 g, 5 mmol) and 2-thiobarbituric acid (0.72 g, 5 mmol), in ethanol (20 mL). The mixture was heated under reflux on a boiling water bath for 4 h.

The solid was filtered, washed with water, and crystallized to afford pyrimidine **23**.

6-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydroisoxazol-5-yl]-7-(2-hydroxyphenyl)-2-thioxo-2,3-dihydropyrano[2,3-*d*]pyrimidin-4-one (24) and 7-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)-5-[5-(2-hydroxy-phenyl) isoxazol-4-yl]-2-thioxo-1,2,3,5-tetrahydropyrano[2,3-*d*]pyrimidin-4-one (25)

Procedure A

A mixture of compound **22** or **23** (2.5 g, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol), in pyridine (5 mL) and/or DMF (20 mL), was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and diluted with acidified cold water (20 mL). The solid was collected by filtration and crystallized to give isoxazoline **24** and isoxazole **25**, respectively.

Procedure B

A mixture of either compound **9** (1.94 g, 5 mmol) and sodium ethoxide (0.23 g of sodium in 5 mL of ethanol; 10 mmol) or compound **8** (1.94 g, 5 mmol) and piperidinium acetate (0.44 g, 3 mmol), in absolute ethanol (30 mL), was treated with 2-thiobarbituric acid (0.72 g, 5 mmol). The mixture was then refluxed for 4 h on a boiling water bath. After that, it was cooled and acidified with dilute HCl (50 mL, 6 M). The solid was filtered off and crystallized to give the isoxazoline **24** and isoxazole **25**, respectively.

ACKNOWLEDGMENTS

The authors thank E. A. Mohamed and M. M. Ismail of the Chemistry Department, Faculty of Education, Ain Shams University, and Akram Hassan, of the Ministry of Education, for their valuable services and facilities.

REFERENCES

1. Abass, M. *Heterocycles* **2005**, *65*, 901.
2. Abass, M.; Mostafa, B. B. *Bioorg. Med. Chem.* **2005**, *13*, 6133.
3. Tzeng, C.-C.; Chen, Y.-L. *Chin. Pharm. J.* **2002**, *54*, 229.

4. Passarotti, C. M.; Valenti, M.; Passarella, D.; Martinelli, M. *Boll. Chim. Farm.* **1999**, *138*, 311.
5. Tougou, K.; Nakamura, A.; Watanabe, S.; Okuyama, Y.; Morino, A. *Drug. Metab. Disp.* **1998**, *26*, 355.
6. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 11.
7. Sharma, A. K.; Khosla, R.; Kela, A. K.; Mehta, V. L. *Indian J. Pharm.* **1994** *26*, 249.
8. Abass, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *170*, 1413.
9. Abass, M.; Hassan, A. *Chem. Papers* **2003**, *57*, 267.
10. Abass, M. *Synth. Commun.* **2000**, *30*, 2735.
11. (a) Abass, M.; Othman, E. S. *Synth. Commun.* **2001**, *31*, 3361; (b) Abass, M.; Ismail, M. M. *Chem. Papers* **2000**, *54*, 187.
12. (a) Abdel-Megid, M.; Ismail, M. M. *Int. J. Chem.* **2002**, *12*, 287; (b) Ismail, M. M.; Abdel-Megid, M.; Hassan, M. M. *Chem. Papers* **2004**, *58*, 117.
13. Chimenti, F.; Bizzari, B.; Manna, F.; Bolasco, A.; Secci, A.; Chimenti, P.; Granese, A.; Riveanera, D.; Lilli, D.; Scaltrito, M. M.; Branciaglia, M. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 603.
14. Jeong, T. S.; Kim, K. S.; An, S.-J.; Cho, K.-H.; Lee, S.; Lee, W. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2715.
15. Ahn, J. H.; Kim, H.-M.; Jung, S.-D.; Yang, S.-D.; Cheon, H. G.; Kim, S. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4461.
16. Palaska, E.; Aytamir, M.; Uzbay, I. T.; Erol, D. *Eur. J. Med. Chem.* **2001** *36*, 539.
17. Li, X. B.; Inouei, T.; Abekawai, T.; Yirui, F.; Koyama, T. *Eur. J. Pharm.* **2004** *50*, 145.
18. Silver, K. S.; Soderlund, D. M. *Pesticid. Biochem. Physiol.* **2005**, *81*, 136.
19. Silva, N. M.; Tributino, J. L.; Miranda, A. L. P.; Barreirg, E. J.; Fraga, C. A. *Eur. J. Med. Chem.* **2002**, *37*, 163.
20. Sperandeo, N. R.; Brinon, M. C.; Brun, R. *Il Farmaco* **2004**, *59*, 431.
21. Kai, H.; Matsumoto, H.; Hattori, N.; Takase, A.; Fujiwara, T.; Sugimoto, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1997.
22. Bassapa, M.; Sadashiva, M. P.; Mantelingu, K.; Swamy, S. N. *Bioorg. Med. Chem.* **2003**, *11*, 4539.
23. Lee, J. S.; Cho, Y. S.; Chang, M. H.; Koh, H. R.; Chung, B. Y.; Pae, A. N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4117.
24. Pastor, J.; Alcazar, J.; Alvarez, R. M.; Andres, J. I.; Cid, J. M.; De Lucas, A. I.; Diaz, A.; Fernandez, J.; Font, L. M.; Itorrino, L.; Lafuento, C.; Martine, S.; Bakker, M. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2917.
25. Matucz, E.; Moricz, K.; Gigler, G.; Simo, A.; Barkoczy, J.; Levay, G.; Harsing, L. G., Jr.; Szenas, G. *Brain Res.* **2004**, *10*, 210.
26. Kumar, M. S.; Swamy, S. N.; Mahendra, M.; Prasad, J. S.; Veswanath, B. S.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3679.
27. Seebacher, W.; Michi, G.; Belaj, F.; Brun, R.; Saf, R.; Weis, R. *Tetrahedron* **2003**, *59*, 2811.
28. Sabitha, G. *Aldrichimica Acta* **1996**, *29*, 15.
29. Shanker, M. S. S.; Reddy, R. B.; Chandra, G. V. P.; Reddy, Y. D. *Asian. J. Chem.* **1992**, *4*, 166.
30. Nazzei, M.; Sottafattori, E.; Dondero, R.; Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmacher, A. A. *Synlett* **2004**, *8*, 2287.
31. Tomita, K. J. *Pharm. Soc. Jpn.* **1951**, *71*, 1100.
32. Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron* **1974**, *30*, 3553.