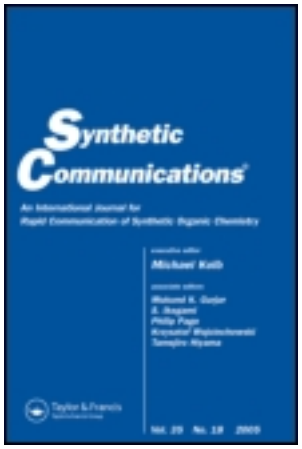

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Spectral Characterization of Novel 3-Phenyl-2-Substituted Quinazoline and Fused Quinazoline Derivatives

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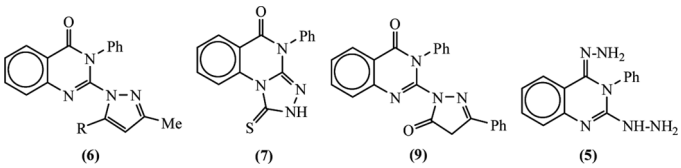
GRAPHICAL ABSTRACT



Abstract *3-phenyl-2-thioxo-quinazolin-4(3*H*)one* ***1*** *was utilized for the construction of some novel 2-substituted quinazolin-4(3*H*)one derivatives through the formation of 2-hydrazinyl quinazolinone, which was used as the key starting material for the synthesis of 2-heteryl quinazolines via the reaction with one carbon donors, -diketones and -ketoester. Infrared,* ^{1}*H NMR, and mass spectra of the synthesized compounds were discussed. Some of them showed promising anti-inflammatory activity.*

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Keywords Anti-inflammatory; hydrazino; pyrazolone; pyrazolo quinazoline; quinazolin-4(3*H*)one; triazolthione

INTRODUCTION

The selective pressure exerted by antibiotic treatment has made many pathogenic bacteria resistant to common antibiotics. New drugs are needed to resolve this serious public health problem. Special attention was recently paid to the quinazoline derivatives. Many derivatives of this system showed antifungal,[1] antibacterial,[2] antitumor,[3] anti-inflammatory,[4] anticonvulsant,[5–7] analgesic,[8,9] and antitubercular[10] activities. Moreover, quinazoline derivatives have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficiency against solid tumors.[11–13]

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These diverse biological activities initiated our interest in the synthesis of some quinazoline derivatives bearing other heterocycles that have a broad spectrum of biological activities, like pyrazole, triazole, and oxadiazole.

RESULTS AND DISCUSSION

These findings prompted us to synthesize a variety of quinazolinone derivatives via the reaction of anthranilic acid with arylisothiocyanate[14] with the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds. The key intermediate, 3-phenyl-2-thioxo- quinazolin-4 (3*H*)one **1**, was prepared.[15] Structure **1** was confirmed by its low R_f value, high melting point, and solubility in sodium hydroxide solution, beside the correct analytical and spectroscopic data. Full analysis of the mass spectrum of **1** shows the correct molecular ion peak at $m/z = 254$ (69.49%), which upon loss of the hydrogen radical yielded the cation (M − 1) at $m/z = 253$ (100%) as the base peak.

Furthermore, acylation of compound **1** with lauroyl chloride in refluxing pyridine afforded the N-acylation product **2**. The structure **2** was substantiated from the correct molecular weight determination and analytical and spectral data. The infrared (IR) spectrum of **2** displayed $\upsilon_{C=O}$ at 1737 cm^{-1} and 1687 cm^{-1}, and no band appeared for the NH group. Moreover, the electron-impact–mass (EI-MS) spectrum shows the correct molecular ion peak at $m/z = 436$ (0.04%).

When compound **1** was reacted with ethyl iodide in boiling ethanol in the presence of sodium hydroxide, the *S*-alkylation product 2-(ethylthio)-3-phenyl-quinazolin-4(3*H*)one **3** was obtained. The structure of **3** was confirmed from the correct analytical and spectroscopic data.

The mass spectrum of **3** is completely in accord with the proposed structure. The EI fragmentation pattern of **3** shows the correct molecular ion peak at $m/z = 282$ (30.61%), which upon loss of the ethyl radical afforded the daughter ion at $m/z = 253$ (45.22%). Loss of the thioethyl radical gave the cation at $m/z = 221$ (44.79%).

Treatment of compound **1** with hydrazine hydrate (1:1) in refluxing dioxane afforded 2-hydrazinyl-3-phenyl quinazolin-4(3*H*)one **4**. The same product was obtained upon treatment of **3** with hydrazine hydrate. The long duration of the reaction (22 h) might be due to the presence of a bulky phenyl ring at position 3, which might reduce the reactivity of the quinazolinone ring system at C-2 position. The reaction of **1** with excess hydrazine hydrate yielded 2-hydrazinyl-4-hydrazono-3-phenyl-3,4-dihydroquinazoline **5**. The structures of **4** and **5** were confirmed from the correct analytical and spectroscopic data.

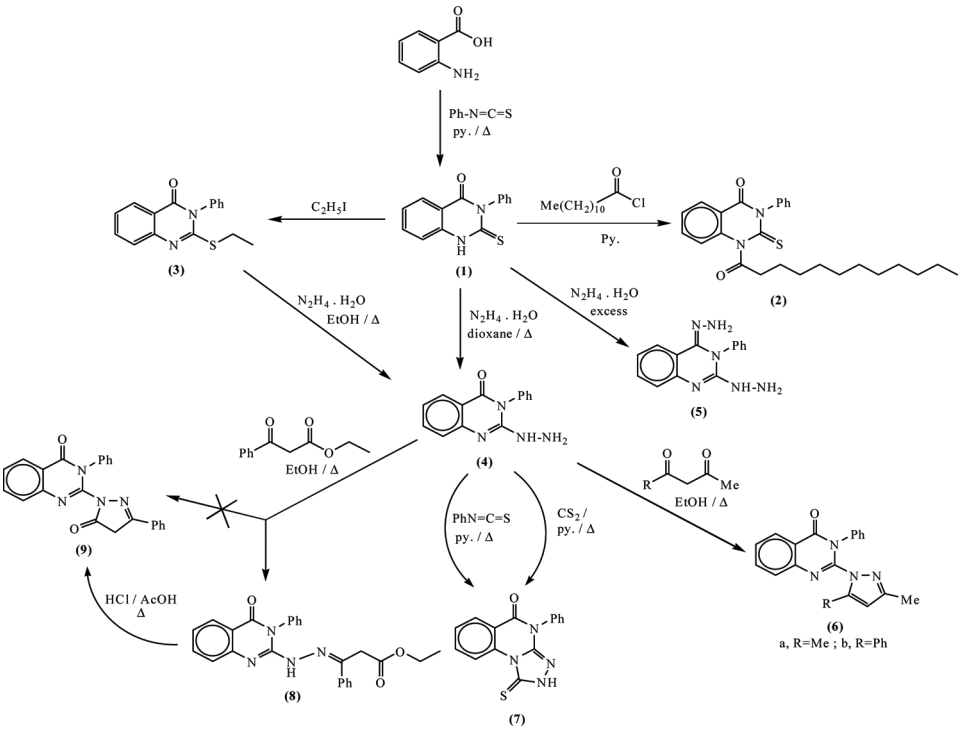
The EI fragmentation pattern for the mass spectrum of **4** shows the correct molecular ion at $m/z = 252$ (70.2%).

The conversion of **1** and **3** to **4** could be summarized according to the mechanism shown in Scheme 2.

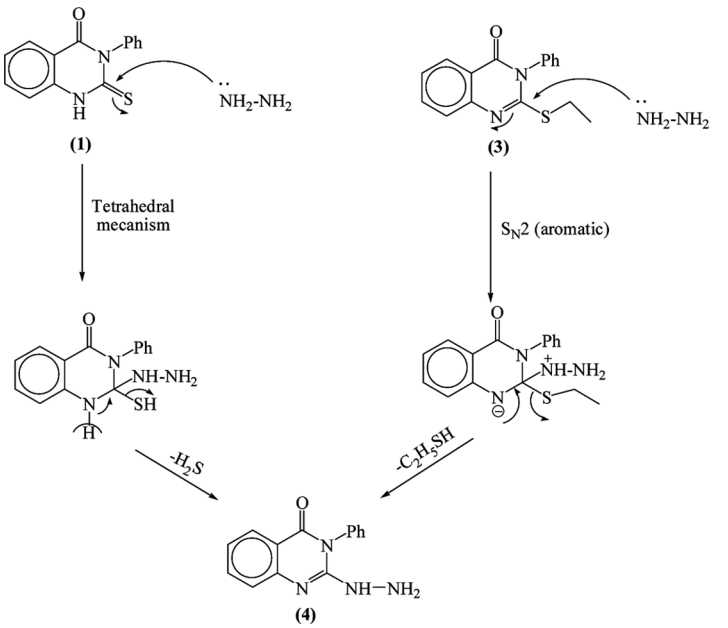
Compound **1** in the presence of excess hydrazine yielded **5**, whose structure was confirmed by IR and ^{1}H NMR spectra.

The formation of compound **5** could be visualized as shown in Scheme 3.

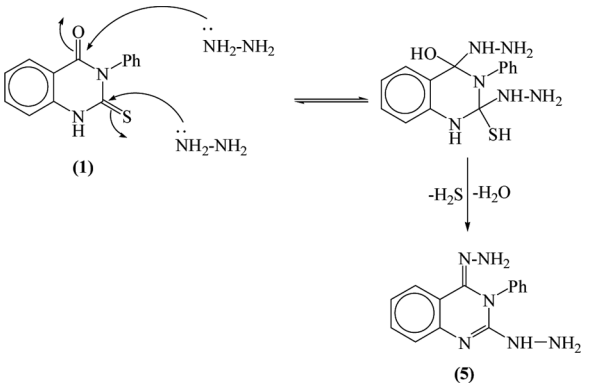
It has been reported[16] that hydrazinopyrimidine can be considered as a key starting material for the synthesis of diverse nitrogen bridgehead compounds. Thus,



Scheme 1.



Scheme 2.



Scheme 3.

compound **4** was subjected to react with electrophilic reagents, such as β-diketones, carbon disulfide, phenyl isothiocyanate, and ethylbenzoylacetate.

When compound **4** was allowed to react with acetyl acetone and/or benzoyl acetone in boiling ethanol, 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-phenyl quinazolin-4-(3*H*)-one **6a** and 2-(3-methyl-5-phenyl-1*H*-pyrazol-1-yl)-3-phenyl quinazolin-4 (3*H*)-one **6b** were afforded, respectively. Structure **6** was substantiated from the analytical and spectroscopic data.

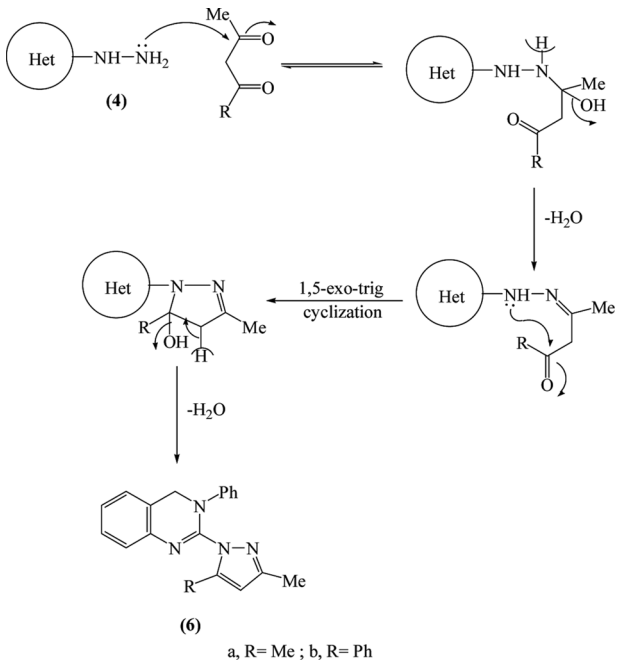
Full analysis for the mass spectrum of **6a** shows the correct molecular ion peak at $m/z = 316$ (100%), which represents the base peak. The mass spectrum of compound **6b** shows the molecular ion peak at $m/z = 378$ (16.6%), which upon loss of pyrazolyl moiety yielded the cation at $m/z = 221$ (14.1%). The base peak at $m/z = 77$ (100%) represents the phenyl cation $C_6H_5^+$. Compound **4** was converted to the pyrazole derivatives **6a** and **6b** according to the pathway shown in Scheme 4.

Heterocyclic *o*-aminocarbonitriles including furans, pyrimidines, and quinazolines reacted with carbon disulfide under different conditions to afford biologically interesting fused thiazines and/or pyrimidinedithione. However, when compound **4** was treated with carbon disulfide in refluxing pyridine, it yielded 4-phenyl-1-thioxo-1,2-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)one **7**. The structure of compound **7** was deduced from the spectral data.

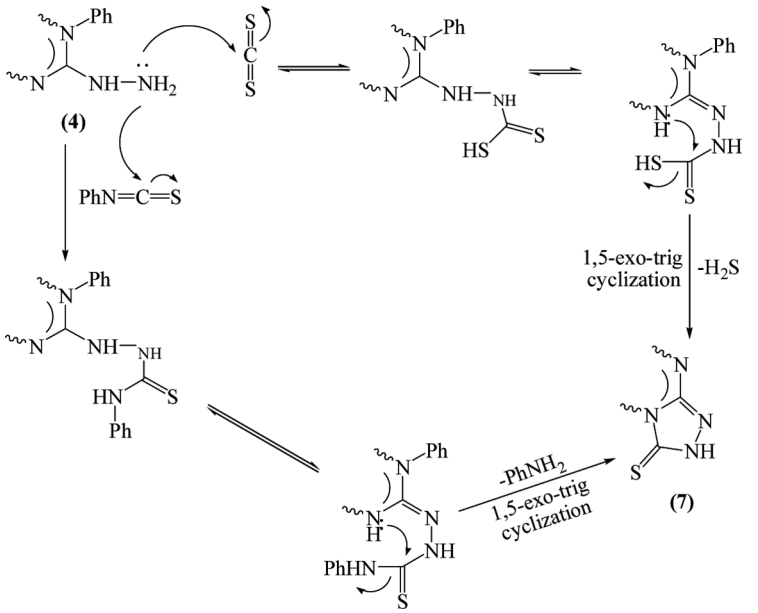
The ^{1}H NMR indicates the presence of thiolactam⇌thiolactim form. The EI fragmentation pattern of the mass spectrum of compound **7** supported the assigned structure, which shows the correct molecular ion peak at $m/z = 294$ (54.1%).

Treatment of compound **4** with phenylisothiocyanate in refluxing pyridine afforded the compound **7** as the sole product in fairly good yield. This is confirmed by comparison with the previous product obtained from the reaction of **4** with carbon disulfide M = 294 (100%). The reaction of **4** with CS_2 and/or phenylisothiocyanate to give **7** could be summarized as shown in Scheme 5.

It was reported that the reaction of hydrazino-pyrimidine derivative with β-ketoester was claimed to afford the pyrazolone derivative.[16] Herein, when compound **4** was allowed to react with ethyl benzoacetate in boiling ethanol, it afforded the condensation product ethyl-3-[2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)hydrazono]-3-phenyl



Scheme 4.



Scheme 5.

propanoate **8** and no pyrazolone derivative **9** was obtained. The spectroscopic data of the product obtained confirm structure **8**.

Furthermore, the EI fragmentation pattern of the mass spectrum of **8** confirmed the assigned structure. On the other hand, ring closure of the latter compound **8** in the HCl/AcOH mixture led to the construction of a new pyrazolone ring linked to the quinazoline nucleus with the formation of **9**. The structure of **9** was illustrated from their analytical and spectral data.

EXPERIMENTAL

Melting points are measured on an electrothermal melting-point apparatus. Elemental analyses were carried out at the microanalytical unit at Cairo Univeristy. The IR spectra were measured on a Unicam SP-1200 spectrometer using the KBr wafer technique. The ^{1}H NMR spectra were measured in dimethylsulfoxide (DMSO-d_6) on a Varian Plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP-1000EX instrument operating at 70 eV.

General Procedure for the Preparation of 1[15]

A mixture of anthranilic acid (0.02 mol, 2.74 g) and phenyl isothiocyanate (0.02 mol, 2.5 ml) in dry toluene (30 ml) was heated under reflux for 4 h. The product deposited during reflux was collected by suction, washed by ethanol, dried, and then recrystallized from dioxane to give 3-phenyl-2-thioxo quinazolin-4(3*H*)-one **1**.

3-Phenyl-2-thioxo quinazolin-4(3*H*)-one (1, $C_{14}H_{10}N_2OS$)

Pale yellow crystals (86% yield); mp: 305–306 °C. IR: υ_{max} 3243 (NH), 1663 (C=O), 1621 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ (ppm) 7.26–7.97 (m, 9H, ArH), 13.01 (s, 1H, NH, exchangeable). MS: *m/z* (%) 254 ($M^{\cdot+}$, 69), 253 (100), 119 (26), 92 (25), 90 (16), 77 (26), 64 (15). Anal. calcd. for $C_{14}H_{10}N_2OS$ (254): C, 66.14; H, 3.93; N, 11.02; S, 12.59. Found: C, 66.19; H, 4.07; N, 11.43; S, 12.71.

General Procedure for Hydrazinolysis of 1 or 3

An equimolar amount of **1** or **3** (0.003 mol) and hydrazine hydrate (0.003 mol) in ethanol (30 ml) were refluxed for 6 h. The solid product formed was filtered off and recrystallized from ethanol to give 2-hydrazinyl-3-phenyl quinazolin-4(3*H*)-one **4**.

2-Hydrazinyl-3-phenyl quinazolin-4(3*H*)-one (4, $C_{14}H_{12}N_4o$)

Colorless crystals (50% yield); mp: 205–207 °C. IR: υ_{max} 3472, 3303, 3173 (NH_2, NH), 1648 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ (ppm) 4.2 (br.s, 2H, NH_2, exchangeable), 7.08–7.92(m, 9H, ArH), 8.17 (br.s, 1H, NH, exchangeable). MS: *m/z* (%) 252 ($M^{\cdot+}$, 65.4), 251 (20), 222 (41), 221 (49), 207 (24), 133 (25), 120 (42), 119 (42), 118 (22), 104 (28), 92 (52), 91 (41), 77 (100). Anal. calcd. for $C_{14}H_{12}N_4O$ (252): C, 66.66; H, 4.76; N, 22.22. Found: C, 66.90; H, 4.95; N, 22.53.

Complete experimental details can be found online in the Supplemental Materials.

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