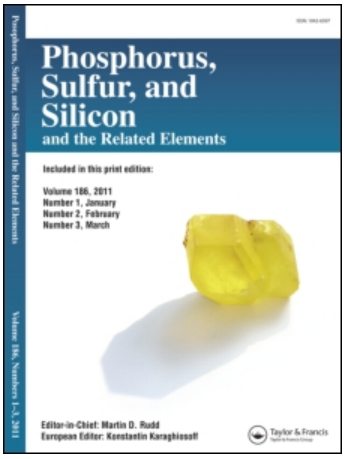

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Novel Quinazolinone Derivatives as Possible Antitumor Agents

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*The synthesis of a novel series of quinazolinone derivatives **6–15** having the biologically active thioxo group utilizing 2-isothiocyanato-benzoic acid methyl ester **2** is reported. Their structures have been confirmed on the basis of elemental analyses and (IR, ^{1}H NMR, and mass) spectral data. Preliminary testing for the in vitro antitumor activity of some synthesized compounds against Ehrlich Ascities Carcinoma cells was carried out.*

Keywords Antitumor activity; quinazoline-4(3H)-one

INTRODUCTION

Quinazolines and condensed quinazolines have received much attention over the years because of their interesting pharmacological properties.[1–6] In our laboratory considerable effort recently has been invested in the synthesis and evaluation of heterocyclic compounds containing the quinazoline and thienopyrimidine nucleus, leading to numerous compounds with promising antitumor activity.[7–12] Moreover, the quinazoline function is quite stable[13] and has inspired medicinal

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TABLE I Physical Properties and Molecular Formula of the Synthesized Compounds

Compound No.	M.P. (°C)	Yield %	Mol. Formula (Mol-wt)
3	78	90	$C_{11}H_{13}NO_3S$ (239.29)
4	40	80	$C_{12}H_{15}NO_4S$ (269.32)
5	232	60	$C_{14}H_{12}N_2O_3S$ (288.32)
6	238	75	$C_{10}H_{10}N_2O_2S$ (222.26)
7	240	85	$C_{11}H_{12}N_2O_2S$ (236.29)
8	222	89	$C_{13}H_{12}N_2O_3S$ (276.31)
9	254	90	$C_{16}H_{12}N_2O_3S$ (312.06)
10	250	60	$C_{15}H_{10}N_2O_3S$ (298.32)
11	252	85	$C_{16}H_{12}N_2O_3S$ (312.06)
12	220	80	$C_{15}H_9BrN_2O_3S$ (377.21)
13	250	70	$C_{11}H_{10}N_2O_3S$ (250.27)
14	>300	65	$C_{17}H_{14}N_2O_3S$ (326.37)
15	218	50	$C_{13}H_8ClN_3OS$ (289.74)

chemists to introduce this stable fragment on bioactive moieties to synthesize new potential medicinal agents. In the present study the thioxo group has been incorporated at position-2 of the quinazolinone to result in 2-thioxo or mercaptoquinazolinone likely to have superior antitumor properties.

MATERIALS AND METHODS

General Considerations

Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the micronalytical unit of Cairo University. All compounds were within ±0.4% of the theoretical values.

Melting points (Table I) are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK). IR

spectra were measured on an Infinity gold FTIR spectrophotometer (Unicam, UK). ^{1}H NMR spectra were obtained on Bruker 300 MHz NMR spectrophotometer (Bruker, Munich, Switzerland) in Deuterated chloroform ($CDCl_3$) as a solvent, using tetramethylsilane (TMS) as an internal standard. Mass spectra were run on a Varian MAT 311-A 70 e.v. (Varian, Fort Collins, USA) and MS. model 5988 (Hewlett-Packard, USA).

Synthesis

2-Ethoxythiocarbonylamino-benzoic Acid Methyl Ester (3)

A solution of **2** (0.01 mol) in absolute ethanol (10 mL) was refluxed for 8 h. The solid obtained was recrystallized from ethanol to give **3** (Table I). **IR (kBr, cm^{-1})**: 3188 (NH), 2990, 2900 (CH aliph.), 1692 (C=O), 1260 (C=S). δ 1.4 [t, 3H, CH_3], 3.7 [s, 3H, OCH_3], 4.65 [q, 2H, CH_2], 7.0–8.4 [m, 4H, Ar-H], 11.7 [s, 1H, NH].

2-(2-Methoxy-ethoxythiocarbonylamino)-benzoic Acid Methyl Ester (4)

A solution of **2** (0.01 mol) in 2-methoxy ethanol (10 mL) was refluxed for 8 h. The solid obtained was recrystallized from ethanol to give **4** (Table I). **IR (kBr, cm^{-1})**: 3176 (NH), 2892 (CH aliph.), 1696 (C=O), 1264 (C=S). δ 3.5, 3.8 [2s, 6H, $2OCH_3$], 3.99 [t, 2H, OCH_2], 4.75 [t, 2H, OCH_2], 7.1–8.5 [m, 4H, Ar-H], 11.7 [s, 1H, NH].

2-(Pyridin-3-yloxythiocarbonylamino)-benzoic Acid Methyl Ester (5)

A mixture of **2** (0.01 mol) and 3-hydroxypyridine (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 10 h. The reaction mixture was cooled, and the solid obtained was recrystallized from dioxane to give **5** (Table I). **IR (kBr, cm^{-1})**: 3306 (NH), 1700 (C=O), 1620 (C=N), 1274 (C=S). δ 3.7 [s, 3H, OCH_3], 7.1–8.2 [m, 8H, Ar-H], 10.5 [s, 1H, NH].

3-(2-Hydroxy-ethyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (6) and 3-(3-hydroxy-propyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (7)

A mixture of **2** (0.01 mol) and the ethanolamine and/or propanol amine (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 8 h. The reaction mixture was cooled, and the solid obtained was recrystallized from ethanol to give **6** and **7**, respectively (Table I). **IR (kBr, cm^{-1}) 6:** 3362 (OH), 3300 (NH), 3018 (CH arom.), 2956 (CH aliph.), 1664 (C=O), 1278 (C=S). δ 4.1 [m, 2H, CH_2OH], 4.85 [t, 2H, NCH_2], 7.2–8.35 [m, 4H, Ar-H], 10.2 [hump, 1H, OH]. **IR**

(kBr, cm^{-1}) 7: 3306 (NH, OH), 1696 (C=O), 1276 (C=S). δ 2.16 [t, 2H, NCH_2], 3.60–3.76 [m, 2H, CH_2], 4.75 [t, 2H, OCH_2], 7.1–8.2 [m, 4H, Ar-H], 8.25, 8.3 [2s, 2H, NH + OH].

3-(4-Oxo-2-thioxo-1, 4-dihydro-2H-quinazolin-3-yl)–but-2-enoic Acid Methyl Ester (8)

A mixture of **2** (0.01 mol) and methyl-3-aminocratonate (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 9 h. The reaction mixture was cooled, and the solid obtained was recrystallized from dioxane to give **8** (Table I). **IR (kBr, cm^{-1})**: 3306 (NH), 2924 (CH aliph.), 1698 (C=O), 1274 (C=S). δ 1.5 [s, 3H, CH_3], 3.7 [s, 3H, OCH_3], 7.0–8.25 [m, 5H, Ar-H , CH], 10.4 [s, 1H, NH].

3-(Methylbenzoate-2-yl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (9)

A mixture of **2** (0.01 mol) and methylanthranilate (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 8 h. The reaction mixture was cooled, and the solid obtained was recrystallized from ethanol to give **9** (Table I). **IR (kBr, cm^{-1})** 3304 (NH), 1700, 1710 (2C=O), 1274 (C=S). **MS (m/z):** 312 (M^+, 12.4%), 253 (100%) (Chart 1).

2-(1,2-Dihydro-4-oxo-2-thioxoquinazolin-3(4H)-yl) Benzoic Acid (10), 2-(1,2-dihydro-4-oxo-2-thioxoquinazolin-3(4H)-yl)-5-methyl Benzoic Acid (11), and 2-(1,2-dihydro-4-oxo-2-thioxoquinazolin-3(4H)-yl)-5-bromo Benzoic Acid (12)

A mixture of **2** (0.01 mol) and anthranilic acid derivatives (0.01 mol) in dioxane (30 mL) containing triethylamine (0.5 mL) was refluxed for 8 h. The reaction mixture was cooled, and the solid obtained was recrystallized from dioxane to give **10–12**, respectively (Table I). **IR (kBr, cm^{-1})10:** 3250 (NH), 1680, 1660 (2C=O), 1274 (C=S).

IR(kBr, cm^{-1})11: 3310 (NH), 1710, 1696 (2C=O), 1276 (C=S). **MS (m/z)11:** 312 (M^+, 13.7%), 253 (100%) (Chart 2).

IR (kBr, cm^{-1})12: 3208 (NH), 3034 (CH arom.), 1688, 1668 (2C=O), 1268 (C=S). **MS (m/z) 12:** 377 (M^+, 7.5%), 331 (100%) (Chart 3).

4-Oxo-2-thioxo-1,4-dihydro-2H-quinazoline-3-carboxylic Acid Ethyl Ester (13)

A mixture of **2** (0.01 mol) and ethylcarbamate (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 4 h. The reaction mixture was cooled, and the solid obtained was recrystallized from ethanol to give **13** (Table I). **IR (kBr, cm^{-1})** 3302 (NH), 1700, 1690

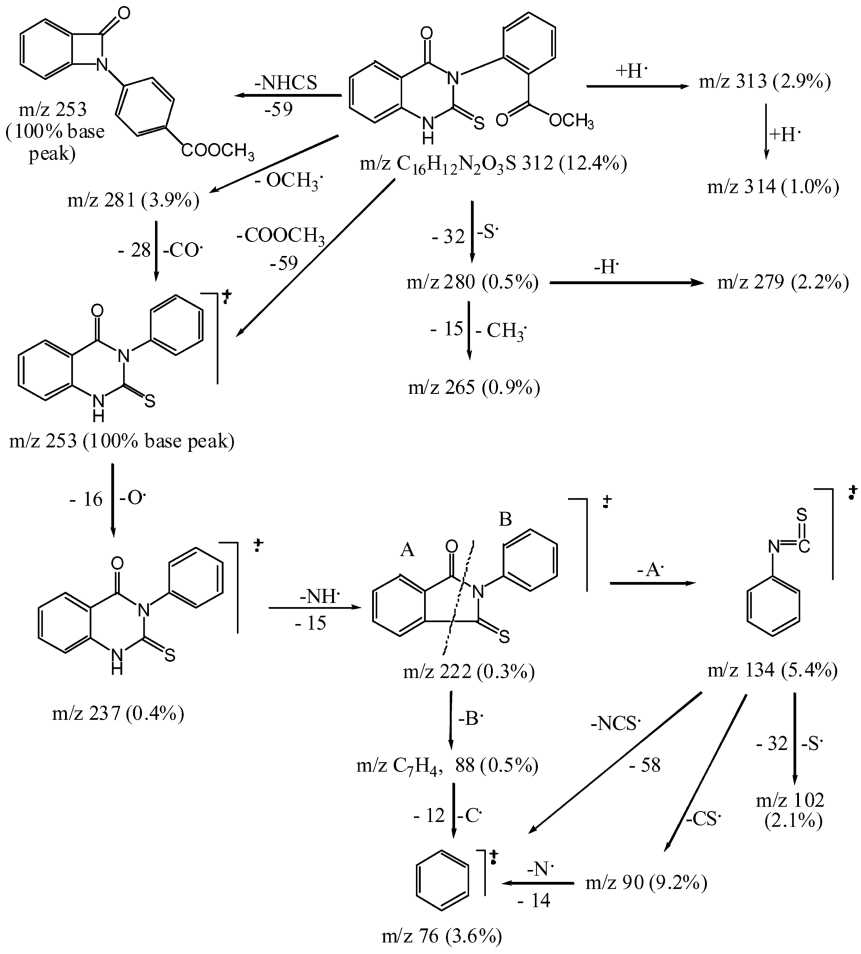


CHART 1 The mass fragmentation pattern of compound **9**.

(2C=O), 1274(C=S). δ 1.6 [t, 3H, CH_3], 4.0 [q, 2H, CH_2], 7.1–8.4 [m, 4H, Ar-H], 10.8 [s, 1H, NH].

4-(4-Oxo-2-thioxo-1,4-dihydro-2H-quinazoline-3-yl)-benzoic Acid Ethyl Ester (14)

A mixture of **2** (0.01 mol) and ethyl-p-aminobenzoate (0.01 mol) in dioxane (25 mL) containing triethylamine (0.5 mL) was refluxed for 10 h. The reaction mixture was cooled, and the solid obtained was recrystallized from dioxane to give **14** (Table I). **IR (kBr, cm^{-1})** 3246 (NH), 1722, 1664 (2C=O), 1270 (C=S). δ 1.25 [t, 3H, CH_3], 4.4 [q, 2H,

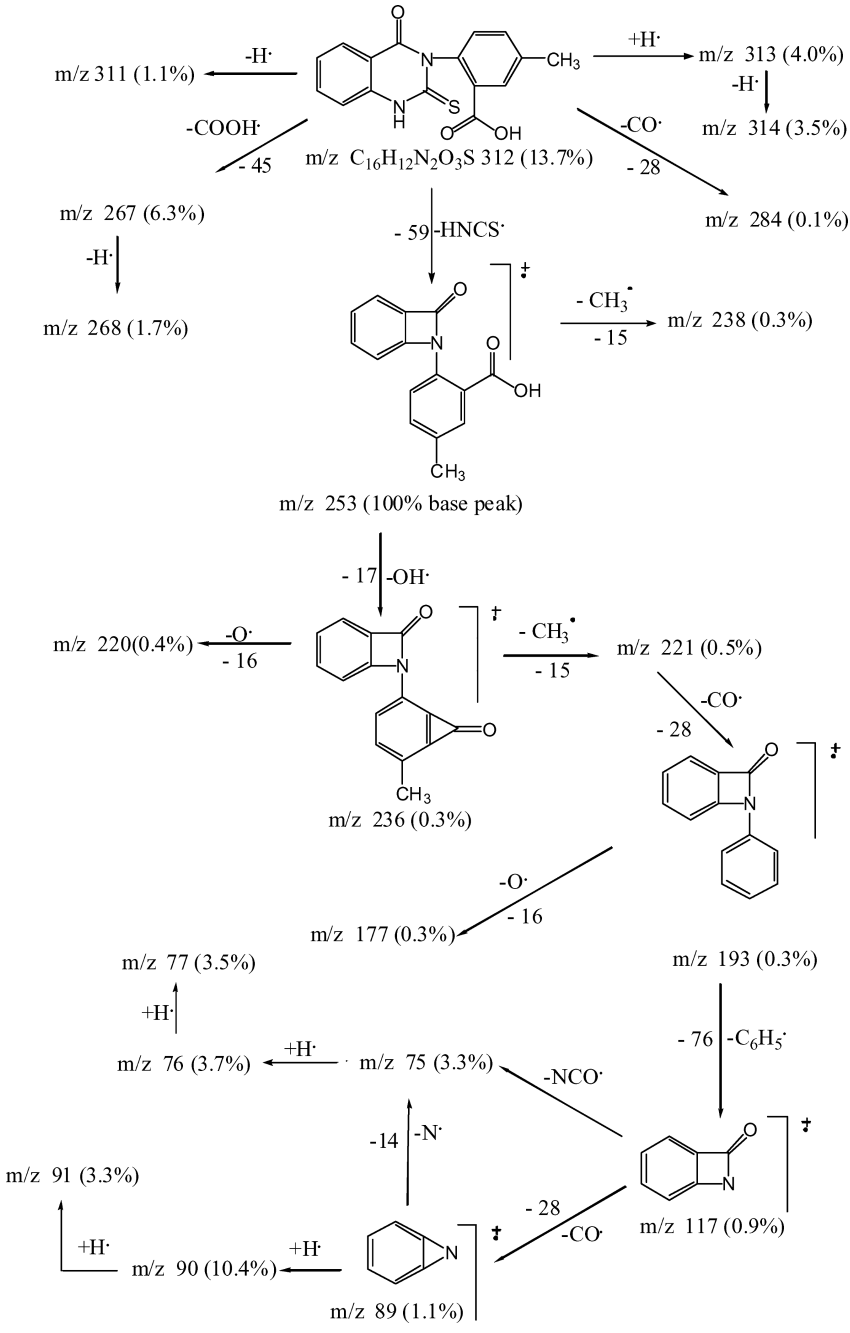


CHART 2 The mass fragmentation pattern of compound **11**.

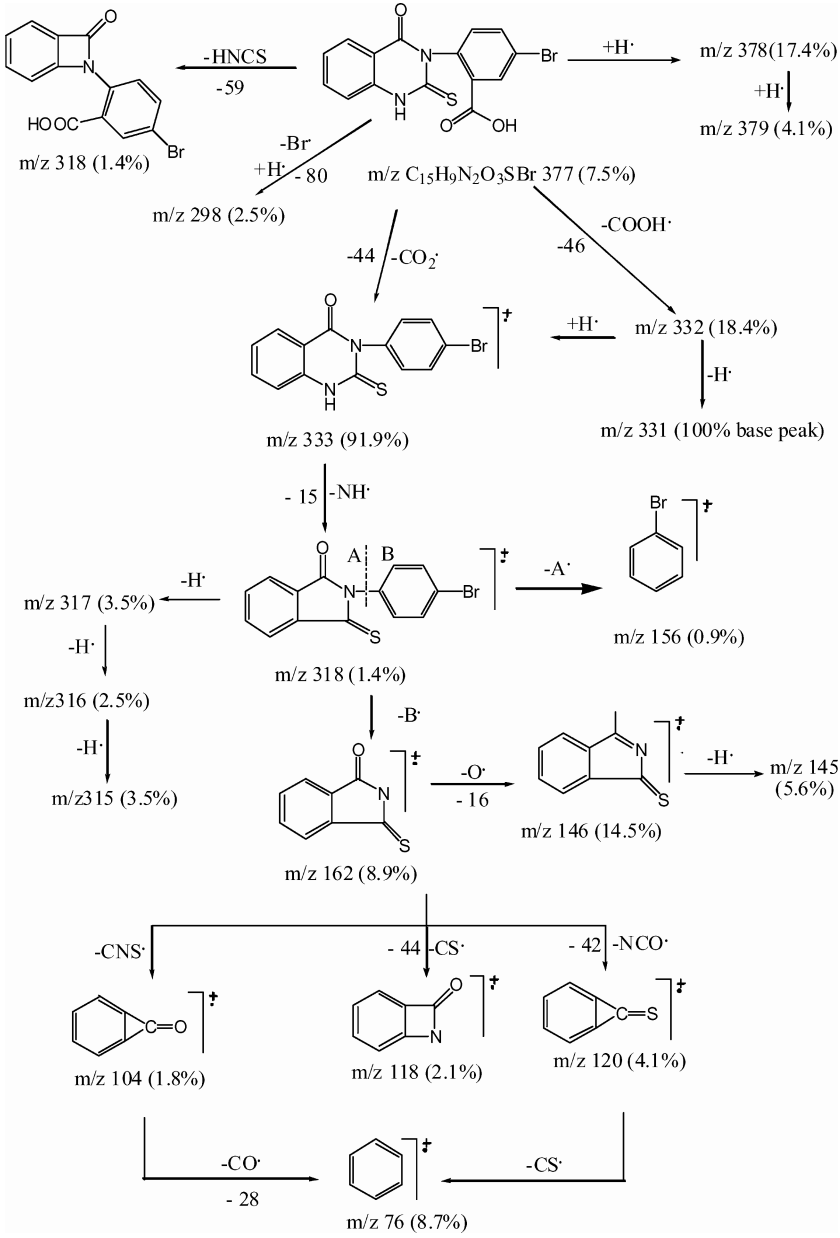


CHART 3 The mass fragmentation pattern of compound **12**.

CH_2], 7.2–8.2 [m, 8H, Ar-H], 9.6 [s, 1H, NH]. **MS (m/z):** 326 (M^+, 1.1%), 253 (100%) (Chart 4).

3-(5-Chloro-pyridin-2-yl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (15)

A mixture of **2** (0.01 mol) and 2-amino-5-chloro-pyridine (0.01 mol) in dioxane (30 mL) containing triethylamine (0.5 mL) was refluxed for 12 h. The reaction mixture was cooled, and the solid obtained was recrystallized from dioxane to give **15** (Table I). **IR (kBr, cm^{-1}):** 3306 (NH), 3086 (CH arom.), 1702 (C=O), 1268 (C=S). δ 7.1–8.0 [m, 7H, Ar-H], 9.2 [s, 1H, NH].

Antitumor Activity (In Vitro Study)

Reagents

1. Roswell Park Memorial Institute (RPMI) 1640 medium (sigma).
2. Ehrlich Ascites Carcinoma (EAC) cells suspension ($2.5.10^5$/mL).
3. Trypan blue dye. A stock solution was prepared by dissolving 1 g of the dye in distilled water 100 mL. The working solution was then prepared by diluting 1 mL of the stock solution with 9 mL of distilled water. The stain was used then for staining the dead EAC cells.
4. The compounds tested were (**3–15**), (Table II).

Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[14]
2. The cells were tested for viability and contamination by staining a certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye.[15,16]
3. The ascetic fluid was diluted with saline (1:10) to contain $2.5.10^6$ cells on a hemocytometer.
4. In a set of sterile test tubes 0.1 mL of tumor cells suspension, 0.8 mL RPMI 1640 media, and 0.1 mL of each tested compound (corresponding to 100, 50, and 25 μg/mL) were mixed. The test tubes were incubated at 37°C for 2 h. Trypan blue exclusion test[15,16] was carried out to calculate the percentage of nonviable cells. Compounds producing more than 70% nonviable cells were considered active.[17]
5. Doxorubicin (Adriablastina)^R was taken as a reference.

$$\% \text{ of nonviable cells} = \frac{\text{No. of nonviable}}{\text{Total No. of cells}} \times 100 \qquad (1)$$

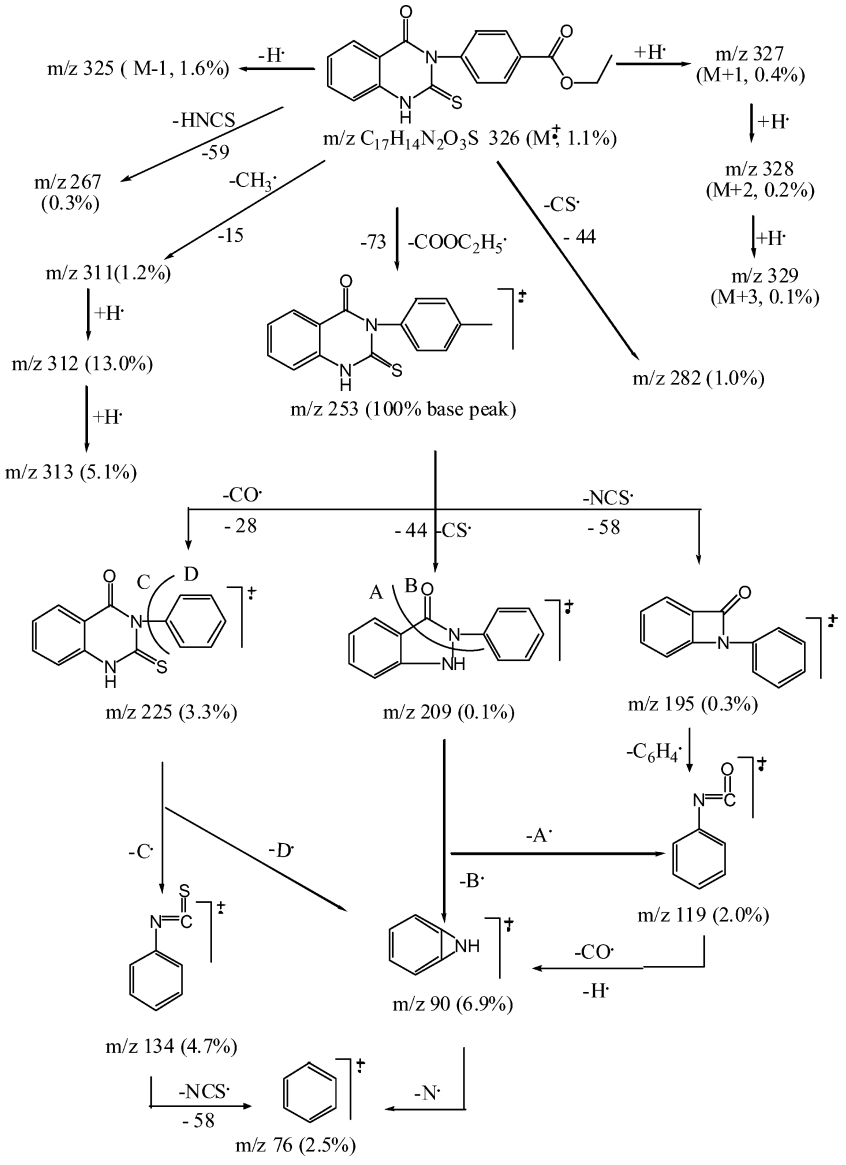


CHART 4 The mass fragmentation pattern of compound **14**.

TABLE II In Vitro Cytotoxic Activity of Some Selected Synthesized Compounds

	Nonviable cells (%)			
	Concentration (μg/mL)			
Compound No.	100	50	25	IC_{50} (μg/mL)*
3	10	0	0	>100
4	0	0	0	—
5	20	10	0	>100
6	0	0	0	—
7	0	0	0	—
8	20	10	0	>100
9	0	0	0	—
11	10	0	0	>100
12	20	10	0	>100
14	0	0	0	—
15	30	20	0	>100
Doxorubicin (reference)	100	55	20	35

*IC_{50} > 100 (μg/mL) is considered to be inactive.

RESULTS

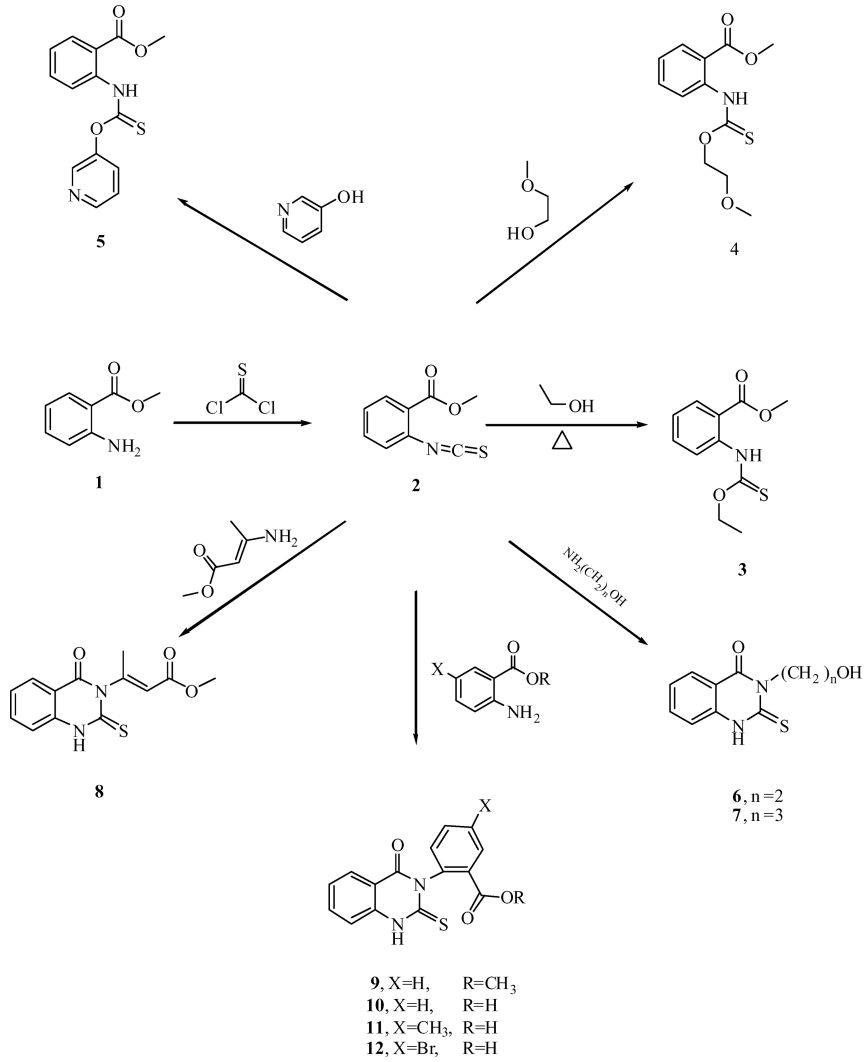
Chemistry

The treatment of methylanthranilate **1** with thiophosgene gave the corresponding 2-isothiocyanato derivative **2**[18] (Scheme 1). The reactivity of isothiocyanato **2** towards some oxygen nucleophiles was investigated. Thus, the reaction of isothiocyanato **2** with ethanol as oxygen nucleophile under reflux yielded the corresponding 2-ethoxythiocarbonylamino-benzoic-acid methyl ester **3** (Scheme 1).

Also, 2-(2-methoxy-ethoxythiocarbonylamino)-benzoic acid methyl ester **4** was obtained via a reaction of isothiocyanato derivative **2** with methoxyethanol (Scheme 1).

It was planned to investigate the reactivity of isothiocyanato **2** toward an aromatic hydroxy compound. Thus, 3-hydroxypyridine was reacted with isothiocyanato **2** to produce 2-(pyridine-3-yloxythiocarbonylamino)-benzoic acid methyl ester **5** (Scheme 1).

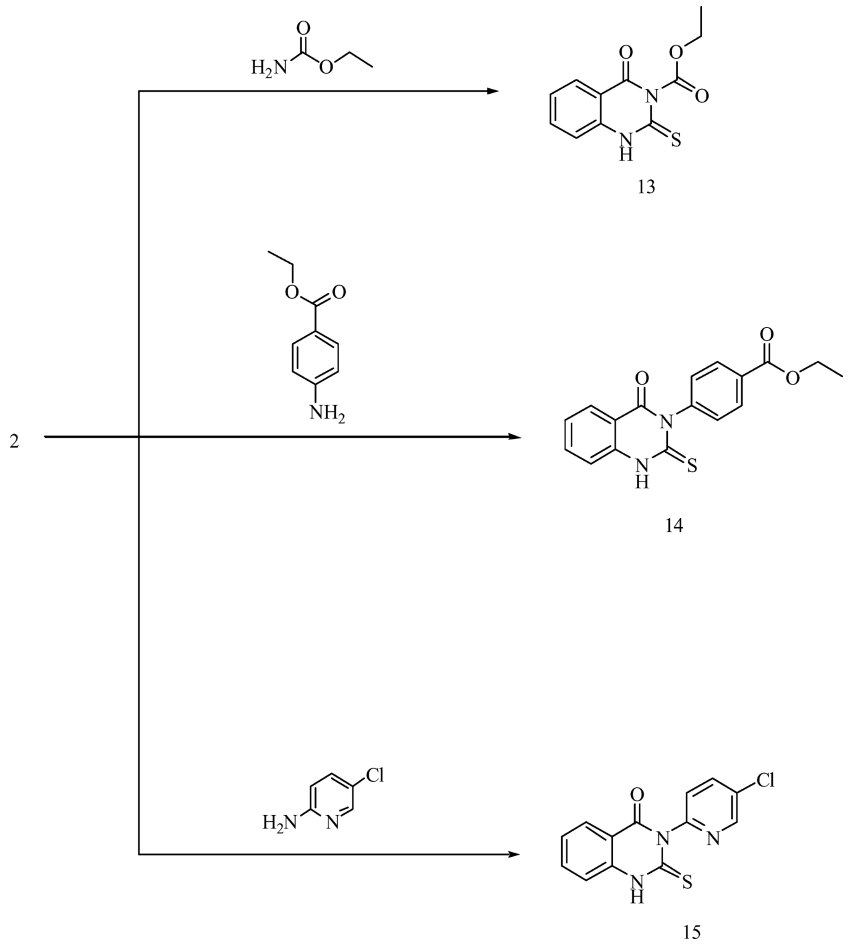
On the other hand, the reactivity of isothiocyanato **2** toward some nitrogen nucleophiles was investigated. Thus, the reaction of isothiocyanato **2** with ethanolamine and/or propanolamine in dioxane containing a catalytic amount of triethylamine afforded the quinazolinone derivatives **6** and **7**, respectively (Scheme 1).



SCHEME 1

In addition, reaction of isothiocyanato **2** with methyl-3-amino-crotonate yielded 3-(4-oxo-2-thioxo-1,4-dihydro-2H-quinazolin-3-yl)-but-2-enoic acid methyl ester **8** in a good yield (Scheme 1).

The cyclocondensation of methylanthranilate 1 and/or anthranilic acid derivatives with isothiocyanato 2 in dioxane/TEA furnished the novel quinazolinone derivatives **9–12**, respectively (Scheme 1).



SCHEME 2

Finally, the interaction of isothiocyanato derivative **2** with ethyl carbamate or ethyl-p-aminobenzoate and/or 2-amino-5-chloro-pyridine yielded the corresponding quinazolinone derivatives **13–15**, respectively (Scheme 2).

Antitumor Activity

The results of antitumor activity for the synthesized compounds showed no activity against EAC.

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