Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-020-01896-0

ORIGINAL PAPER

Synthesis and antimicrobial evaluation of new series of quinazolin-5-one derivatives

Reda A. Haggam[1,2] · Essam. A. Soylem[2] · Mohamed. G. Assy[2] · Marium. F. Arastiedy[2]

Received: 31 August 2019 / Accepted: 29 February 2020

Abstract
A new series of quinazolinone derivatives were synthesized starting with anthranilic acid and cinnamoylisothiocyanate in high yields 55–99%. Their structures were elucidated by $^{1}H/^{13}C$ NMR, FTIR spectroscopy, MS and elemental analysis. The study of the biological activity of all the novel compounds is reported. The minimal inhibitory concentration of some quinazolin-5-one derivatives showed potential activity against both Gram (+ve) and Gram (−ve) microorganisms more than the reference cefotaxime. In addition, some derivatives of quinazolin-5-one can be considered as antifungal agents comparing with the standard drug nystatin.

Keywords Anthranilic acid · Cinnamoylthiourea · Mercaptopyrimidine · Thiadiazoloquinazolin-5-one · Antimicrobial activity

Introduction

Nitrogen-rich heterocycles, particularly quinazolines and quinazolinones, are useful bioactive scaffolds in medicinal chemistry and synthetic applications [1]. Quinazolinone derivatives showed inhibitory activities on α-glucosidase in a non-competitive manner [2]. Also, 2-(4-Fluorophenyl)-quinazolin-4(3H)-one acts as a novel tyrosinase inhibitor [3]. Recent developments in the green protocols were presented for the construction of highly bioactive quinazoline and quinazolinone compounds aiming at the treatment of different disorders [4]. The simple and condensed quinazoline derivatives have drawn much attention owing to their applications particularly in a wide range of antitumor activities [5]. Interest in quinazolinones as anticancer agents has further increased since the discovery of raltitrexed and thymitaq and their activity as thymidylate enzyme inhibitors [6]. Compounds containing 2(1H)-quinazolinone ring structure have also shown prominent anticancer activities [7]. Moreover, quinazolinone heterocycles possess diverse pharmacological activities including antiviral [8] and antihistaminic [9, 10]. Among other pharmacological activities, quinazoline derivatives show remarkable antimicrobial properties [11]. Quinazoline derivatives displayed outstanding biological properties involving anticonvulsant, diuretic and antihypertensive activities as well [12–14]. Quinazoline and quinazolinone are also used in preparation of various functional materials for synthetic chemistry and also present in several drug molecules such as albaconazole that have been used as antifungal and nolatrexed as antisolid tumours (Fig. 1) [15–17].

Owing to the importance of quinazolinone derivatives, some synthetic procedures have been reported, for example synthesis of 2-substituted-2,3-dihydro-4(1H)-quinazolinone derivatives by one-pot condensation of anthranilamide with aldehydes or ketones in the presence of boric acid under solvent-free conditions [18]. 2,3-Dihydroquinazolin-4(1H)-ones was prepared via Ferrite/Chitosan as a green and reusable nanocatalyst [19]. In addition, several organic reactions based on green chemistry concerned with synthesis of substituted quinazolinones derivatives were reported [20–23]. It is notable that most of these methods have drawbacks such as using expensive reagents, non-recyclable and excess amount of catalysts, long reaction times and toxic solvents. In this regard, our interest has been recently directed towards the synthesis of some novel azoles and azines of expected

✉ Reda A. Haggam
rhaggan99@hotmail.com

[1] Department of Chemistry, Faculty of Science, Islamic University in Almadinah Almonawara, Medina 42351, Saudi Arabia

[2] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig 44511, Egypt

Published online: 16 March 2020

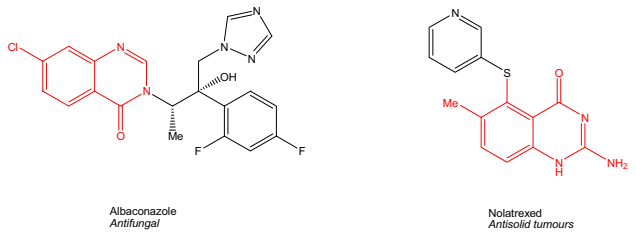


Fig. 1 Structure of albaconazole and nolatrexed

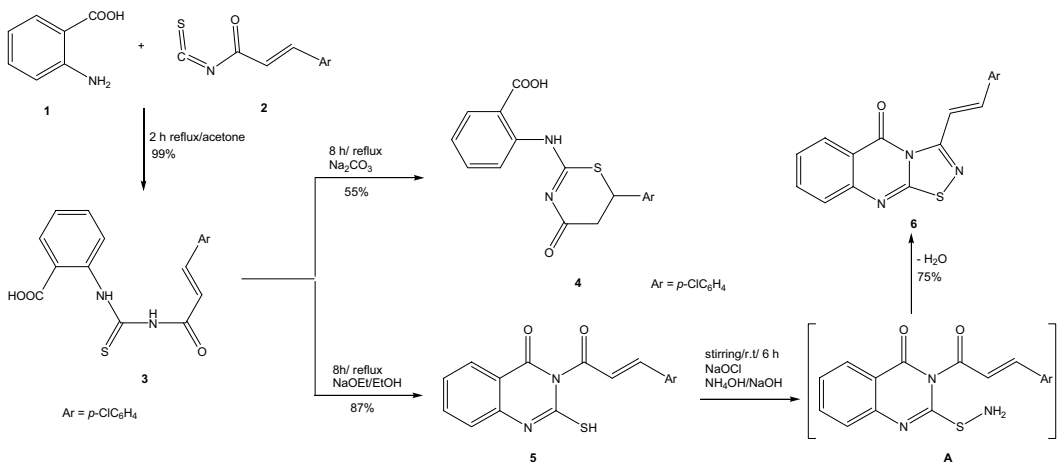
antitumor activity [24–29]. Inspired by these findings, we attempted to synthesize new quinazolinone derivatives using commercially available reagents through a novel, easy, high-yielding, and clean synthetic route to evaluate their biological activities as antibacterial and antifungal agents.

Results and discussion

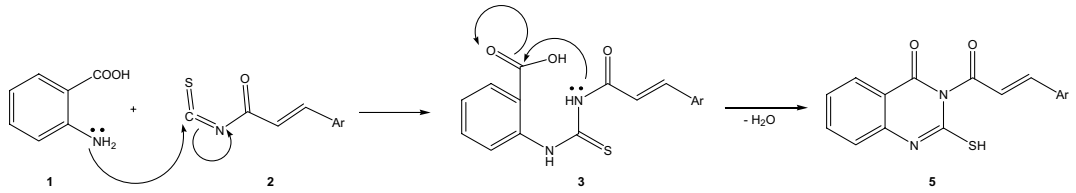
The present work is aiming at utilization of cinnamoyl thiourea via isothiocyanates for synthesis of new quinazolinone derivatives by using simple available laboratory reagents. Isothiocyanates are versatile reagents that have been used as synthetic moiety to synthesize biologically active heterocycles [30, 31]. At the beginning, the nucleophilic nitrogen of anthranilic acid (**1**) was added to cinnamoylisothiocyanate (**2**) [32] in acetone under reflux for 2 h to build the cinnamoyl thiourea derivative **3** in 99% yield (Scheme 1). Upon heating of **3** with sodium carbonate for 8 h produced thiazine ring system **4** in 55% yield via deprotonation the acidic hydrogen NH flanked between CO and CS groups. On the other hand, performing the reaction in strong base as ethanolic sodium ethoxide for 8 h resulted in mercaptoquinazoline **5** in 87% yield throughout an intramolecular nucleophilic addition on the carboxylic carbonyl group (Scheme 1). It is notable that compound **5** is a functionally suitable starting material for further construction of a novel class of fused heterocycles such as thiadiazoloquinazoline of type **6** and thiazoloquinazoline **10**. Stirring of **5** with sodium hypochlorite at r.t for 6 h afforded thiadiazoloquinazolin-5-one **6** in 75% yield via the amination of sulphenyl intermediate **A**, as outlined in (Scheme 1).

The suggested mechanism for building of quinazoline **5** started with the addition of the nucleophilic nitrogen of anthranilic acid (**1**) to cinnamoylisothiocyanate (**2**) [32] to afford thiourea derivative **3** which underwent an intramolecular nucleophilic cyclization followed by dehydration forming the target molecule mercaptoquinazoline **5,** as shown in (Scheme 2).

The structure of compound **5** was elucidated by the spectral analysis. The IR spectrum of mercaptoquinazoline derivative **5** displayed distinguishable absorption bands at 2260, 1693, 1686, 1629, 1588 cm^{-1} for (SH), (2C=O), (C=N) and (C=C), respectively. In addition, the absence of carbonyl stretching peak at 1705 cm^{-1} that was attributed to acidic carbonyl supported that the (COOH) group was involved in the cyclization. The ^1H NMR of **5** showed a broad singlet at $\delta = 12.49$ ppm for (SH) group. There is multiplet in between $\delta = 7.93–7.28$ ppm for eight aromatic protons. Moreover, there are two doublets at $\delta = 6.53$ and 7.56 ppm with J = 14.9 Hz for the two vinylic protons (–CH=CH–) (Fig. 1). Disappearance the peak at $\delta = 12.49$ ppm in D_2O spectrum emphasized that the SH proton was exchangeable with D_2O. This is an evidence for the correct suggested structure of mercaptoquinazoline **5**. Also, the mass spectrometry of compound **5** is in agreement with its structure as well as its molecular weight. The IR spectrum of thiadiazoloquinazolin-5-one **6** revealed absorption bands at 1683 and 1627 cm^{-1} for (amidic C=O) and (C=N) groups,



Scheme 1 Basic cyclizations of cinnamoyl thiourea **3** under different conditions



Scheme 2 Proposed mechanism for formation of mercaptoquinazoline **5**

respectively. In the ^{1}H NMR of **6**, it was observed multiplet in between $\delta = 7.73–7.45$ ppm for eight aromatic protons. In addition, there are two doublets with coupling constant $J = 14.9$ Hz at $\delta = 6.52$ and 7.57 ppm for the two vinylic protons –CH=CH–. The high value of the coupling constant supports that the two olefinic protons exist in *trans* configuration. Basic alkylation of 2-mercapto-3-cinnamoylquinazolinone **5** with appropriate halogenated activated methylene reagents such as *N*-phenylchloroacetamide, ethyl chloroacetate and chloroacetamide under reflux for 9–14 h resulted in the synthesis of thiazoloquinazolineone derivatives **8** and **9** (Scheme 2). Reaction of **5** with *N*-phenylchloroacetamide gave the *S*-alkylated quinazolinone **7** that could be isolated in 65% yield. Upon heating compound **7** in xylene for 10 h delivered thiazoloquinazolinone **8** in 85% yield. Refluxing of **5** with ethyl chloroacetate or chloroacetamide for 14 h gave thiazoloquinazolinone derivatives **9a** and **9b** directly in 65% yield via the *S*-alkylated intermediate **B** that could not be isolated. An intramolecular basic cyclization of compound **5** in xylene provided thiazinoquiazolinone derivative **10** in 79% yield. Also, [2 + 4] intramolecular cycloaddition of 2-mercaptoquinazolinone **5** and maleic anhydride afforded thiazine intermediate **C** that underwent hydrolysis and subsequently decarboxylation forming the final product **11** in 69% yield (Scheme 3).

The IR spectrum of quinazolinone 7 showed disappearance of the characteristic band for (SH) at 2250 cm^{-1}, indicating that *S*-alkylated product 7 was formed. Other bands are present at 3345, 1693, 1686, 1665 cm^{-1} for (NH) and (3C=O amide), respectively. The ^{1}H NMR of **7** revealed singlet at $\delta = 4.17$ ppm for (SCH_2) group. In addition, a broad singlet at $\delta = 12.51$ ppm for (NH). The broad singlet was exchangeable with D_2O. The mass spectrometry of quinazolinone **7** is in agreement with its molecular weight and structure. Stirring of **5** with hydrogen peroxide in acidic medium led to desulphurization producing quinazoline derivative **12** in 88% yield, but the structure **13** is not observed (Scheme 3). On the other hand, reaction of **5** with hydrogenperoxide in alkaline medium at r.t for 4 h gave the oxidative product **14** in 75% yield. Finally, the disulphide of type **15** was formed in 87% yield due to oxidative dehydrogenation of cinnamoylquinazolinone **5** with iodine in the presence of acetic acid as in (Scheme 4).

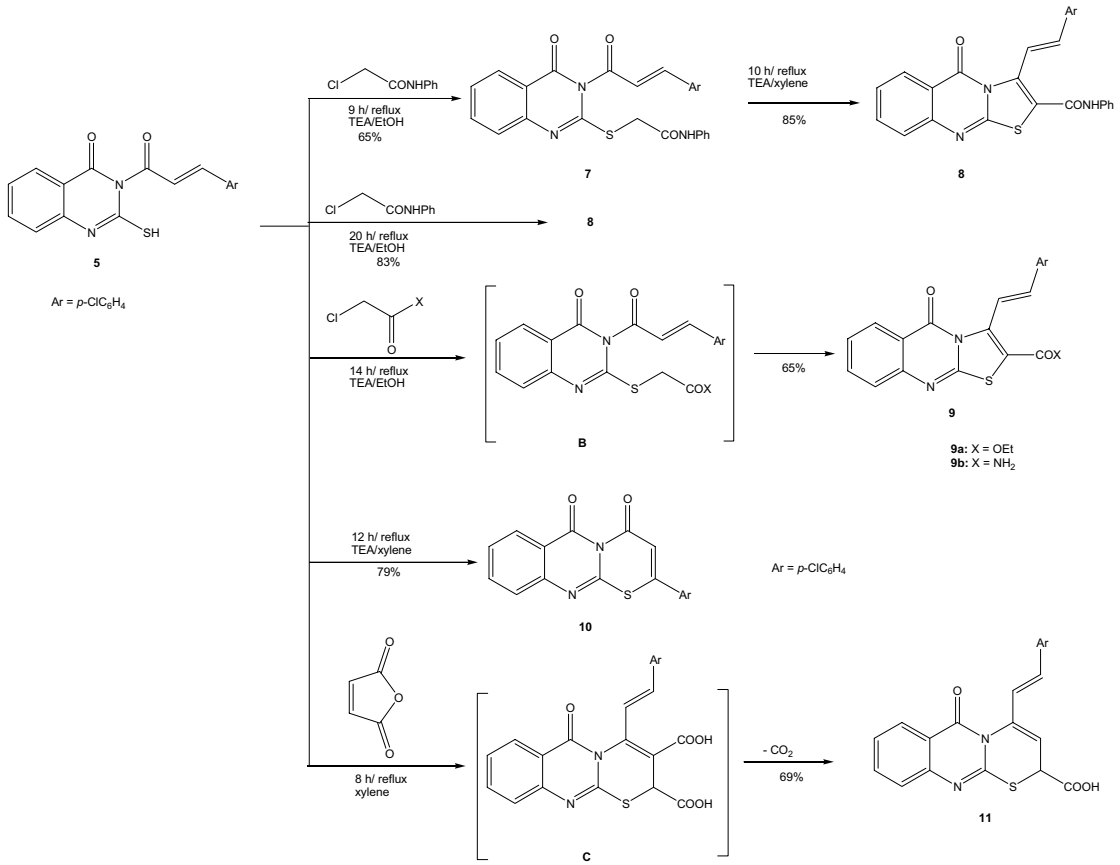
The IR spectrum of **12** displayed absorption bands at 1694, 1686 cm^{-1} for (2C=O). Moreover, disappearance of the band for SH indicated that desulphurization occured. In its ^{1}H NMR, there are no signals at δ value greater than 7.90 ppm. This is a clue the SH proton disappeared. The mass spectrometry of compound **12** is in agreement with its molecular weight $M^+ = 310$.

Pharmacological studies

Antimicrobial evaluation

We studied the *invitro* antimicrobial activities for the synthesized compounds **4, 5, 6, 7, 8, 9a, 10, 11, 12, 14** and **15** against *Staphylococcus epidermidis* ATCC 12228, *Staphylococcus aureus* ATCC 6538, as (Gram +ve), *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 10536, as (Gram −ve) (Table 1) and fungi, namely (*Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404) (Table 3). It is clearly observed that, from the obtained results in Table 1, approximately all the tested compounds exhibited significant antibacterial activity against both Gram (+ve) and Gram (−ve) microorganisms, especially compounds **6**, **7** and **12** that exhibited activity against Gram (+ve) bacteria more than the standard drug activity (cefotaxime) using the agar well diffusion method [33]. The effect of concentration gradient of the most active compound, 6, on Gram +ve bacteria (percentage of inhibition) showed the maximum antibacterial at 70 µg (Table 2).

The results showed that compounds **8**, **12** and **14** have exhibited antifungal activity more than the standard drug (nystatin), as shown in Table 3. Compound **8** is the most active one on fungi (*Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404) with optimum concentration (70 µg), as shown in Table 4. By studying the effect of time on the antifungal activity for compound **8**, we found that after 8 days, we obtain the highest percentage of getting rid of fungi (Table 5).



Scheme 3 Cyclizations of 2-mercapto-3-cinnamoylquinazolinone **5**

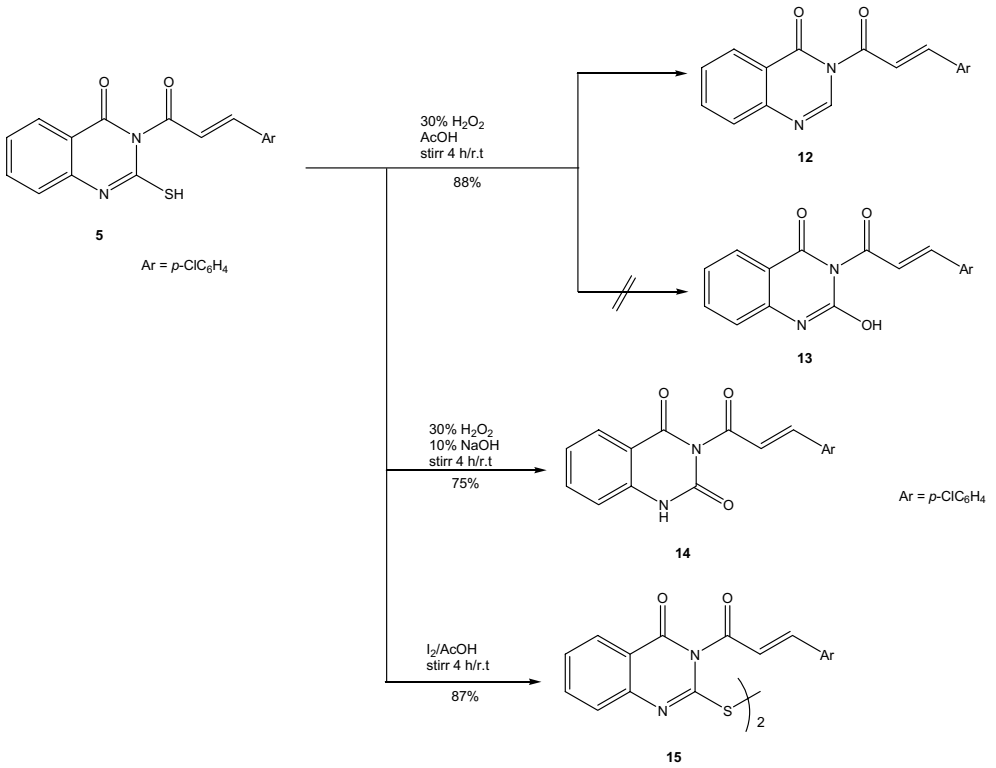
Experimental

Chemistry

All starting materials, reagents and solvents were purchased from Aldrich Chemical Co., Merck Chemical Co. All melting points were measured using an Electrothermal IA 9100 apparatus and are uncorrected. The experiments were done using dry solvents. The obtained products have been purified by recrystallization. IR spectra (KBr discs) were recorded on a Shimadzu FTIR, 8300 PC infrared spectrophotometer. The $^{1}H/^{13}C$ NMR was measured with a JEOL-JNM-LA 400 MHz spectrometer using DMSO-d6 as a solvent. The coupling constants (*J*) are given in *Hz*. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Mass spectra were recorded with a Shimadzu QP-2010 plus instrument at 70 eV. TLC was performed on Merck Silica Gel 60F254 with detection by way of UV light. Elemental analyses were determined on a PerkinElmer 240 (Microanalysis Center, Cairo University, Cairo; Egypt).

2-({[3-(E)-(4-Chlorophenyl)prop-2-enoyl]carbamothioyl}amino)benzoic acid (3)

A mixture of anthranilic acid (**1**) (0.137 g, 1 mol) and *p*-chlorocinnamoylisothiocyanate (MP. 44–45 °C; Lit. 42–44 °C) (**2**) [32] (0.239 g, 1 mol) in dry acetone (50 ml) was refluxed for 2 h. After concentration and cooling the reaction mixture, the formed product was filtered off, dried and recrystallized from methanol to give yellow crystals in 99% Yield. Mp. 230–231 °C. IR (KBr, cm^{-1}): 3424 (OH), 3363, 3321 (2 NH), 1710, 1686 (2 C=O), 1628 (C=N), 1506 (C=C). Elem. Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S$ (360.81): C, 56.59; H, 3.63; N, 7.76%. Found: C, 56.42; H, 3.51; N, 7.65%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.51, 7.55 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.35–8.48 m (8H, m, 2Ar–H), 10.78, 11.55 (2H, 2 s, exch. with D_2O, 2NH), 13.09 (1H, s, exch. with D_2O, OH). m/z (EI, 70 eV) 363 (8), 361 (25), 342 (70), 238 (90), 165 (100).



Scheme 4 Oxidation of 2-mercapto-3-cinnamoylquinazolinone **5** under different reaction conditions

Table 1 The minimal inhibitory concentration (MIC) of **4, 5, 6, 7, 8, 9a, 10, 11, 12, 14** and **15**

Comp. no.	Gram (+ve) *S. epidermidis* ATCC 12228	*S. aureus* ATCC 6538	Gram (-ve) *P. aeruginosa* ATCC 9027	*E. coli* ATCC 10536
4	4.0	10.0	3.0	5.0
5	10.0	12.0	4.0	9.0
6	12.0	18.0	6.0	11.0
7	11.0	17.0	6.0	10.0
8	8.0	14.0	4.0	10.0
9a	6.0	12.0	2.0	4.0
10	7.0	8.0	3.0	5.0
11	5.0	9.0	6.0	8.0
12	12.0	17.0	7.0	12.0
14	9.0	14.0	6.0	11.0
15	7.0	13.0	3.0	6.0
Cefotaxime (5 mg/mL)	10.0	16.0	5.0	10.0
(control) DMF (control)	–	–	–	–

(MIC), concentration of compound inhibiting the microbial growth (μg/ml)

2-(6-(4-Chlorophenyl)-5,6-dihydro-4-oxo-4H-1,3-thiazin-2-ylamino)benzoic acid (4)

A mixture of cinnamoyl thiourea **3** (0.361 g, 1 mol) in 10% sodium carbonate (50 ml) was refluxed for 8 h and followed by TLC. The alkaline residue was acidified with dil. HCl. The formed product was filtered off, washed with cold water, dried and then recrystallized from ethanol to give yellowish crystals in 55% Yield. Mp. 206–207 °C. IR (KBr, cm^{-1}): 3340 (OH), 3143 (NH), 1705, 1685 (2 C=O), 1628 (C=N). Elem. Anal. Calcd. for $C_{18}H_{16}ClN_2O_3S$ (375.85): C, 57.52; H, 4.29; N, 7.45%. Found: C, 57.39; H, 4.20; N, 7.38%. ^{1}H-NMR

Table 2 Effect of concentration gradient for the most active compound on Gram +ve bacteria (percentage of inhibition)

Comp. no.	Concentration (µg)	*S. epidermidis* (%) ATCC 12228	*P. S. aureus* (%) ATCC 6538
6	10.0	12.0	16.0
	20.0	22.0	31.0
	30.0	35.0	45.0
	40.0	49.0	58.0
	50.0	58.0	67.0
	60.0	72.0	81.0
	70.0	85.0	90.0
	80.0	85.0	90.0
	90.0	84.0	89.0

Table 3 The minimal inhibitory concentration (MIC) of **4, 5, 6, 7, 8, 9a, 10, 11, 12, 14** and **15**

Comp. no.	Fungi *Candida albicans* ATCC 10231	*Aspergillus niger* ATCC 16404
4	10.0	5.0
5	8.0	7.0
6	7	9.0
7	8.0	8.0
8	14.0	10.0
9a	7.0	7.0
10	5.0	4.0
11	7.0	3.0
12	12.0	10.0
14	13.0	11.0
15	9.0	6.0
Nystatin (5 mg/mL) (control) DMF (control)	12.5 –	8.5 –

(MIC), concentration of compound inhibiting the microbial growth (µg/ml)

Table 4 Effect of concentration gradient for the most active compound on fungi (percentage of inhibition)

Comp. no.	Concentration (µg)	*Candida albicans* (%) ATCC 10231	*Aspergillus niger* (%) ATCC 16404
8	10.0	18.0	21.0
	20.0	29.0	35.0
	30.0	41.0	49.0
	40.0	53.0	61.0
	50.0	63.0	70.0
	60.0	75.0	81.0
	70.0	83.0	87.0
	80.0	82.0	87.0
	90.0	82.0	87.0

Table 5 Effect of time on the antifungal activity of optimum concentration (70 µg) for compound **8**

Comp. no.	Time	*Candida albicans* (%) ATCC 10231	*Aspergillus niger* (%) ATCC 16404
8	12 h	18.0	21.0
	1 day	33.0	35.0
	2 days	44.0	42.0
	3 days	52.0	54.0
	4 days	59.0	61.0
	5 days	66.0	68.0
	6 days	73.0	76.0
	7 days	79.0	83.0
	8 days	84.0	89.0
	9 days	84.0	89.0
	10 days	84.0	88.0
	11 days	83.0	89.0

(DMSO-d6, 400 MHz) δ: 2.75 (2H, d, $J=2.6$ Hz, CH_2CO), 3.25 t (1H, t, $J=2.6$ Hz, CHAr), 6.59–7.93 m (8H, m, 2Ar-H), 12.62 (1H, s, exch. with D_2O, NH), 13.39 s (1H, s, exch. with D_2O, OH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 35.4 (CH_2CO), 110.2, 115.3, 118.5, 128.4, 129.3, 130.4, 133.1, 135.7, 139.8, 142.0, 149.4, 162.2, 168.7 (CO amide), 171.1 (CO acid). m/z (EI, 70 eV) 376 (100), 348 (40), 273 (50), 160 (10).

3-[(E)-3-(4-Chlorophenyl)acryloyl]-2-mercapto-quinazolin-4(3H)-one (5)

A mixture of cinnamoyl thiourea derivative **3** (0.361 g, 1 mol) in sodium ethoxide solution (50 ml) was refluxed for 8 h and followed by TLC. The solvent was removed under reduced pressure. The alkaline residue was acidified with dil. HCl. The formed product was filtered off, washed with water, dried and recrystallized from ethanol to give pale yellow crystals in 87% Yield. Mp. 160–161 °C. IR (KBr, cm^{-1}): 2260 (SH), 1693, 1686 (2C=O), 1629 (C=N), 1588 (C=C). Elem. Anal. Calcd. for $C_{17}H_{11}ClN_2O_2S$ (342.80):C, 59.56; H, 3.23; N, 8.17%. Found: C, 59.53; H, 3.20; N, 8.13%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.53, 7.56 (2H, 2d, $J=14.9$ Hz, –CH=CH–), 7.28–7.93 (8H, m, Ar-H), 12.49 (1H, br s, exch. with D_2O, SH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 121.2, 122.1, 123.6, 125.1, 126.5, 127.8, 128.6, 129.2, 133.3, 134.6, 137.4, 144.5, 165.8 (NCS), 166.2 and 169.4 (2C=O). m/z (EI, 70 eV) 342 (20), 301 (100), 282 (80), 178 (69), 165 (55).

3-[2-(4-Chlorophenyl)ethenyl]-7,8-dihydro-5H-[1, 2, 4] thiadiazolo[5,4-b]quinazolin-5-one (6)

A mixture of mercaptoquinazoline derivative **5** (0.343 g, 1 mol), sodium hypochlorite (1 mol), 30% ammonium

hydroxide solution (10 ml) and 10% sodium hydroxide (15 ml) was stirred at r.t for 6 h. The alkaline reaction mixture was then acidified with dil. HCl. The formed product was filtered off, washed with cold water, dried and recrystallized from acetic acid to give yellowish crystals in 75% Yield. Mp. 340–341 °C. IR (KBr, cm^{-1}): 1683 (C=O), 1627 (C=N), 1588 (C=C). Elem. Anal. Calcd. for $C_{17}H_{10}ClN_3OS$ (339.80): C, 60.09; H, 2.97; N, 12.37%. Found: C, 59.99; H, 2.84; N, 12.31%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.52, 7.57 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.45–7.73 (8H, m, 2Ar-H). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 118.3, 121.9, 122.6, 125.5, 126.3, 127.6, 129.6, 130.2, 134.5, 135.3, 138.6, 139.2, 163.3 (NCN), 164.3 (NCS), 170.8 (C=O).

General procedure for synthesis of compounds 7, 8, 9a, b, 10 and 11

A mixture of 2-mercapto-3-cinnamoylquinazolinone (**5**) (0.343 g, 1 mol) in ethanol or xylene (10 ml), appropriate halogenated methylene or anhydride reagents such as *N*-phenylchloroacetamide, ethyl chloroacetamide, chloroacetamide and maleic anhydride (10 mmol) in ethanol or xylene (15 ml), and a few drops of TEA was refluxed for 8–20 h and followed by TLC. The formed product obtained after concentration and cooling was filtered off and recrystallized from the proper solvent.

2-((E)3-(3-(4-Chlorophenyl)acryloyl)-3,4-dihydro-4-oxoquinazolin-2-ylthio)-*N*-phenylacetamide (7)

The formed product was filtered off, washed with water and crystallized from ethanol to give yellowish-white crystals in 65% Yield. Mp. 187–188 °C. IR (KBr, cm^{-1}): 3345 (NH), 1693, 1686, 1665 (3 C=O amide), 1606 (C=N), 1588 (C=C). Elem. Anal. Calcd. for $C_{25}H_{18}ClN_3O_3S$ (475.95): C, 63.09; H, 3.81; N, 8.83%. Found: C, 63.03; H, 3.76; N, 8.77%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 4.17 (2H, s, SCH_2), 6.51, 7.57 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 6.81–7.87 (13H, m, 3Ar-H), 12.51 (1H, s, exch. with D_2O, NH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 32.8 (SCH_2), 121.8, 122.4, 123.1, 124.0, 124.2, 125.6, 126.7, 127.9, 128.6, 129.2, 131.3, 132.1, 134.4, 137.4, 138.5, 139.8, 164.2 (NCS), 165.8, 168.8, 169.3 (3 C=O). m/z (EI, 70 eV) (100), 463 (30), 301 (40), 218 (25), 93 (26).

3-[2-(4-Chlorophenyl)ethenyl]-5-oxo-N-phenyl-5H-[1, 3] thiazolo[2,3-b]quinazoline-2-carboxamide (8)

The formed product was filtered off, washed with water and crystallized from toluene to give deep yellowish brown crystals in 85% Yield. Mp. 209–210 °C. IR (KBr, cm^{-1}): 3437 (NH), 1696, 1684 (2 C=O amide), 1627 (C=N), 1588 (C=C). Elem. Anal. Calcd. for $C_{25}H_{16}ClN_3O_2S$ (457.07): C, 65.57; H, 3.52; N, 9.18%. Found: C, 65.42; H, 3.38; N, 9.10%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.51, 7.58 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 6.89–7.94 (13H, m, 3Ar-H), 10.68 (1H, br s, exch. with D_2O, NH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 121.8, 123.4, 123.7, 123.9, 124.3, 125.4, 126.7, 127.3, 128.6, 129.3, 129.5, 132.2, 134.8, 136.3, 138.3, 140.6, 141.5, 145.7, 156.9 (NCN), 161.8, 169.5 (2 C=O).

Ethyl-3-[2-(4-Chlorophenyl)ethenyl]-5-oxo-5H-thiazolo[2,3-b]quinazoline-2-carboxylate (9a)

The formed product was filtered off, washed with water and crystallized from benzene to give greenish yellow crystals in 65% Yield. Mp. 201–202 °C. IR (KBr, cm^{-1}): 1727 (C=O ester), 1693 (C=O amide), 1606 (C=N), 1589 (C=C). Elem. Anal. Calcd. for$C_{21}H_{15}ClN_2O_3S$ (410.87): C, 61.39; H, 3.68; N, 6.82%. Found: C, 61.26; H, 3.50; N, 6.74%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 1.23 (3H, t, $J = 7.1$ Hz, CH_3), 2.42 (2H, q, $J = 7.1$ Hz, CH_2), 6.51, 7.57 (2H, 2d, $J = 14.9$ Hz,–CH=CH–), 6.64–8.61 (8H, m, 2Ar-H), 12.43 (2H, s, exch. with D_2O, NH_2).

3-[2-(4-Chlorophenyl)ethenyl]-5-oxo-5H-thiazolo[2,3-b]quinazoline-2-carboxamid (9b)

The formed product was filtered off, washed with water and crystallized from ethanol to give white crystals in 65% Yield. Mp. 170–171 °C. IR (KBr, cm^{-1}): 3438, 3412 (NH_2), 1692, 1667 (2 C=O amide), 1606 (C=N), 1588 (C=C). Elem. Anal. Calcd. $C_{19}H_{12}ClN_3O_2S$ (381.84): C, 59.76; H, 3.17; N, 11.00%. Found: C, 59.72; H, 3.12; N, 11.08%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.53, 7.54 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.45–8.61 (8H, m, 2Ar-H), 5.80 (2H, br s, exch. with D_2O, NH_2). m/z (EI, 70 eV) 384 (20), 382 (55), 316 (45), 165 (95), 141 (55), 137 (70).

2-(4-Chlorophenyl)-[1, 3] thiazino[2,3-b]quinazoline-4,6-dione (10)

The formed product was filtered off, washed with water and crystallized from ethanol to give yellow crystals in 79% Yield. Mp. 210–211 °C. IR (KBr, cm^{-1}): 1689, 1666 (2 C=O amide), 1628 (C=N), 1589 (C=C). Elem. Anal. Calcd. $C_{17}H_9ClN_2O_2S$ (340.78): C, 59.92; H, 2.66; N, 8.22%. Found: C, 59.87; H, 2.60; N, 8.16%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.44 (1H, s, olefinic –COCH=), 7.58–8.23 (8H, m, 2Ar-H). m/z (EI, 70 eV) 343 (10), 341 (31), 236 (20), 146 (40), 135 (45), 91 (100).

4-[2-(4-Chlorophenyl)ethenyl]-6-oxo-2H,6H-[1, 3] thiazino[2,3-b]quinazoline-2-carboxylic acid (11)

The formed product was filtered off, washed with water and crystallized from *n*-butanol to give grey crystals in 69% Yield. Mp. 228–229 °C. IR (KBr, cm^{-1}): 3419 (OH), 1710, 1683 (2 C=O amide), 1628 (C=N), 1589 (C=C). Elem. Anal. Calcd. $C_{20}H_{13}ClN_2O_3S$ (396.85): C, 60.53; H, 3.30; N, 7.06%. Found: C, 60.44; H, 3.24; N, 7.01%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 3.45 (1H, d, $J = 1.8$ Hz, CH–S), 6.23 (1H, d, $J = 1.8$ Hz, olefinic –CH=C–N), 6.50, 7.57 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.23–8.61 (8H, m, 2Ar-H), 11.46 (1H, s, exch. with D_2O, OH). m/z (EI, 70 eV) 399 (55), 397 (28), 260 (15), 181 (40), 164 (70), 92 (100), 85 (28).

General procedure for synthesis of compounds 12, 14

To a solution of 2-mercapto-3-cinnamoylquinazolinone (**5**) (0.343 g, 1 mol) in 10% sodium hydroxide solution and/or acetic acid (20 ml), H_2O_2 (0.02 mol) was added dropwise with stirring at r.t. The reaction mixture was stirred furthermore for 4 h and followed by TLC as well. The mixture was worked up as usual, and the formed product was filtered off, washed with water, dried and recrystallized from the proper solvent.

3-[(E)-3-(4-Chlorophenyl)acryloyl]quinazolin-4(3H)-one (12)

The formed product was filtered off, washed with water and crystallized from *n*-butanol to give yellowish-white crystals in 88% Yield. Mp. 342–343 °C. IR (KBr, cm^{-1}): 1694, 1686 (2 C=O amide), 1629 (C=N), 1590 (C=C). Elem. Anal. Calcd. $C_{17}H_{11}ClN_2O_2$ (310.73): C, 65.71; H, 3.57; N, 9.02%. Found: C, 65.61; H, 3.49; N, 8.92%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.52, 7.57 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.15–7.89 (9H, m, 2Ar-H and N=CH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 122.8, 123.1, 123.8, 125.3, 126.8, 127.2, 128.6, 129.5, 133.2, 135.6, 138.2, 145.0, 153.4 (NCN), 166.4, 169.3 (2 C=O). m/z (EI, 70 eV) 310 (100), 301 (35), 282 (45), 275 (80), 137 (55), 119 (35).

3-[(E)-3-(4-Chlorophenyl)acryloyl]quinazoline-2,4(1H,3H)-dione (14)

The formed product was filtered off, washed with water and crystallized from benzene to give yellowish-white crystals in 75% Yield. Mp. 240–241 °C. IR (KBr, cm^{-1}): 3320 (NH), 1697, 1690, 1686 (3 C=O amide), 1606 (C=N), 1588 (C=C. Elem. Anal. Calcd. $C_{17}H_{11}ClN_2O_3$ (326.73): C, 62.49; H, 3.39; N, 8.57%. Found: C, 62.37; H, 3.33; N, 8.43%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.52, 7.57 (2H, 2d, $J = 14.9$ Hz, –CH=CH–), 7.83–8.61 (8H, m, 2Ar-H), 11.60 (1H, s, exch. with D_2O, NH). ^{13}C-NMR (DMSO-d6, 100 MHz) δ: 121.4, 122.3, 124.6, 125.5, 126.4, 127.3, 128.3, 129.6, 133.7, 134.6, 139.2, 144.8, 162.2 (NCONH), 166.8, 169.3 (2 C=O). m/z (EI, 70 eV) 329 (15), 327 (43), 182 (60), 162 (70), 92 (100), 64(60).

3-[(E)-3-(4-Chlorophenyl) acryloyl]-2-(2-(3-[(E)-3-(4-chlorophenyl) acryloyl]-3,4-dihydro-4-oxoquinazolin-2-yl]disulphanyl)quinazolin-4(3H)-one (15)

To a solution of 2-mercapto-3-cinnamoylquinazolinone (**5**) (0.343 g, 1 mol) of in acetic acid (20 ml), iodine (1 mol) in acetic acid (10 ml) was added dropwise with stirring at r.t for 4 h. The reaction mixture was poured into ice-cold water (50 ml), and the formed product was filtered off, washed with water, dried and recrystallized from ethanol to give purple crystals in 87% Yield. Mp. 252–253 °C. IR (KBr, cm^{-1}): 1694, 1688 (2 C=O amide), 1627 (C=N), 1589 (C=C). Elem. Anal. Calcd. $C_{34}H_{20}Cl_2N_4O_4S_2$ (683.58): C, 59.74; H, 2.95; N, 8.20%. Found: C, 59.70; H, 2.88; N, 8.17%. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 6.52, 7.58 (4H, 2d, $J = 14.9$ Hz, 2–CH=CH–), 7.90–8.60 (16H, m, 4Ar-H). m/z (EI, 70 eV) 686 (60), 301 (15), 178 (10), 165 (100), 65 (35).

Antimicrobial evaluation

Mueller–Hinton agar plates were surface-inoculated with the tested strains suspensions adjusted to match 0.5 McFarland standards, and the inoculated were spread over the surfaces of plates using sterile cotton swabs. After drying of the plates, cups (10 mm diameter) were punched in the agar. Samples were dissolved in DMF. Different concentrations of each tested compound were calculated (100–500 µg), using the MIC (Minimal Inhibitory Concentration). The (MIC) of each compound was calculated from the authentic concentration. Then 100 µL from each tested sample or the antimicrobial agents (control) was added into the cups. The plates were incubated at 37 °C for 24 h for bacteria and at 30 °C for 5 days for fungi growth [33]. The antibacterial activity was determined by measuring the diameter of the zone of inhibition and comparing to the antimicrobial agents (control). The experiment was repeated three times, and the mean inhibition zones were calculated. The plate cultures were incubated, and the development of the inhibition growth zones was observed.

Conclusion

In summary, we succeeded in preparation a novel series of quinazolin-5-one derivatives with in high yields via commerciable available reagents. The molecular structures of the new compounds were confirmed via spectroscopic data. The minimal inhibitory concentration (MIC) for quinazolin-5-one derivatives **6**–**8**, **12** and **14** exhibited more potential activity as antibacterial and antifungal agents in comparison with the standard references.

Acknowledgements The authors are so grateful to Dr. Zainab Fathy Elsawah in pharmacology dept., Faculty of Science, Zagazig University, for performing and explaining the biological activity section in this report. Also, the authors thank all the associated personnel in any reference that contributed in/for the achievement of this article.

Compliance with ethical standards

Conflict of interest This research holds no conflict of interest and is not funded through any source.

References

1. I. Khan, S. Zaib, S. Batool, N. Abbas, Z. Ashraf, J. Iqbal, A. Saeed, Bioorg. Med. Chem. **24**(11), 2361–2381 (2016)
2. M. Wei, W.M. Chai, R. Wang, Q. Yang, Z. Deng, Y. Peng, Bioorg. Med. Chem. **25**(4), 1303–1308 (2017)
3. R. Wang, W.M. Chai, Q. Yang, M.K. Wei, Y. Peng, Bioorg. Med. Chem. **24**(19), 4620–4625 (2016)
4. I. Khan, A. Ibrar, W. Ahmed, A. Saeed, Eur. J. Med. Chem. **90**, 124–129 (2014)
5. A.A. Khalil, S.G.A. Hamide, A.M. Al-Obaid, H.I. El-Subbagh, Arch. Pharm. **2**, 95–103 (2003)
6. V. Bavetsias, A.L. Jackman, J.H. Marriott, R. Kimbell, W. Gibson, F.T. Boyle, G.M. Bisset, J. Med. Chem. **40**, 1495–1510 (1997)
7. J. Jampilek, R. Musiol, J. Finster, Molecules **40**(10), 4246–4265 (2009)
8. V. Alagarsamy, R. Revathi, S. Meena, K.V. Ramaseshu, S. Rajasekaran, E.D. Clercq, Indian J. Pharm. Sci. **66**, 459–462 (2004)
9. V. Alagarsamy, R. Giridhar, M.R. Yadav, Bioorg. Med. Chem. Lett. **15**, 1877–1880 (2005)
10. V. Alagarsamy, R. Giridhar, M.R. Yadav, J. Pharm. Pharmacol. **58**, 1249–1255 (2006)
11. T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger, M. Marschall, Antimicrob. Agents Chemother. **48**, 4154–4162 (2004)
12. A. Maleki, RSC Adv. **4**, 64169–64173 (2014)
13. A. Maleki, Tetrahedron Lett. **54**, 2055–2059 (2013)
14. A. Maleki, Tetrahedron **68**(38), 7827–7833 (2012)
15. D.J. Connolly, D. Cusack, T.P. O'Sullivan, P.J. Guiry, Tetrahedron **61**(43), 10153–10202 (2005)
16. P.N. Abida, M. Arpanarana, Int. J. Pharm. Biol. Arch. **2**(6), 1651–1657 (2011)
17. A. Mohammad, Int. J. Med. Chem. **8**(3), 1–27 (2014)
18. Z.K. Jaberi, L. Zarei, S. Afr, J. Chem. **65**, 36–38 (2012)
19. A. Maleki, M. Aghaei, N. Ghamari, M. Kamalzare, Int. J. Nanosci. Nanotechnol. **12**(4), 215–222 (2016)
20. A. Maleki, Z. Hajizadeh, R. Firouzi-Haji, Micropor. Mesopor. Mater. **259**(15), 46–53 (2018)
21. A. Maleki, M. Aghaei, N. Ghamari, Chem. Lett. **44**, 259–261 (2015)
22. A. Maleki, T. Kari, M. Aghaei, J. Porous Mater. **24**, 1481 (2017)
23. A. Shaabani, A. Maleki, H. Mofakham, Synth. Commun. **38**, 3751–3759 (2008)
24. M.H. Sherif, M.G. Assy, N. Yousif, M.M. Galahom, J. Iran. Chem. Soc. **10**, 85–91 (2013)
25. R.A. Haggam, M.G. Assy, M.H. Sherif, M.M. Galahom, Res. Chem. Intermed. **43**, 6299–6315 (2017)
26. R.A. Haggam, M.G. Assy, M.H. Sherif, M.M. Galahom, Eur. J. Chem. **9**(2), 99–106 (2018)
27. R.A. Haggam, E.A. Soylem, M.G. Assy, M.F. Arastiedy, Curr. Sci. **115**(10), 1893–1903 (2018)
28. R.A. Haggam, M.G. Assy, E.K. Mohamed, A.S. Mohamed, J. Heterocycl. Chem. **57**(2), 1–9 (2019)
29. R.A. Haggam, H.Y. Moustafa, M.G. Assy, H.M. Abdelrahman, Russ. J. Org. Chem. 2, (**in Print**), (2020)
30. G.B. Kibrom, S.S. Girija, Arkivoc **4**, 206–245 (2015)
31. A.K. Mukerjee, R. Ashare, Chem. Rev. **91**, 1–24 (1991)
32. S. El-Bahaie, M.G. Assy, A. Kadry, Collect. Czech. Chem. Commun. **55**, 1049–1054 (1990)
33. A.L. Barry, *In procedures antibiotics in laboratory medicine* (Lorin Williams Wilkians Co., Baltimore, 1980), pp. 1–23