SYNTHESIS OF SOME NEW QUINAZOLINE ANALOGS AND THEIR ANTIMICROBIAL ACTIVITY

Adel S. El-Azab, Adnan A. Kadi, Ahmed M. Alafeefy and S.G. Abdel-Hamide*

Department of Pharmaceutical Chemistry, College of Pharmacy,
King Saud University, P.O. Box 2457, Riyadh 11451,
Saudi Arabia

Abstract

Two new series of 6-iodo-2,4-dithio-4(3*H*)quinazoline (**2**-**9**) and 6-iodo-2-thio-4-oxo-quinazoline (**10**-**21**) were prepared and screened for their antimicrobial activity. Compounds **10**, **19** and **20**, showed marked broad spectrum antimicrobial activity against a panel of Gram-positive and Gram-negative bacteria and pathogenic fungi. It seems that the connected heterocyclic rings such as benzimidazole and pyridazine, has improved the antimicrobial activities. The detailed synthesis and the antimicrobial screening of the new compounds are reported.

Keywords: Synthesis, 2-mercaptoquinazoline, quinazoline-2,4-dithione, 2-amino-quinazoline, benzimidazole, pyridazine, antimicrobial screening.

1. Introduction

In recent years much attention has been focused on the synthesis of some iodoquinazoline compounds as potential antimicrobial agents (1-6). In the present investigation, the quinazoline analogs were designed to contain a proper side chain bearing sulphur or sulphonyl group which are believed to contribute to the antimicrobial activity, in addition, some heterocyclic rings that known to have antimicrobial activity such as benzimidazole and pyridazine has been incorporated into the quinazoline nucleus (3, 7, 8). The newly synthesized compounds were screened for their activity against a panel of Gram-positive and Gram-negative bacteria and pathogenic fungi.

2. Results and Discussion

A) Chemistry

The synthetic strategy to obtain the target compounds **1-21** is depicted in Schemes 1-3.

* To whom all correspondence should be addressed. gabersami@yahoo.com

The starting material 2-mercapto-3-(4-chlorophenyl)-6-iodo-4(3*H*)-quinazolinone **1** was treated with phosphorous pentasulphide in boiling xylene to afford the 4-thioxo derivative **2** in high yield. The latter was alkylated with ethyl or benzyl halides to give the ethylthio and benzylthio derivatives, respectively **3**, **4**. Oxidation of **3** and **4** with potassium permanaganate afforded the corresponding sulphone analogs **5**, **6**. The reaction of **2** with 4-chlorophenacyl bromide and chloroacetonitrile afforded the targets **7**, **8**, respectively. Further alkylation of **2** using cyclohexyl bromide in dimethyl formamide yielded the target compound **9** (Scheme 1). Treatment of **1** with 2-chloromethylbenzimidazole or 2-chloro-4-substituted acetanilides afforded **10** and $\mathbf{11_{a-g}}$, respectively. Interaction of **1** with formamide furnished 2-amino-3-(4-chlorophenyl)-6-iodo-4-oxo-3*H*-quinazoline **12**. Alkylation of **1** with chloroacetone gave the 2-oxopropylthio analog **13** which upon reaction with 4-substituted benzaldehydes failed to give the corresponding α,β-unsaturated ketone derivatives $\mathbf{14_{a-c}}$ but gave 3-(4-chlorophenyl)-6-iodo-2,4-(1H, 3H)quinazoline-2,4-dione **15** (Scheme 2). Reaction of **16** with o-aminophenol in polyphosphoric acid failed to give compound **17** but afforded 2,4-quinazolinedione **15**. Interaction of the acid hydrazide **18** with diethyloxalate and/or chloroacetaldehyde diethylacetal yielded the corresponding heterocycles **19**, **20** respectively. Condensation of the hydrazide **18** with appropriate aldehyde in acetic acid afforded the hydrazones $\mathbf{21_{a-c}}$. Cyclocondensaton of $\mathbf{21_{a,b}}$ by boiling with acetic anhydride failed to afford the substituted oxadiazole analogs $\mathbf{22_{a,b}}$ but gave 2-mercapto-3-(4-chlorophenyl)-6-iodo-4-(3*H*)quinazoline **1**. Interaction of $\mathbf{21_{a-c}}$ with mercaptoacetic acid failed to give the corresponding thiazolidinone analogs $\mathbf{23_{a-c}}$ but afford quinazolinedione **15** (Scheme 3).

Antimicrobial Screening

All of the newly synthesized compounds were subjected to antimicrobial screening by the *in vitro* cup-plate technique using ampicillin, streptomycin and nystatin as positive controls. Compounds **4**, **6**, **8**, **9**, **19** and $\mathbf{21_b}$, showed remarkable activity toward the Gram negative bacteria *E. coli.*

The Gram positive bacteria *S. aureus* and *B. subtilis* proved to be sensitive toward compounds **8**, **10**, **12, 19**, **20**, and $\mathbf{21_b}$. Compounds **4**, **10**, **19** and **20** showed remarkable activity towards the used fungi *S. cerevisiae* and *C. albicans*. All of the aforementioned compounds showed antimicrobial activity comparable to the used positive control drug. In addition compounds **10**, **19**, and **20** proved to be the most active broad spectrum antimicrobial agents in this study.

In conclusion, the present study revealed that attachment of 1,3,4-oxadiazole, benzimidazole, pyridazine and thiazolidinone to the quinazoline nucleus could be useful as a template for further development through modification or derivatization to design a more potent antimicrobial agents.

3. Experimental

All melting points (°C) were taken in open capillaries and are uncorrected. Microanalyses were conducted on a Heraeus instrument, results are within ± 0.4% of

the theoretical values. Thin layer chromatography was performed on Merck 50020 10 cm plates, precoated with silica gel GF_{254} using short wavelength UV light for visualization and elution with $CHCl_3$: EtOH (9:1). All of the fine chemicals and reagents used were purchased from Aldrich Chemical Co., USA. ^{1}H NMR were recorded on a Varian Gemini 200, 200 MHz spectrometer. Chemical shifts are given in δ (ppm) values downfield from Me_3Si as an internal standard. IR spectra were recorded on a Pye Unicam SP 1000 using KBr discs. The following organisms were used in the antimicrobial screening *Escherichia coli* ATCC 10536, *Staphylococcus aureus* ATCC 06538, *Bacillus subitilis* RTCC 6633, *Saccharomyces* ATCC 9763, and *Candida albicans* ATCC 1023. The starting materials 2-mercapto-3-(4-chlorophenyl)-6-iodo-4-(3*H*)-quinazoline, 1,2-(Ethoxycarbonylmethyl)thio-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (16) and 2[(3-(4-chlorophenyul)-4-oxo-3*H*-quinazolin-2-yl)thio]acetyl-hydrazine (18) were synthesized according to not yet reported procedures (9).

3-(4-Chlorophenyl)-6-iodoquinazoline-2,4(1*H*, 3*H*)-dithione (2)

To a solution of 3-(4-chlorophenyl-6-iodo-2-mercapto-3*H*-quinazolin-4-one **1** (4.145 g in 0.01 mol) in dry xylene (40 ml) phosphorous pentasulfide (2.3 g, 0.01 mol) was added. The reaction mixture was refluxed for 18 hr, cooled and solvent was evaporated under *vacuo*. The obtained solid was treated with acidulated cold water (100 ml) with stirring for 15 min. The obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6): δ 7.38 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.66 (d, 2H, J = 8.5 Hz, Ar-H), 8.06–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 12.3 (brs, 1H, NH).

3-(4-Chlorophenyl)-2-ethylthio-6-iodo-4(3*H*)quinazoline-4-thione (3) and 3-(4-chlorophenyl)-2-benzylthio-6-iodo-4(3*H*)quinazoline-4-thione (5)

To a solution of **2** (2.15 g, 0.005 mol) in dry acetone (50 ml), anhydrous K_2CO_3 (2.0 g) was added followed by either ethyl bromide or benzyl bromide (0.0075 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was evaporated under *vacuo* and the obtained solid was crystallized from the appropriate solvent (Table 1, 2). ^{1}H NMR (acetone-d_6) **3**: δ 1.09 (t, 2H, J = 8 Hz, $\underline{CH_3}CH_2$), 3.43 (q, 2H, J = 8 Hz, $\underline{CH_2}CH_3$), 7.39 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.5 Hz, Ar-H), 8.03–8.17 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.30 (d, 1H, J = 2 Hz, Quin-H), **5**: δ 4.46 (s, 2H, CH_2Ph), 7.16–7.73 (m, 10 H, Ar-H and Quin-H), 8.05–8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

3-(4-Chlorophenyl)-2-ethylsulfonyl-6-iodo-4-(3*H*)quinazoline-4-thione (4) and 2-Benzylsulphonyl-3-(4-chlorophenyl)-6-iodo-4(3*H*)quinazoline-4-thione (6)

To a solution of **3** or **5** (0.005 mol) in acetic acid (30 ml) potassium permanagante solution (0.8 g, 0.005 mol) in 10 ml water was added. The reaction

mixture was stirred at room temperature for 3 hr, concentrated to half of its volume under reduced pressure and cooled. The obtained solid was filtered, dried and crystallized from the suitable solvent (Table 1, 2). ^{1}H NMR (DMSO-d_6) **4**: δ 1.2 (t, 3H, J = 8 Hz, $\underline{CH_3}$-CH_2), 3.69 (q, 2H, J = 8 Hz, $\underline{CH_2}CH_3$), 7.38 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.66 (d, 2H, J = 8.5 Hz, Ar-H), 8.01–8.18 (dd, 1H, J = 2, 7.5t Hz, Quin-H), 8.1 (d, 1H, J = 2 Hz, Quin-H), **6**: δ 4.91 (s, 2H, CH_2Ph), 7.18–7.79 (m, 10 H, Ar-H) and Quin-H), 8.05–8.19 (dd, 1H, J = 2.0, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

2-(4-Chlorobenzoylmethylthio)-3-(4-chlorophenyl)-6-iodo-4(3*H*)quinazoline-4-thione (7)

A mixture of **2** (2.3 g, 0.005 mol), 4-chlorophenacyl bromide (1.25 g, 0.0075 mol) and anhydrous potassium carbonate (2 g) in dry acetone (50 ml) was heated under reflux for 24 hr. The reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure. The obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1, 2). ^{1}H NMR (acetone-d_6), **7**: δ 4.71 (s, 2H, CH_2CO), 7.29–7.73 (m, 9H, Ar-H and Quin-H), 8.03–8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

3-(4-Chlorophenyl)-2-cyanomethylthio-6-iodo-4(3*H*)quinazin-4-thione (8)

To a solution of **2** (2.3 g, 0.005 mol) in dry acetone (40 ml), anhydrous potassium carbonate (2.0 g) was added, followed by 2-bromoacetonitrile (0.89 g, 0.0075 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was evaporated in *vacuo* to give the crude product which was crystallized from ethanol (Table 1, 2). ^{1}H NMR ($CDCl_3$) **8**: δ 4.23 (s, 2H, CH_2), 7.38 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5), Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.03–8.11 (d, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2Hz, Quin-H).

2-(Cyclohexylthio)-3-(4-chlorophenyl)-6-iodo-4(3*H*)quinazoline-4-thione (9)

To a solution of **1** (4.14 g, 0.01 mol) in dry dimethylformamide (30 ml), anhydrous K_2CO_3 (2.0 g) was added followed by cyclohexyl bromide (0.015 mol). The reaction mixture was heated under reflux for 20 h. The solvent was removed in *vacuo* and the obtained solid was recrystallized from ethanol (Table 1, 2). ^{1}H NMR ($CDCl_3$), δ 0.9–2.1 (m, 10, cyclohexyl), 3.1–3.3 (m, 1H, SCH), 7.36 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.01–8.15 (dd, 1H, J = 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

2-(2-Benzimidazolylmethylthio)-3-(4-chlorophenyl)-6-iodo-(3*H*)-quinazoline-4-one (10)

To a solution of **1** (2.07 g, 0.005 mol) in acetone (40 ml), anhydrous potassium carbonate (2.0 g) was added, followed by 2-chloromethylbenzimidazole (1 g, 0.006

mol). The reaction mixture was heated under reflux for 20 h. The solvent was removed in *vacuo* and the obtained solid was crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 3.91 (s, 2H, S-CH_2-Hetero), 7.26–7.72 (m, 10H, Ar-H, benzimidazole-H, NH and Quin-H), 8.05–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2Hz, Quin-H).

3-(4-Chlorophenyl)-6-iodo-2[N-substituted phenyl)carbamoylthio]-4-(3*H*)-quinzoline-4-one (11_{a-g})

To a solution of **1** (4.14 g, 0.01 mol) in acetone (60 ml), anhydrous K_2CO_3 (2.0 g) was added, followed by the appropriate 2′-chloro-4-substituted acetanilide (0.012 mol). The reaction mixture was heated under reflux for 20 h, then filtered while hot and the filtrate was concentrated in *vacuo*. The separated solid was filtered, washed with water, dried and crystallized from the suitable solvent (Table 1, 2). ^{1}H NMR (DMSO-d_6) **11_a:** δ 4.26 (s, 2H, S-CH_2CO), 7.06–7.69 (m, 10H, Ar-H and Quin-H), 8.05–8.21 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.32 (d, 1H, J = 2 Hz, Quin-H), 11.8 (brs, 1H, NH). **11_b:** 4.28 (s, 2H, S-CH_2CO), 7.08–7.81 (m, 9H, Ar-H and Quin-H), 3.03–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 11.86 (brs, 1H, NH). **11_c:** 4.26 (s, 2H, S-2H, S-CH_2CO), 7.02–7.88 (m, 9H, Ar-H and Quin-H), 8.04–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.32 (d, 1H, J = 2 Hz, Quin-H), 11.91 (brs, 1H, NH). **11_d:** 4.0 (s, 1H, OH), 4.26 (s, 2H, S-CH_2CO), 6.71–7.61 (m, 9H, Ar-H and Quin-H), 8.02–8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.3 (d, 1H, J = 2 Hz, Quin-H), 11.71 (brs, 1H, NH). **11_e:** 4.25 (s, 2H, S-CH_2CO), 4.71 (s, 1H, OH), 7.21–7.94 (m, 8H, Ar-H and Quin-H), 8.03–8.17 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 11.21 (brs, 1H, COOH), 11.69 (brs, 1H, NH). **11_f:** 2.35 (s, 3H CH_3), 4.11 (s, 1H, OH), 4.25 (s, 2H, SCH_2CO), 6.59–7.55 (m, 8H, Ar-H and Quin-H), 8.01–8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.32 (d, 1H, J = 2 Hz, Quin-H), 11.71(brs, 1H, NH). **11_g:** 4.13 (s, 1H, OH), 4.25 (s, 2H, SCH_2CO), 6.61–7.71 (m, 9H, Ar-H and Quin-H), 8.03–8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 11.73 (brs, 1H, NH).

2-Amino-3-(4-chlorophenyl)-6-iodo-4(3*H*)quinazoline-4-one (12)

A solution of **1** (2.07 g, 0.005 mol) in formamide (20 ml) was heated under reflux for 20 h. On cooling, the obtained precipitate was filtered, washed with water and crystallized from ethanol (Table 1). ^{1}H NMR (DMSO-d_6): δ 5.92 (brs, 2H, NH_2), 7.41 (d, 1H, J = 7.5 Hz, Quin-11), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.5 Hz, Ar-H), 8.04–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-11), 8.31 (d, 1H, J = 2 Hz, Quin-H).

3-(4-Chlorophenyl)-6-iodo-2-(2-oxo-propylthio)-4(3*H*)quinazoline-4-one (13)

To a solution of **1** (4.15 g, 0.01 mol) in dry acetone (50 ml), anhydrous potassium carbonate (2.0 g) was added, followed by chloroacetone (0.015 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was concentrated in *vacuo*. The separated crude product was filtered, dried and crystallized from ethanol (Table 1). ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3CO), 4.32 (s, 2H, CH_2CO), 7.41 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.02–8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

3-(4-Chlorophenyl)-6-iodo-2,4-(1*H*, 3*H*)quinazoline-2,4-dione (15)

Method (A)

A solution of **13** (1.175 g, 0.0025 mol) and NaOEt (0.25 g, 0.0036 mol) in ethanol (20 ml) was stirred at room temperature for 2 h. Substituted benzaldehyde (0.0035 mol) was added dropwise and stirring was continued for another 24 h. The reaction mixture was adjusted to pH 6 using dilute HCl, the obtained solid was filtered and recrystallized from acetic acid (Table 1).

Method (B)

A solution of **13** (1.175 g, 0.0025 mol) in ethanol (30 ml) containing piperidine (1 ml) was refluxed for 1 h. Substituted benzaldehyde (0.0035 mol) was added slowly. The reaction mixture was refluxed for 20 h, concentrated under reduced pressure, cooled and treated with cold acidulated water (20 ml). The obtained solid was filtered, washed with water and crystallized from acetic acid (Table 1).

Method (C)

A mixture of 2-(ethoxycarbonylmethyl)thio-3-(4-chlorophenyl)-6-iodo-4(3*H*)-quinazoline-4-one (**16**, 2.5 g, 0.05 mol) and 2-aminophenol (0.0075 mol) in polyphosphoric acid (20 ml) were heated under reflux on an oil bath at 120°C for 4 hr. On cooling, the mixture was neutralized with 10% sodium hydrogen carbonate solution and separated product was filtered, washed with water, dried and crystallized from acetic acid (Table 1, 2).

^{1}H NMR (DMSO-d_6): δ 7.39 (d, 1H, J = 7.5 Hz, Quin-H, 7.51 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.05–8.21 (dd, 1H, J = 2, 7.5 Hz, Quin-H, 8.33 (d, 1H, J = 2 Hz, Quin-H), 12.67 (brs, 1H, NH).

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]pyridazine-3,4,6-trione (19)

An equimolar mixture of **18** (4.86 g, 0.01 mol), diethyl oxalate (1.4 6 g, 0.01 mol) and sodium metal (0.23 g) in ethanol (30 ml) was heated under reflux for 12 hr.

On cooling, the mixture was acidified with dil. HCl and the separated solid was filtered, dried and crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6): δ 7.03 (brs, 1H, NHCO), 7.24 (d, 1H, J = 7.5 Hz, Quin-H), 7.35 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 7.81 (s, 1H, OH), 8.03–8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 10.11 (s, 1H, OH).

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-quinazolin-2-yl)thio]-pyridazin-6-one (20)

An equimolar amount of **18** (4.86 g, 0.01 mol), chloroacetaldehyde diethyl-acetal (1.52 g, 0.01 mol) and sodium ethoxide (0.068 g, 0.01 mol) in ethanol (50 ml) was heated under reflux for 20 h. The reaction mixture was cooled and acidified with dilute HCl. The separated solid was filtered, washed with cold water and crystallized from ethanol (Table 1). ^{1}H NMR (DMSO-d_6): 2.31 (d, 1H, J = 10 Hz, CH_2), 4.92 (t, 1H, J = 10 Hz, CH), 7.24 (d, 1H, J = 7.5 Hz, Quin-H), 7.41 (t, 1H, J = 10 Hz, N=CH), 7.53 (d, 2H, J = 8.5 Hz, Ar-H0, 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.03–8.17 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

N-(4-Substituted benzylidene)-N-[2-(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]hydrazine (21_{a-c})

A mixture of **18** (4.86 g, 0.01 mol) and appropriate aldehyde (0.015 mol) in acetic acid (20 ml) was heated under reflux for 12 h. The reaction mixture was cooled, and the separated solid was filtered, washed with petroleum ether, dried and recrystallized from acetic acid (Table 1). ^{1}H NMR (DMSO-d_6) **21_a:** δ 4.14 (s, 2H, S-CH_2CONH), 7.21–7.69 (m, 10, Ar-H and Quin-H), 8.03–8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.59 (s, 1H, CH=N), 10.31 (brs, 1H, NH). **21_b:** δ 3.73 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2CO), 6.8–7.69 (m, 9H, Ar-H and Quin-H), 8.01–8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.67 (s, 1H, CH=N), 10.13 (brs, 1H, NH). **21_c:** δ 4.0 (s, 1H, 0H), 4.19 (s, 2H, S-CH_2CONH), 6.71–7.67 (m, 9H, Ar-H and Quin-H), 8.01–8.16 (dd, 1H, J = 2, 7.5 Hz, Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 9.57 (s, 1H, CH=N), 10.39 (brs, 1H, NH).

Antimicrobial Testing

Nutrient agar plates were seeded using 0.1 ml of overnight cultures. Cylindrical plugs were removed from agar plate using a sterile cork borer and 100 µ gram of the tested compounds (1 mg/ml, DMSO) were added to the well in triplicates. Blank solvent was used as control. Plates inoculated with tested bacteria were incubated at 37°C, while those of fungi were incubated at 30°C. Results were taken after 24 h of incubation and were recorded as average diameter of the inhibition zone in mm (1, 2, 10, 11).

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5. References

(1) Abdel-Hamide SG. Synthesis and Antimicrobial Activity of Some New Substituted Quinazoline Derivatives. *Saudi Pharm. J*. **2001**; 9:72-84.

(2) Al-Omar MA, Abdel-Hamide SG, Alkhamees HA, El-Subbagh HI. Synthesis and Biological Screening of Some New Substituted 3H-Quinazolin-4-one Analogs as Antimicrobial Agents. *Saudi Pharm. J*. **2004**; 12:63-71.

(3) Abdel-Hamide SG, Ghorab MM, El-Hifnawy HN. Effect of Novel Biologically Active Oxadiazino, Oxadiazolo, and Oxathiadiazoloquinazolines on Non-irradiated and Radioresistant *Staphylococcus aureus*. *Acta Pharm*. **1998**; 48:249-258.

(4) Mosad SM, Mohammed KI, Ahmed MA, Abdel-Hamide SG. New Quinazoline Related Derivatives with antimicrobial Activity: Part I. *Pak. J. Biol. Sci*. **2004**; 7(7):1263-1268.

(5) Misra HK, SenGupta AK. Synthesis and Evaluation of Substituted 4(3H)-Quinazoline Derivatives for Antimicrobial and Antiacetylcholinesterase Activity. *Pharmazie*, **1982**; 37:254-256.

(6) Al-Omar MA, El-Azab AS, El-Obeid HA, Abdel-Hamide SG. Synthesis of Some New 4-(3H)-Quinazoline Analogs as Potential Antioxidant Agents. *J. Saudi Chem. Soc*. **2006**; 10(1):113-128.

(7) Abdel-Hamide SG, El-Hakim AE, Abdel-Rahman RM. Synthesis and Biological Activities of Some New Heterocyclic Compounds Bearing 2-Phenyl-6-iodo-quinazolinyl-4-oxy Moiety: Part-II. *Indian J. Heterocyclic Chem*. **1996**; 5:189-192.

(8) Aziza MA, Nassar MW, Abdel-Hamide SG, El-Hakim AE, El-Azab AS. Synthesis of Some New Heterocyclic Systems Bearing 2-Ethyl-6-iodo-4(3H)-quinazolino-n-3-yl Moiety as Antibacterial Agents. *Az. J. Pharm. Sci*. **1998**; 21:65-74.

(9) El-Azab AS. 2-Mercaptoquinazoline Analogs as Potential Antimicrobial Agents, Phosphorous, Sulfur and Silicon. *Phosphorous, Sulfur, Silicon and Relat. Elem*. **2007**; 182:333-348.

(10) Colle JG, Duguid JP, Fraser AG, Marmion BP. (eds) 1989: Mackie & Mc-Carthey, Practical Medical Microbiology, 13th ed, Churchill Livingstone, London, UK.

(11) Shehata, IA, Nasr MN, El-Subbagh HI, Gineinah MM, Kheira SM. Synthesis and Biological Testing of Certain 1,3,4-Oxadiazole and 1,2,4-Triazole Derivatives as Potential Antimicrobial Agents. *Sci. Pharm*. **1996**; 64:133-143.

Table 1: The physiochemical properties of the new synthesized compounds.

Compd	Solvent	M.P. °C	Yield	Molecular formula (Mol. wt.)
2	EtOH	290-2	70	$C_{14}H_8ClIN_2S_2$
3	$CHCl_3$, hexane	197-9	78	$C_{16}H_{12}ClIN_2S_2$
4	Dioxane	190-2	60	$C_{16}H_{12}ClIN_2O_2S_2$
5	$CHCl_3$, hexane	187-9	80	$C_{21}H_{14}ClIN_2S_2$
6	Dioxane	215-7	66	$C_{21}H_{14}ClIN_2O_2S_2$
7	EtOH	>340	56	$C_{22}H_{13}Cl_2IN_2OS_2$
8	EtOH	331-3	54	$C_{16}H_9ClIN_3S_2$
9	EtOH	>340	61	$C_{20}H_{18}ClIN_2S_2$
10	EtOH	260-2	40	$C_{22}H_{14}ClIN_4OS$
11_a	EtOH, dioxane	227-9	60	$C_{22}H_{15}ClIN_3O_2S$
11_b	EtOH, dioxane	245-7	66	$C_{22}H_{14}BrClIN_3O_2S$
11_c	EtOH, dioxane	230-2	71	$C_{22}H_{14}Cl_2IN_3O_2S$
11_d	AcOH	190-3	69	$C_{22}H_{15}ClIN_3O_3S$
11_e	AcOH	240-2	50	$C_{23}H_{15}ClIN_3O_5S$
11_f	AcOH	187-9	73	$C_{23}H_{17}ClIN_3O_3S$
11_g	EtOH	220-2	75	$C_{22}H_{15}ClIN_3O_3S$
12	EtOH	240-2	41	$C_{14}H_9ClIN_3O$
13	EtOH	195-7	68	$C_{17}H_{12}ClIN_2O_2S$
15	AcOH	>350	77	$C_{14}H_8ClIN_2O_2$
19	EtOH	320-2	61	$C_{18}H_{10}ClIN_4O_4S$
20	EtOH	>350	57	$C_{18}H_{11}ClIN_4O_2S$
21_a	AcOH	225-7	70	$C_{23}H_{16}ClIN_4O_2S$
21_b	AcOH	235-7	80	$C_{24}H_{18}ClIN_4O_3S$
21_c	AcOH	265-6	70	$C_{23}H_{16}C_{11}N_4O_3S$

Table 2: Mass spectral data of some compounds.

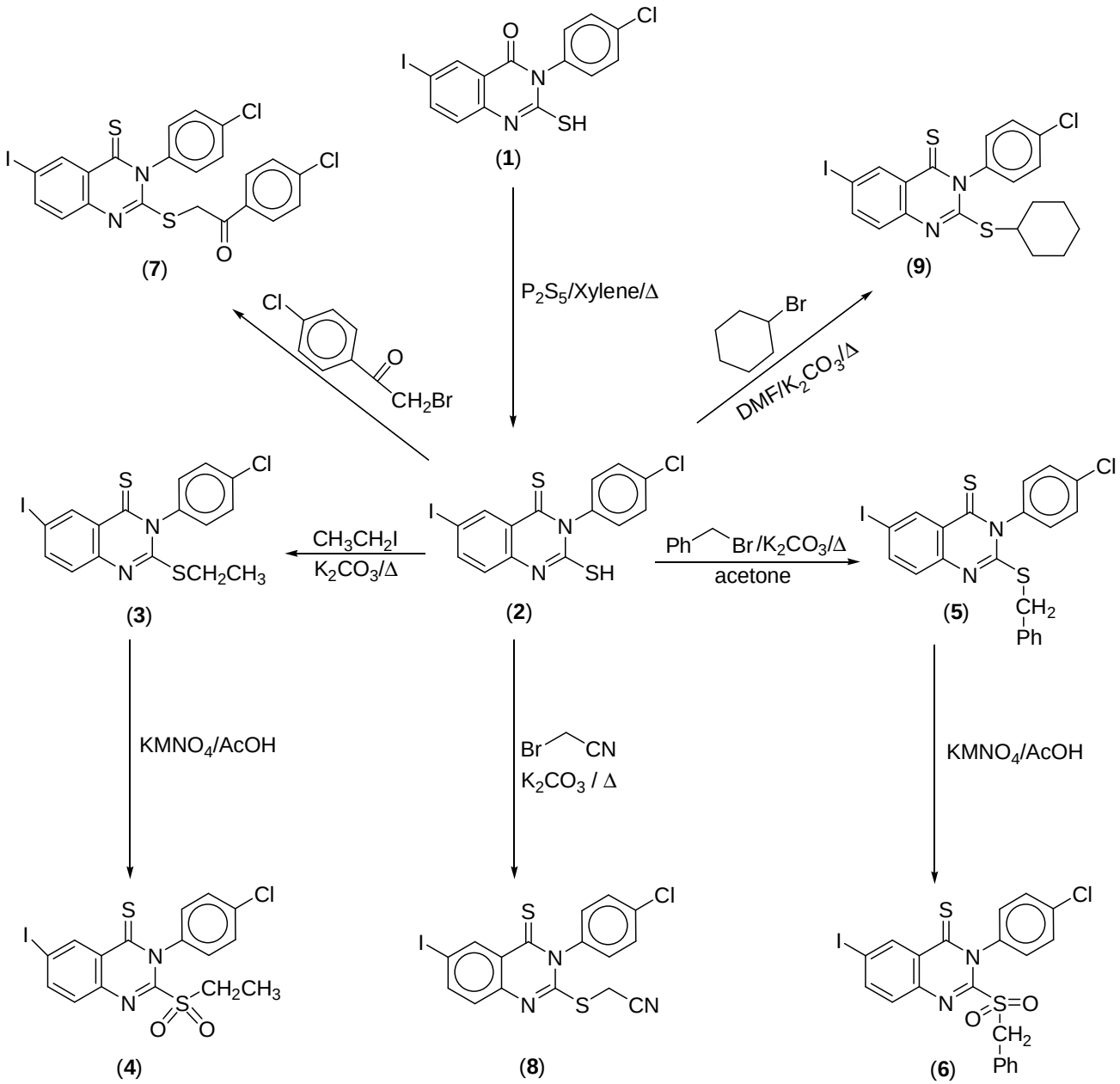
Compound	MS (Relative Intensity)
2	m/z 430 (M^+, 32.82), 432 (M + 2, 11.40); 319 (1.81), 287 (37.69), 144 (70.59).
3	m/z 458 (M^+, 13.21), 460 (M + 2, 4.71), 443 (16.2), 397.05 (18.06), 347 (22.61).
4	m/z 490.25 (M^+, 25.90), 492.15 (M + 2, 8.61%), 397 (100), 379.36 (29.96).
5	m/z 520 (M^+, 39.16), 522 (M + 2, 14.12), 488 (32.36), 429.1 (12.7).
6	m/z 552 (M^+, 44.37); 554 (M + 2, 14.71), 522 (53.54), 441.2 (41.17), 409.10 (65.81), 398.1 (46.47).
7	m/z 583 (M^+, 32.45), 585 (M + 2, 20.19), 587 (M + 4, 4.11), 472.25 (17.30), 443 (19.22), 397 (23.92).
8	m/z 469 (M^+, 29.36), 471 (M + 2, 9.21), 443 (13.21), 429 (11.21), 397 (19.31), 358 (31.21).
10	m/z 544 (M^+, 2.93), 427 (1.23), 413 (2.13), 381 (0.8).
11_b	m/z 625 (M^+, 0.71), 627 (M + 2, 0.23), 514 (14.31), 455 (6.47), 427 (9.31), 413 (3.61), 381 (2.12).
11_f	m/z 577 (M^+, 2.18), 579 (M^+ + 2, 0.83), 455 (4.50), 413.2 (2.61), 381 (3.31).
12	m/z 397 (M^+, 91.96), 399 (M + 2, 30.23), 258.3 (38.20), 244 (63.61).
21_a	m/z 574 (M^+, 31.81), 576 (M + 2, 9.81), 455 (8.31), 427 (13.39), 413.31 (20.31).

Table 3: Antimicrobial screening results for the tested compounds at 1 mg/ml concentration.[a]

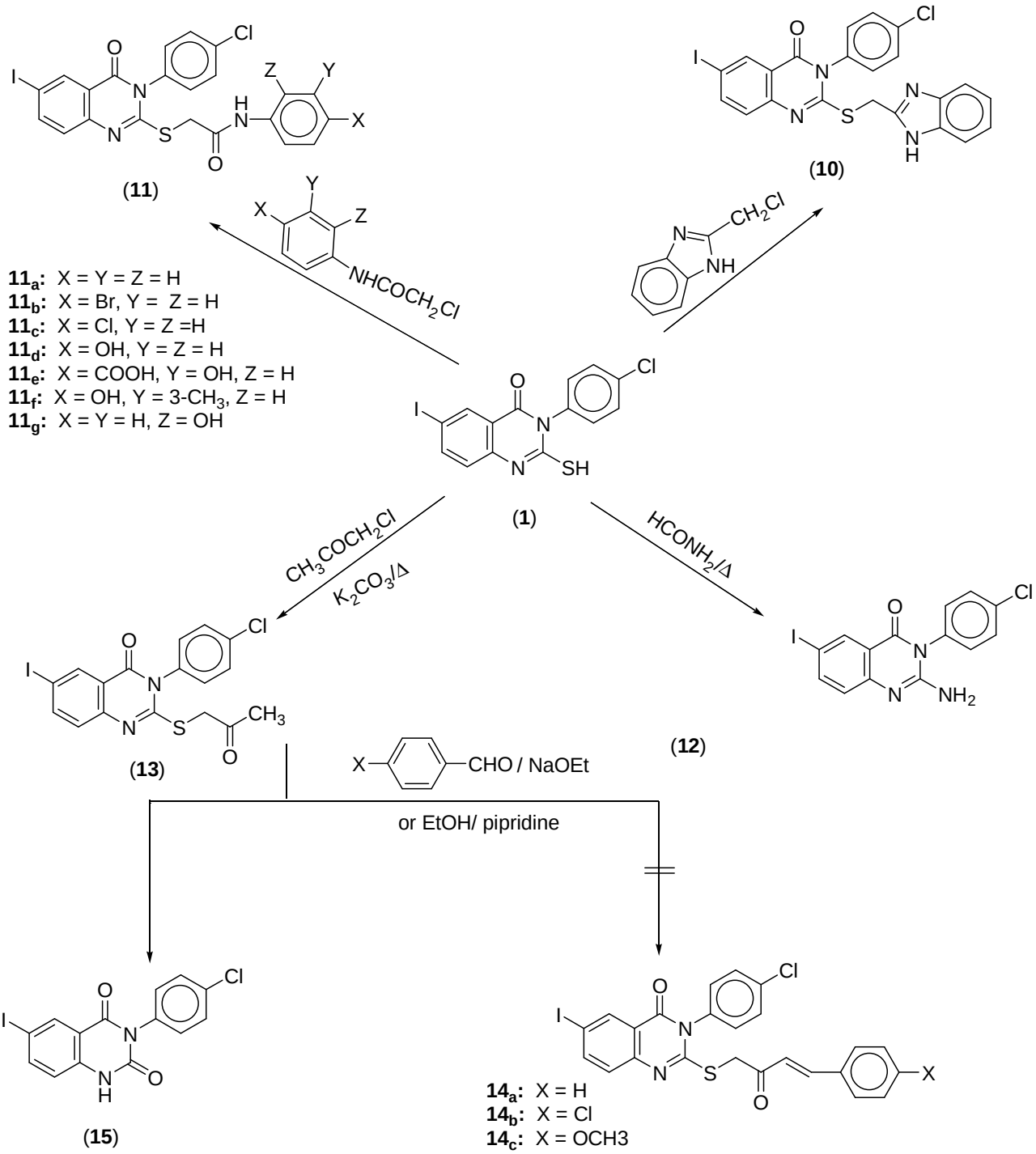
Compd	*E. coli*	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
2	—	—	+	++	++
3	—	+	—	—	—
4	+++	—	—	++	++
5	+	+	+	+	—
6	+++	+	+	+	+
7	—	—	—	—	+
8	+++	++	++	—	—
9	+++	—	+	—	—
10	++	++	++	++	++
11_a	+	+	—	—	—
11_b	++	++	—	+	—
11_c	—	—	++	++	—
11_d	+	—	—	—	—
11_e	—	+	+	—	—
11_f	++	—	++	—	—
11_g	—	++	—	+	+
12	++	++	++	—	—
13	+	+	+	—	—
15	+	+	+	+	+
19	+++	++	++	++	++
20	++	+++	+++	++	++
21_a	++	++	—	+	+
21_b	+++	++	++	+	—
21_c	—	++	—	++	—
Ampicillin	+++	+++	+++	NT	NT
Streptomycin	+++	+++	++	NT	NT
Nystation	NT	NT	NT	++	+++

[a] : Inactive (inhibition zone < 10 mm), +, moderately activity (inhibition zone 10–15 mm), ++: active (inhibition zone 15–20 mm), +++: marked activity (inhibition zone > 20 mm), NT : not tested.

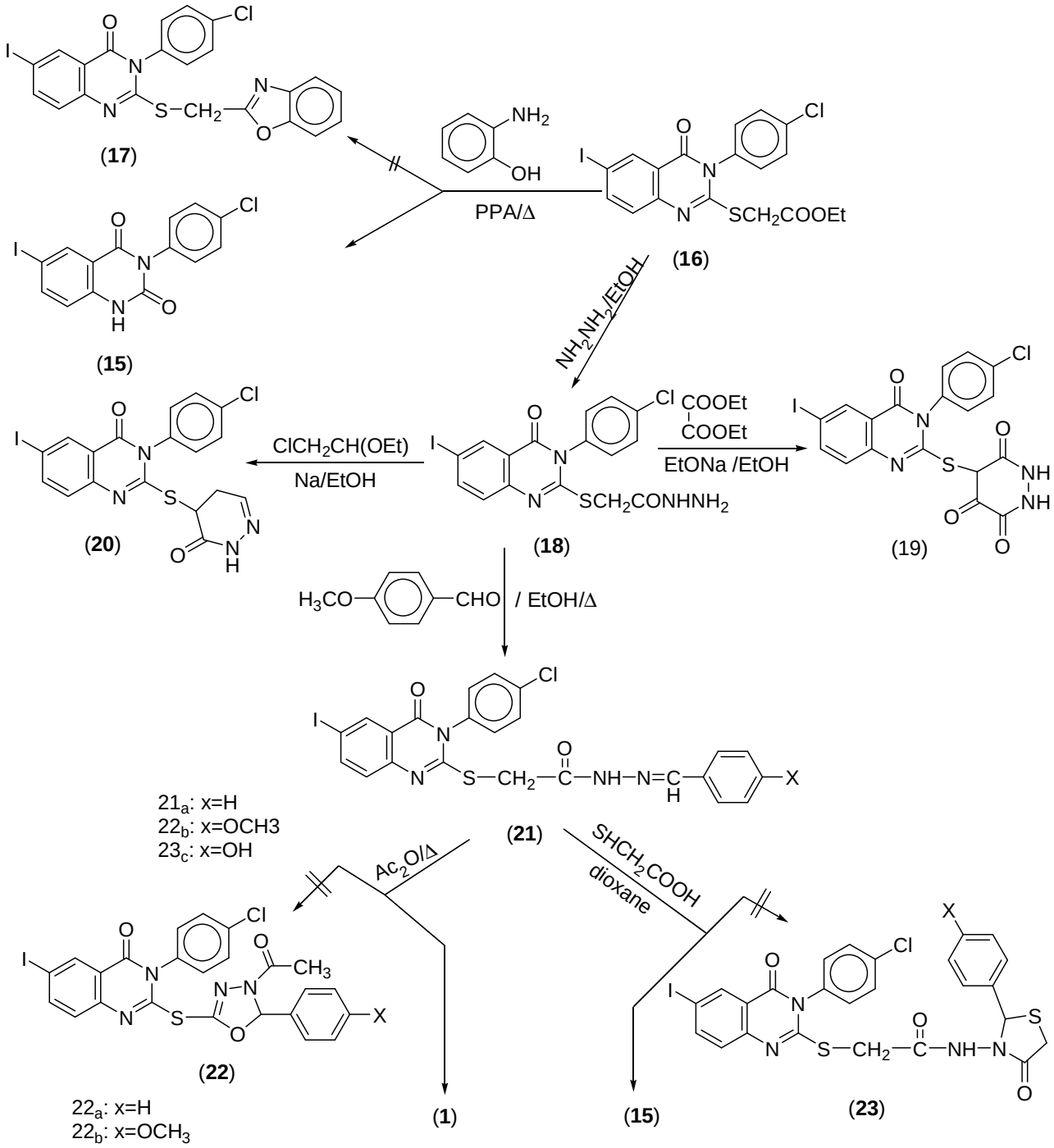
Scheme 1


(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
(9)
P2S5/Xylene/Δ
CH3CH2I
K2CO3/Δ
Ph Br /K2CO3/Δ
acetone
DMF/K2CO3/Δ
KMNO4/AcOH
KMNO4/AcOH
Br CN
K2CO3 / Δ

Scheme 2


(11)
(10)
(1)
(13)
(12)
(15)
(14)
11a: X = Y = Z = H
11b: X = Br, Y = Z = H
11c: X = Cl, Y = Z =H
11d: X = OH, Y = Z = H
11e: X = COOH, Y = OH, Z = H
11f: X = OH, Y = 3-CH3, Z = H
11g: X = Y = H, Z = OH
CH3COCH2Cl
K2CO3/Δ
HCONH2/Δ
CHO / NaOEt
or EtOH/ pipridine
14a: X = H
14b: X = Cl
14c: X = OCH3

Scheme 3:


(17)
(15)
PPA/Δ
(16)
NH2NH2/EtOH
ClCH2CH(OEt)
Na/EtOH
(20)
(18)
COOEt
COOEt
EtONa /EtOH
(19)
H3CO
CHO
/ EtOH/Δ
21a: x=H
22b: x=OCH3
23c: x=OH
(21)
Ac2O/Δ
SHCH2COOH
dioxane
(22)
22a: x=H
22b: x=OCH3
(1)
(15)
(23)