SYNTHESIS AND BIOLOGICAL SCREENING OF SOME NEW SUBSTITUTED 2-MERCAPTO-4-(3*H*)-QUINAZOLINONE ANALOGS AS ANTICONVULSANT AGENTS

Adnan A. Kadi, Adel S. El-Azab, 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

A new series of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodo-quinazoline was synthesized and characterized by their elemental analysis, ^{1}H NMR and mass spectral data. The anticonvulsant activities of prepared compounds have been examined using the PTZ-seizure threshold test. Compounds **2**$_{a,b}$, **3**$_a$, **4**$_{a,b}$, **12** and **13**$_{a-c}$ showed a significant anticonvulsant activity (at 200 mg/kg dose/level).

Introduction

Epilepsy is a very common disorder, characterized by seizures, which takes various form and result from episodic neuronal discharges. Current antiepileptic drugs are effective in controlling seizures in about 70% of patients but their use is often limited by side effects.[1-3] Mercaptoquinazolines are reported to possess a potent anticonvulsant activity.[4-7] In this study a new series of mercaptoquinazoline bearing iodine at the 6-position was synthesized. The thiol function was used to introduce variety of polar moieties (ureide structure or imide functionality), aliphatic and aromatic substituents, esters, hydrazides and 1,3,4-oxadiazole nucleus to the

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

quinazoline nucleus to explore their influence on anticonvulsant activities. The present study is a continuation to our previous efforts, hoping to come up with a novel lead compound(s). For further development as anticonvulsant agent(s) with minimal side effects.

Experimental

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. IR spectra were recorded on a Perkin-Elmer spectrometer. ^{1}H NMR were recorded in DMSO-d_6 on a Jeol 400 MHz instrument using TMS as internal standard (chemical shifts in δ ppm). Microanalytical data (C, H, N) were performed on Perkin Elmer 240 B analyzer and they agreed with proposed structures within ± 0.4% of the calculated values. Mass spectra were recorded on a Shimadzu PQ-5000 GC-MS apparatus. Solvent evaporation was performed under reduced pressure using Buchi Rotatory Evaporatory unless otherwise stated. T.L.C. was performed on precoated silica gel plates (60-F_{254}, 0.2 mm), manufactured by E.M. Sciences, Inc, and shortwave UV (254) nm was used to detect the U.V. absorbing compounds (CH_2Cl_2, EtOH 10:1). All test animals were obtained from Animal Care Center, College of Pharmacy, Al-Azhar University, Cairo, Egypt. The starting material 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodo-quinazoline (1), 2-(Ethoxycarbomethyl)thio-3-(4-chloro-phenyl)-4-oxo-6-iodo-3*H*-quinazoline (6) and its corresponding acid hydrazide (11) were prepared using reported procedures.[8]

2-Substitued methylthio-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (2_{a-c})

To a solution of 2-mercapto-3-(4-chlorophenyl)-6-iodo-3*H*-quinazoline-4-one **1** (0.01 mol) in dry acetone (60 ml) anhydrous potassium carbonate (2 g) was added, followed by either 2-chloroacetamide, 2-chloroacetic acid or 2-chloroethanol (0.015 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was concentrated in *vacuo* to give crude product which was crystallized from the suitable solvent (Table 1, 2). ^{1}H NMR ($CDCl_3$), **2_a**: δ 4.23 (s, 2H, CH_2CO), 7.37 (d, 1H, J = 7.5 Hz, Quin-H), 7.49 (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), 8.29 (d, 1H, J = 2 Hz, Quin-H), 9.11 (brs, 2H, NH_2), **2_b**: δ 4.25 (s, 2H, CH_2CO), 7.32 (d, 1H, J = 7.5 Hz, Quin-H), 7.51 (d, 2H, J = 8.5 Hz, Ar-H), 7.63 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.17 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 11.12 (brs, 1H, COOH), **2_c**: δ 2.78 (t, 2H, J = 7.5 Hz, $\underline{CH_2}$-CH_2), 2.89 (brs, 1H, OH), 3.59 (t, 2H, J = 7.5 Hz, $CH_2\underline{CH_2}$), 7.36 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.63 (d, 2H, J = 8.5 Hz, Ar-H), 8.01-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

2-(Substitutedphenyl or pyridyl)thio-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline 3_{a-c}

A mixture of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline **1** (0.005 mol), the appropriate chloronitrobenzene, chloro-dinitrobenzene or chloro-nitropyridine (0.005 mol) and potassium carbonate (2.0 g) in dimethylformamide (20 ml) was heated under reflux for 12 h. Solvent was evaporated in *vacuo* and the obtained residue was washed with water, dried and crystallized from appropriate

solvent (Table 1, 2), ^{1}H NMR (DMSO-d_6), **3_a**: δ 6.92-7.73 (m, 7H, Ar-H and Quin-H), 8.01-8.14 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 8.36-8.46 (m, 2H, Ar-H), **3_b**: δ 7.31 (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), 8.01-8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.26 (d, 1H, J = 2 Hz, Quin-H), 8.5 (m, 1H, Ar-H), 8.96-9.15 (m, 2H, Ar-H). **3_c**: δ 7.28 (d, 1H, J = 7.5, Quin-H), 7.51 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.01-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.25 (d, 1H, J = 2 Hz, Quin-H), 8.6 (m, 1H, Pyr-H), 8.81-8.92 (m, 2H, Pyr-H).

3-(4-Chlorophenyl)-6-iodo-2-[2-(1-phthalimido)alkylthio]-4-(3*H*)-quinazolin one (4_{a-c})

To a solution of **1** (4.14, 0.01 mol) in acetone (50 ml), anhydrous K_2CO_3 (2.0 g) was added, followed by N-(chloroalkyl)phthalimide (0.012 mol). The reaction mixture was heated under reflux for 12 h, filtered while hot, concentrated in *vacuo* and the separated solid was filtered, dried and crystallized from AcOH (Tables 1 and 2), ^{1}H NMR (DMSO-d_6) **4_a**: δ 2.81 (t, 2H, J = 11 Hz, S-$\underline{CH_2}$-CH_2-N), 3.43 (t, 2H, J = 11 Hz, S-$CH_2\underline{CH_2}$-N), 7.21-7.64 (m, 9H, Ar-H and Quin-H), 8.01-8.13 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H). **4_b**: δ 1.21 (m, 2H, S-CH_2-$\underline{CH_2}$-CH_2-N), 2.81 (t, 2H, J = 10 Hz, S-$\underline{CH_2}CH_2CH_2$N), 3.41 (t, 2H, J = 10 Hz, S-$CH_2CH_2\underline{CH_2}$-N), 7.19-7.76 (m, 9H, Ar-H and Quin-H), 8.03-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H). **4_c**: δ 1.11 (m, 2H, S-$CH_2\underline{CH_2}CH_2CH_2$-N), 1.36 (m, 2H, S-$CH_2CH_2\underline{CH_2}CH_2$-N), 2.38 (t, 2H, J = 12 Hz, S-$\underline{CH_2}CH_2CH_2$-N), 3.38 (t, 2H, J = 12 Hz, S-$CH_2CH_2CH_2\underline{CH_2}$N), 7.21-7.78 (m, 9H, Ar-H and Quin-H), 8.02-8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

2-Hydrazino-6-iodo-3-(4-chlorophenyl)-4(3*H*)quinazoline-4-one (5)

A mixture of **1** (4.14 g, 0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (30 ml) was heated under reflux for 24 h. The reaction mixture was cooled, the obtained solid was filtered and crystallized from ethanol-benzene (Table 1). ^{1}H NMR (DMSO-d_6), δ 3.6 (brs, 2H, NH<u>NH</u>$_2$), 5.3 (brs, 1H, <u>NH</u>NH$_2$), 7.29 (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), 8.01-8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.3 (d, 1H, J = 2 Hz, Quin-H).

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

A mixture of **1** (4.14 g, 0.01 mol) was heated under reflux with hydroxylamine hydrochloride (1.04 g, 0.015 mol) in ethanol (40 ml) containing 3 ml of dry pyridine. Solvents were evaporated in *vacuo* to give the crude product which was washed with dilute HCl (30 ml), water, dried and crystallized from dioxane (Tables 1 and 2). ^{1}H NMR (DMSO-d_6), δ 3.12 (brs, 1H, NHO<u>H</u>), 4.31 (brs, 1H, <u>NH</u>OH), 7.25 (d, 1H, J = 7.5 Hz, Quin-H), 7.49 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

N^1-[(3-4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]thiosemi-carbazide (8)

A mixture of **7** (2.5 g, 0.005 mol) and thiosemicarbazide (0.3 g, 0.006 mol) in dry dimethylformamide (20 ml) was heated under reflux for 20 h. Solvent was removed under reduced pressure, the obtained residue was treated with water (20 ml) stirred and filtered. The crude product was washed with distilled water, dried and crystallized from dioxane (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 4.17 (s, 2H, CH_2CO),

7.41 (d, 1H, J = 7.5 Hz, Quin-H), 7.51 (d, 2H, J = 8.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.13 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.11 (brs, 1H, NH), 9.31 (brs, 1H, NH), 10.12 (brs, 2H, NH_2).

2-Mercapto-5-[3′-(4-Chlorophenyl)-4′-oxo-6′-iodo-3′*H*-quinazolin-2′-yl)thio-methyl]-1,3,4-triazole (9)

A mixture of **8** (1.36 g, 0.0025 mol) and 8 ml of NaOH (10%) was heated under reflux for 4 hr, then cooled and neutralized with dilute hydrochloric acid. The obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 3.4 (brs, 1H, SH), 4.21 (s, 2H, S-CH_2), 5.1 (brs, 1H, NH), 7.32 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.13 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

2-Amino-5-[3′-(4-chlorophenyl)-4′-oxo-6′-iodo-3′*H*-quinazolin-2′-yl)thiomethyl]-1,3,4-thiadiazole (10)

A suspension of **8** (1.36 g, 0.0025 mol) in conc. H_2SO_4 (10 ml) was stirred at room temperature for 4 hr, then neutralized with aq. NaOH/ice. The obtained solid was filtered, washed with water, dried and crystallized from methanol (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 3.21 (brs, 2H, NH_2), 4.16 (s, 2H, SCH_2), 7.31 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.13 (dd, 1H, J = 2, 7.5 hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

N-(1-Succinimido)-2-[3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]-acetamide (12)

A mixture of the acid hydrazide **11** (4.86 g, 0.01 mol), succinic anhydride (0.8 g, 0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 20 h. The

precipitate was filtered while hot, dried and crystallized from dioxane (Table 1). ^{1}H NMR (DMSO-d_6), δ 2.34 (m, 2H, CO$\underline{CH_2}CH_2$CO), 2.41 (m, 2H, COCH$_2\underline{CH_2}$CO), 4.26 (s, 2H, S$\underline{CH_2}$CO), 7.26 (d, 1H, J = 7.5 Hz, Quin-H), 7.48 (d, 2H, J = 8.5 Hz, Ar-H), 7.70 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.32 (d, 1H, J = 2 Hz, Quin-H), 8.91 (brs, 1H, NH).

N-(1-Substitutedphthalimido)-2-[3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]acetamide (13_{a-c})

A mixture of the acid hydrazide **11** (4.86 g, 0.01 mol), phthalic anhydride, tetrabromophthalic anhydride or tetrachlorophthalic anhydride (0.015 mol) in glacial acetic acid (30 ml) was heated under reflux for 18 h. The precipitate was filtered while hot dried and crystallized from the suitable solvents (Tables 1 and 2). ^{1}H NMR (DMSO-d_6), **13_a**: δ 4.19 (s, 2H, CH_2CO), 7.26-7.88 (m, 9H, Ar-H and Quin-H), 8.02-8.14 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.28 (d, 1H, J = 2 Hz, Quin-H), 11.05 (brs, 1H, NH). **13_b**: δ 4.21 (s, 2H, SCH_2CO), 7.26 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.05-8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 11.51 (brs, 1H, NH), **13_c**: δ 4.21 (s, 2H, S-CH_2CO), 7.23 (d, 1H, J = 7.5 Hz, Quin-H), 7.56 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.01-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H J = 2 Hz, Quin-H), 11.13 (brs, 1H, NH).

6-Iodo-2-(2′-mercapto-1′,3′,4′-oxadiazoline-2′-yl-methylthio)-3-(4-chlorophenyl)-4-(3*H*)quinazolinone (14)

A mixture of **11** (4.86 g, 0.01 mol), potassium hydroxide (0.01 mol) and carbon disulphide (0.02 mol) in ethanol (40 ml) was heated under reflux for 8 h. The

solvent was removed under reduced pressure and the residue was dissolved in water, acidified with dilute HCl and the separated solid was filtered, dried and crystallized from ethanol (Tables 1 and 2). ^{1}H NMR (DMSO-d_6), δ 3.82 (s, 2H, S-CH_2), 7.31 (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), 8.01-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 10.12 (s, 1H, SH).

N-(4-Chlorobenzoyl)-N′-[3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]hydrazine (15)

A mixture of **11** (4.86 g, 0.01 mol) and 4-chlorobenzoyl chloride (2.63 g, 0.015 mol) in dimethyl formamide (25 ml) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto crushed (100 ml) ice and stirred. The solid was filtered, washed with water, dried and crystallized from acetic acid (Tables 1 and 2). ^{1}H NMR (DMSO-d_6), δ 4.15 (s, 2H, CH_2CO), 7.19-7.81 (m, 9H, Ar-H and Quin-H), 8.01-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.12 (brs, 1H, NH), 9.68 (brs, 1H, NH).

2-[2′-(4-Chlorophenyl)-1,3,4-oxadiazoline-2-yl)methylthio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline (16)

Method (A)

To a suspension of **15** (0.625 g, 0.001 mol) in dry xylene (20 ml) phosphorous pentoxide (0.7 g) was added portionwise. The reaction mixture was heated under reflux for 7 h and filtered while hot. The filtrate was removed under reduced pressure and the residue was crystallized from ethanol (Tables 1 and 2). ^{1}H NMR ($CDCl_3$), δ

4.13 (s, 2H, SCH_2), 7.21-7.71 (m, 9H, Ar-H and Quin-H), 8.01-8.14 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

Method (B)

A mixture of **11** (2.43 g, 0.005 mol), p-chlorobenzoic acid (0.78 g, 0.005 mol) and phosphorous oxychloride (10 ml) was heated under reflux on a water bath for 5 h. The reaction mixture was poured into a beaker containing crushed ice (100 ml). The obtained solid was filtered, washed with water, dried carefully and crystallized from ethanol.

N^1-[(3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thioacetyl]-N^2-ethylthiosemicarbazide (17)

A mixture of **11** (0.486, 0.001 mol) and ethylisothiocyanate (0.0015 mol) in dioxane (15 ml) was heated under reflux for 18 h. The obtained solid upon cooling was filtered, dried and crystallized from acetic acid (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 1.13 (t, 3H, J = 7 Hz, $\underline{CH_3}$-CH_2), 3.21 (m, 2H, CH_3-$\underline{CH_2}$), 4.17 (s, 2H, S$\underline{CH_2}$CO), 7.31 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.15 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.32 (d, 1H, J = 2 Hz, Quin-H), 9.06 (brs, 2H, NH), 10.21 (brs, 1H, NH).

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]-3,4-diphenyl-pyridazin-6-one (18)

A mixture of **11** (1.215 g, 0.0025 mol) and benzoin (0.52 g, 0.0025 mol) in ethanol (20 ml) containing few drops of acetic acid was heated under reflux for 4 h, and cooled. The obtained solid was filtered and crystallized from acetic acid (Table 1). ^{1}H NMR (DMSO-d_6), δ 4.56 (d, 1H, J = 9 Hz, S-CHCO), 5.11 (d, 1H, J = 9

Hz, -CHPh), 7.03-7.71 (m, 15H, Ar-H and Quin-H), 8.01-8.13 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 8.91 (brs, 1H, NHCO).

2-[3-(4-Chlorophenyl)-6-iodo-4-oxo-3*H*-quinazolin-2-yl]thiomethyl]-6-(4-Bromophenyl)-1,3,4-oxadiazine (19)

A mixture of **11** (1.215 g, 0.0025 mol) and p-bromophenacyl bromide (0.67 g, 0.0025) in ethanol (30 ml) was heated under reflux for 3 h, followed by the addition of triethylamine (0.5 ml) with continuous heating for extra 5 h. The reaction mixture was concentrated, cooled and filtered. The separated solid was crystallized from dioxane (Table 1). ^{1}H NMR (DMSO-d_6), δ: 4.12 (s, 2H, S-CH_2-COR=N), 6.89 (d, 1H, J = 11 Hz, O-CH-Ph), 7.08-7.71 (m, 9, Ar-H, oxadiazine-H and Quin-H), 8.03-8.14 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.24 (d, 1H, J = 11 Hz, CH = N), 8.31 (d, 1H, J = 2 Hz, Quin-H).

4-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl]thio]pyridazine-3,6-dione (20)

Chloracetyl chloride (0.45 g, 0.0045 mol) was added to a solution of compound **11** (1.44 g, 0.003 mol) in dry dimethylformamide (15 ml). The reaction mixture was stirred at room temperature for 2 h, then heated under reflux for 5 h. Solvent was removed under reduced pressure and the residue was crystallized from dioxane (Table 1). ^{1}H NMR (DMSO-d_6), δ: 2.71 (d, 2H, J = 9 Hz, CH_2CO), 4.08 (t, 1H, J = 9 Hz, SCHCO), 7.29 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8 Hz, Ar-H), 7.69 (d, 2H, J = 8 Hz, Ar-H), 8.03-8.13 (dd, 1H, J = 2, 75 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 10.5 (brs, 2H, 2NHCO).

[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thiomethylcarbonyl]-biacetylmonoxime hydrazone (21)

A mixture of **11** (2.4 g, 0.005 mol) and biacetyl monoxime (0.5 g, 0.005 mol) in ethanol (30 ml) was heated under reflux for 2 h, then cooled. The produced solid was separated and crystallized from ethanol (Table 1). ^{1}H NMR (DMSO-d_6), δ 1.9 (s, 3H, NH-N=C-CH_3), 1.98 (s, 3H, O-N=C-CH_3), 3.98 (s, 2H, SCH_2CO), 4.6 (s, 1H, OH), 7.33 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8 Hz, Ar-H), 7.69 (d, 2H, J = 8 Hz, Ar-H), 8.03-8.12 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 8.92 (brs, 1H, CONH-N=).

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]-3,4-dimethyl-pyridazine-6-one (22)

A solution of **21** (0.57 g, 0.0005 mol) in acetic acid (10 ml) was heated under reflux for 4 h, cooled and poured into ice (20 ml). The obtained solid was filtered and crystallized from acetic acid (Table 1). ^{1}H NMR (DMSO-d_6), δ 1.13 (d, 3H, J = 8 Hz, CH_3), 1.88 (s, 3H, N=C-CH_3), 2.89 (m, 1H, CH(CH_3)-C=N-), 4.22 (d, 1H, J = 8 Hz, S-CH-C=O), 7.38 (d, 1H, J = 7.5 Hz, Quin-H), 7.54 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.13 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.61 (brs, 1H, NH).

Chemistry

The starting material, 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline **1** was prepared using reported procedures.[8] The 2-sulfhydryl moiety at **1** was alkylated with 2-chloroacetonitrile, 2-Chloroacetic acid and 2-chloroethanol to produce compounds $\mathbf{2_{a-c}}$, respectively.[6] The 2-mercapto function was further alkylated using 2-nitrochlorobenzene, 2,4-dinitrochlorobenzene or 2-chloro-3-nitropyridine to

give $\mathbf{3_{a\text{-}c}}$.[6] Reaction of **1** with N-(chloroalkyl)-phthalimide gave the targets 1,3-isoindoledinone analogs $\mathbf{4_{a\text{-}c}}$, respectively.[9] Condensation of **1** with hydrazine hydrate[10] or hydroxylamine[11] in boiling ethanol afforded compounds **5** and **6**, respectively (Scheme 1, Tables 1 and 2). Compound **7** was reacted with thiosemi-carbazide in dimethyl formamide to afford **8** which was reacted with sodium hydroxide or conc. Sulphuric acid to afford compounds **9** and **10**, respectively.[12] The acid hydrazide **11** was allowed to react with succinic anhydride, phthalic and substituted phthalic anhydrides to give 1-succinimido, 1-phthalimido, 1-tetrabromo-phthalmide and 1-tetrachlorophthalimido analogs **12** and $\mathbf{13_{a\text{-}c}}$, respectively (Scheme 2, Tables 1 and 2). Reaction of **11** with carbon disulfide under basic conditions afforded the 5-thioxo-1,3,4-oxadiazole derivative **6**.[13] The hydrazide analog **11** was allowed to react with 4-chlorobenzoyl chloride to afford the benzamide analog **15** which was subjected to cyclodehydration *via* refluxing in dry xylene containing phosphorous pentaoxide to afford the 5-(4-chlorophenyl)-1,3,4-oxadiazole analog **16**. The latter compound was obtained by reacting the hydrazide derivative with 4-chlorobenzoic acid in the presence of $POCl_3$.[5] The hydrazide **11** was reacted with ethylisothiocyanate to afford the thiosemicarbazide derivative **17**[14] (Scheme 3, Tables 1 and 2). The reaction of **11** with benzoin in acetic acid, 4-bromophenacyl bromide in ethanol and/or chloroacetyl chloride in dimethylformamdie afforded the corresponding heterocyclic analogs **18**-**20**, respectively. On the other hand, condensation of **11** with biacetyl monoxime afforded the hydrazone **21** which upon refluxing with acetic acid gave the pyridiazinone analog **22** (Scheme 4, Tables 1 and 2).[15]

Pharmacological Testing

All of the synthesized compounds were screened for their anticnvulsant activity following the method of Swinyard et al. (1982).[16] Each of the tested compounds was suspended in sterile water with few drops of tween 80, injected intraperitoneally in a dose range of 30-600 mg/kg in a group of six mice. The convulsant dose (CD_{98}) of pentylenetetrazole (85 mg/kg, mice) was injected subcutaneously in a volume of 0.01 ml/g body weight into each mouse at the previously determined time of the peak effect (30 minutes).

The animals were observed for the next thirty minutes for the presence or absence of a threshold seizure which is defined as one episode of clonic spasm that persist for at least five seconds.

Compounds **$2_{a,b}$**, **3_a**, **$4_{a,b}$**, **12** and **13_{a-c}** and showed a significant anticonvulsant activity (at 200 mg/kg, dose level) manifested by the absence of any seizures during the thirty minutes period of observation. Moreover, these compounds in the tested doses showed marked CNS depressant activities associated with sedation and hypnosis.

Compounds **4_c**, **14**, **16**, **20**, **21** and **22** elevated the threshold level of seizure from five to 23-30 minutes, yet they didn't protect the animals completely against pentylenetetrazole induced convulsion and they showed weak CNS depressant activities.

It seems that compounds **$2_{a,b}$**, **3_a**, **$4_{a,b}$**, **12**, and **13_{a-c}** may interfere with the direct stimulating effect of pentylenetetrazole on the neuronal membrane. Further

investigations are required to evaluate the other possible mechanisms of the observed anticonvulsant activity.

Acknowledgement

The authors are grateful to Dr. Adel Mostafa, Professor of Pharmacology, Faculty of Pharmacy, Helwan University for carrying out the anticonvulsant testing.

References

(1) Shoravon, S.D. Lancet 1990, 336, 93-96.

(2) Flaherty, P.T.; Greenwood, T.D.; Manheim, A.L.; Wolfe, J.F. J. Med. Chem. 1996, 39, 1509-1513.

(3) Meldrum, B.S.; Porter, R.J.; Eds. In New Anticonvulsant Drugs. Current Problems in Epilepsy 4; John Libby: London 1986.

(4) El-Helby, A.A.; Abdel-Hamide, S.G.; El-Hakim, A.E. Az. J. Pharm. Sci. 1995, 15, 1-13.

(5) Abdel-Hamide, S.G. Ghorab, M.M.; Badary, O.A. Egypt J. Biotechnol. 1997, 1, 36-45.

(6) Abdel-Hamid, S.G.; El-Obeid, H.A.; Al-Majed, A.A.; El-Kashef, H.A.; El-Subbagh, H.I. Med. Chem. Res. 2001, 10(6), 378-389.

(7) Abdel-Hamide, S.G.; El-Hakim, A.E.; El-Helby, A.A. Az. J. Pharm. Sci. 1996, 17, 35-40.

(8) El-Azab, A.S. Phosphorus, Sulfur, Silicon and Relat. Elem (in press).

(9) Abdel-Hamid, S.G.; El-Obeid, H.A.; al-Rashood, K.A.; Khalil, A.A.; El-Subbagh, H.I. Sci. Pharm. 2001, 69, 351-366.

(10) Ghorab, M.M.; Abdel-Hamide, S.G.; El-Gaby, M.S.; El-Sayed, S.M. Acta Pharm. 1999, 49, 1-10.

(11) Abdel-Hamide, S.G., Ghorab, H.H.; El-Hifnawi, H.N. Acta Pharm. 1998, 48, 249-258.

(12) Shehata, I.A.; Nasr, M.N.; El-Subbagh, H.I., Gineinah, M.M.; Kheira S.M. Sci. Pharm. 1996, 64, 133-143.

(13) Heiba, H.I.; Ghorab, M.M.; Hifnawi, H.N. Egypt J. Biotechnol. 1998, 4, 46-97.

(14) Khalil, A.A., Abdel-Hamide, S.G., Al-Obaid, A.M., El-Subbagh, H.I. Arch. Pharm. Pharm. Med. Chem. 2003, 2, 95-103.

(15) Abdel-Hamide, S.G.; El-Hakim, A.E.; Abdel-Rahman, R.M. Indian J. of Heterocyclic Chem. 1996, 5, 189-192.

(16) Swinyard, E.A., Woodhead, J.H. In Antiepileptic Drugs, 2nd ed.; Woodburgy, D.M.; Penny, J.K.; Pippenger C.E.; Eds, Raven Press; New York, 1982, pp. 111-126.

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

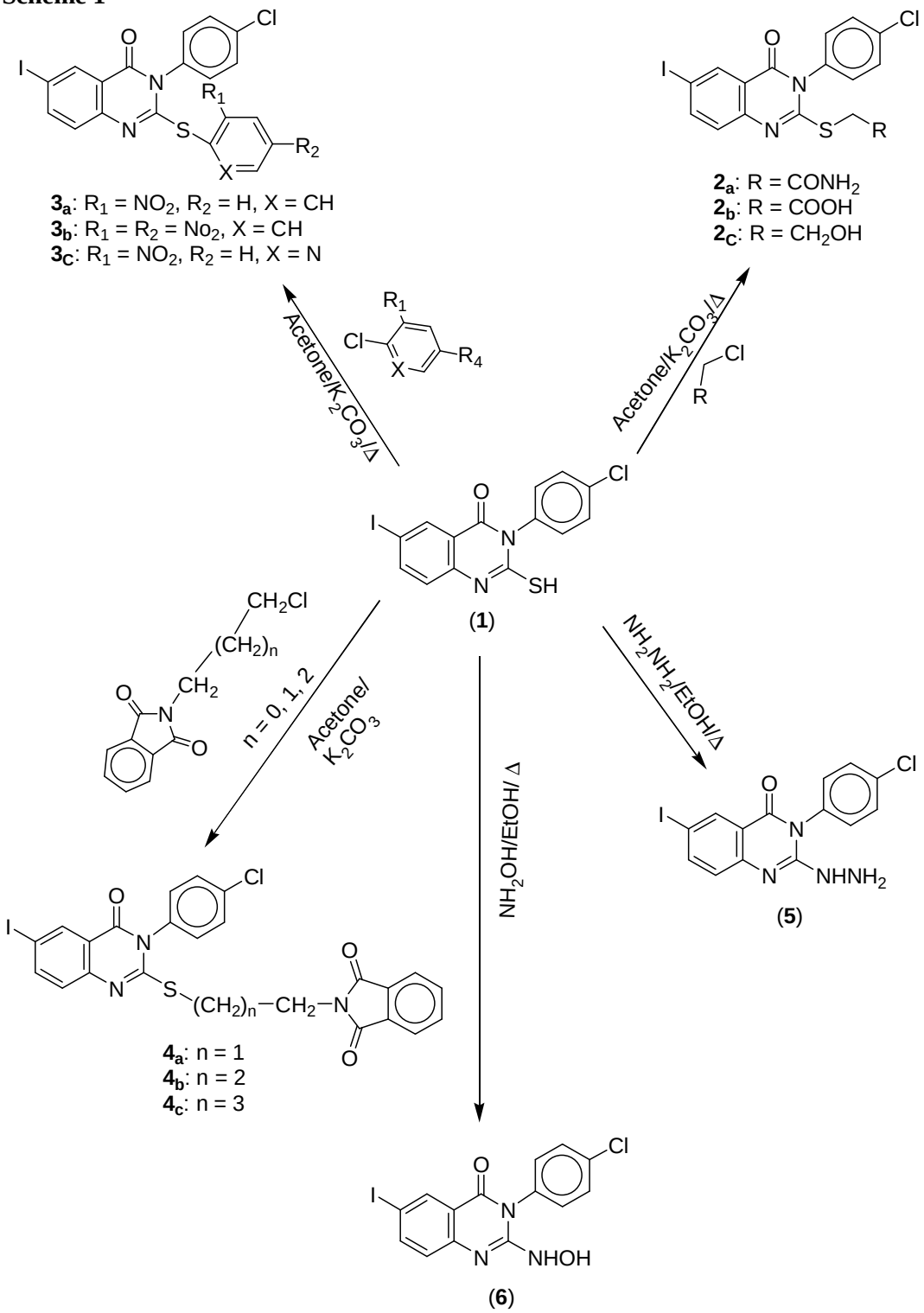
Compd	Solvent	Yield	M.P. °C	Molecular formula
1				Ref.
2_a	EtOH	70	>350	$C_{16}H_{11}ClIN_3O_2S$
2_b	EtOH	50	325-6	$C_{16}H_{10}ClIN_2O_3S$
2_c	EtOH	60	295-7	$C_{16}H_{12}ClIN_2O_2S$
3_a	AcOH	50	290-2	$C_{20}H_{11}ClIN_3O_3S$
3_b	AcOH	55	129-131	$C_{20}H_{10}ClIN_4O_5S$
3_c	AcOH	63	180-2	$C_{19}H_{10}ClIN_4O_3S$
4_a	AcOH	46	>350	$C_{24}H_{15}ClIN_3O_3S$
4_b	AcOH	60	210-2	$C_{25}H_{17}ClIN_3O_3S$
4_c	AcOH	39	190-2	$C_{26}H_{19}ClIN_3O_3S$
5	EtOH, benzene	40	230-1	$C_{14}H_{10}ClIN_4O$
6	Dioxane	73	290-2	$C_{14}H_9ClIN_3O_2$
7				Ref.
8	Dioxane	66	305-7	$C_{17}H_{13}ClIN_5O_2S_2$
9	EtOH	68	>350	$C_{17}H_{11}ClIN_5OS_2$
10	MeOH	59	237-9	$C_{17}H_{11}ClIN_5OS_2$
11				Ref.
12	Dioxane	71	>350	$C_{20}H_{14}ClIN_4O_4S$
13_a	AcOH	64	265-7	$C_{24}H_{14}ClIN_4O_4S$
13_b	AcOH	80	290-2	$C_{24}H_{10}\ Br_4ClIN_4O_4S$
13_c	AcOH	77	276-8	$C_{24}H_{10}Cl_5IN_4O_4S$
14	EtOH	60	294-6	$C_{17}H_{10}ClIN_4O_2S_2$
15	AcOH	81	330-2	$C_{23}H_{15}Cl_2IN_4O_3S$
16	EtOH	54	220-2	$C_{23}H_{13}Cl_2IN_4O_2S$
17	Dioxane	65	246-8	$C_{19}H_{17}ClIN_5O_2S_2$
18	AcOH	78	127-9	$C_{30}H_{20}ClIN_4O_2S$
19	EtOH, dioxane	56	182-4	$C_{24}H_{15}BrClIN_4O_2S$
20	Dioxane	71	200-2	$C_{18}H_{12}ClIN_4O_2S$
21	EtOH, benzene	58	255-7	$C_{20}H_{17}ClIN_5O_3S$
22	AcOH	49	150-2	$C_{20}H_{16}ClIN_4O_2S$

All the compounds were analyzed for C, H, N and analytical results were within ± 0.4-0.5%.

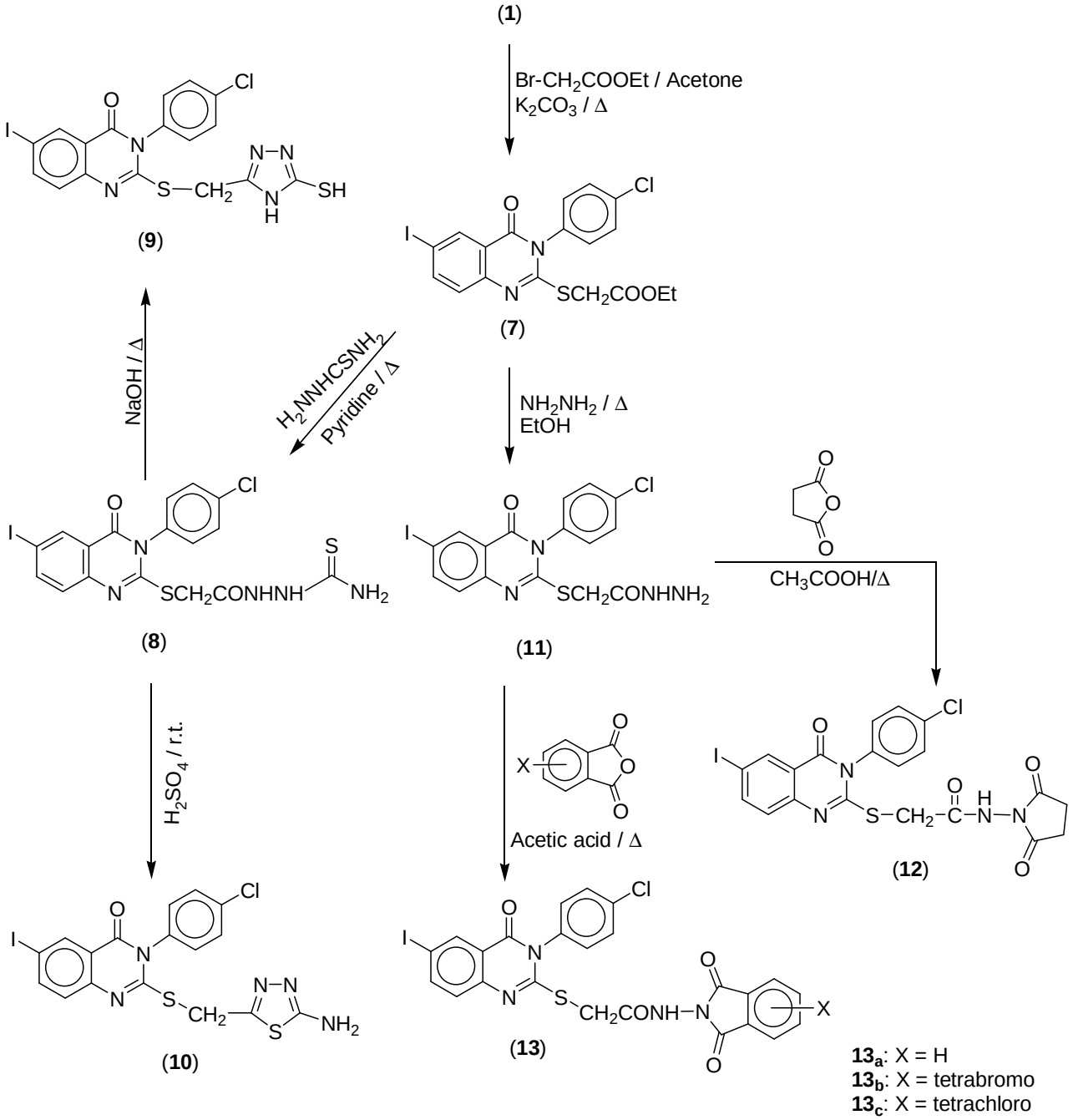
Table 2: Mass spectral data of some compounds.

Compound	MS (Relative Intensity)
2_a	m/z 471 (M^+, 10.61), 473 (M + 2, 3.61), 455 (1.08), 427 (3.01), 413 (6.55), 360 (0.53), 346 (1.41).
3_c	m/z 536 (M^+, 16.31), 538 (M + 2, 5.73), 381 (1.74).
4_a	m/z 587 (M^+, 25.7), 589 (M + 2, 8.31), 441 (1.6), 427 (2.43), 413 (7.26), 434 (1.47), 381 (2.30).
4_c	m/z 615 (M^+, 3,39), 617 (M + 2, 1.21), 469 (4.54), 455 (2.44), 441 (2.61), 427 (1.68), 413 (2.10), 381 (1.63).
6	m/z 413 (M^+, 1.05), 135 (10.38), 91 (83.21).
8	m/z 545 (M^+, 14.98), 547 (M + 2, 4.81), 529.3 (100), 475.35 (15.65), 459.71 (28.68), 427.2 (23.13), 413.32 (42.13), 381.1 (16.51).
9	m/z 527 (M^+, 52.25), 529 (M + 2, 17.31), 427.15 (46.48), 413.10 (29.31), 381.05 (35.80).
10	m/z 527 (M^+, 39.37, 529 (M + 2, 13.31), 427.15 (29.25), 413.21 (12.31), 381.12 (29.25).
13_a	m/z 616.2 (M^+, 2.03), 618.2 (M + 2, 0.91), 470 (1.98), 455 (3.21), 427 (1.48), 413 (1.86), 381 (1.08).
14	m/z 528 (M^+, 0.71), 427 (2.61), 413 (1.51), 381 (0.58).
15	m/z 624 (M^+, 0.51), 455 (0.79), 427 (1.31), 413 (0.81), 381 (1.21).
16	m/z 606 (M^+, 3.42), 427 (2.29), 413 (1.31), 381 (1.31).
19	m/z 664 (M^+, 1.11), 427 (15.07), 413.1 (13.09), 381 (19.33), 237 (16.62).
22	m/z 538 (M^+, 1.34).

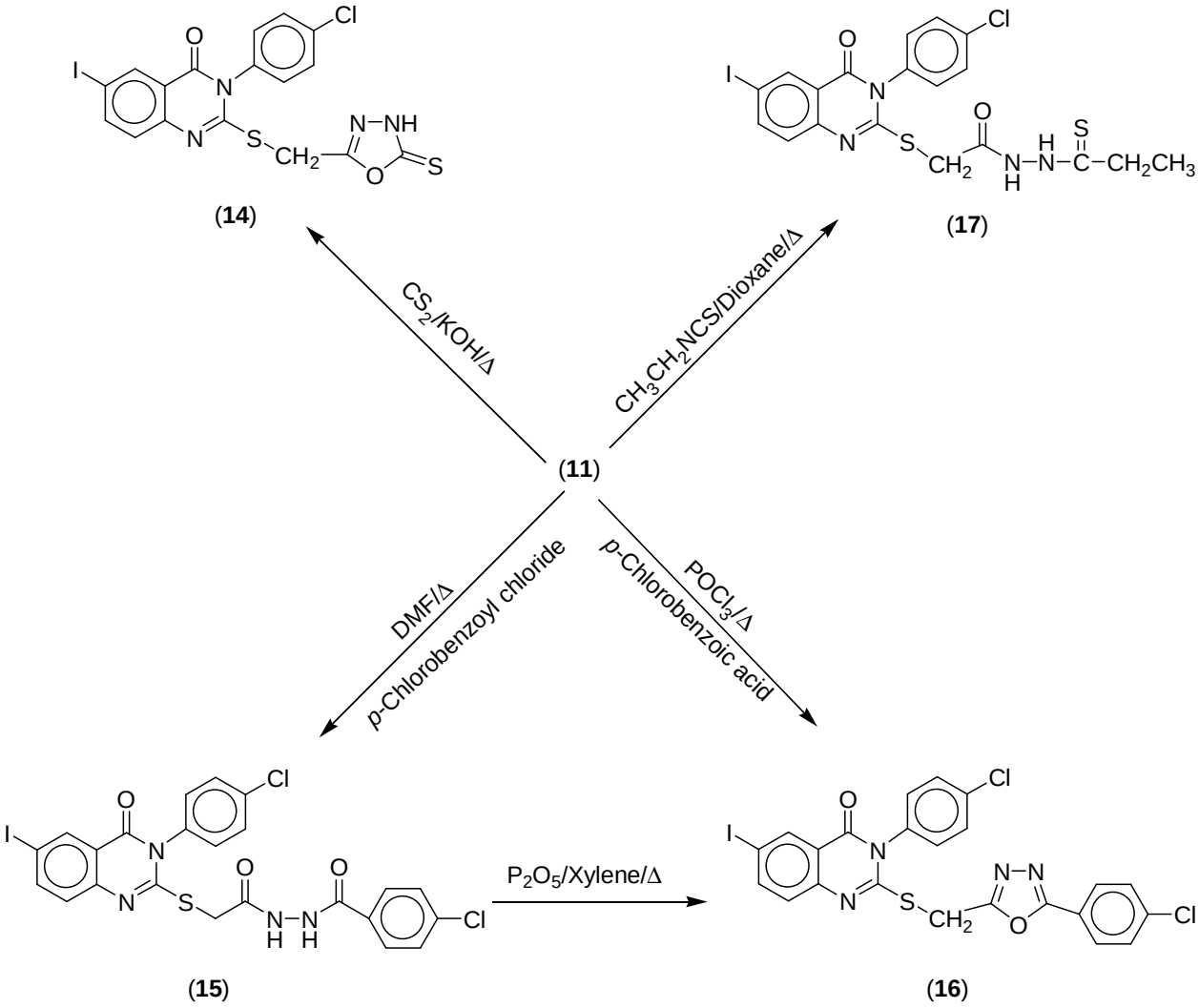
Scheme 1


3a: R1 = NO2, R2 = H, X = CH
3b: R1 = R2 = No2, X = CH
3C: R1 = NO2, R2 = H, X = N
2a: R = CONH2
2b: R = COOH
2C: R = CH2OH
Acetone/K2CO3/Δ
Acetone/K2CO3/Δ
(1)
n = 0, 1, 2
Acetone/ K2CO3
NH2NH2/EtOH/Δ
NH2OH/EtOH/ Δ
4a: n = 1
4b: n = 2
4c: n = 3
(5)
(6)

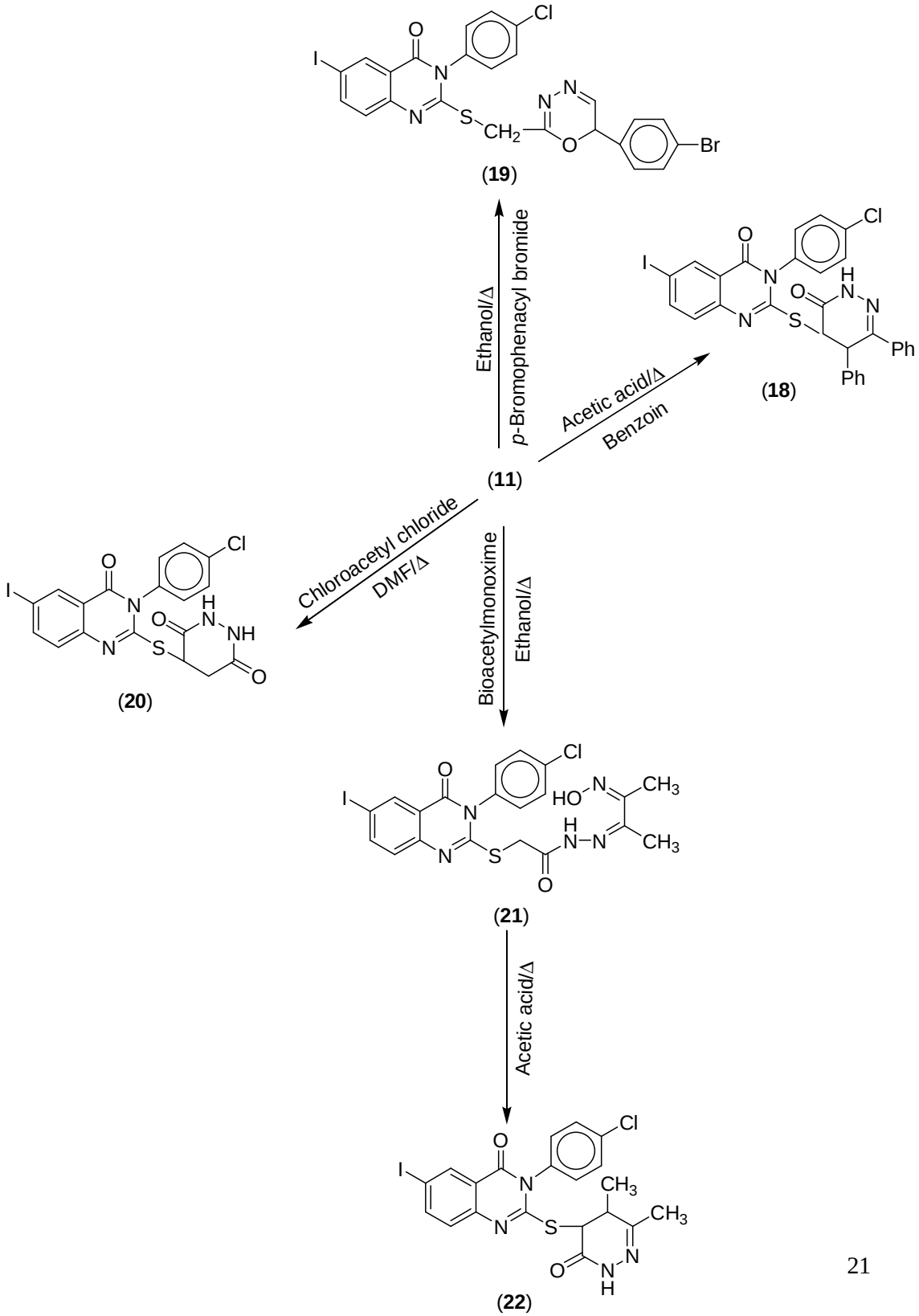
Scheme 2


(1)
Br-CH2COOEt / Acetone
K2CO3 / Δ
(9)
(7)
NaOH / Δ
H2NNHCSNH2
Pyridine / Δ
NH2NH2 / Δ
EtOH
(8)
(11)
CH3COOH/Δ
H2SO4 / r.t.
Acetic acid / Δ
(10)
(13)
(12)
13a: X = H
13b: X = tetrabromo
13c: X = tetrachloro

Scheme 3


(14)
(17)
(11)
CS2/KOH/Δ
CH3CH2NCS/Dioxane/Δ
DMF/Δ
p-Chlorobenzoyl chloride
p-Chlorobenzoic acid
POCl3/Δ
P2O5/Xylene/Δ
(15)
(16)

Scheme 4


(19)
Ethanol/Δ
p-Bromophenacyl bromide
(18)
Acetic acid/Δ
Benzoin
(11)
Chloroacetyl chloride
DMF/Δ
(20)
Bioacetylmonoxime
Ethanol/Δ
(21)
Acetic acid/Δ
(22)