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Uses of quinazolin-2-[(β-propionoyl)isothiocyanate]-4-one as a building block in synthesis of some heterocyclic compounds of expected biological activity

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The behaviour of quinazaline-2 [(β-propionoyl)isothiocyanate] **1** towards different nucleophilic reagents as phenylhydrazine, aroyl hydrazine, glycine, anthranilic acid (nitrogen nucleaphile), sulphut nucleaphile as a thioglycolic acid and oxygen nucleaphile as ortho amino phenol has been investigated and found that it proceeds via isothiocyanate heterocyclization to furnish non-condensed heterocyclic compounds containing triazoles, oxazole, thiazole and benzoxazale nuclei besides the quinazoline nucleus.

It has been well established that various triazoles, oxazoles, benzoxazoles and thiazoles are of biological interest[1-3]. This encouraged us to synthesise those nuclei in a molecule along with quinazoline nucleus, which possess a bactericidal and virocidal activities[4-7]. In continuation to our work on synthesis of heterocyclic compounds having biological interest[8-10], quinazolin-2-[(β-propionoyl)isothiocyanate]-4-one **1** was prepared by treating the acid chloride solution of quinazolinoyl propionic acid in dry acetone with ammonium thiocyanate. The isothiocyanate solution obtained was used *in situ* to prevent its decomposition.

Reactions of hydrazine or their derivatives with isothiocyanate serve as a key intermediate in the preparation of various triazoles[11]. Thus when solution of isothiocyanate **1** was treated with phenylhydrazine, 2[3′-(2′-phenyl-1,2,4-triazolinyl-5-thione)] ethyl-quinazolin 3*H*-4-one **2** was obtained.

Reaction of isothiocyanate **1** with aroylhydrazine such as benzoylhydrazine and *p*-nitrobenzoylhydrazine gave *N*-aroyl-*N*′-[2-(propionoyl) quinazolin-3*H*-4-one] thiosemicarbazide **3a,b**. Treatment of thiosemicarbazide **3a,b** with polyphosphoric acid (PPA) afforded the cyclized product[12] 2-[4′(3-aryl-1,2,4-triazolinyl-5-thione] propionoyl-quinazolin-3*H*-4-one **4a,b**. Addition of anthranilic acid to isothiocyanate leads to the formation of thiourea **5**. Cyclization of thiourea **5** with acetic anhydride yields 1,3-quinazolinone-2-thione derivative **6**.

When glycine was reacted with isothiocyanate **1** in the presence of pyridine as a base, thiourea derivative produced cyclized to 2-amino-2-thiol-1,3-oxazolidin-5-one **7** (Scheme I).

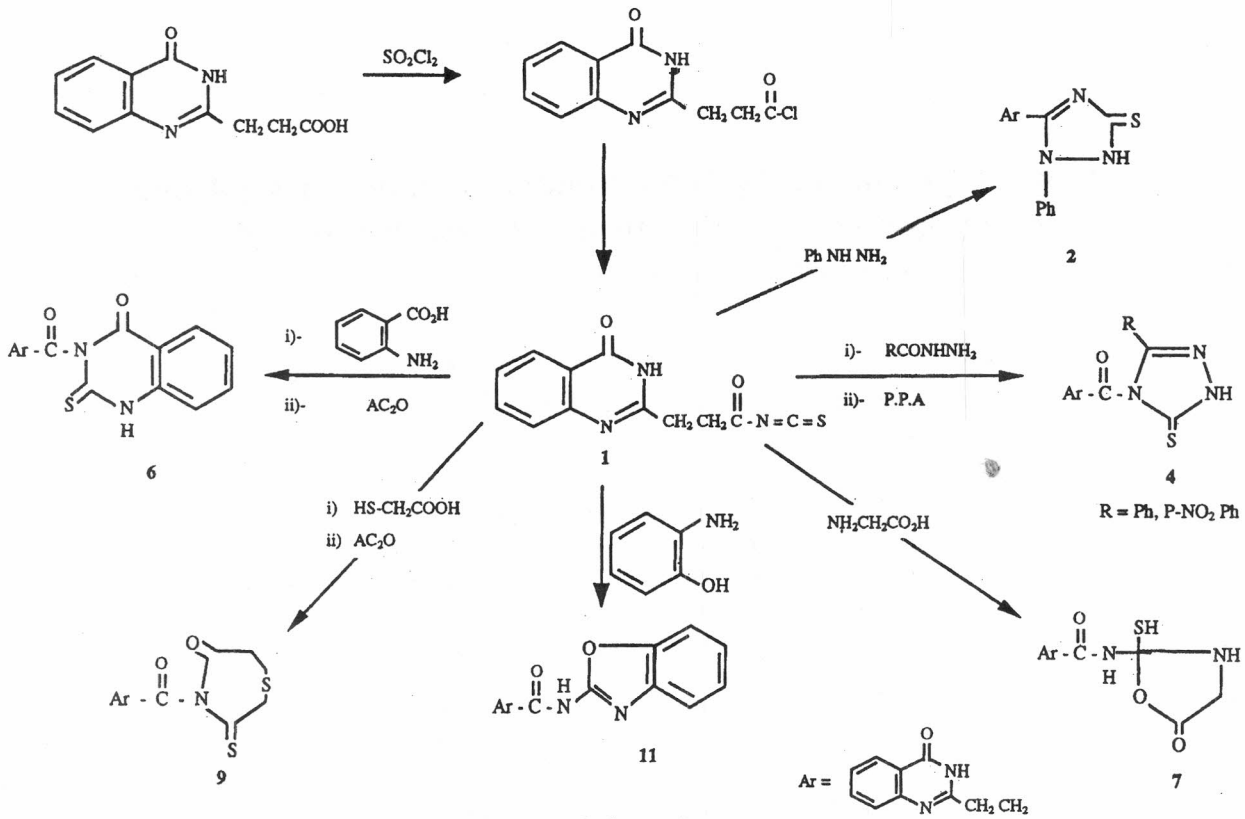
The behaviour of isothiocynate **1** towards sulphur nucleophile, was investigated by its reaction with thioglycollic acid in which the adduct **8** was produced.

When compound **8** was treated with Ac_2O[13,14] 3-[2-propionoyl) quinazolin-2-*H*-4-one]-1,3-thiazolidine-5-one-2-thione **9** was produced.

o-Aminophenol can act as oxygen nucleophile when it reacts with isothiocyanate **1**; the oxygen atom of *o*-aminophenol attacks the isothiocyanate to produce the thiocarbamate **10**. Fusion of **10** leads to evolution of H_2S gas and formation of 2-amino-[2-(β-propionoyl)-quinazolin-3*H*-4-one]-1,3-benzoxazole **11** via nucleophilic attack of nitrogen atom of primary amine to C=S (Scheme I).

Experimental Section

All melting points are uncorrected, IR spectra were recorded on PYE Unicam SP 200 spectrophotometer and ^{1}H NMR spectra on a Perkin-Elmer 90 MHz spectrometer. All chemical shifts are given in δ, ppm using TMS as an internal standard and $CDCl_3$ as a solvent. Mass spectra were recorded on HP MODEL MS 5989 electron



Scheme I

impact 70 ev. The antimicrobial activities of some of the synthesised compounds were determined in Botany Department, Faculty of Science, Benha University, *in vitro* using the hale plate and filter paper discs method[15,16]. Four different species of gram positive and gram negative bacteria were used. The culture medium was normal nutrient agar (NA) and the solvent (acetone-water) mixture 10%. The microbial activity data are listed in Table I.

Synthesis of quinazolin-2-[(β-propionoyl)-isothiocyanate)-4-one 1. To a stirred solution of quinazoline-2-propionoyl chloride-4-one **1** (0.01 mole) in dry acetone (50 mL) a solid ammonium thiocyanate (0.01 mole) was added. The reaction mixture was stirred for 1 hr at room temperature. Ammonium chloride was precipitated during the progress of the reaction. It was filtered and a clear solution of isothiocyanate **1** was obtained.

Reaction of isothiocyanate 1 with phenyl-hydrazine: Formation of 2-[3′-(2′-phenyl-1,2,4-triazolinyl-5-thione)]ethyl quinazoline-3*H*-4-one 2. A solution of isothiocyanate **1** (0.01 mole) and phenylhydrazine (0.01 mole) in dry acetone was heated under reflux for 30 min, concentrated then treated with methanol to give crystals of **2**, yield

Table I—Response of various micro-organisms to some synthesized compounds

Compd	*Bacillus subtil*		*Asperogillus* SP		*Penicillum* SP		*Megaterium bacillus*	
	A	MIC	A	MIC	A	MIC	A	MIC
4	+++	250	+	250	+	250	++	250
6	+++	500	++	500	+	250	+	250
7	+	250	+	500	–	–	++	500
9	+	125	–	–	–	–	+	250
11	+	125	–	500	–	–	+++	250

A = Antimicrobial activity of tested compounds, +, ++ and +++ represent the extent of the zone diameter (mm); inhibition of either fungal growth or bacterial cells, for each dose level for each compound.

(–) = No inhibition was observed i.e. compound is not active (+) >5 mm, slightly active, (++) >7 mm, moderately active and +++ 9 mm highly active.

MIC = Minimum inhibitory concentration.

62%, m.p. 110-12°. Anal. Found: C, 61.7; H, 4.5; N, 20.3. Calc. for $C_{18}H_{15}N_5OS$: C, 61.9; H, 4.3; N, 20.1%; IR: νNH's at 3300 and 3250, νC=O of quinazolinone at 1670, νC=N at 1610 and νC=S at 1330 cm^{-1} beside three characteristic bands for quinazoline moiety[17] in the region 1630-1620, 1580-1570 and 1515-1480 cm^{-1}; ^1H NMR spectrum shows signals at δ 2.5 (2H), 2.7 (2H) for the two CH_2 protons, at 4.0 (s, 1H) and 8.2 (s, 1H) for the two NH which disappeared on addition of D_2O and 7.2-8.0 (m, 9H) for the aromatic protons. Mass spectrum shows no molecular ion. It fragmented into two distinguished ions m/z 146 (94%) and m/z 201 (59%) corresponding to quinazolinone nucleus and (M^+-quinazolinone).

Reaction of isothiocyanate 1 with aroylhydrazine: Formation of thiosemicarbazide derivative 3a,b. The solution of isothiocyanate **1** (0.01 mole) in dry acetone (50 mL) and the aroyl hydrazine, namely benzoylhydrozine and *p*-nitrobenzoyl hydrazine (0.01 mole) was heated under reflux for 1 hr. The solid product was filtered off and recrystallized from acetic acid to give **3a,b: 3a**, yield 50%, m.p. 230-32°. Anal. Found: C, 57.9; H, 4.5; N, 17.9. Calc. for $C_{19}H_{17}N_5O_3S$: C, 57.8; H, 4.3; N, 17.7. IR spectrum exhibits νNH at 3400-3300 cm^{-1}, νC=O at 1710, 1690 and 1670 cm^{-1} and νC=S of thiosemicarbazide at 1320 cm^{-1}; **3b**, yield 60%, m.p. 252-53°. Anal. Found: C, 51.6; H, 3.5; N, 19.3. Calc. for $C_{19}H_{16}N_6O_5S$: C, 51.8; H, 3.6; N, 19.1%.

Reaction of thiosemicarbazide 3a,b with polyphosphoric acid: Formation of 2[4′-(3-aryl-1, 2, 4-triazolinyl-5-thione]propionoyl-1-quinazolin-3-*H*-4-one 4a,b. The solution of **3a,b** (0.01 mole) in acetic acid (20 mL) was added dropwise to 20 mL of PPA at 80°C. After the addition, the solution was maintained at 140-50°C for 1 hr. The reaction mixture was poured onto ice-cold water, the solid product obtained was filtered off and recrystallized from acetic acid to give **4a,b: 4a,** yield 40% m.p. 205-7°. Anal. Found: C, 60.5; H, 4.0; N, 18.7. Calc. for $C_{19}H_{15}N_5O_2S$: C, 60.4; H, 3.9; N, 18.5. **4b**, yield 43%, m.p. 210-12°. Anal. Found: C, 54.1; H, 3.5; N, 19.7. Calc. for $C_{19}H_{14}N_6O_4S$: C, 54.1; H, 3.5; N, 19.7. IR Specrum of **4a,b** exhibits νNH at 3380-3320, νC=O (1740-1720) and νC=S at 1345 cm^{-1}. Mass spectrum of **4a** shows molecular ion peak [M^+] at 423 (20%) and base peak at m/z 146 (100%) corresponding to quinazolinone nucleus.

Reaction of isothiocyanate 1 with anthranilic acid: Formation of *N*-CO-carboxyphenyl-*N*-[2-(propionoyl)-quinazolin-4-one] thiourea 5. To a solution of isothiocyanate (0.01 mole) anthranilic acid was added. The reaction mixture was refluxed for 1 hr and then cooled. The solid precipitated was filtered off and recrystalized from acetic acid to give thiourea **5**, yield 85%, m.p. 130-32°. Anal. Found: C, 57.7; H, 4.2; N, 14.2. Anal. calc. for $C_{19}H_{16}N_4O_4S$: C, 57.5; H, 4.0; N, 14.1. IR shows νOH and νNH (broad) in the region 3530-3100, νC=O at 1720, 1700 and 1690 and νC=S at 1340 cm^{-1}. ^1H NMR spectrum shows signals at δ 2.4 (2H), 2.6 (2H) for two CH_2 protons, 7.6-9.2 (8H, Ar), 10.2 (3H) for three NH and at 11.5 (s, 11.5) for the carboxylic proton which disappeared on addition of D_2O.

Cyclization of 5 with acetic anhydride: Formation of 1,3-quinazolinone-2-thione derivative 6. A solution of **5** (0.01 mole) in acetic anhydride (50 mL) was heated on water-bath for 1 hr. A solid product was obtained during heating. At the end of the reaction period the solid product was filtered off while hot and recrystalized from acetic acid to give **6**, yield 80%, m.p. 180-82°. Anal. Found: C, 60.5; H, 3.7; N, 14.6. Calc. for C, 60.5; H, 3.9; N, 14.6. ^1H NMR spectrum of **6** shows signals at δ 2.2 (2H), 2.5 (2H) of the two CH_2, 7.5-9.2 (8H, Ar), 11.2 (s, 1H) of the NH which disappeared on addition of D_2O. Mass spectrum of **6** shows no molecular ion but the two distinguish ions of the two quinazoline moiety appeared at m/z 146 (15%) and m/z 179 (22%).

Reaction of isothiocyanate 1 with glycine: Formation of 2-amino-2-thiol-1,3-oxazolidin-5-one derivative 7. To a solution of isothiocyanate **1** (0.01 mole) in dry acetone, glycine (0.01 mole) and few drops of pyridine were added and the reaction mixture refluxed for 1 hr. A solid product was precipitated after cooling which was filtered off, washed with water and recrystallized from ethanol to give **7**, yield 60%, m.p. >300°. Anal. Found: C, 50.5; H, 4.3; N, 16.5. Calc. for $C_{14}H_{14}N_4O_4S$: C, 50.3; H, 4.2; N 16.7. IR spectrum inhibits νNH at 3200-3150, νSH at 2300 and νC=O at 1700 and 1690 cm^{-1}. ^1H NMR spectrum of **7** shows signals concentrated at δ 2.5 (6H) for the three CH_2

protons, 7.4 (s, 3H) for the three NH which disappeared on addition of D_2O, 3.0 (s, 1H) for SH and at 7.8-8.0 (4H, Ar).

Reacion of isothiocyanate 1 with thioglycollic acid: Formation of adduct 8. To a solution of isothiocyanate **1** (0.01 mole) in dry acetone thioglycollic acid (0.01 mole) was added. The reaction mixture was refluxed for 1 hr. A solid product was obtained after cooling to give the adduct **8** which was recrystallized from ethanol, yield 80%, m.p. 120-22°. Anal. Found: C, 48.0; H, 3.9; N, 11.9. Calc. for $C_{14}H_{13}N_3O_4S_2$: C, 47.8; H, 3.7; N, 11.9. IR spectrum shows νOH and νNH in the region 3500-3350, νC=O at 1700, 1690 and 1670 and νC=S at 1385 cm^{-1}.

Cyclization of the adduct 8 with acetic anhydride: Formation of 3-[2-(propionoyl)-quinazolin-3*H*-4-one]-1, 3-thiazolidine-5-one-2-thione 9. A solution of adduct **8** (0.01 mole) in acetic anhydride (30 mL) was refluxed for 1 hr. A solid product was obtained after cooling which upon recrystallization from benzene-pet. ether (60-80°) mixture gave the product **9**, yield 60%, m.p. 90-92°. Anal. Found: C, 50.5; H, 3.3; N, 12.4. Calc. for $C_{14}H_{11}N_3O_3S_2$: C, 50.4; H, 3.3; N, 12.6%. IR spectrum shows νNH at 3230, νC=O's at 1690 and1680 cm^{-1} and νC=S at 1370 cm^{-1}.

Reaction of isothiocyanate 1 with *o*-aminophenol: Formation of the adduct 10. To a solution of isothiocyanate **1** (0.01 mole) in dry acetone *o*-aminophenol (0.01 mole) was added. The reaction mixture was refluxed for 1 hr. After cooling a solid product was obtained. It was filtered and recrystallized from acetic acid to give solid crystals of the product **10**, yield 80%, m.p. 210-12°. Anal. Found: C, 58.5; H, 4.5; N, 15.2. Calc. for $C_{18}H_{16}N_4O_3S$: C, 58.7; H, 4.3; N, 15.2%.

Cyclization of the thiocarbamate derivative 10: Formation of 2-amino[2-(2-propionoyl)-quinazolin-3*H*-4-one]-1,3-benzoxazole 11. The thiocarbamate derivative **10** was heated at 220°C. H_2S gas was liberated during the fusion process and after approximately 1 hr H_2S evolution ceased. The reaction mixture was left to cool. A solid product was obtained which was recrystallized from acetic acid to give **11**, yield 60%, m.p. 160-62°. Anal. Found: C, 64.6; H, 4.3; N, 16.5. Calc. for $C_{18}N_{14}N_4O_3$: C, 64.6; H, 4.2; N, 16.7%. ^1H NMR spectrum shows signals at δ 1.8 (2.5, 4H) of the two CH_2, at δ 7.2 (8H Ar) and at δ 8.2 (2H, NH) which disappeared on addition of D_2O.

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