

Synthesis and biological studies of N³ substituted dithiocarbamoyl of quinazalone-4

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Manuscript received online 29 March 2023, accepted on 20 April 2023

Abstract : Dithiocarbamates of quinazalone-4 was synthesized by incorporating dithiocarbamic ester moiety and quinazalone-4 ring system in one skeleton. This goal was achieved by synthesising some novel dithiocarbamates of quinazalone-4. All the structures of the final compounds were ascertained based on spectral studies. It has broad applications and has been found that some of the synthesized compounds showed antibacterial and anti fungal activities.

(Keywords: Dithiocarbamates; quinazalone-4, dithiocarbamic ester; anti bacterial activity; anti fungal activity)

Introduction

Dithiocarbamates of quinazalone-4 is a nitrogen heterocyclic compound exhibiting diverse, chemical and medicinal versatility and its derivatives have wide applications in chemical, agricultural and pharmaceutical industries.

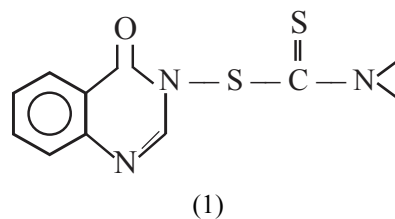
The chemistry of quinazalone-4 system has received an increasing interest because of its biological significance. These are an important class of fused heterocyclic ring system with a wide range of biological activities such as antimicrobial¹⁻², antibacterial³, antiviral, anti-inflammatory⁴⁻⁵, antitubercular⁶, antitumor⁷ and cytotoxic⁸. Numerous reasons have shown that the quinazalone-4 nucleus showed potent anti microbial activity. Substitution at position N-3 of quinazalone -4 has been associated with anti microbial properties.

Dithiocarbamate derivatives are a common class of organic molecules with various

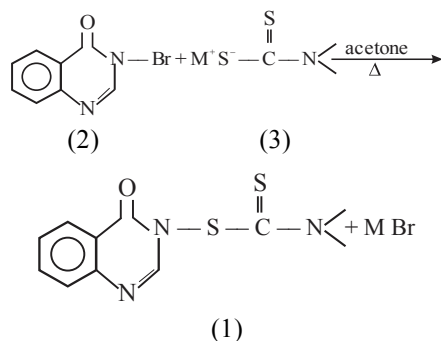
valuable biological effects. These are the simplest occurring organo sulphur compounds exhibiting diverse chemical and medicinal versatility and have been used as pesticide in the 20th Century but thereafter they have attracted the interest of medicinal chemists due to their metal binding capacity. They are well known to be used as fungicides, antibiotics and anti inflammatory agents.

Dithiocarbamate has been proved to be an effective pharmacophore with cancer chemo preventive and anti tumor activity. In my work I have incorporated dithiocarbamate moieties with quinazalone-4. A series of quinazalone-4 bearing various dithiocarbamate side chains were synthesized. All these derivatives were evaluated for anti bacterial and anti fungal activity.

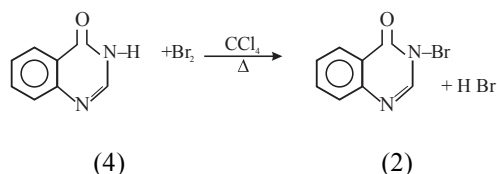
In the present investigation, we therefore, thought to synthesize some dithiocarbamates of general formula.



The goal was achieved by reacting N³-Bromoquinazalone-4 (2) with sodium/ammonium salt (3) of appropriate dithiocarbamic acid in acetone solution under refluxing condition according to following scheme.

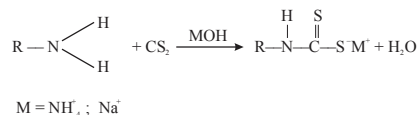


The N³- bromoquinazalone-4-required for the present work was prepared by direct interaction between quinazalone-4(4) and bromine in Carbon tetrachloride.

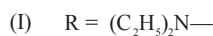
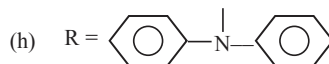
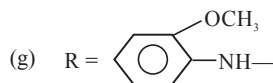
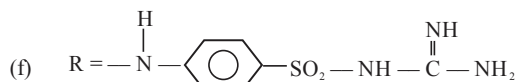
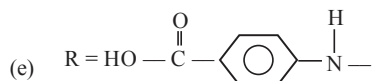
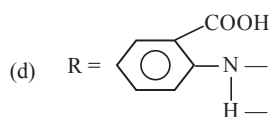
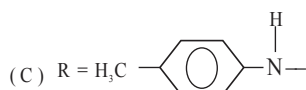
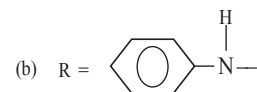
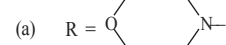
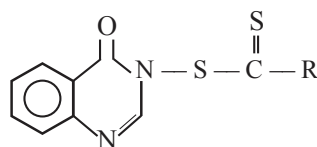


Quinazalone-4 (4) was prepared from freshly crystallised sample of commercial anthranilic acid by heating with excess of formamide. Following method described in the literature.

The second component sodium/ ammonium salt of dithiocarbamic acid was prepared by the most convenient and widely used method by following scheme.



Following the aforementioned scheme. The following compounds were prepared.



Experimental

All the melting points were taken in open capillary tube in sulphuric acid bath and are uncorrected. The i.r. spectra were recorded on FTIR in the Lab. Of CIMFR, Dhanbad.

Preparation of quinazalone-4(4)⁹

Anthranilic acid (13.710g; 0.01) was heated with excess of formamide (7.56) for 1.1.5

hr at 120-125°C. The reaction mixture filtered and the filtrate was cooled. White solid was obtained which was recrystallized from ethanol. White crystals were obtained m.p -215-216°
Yield = 8.65

Preparation of N3- Bromo- quinazalone- 4 (2)

Quinazalone- 4 (1.46 g : 0.01 m) was suspended in carbontetrachloride (20 ml). To this suspension Bromine in carbontetrachloride (16 ml, 10%) was added slowly with vigorous shaking. the mixture was refluxed on a water bath for 15-20 minutes using water condenser. Hydrogen bromide evolved briskly. The reaction mixture was cooled. The crystals were separated by filtration. It was crystallized from methanol m.pt= 116°
Yield = 1.19 gm

General Method of the preparation of sodium (or Potassium) salt of dithiocarbamic acid (3a)

To a vigorously stirred solution of the amine (0.05m), sodium (or Potassium) hydroxide in ethanol. carbondisulphide (0.075m) was added dropwise. The temperature during addition was maintained below 10°. The salt which separated in the reaction mixture was collected and washed with chloroform to remove the dimeric product that might have formed as a by: product. The residue was then washed with little absolute ethanol and used as such.

General method of the preparation of ammonium salt of dithiocarbamic acids: (3 b)

In a loosely stoppered conical flask (100 ml) cooled in freezing mixture concentrated ammonia (9.0 ml, d = 0.88) and carbondisulphide (0.07m) was added. The solution was stirred and the aromatic amine (0.05 m) was added in small portions with vigorous shaking for one hour. The reaction was then allowed to stand for further one hour. The separated crystalline salt was collected and dried. It was extracted with chloroform to remove small amount of dimeric material. which might have been formed as a bye-product. The residue was then washed with little ethanol. It was used without further purification.

General Method of the preparation of N-3 [Aryl/Alky/Dithiocarbamoyl]

Quinazalone-4 (1) :

Separate solution of N-3 Bromo-quinazalone-4 (2) (2.24 g; 0.01m in 20 ml. acetone) and salt of appropriate dithiocarbamic acid (3) in 20 ml dry acetone were mixed together and shaken well at room temperature for 5-10 minutes. The reaction mixture was then heated under reflux on a water bath for one hour. Then it was filtered and the filtrate was cooled. Solid was separated, which was washed thoroughly with distilled water and dried. The product was recrystallised mostly from ben zene to obtain pure samples of the desired compounds. The yield were invariably good.

Following compounds were prepared by the method :

1. N³ [Morpholinyldithiocarbamoyl]- Quinazalone-4 (1a)

It was prepared by the reaction of ammonium morpholinyldithiocarbamate (0.9 g. 0.005m) and N³- Bromoquinazalone-4 (2) (1.12g, 0.005m). It was crystallized from benzene to get cream coloured crystals.

m.pt 175-176°, Yield, 1.5g

Analysis Found : C= 50.75 H= 4.19. N= 13.61% S= 20.76%

C₁₃H₁₃O₂N₃S₂ requires C= 50.81, H= 4.23
N= 13.68% S= 20.85%

2. N³ [Phenyldithio carbamoyl]- quinazalone-4(1b)

It was prepared by the reaction of ammonium phenyldithiocarbamate (0.93g, 0.005m) and (103) (1.12g; 0.005m)

It was Crystallised as light cream crystals from benzene

m.pt. 179-180°, Yield : 1.4 g

Analysis : found C= 57.49, H= 3.46,
N= 13.40%, S= 20.31 %

C₁₅H₁₁N₃OS₂ requires C= 57.51, H= 3.51,

N= 13.42%, S= 20.45 %

3. N³ [P- Tolyldithiocarbamoyl]- quinazolone-4(1c) :

It was prepared by the reaction of ammonium-tolyldithiocarbamate (1.0g : 0.005m) and (103) (1.12g : 0.005 m)

It was crystallized from benzene as colourless needles shaped crystals.

m.pt 136-137⁰

Yield 1.32 g

Analysis found C= 58.69, H= 3.82,

N= 12.83% S= 19.43%

C₁₆H₁₃N₃O₃S₂ C= 53.78; H= 3.08,

N= 11.76%, S= 17.93%

4. N³ [2'- Carboxyphenyldithiocarbamoyl] - quinazolone - 4 (1d) :

It was prepared by the reaction of ammonium -2- carboxy phenyldithiocarbamate (1.15 g, 0.005 m) and (2) (1.12g, 0.005m). It was crystallized from benzene as shining brown crystals.

m. pt. 122⁰

Yield 1.3g

Analysis : found C= 53.66, H = 3.01,

N = 11.72%, S = 17.86%

C₁₆H₁₁N₃O₃S₂ requires C=53.78; H=3.08;

N= 11.76%, S= 17.93%

5. N³ [4'- Carboxy phenyldithiocarbamoyl] - quinazolone - (1e) :

It was prepared by the reaction of ammonium -4- carboxy phenyldithiocarbamate (1.15 g, 0.005 m) and (2) (1.12g, 0.005m).

It was crystallized from benzene as coffee coloured crystals.

m. pt. 126⁰

Yield 1.2g

Analysis : found

C= 53.69, H = 3.02, N =11.73%, S = 17.86%

C₁₆H₁₁N₃O₃S₂ requires C=53.78; H=3.08;

N= 11.76%, S= 17.93%

6. N³- [Sulphaquinadinyldithiocarbamoyl]- quinazolone- 4 (1f) :

It was prepared by the reaction of ammonium sulphaquinadinyldithiocarbamate (1.535g; 0.005m) and (2) (1.12g; 0.005m)

It was crystallized from benzene as deep cream coloured crystals

m.pt 125-126⁰,

Yield 1.25g

Analysis Found

C= 44.21, H= 3.17: N= 19.29% S= 22.01%

C₁₆H₁₄N₆O₃S₃ requires

C=44.24; H=3.23; N= 19.35%, S= 22.12%

7. N³- [4-Methoxyphenyldithiocarbamoyl]- quinazolone- 4(1q)

It was prepared by the reaction of ammonium p anisidinyldithiocarbamate (1.06g; 0.005m) and (2) (1.12g, 0.005)

It was crystallized from benzene as light brown coloured crystals

m.pt 168⁰

Yield 1.3g

Analysis Found

C= 55.92, H= 3.75, N= 12.21%, S= 18.54%

C₁₆H₁₃N₃O₂S₂ requires,

C= 55.98, H= 3.79, N= 12.24%, S= 18.66%

8. N³- [Diphenyl dithiocarbamoyl]- quinazolone- 4 (1h)

It was prepared by the reaction of ammonium diphenyl-dithiocarbamate (1.31g;0.005m) and (2) (1.12g; 0.005m)

It was crystallized from benzene as shining steel grey coloured crystals.

m.p. 46-47⁰

Yield 1.13g

Analysis Found

C= 64.71; H=3.82; N= 10.74%, S= 16.33%

C₁₆H₁₃N₃O₂S₂ requires,

C= 64.78, H= 3.86, N= 10.80%, S= 16.45%

9. N³-[Diethyldithiocarbamoyl] quinazalone-4(1i)

It was prepared by the reaction of ammonium diethyl dithiocarbamate (0.83g, 0.005m) and (2) (1.12g; 0.005m)

It was crystallized from benzene as light brown crystals

m.pt 157-158⁰.

Yield : 1.29g

Analysis Found

C= 53.21; H=5.08; N= 14.29%, S= 21.71%

C₁₆H₁₃N₃O₂S₂ requires,

C= 53.24, H= 5.12, N= 14.33%, S= 21.84%

Biological tests:

For the preparation of the media for the culture of staphylococcus aureus and other test bacteria the following material was required.

Peptone : 20g

Sodium taurocholate (conium) : 5g

Water : 11g

Agar : 20g

Lactose : 10% aqueous solution- 100ml

Neutral red solution (2% in 50% ethanol) :- 3.5 ml. Peptone and taurocholate were dissolved in water by heating Agar was added to it and heated in autoclave. It was filtered to make it clear. The pH was adjusted to 7.5. The lactose and neutral red solution was added and mixed well. The whole maternal was heated in an

autoclave at 100⁰. for one hour, then at 115⁰ for 15 minutes. The molten media (14ml) was then poured into petridish of 88m diameter and was left undisturbed until it had set. The plate was dried by heating at 37⁰. for 1 hour in an oven. The media acquired reddish brown colour.

The test bacteria was then cultured in the usual manner.

Biological activities

The compound synthesized 1(a) to 1(i) were separately screened (1mg/disk and 0.5 mg/dsk) against both gram +ve and gram -ve bacteria. *S. albus*, *B. subtilis* and *S. aurus* were taken as the gram +ve bacteria while *E.coli* and *S. dysenteriae* as gram -ve bacteria. They were also screened (1mg/ disk level) against fungi such as *A. niger* and *N. cressa*.

Antibacterial Acitivity

Among the compounds tested, (1a) was found to reactive against *B. subtilis*, *E. coli* & *S. dysentriae* while (1c) was active against all the test bacteria, (1e) was against *S. aurus*, *B. subtilis*, *E.coli* & *S. dysentrie*. Other compounds did not show any activity.

Antifungal Activity

Compound (1e) showed mild activity against both *A. niger* & *N.cressa*, while (1e) was moderately active *A.niger* only. None of other compounds did show any antifungal activity.

The determination of sensitivity¹⁰

The sensitivity test was done by paper disk method.

The result of the sensitivity tests has been presented in table 1, 2 and 3.

Table – 1
Anti bacterial Activity of Compounds Against Gram Positive Bacteria

<i>S aureus</i>	<i>S albus</i>		<i>B. subtilis</i>	
1 mg disk ⁻¹ 0.5 mg disk ⁻¹ Compound no. 102	1 mg disk ⁻¹	0.5 mg disk ⁻¹	1 mg disk ⁻¹	0.5 mg disk ⁻¹
a) - -	-	-	+	-
b) - -	-	-	-	-
c) ++ +	+	-	+	-
d) - -	-	-	-	-
e) + +	-	-	+	-
f) - -	-	-	-	-
g) - -	-	-	-	-

+ = ≤ 20 mm

++ 20 to 40 mm

- no inhibition

Table – 2
Anti bacterial Activity of Compounds Against Gram Negative Bacteria

<i>E. coli</i>		<i>S. dysenteriae</i>	
1 mg disk ⁻¹ Compound no. 102	0.5 mg disk ⁻¹	1 mg disk ⁻¹	0.5 mg disk ⁻¹
a) +	—	+	—
b) —	—	—	—
c) ++	+	++	+
d) —	—	—	—
e) ++	+	+	—
f) —	—	—	—
g) —	—	—	—

+ = ≤ 20 mm

++ 20 to 40 mm

- no inhibition

Table - 3
Anti Fungal Activity of Compounds
(Zone of inhibition in 24 hours.)

Compound No. 102	<i>A niger</i> 1 mg/disk	<i>N cressa</i> 1 mg/disk
a)	-	-
b)	-	-
c)	+	-
d)	-	-
e)	+	+
f)	-	-
g)	-	-

+ = ≤ 20 mm

++ 20 to 40 mm

- no inhibition

Results and Discussion

The compounds of general formula (1) synthesized. These compounds have been screened *in vitro*, separately against gram +ve and gram -ve bacteria. They also have been screened against some fungi. The tests were done

at 1mg /disk and 0.5mg /disk level in a case of bacteria while 1mg/disk level against fungi. Some of the compounds were found to be reactive against bacteria and some against fungi.

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