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Synthesis and biological evaluation of some novel substituted 4-chloro quinolin 2-(1*H*)-one dithiocarbamates

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ABSTRACT

Organic dithiocarbamate (DTC) derivatives have received much attention in the field of organic chemistry due to their interesting chemistry and wide utility. They are well known used as organic intermediates, rubber additive, additive of polluted water, vulcanizing agents, pharmaceuticals, agrochemicals, protection of amino groups, linkers in solid phase organic synthesis and recently in the synthesis of ionic liquids. Quinolinones are an interesting class of molecules present in a number of biologically active natural products. Hence, a series of quinolinone derivatives bearing diverse dithiocarbamate moieties with secondary amines were designed and synthesized via a three-component reaction protocol. The compounds were characterized for IR, mass and ^{1}H NMR and screened for anti-microbial activities and DNA protection. Some of the compounds showed significant properties.

Keywords: Quinolines, Dithiocarbamates, antimicrobial activities, DNA protection.

INTRODUCTION

Organic dithiocarbamates have received much attention due to their interesting chemistry and wide utility. This is due to their pivotal role in agriculture [1] and their intriguting biological activities [2]. They have been extensively used as pharmaceuticals, agro-chemicals, and intermediate in organic synthesis, for the protection of amino groups in peptide synthesis, as linkers in solid phase organic synthesis, as radical precursors and recently in synthesis of ionic liquids [3]. Besides being widely used as fungicides to protect crops from fungal diseases, dithiocarbamic acid esters have a number of other applications such as in photo chemistry, catalysis in the sulfur vulcanization of rubber, detection and analysis of biological NO produced endogenously from NO syntheses and polymerization. Because of the reasons mentioned above, the syntheses of dithiocarbamates have received considerable attention. Recently, one pot reaction of amines with CS_2 and electrophillic reagents has been developed. Much effort has been focused on the exploration of reaction conditions for one-pot reaction [4].

Quinoline derivatives represent an important class of heterocycles, as there ring system occurs in various natural products, especially in alkaloids and exhibit exceptionally broad spectrum of biological activities [5-7]. After the discovery of cinchona alkaloids as anti-malarial agents several anilino-quinolines were also established as synthetic anti-malarials [8]. There is potent antimicrobial and anti-malarial activity of chloroquinolines. Very recently, quinolinyl iso-quinolines were reported to possess antiviral activity [9]. Many quinolinone derivatives have found active as antimalarial parasite agents [10], antiamebics and antischistosomal agents [11-13] and to have antibacterial [14,15], antiproliferative and antitubulin [16], anti-hepatitis *B* virus (HBV) [17,18] anti-HIV-1 [19] activities.

In the present study, 2,4 dichloroquinolines are acid hydrolysed to get 4-chlorocarbostyril. This was treated with carbon disulphide and various secondary amines in presence of sodium methoxide and DMF to form dithiocarbamate substituted quinolines.

The in vitro anti bacterial and antifungal activities were evaluated by agar disc diffusion method [21]. The DNA protection of the compounds was also done and some of the compounds showed good activity.

MATERIALS AND METHODS

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary electric melting point apparatus (Shital scientific industries, Mumbai) and are uncorrected. ^{1}H NMR spectra were recorded on Bruker spectrometer in $CDCl_3$ and DMSO (400 MHz and 500 MHz) with TMS as internal standard. IR spectra (KBr) were run on a Nicolet impact 410 FT-IR spectrometer (v_{max} in cm^{-1}). Mass spectrum was recorded on Finnigan MAT (Model MAT8200) spectrometer. Column chromatography was conducted on silica gel 200-400 mesh (Merck) and preparative thin-layer chromatography was carried out using SILICA GEL GF-254.

All the compounds gave satisfactory chemical analysis the homogenicity of the compounds was checked by TLC on aluminum foil packed precoated silica gel plates using n-hexane and ethyl acetate (8:2) as mobile phase and visualized under UV lamp. The results are in **Table I.**

Table I. Physicochemical Parameters

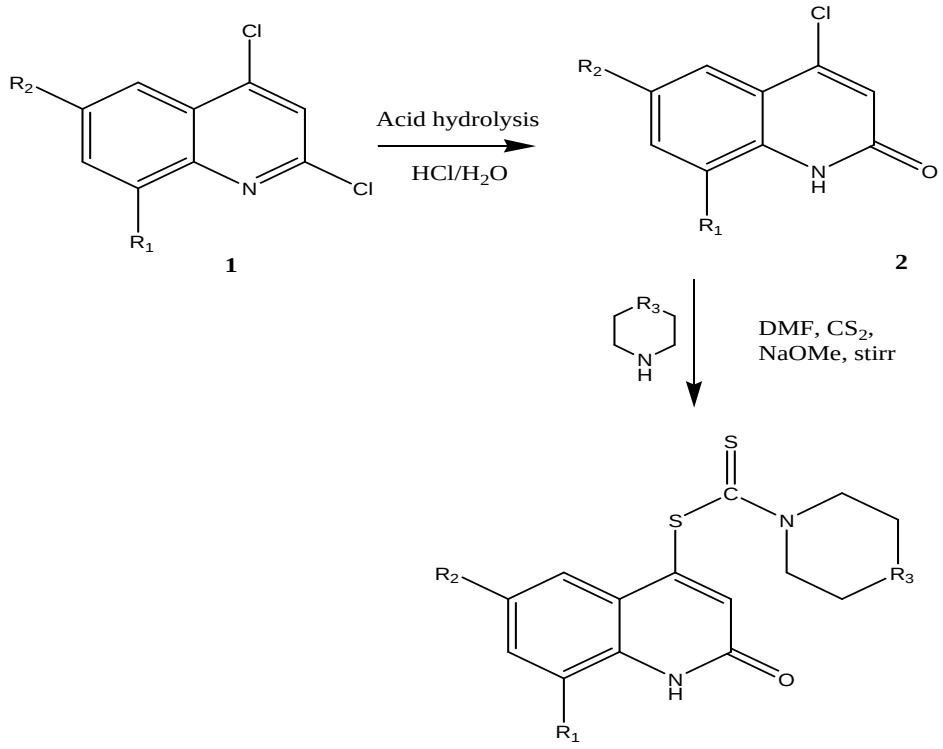
Sl. No	Compound	Mol. formula	Mass	% (Yield)	M. P. °C
1	3a	$C_{16}H_{18}N_2OS_2$	319	84	178-181
2	3b	$C_{16}H_{18}N_2OS_2$	319	81	184-187
3	3c	$C_{15}H_{15}N_3O_3S_2$	349	72	176-178
4	3d	$C_{16}H_{18}N_2O_2S_2$	334	79	189-192
5	3e	$C_{17}H_{20}N_2OS_2$	332	82	184-186
6	3f	$C_{15}H_{16}N_2O_2S_2$	320	81	179-182
7	3g	$C_{15}H_{16}N_2O_2S_2$	320	83	182-184
8	3h	$C_{14}H_{13}N_3O_4S_2$	351	76	181-183
9	3i	$C_{15}H_{16}N_2O_3S_2$	336	82	189-193
10	3j	$C_{16}H_{18}N_2O_2S_2$	334	83	191-193
11	3k	$C_{15}H_{17}N_3OS_2$	320	84	185-187
12	3l	$C_{15}H_{17}N_3OS_2$	320	86	189-191
13	3m	$C_{14}H_{14}N_4O_3S_2$	350	78	178-179
14	3n	$C_{15}H_{17}N_3O_2S_2$	335	83	179-182
15	3o	$C_{16}H_{19}N_3OS_2$	333	79	186-188

General procedure for the synthesized compounds
Compound **1** 2, 4 dichloroquinoline was prepared as previously described in the literature [20].

Synthesis of 4-Chloro-quinoline 2-(1*H*)-one: (2)
A solution of dichloroquinoline **1** (2.12g, 10mM) in dilute dichloroacetic acid (50mL, 90%) was heated under reflex for 1h. A clear solution was then poured on to ice cold water and the precipitate that formed was collected by filtration and crystallized.

Synthesis of 4- dithiocarbamate substituted quinoline 2-(1*H*)-one: 3(a-o)
To a solution of amine (1mM) in DMF (2mL) was added drop wise Carbon disulphide (2mM) and anhydrous Sodium Methoxide (1mM). The resulted mixture was stirred at room temperature for 30 min. The 4-Chloro Quinoline **2** (1mM) was added by one portion and stirring was continued. After completion of the reaction (monitored by TLC), the mixture was diluted with ice cold water (20mL) and the precipitate was filtered, and re-crystallized from Ethanol to give the target compound **3**.

Scheme-1: Synthesis of 4-chloro quinolin 2-(1H)-one dithiocarbamates.



3a- R_1=H, R_2=CH_3, R_3=CH_2
3b- R_1=CH_3, R_2=H, R_3=CH_2
3c- R_1=H, R_2=NO_2, R_3=CH_2
3d- R_1=H, R_2=OCH_3, R_3=CH_2
3e- R_1=CH_3, R2=CH_3,R_3=CH_2
3f- R_1=H, R_2=CH_3, R_3=O
3g- R_1=CH_3, R_2=H, R_3=O
3h- R_1=H, R_2=NO_2, R_3=O
3i- R_1=H, R_2=OCH_3, R_3=O
3j- R_1=CH_3,R_2=CH_3, R_3=O
3k- R_1=H, R_2=CH_3, R_3=NH
3l- R_1=CH_3, R_2=H, R_3=NH
3m- R_1=H, R_2=NO_2, R_3=NH
3n- R_1=H, R_2=OCH_3, R_3=NH
3o- R_1=CH_3, R_2=CH_3, R_3=NH

Spectral Data

1,2-dihydro-6-methyl-2-oxoquinolin-4-yl piperidine-1-carbodithioate **3a**: IR (KBr) cm^{-1} 3210 (N-H); 1667 (C=O); 1180 (C-N); 1352 (C=S); ^{1}H NMR (DMSO) δ 2.34 (s, 3H, 6CH_3), 7.26 7.70 (m, 4H, Ar-H), 1.48-2.6 (m, 10H, pip CH_2's), 10.55 (bs, 1H, N-H_{qui}).

1,2-dihydro-8-methyl-2-oxoquinolin-4-yl piperidine-1-carbodithioate **3b**: IR (KBr) cm^{-1} 3190 (N-H); 1660 (C=O); 1165 (C-N); 1359 (C=S); ^{1}H NMR (DMSO) δ 2.30 (s, 3H, 8-CH_3), 7.15-7.62 (m, 4H, Ar-H) 1.46-2.50 (m, 10H, pip CH_2's) 10.60 (bs, 1H, N-H_{qui})
1,2-dihydro-6-nitro-2-oxoquinolin-4-yl piperidine-1-carbodithioate **3c**: IR (KBr) cm^{-1} 3184 (N-H); 1672 (C=O); 1156 (C-N) 1357 (C=S); ^{1}H NMR (DMSO) δ 7.26-8.66 (m, 4H, Ar-H), 1.43-2.70 (m, 10H, pip CH_2's) 10.68 (bs, 1H, N-H_{qui})

1,2-dihydro-6-methoxy-2-oxoquinolin-4-yl piperidine-1-carbodithioate **3d**: IR (KBr) cm^{-1} 3211 (N-H); 1678 (C=O); 1156 (C-N); 1357 (C=S); ^{1}H NMR (DMSO) δ 7.68-8.96 (m, 4H, Ar-H), 3.67 (s, 3H, 6-OCH_3), 7.18-7.98 (m, 10H, pip CH_2's), 11.23 (bs, 1H, N-H_{qui})

1,2-dihydro-6,8-dimethyl-2-oxoquinolin-4-yl piperidine-1-carbodithioate **3e**: IR (KBr) cm^{-1} 3198 (N-H); 1684 (C=O); 1174 (C-N); 1345 (C=S); ^{1}H NMR (DMSO) δ 2.56 (s, 3H, 6CH_3), 2.98 (s, 3H, 8CH_3), 7.14-7.75 (m, 3H, Ar-H), 1.78-2.76 (m, 10H, pip CH_2's), 11.67 (bs, 1H, N-H_{qui})

1,2-dihydro-6-methyl-2-oxoquinolin-4-yl morpholine-4-carbodithioate **3f**: IR (KBr) cm^{-1} 3215 (N-H); 1689 (C=O); 1153 (C-N); 1356 (C=S); ^{1}H NMR (DMSO) δ 2.59 (s, 3H, 6-CH_3), 8.19-8.49 (m, 4H, Ar-H), 2.94-3.78 (m, 8H, mor CH_2's), 11.64 (bs, 1H, N-H_{qui})

1,2-dihydro-8-methyl-2-oxoquinolin-4-yl morpholine-4-carbodithioate **3g**: IR (KBr) cm^{-1} 3154 (N-H); 1620 (C=O); 1163 (C-N); 1359 (C=S); ^{1}H NMR (DMSO) δ 2.79 (s, 3H, 8CH_3), 8.49-8.98 (m, 4H, Ar-H), 3.27-3.91 (m, 8H, mor CH_2's), 10.87 (bs, 1H, N-H_{qui})

1,2-dihydro-6-nitro-2-oxoquinolin-4-yl morpholine-4-carbodithioate **3h**: IR (KBr) cm^{-1} 3214 (N-H); 1650 (C=O); 1172 (C-N); 1354 (C=S); ^{1}H NMR (DMSO) δ 7.78-8.94 (m, 4H, Ar-H), 3.14-3.84 (m, mor, CH_2's), 11.87 (bs, 1H, N-H_{qui})

1,2-dihydro-6-methoxy-2-oxoquinolin-4-yl morpholine-4-carbodithioate **3i**: IR (KBr) cm^{-1} 3154 (N-H); 1670 (C=O); 1189 (C-N); 1358 (C=S); ^{1}H NMR (DMSO) δ 3.56 (s, 3H, 6-OCH_3), 8.14-8.94 (m, 4H, Ar-H), 2.95-3.84 (m, 8H, mor CH_2's),11.42 (bs, 1H, N-H_{qui})

1,2-dihydro-6,8-dimethyl-2-oxoquinolin-4-yl morpholine-4-carbodithioate **3j**: IR (KBr) cm^{-1} 3160 (N-H); 1675 (C=O); 1195 (C-N); 1353 (C=S); ^{1}H NMR (DMSO) δ 2.75 (s, 3H, 6-CH_3), 2.92 (s, 3H, 8-CH_3), 7.48-8.14 (m, 7H, Ar-H), 2.87-3.97 (m, 8H, mor CH_2's), 11.43 (bs, 1H, N-H_{qui})

1,2-dihydro-6-methyl-2-oxoquinolin-4-yl piperazine-1-carbodithioate **3k**: IR (KBr) cm^{-1} 3150 (N-H); 1690 (C=O); 1167 (C-N); 1354 (C=S), 3191 (NH); ^{1}H NMR (DMSO) δ 2.67 (s, 3H, 6-CH_3), 7.45-7.99 (m, 4H, Ar-H), 2.16-2.94 (m, 8H, piz CH_2's), 1.76 (s, 1H, NH, disappeared with D_2O), 10.62 (bs, 1H, N-H_{qui})

1,2-dihydro-8-methyl-2-oxoquinolin-4-yl piperazine-1-carbodithioate **3l**: IR (KBr) cm^{-1} 3195, 3215 (N-H); 1643 (C=O); 1184 (C-N); 1357 (C=S); ^{1}H NMR (DMSO) δ 2.64 (s, 3H, 8-CH_3), 7.15-7.79 (m, 4H, Ar-H), 2.67-2.84 (m, 8H, piz CH_2's), 1.72 (s, 1H, NH, disappeared with D_2O), 11.72 (bs, 1H, N-H_{qui})

1,2-dihydro-6-nitro-2-oxoquinolin-4-yl piperazine-1-carbodithioate **3m**: IR (KBr) cm^{-1} 3178, 3247 (N-H); 1576 (C=C); 1165 (C-N); 1359 (C=S); ^{1}H NMR (DMSO) δ 7.17-8.58 (m, 4H, Ar-H), 2.45-2.98 (m, 8H, piz CH_2's), 1.89 (s, 1H, NH, disappeared with D_2O), 10.34 (bs, 1H, N-H_{qui})

1,2-dihydro-6-methoxy-2-oxoquinolin-4-yl piperazine-1-carbodithioate **3n**: IR (KBr) cm^{-1} 3197, 3216 (N-H); 1565 (C=C); 1176 (C-N); 1349 (C=S); ^{1}H NMR (DMSO) δ 3.45 (s, 3H, 6-OCH_3), 7.74-8.43 (m, 8H, piz CH_2's), 1.94 (s, 1H, NH, disappeared with D_2O), 10.76 (bs, 1H, N-H_{qui})

1,2-dihydro-6,8-dimethyl-2-oxoquinolin-4-yl piperazine-1-carbodithioate **3o**: IR (KBr) cm^{-1} 3179, 3243 (N-H); 1567 (C=C); 1167 (C-N); 1357 (C=S); ^{1}H NMR (DMSO) δ 2.58 (s, 3H, 6-CH_3), 2.73 (s, 3H, 8-CH_3), 7.54-7.84 (m, 3H, Ar-H), 2.65-3.31 (m, 8H, piz CH_2's), 1.74 (s, 1H, NH, disappeared with D_2O), 11.83 (bs, 1H, N-H_{qui})

***In vitro* Antimicrobial activity**

For the antimicrobial assay standard inoculums were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 8.0 mm in diameter were prepared from Whattman no. 1 filter paper and sterilized by dry heat at 120 °C for 1 h. The sterile discs previously soaked in a known concentration (100m g/8 mm disc) of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 °C. The inhibition zones were measured and compared with the standard

Antibacterial Activity

The newly synthesized compounds **3(a-o)** were tested for their *in vitro* antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* by using the agar disc diffusion method [21]. The results of the preliminary antimicrobial testing of the prepared compounds and the standard of antibacterial drug ciprofloxacin are shown in **Table 3**. Among the tested compounds**, 3a, 3d, 3j, 3l** and **3o** showed considerable activity almost equal to the activity of ciprofloxacin. The other compounds were found to be moderate or least effective.

Antifungal Activity

All the newly synthesized compounds **3(a-o)** were also screened for their antifungal activity against *Aspergillus niger* and *Alternaria alternate* by Disc diffusion method [22]. The results of the preliminary antifungal testing of the prepared compounds and the standard antifungal drug amphotericin B are shown in **Table 3.** The antifungal activity data reveal that compounds **3b, 3f, 3k** and **3m** showed good activity against the test fungi and nearly equal to the standard amphotericin B.

Table II. Antimicrobial Activity of Compounds 3(a-o)

Growth inhibition zone diameter (mm)				
Compound	**Antibacterial activity**		**Antifungal activity**	
	S. aureus	*E. coli*	*A. niger*	*A. alternata*
3a	20	21	14	13
3b	13	16	18	17
3c	14	15	12	14
3d	18	19	13	11
3e	12	14	10	12
3f	13	15	17	17
3g	13	12	09	06
3h	11	14	08	09
3i	10	13	11	10
3j	16	18	13	12
3k	13	15	16	18
3l	18	20	11	12
3m	12	14	18	17
3n	13	15	10	12
3o	17	21	11	09
Ciprofloxacin	22	25	---	---
Amphotericin B	---	---	20	20

The compounds **3(a-o)** and the standards used were of 100 mg/8 mm discs.

DNA Protection Analysis

Sample stock was prepared in DMSO, Bacterial DNA was isolated from *Eschericha coli* was used for the assay. Various volumes of samples were added to 10µl DNA in a vial. Ferrous sulphate (10µl; 1mM) and Hydrogen peroxide (10µl: 10mM) were added to the reaction vial. The mixture was incubated at 37˚C for 60 min. Agarose gel electrophoresis of this reaction mixture was carried out using 0.8% gel.

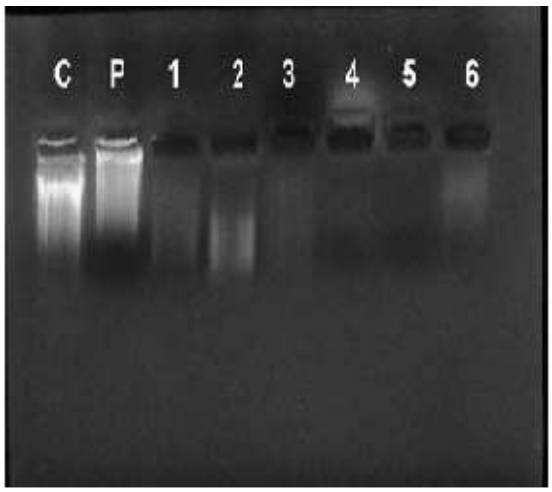


Fig.1. DNA protection activity of samples: Gel 1 – Samples 1-6

Table III. DNA Protection of some compounds

DNA Protection		
Lane	**Sample and concentration tested**	**Results**
Lane Label C	Control DNA (untreated)	Clear band
Lane Label P	Positive control (Treated)	Smear
1 (3c)	Sample 7 -100µg	Faded nuclear band – partial protection
2 (3d)	Sample 8- 100µg	Faded nuclear band – partial protection
3 (3h)	Sample 9-100µg	Smear -No protection
4 (3i)	Sample 10-100µg	Smear -No protection
5 (3m)	Sample 11 -100µg	Smear -No protection
6 (3n)	Sample 12 -100µg	Smear -No protection

RESULTS AND DISCUSSION

The results of the preliminary antimicrobial testing of the prepared compounds and the standard of antibacterial drug ciprofloxacin are shown in **Table II**. Among the tested compounds**, 3a, 3d, 3j, 3l** and **3o** showed considerable activity almost equal to the activity of ciprofloxacin. The other compounds were found to be moderate or least effective. The results of the preliminary antifungal testing of the prepared compounds and the standard antifungal drug amphotericin B are shown in **Table II.** The antifungal activity data reveal that compounds **3b, 3f, 3k** and **3m** showed good activity against the test fungi and nearly equal to the standard amphotericin B. The DNA protections of some compounds were done, two of which showed good results. The protection of compound is tabulated in **Table III**.

The synthetic route for compound **3** is outlined in scheme 1. According to the reported procedures dichloroquinoline **1** undergoes acid hydrolysis to get the desired compound **2** in good yields. Then, at the prescence of sodium methoxide as base, a subsequent three-component reaction of the corresponding amine, carbon disulphide and the intermediate **2** produced compound **3**. All the compounds were analysed by TLC.

In conclusion, a new series of dithiocarbamate substituted quinolines **3(a-o)** has been synthesized and evaluated for their antimicrobial activity and DNA protection. Most of the new compounds showed appreciable antimicrobial activity. Among them, some compounds showed marked inhibition of bacterial and fungal growth nearly equal to the standards and two of the compounds showed partial DNA protection.

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