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SYNTHESIS AND IN VITRO ANTITUMOR ACTIVITY OF QUINAZOLINE-4(3H)-ONE DERIVATIVES WITH DITHIOCARBAMATE SIDE CHAINS

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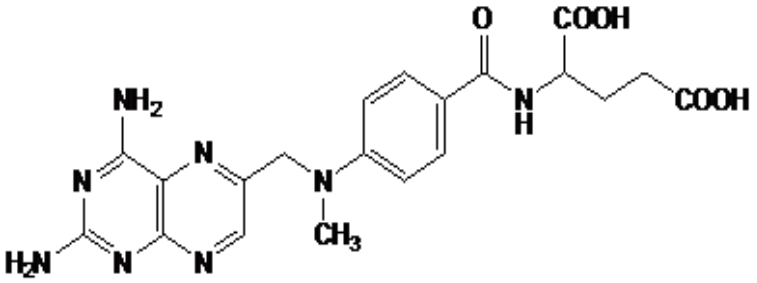
ABSTRACT
A series of quinazoline-4(3*H*)-one derivatives with dithiocarbamate side chains were synthesized to investigate cytotoxic activity. Final compounds **(5a-5o)** were confirmed by spectral data and elemental analysis. Synthesized compounds were tested for antitumor activity against K562 (leukemia), Colo-205 (colon cancer) and MDA-MB (Breast cancer) by MTT assay method. Title compounds were prepared by reacting corresponding 3-amino-2-phenylquinazoline-4(3*H*)-ones with carbon disulfide and various alkyl/aralkylhalides in dimethylformamide. Physicochemical and spectral data were consistent with newly synthesized compounds. Among the series, compound **5p** (IC50 = 14.6 µM) showed significant antitumor activity against K562 cells.

KEYWORDS: Quinazoline-4(3*H*)-one, dithiocarbamates, anticancer activity, MTT assay.

INTRODUCTION
Quinazoline-4(3*H*)-ones and their derivatives constitute an important class of heterocyclic compounds as they have a broad spectrum of pharmacological activities like antifungal,[1] antimicrobial,[2] anti HIV,[3] anticancer,[4] anti-inflammatory,[5] anticonvulsant,[6] antidepressant,[7] hypolipidemic,[8] antiulcer [9] and analgesic.[10] A steadily increasing number of studies have been carried out on quinazoline-4(3*H*)-ones and their antitumor activity.[11,12] On the other hand, dithiocarbamates are a common class of organic molecules, they form mono and bi-dentate co-ordination to transition metal centers. Transition metal complexes of dithiocarbamates present a wide range of biological activities [13,14] and have found application in the treatment of cancer.[15,16] Recent reports indicate that quinazolinones linked to dithiocarbamates showed significant *in vitro* antitumor activity,[17] against human myelogenous leukemia K562 cells with IC_{50} = 0.5 µM and more potent than Methotrexate (IC_{50} = 419 µM) and Brassinin (IC_{50} = 128 µM) (Fig. 1). In view of the above literature indicating that quinazolinone and dithicarbamates possessing antitumor activity, it is thought worthwhile to synthesize molecules with quinazoline-4(3*H*)-one nucleus having 2-phenyl substituent and alkyl/aralkyl dithiocarbamate chain at 3rd position and evaluate them for their anticancer activity against human cell lines by MTT assay.



Methotrexate I

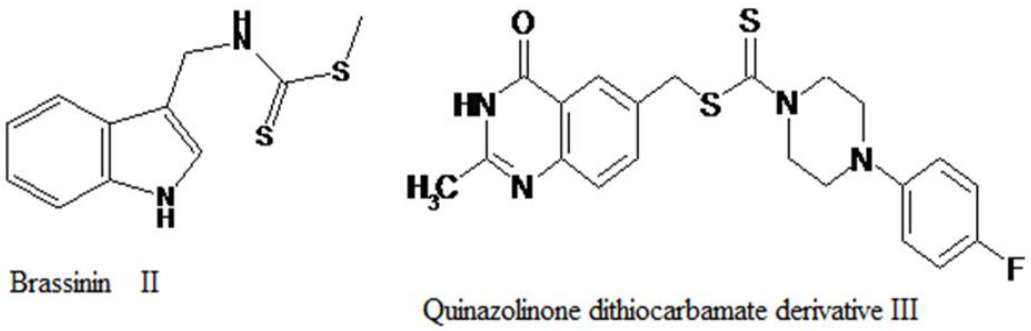
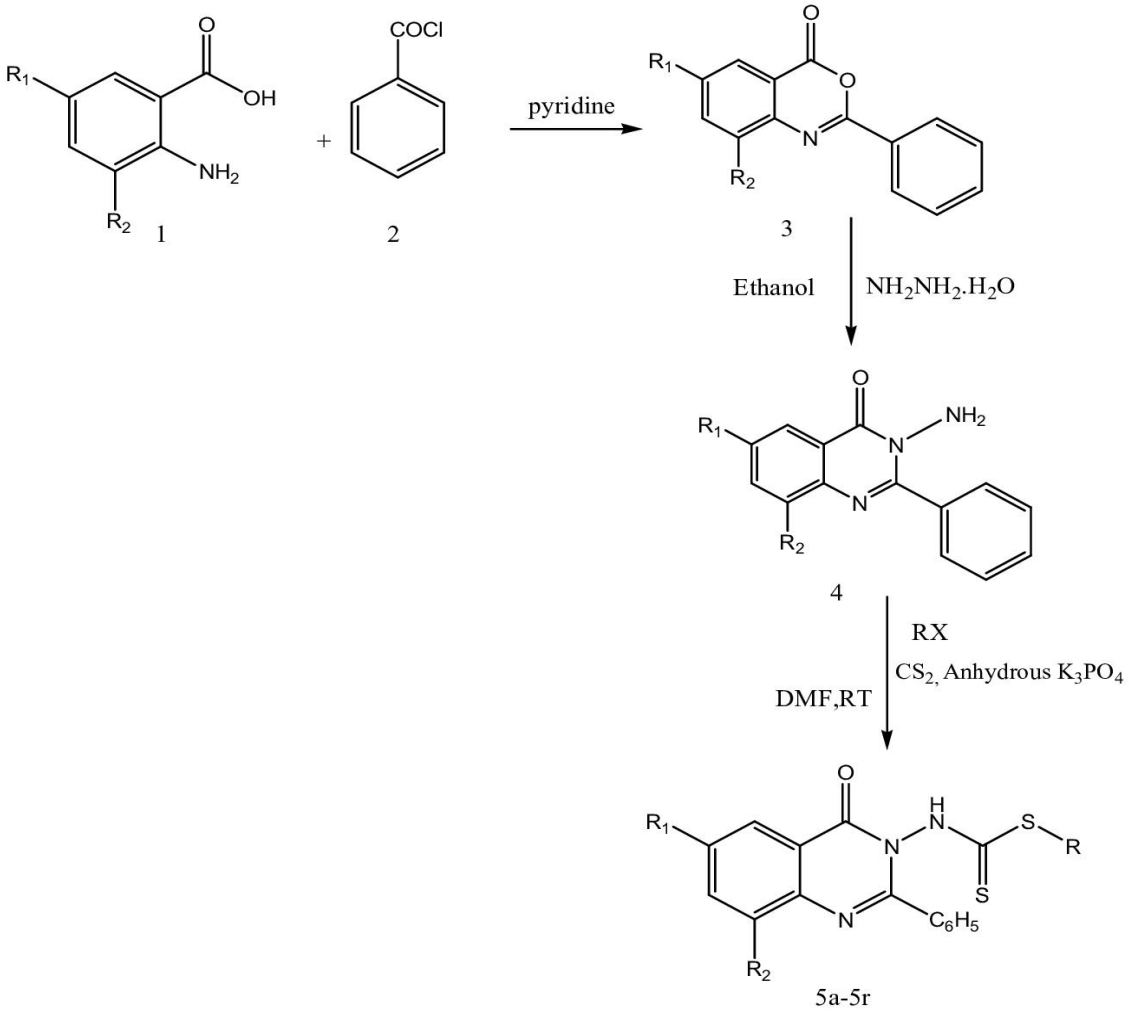


Figure 1: Structures of known dithiocarbamate derivatives.

Experimental

General. Melting points were determined in one-end-open capillary tubes on Shital scientific melting point apparatus and are uncorrected. Infrared spectra recorded on Schimadzu infrared spectrophotometer in KBr pellets. ^{1}H NMR spectra were determined on a Bruker AVANCE-300 spectrometer. All NMR spectra were measured in $CDCl_3$ solution using tetra methyl silane as an internal standard and ^{1}H chemical shifts are reported as ppm. Mass spectra were recorded by using electrospray ionization technique (ESI) on the VG170708H mass spectrometer. The CHN analyses were conducted using the Perkin Elmer 240B analyzer. Silicagel 60-120 mesh (Merck) was used as an adsorbent for column chromatography. TLC was performed on 5 – 10 cm aluminum plates coated with silicagel 60F-254 (Merck) in an appropriate solvent.

Scheme



Scheme1 ***reagents and condition (*****1) pyridine, (2) Ethanol, $NH_2NH_2.H_2O$ (3) CS_2, Anhydrous K_3PO_4**

	R	R_1	R_2
A	Me	H	H
B	Et	H	H
C	Pr	H	H
D	i-Pr	H	H
E	i-Bu	H	H
F	Benzyl	H	H
G	Me	Me	H
H	Et	Me	H
I	Pr	Me	H
J	i-Pr	Me	H
K	i-Bu	Me	H
L	Benzyl	Me	H
M	Me	Br	Br
N	Et	Br	Br
O	Pr	Br	Br
P	i-Pr	Br	Br
Q	i-Bu	Br	Br
R	Benzyl	Br	Br

Synthesis of 6 or 6,8-disubstituted-2-phenyl-3,1-benzoxazin-4-one (3)

The different 2-phenyl-3,1-benzoxazin-4-one derivatives were prepared as reported in the literature.[18,19]

Synthesis of 3-amino-6 or 6,8-disubstituted-2-phenylquinazolin-4(3*H*)-one (4)

3-amino-6 or 6,8-disubstituted-2-phenylquinazolin-4(3*H*)-one derivatives (4) prepared from benzaxazin-4-ones **(3)** as reported in the literature.[19]

General method of Synthesis of quinazolin-4(3*H*)-onedithiocarbamates (5a-5r).

Appropriate quinazolin-4(3*H*)-one dithiocarbamates (4); (0.02 mol) and anhydrous potassium phosphate (0.02 mol) were stirred in dimethylformamide (10 mL) at room temperature for 5 minutes and then carbondisulfide (0.026 mol) was added dropwise. The reaction mixture was stirred for additional 20 min, and then various alkyl/aralkylhalides (RX, 0.02 mol) were added. Stirring was continued at room temperature until the reaction was completed as monitored by TLC. The mixture was poured into cold water then extracted with ethylacetate (3x30 mL), the organic phase was washed one time with water and dried with sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the resultant residue obtained in each case was chromatographed over silica gel using mixture of petroleum ether and ethylacetate as eluent to afford title compounds.

Analutical data for methyl-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl) dithiocarbamate (5a)

^{1}H NMR (200 MHz, $CDCl_3$): δ =2.82 (s, 3H, Me), 7.19-9.02 (m, 9H, Ph & H5-8), 11.62 (bs, 1H, NH). IR (KBr) ν /cm^{-1}: 3269.38 (NH), 1647.97 (C=O), 1598.32 (C=N). Yield 78%; m.p. 112-116 ^{0}C; ESI-MS (*m/z)* 328$[M+H]^+$; calcd. for $C_{16}H_{13}N_3OS_2$: C, 58.71; H, 3.97; N, 12.84. found: C, 58.74; H, 3.95; N, 12.81 %.

Analutical data for Ethyl-*N*-(2-phenylquinazolin-3-yl-4(3*H*)-one)dithiocarbamate (5b)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55 (t, 3H, Me), 3.38 (q, 2H, SCH_2) 7.17-9.03 (m, 9H, Ph & H5-8),11.63 (bs, 1H, NH).; IR (KBr) ν / cm^{-1}: 3310.27 (NH), 1662.97 (C=O), 1585.32 (C=N) Yield 74%; m.p. 104-106^{0}C; ESI-MS (*m/z)* 342 $[M+H]^+$.

Analutical data for n-Propyl-*N*-(2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5c)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (t, 3H, Me), 1.88 (m, 2H, CH_2), 3.25 (t,2H, SCH_2) 7.12-8.95 (m, 9H, Ph & H5- 8),11.5(bs, 1H, NH); IR (KBr) ν / cm^{-1}: 3290.16 (NH), 1674.20 (C=O),1594.50 (C=N). Yield 71%; m.p. 92-94 ^{0}C; ESI-MS (*m/z)* 356 $[M+H]^+$;Anal. Calcd. for $C_{18}H_{17}N_3OS_2$: C, 60.83; H, 4.78; N, 11.83%; Found: C, 60.79; H, 4.76; N, 11.86 %.

Analutical data for 2-Propyl-*N*-(2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5d)

^{1}H NMR (200 MHz, $CDCl_3$): δ=1.50 (d, 6H, 2xMe), 3.98 (m, 1H, SCH) 7.13-8.96(m, 9H, Ph & H5-8),1159 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3260.93 (NH),1658.90 (C=O),1601.80 (C=N).Yield 64 %; m.p. 90-92 ^{0}C; ESI-MS *m/z* 356 $[M+H]^+$.

Analutical data for 2-Methyl propyl-*N*-(2-phenylquinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5e)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.09 (d, 6H, 2xMe), 2.13 (m, 1H, CH), 3.23 (d, 2H, SCH_2) 7.17-9.03 (m, 9H, Ph & H5-8), 11.62 (bs, 1H, NH);IR (KBr) ν / cm^{-1} 3289.32 (NH),1647.97 (C=O)1588.62 (C=N).Yield 63 %;m.p. 72-74 ^{0}C; ESI-MS *m/z* 370 $[M+H]^+$.

Analutical data for Benzyl-*N*-(2-phenylquinazolin-3-yl-4(3*H*)-one)dithiocarbamate (5f)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 4.59 (s, 1H, SCH_2), 7.21-9.06 (m, 14H, Ph & H5-8), 11.65 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3282.73 (NH),1671.50 (C=O),1595.80 (C=N). Yield 64 %; m.p. 118-120 ^{0}C; ESI-MS (*m/z)* 404$[M+H]^+$;Anal. Calcd. for $C_{22}H_{17}N_3OS_2$: C, 65.50; H, 4.21; N, 4.21. Found: C, 65.48; H, 4.24; N, 10.41 %.

Analutical data for Methyl-*N*-(6-methyl-2-phenylquinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5g)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.33 (s, 3H, Ph-Me), 2.74 (s, 3H, SMe), 7.18-8.83 (m, 8H, Ph & H5,7,8),11.45 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3300.14 (NH),1657.80 (C=O),1599.20 (C=N). Yield 76 %; m.p. 124-126 ^{0}C; ESI-MS (*m/z)* 342 $[M+H]^+$.

Analutical data for Ethyl-*N*-(6-methyl-2-phenylquinazolin-3-yl-4(3*H*)-one)dithiocarbamate (5h)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.47 (t, 3H, Me), 2.33 (s, 3H, Ph-Me), 3.26 (q, 2H, SCH_2), 7.18-8.82 (m, 8H, Ph & H5,7,8),11.46 (bs, 1H, NH); IR (KBr) ν/ cm^{-1}3299.04 (NH),1687.80 (C=O),1587.40 (C=N) Yield 73 %; m.p. 116-118 ^{0}C; ESI-MS (*m/z)* 356 $[M+H]^+$.

Analutical data for n-Propyl-*N*-(6-methyl-2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5i)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.13 (t, 3H, Me), 1.92 (m, 2H, CH_2), 2.43 (s, 3H, Ph-Me), 3.34 (t, 2H, SCH_2), 7.02-8.92(m, 8H, Ph& H5,7,8),11.56 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3298.12 (NH),1662.32 (C=O),1597.21 (C=N) Yield 69 %: m.p. 112-114 ^{0}C;ESI-MS (*m/z)* 370 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{19}N_3OS_2$: C, 61.78; H, 5.14; N, 11.38. Found: C, 61.75; H, 5.17; N, 11.40 %.

Analutical data for 2-Propyl-*N*-(6-methyl-2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5j)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.49 (d, 6H, 2xMe), 2.33 (s, 3H, Ph-Me), 3.93 (m, 1H, SCH) 7.19-8.83 (m, 8H, Ph & H5,7,8),11.49 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3271.12 (NH), 1674.32 (C=O), 1588.51 (C=N). Yield 63 %; m.p 110-112 ^{0}C; ESI-MS (*m/z)* 370 $[M+H]^+$.

Analutical data for 2-Methylpropyl-*N*-(6-methyl-2-phenylquinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5k)

^{1}H NMR (200 MHz, $CDCl_3$): δ =1.04 (d, 6H, 2xMe), 2.06 (m, 1H, CH), 2.33 (s, 3H, Ph-Me), 3.19 (d, 2H, SCH_2) 7.19-8.82 (m, 8H, Ph & H5,7,8),11.46 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3298.00 (NH),1686.25 (C=O),1592.50 (C=N). Yield 72 %; m.p. 96-98 ^{0}C; ESI-MS (*m/z)* 3384 $[M+H]^+$; Anal. Calcd. for $C_{20}H_{21}N_3OS_2$: C, 62.66; H, 5.48; N, 10.96. Found: C, 62.68; H, 5.47; N, 10.93 %.

Analutical data for Benzyl-*N*-(6-methyl-2-phenylquinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5l)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3H, Ph-Me), 4.59 (s, 1H, SCH_2), 7.28-8.92 (m, 13H, Ph & H5,7,8), 11.55 (bs, 1H, NH); IR (KBr) ν/ cm^{-1} 3292.09 (NH),1671.20 (C=O),1590.70 (C=N). Yield 64 %; m.p. 124-126 ^{0}C; ESI-MS (*m/z)* 418 $[M+H]^+$.

Analutical data for Methyl-*N*-(6,8-dibromo-2-phenylquinazolin-3-yl-4(3*H*)-one)dithiocarbamate (5m)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.73(s, 3H, Me), 7.25-8.05 (m, 7H, Ph & H5,7), 9.48 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3299.13 (NH),1657.80 (C=O),1594.70 (C=N). Yield 61 %;m.p. 164-166 ^{0}C; ESI-MS (*m/z)* 486 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{11}N_3OS_2Br_2$: C, 39.58; H, 2.26; N, 8.65. Found: C, 39.56; H, 2.27; N, 8.67 %.

Analutical data for Ethyl-*N*-(6,8-di bromo-2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5n)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.47 (t, 3H, Me), 3.29 (q, 2H, SCH_2), 7.25-8.04 (m, 7H, Ph & H5,7), 9.50 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3287.46 (NH),1662.91 (C=O),1573.60 (C=N).Yield 60 %; m.p. 148-150 ^{0}C; ESI-MS (*m/z)* 500 $[M+H]^+$.

Analutical data for n-Propyl-*N*-(6,8-di bromo-2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5o)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.05 (t, 3H, Me), 1.85 (m, 2H, CH_2), 3.24 (t, 2H, SCH_2), 7.25-8.04 (m, 7H, Ph & H5,7), 9.51 (bs, 1H, NH); IR (KBr) ν cm^{-1} 3279.61 (NH),1659.46 (C=O),1572.15 (C=N).Yield 60 %; m.p. 136-138 ^{0}C; ESI-MS (*m/z)* 514 $[M+H]^+$.

Analutical data for 2-Propyl-*N*-(6,8-di bromo-2-phenyl quinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5p)

^{1}H NMR ($CDCl_3$) (200 MHz, $CDCl_3$) δ (ppm): 1.48 (d, 6H, 2xMe), 3.93 (q, 1H, SCH), 7.51-8.10 (m, 7H, Ph & H5,7), 9.52 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3269.11 (NH),1673.18 (C=O),1589.39 (C=N).Yield 59 %; m.p. 122-124 ^{0}C; ESI-MS (*m/z)* 514 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{15}N_3OS_2Br_2$: C, 42.10; H, 2.92; N, 8.18. Found: C, 42.98; H, 2.93; N, 8.21 %.

Analutical data for 2-Methylpropyl-*N*-(6,8-dibromo-2-phenylquinazolin-3-yl-4(3*H*)-one) dithiocarbamate (5q)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.03 (d, 6H, 2xMe), 2.06 (m, 1H, CH), 3.15 (d, 2H, SCH_2) 7.26-8.04 (m, 7H, Ph & H5,7), 9.51 (bs, 1H, NH). IR (KBr) ν/ cm^{-1} 3271.24 (NH),1674.82 (C=O),1590.70 (C=N). Yield 57 %; m.p. 110-112 ^{0}C; ESI-MS (*m/z)* 528 $[M+H]^+$.

Analutical data for Benzyl-*N*-(6,8-dibromo-2-phenylquinazolin-3-yl-4(3*H*)-one)dithiocarbamate (5r)

^{1}H NMR (200 MHz, $CDCl_3$): δ= 4.41 (s, 1H, SCH_2), 7.19-7.97 (m, 12H, Ph & H5,7), 9.39 (bs, 1H, NH); IR (KBr) ν /cm^{-1} 3299.10 (NH),1669.94 (C=O),1584.81 (C=N).Yield 62 %: m.p. 160-162 ^{0}C; ESI-MS (*m/z)* 562 $[M+H]^+$.

BIOLOGICAL ACTIVITY

Evaluation of in vitro anticancer activity

Evaluation of in vitro anticancer activity against *K562, Colo-205* and *MDA-MB cancer cell lines*. K562 (Leukemia), Colo-205 (Colon cancer) and MDA-MB (Breast cancer) cell lines were obtained from National Center for Cell Science (NCCS) (University of Pune Campus, Pune). All the cells were grown in plastic T-25 culture flask in Dulbecco's Modified Eagle's Medium which were supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 100 µg mL penicillin, 200 µg mL streptomycin in a humidified atmosphere with 5% CO2 at 37^{o}C. The test compounds were dissolved in DMSO, in a final concentration never exceeding 0.1%, which have no substantial effect on cell growth. 1x104 cells (counted by Trypan blue exclusion dye method) in 96-well plates were incubated with test compounds for 48 h. Then the above media was replaced with 90 µL of fresh serum free media and 10 µL of 3-(4,5-dimethlthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) reagent (5 mg mL) and plates were incubated at 37oC for 4 h, there after the above media was replaced

with 200 µL of of Dimethyl Sulfoxide (DMSO) and incubated at 37^{o} C for 10 min. Finally, the absorbance at 570 nm was measured on a spectrophotometer (spectra max, Molecular devices). The assay was performed in triplicate for three independent determinations. Cisplatin taken as standard drug as it forms complexes with metals, used in the treatment of cancer. IC-50 values were determined from plot: % inhibition versus concentration.

RESULTS AND DISCUSSION

Quinazoline-4(3*H*)-onedithiocarbamates **(5a-r)** were obtained (Scheme) by stirring 3-amino-2-phenylquinazolin-4(3*H*)-one with carbondisulfide and various alky/aralkyl halides in dimethylformamide. The preparation of the title compounds were shown in scheme-1. The physical data of all synthesized compounds were shown in Table-1. All the synthesized compounds were purified by column chromatography using petroleum ether and ethyl acetate as solvent and the reactions were monitored by TLC. The chemical structures of new compounds were elucidated by analytical as well as spectroscopic measurements. The mass spectra of the compounds revealed the molecular ion as the base peak for almost all compounds. In the ^{1}H NMR spectra, NH proton of quinazolinone appeared at δ 9.39-11.65 and aromatic protons of quinazolinones appeared at δ 7.00-9.06.The synthesized quinazolin-4(3*H*)-one dithiocarbamates **(5a-r)** were screened for *in vitro* antitumor activity by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) method to determine the IC-50 values (Table 2).

Compound **5p**, with Isopropyl side chain showed the highest potency with IC50 of 14.6 µM against K562 cells, while it exhibited only mild activity against Colo-205 and MDA-MB cells with same IC50 values (31.8 µM) against both. However compound **5d**, the isopropyl derivative without bromo substituents, at 6th and 8th positions exhibited greater potency (IC50 = 20.0 µM) against K562 and less potency (IC50 = 28.0 µM) against Colo-205 than the corresponding dibromo analogue **(5p)** indicating selective toxicity of derivatives against different cell lines. In general, size and bulkiness of alkyl group (R) increased from methyl to isobutyl, the potency increased against all the cell lines as evidenced from the IC50 values of compound **5a** (R= Me; IC50 = 61.1 µM, Colo-205) and **5e** (R=i-Bu; IC50 = 23.1 µM).

Similarly methyl substitution (R1= Me) at 6th position decreased the activity as indicated by the IC50 values of compound **(5c)** (R = n-Pr; R1= H, IC50 = 26.0 µM) and **(5i)** (R= n-Pr; R1= Me, IC50 = 29.9 µM) against Colo-205 cells. Similar trend is observed against K562 cells. Such a decrease in activity with methyl substitution is seen in case of Isobutyl dithiocarbamates (R = i-Bu) against all three cell lines tested. Among the dibromo compounds (R1=R2=Br), the isopropyl analog **(5p)** R= i-Pr); IC50 = 14.6 µM) exhibited about two times greater potency than the corresponding methyl analogue **(5m)** R= Me, IC50 = 26.3 µM) against K562 cells whereas methyl analogue **(5m)** showed greater potency than the isopropyl analogue against Colo-205 as well as MDA-MB cells.

Over all the activity of the compounds against all the three cell lines increased by replacement of isopropyl chain (R) with isobutyl group except compound **(5k)** (R = i-Bu) which showed much less potency than the corresponding isopropyl analog **(5j)** against MDA-MB cells and **(5q)** (R= i-Bu) showed less potency than **(5p)** (R= i-Pr) against K562 cells.

Table 1: Physicochemical properties of quinazolin-4(3*H*)-one dithiocarbamates (5a-r)

Comp	Molecularformula	Mol. wt.	m.p (O^{0})	% yield
5a	C16H13N3OS2	327	112-116	78
5b	C17H15N3OS2	341	104-106	74
5c	C18H17N3OS2	355	92-94	71
5d	C18H17N3OS2	355	90-92	64
5e	C19H19N3OS2	369	72-74	63
5f	C22H17N3OS2	403	118-120	64
5g	C17H15N3OS2	341	124-126	76
5h	C18H17N3OS2	355	116-118	73
5i	C19H19N3OS2	369	112-114	69
5j	C19H19N3OS2	369	110-112	63
5k	C20H21N3OS2	383	96-98	72
5l	C23H19N3OS2	417	124-126	64
5m	C16H11N3OS2 Br2	485	164-166	61
5n	C17H13N3OS2 Br2	499	148-150	60
5o	C18H15N3OS2 Br2	513	136-138	60
5p	C18H15N3OS2 Br2	513	122-124	59
5q	C19H17N3OS2 Br2	527	110-112	57
5r	C22H15N3OS2 Br2	561	160-162	62

Table 2: *In-vitro* anticancer activity of quinazolin-4(3*H*)-one dithiocarbamates

	Cell line (IC_{50} µM)[a]		
Compound	**Colo-205**	**K562**	**MDA-MB**
5a	61.10±1.5	30.0±1.2	61.10±2.0
5b	58.6±2.9	29.95±2.3	58.65±0.9
5c	26.0±1.8	22.3±1.9	56.38±2.1
5d	28.9±2.2	20.67±0.9	50.70±1.4
5e	23.95±1.9	18.98±0.3	28.00±1.8
5f	32.0±1.5	24.6±1.3	49.22±2.1
5i	29.2±0.9	25.7±1.9	54.0±1.2
5j	46.6±2.2	48.7±1.8	28.0±0.5
5k	22.6±1.9	28.0±1.2	52.0±1.9
5l	22.6±1.3	31.33±2.3	50.9±1.9
5m	28.1±0.9	26.3±2.1	29.6±1.2
5p	31.8±2.5	14.6±1.8	31.8±0.5
5q	31.5±2.1	25.7±2.3	31.2±2.2
5r	31.0±0.8	56.1±1.2	56.1±0.9
Cisplatin	13.6±1.4	12.3±1.5	14.7±0.9

a-Concentration required to inhibit cell growth by 50%. Data are presented as means±S.D(n=3

CONCLUSION

In conclusion a series of quinazolin-4(3*H*)-one linked dithiocarbamates have been synthesized, a few molecules showed significant antiproliferative activity against different cancer cell lines. More importantly, compound **(5p)** exhibited potential in vitro cytotoxic activity against k562 cancer cell lines, indicating that isopropyl side chain with dibromo substitution at position 6 and 8 of quinazolin-4(3*H*)-one contribute positively for the activity. The toxicity profiles of this potent molecule could be studied further to establish its safety and it could be an interesting candidate for further in vivo testing.

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