Pharmacophore 2014, Vol. 5 (5), 684-692 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

SYNTHESIS AND EVALUATION OF SOME NEW QUINAZOLINONES FOR THEIR PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

The present work is aimed to synthesize a new series of quinazolin-4(3H)-one derivatives with substituted dithiocarbamate side chain. The proposed derivatives were synthesized by reacting 3-aminoquinazolin-4(3H)-one with carbon disulphide and alkyl/aralkyl halides. All the structures of the final compounds were ascertained based on spectral studies (IR, ^{1}H-NMR, and Mass). The compounds were evaluated for *in vitro* cytotoxicity against MCF 7 human breast cancer cell lines at concentrations of 1µg/ml, 10 µg/ml and 50 µg/ml. The antibacterial activity was assayed against four different strains, *Escherichia coli, Klebsiella pneumonia* Gram-negative bacteria and *Bacillus subtilis, Staphylococcus aureus* Gram-positive bacteria. Among all the compounds tested, the compound 5l (X, X'=Br; R = -$CH_2C_6H_5NO_2$ (*m*)) showed 45% inhibition at 50 µg/ml in cytotoxic assay. The same compound 5l exhibited highest antibacterial activity with MIC of 16.4 µg/ml and 12.6 µg/ml against *E. coli* and *K. pneumonia* respectively. The compound 5k (X, X' = Br; R = $CH_2C_6H_5$) next in the order showed MIC of 27.6 µg/ml of 16.7 µg/ml against *B. subtilis* and *S. aureus* respectively.

Keywords: Quinazolin-4(3H)-One, Dithiocarbamate, Cytotoxicity, Antibacterial activity.

INTRODUCTION

The chemistry of quinazolin-4(3H)-one system has received an increasing interest because of its biological significance.[1] 4-(3H)-Quinazolinones are an important class of fused heterocyclic ring system with a wide range of biological activities such as antimicrobial[2], antitubercular[3], anti-inflammatory[4, 5], antitumor[6], antibacterial[7], antiviral and cytotoxic.[8,9] Numerous researches have shown that the quinazolin-4(3H)-one nucleus possesses potent activity against human cancer particularly by killing the cells in a tumor specific manner.[10] The nucleus also showed potent antimicrobial activity. Substitution at position N-3 of quinazolin-4(3H)-one has been associated with antimicrobial properties. Introduction of bromine or chlorine atom at position 6 and 8 improved their antimicrobial activities.[11] Dithiocarbamate derivatives are a common class of organic molecules with various valuable biological effects. They are well-known to be used as fungicides, antibiotics and anti-inflammatory agents and promote nitrogen monoxidum elimination from the body, as well as chelate heavy metals in the body.[12] In addition, dithiocarbamate derivatives brassinin and sulforamate were reported to have cancer chemopreventive activity.[13] Dithiocarbamate has been proved to be an effective pharmacophore with cancer chemopreventive and antitumor activity.[14] In our research programme, we have

incorporated dithiocarbamate moieties with 4-(3H)-quinazolinones. A series of 2-methyl-4(3H)-quinazolinones bearing various dithiocarbamate side chains were synthesized. Some of the derivatives with dibromo substitution at 6th and 8th position were synthesized. All these derivatives (5a-l) were evaluated for *in vitro* cytotoxic activity and antibacterial activity.

MATERIALS AND METHODS

Chemistry

All the chemicals for the synthesis of title compounds were obtained from Sigma Aldrich /Qualigens/ E-Merck. Melting points reported were recorded in open capillaries, using Toshniwal or Cintex melting point apparatus, expressed in ^{0}C and are uncorrected. ^{1}H NMR spectra were recorded on Avance 300 MHz instrument in $CDCl_3$ using TMS (tetra methyl silane) as the internal standard and chemical shift (δ) values are given parts per million along with coupling constant (J) values. The standard abbreviations s, d, dd, t and m refer to singlet, doublet, doublet of doublet, triplet, quartet and multiplet respectively. Electro Spray Ionization (ESI) Mass spectra were reported. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60-F (0.5 mm) plates. Visualization of the spots on TLC plates was achieved by dipping them in anisaldehyde solution & subsequent charring and expose to UV light in a chamber. Column chromatography was performed using silica gel (60 - 120 and 100 - 200 mesh).

Synthesis

Synthesis of 3,5-dibromo anthranilic acid (1b)[15]

Anthranilic acid was dissolved in glacial acetic acid in one conical flask. In another conical flask bromine was added to glacial acetic acid. Both flasks were cooled to 5-10^{0}C by keeping them in ice bath. Then the bromine in acetic acid was added to anthranilic acid in portion wise with continuous stirring. The separated solid was washed with water to remove the excess of bromine. Then the product 3,5-dibromo anthranilic acid was purified by recrystallization or by column chromatographic method. (**1b** m.p. 228-230^{0}C: lit 224-226^{0}C, Yield: 85%).

Synthesis of 2-methylbenzo [d] (1,3)oxazin-4-ones (2a-b)[16]

A mixture of unsubstituted/substituted anthranilic acid **(1a-b)** (0.01 mol) and acetic anhydride (10.2 ml; 0.1 mol) was refluxed on gentle flame (70-75^{0}C) for 2hrs. The excess of acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether in each case and kept aside for 1hr. The solid separated was filtered and dried. (**2a** m.p. 84-88^{0}C: lit 80-82^{0}C, Yield: 64%; **2b** m.p. 238-242^{0}C: lit 244-248^{0}C, Yield: 73%).

Note: The above products were highly unstable and proceeded with the next step immediately. The products were sensitive to water and extraction was done with organic solvents.

Synthesis of 3-amino-(unsubstituted/6, 8-dibromo)-2-methyl-3H-quinazolin-4-ones (3a-b)[16]

Appropriate 2-methyl-benzo [d] (1, 3) oxazin-4-one **(2a-b,** 0.01 mol.**)** was dissolved in ethanol and treated with hydrazine hydrate (0.03 mol) with continuous stirring. The addition was done in portion wise as the reaction was exothermic. Stirring was continued for 6 hrs and the separated solids were purified by column chromatography. (**3a** m.p. 138-146^{0}C: lit 140-142^{0}C, Yield: 71%; **3b** m.p. 214-218^{0}C: lit 220-222^{0}C, Yield: 86%).

Synthesis of (2-methyl-4-oxo-3H-quinazolin-3-yl) dithiocarbamic acid esters (5a-b)

To a vigorously stirred solution of 3-amino-2-methyl-3H-quinazolin-4-ones **(3a-b)** (0.0017 mol.) in 10 ml of N, N-dimethylformamide, anhydrous sodium phosphate (0.0019 mol.) was added. After 15 min. carbon disulphide (260 mg; 0.0034 mol. 0.24 ml) was added. The reaction mixture was allowed to stir for overnight. Then the reaction mixture **(4a-b)** was kept in ice bath until the temperature reached to 5-10^{o}C. To this, appropriate alkyl halides or aralkyl halides (0.0017 mol) was added and stirred for 2hrs. The reaction mixture was poured into ice cold water and the product was extracted with diethyl ether. The ether layer was separated and concentrated under reduced pressure. The crude products

obtained were purified by column chromatography.

By adopting the above general procedure compounds **(5a-l)** were prepared using 3-amino-6,8-dibromo/unsubstituted-2-methyl-3H-quinazolin-4-ones **(3a-b)** and appropriate alkyl/aralkyl halides *viz.,* 1-Bromoethane ; 1-Bromopropane ; 1-Chlorobutane ; 1-Bromopentane ; Isopentylbromide ; 1-Bromohexane ; Benzylchloride and *m*-Nitrobenzyl chloride. The structures of the compounds **(5a-l)** were ascertained based on their spectral data.

(2-Methyl-4-oxo-3H-quinazolin-3-yl) ethyl dithiocarbamate (5a)

IR DATA: 3494.37 (N-H str); 3104 (Aromatic C-H); 2923.25, 2853.48 (Aliphatic C-H); 1685.63 (C=O str); 1604.11 (C=S); 1469.50 (N-H bend); 1302.04 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J=8.30, Ar-H, C-5); 7.72 (t, 1H, J=7.55, Ar-H, C-6); 7.63 (d, 1H, J=8.30, Ar-H, C-8); 7.38 (t, 1H, J=7.55, Ar-H, C-7); 3.20 (q, 2H, J=7.55, S–C***H*****$_2$**– CH_3); 2.58 (s, 3H, C-2 methyl); 1.30 (t, 3H, J=7.55, S–CH_2–C***H*****$_3$**).

Mass :(ESI-MS) *(m/z):* 279 (M^++H)

(2-Methyl-4-oxo-3H-quinazolin-3-yl) propyl dithiocarbamate (5b)

IR DATA: 3451.23 (N-H str); 3178.42 (Aromatic C-H); 2962.34, 2926.13 (Aliphatic C-H); 1683.81 (C=O str); 1608.72 (C=S); 1468.94 (N-H bend); 1295.13 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J=7.55, Ar-H, C-5); 7.72 (t, 1H, J=6.79, Ar-H, C-6); 7.62 (d, 1H, J=7.55, Ar-H, C-8); 7.38 (t, 1H, J=6.79, Ar-H, C-7); 3.23-3.13 (t, 2H, J=7.55, S-C***H*****$_2$**–C_2H_5); 2.58 (s, 3H, C-2 met); 1.72-1.60 (m, 2H, S-CH_2–C***H*****$_2$**–CH_3); 0.97 (t, 3H, J=7.55, S-C_2H_4– C***H*****$_3$**).

Mass :(ESI-MS) *(m/z*): 294 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) butyl dithiocarbamate (5c)

IR DATA: 3456.97 (N-H str); 3178.74 (Aromatic C-H); 2958.10, 2925.63, 2858.69 (Aliphatic C-H); 1688.07 (C=O str); 1608.40 (C=S); 1468.35 (N-H bend); 1295.00 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.14 (d, 1H, J=7.80, Ar-H, C-5); 7.70 (t, 1H, J=6.83, Ar-H, C-6); 7.61 (d, 1H, J=7.80, Ar-H, C-8); 7.36 (t, 1H, J=6.83, Ar-H, C-7); 3.17 (t, 2H, J=6.83, S-C***H*****$_2$**–CH_2–CH_2–CH_3); 2.56 (s, 3H, C-2 methyl); 1.65-1.57 (m, 2H, S-CH_2–C***H*****$_2$**–CH_2–CH_3); 1.41-1.33 (m, 2H, S-CH_2–CH_2–C***H*****$_2$**–CH_3); 0.90 (t, 3H, J=7.55, S-CH_2–CH_2–CH_2–C***H*****$_3$**).

Mass :(ESI-MS) *(m/z):* 308 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) pentyl dithiocarbamate (5d)

IR DATA**:** 3539.76 (N-H str); 3206.31 (Aromatic C-H); 3008.69, 2925.98 (Aliphatic C-H); 1664.80 (C=O str); 1601.99 (C=S); 1468.51 (N-H bend); 1250.12 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.12 (d, 1H, J=7.55, Ar-H, C-5); 7.72 (t, 1H, J=6.83, Ar-H, C-6); 7.64(d, 1H, J=7.55, Ar-H, C-8); 7.36 (t, 1H, J=6.83, Ar-H, C-6); 3.21 (t, 2H, J=6.83, S-C***H*****$_2$**–CH_2– CH_2–CH_2–CH_3); 2.56 (s, 3H, C-2 methyl); 1.72-1.56 (m, 6H, S-CH_2–C***H*****$_2$**– C***H*****$_2$**–C***H*****$_2$**–CH_3) ; 0.87 (t, 3H, J=7.55, S-CH_2–CH_2– CH_2–CH_2–C***H*****$_3$**).

Mass :(ESI-MS) *(m/z):* 322 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) isopentyl dithiocarbamate (5e)

IR DATA: 3358.13 (N-H str); 3189.21 (Aromatic C-H); 2956.04, 2866.06 (Aliphatic C-H); 1676.61 (C=O str); 1608.99 (C=S); 1469.58 (N-H bend); 1262.73 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, J=8.30, Ar-H, C-5) ; 7.75 (t, 1H, J=7.55, Ar-H, C-6); 7.64 (d, 1H, J=8.30, Ar-H, C-8); 7.44 (t, 1H, J=7.55, Ar-H, C-7); 3.33-3.16 (t, 2H, J=6.79, S-C***H*****$_2$**–CH_2–CH (CH_3)–CH_3); 2.59 (s, 3H, C-2, methyl); 1.75-1.34 (m, 3H, S-CH_2–C***H*****$_2$**–C***H*** (CH_3)–CH_3); 0.93 (d, 6H, J=6.79, S-CH_2–CH_2–CH (C***H*****$_3$**)–C***H*****$_3$**).

Mass :(ESI-MS) *(m/z):* 322 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) hexyl dithiocarbamate (5f)

IR DATA: 3433.58 (N-H str); 3179.93 (Aromatic C-H); 2926.16, 2856.68 (Aliphatic C-H); 1682.87 (C=O str); 1609.48 (C=S); 1468.63 (N-H bend); 1294.21 (C-N).

^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J=8.30, Ar-H, C-5); 7.70 (t, 1H, J=6.79, Ar-H, C-6); 7.63 (d,

1H, J=8.30, Ar-H, C-8); 7.37 (t, 1H, J=6.79, Ar-H, C-7); 3.23-3.13 (t, 2H, J=6.04, S-C***H₂***–CH_2–CH_2–CH_2–CH_3); 2.58 (s, 3H, C-2 methyl); 1.68-1.54 (m, 2H, S-CH_2–CH_2–CH_2–CH_2–C***H₂***–CH_3); 1.39-1.25 (m, 6H, S-CH_2–C***H₂***–C***H₂***–C***H₂***–CH_2–CH_3); 0.88 (t, 3H, J=6.79, S-CH_2–CH_2–CH_2–CH_2–CH_2–C***H₃***).
Mass :(ESI-MS) *(m/z):* 336 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) benzyl dithiocarbamate (5g)
IR DATA: 3328.52 (N-H str); 3164.18 (Aromatic C-H); 2967.59, 2926.19 (Aliphatic C-H); 1663.94 (C=O str); 1605.73 (C=S); 1465.57 (N-H bend); 1293.53 (C-N).
^{1}H NMR ($CDCl_3$): δ 8.14(d, 1H, J=7.34, Ar-H, C-5); 7.76 (t, 1H, J=6.29, Ar-H, C-6); 7.61 (d, 1H, J=7.34, Ar-H, C-8); 7.46 (t, 1H, J=6.29, Ar-H, C-7); 7.44-7.21 (m, 5H, phenyl-C_6***H₅***); 4.63-4.56 (m, 2H, S-C***H₂***-) ; 2.54 (s, 3H, C-2 methyl).
Mass :(ESI-MS) (*m/z*): 342 (M^++H).

(2-Methyl-4-oxo-3H-quinazolin-3-yl) m-Nitro benzyl dithiocarbamate (5h)
IR DATA: 3315.74 (N-H str); 3179.93 (Aromatic C-H); 2926.80, 2856.68 (Aliphatic C-H); 1669.60 (C=O str); 1605.47 (C=S); 1345.88 (N-H bend); 1253.67 (C-N).
^{1}H NMR ($CDCl_3$): δ 8.25 - 8.17(m, 2H, Ar-H); 7.78 - 7.68 (m, 2H, Ar-H); 7.66 - 7.59 (m, 2H, phenyl); 7.51 - 7.42 (m, 2H, phenyl); 4.84 (s, 2H, S-CH_2-); 2.70 (s, 3H, C-2 methyl).
Mass :(ESI-MS) *(m/z):* 387 (M^++H).

(2-Methyl- 6, 8-dibromo-4(3H)-quinazolinon-3yl) ethyl dithiocarbamate (5i):
IR DATA: 3424.36(N-H str); 3124.60 (Aromatic C-H); 2892.65, 2853.48 (Aliphatic C-H); 1645.23 (C=O str); 1611 (C=S); 1443.70 (N-H bend); 1314 (C-N); 716.24 (C-Br str).
^{1}H NMR ($CDCl_3$): δ 8.32 (d, 1H, Ar-H); 8.07 (d, 1H, Ar-H); 3.12 - 3.02 (q, 2H, S–C***H₂***–CH_3); 2.46 (s, 3H, C-2 methyl); 1.50 (t, 3H, S–CH_2–C***H₃***).
Mass :(ESI-MS) *(m/z):* 437 (M^+).

(2-Methyl-6, 8-dibromo-4-oxo-3H-quinazolin-3-yl) propyl dithiocarbamate (5j):
IR DATA: 3442.73 (N-H str); 3164.60 (Aromatic C-H); 2923.35, 2856.39 (Aliphatic C-H); 1661.37 (C=O str); 1600.81(C=S); 1440.87 (N-H bend); 1238.77 (C-N); 713.49 (C-Br str).
^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, J=2.26, Ar-H); 8.14 (d, 1H, J=2.26, Ar-H); 3.29-3.23 (t, 2H, J=7.55, S-C***H₂***–CH_2–CH_3); 2.63 (s, 3H, C-2 methyl); 1.79-1.70 (m, 2H, S-CH_2–C***H₂***–CH_3); 1.04 (t, 3H, J=7.55, S-CH_2–CH_2–C***H₃***).
Mass :(ESI-MS) *(m/z):* 451 (M^+).

(2-Methyl- 6, 8-dibromo-4-oxo-3H-quinazolin-3-yl) benzyl dithiocarbamate (5k):
IR DATA: 3419.14 (N-H str); 3081.36 (Ar C-H); 3026.36, 2934.31 (Aliphatic C-H); 1684.26 (C=O str); 1589.47 (C=S); 1442.23 (N-H bend); 1312.76 (C-N); 693.97 (C-Br str).
^{1}H NMR ($CDCl_3$): δ 8.28 (d, 1H, Ar-H); 8.13 (d, 1H, Ar-H); 7.34-7.27 (m, 5H, C_6***H₅***); 4.54 - 4.49 (s, 2H, S-C***H₂***); 2.64 (s, 3H, C-2 methyl).
Mass :(ESI-MS) *(m/z):* 499 (M^+).

(2-Methyl- 6, 8-dibromo-4-oxo-3H-quinazolin-3-yl) m-nitro benzyl dithiocarbamate (5l):
IR DATA: 3415.40 (N-H str); 3184.58 (Aromatic C-H); 2865.80 (Aliphatic C-H); 1673.26 (C=O str); 1595.73 (C=S); 1415.88 (N-H bend); 1183.67 (C-N); 703.72 (C-Br str).
^{1}H NMR ($CDCl_3$): δ 8.16 (d, 1H, C-6); 8.09 (d, 1H, C-8); 7.98-7.62 (m, 2H, phenyl); 7.36 - 7.15 (m, 2H, phenyl); 4.64 (s, 2H, S-C***H₂***); 2.90 (s, 3H, C-2 methyl).
Mass :(ESI-MS) *(m/z):* 544 (M^+).

Cytotoxic Activity

The synthesized compounds (5a) to (5l) were tested against MCF-7 human breast cancer cell lines for their growth inhibitory activity. The cytotoxic activity was measured spectrophotometrically by "MTT assay" method.

Preparation of Test Compounds

Solutions of the test compounds were prepared by dissolving the weighed quantity of the compounds in a sufficient quantity of dimethylsulfoxide (DMSO). (1 µg/ml, 10 µg/ml and 50 µg/ml).

Preparation of Control Solutions

Solutions containing only phosphate buffer saline and dimethylsulfoxide at identical dilutions were prepared and used as controls.

MTT Assay Procedure

The MTT assay was based on the reduction of the yellow colored 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase enzyme of metabolically active cells to a blue formazan. MCF-7 cell lines were plated in 96-well plates (100 µl) and the test compounds **(5a-l)** were added in increasing dose ranging from 1 µg/ml, 10 µg/ml and 50 µg/ml. These plates were incubated for 0-48 hrs at 37^0C. After, each well of the micro titer plate was added 10 µl of a solution of MTT (5 mg/ml) in phosphate-buffer saline. The trays were further incubated at 37^0C in a CO_2 incubator for additional 2hrs and 100 µl of DMSO was added. A fixed volume of medium was then removed from each cup without disturbing the MCF-7 cells clusters containing the formazan crystals. Solubilization of the formazan crystals was achieved by adding 100 µl of 10% (v/v) triton X-100 in acidified isopropanol (2 ml concentrated HCl per 500 ml solvent) using M-96 washer. Complete dissolution of the fomazan crystals could be obtained after the trays had been placed on a plate shaker for 10 min. Finally, the absorbance was read in spectrophotometer at wavelength of 562 nm. A blank was carried out directly on the micro titer plates by omitting the drug (control). The absorbance obtained for the test compounds were compared with the absorbance of control.

ANTIBACTERIAL ACTIVITY

The synthesized compounds (5a-l) were assayed for antibacterial activity against Gram-positive bacteria *Bacillus subtilis, Staphylococcus aureus and* Gram-negative bacteria *Escherichia coli, Klebsiella pneumonia.* The minimum inhibitory concentration (MIC) was measured by using Serial dilution method.

Serial Dilution Method

In this method, serial dilution of the standard and test compounds were made in a liquid medium, which was inoculated separately with four strains of bacteria and incubated at 37^0C for 24 hrs. The lowest concentration (highest dilution) of the compound preventing the appearance of turbidity is considered to be the *minimal inhibitory concentration* (MIC). At this dilution the compound is known to be "Bacteriostatic".

The method is carried under aseptic conditions. Sterile, capped, numbered tubes from 1-9 were taken and added 1 ml of sterile broth to each of them. To the first tube, 2 ml of the stock solution (150 µg/ml) was added and then transferred 1ml from first tube to 2nd tube. The contents were mixed and 1ml of it was transferred to the 3rd tube. Likewise dilutions were continued and 1ml from 8th tube was discarded. The 9th tube served as control. The final concentration of the compound was now one-half of the original concentration in each tube. These tubes were incubated at 37^0C for 24 hrs. The sub-cultures were prepared by suspending several colonies of the culture that were to be tested in 5ml of nutrient broth to give a slightly turbid suspension. This suspension was diluted by aseptically pipetting 0.2 ml of suspension into 40 ml of nutrient broth. Stock solution of the test compounds were prepared by dissolving 10 mg each in dimethylsulfoxide (DMSO – 10 ml). Further required dilutions were made to prepare 150 µg/ml. A reference standard was prepared by dissolving weighed quantities of Ampicillin in DMSO to obtain 50 µg/ml.

RESULTS AND DISCUSSION

Cytotoxic Activity

The synthesized compounds were tested for *in vitro* cytotoxic activity against MCF-7 human breast cancer cell lines by "MTT assay" method. Among the compounds tested, the compound 5l (X, X'=*6, 8-dibromo; R=m-nitro benzyl*) showed highest activity with 45% inhibition at 50 µg/ml. The aromatic substituted compounds 5g (R=*benzyl*) and 5h (R=*m-nitro benzyl*) exhibited potent activity with 29% and 44% inhibition respectively than the alkyl substituted compounds. The alkyl substituted compounds 5a (R=*ethyl*), 5b (R=*propyl*), 5c (R=*butyl*), 5d (R=*pentyl*) exhibited increasing order of activity with 20%, 21%, 25% & 26% inhibition with increase in the chain length from C-2 to C-5. Further increase in the chain length led to

compound 5f (R=*hexyl*) with decrease in the activity (17%).

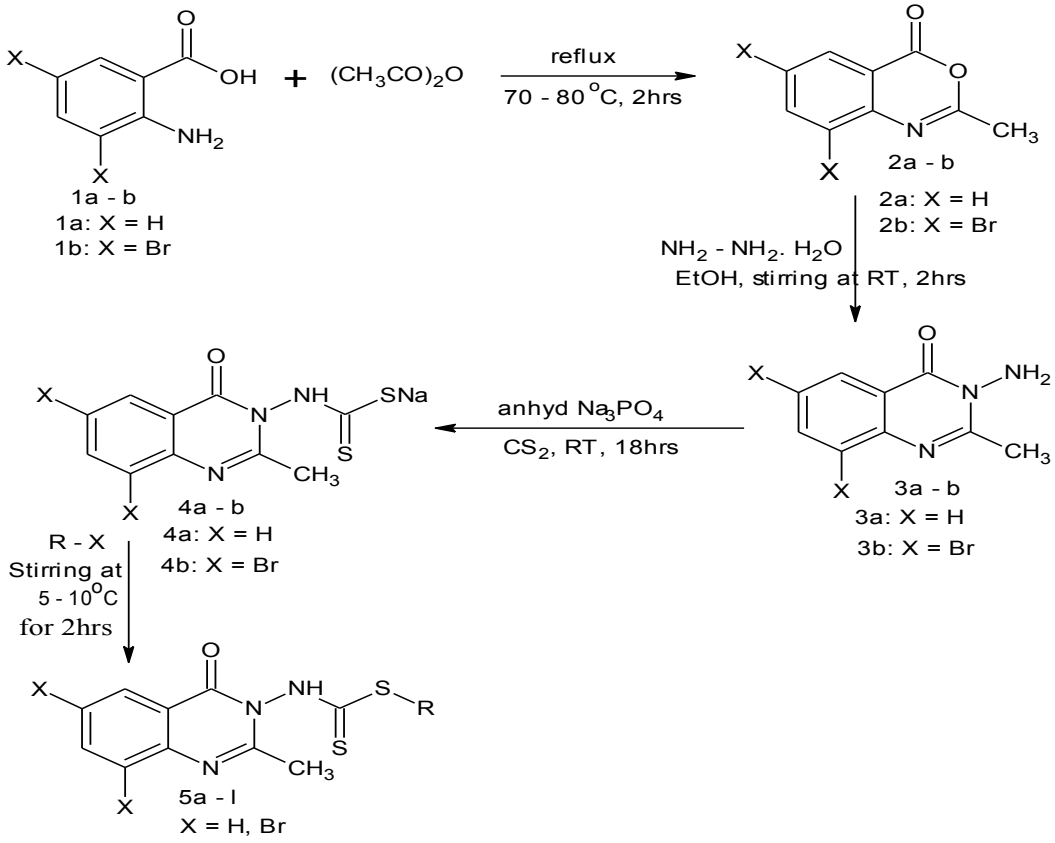
The substitution on quinazolinone ring led to compounds 5i, 5j, 5k & 5l. The compound 5k (X, X'=*6, 8-dibromo; R=benzyl*) showed 40% inhibition whereas the compound 5g (R=*benzyl*) showed 29% inhition. In the same series compound 5j (X, X'=*6, 8-dibromo; R=propyl*) showed 23% inhibition and 5b (R=*propyl*) showed 21% inhibition at the 50 µg/ml. Thus the dibromo substitution resulted in slight increase in the potency.

Antibacterial Activity

The antibacterial activity data revealed that the title compounds showed significant activity. The compounds 5a, 5b & 5i were equipotent and 5g, 5k & 5l were more potent when compared with the standard Ampicillin. The compound 5l (X, X' = Br; R = -$CH_2C_6H_5NO_2$(*m*)) showed highest activity towards gram negative bacteria with MIC 16.4 µg/ml and 12.6 µg/ml against *E. coli* and *K. pneumonia* respectively and the compound 5k (X, X' = Br; R = $CH_2C_6H_5$) showed potent activity against gram positive bacteria with MIC 27.6 µg/ml and 16.7 µg/ml against *B. subtilis* and *S. aureus* respectively.

CONCLUSION

A series of 3-amino-quinazolin-4(3H)-one derivatives with dithiocarbamate side chain and bromine at 6, 8-positions were synthesized and screened for *in vitro* cytotoxic and antimicrobial activity. All the derivatives showed significant activity. Substitution of aliphatic alkyl side chains like ethyl, propyl, butyl, pentyl, isopentyl and hexyl on the dithiocarbamate showed varied anticancer and antibacterial activity. Substitution of aralkyl side chains like benzyl and m-nitro benzyl on the dithiocarbamate showed increase in cytotoxic and anti-microbial activity, when compared to compounds with aliphatic substitution. Substitution of the quinazolinone ring with bromine at 6, 8- positions resulted in retention of cytotoxic activity and increase in anti-microbial activity.



X= H, Br; R = C_2H_5; n-C_3H_7; n-C_4H_9;n-C_5H_{11}; *iso*-C_5H_{11}; n-C_6H_{13}; $CH_2C_6H_5$; $CH_2C_6H_4NO_2$*(m)*.

Scheme 1

Table 1: Physical data of the synthesized compounds (5a-l)

Compound	Substitution		Chemical Formula	Molecular Weight	Melting Point(^{0}c)	% Yield
	X	**R**				
5a	H	C_2H_5	$C_{12}H_{13}N_3OS_2$	279	104-108	55
5b	H	C_3H_7	$C_{13}H_{15}N_3OS_2$	293	113-119	62.55
5c	H	C_4H_9	$C_{14}H_{17}N_3OS_2$	307	123-128	66.2
5d	H	C_5H_{11}	$C_{15}H_{19}N_3OS_2$	321	-----	68.73
5e	H	(*iso*)C_5H_{11}	$C_{15}H_{19}N_3OS_2$	321	137-144	74.55
5f	H	C_6H_{13}	$C_{16}H_{21}N_3OS_2$	335	-----	68.3
5g	H	$CH_2C_6H_5$	$C_{17}H_{15}N_3OS_2$	341	177-182	69.7
5h	H	$CH_2\,C_6H_4\,NO_2$(*m*)	$C_{17}H_{14}N_4O_3S_2$	386	183-189	64.55
5i	Br	C_2H_5	$C_{12}H_{11}N_3OS_2Br_2$	437	157-165	60.56
5j	Br	C_3H_7	$C_{13}H_{13}N_3OS_2Br_2$	451	173-179	62
5k	Br	$CH_2C_6H_5$	$C_{17}H_{13}N_3OS_2Br_2$	499	187-192	68.4
5l	Br	$CH_2\,C_6H_4\,NO_2$*(m)*	$C_{17}H_{12}N_4O_3S_2Br_2$	544	208-212	63.93

Table 2: The cytotoxic activity of compounds (5a-l)

Compound	**Concentration (Ug/Ml)**	**% Inhibition**
5a	1	15.58112979
	10	17.91863511
	50	20.65915859
5b	1	15.99310391
	10	18.06193046
	50	21.17263357
5c	1	19.96059378
	10	22.09882901
	50	25.91630656
5d	1	21.40847383
	10	23.50939256
	50	26.09542574
5e	1	18.96648232
	10	21.37339632
	50	24.54007419
5f	1	11.38675563
	10	14.22206301
	50	17.56338207
5g	1	25.3461105
	10	27.13655599
	50	29.41510124
5h	1	35.31409295
	10	38.36061169
	50	44.15959519
5i	NT	NT
5j	1	20.28897895
	10	22.59588474

	50	23.50118293
5k	1	33.69007904
	10	37.38217316
	50	40.79215458
5l	1	37.1560352
	10	41.30488324
	50	45.27311944
Control		0
DMSO		0

NT = Not tested

Table 3: The antibacterial activity (MIC, ug/ml) of compounds (5a-l)

Compound	Antibacterial activity MIC (ug/ml)			
	E. coli	*K.pneumoniae*	*B.subtilis*	*S.aureus*
5a	29.5	27.6	76.2	56.3
5b	34.6	88.3	93.4	67.4
5c	106.4	102.5	97.6	62.8
5d	107.6	98.4	102.8	97.3
5e	103.8	96.8	104.5	88.4
5f	82.6	74.2	107.2	103.5
5g	19.5	18.5	36.8	58.6
5h	96.2	43.7	42.3	73.2
5i	36.8	29.3	38.3	43.4
5j	80.7	52.8	40	45.8
5k	17.5	14.7	27.6	16.7
5l	16.4	12.6	32.6	24.9
Ampicillin	30.5	58.2	23.6	19.3

ACKNOWLEDGEMENTS

The author N. Sukanya is thankful to IICT-Hyderabad, Telangana, India for providing laboratory facilities, spectral studies and pharmacological studies and to UGC (University Grant Commission), New Delhi for providing financial assistance in the form of Fellowship during my course.

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Cite This Article: Achaiah, Garlapati and Sukanya, N (2014), "Synthesis and evaluation of some new quinazolinones for their pharmacological activities", ***Pharmacophore***, Vol. 5 (5), 684-692.