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# Synthesis and Antimicrobial Evaluation of some new Quinazoline based Thiosemicarbazones

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**Abstract:** A series of 1-[2-hydroxyl–5–(substituted phenyl)diazyl benzylidene-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) thiourea (III $TS_1$ – $TS_7$ **)** have been synthesized by the reaction of substituted 2- hydroxyl 5-(phenyldiazenyl) benzaldehyde (I) and quinazoline derivative of thiosemicarbazide (II) in DMF. Structure of all synthesized compounds was established on the basis of elemental analysis and IR, NMR spectroscopic data. The antimicrobial activities of the synthesized compounds were evaluated by screening on different human pathogens using the disc diffusion assay.
**Keywords:** Quinazoline , Thiosemicabazide, Thiosemicarbazone, Antimicrobial Screening.

## Introduction

In spite of a large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotics resistance developed in the last decades, has created a substantial medical need for new classes of antimicrobial agents[1-5]. Quinazoline derivatives have a therapeutic benefit as an anti - invasive agents with potential activity in early and advanced solid tumors, metastatic bone disease and leukemias[6-10]. Some of the known quinazoline derivative are reported to exhibit remarkable anticancer activity[11]. In addition several quinazoline derivatives posses diverse biological activities viz. antimicrobial[12], anticonvulsant[13], hyponotics[14], anti-inflammatory[15], diuretics antihypertensive[16,] antituberculor[17] etc. Thiosemicarbazones possessing both–N-C=S and –CH=N- moieties as a pharmacophore. Furthermore, interest in the chemistry, synthesis and biology of these pharmacophore continues to be fuelled by their wide range of biological properties viz. antifungal, antibacterial, antimalarial, antiviral, antitubercular, anticonvulsant, antitumor activities[18-20].

## Experimental Methods

The synthetic route to the required compounds is outlined in scheme- 1. For the synthesis of the titled compounds, substituted 2- hydroxyl 5-(phenyl

diazenyl) benzaldehyde (**I**) required as a starting material was prepared by the diazotization and coupling method and quinazoline derivative of thiosemicarbazide (**II**) was prepared by reacting benzoylated anthranilic acid and thiosemicarbazide in the presence of ethanol. The reaction of equimolar quantities of (**I**) with (**II**) in the presence of DMF resulted in the formation of compounds **(III $TS_1$- $TS_7$).**

**Synthesis of substituted 2- hydroxyl 5- (phenyldiazenyl) benzaldehyde (I).**

Substituted primary amine (0.01M) were dissolved in aqueous hydrochloric acid (28mL, 6N) and mechanically stirred at 0 - 5°C. A cold solution of sodium nitrite (5gm/10 mL water ) was added drop wise to the constantly stirred reaction mixture. The diazotized solution was immediately added in small portion to salicylaldehyde ( 5 mL dissolved in 40 mL,6N NaOH), with constant stirring at 0-5°C. The stirring was continued for 4h. The solid obtained was filtered under suction washed with cold water and recrytallised from glacial acetic acid.

**Synthesis of quinazoline derivatives of thio semicarbazide (II)**

Thiosemicarbazide has been synthesized in two steps.

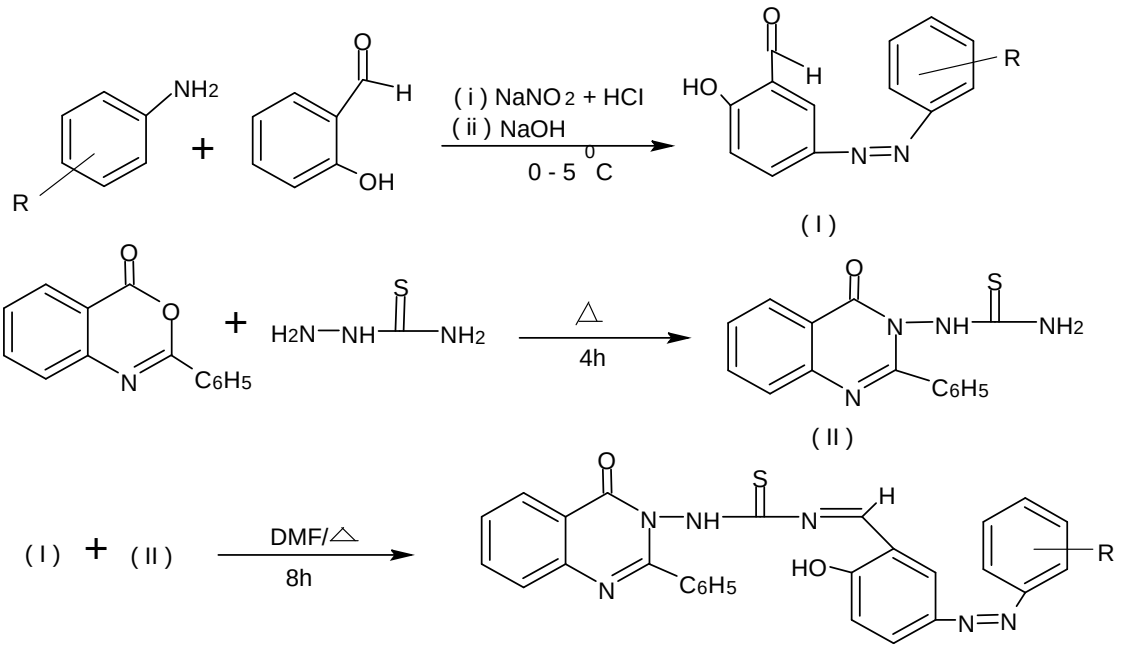
**1) Synthesis of 2- phenyl 3,1- benzoxazine – 4 (3H) – one**

To a stirred solution of anthranilic acid (0.01M) in pyridine (0.01M), benzoyl chloride (0.01M) were added drop wise maintaining the temperature near 8° C for 1h. Reaction mixture was stirred for another 2 hour at room temperature while stirring a solid product separates out whole reaction mixture was neutralized with $NaHCO_3$ solution. A pale yellow solid deposited which was filtered, washed with water and recrystallised from ethanol.

**2) Synthesis of N - [ 2- phenyl-4 (3H )- oxo- quinazoline-3-yl ] thiourea**

2- phenyl 3,1- benzoxazine – 4 (3H) – one (0.01M) were dissolved in ethanol and thiosemicarbazide (0.01M) in ethanol were added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 4 hours and after cooling at room temperature a crystalline product was obtained. It was filtered and recrystallised from ethanol to yield needle shaped shiny white crystals.

**SCHEME**




(III $TS_1$- $TS_7$)

**Synthesis of 1-[2-hydroxyl–5–(Substituted phenyl) diazyl benzylidene -3- (4-oxo-2- phenyl quinazolin-3(4H) - yl)thiourea (III)**

A mixture of the appropriate, 2-hydroxy–5–(phenyldiazenyl) benzaldehyde (**I**)(0.01M) and N - [ 2- phenyl-4 (3H )- oxo-quinazoline-3-yl ] thiourea (**II**) (0.01M) were refluxed for 8h in DMF (30 mL). The mixture was then cooled in an ice bath and the product separated was repeatedly washed with water followed by ethanol and recrystallised from diethyl ether.

**Compound No: $TS_1$**

IR (KBr)ν $cm^{-1}$ : 3427 (-OH), 3224(-NH ), 3066 (Ar C-H), 1604 ( C=O), 1514 (-CH=N-), 1490(-N=N-), 1271(-C=S ). $^1$HNMR (DMSO) δ in ppm: 12.20(s, 1H, NH ) ,8.73( s, 1H, -CH=N-), 7.19-8.07( m, Ar C-H), 4.0(-OH), 2.4-3.05 ( s, $C_6H_5$ ).

**Compound No: $TS_3$**

IR (KBr)ν $cm^{-1}$ : 3428 (-OH), 3220(-NH ), 3056 (Ar C-H), 1650( C=O), 1515 (-CH=N-), 1495(-N=N-),1338 ($NO_2$), 1270(-C=S ). $^1$HNMR (DMSO) δ in ppm: 12.21(s, 1H, NH), 8.70 ( s, 1H, -CH=N-), 7.19-8.07 ( m, Ar C-H), 4.4(-OH), 2.4-3.05(s,$C_6H_5$ ).

**Compound No: $TS_5$**

IR (KBr)ν $cm^{-1}$ : 3427 (-OH), 3222(-NH ), 3050 (Ar C-H), 1655( C=O), 1510 (-CH=N-), 1493(-N=N-), 1260(-C=S ). $^1$HNMR (DMSO) δ in ppm: 12.22 (s, 1H, NH) ,8.77 ( s, 1H, -CH=N-), 7.19-8.07( m, Ar C-H), 4.5(-OH), 3.4(s,3H, $OCH_3$ ) 2.4-3.05 ( s, $C_6H_5$ ).

**Compound No: $TS_7$**

IR (KBr)ν $cm^{-1}$ : 3427 (-OH), 3223(-NH ), 3064 (Ar C-H), 1620 ( C=O), 1512 (-CH=N-), 1488(-N=N-), 1272(-C=S ), 754( C-Cl) . $^1$HNMR (DMSO) δ in ppm: 12.22 (s, 1H, NH), 8.72 ( s, 1H, -CH=N-), 7.19-8.07( m, Ar C-H), 4.3(-OH),) 2.4-3.05(s,$C_6H_5$ ).

All melting points were determined in open capillaries and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck) with Benzene : Ethanol (5:1). Spectroscopic data were recorded using following instruments-IR: Shimadzu (FTIR) spectrophotometer, NMR : Bruker DRX 300 (300 MHz, FT NMR) and elemental ( C, H, N ) analysis.

**Antimicrobial Screening**

All the synthesised compounds were screened for their in-vitro antimicrobial activity against 24h old cultures of bacterial and fungal pathogens. Antimicrobial activity was determined against Escherichia coli, Salmonella typhimurium, Klebisiella pneumoniae and Aspergillus niger, Aspergillus fumigatus, Curvularia lunata strains using the disc diffusion assay. For this, a sterile filter paper disc (5 mm) impregnated with fixed doses (600 µg/mL) of the synthesized compounds under investigation were placed upon the seeded petridishes. Similar disc were prepared for the standard drugs, chloramphenicol, fluconazole and the solvent control, dimethyl formamide. The plates were incubated for 24h at 37˚C for the bacterial and fungal strains. The zone of inhibition, observed around the disc after incubation was measured. The results are represented in Table 2.

**Table 1 Physical parameters of newly synthesized compounds**

| compounds | R | Molecular Formula | Molecular Weight | M.P.° C | % Yield |
|---|---|---|---|---|---|
| III $TS_1$ | -H | $C_{28}H_{20}O_2N_6S$ | 504.56 | 202 | 65% |
| III $TS_2$ | p - $NO_2$ | $C_{28}H_{19}O_5N_7S$ | 549.56 | 200 | 42 % |
| III $TS_3$ | m – $NO_2$ | $C_{28}H_{19}O_5N_7S$ | 549.56 | 198 | 54 % |
| III $TS_4$ | p –$OCH_3$ | $C_{29}H_{22}O_4N_6S$ | 534.58 | 146 | 55% |
| III $TS_5$ | m –$OCH_3$ | $C_{29}H_{22}O_4N_6S$ | 534.58 | 148 | 60% |
| III $TS_6$ | p-Cl | $C_{28}H_{19}O_2N_5SCl$ | 539.00 | 132 | 48% |
| III $TS_7$ | m -Cl | $C_{28}H_{19}O_2N_5SCl$ | 539.00 | 138 | 52% |

**Table 2 Antimicrobial data of the compounds ( III $TS_1$ - $TS_7$ )**

| Comp | R | *E.coli* | *S.typhimurium* | *K.pneumoniae* | *A. niger* | *A. fumigatus* | *C. lunata* |
|---|---|---|---|---|---|---|---|
| IV $TS_1$ | -H | 04 | 08 | 09 | 05 | 07 | 09 |
| IV $TS_2$ | p - $NO_2$ | 11 | 13 | 16 | 10 | 12 | 15 |
| IV $TS_3$ | m – $NO_2$ | 10 | 11 | 14 | 08 | 08 | 10 |
| IV $TS_4$ | p –$OCH_3$ | 06 | 09 | 12 | 05 | 06 | 08 |
| IV $TS_5$ | m –$OCH_3$ | 05 | 08 | 11 | 05 | 05 | 07 |
| IV $TS_6$ | P -Cl | 06 | 09 | 13 | 06 | 09 | 10 |
| IV $TS_7$ | m -Cl | 05 | 08 | 12 | 06 | 08 | 09 |
| Chloramphenicol | | 26 | 28 | 30 | - | - | - |
| Fluconazole | | - | - | - | 20 | 22 | 24 |

600 µg/mL
Zone of inhibition in ( mm. )

## Results and discussion

In the IR spectra, some significant stretching bands due to –OH and –C=O, -N=N-, and–C=S, were observed at 3427 -3242, 1664-1604, 1495-1488 and 1272-1260, respectively. The specific band for thiosemicarbazones (-CH=N-), was observed at 1515-1510 $cm^{-1}$. In the $^1$NMR spectra, the signal due (-CH=N-), protons present in all compounds appeared at 8.70-8.77ppm as a siglet. The NHC=S and, -OH protons were observed at 12.20 - 12.22, and 4.0-4.5 ppm, respectively. All the aromatic protons were observed in the expected regions.
The antimicrobial activities of the synthesized compounds were screened *in vitro* using the Disc Diffusion technique against different human pathogens at 600 µg /mL. showed moderate activity (Table 2). Compounds $TS_2$ & $TS_2$ having p-Nitro and m-Nitro substituents showed marked activity against *Klebisiella pneumonia* and *Curvularia lunata.* All the compounds showed moderate activity against *Aspergillus fumigatus* and minimum to *Escherichia coli.*

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