# A CONVENIENT WAY FOR THE PREPARATION OF NOVEL THIOUREA DERIVATIVES CONTAINING BIOLOGICALLY ACTIVE QUINAZOLINE MOIETY

**Sohail Saeed[a,b]* and Rizwan Hussain[b]**

**Keywords:** Heterocyclic thiourea derivatives, quinazolin-4(3H)-one moiety, phenyl isothiocyanates

A series of new thiourea derivatives containing quinazoline-4(3H)-one framework (**3a-d**) was successfully synthesized and characterized by IR, $^{1}$H NMR, $^{13}$C NMR spectroscopy, ESI mass spectrometry and elemental analysis. Variation in the functional group at the phenyl ring led to set of compounds bearing quinazoline-4(3H)-one accommodated substituted phenyl thioureas.

Corresponding Authors
Tel: + 0092-51 - 9250081
Fax: + 0092-51 - 9250081
E-Mail: sohail262001@yahoo.com
[a] Department of Chemistry, Research Complex, Allama Iqbal Open University, Islamabad-44000, Pakistan
[b] National Engineering & Scientific Commission, P.O. Box. 2801, Islamabad, Pakistan

## Introduction

Thioureas are potentially very versatile ligands, able to coordinate to a range of metal centers as neutral ligands, monoanions or dianions.[1-9] In addition, the oxygen, nitrogen and sulfur donor atoms provide a multitude of bonding possibilities. The coordination chemistry of substituted thioureas has led to some interesting practical applications, including liquid-liquid extraction, pre-concentration and highly efficient chromatographic separation, fluorimetric detection of the platinum group metals, and the selective on-line pre-concentration of ultra-traces of Pd, followed by its determination using graphite furnace atom absorption spectrometry.[10, 11]

Thiourea and its derivatives have found extensive applications in the fields of medicine, agriculture and analytical chemistry. They are known to exhibit a wide variety of biological activities such as antiviral, antibacterial, antifungal,[12] antitubercular, herbicidal, insecticidal,[13] and to act as chelating agents,[14] in catalysis,[15] in anion recognition [16] and to play a role in some epoxy resin curing agents containing amino functional groups.[12]

Substituted thioureas are an important class of compounds, precursors or intermediates towards the synthesis of a variety of heterocyclic systems such as imidazole-2-thiones, [17] 2-imino-1,3-thiazolines,[18] pyrimidine-2-thiones and (benzothiazolyl)-4-quinazolinones[19] N-(Substituted phenyl)-N-phenylthioureas have been developed as anion-binding sites in a hydrogen-bonding receptor,[20] calixarenes containing thioureas as neutral receptors towards α,α-dicarboxylate anions,[21] and N-4-substituted-benzyl-N-*tert*-butylbenzyl thioureas as vanilloid receptor ligands and antagonists in rate DRG neurons.[22] As part of our research on biological activity and coordination chemistry of thioureas,[23-30] we are interested in the study of the influence of non-covalent interactions, especially hydrogen bonds and π-π stacking interactions, on the coordination modes of thiocarbonyl donor groups with transition metal ions.

Since varying substituents is a common method for drug design in medicinal chemistry and a useful medical value of substituted thiourea derivatives containing quinazolin moiety, we aimed to synthesize new thiourea derivatives and to investigate their antimicrobial and antitumor activities. Based on these reports, we herein report the synthesis and characterization of a series of novel thiourea derivatives bearing quinazolin moiety. However, a thorough investigation relating structure and activity of thiourea derivatives and their stability under biological conditions is required.

## Experiments

### Chemicals and measurements

Synthetic starting material, reagents and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co., Merck Chemical Co. and were dried when necessary. Melting points were recorded on Electrothermal IA9000 series digital melting point apparatus. The proton NMR and $^{13}$C spectra were recorded in DMSO-$d_6$ solvent on Jeol ECS- 400 and 300 MHz spectrophotometer using tetramethylsilane as an internal reference, respectively. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). Infrared measurements were recorded in the range 400 - 4000 cm$^{-1}$ on spectrum 2000 by Perkin Elmer. Thin layer chromatography (TLC) analysis were carried out on 5 × 20 cm plate coated with silica gel $GF_{254}$ type 60 (25-250 mesh) using an ethyl acetate-petroleum ether mixture (1:2) as solvent.

### Procedures for the synthesis of compounds (3a-d)

Intermediate-1 was synthesized by following the Niementowski hetero cyclization reaction of 2-amino-5-nitrobenzolic acid with benzoyl chloride using pyridine as a

solvent as reported earlier.[31] Yielded intermediate-1 was followed by nucleophillic substitution reaction by using ethylene diamine as a nucliophile to yield intermediate-2. The synthesized intermediate-2 was dissolved in DMF and equimolar amount of the substituted phenyl isothiocyanate were added drop-wise to it and anhydrous acetone was also added in an equimolar amount. After the completion of the addition, the reaction mixture was refluxed for about 6-8 hours. The status of the reaction was monitored by TLC using ethanol: ethyl acetate (1.0: 9.0) as an eluent. After complete conversion, the reaction mixture was poured in crushed ice to separate the product. The obtained product was filtered, washed and dried.

**1-[2-(6-Nitro-4-oxo-2-phenyl-4H-quinazolin-3-yl)-ethyl]-3-p-tolyl-thiourea (3a)**

Elemental analysis for $C_{24}H_{21}N_5O_3S$ (MW = 459.14) in wt % calc. C=62.73, H= 4.61, N=15.24, S=6.98 and found to be C= 62.75, H=4.68, N=15.25, S= 6.96. m.p. 175$^oC$, yield 69 %. IR (KBr, $cm^{-1}$): 3352.68 (-NH str.), 1683.08 (C=O str.), 1504.75 (ArC-H str.), 1339.44 (-$NO_2$ str.), 1284.71 (C=S str.); $^1H$ NMR (400 MHz, DMSO-$d_6$, δppm): 12.35 (1H, s, -NH, exchangeable with $D_2O$), 10.84 (1H, s, -NH, exchangeable with $D_2O$), 7.03-8.86 (12H, m, Ar-H), 3.12 (2H, q, -$CH_2$), 2.79 (2H, t, -$CH_2$); 2.41 (3H, s, -$CH_3$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$, δppm): 166.47 (C=O), 165.79 (C=O), 145.25 (C=N, quinazolinone ring), 142.40 (C-$NO_2$), 135.49-120.67 (Ar-C), 41.54 ($CH_2$), 39.46 (-$CH_2$), 22.36 (-$CH_3$); TOF-MS (m/z): 460.34 (M+1, 12%), 144.20 (100%).

**1-[2-(6-Nitro-4-oxo-2-phenyl-4H-quinazolin-3-yl)-ethyl]-3-m-tolyl-thiourea (3b)**

Elemental analysis for $C_{24}H_{21}N_5O_3S$ (MW = 459.14) in wt % calc. C=62.73, H= 4.61, N=15.24, S=6.98 and found to be C= 62.76, H=4.69, N=15.25, S= 6.95. m.p. 180-181 $^oC$, yield 73%. IR (KBr, $cm^{-1}$): 3351.23 (-NH str.), 1683.19 (C=O str.), 1505.18 (ArC-H str.), 1339.34 (-$NO_2$ str.), 1284.47 (C=S str.); 1160.31 (C-N str.); $^1H$ NMR (400 MHz, DMSO-$d_6$, δppm): 12.29 (1H, s, -NH, exchangeable with $D_2O$), 10.78 (1H, s, -NH, exchangeable with $D_2O$), 6.92-8.92 (12H, m, Ar-H), 3.11 (2H, q, -$CH_2$), 2.77 (2H, t, $CH_2$); 2.51 (3H, s, -$CH_3$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$, δppm): 166.53 (C=O), 165.83 (C=O), 145.28 (C=N, quinazolinone ring), 142.37 (C-$NO_2$), 133.88-121.64 (Ar-C), 41.23 ( $CH_2$), 39.83 (-$CH_2$), 22.61 (-$CH_3$); TOF -MS (m/z): 460.09 (M+1, 13%), 144.58 (100%).

**1-[2-(6-Nitro-4-oxo-2-phenyl-4H-quinazolin-3-yl)-ethyl]-3-phenyl-thiourea (3c)**

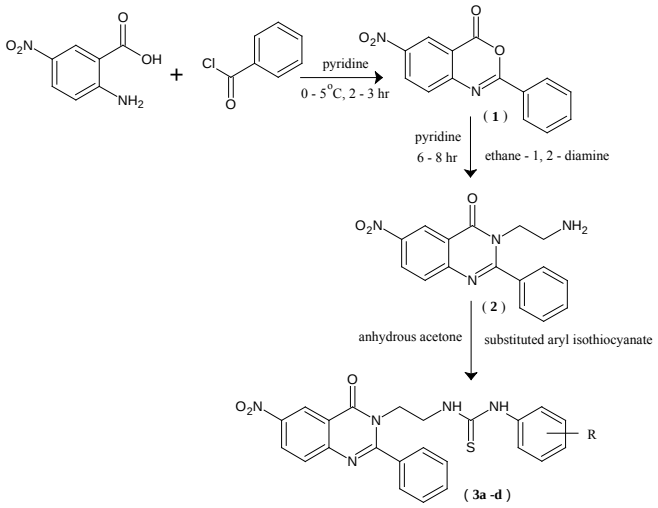
Elemental analysis for $C_{23}H_{19}N_5O_3S$ (MW = 445.49) in wt % calc. C=62.03, H= 4.29, N=15.73, S=7.20 and found to be C= 62.06, H=4.33, N=15.71, S= 7.21. m.p. 208$^oC$, yield 70.4 %. IR (KBr, $cm^{-1}$): 3352.88 (-NH str.), 1682.32 (C=O str.), 1504.80 (ArC-H str.), 1339.53 (-$NO_2$ str.), 1284.48 (C=S str.); $^1H$ NMR (400 MHz, DMSO-$d_6$, δppm): 12.06 (1H, s, -NH, exchangeable with $D_2O$), 10.87 (1H, s, -NH, exchangeable with $D_2O$), 7.13-8.81 (13H, m, Ar-H), 3.05 (2H, q, -$CH_2$), 2.83 (2H, t, -$CH_2$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$, δppm): 166.51 (C=O), 165.83 (C=O), 145.22 (C=N, quinazolinone ring), 142.37 (C-$NO_2$), 134.35-121.77 (Ar-C), 40.62 (-$CH_2$), 39.37 (- $CH_2$); TOF-MS (m/z): 445.42 (M+1, 14 %), 144.73 (100%).

**1-[2-(6-Nitro-4-oxo-2-phenyl-4H-quinazolin-3-yl)-ethyl]-3-o-tolyl-thiourea (3d)**

Elemental analysis for $C_{24}H_{21}N_5O_3S$ (MW = 459.14) in wt % calc. C=62.73, H= 4.61, N=15.24, S=6.98 and found to be C= 62.73, H=4.64, N=15.25, S= 6.96. m.p. 182-183 $^oC$, yield 89 %. IR (KBr, $cm^{-1}$): 3353.64 (-NH str.), 1685.20 (C=O str.), 1504.55 (ArC-H str.), 1340.11 (-$NO_2$ str.), 1284.58 (C=S str.); $^1H$ NMR (400 MHz, DMSO-$d_6$, δppm): 11.92 (1H, s, -NH, exchangeable with $D_2O$), 10.93 (1H, s, -NH, exchangeable with $D_2O$), 6.95-8.92 (12H, m, Ar-H), 2.72 (2H, t, -$CH_2$); 2.42 (3H, s, -$CH_3$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$, δppm): 1673.13 (2H, q, -$CH_2$), 49 (C=O), 166.73 (C=O), 145.19 (C=N, quinazolinone ring), 142.67 (C-$NO_2$), 132.82-121.86 (Ar-C), 40.57 (-$CH_2$), 39.43 (-$CH_2$), 21.96 (-$CH_3$); TOF-MS (m/z): 460.13 (M+1, 14%), 144.49 (100%).

## Results and Discussion:

Quinazoline-4-one based derivatives were prepared by a series of reaction as illustrated in scheme. The intermediate-1 and intermediate-2 was synthesized by following the procedure reported earlier.[31] Intermediate-3 was confirmed by C-O stretching of benzoxacine moiety observed at 1178 $cm^{-1}$ along with C=O stretching of cyclic ketone at 1772 $cm^{-1}$.




**Scheme**. Schematic diagram for the synthesis of target compounds (3a-d); 3a-d: R =3a= 3-$CH_3$, 3b; 4-$CH_3$, 3c; H, 3d; 2-$CH_3$

Reaction of intermediate-1 with ethylene diamine as a nucliophile leads to yield intermediate-2. Successful formation of intermediate-2 was confirmed by -$NH_2$ stretching frequencies observed at 3315 $cm^{-1}$ and disappearance of C-O stretching frequency at 1178 $cm^{-1}$. Reactions of the intermediate-2, [3-(2-aminoethyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one], with different phenyl isothiocyanate derivatives were carried out by using DMF as a solvent along with equimolar amount of triethyl amine, resulted in the synthesis of final compounds (**Scheme**). $^1H$ NMR spectra of compound-**3c** revealed signals in the downfield region at 12.06 δppm and 10.87 δppm as a singlet indicating the presence of two protons of thiourea in the linkage at N3 position of quinazoline-4-one moiety. Two aromatic protons adjacent to the -$NO_2$ group were observed in the downfield region between 8.81 to 8.66 δppm as a singlet and doublet, respectively. While remaining 11

aromatic protons were observed as a multiplet in the aromatic region between 7.13 to 7.92 δppm. In $^{13}$C NMR spectra of final compound **3c**, two downfield peaks were obtained at 166.51 and 165.83 δppm, accounting for a C=S and C=O present in the compound, respectively. Carbon attached with Nitrogen heteroatom on both side in the quinazolinone moiety was observed in the downfield region at 145.23 δppm. Further the aromatic carbon attached with the nitro group was observed in the downfield region at 141.91 δppm. Peaks between 138.56-121.77 δppm were for the rest aromatic carbons. Peaks for aliphatic carbon present in the final structure were observed at 40.62 and 39.37 δppm.[32]

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Received: 16.02.2013.
Accepted: 10.03.2013.