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Research Article

Synthesis and *In vitro* Anti-Mycobacterial Activity Evaluation of Some Quinazolinyl Thioureido Scaffolds

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Abstract

The current study reports design and diversity oriented synthesis of novel heterocycles incorporating of thioureido linkage on position no C-4 which not yet been explored and could find new applications in biology. Employing reagent based skeletal diversity approach; a facile synthesis of heterocycles with thioureido linkage at C-4 position of the quinazoline moiety has been accomplished. All the newly synthesized compounds were subjected to in vitro screening against various mycobacterial, bacterial and fungal strains. The bioassay results indicate some compounds could be emerged as the most promising anti tubercular and antimicrobial agents. All the intermediates and products have been isolated and fully characterized by IR, ^{1}H NMR and ^{13}C NMR.

INTRODUCTION

Discovery is the identification of novel active chemical compounds, often called "hits", which are typically found by assay of compounds for a desired biological activity. Initial hits can come from repurposing existing agents toward new pathologic processes. Tuberculosis (TB) has been a leading cause of death since time immemorial and it continues to cause immense human misery even today. Tuberculosis control requires new drugs that act at novel drug targets to help combat resistant forms of Mycobacterium tuberculosis and reduce treatment duration. In view of the fact there is need for the discovery of new, selective and promising inhibitor with an improved safety and efficacy profile has stimulated us to present an attractive approach towards design and development of new antimycobacterial scaffolds. Literature study reveals that more effectual new chemical scaffolds can be envisaged by incorporating two cyclic systems into a single molecule via linkage. With proven pharmacological significance, quinazolines have become a favourite field for many investigators and their efforts are quite significant in literature. According to recent data, quinazoline nucleus has attracted the attention of medicinal chemists due to its well known antifungal, anticancer & antitumor activity [1,2]. Quinazoline derivatives also known to show antibacterial and antitubercular activity [3,4]. This wide range of biological activities displayed by quinazolines is conferred by the diversity of the substituents that can be combined on the C-2,C-3 and C-6 centres. It is therefore of great interest to explore new type of substituent on the quinazoline ring in which incorporating of thioureido linkage on position C-4 which not yet been explored and could find new applications in biology.

Thioureas are of novel class of molecules found in many natural products. Their synthesis becomes a significant aspect in these days as many surrogates or substituents on the thiourea linkage may enhance its activity. In addition, thiourea compounds are associated with series of biological activities [5,6]. Thiourea are mimicking the urease in many functions; with growing application and versatile activity as active motif leads the chemists to make such thioureido [7] moieties. For these reasons synthesis of quinazoline moiety incorporated with thioureido linkage is of high interest. These novel compounds open up new perspectives in drug design by providing an entire range of highly specific, selective and non-toxic pharmaceuticals. Considering the advantage of biocompatibility and structural diversity of thiourea residues with the biological system, currently there is huge tendency of conjugating thiourea residues with bioactive heterocyclic motifs in the field of biomedical research. So here we designed synthetic route wherein the central key Quinazoline and different cyclic moieties built at C_4 position employing diversity oriented synthesis.

R = **7a** 4-NO_2, **7b** 3-NO_2, **7c** 2-NO_2, **7d** 4-F, **7e** 3-CH_3, **7f** 2-Cl: 3-Cl, **7g** 4-CH_3, **7h** 4-OCH_3, **7i** 2-Cl, **7j** 3-Cl

Scheme 1. Reagents: a) $HCONH_2$, 150°C b) PCl_5, $POCl_3$, 115-118°C c) IPA, K_2CO_3, NH_2CH_2COOH, reflux 5-6 hrs. d) $SOCl_2$ e) Acetone, NH_4NCS f) Acetone, sub. amine.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the quinazolinyl thioureido unreported title compounds is as outlined in Scheme 1.In general, the basic strategy was the same as was used to make the lead structure; the combination of aromatic electrophilic and aromatic nucleophilic moieties corresponding to the target analogues. Hence in continuation of our work on quinazolines, we have incorporated thioureido linkage with quinazoline moiety. In this work, the lead structure, (6-nitroquinazolin-4(3h)-one) compound **2** was synthesized using the Niementowski cyclization according to the literature [8]. Compound **2** on reaction with phosphorous pentachloride and phosphorous oxychloride gave compound **3** which was synthesized according to literature [9]. Compound **3** on reaction with glycine gave quinazolinyl glycine derivative compound **4.** The latter was then treated with thionyl chloride to produce compound **5** which on subsequent treatment with ammonium thiocyanate according to literature [10] gave compound **6** which on treatment with various aryl amines in acetone gave **7a-j.** All the synthesized compounds were fully characterized by IR, ^{1}H-NMR, ^{13}C NMR spectroscopy and elemental analysis.

The titled compounds were prepared through the reaction sequences depicted in Scheme 1. Compound **2** showed the presence of >NH group in IR (3170 cm^{-1}) and ^{1}H NMR spectra which showed a broad signal around δ 7.17 (NH). The IR spectrum of compound **3** showed peak at 760 cm^{-1} for C-Cl**.** The IR spectrum of titled compound **7a** showed peak at 1211 cm^{-1} (thioureido CS group) and its ^{1}H NMR spectrum showed a singlet at δ 8.62 (NHCSNH). In addition to that, the absence of a peak at 760 cm^{-1} for chloro group and presence of a peak at 1211 cm^{-1} (thioureido CS group) in compound **7a** reveals that p-nitro phenyl thioureido linkage is present as a linker between phenyl ring and quinazoline moiety. The ^{13}C NMR spectrum of **7a** reveals carbon signals at δ 180.25, 169.29, 159.11 and 155.90 assigned to C=S, C=O, C_2 and C_4, respectively.

Biological Activity

Antibacterial Activity:

1. Compounds

Test compounds were dissolved in DMF at an initial concentration of 40 mg\ ml and then were serially diluted in culture medium.

2. Cells

Bacterial strains: Staphylococcus aureus, Bacillus subtillis, Salmonella typhi, Klebsiella pneumonia

Fungal strain: Aspergillus niger

The minimum inhibitory concentrations (MICs) of the chemical compounds assays were carried out as described by Clause [11] with minor modifications. References viz., ampicillin trihydrate and ciprofloxacin (antibacterial agent) and fluconazole (antifungal agent) were used. Solutions of the test compounds and reference drugs were dissolved in DMF at a conc. of 20 mg ml^{-1}. The two fold dilution of the compounds and reference drugs were prepared (40, 30, 20, 10, 05, etc.) mg ml^{-1}. Antibacterial activities of the bacterial strains were carried out in Muller–Hinton broth (Difco) medium, at pH 6.9, with an inoculum of (1–2) × 10^3 cells ml^{-1} by the spectrophotometric method and an aliquot of 100 µl was added to each tube of the serial dilution. The chemical compounds–broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37°C for 24 h at 150 rpm. The MICs of the chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e.,no turbidity) of inoculated bacteria. The results obtained is summarized in Table 1.

Table 1 represents the antibacterial effect of the substituted quinazoline-4(3H)-ones and their thioanalogues. Two compounds of the obtained series owed high *in vitro* antimicrobial activity. Amongst the entire tested compounds, **7c** showed excellent activity against S.Typhi and Kleb; **7f** showed good activity against Bacillus subtillis and displayed excellent activity against fungus Aspergilus Niger.

Antitubercular Activity: All compounds 7(a-j) were screened at 62.5 µg/ml for their in vitro antimycobacterial activity against M. tuberculosis $H_{37}R_v$ strain using Lowenstein-Jensen medium method [12]. Positive and negative growth controls were run in each experiment and Rifampicin was used as standard drug.

The antitubercular effects of new synthesized compounds **7a-j** were investigated against M. tuberculosis $H_{37}R_v$ strain and the results are shown in Figure 1. The compounds **7c** (2-NO_2)**, 7d** (4-F) and **7i** (2-Cl) possess elevated activity against M. tuberculosis $H_{37}R_v$ strain while all the remaining compounds possess moderate to poor efficiency.

CONCLUSION

A series of quinazoline moiety incorporated with thioureido linkage were successfully synthesized and screened for antimicrobial and antitubercular activity. It is seen from the biological screening result that the several quinazoline moiety incorporated with thioureido linkage were interestingly found to be more active than their corresponding precursors. The probable reason for such behaviour with Gram –ve is the ortho position of nitro group on the aromatic ring compared to Meta and para position. In addition to this the presence of more than one electron-donating group on the aromatic ring in general influences the antifungal activity compared to compounds with electron withdrawing groups. Besides this, presence and the position of thioureido (–NHCSNH-) group as the connecting linker between the aromatic ring and quinazoline ring seem to be very significant for antimicrobial effect. The tested compounds were found to be active against S.typhi, Kleb and A.niger as paralleled to standards. Antitubercular activity of some compounds was found good against M. tuberculosis $H_{37}R_v$ as compared to that of Rifampicin.

Table 1: Antimicrobial Activity.

Compound No.	MIC in mM Antibacterial Strains		MIC in mM Antibacterial Strains		Antifungal Strains *A. niger*
	B. subtilis	*S. aureus*	*S. typhi*	*Kleb*	
7a	0.70	0.70	0.70	0.47	0.70
7b	0.70	0.70	0.70	0.70	0.47
7c	0.70	0.70	**0.23**	**0.18**	0.70
7d	0.74	0.50	0.50	0.75	0.50
7e	0.50	0.76	0.76	0.50	0.50
7f	**0.44**	0.66	0.66	0.44	**0.44**
7g	0.81	0.81	0.81	0.54	0.81
7h	0.72	0.72	0.72	0.73	0.72
7i	0.72	0.72	0.48	0.48	0.71
7j	0.72	0.72	0.48	0.72	0.71
Ampicillin	0.27	0.13	0.20	0.13	-
Ciprofloxacin	0.25	0.19	0.19	0.12	-
Fluconazole	-	-	-	-	0.35

Abbreviations: B. Subtilis-Bacillus Subtilis; S. Aureus-Staphylococcus Aureus; S. Typhi-Salmonella Typhi; Kleb- Klebsiella Pneumonia; A. Niger-Aspergillus Niger

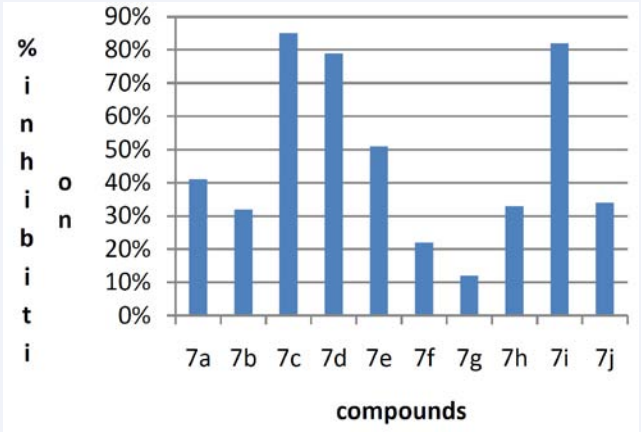

Figure 1 Antitubercular Activity of synthesized compounds 7(a-j).

EXPERIMENTAL

Reagents, Instrumentation and Measurements

All chemicals and solvents were of analytical grade and used directly. All the melting points were determined in open capillaries and are uncorrected. TLC analysis was done using pre-coated silica gel plates and visualization was done using iodine.

Apparatus

IR spectra (υmax in cm^{-1}) were recorded on Nicolet is10 FTIR spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively (Bruker Avance II), using DMSO as solvent and TMS as internal reference (chemical shifts in δ, ppm).The elemental analysis (C, H, N) of compounds were performed on Carlo Erba–1108 elemental analyzer. Their results were found to be in good agreement with the calculated values.

Synthesis of 6-nitroquinazolin-4(3h)-one (Compound 2)

A mixture of 5-Nitroanthranilic acid (0.01 mole) and formamide (20 ml) were heated for 8-10 hrs at 150-160°C under stirring with a magnetic stirrer. The mixture was then allowed to cool, and the precipitates were filtered off and dried at 80°C to give 6-nitro quinazolin-4(3H)-one (M.P.283-285°C).

Synthesis of 4-chloro-6-nitroquinazoline (Compound 3)

A mixture of 6-Nitro quinazoline-4(3H)-one (0.01mole), phosphorus pentachloride (0.05mole) and phosphorus oxychloride (16 ml) were heated and stirred under reflux for 8 hr at 115-118°C. Excess of phosphorus oxychloride was then removed by distillation. The residue obtained was acidified with sodium bicarbonate solution (5%w/v). The resulting precipitate was collected by filtration, washed with water, and dried to give 4-chloro-6-nitroquinazoline (M.P.220-223°C).

Synthesis of [(6-nitroquinazolin-4-yl) amino] acetic acid (compound 4)

A mixture of 4-Chloro-6-nitroquinazoline (0.01mole) and anhydrous K_2CO_3 (0.02mole) were taken in isopropyl alcohol. To this drop wise addition of glycine (0.01mole) in IPA with continuous stirring was done for half an hour. Then the reaction mixture was refluxed for 5-6 hrs. After the completion of reaction (checked by TLC), reaction mixture was then poured over crushed ice. The resulting precipitate was neutralized by conc. HCl. The product was collected by filtration, washed with water and dried to give [(6-nitro quinazoline-4-yl) amino] acetic acid. (M.P.157-159°C).

Synthesis of n-[(substituted phenyl) carbamothioyl]-2-[6-nitroquinazolin-4-yl) amino] acetamide (Compound 5,6 &7)

A mixture of [(6-nitroquinazolin-4-yl) amino] acetic acid

(0.01mole) and thionyl chloride (0.015mole) were refluxed for 3 hrs. Excess of thionyl chloride was distilled off. The product was then cooled and was dissolved in acetone (40 ml). Ammonium thiocyanate in acetone was then added slowly with constant stirring at room temperature. The reaction mixture was kept under reflux condition for 1 hr. Afterwards the solution of amine (0.01mole) in acetone was added slowly with constant stirring at room temperature. The reaction mixture was then refluxed for 3-4 hrs. The solution was poured into ice-cold water and the above product was recrystallized by using ethanol.

Spectral data of Compounds 7(a-j)

Compound (7a). Yield 67%, brown; mp 150 °C; Anal. Calcd for $C_{17}H_{13}N_7O_5S$ (427.39): C, 47.77%; H, 3.07%; N, 22.94%. found: C, 47.54%; H, 2.58 %; N, 22.87%; **IR (KBr)/cm^{-1}:** 3172 cm^{-1} (-NH-), 1680 cm^{-1} (>C=O), 1615 cm^{-1} (-C=N-), 1211 cm^{-1} (C=S), 1339 cm^{-1} (-C-N), 1557,1283 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.28 (s, 2H, CH_2), 7.11 (s, 1H, Ar-NH), 8.62 (s, 1H, CSNH), 9.08 (s, 1H, CONH), 7.30-8.11 (m, 8H, Ar-H);**^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 180.25 (C=S), 169.29 (C=O), 159.11 (C=N, C_2), 155.90 (C=N, C_4), 151.54 (CHAr), 137.31 (CHAr), 134.58 (CHAr), 131.12 (CHAr), 129.84 (CHAr), 128.68 (CHAr), 127.79 (CHAr), 120.60 (CHAr), 118.79 (CHAr), 115.62 (CHAr), 112.58 (CHAr), 48.27 (NCH_2).

Compound (7b). Yield 64%, yellow; mp 170 °C; Anal. Calcd for $C_{17}H_{13}N_7O_5S$ (427.39): C, 47.77%; H, 3.07%; N, 22.94%. found: C, 47.57%; H, 2.86 %; N, 22.78%;**IR (KBr)/cm^{-1}:** 3175 cm^{-1} (-NH-), 1676 cm^{-1} (>C=O), 1612 cm^{-1} (-C=N-), 1210 cm^{-1} (C=S), 1334 cm^{-1} (-C-N), 1555,1281 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.31 (s, 2H, CH_2), 7.09 (s, 1H, Ar-NH), 8.59 (s, 1H, CSNH), 9.09 (s, 1H, CONH), 7.28-8.12 (m, 8H, Ar-H); **^{13}C NMR** (75.5 MHz,CDCl3): δ 180.23 (C=S), 170.01 (C=O), 159.08 (C=N, C_2), 155.87 (C=N, C_4), 152.34 (CHAr), 137.05 (CHAr), 133.28 (CHAr), 130.08 (CHAr), 128.82 (CHAr),127.88 (CHAr), 126.19 (CHAr), 120.56 (CHAr), 118.58 (CHAr), 115.31 (CHAr), 113.80 (CHAr), 48.22 (NCH_2).

Compound (7c). Yield 65%, yellow; mp 146 °C; Anal. Calcd for $C_{17}H_{13}N_7O_5S$ (427.39): C, 47.77%; H, 3.07%; N, 22.94%. found: C 47.46%; H,2.86 %; N,22.75%; **IR (KBr)/cm^{-1}:** 3198 cm^{-1} (-NH-), 1684 cm^{-1} (>C=O), 1610 cm^{-1} (-C=N-), 1208 cm^{-1} (C=S), 1339 cm^{-1} (-C-N), 1560,1283 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.28 (s, 2H, CH_2), 7.09 (s, 1H, Ar-NH), 8.63 (s, 1H, CSNH), 9.13 (s, 1H, CONH), 7.15-8.08 (m, 8H, Ar-H); **^{13}C NMR** (75.5 MHz,$CDCl_3$): δ 180.15 (C=S), 169.75 (C=O), 159.16 (C=N, C_2), 154.87 (C=N, C_4), 152.56 (CHAr), 138.31 (CHAr), 134.28 (CHAr), 133.02 (CHAr), 130.62 (CHAr),129.68 (CHAr), 127.45 (CHAr), 121.60 (CHAr), 119.61 (CHAr), 114.62 (CHAr), 112.24 (CHAr), 48.25 (NCH_2).

Compound (7d). Yield 68%, brown; mp 200 °C; Anal. Calcd for $C_{17}H_{13}FN_6O_3S$ (400.38): C, 51.00%; H, 3.27%; N, 20.99%. found: C, 50.82%; H,3.11 %; N, 20.56%; **IR(KBr)/cm^{-1}:** 3169 cm^{-1} (-NH-), 1684 cm^{-1} (>C=O), 1617 cm^{-1} (-C=N-), 1211 cm^{-1} (C=S), 1337 cm^{-1} (-C-N), 1559,1281 cm^{-1} (-NO_2), 1132 cm^{-1} (C-F); **^{1}H NMR CDCl$_3$**: 4.30 (s, 2H, CH_2), 7.10 (s, 1H, Ar-NH), 8.60 (s, 1H, CSNH), 9.08 (s, 1H, CONH), 7.30-8.10 (m, 8H, Ar-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 180.14 (C=S), 169.62 (C=O), 158.43 (C=N, C_2), 155.75 (C=N, C_4), 152.04 (CHAr), 137.89 (CHAr), 135.56 (CHAr), 132.52 (CHAr), 130.64 (CHAr),128.68 (CHAr), 127.21 (CHAr), 121.93 (CHAr), 119.34 (CHAr), 115.12 (CHAr), 113.87 (CHAr), 48.19 (NCH_2).

Compound (7e). Yield 70%, white; mp 238 °C; Anal. Calcd for $C_{18}H_{16}N_6O_3S$ (396.42): C, 54.54%; H, 4.07%; N, 21.20%. found: C, 54.26%; H,3.85 %; N, 21.01%; **IR (KBr)/cm^{-1}:** 3185 cm^{-1} (-NH-), 1661 cm^{-1} (>C=O), 1615 cm^{-1} (-C=N-), 1217 cm^{-1} (C=S), 1337 cm^{-1} (-C-N), 1558,1287 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.28 (s, 2H, CH_2), 7.07 (s, 1H, Ar-NH), 8.54 (s, 1H, CSNH), 9.10 (s, 1H, CONH), 7.15-8.22 (m, 8H, Ar-H);**^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 181.05 (C=S), 170.29 (C=O), 158.11 (C=N, C_2), 156.90 (C=N, C_4), 152.60 (CHAr), 138.51 (CHAr), 135.42 (CHAr), 132.02 (CHAr), 131.32 (CHAr),127.55 (CHAr), 126.79 (CHAr), 125.30 (CHAr), 120.52 (CHAr), 119.12 (CHAr), 113.70 (CHAr), 48.22 (NCH_2).

Compound (7f). Yield 75%, white; mp 210 °C; Anal. Calcd for $C_{17}H_{12}Cl_2N_6O_3S$ (451.28): C, 45.24%; H, 2.68%; N, 18.62%. found: C, 45.21%; H,2.55 %; N, 18.52%; **IR (KBr)/cm^{-1}:** 3177 cm^{-1} (-NH-), 1672 cm^{-1} (>C=O), 1616 cm^{-1} (-C=N-), 1217 cm^{-1} (C=S), 1340 cm^{-1} (-C-N), 1557,1282 cm^{-1} (-NO_2), 757 cm^{-1} (C-Cl); **^{1}H NMR CDCl$_3$**: 4.31 (s, 2H, CH_2), 7.08 (s, 1H, Ar-NH), 8.55 (s, 1H, CSNH), 9.05 (s, 1H, CONH), 7.11-8.27 (m, 7H, Ar-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 181.23 (C=S), 170.15 (C=O), 159.20 (C=N, C_2), 155.45 (C=N, C_4), 152.34 (CHAr), 137.92 (CHAr), 135.02 (CHAr), 132.15 (CHAr), 130.65(CHAr), 129.84 (CHAr), 127.79 (CHAr), 121.85 (CHAr), 120.58 (CHAr), 117.35 (CHAr), 112.58 (CHAr), 47.86 (NCH_2).

Compound (7g). Yield 67%, white; mp 190 °C; Anal. Calcd for $C_{18}H_{16}N_6O_3S$ (396.42): C, 54.54%; H, 4.07%; N, 21.20%. found: C, 54.40%; H,3.89 %; N, 21.02%; **IR (KBr)/cm^{-1}:** 3195 cm^{-1} (-NH-), 1676 cm^{-1} (>C=O), 1614 cm^{-1} (-C=N-), 1205 cm^{-1} (C=S), 1328 cm^{-1} (-C-N), 1568,1277 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.30 (s, 2H, CH_2), 7.09 (s, 1H, Ar-NH), 8.54 (s, 1H, CSNH), 9.11 (s, 1H, CONH), 7.21-8.34 (m, 8H, Ar-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 181.25 (C=S), 170.19 (C=O), 160.31 (C=N, C_2), 156.54 (C=N, C_4), 151.54 (CHAr), 138.01 (CHAr), 135.32 (CHAr), 133.54 (CHAr), 130.84 (CHAr), 129.68 (CHAr), 128.79 (CHAr), 122.34 (CHAr), 120.67 (CHAr), 119.19 (CHAr), 113.51 (CHAr), 48.07 (NCH_2).

Compound (7h). Yield 71%, white; mp 215 °C; Anal. Calcd for $C_{18}H_{16}N_6O_4S$ (412.42): C, 52.42%; H, 3.91%; N, 20.38%. found: C, 52.25%; H,3.67 %; N, 20.16%; **IR (KBr)/cm^{-1}:** 3184 cm^{-1} (-NH-), 1672 cm^{-1} (>C=O), 1616 cm^{-1} (-C=N-), 1206 cm^{-1} (C=S), 1330 cm^{-1} (-C-N), 1568,1277 cm^{-1} (-NO_2); **^{1}H NMR CDCl$_3$**: 4.30 (s, 2H, CH_2), 7.09 (s, 1H, Ar-NH), 8.53 (s, 1H, CSNH), 9.11 (s, 1H, CONH), 7.21-8.24 (m, 8H, Ar-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 180.31 (C=S), 170.62 (C=O), 160.45 (C=N, C_2), 155.90 (C=N, C_4), 152.32 (CHAr), 139.33 (CHAr), 135.53 (CHAr), 132.12 (CHAr), 130.52 (CHAr),128.40 (CHAr), 127.61 (CHAr), 119.60 (CHAr), 118.53 (CHAr), 114.62 (CHAr), 113.58 (CHAr), 48.12 (NCH_2).

Compound (7i). Yield 68%, yellow; mp 160 °C; Anal. Calcd for $C_{17}H_{13}ClN_6O_3S$ (416.84): C, 48.98%; H, 3.14%; N, 20.16%. found: C, 48.74%; H,3.01 %; N, 20.03%; **IR (KBr)/cm^{-1}:** 3186 cm^{-1} (-NH-), 1679 cm^{-1} (>C=O), 1621 cm^{-1} (-C=N-), 1208 cm^{-1} (C=S), 1328 cm^{-1} (-C-N), 1570,1281 cm^{-1} (-NO_2), 760 cm^{-1} (C-Cl); **^{1}H NMR CDCl$_3$**: 4.32 (s, 2H, CH_2), 7.13 (s, 1H, Ar-NH), 8.54 (s, 1H, CSNH), 9.12 (s, 1H, CONH), 7.17-8.38 (m, 8H, Ar-H),**^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 180.27 (C=S), 169.65 (C=O), 160.21 (C=N, C_2), 156.55 (C=N, C_4), 152.54 (CHAr), 137.31 (CHAr), 135.46 (CHAr), 131.80 (CHAr), 129.84 (CHAr), 128.32 (CHAr), 127.60 (CHAr), 119.25 (CHAr), 118.90 (CHAr), 114.62 (CHAr), 112.58 (CHAr), 48.20 (NCH_2).

Compound (7j). Yield 70%, yellow; mp 200 °C; Anal. Calcd for $C_{17}H_{13}ClN_6O_3S$ (416.84): C, 48.98%; H, 3.14%; N, 20.16%. found: C,48.81%; H,2.89 %; N, 20.01%; **IR(KBr)/cm^{-1}:** 3189 cm^{-1} (-NH-), 1675 cm^{-1} (>C=O), 1618 cm^{-1} (-C=N-), 1210 cm^{-1} (C=S), 1325 cm^{-1} (-C-N), 1573,1287 cm^{-1} (-NO_2), 762 cm^{-1} (C-Cl); **^{1}H NMR CDCl$_3$**: 4.29 (s, 2H, CH_2), 7.10 (s, 1H, Ar-NH), 8.50 (s, 1H, CSNH), 9.08 (s, 1H, CONH), 7.13-8.27 (m, 8H, Ar-H),**^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 181.22 (C=S), 169.32 (C=O), 160.62 (C=N, C_2), 156.20 (C=N, C_4), 152.90 (CHAr), 138.35 (CHAr), 135.18 (CHAr), 133.02 (CHAr), 128.86 (CHAr), 128.20 (CHAr), 126.19 (CHAr), 121.35 (CHAr), 120.58 (CHAr), 119.79 (CHAr), 113.70 (CHAr), 48.36 (NCH_2).

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