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Search for new pharmacophores for antimalarial activity (Part III): Synthesis and bioevaluation of new 6-thioureido-4-anilinoquinazolines

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Abstract— Syntheses and in vitro antimalarial evaluation of 42 new thioureido quinazolines have been carried out. Several analogs showed promising antimalarial effect in the in vitro investigation against chloroquine-sensitive 3D7 strain of *P. falciparum* whereas one of the compounds shows 50% curative effect in the mouse model at an oral dose of 100mg/kg x 4 days against multi drug resistant *P. yoelii nigeriensis*.

Introduction

The widespread presence of chloroquine (CQ)-resistant *P. falciparum* strains has severely affected global malaria eradication program. The paucity of new affordable drugs has not only complicated the clinical management of malaria in endemic areas, but has also resulted in increase in the mortality rate. This situation underscores the need for urgent discovery of new antimalarial agents. In this context it becomes essential to carry out exploratory studies for finding new pharmacophores which associate with antimalarial activity. Installing these pharmacophores in scaffolds with proven biological property as anti-infectious agent could lead to discovery of new antimalarial compound. In our research program aimed at this objective, we have reported the potent antimalarial effect of new quinazoline derivatives which were afforded by placing a ureido group at 6-position of 4-anilinoquinazolines.[1] In a set of compounds belonging to this prototype, we could identify an analog that displayed 40% curative activity at an oral dose of 100mg/kg x 4 days in mice model against multi drug resistant (mdr) *P. yoelli*

nigeriensis. In continuation of these studies we considered worthwhile to supplement the ureido group in 4-anilinoquinazolines with a thioureido moiety and investigate the antimalarial effect of the resulting compounds. Our decision to evaluate thioureidoquinazolines for antimalarial activity was influenced by several reports disclosing the antimalarial effect of thiourea-based compounds via different mechanisms. For example, Rastelli et al.[2] reported that the thiourea-unit of compound **I** binds with the pfDHFR whereas Kasam et al.[3] disclosed the plasmepsin inhibitory effect of thioureides represented by **II** (Fig. 1). It was also proposed that the thio-group provides opportunity for nucleophilic addition of enzymes through thiol formation resulting in antimalarial effect.[4] The antimalarial efficacy of different thioureides **(III-VI)** has been demonstrated in several other reports too, but in majority of them it is limited to the in vitro examination.[5] We describe herein the synthesis and bioevaluation of new series of 6-thioureido-4-anilinoquinazolines as antimalarial agents.

Insert Figure 1 here

Results and Discussion

The preparation of the targeted compounds was straightforward as outlined in scheme 1. The starting quinazolinamines **(1-6)** were obtained following the procedure recently reported by us.[1] Amines were treated with the commercially available isothiocyanates to afford the desired compounds **(7-12a-g)** in good yields as solids. The new compounds were characterized spectroscopically and analytically. Results of the in vitro antimalarial efficacy against CQ-sensitive *P. falciparum* of the forty two compounds which were investigated during the present study are displayed in Table 1. The MIC of CQ that was used as standard in the bioassay was 0.12μg/mL whereas the IC_{50} was found to be 2.0 ng/mL. Generally, compounds having MIC of 2

μg/mL or less were evaluated for their IC_{50} values. We introduced changes at both the phenyl rings present in the molecule during the synthesis of compounds included herein. In all 6 variations were made in the phenyl ring of the anilino group which included H, 3-OMe, 3-Cl, 3-CF_3, 3,4-$(OMe)_2$, 4-OMe while 7 changes represented by H, 3-F, 3-CN, 3-Cl, 4-Cl, 4-Br or 1-naphthyl were made in the phenyl group of the thiourea subunit.

Insert Scheme 1 here

Insert Table 1 here

In series **7**, the phenyl ring of the anilino moiety was devoid of any substitution. Amongst the compounds of this series, **7a-b,d-e,g** displayed antimalarial effect at MIC of 2 μg/mL whereas **7c** and **7f** bearing 3-CN and 3-Br substitutions, respectively on the aryl ring of the thiourea subunit showed MIC of 10 μg/mL or more. Out of 5 compounds with MIC of 2 μg/mL, the IC_{50} for **7b** and **7d** were examined. Compound **7b** bearing the 3-F substitution showed moderate activity with IC_{50} value of 792 ng/mL whereas **7d** having 3-Cl group had comparable effect with IC_{50} value of 813 ng/mL. Introduction of a methoxy group at 3-position in the phenyl ring of the anilino part resulted in compounds belonging to series **8** which exhibited significant antimalarial activity. Except for compounds **8e** and **8g**, all compounds displayed MIC of either 2 or 1 μg/mL leading to the determination of their IC_{50} values. Thioureides **8b,c,d** bearing 3-F, 3-CN, 3-Cl substitutions, respectively in the phenyl ring on the arylthiourea portion exhibited better antimalarial response with IC_{50} of 26.7, 21.0, 11.5 ng/mL whereas **8a** and **8f** having an unsubstituted phenyl or 4-bromophenyl substitution on thiourea displayed IC_{50} of 258 ng/mL and 151 ng/mL, respectively. However even this activity was low as compared to the standard drug CQ. On the basis of the SI for compounds of this series, **8d** with SI of 1615 was ideal for the in

vivo examination. On replacing the OMe group at 3-position of the phenyl ring of aniline with the Cl-group resulted in compounds of series **9**. However this change led to significant drop in antimalarial efficacy of the compounds. Except for compound **9d** and **9f** incorporating 3-Cl and 4-Br on the phenyl of thiourea group, all other derivatives displayed MIC of 10 μg/mL or more. Compounds **9d** and **9f** showed IC_{50} of 8.8 and 526.1 ng/mL, respectively whereas the SI was found to be 556.3 and 1.0. This implied that among this set of compounds too, the 3-Cl substitution on the phenyl ring of the arylthiourea showed better antimalarial efficacy compared to other analogs in the series.

Next, replacing the 3-Cl with 3-CF_3 in the 4-anilino moiety produced compounds belonging to series **10**. However, analogs of this series did not show any marked improvement in the antimalarial effect and here too except for **10f**, all compounds displayed MIC of 10 μg/mL. The IC_{50} value of **10f** having 4-Br substitution in phenyl ring of the thiourea was found to be 39.2 ng/mL. Previous study with 6-ureido-4-anilinoquinazolines has indicated that installing 3,4-$(OMe)_2$ substitution on phenyl ring of the anilino group furnished compounds displaying best in vitro antimalarial effect. This invoked us to prepare compounds of series **11** in which 3,4-$(OMe)_2$ substitution was placed in the aryl ring of the anilino core. Unlike ureidoquinazolines, the compounds belonging to this series showed moderate antimalarial effect only. Compounds **11c,d,e** bearing 3-CN, 3-Cl, 4-Cl groups, respectively showed MIC of 10 μg/mL whereas other 4 analogs **(11a,b,f,g)** exhibited antimalarial response at MIC value of 2 μg/mL. The IC_{50} values for **11a, 11b, 11f, 11g** ranged between 207.2 and 682.8 ng/mL whereas the SI values were 89.8, 63.7, 85.7 and 133.8, respectively. From this result it was suspected that placing a substitution at the 4-position result in the loss of antimalarial effect. In order to check this, finally we prepared the series **12** wherein the phenyl ring of the aniline core carried methoxy group at 4-position. The

resulting set of compounds **12a-g** was found to be the least active. Except for **12a-b,f** containing an unsubstituted phenyl, 3-F-phenyl or 4-Br-phenyl, respectively in the aryl thiourea part, all other compounds displayed MIC of 10 μg/mL. In terms of IC_{50} **12b** and **12f** had only moderate activity with values of 53.2 ng/mL (SI=206.4) and 50.2 (SI=114.9), respectively. In comparison **12a** was even less active with IC_{50} of 242.6 ng/mL (SI=80.4). These results made it evident that having a substitution at 4-position of the phenyl ring of the aniline-part could result in loss in antimalarial activity in thioureidoquinazolines. The result of the in vitro study also reflected that 3-Cl- or 4-Br-phenyl in the aryl thiourea entity were better suited to show the antimalarial effect.

Essentially to further investigate the utility of these compounds as antimalarial agents it was decided to determine the oral efficacy of a few derivatives in mouse model against mdr *P. yoelii nigeriensis*. Hence the antimalarial effect of compounds **8d, 8f**, **9b, 9d** and **10f** were investigated at a dose of 100 mg/kg x 4d via oral route. The thioureide **8f** showed 100 and 99.9% suppression in parasitaemia in mice on day 4 and 7, respectively. It was encouraging to note that 50% of the treated mice survived on completion of the experiment on 28^{th} day. Compared to this, at identical dose compounds **9b** and **9d** could cause 85.7 and 77.1% reduction in the level of day-4 parasitaemia. By day-7, although the suppression of parasitaemia in animals which were administered **9b** was around 61%, it decreased for animals treated with **9d** to 16% only. Further, for compound **8d** which elicited good antimalarial response in the in vitro assay could cause only 46.5% suppression of parasitaemia on day-4 which further decreased to 28.5% by day-7. Compound **10f** caused only 9.8% of suppression in day-4 level of parasitaemia and all the animals died on day-7 reflecting its inactivity in the in vivo system. Except for compound **8f**, animals treated with different analogs died by day-28 of the experiment. It is assumed that low level of solubility of these compounds could be one of the reasons for their limited efficacy in

the in vivo system. However, the result of the in vivo evaluation indicated that amongst the set of compounds described herein there was no correlation between the in vitro and in vivo antimalarial efficacy.

Conclusions

In summary we have disclosed the antimalarial investigation of new thiourea analogs of 4-anilinoquinazolines. It was observed that compounds display moderate antimalarial efficacy against the CQ-sensitive 3D7 strain of *P. falciparum*. Out of a few analogs evaluated for in vivo efficacy against mdr strain via oral route, one compound was found to show 50% curative effect. These results provide impetus for designing new compounds incorporating thiourea moiety for the discovery of new antimalarials.

Experimental

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS and FABMS were recorded on MICROMASS Quadro-II LCMS and JEOL SX/102/DA 6000 system, respectively. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL *III* microanalyzer. HPLC was performed on Agilent 1100 having a DA detector (λ_{max}= 220 nm and 254 nm) using a gradient run of 10-100% MeCN containing 0.01% TFA in water over a period of 30 min in a RP-18e column (250 x 4.6 mm) with particle size of 5 μm.

General procedure for the preparation of 6-amino-4-arylaminoquinazoline (1-6).[1]

General procedure for the preparation of compounds 7-12a-g. A mixture of appropriate amine from **1-6** (1.0 equiv) and aryl isothiocyanate (1.3 equiv) in anhydrous DMF (2.0 mL) was stirred at room temperature for 6-20 h. Thereafter the reaction mixture was diluted with 50 mL water, and extracted with ethyl acetate (4 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and the residue thus obtained was purified through silica-gel column chromatography using hexanes: EtOAc (30-10:70-90, v/v) as eluent to yield the desired compounds **7-12a-g**.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-phenylthiourea (7a):** 50% (0.55g from 0.70g) as a yellow solid, mp 142-143 °C; ν_{max} (KBr) 1216 (C=S), 3359 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.13 (d, 2H, *J*= 6.4 Hz, ArH), 7.34-7.50 (m, 6H, ArH), 7.73-7.83 (m, 4H, ArH), 8.48 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.75 (s, 1H, NH), 9.95.(s, 1H, NH), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 116.0, 119.3, 123.1, 124.5, 125.0, 125.6, 128.6, 129.3, 132.8, 138.0, 140.1, 148.3, 154.8, 158.3, 181.3; mass (ES+) *m/z*= 372.1 (M^++1). Anal. Calcd. for $C_{21}H_{17}N_5S$ (Exact mass: 371.1205); C, 67.90; H, 4.61; N, 18.85. Found C, 68.05; H, 4.65; N, 18.73.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3-fluorophenyl)thiourea (7b):** 48% (0.55g from 0.70g) as a yellow solid, mp 157-158 °C; ν_{max} (KBr) 1234 (C=S), 3409 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.96 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.29-7.38 (m, 4H, ArH), 7.53 (d, 1H, *J*= 9.5 Hz, ArH), 7.77-7.83 (m, 4H, ArH), 8.48 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.74 (s, 1H, NH), 10.07 (s, 1H, NH), 10.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 111.2, 111.5, 111.8, 112.0, 116.0, 119.3, 120.3, 123.1, 124.5, 128.8, 129.3, 130.7, 130.8, 132.7, 137.8, 140.0, 141.9, 142.1, 148.5, 154.9, 158.2, 161.0, 164.2, 181.2; mass (ES+) *m/z*= 390.1 (M^++1). Anal. Calcd. for

$C_{21}H_{16}FN_5S$ (Exact mass: 389.1110); C, 64.76; H, 4.14; N, 17.98. Found C, 65.00; H, 4.32; N, 18.14.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3-cyanophenyl)thiourea (7c):** 55% (0.46g from 0.50g) as a brown solid, mp 118-120 °C; ν_{max} (KBr) 1216 (C=S), 2215 (CN), 3436 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.12 (t, 1H, *J*= 7.3 Hz, ArH), 7.38 (t, 2H, *J*= 7.8 Hz, ArH), 7.51-7.60 (m, 2H, ArH), 7.75-7.86 (m, 5H, ArH), 8.00 (s, 1H, ArH), 8.48 (d, 1H, *J*= 1.4 Hz, ArH), 8.55 (s, 1H, ArH), 9.75.(s, 1H, NH), 10.10 (s, 1H, NH), 10.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 112.0, 116.1, 119.5, 123.3, 124.7, 128.1, 128.9, 129.0, 129.4, 129.8, 130.6, 132.7, 137.6, 140.0, 141.3, 148.6, 155.0, 158.4, 181.6; mass (ES+) *m/z*= 397.1 (M^++1). Anal. Calcd. for $C_{22}H_{16}N_6S$ (Exact mass: 396.1157); C, 66.65; H, 4.07; N, 21.20. Found C, 66.33; H, 3.84; N, 21.37.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(3-chlorophenyl)thiourea (7d):** 50% (0.60g from 0.70g) as a yellow solid, mp 123-125 °C; ν_{max} (KBr) 1252 (C=S), 3400 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.10-7.21 (m, 2H, ArH), 7.36-7.41 (m, 4H, ArH), 7.69 (s, 1H, ArH), 7.75-7.85 (m, 4H, ArH), 8.49 (s, 1H, ArH), 8.56 (s, 1H, ArH), 9.77 (s, 1H, NH), 10.05 (s, 1H, NH), 10.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 115.7, 119.0, 122.8, 123.0, 124.1, 124.2, 124.8, 128.5, 128.9, 130.5, 132.3, 133.0, 137.3, 139.6, 141.4, 148.1, 154.6, 157.9, 181.0; mass (ES+) *m/z*= 406.1 (M^++1). Anal. Calcd. for $C_{21}H_{16}ClN_5S$ (Exact mass: 405.0815); C, 62.14; H, 3.97; N, 17.25. Found C, 62.42; H, 4.14; N, 17.02.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(4-chlorophenyl) thiourea (7e):** 47% (0.56g from 0.70g) as a brown solid, mp 167-169 °C; ν_{max} (KBr) 1216 (C=S), 3409 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 7.12 (t, 1H, *J*= 7.4 Hz, ArH), 7.36-7.41 (m, 4H, ArH), 7.54 (d, 2H, *J*= 8.8 Hz, ArH),

7.77 (d, 1H, *J*= 8.8 Hz, ArH), 7.85 (d, 3H, *J*= 7.0 Hz, ArH), 8.50 (d, 1H, *J*= 1.3 Hz, ArH), 8.57 (s, 1H, ArH), 9.76 (s, 1H, NH), 10.00.(s, 1H, NH), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 116.1, 119.4, 123.2, 124.6, 126.3, 126.7, 128.8, 129.2, 129.4, 129.6, 132.8, 137.9, 139.2, 139.3, 140.1, 148.5, 155.0, 158.3, 181.5; mass (ES+) *m/z*= 406.1 (M^++1). Anal. Calcd. for $C_{21}H_{16}ClN_5S$ (Exact mass: 405.0815); C, 62.14; H, 3.97; N, 17.25. Found C, 62.34; H, 3.68; N, 17.12.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(4-bromophenyl) thiourea (7f):** 44% (0.25g from 0.30g) as a yellow solid, mp 123-125 °C; ν_{max} (KBr) 1242 (C=S), 3454 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.12 (t, 1H, *J*= 7.3 Hz, ArH), 7.38 (t, 1H, *J*= 7.7 Hz, ArH), 7.46-7.54 (m, 4H, ArH), 7.69 (s, 1H, ArH), 7.75 (d, 1H, *J*= 8.8 Hz, ArH), 7.84 (d, 3H, *J*= 8.0 Hz, ArH), 8.48 (s, 1H, ArH), 8.55 (s, 1H, ArH), 9.74 (s, 1H, NH), 9.97 (s, 1H, NH), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 116.1, 117.6, 118.7, 119.3, 123.2, 123.3, 124.6, 126.9, 129.3, 132.1, 132.8, 138.0, 139.8, 140.1, 141.3, 148.1, 154.9, 158.3, 181.4; mass (ES+) *m/z*= 452.0 (M^++2). Anal. Calcd. for $C_{21}H_{16}BrN_5S$ (Exact mass: 449.0310); C, 56.01; H, 3.58; N, 15.55. Found C, 56.22; H, 3.67; N, 15.58.

***N*-(4-Anilinoquinazolin-6-yl)-*N*'-(2-naphthyl)thiourea (7g):** 50% (0.63g from 0.70g)as a yellow solid, mp 140-142 °C; ν_{max} (KBr) 1254 (C=S), 3352 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.11 (t, 1H, *J*= 7.3 Hz, ArH), 7.38 (t, 2H, *J*= 7.8 Hz, ArH), 7.51-7.61 (m, 4H, ArH), 7.74 (d, 1H, *J*= 8.9 Hz, ArH), 7.83-7.90 (m, 3H, ArH), 7.95 (t, 1H, *J*= 6.7 Hz, ArH), 8.04 (d, 1H, *J*= 8.0 Hz, ArH), 8.48 (s, 1H, ArH), 8.54 (s, 1H, ArH), 8.56 (s, 1H, ArH), 9.76 (s, 1H, NH), 10.05 (s, 1H, NH), 10.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 115.9, 119.7, 123.1, 124.0, 124.5, 126.4, 126.5, 127.0, 127.1, 127.8, 128.5, 128.9, 129.3, 130.8, 133.2, 134.8,

135.8, 138.2, 140.1, 148.5, 154.8, 158.3, 182.8; mass (ES+) *m/z*= 422.1 (M^++1). Anal. Calcd. for $C_{25}H_{19}N_5S$ (Exact mass: 421.1361); C, 71.23; H, 4.54; N, 16.61. Found C, 71.48; H, 4.88; N, 16.94.

***N*-[4-(3-Methoxyanilino)quinazolin-6-yl]-*N*'-phenylthiourea (8a):** 75% (0.28g from 0.25g) as an off white solid, mp 174-175 °C; ν_{max} (KBr) 1259 (C=S), 3417 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 8.2 Hz, J_2= 2.1 Hz, ArH), 7.14 (t, 1H, *J*= 7.3 Hz, ArH), 7.25-7.37 (m, 3H, ArH), 7.47-7.54 (m, 4H, ArH), 7.75 (d, 1H, *J*= 8.9 Hz, ArH), 7.86 (dd, 1H, J_1= 8.9 Hz, J_2= 1.9 Hz, ArH), 8.47 (d, 1H, *J*= 1.6 Hz, ArH), 8.57 (s, 1H, ArH), 9.69 (s, 1H, NH), 9.96 (s, 1H, NH), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 53.8, 98.3, 106.8, 107.7, 113.2, 114.0, 117.2, 122.5, 123.0, 123.6, 126.6, 127.3, 128.0, 130.8, 136.0, 138.0, 139.2, 146.3, 152.7, 156.2, 158.1, 179.3; mass (ES+) *m/z*= 402.8 (M^++1). Anal. Calcd. for $C_{22}H_{19}N_5OS$ (Exact mass: 401.1310); C, 65.81; H, 4.77; N, 17.44. Found C, 66.04; H, 4.96; N, 17.23.

***N*-(3-Fluorophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]thiourea (8b):** 55% (0.26g from 0.30g) as a yellow solid, mp 178-179 °C; ν_{max} (KBr) 1216 (C=S), 3430 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 8.0 Hz, J_2= 1.9 Hz, ArH), 6.94-6.99 (m, 1H, ArH), 7.25-7.41 (m, 3H, ArH), 7.47-7.54 (m, 3H, ArH), 7.76 (d, 1H, *J*= 8.8 Hz, ArH), 7.85 (dd, 1H, J_1= 8.9 Hz, J_2= 1.6 Hz, ArH), 8.48 (d, 1H, *J*= 1.3 Hz, ArH), 8.58 (s, 1H, ArH), 9.68 (s, 1H, NH), 10.06 (s, 1H, NH), 10.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 55.8, 108.8, 109.7, 111.2, 111.5, 111.7, 112.0, 115.2, 116.0, 119.3, 120.3, 128.7, 130.0, 130.7, 130.8, 132.7, 137.8, 141.2, 141.9, 142.0, 148.5, 154.8, 158.2, 160.2, 161.0, 164.2, 181.3;

mass (ES+) *m/z*= 420.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}FN_5OS$ (Exact mass: 419.1216); C, 62.99; H, 4.33; N, 16.70. Found C, 62.68; H, 4.61; N, 16.94.

***N*-(3-cyanophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl] thiourea (8c):** 75% (0.48g from 0.40g) as a yellow solid, mp 160-161 °C; ν_{max} (KBr) 1244 (C=S), 2230 (CN), 3453 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.71 (dd, 1H, J_1= 8.1 Hz, J_2= 2.0 Hz, ArH), 7.29 (t, 1H, *J*= 8.1 Hz, ArH), 7.46-7.61 (m, 4H, ArH), 7.76-7.88 (m, 3H, ArH), 8.01 (s, 1H, ArH), 8.51 (s, 1H, ArH), 8.61 (s, 1H, ArH), 9.80 (s, 1H, NH), 10.20 (s, 1H, NH), 10.33 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 54.3, 107.4, 108.3, 110.3, 113.7, 114.4, 117.8, 126.3, 126.9, 127.3, 128.1, 128.5, 129.0, 131.3, 136.1, 139.5, 139.6, 146.3, 153.1, 156.7, 158.6, 179.9; mass (ES+) *m/z*= 427.0 (M^++1). Anal. Calcd. for $C_{23}H_{18}N_6OS$ (Exact mass: 426.1263); C, 64.77; H, 4.25; N, 19.70. Found C, 64.95; H, 4.47; N, 19.54.

***N*-(3-Chlorophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl] thiourea (8d):** 54% (0.44g from 0.50g) as an off white solid; R_t= 16.06 min; mp 184-185 °C; ν_{max} (KBr) 1257 (C=S), 3305 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.70 (d, 1H, *J*= 6.6 Hz, ArH), 7.19 (d, 1H, *J*= 6.5 Hz, ArH), 7.28-7.52 (m, 5H, ArH), 7.68 (s, 1H, ArH), 7.76 (d, 1H, *J*= 8.1 Hz, ArH), 7.83 (d, 1H, *J*= 8.1 Hz, ArH), 8.46 (s, 1H, ArH), 8.57 (s, 1H, ArH), 9.68 (s, 1H, NH), 10.02 (s, 1H, NH), 10.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 55.9, 108.9, 109.8, 115.3, 116.1, 119.3, 123.3, 124.5, 125.3, 128.8, 130.1, 130.9, 132.8, 133.4, 137.8, 141.2, 141.8, 148.5, 154.9, 158.3, 160.3, 181.4; mass (ES+) *m/z*= 436.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}ClN_5OS$ (Exact mass: 435.0921); C, 60.61; H, 4.16; N, 16.07. Found C, 60.36; H, 4.43; N, 16.25.

***N*-(4-Chlorophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]thiourea (8e)**: 57% (0.47g from 0.50g) as a yellow solid; R_t= 19.27 min; mp 192-193 °C; ν_{max} (KBr) 1205 (C=S), 3411 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 8.2 Hz, J_2= 2.1 Hz, ArH), 7.28 (t, 1H, *J*= 8.1 Hz, ArH), 7.37 (d, 2H, *J*= 8.8 Hz, ArH), 7.49 (d, 1H, *J*= 8.0 Hz, ArH), 7.52-7.60 (m, 3H, ArH), 7.74 (d, 1H, *J*= 8.9 Hz, ArH), 7.87 (dd, 1H, J_1= 8.8 Hz, J_2= 1.7 Hz, ArH), 8.47 (s, 1H, ArH), 8.57 (s, 1H, ArH), 9.67 (s, 1H, NH), 10.44 (s, 2H, 2 x NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.4, 108.3, 109.2, 114.7, 115.6, 118.6, 125.6, 125.9, 128.1, 128.6, 128.7, 129.6, 132.4, 137.8, 139.0, 140.8, 147.9, 154.3, 157.7, 159.7, 180.9; mass (ES+) *m/z*= 436.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}ClN_5OS$ (Exact mass: 435.0921); C, 60.61; H, 4.16; N, 16.07; O, 3.67; S, 7.36. Found C, 60.54; H, 3.84; N, 16.23.

***N*-(4-Bromophenyl)-*N*'-[4-(3-methoxyanilino)quinazolin-6-yl]thiourea (8f):** 46% (0.25g from 0.30g) as a white solid, mp 190-191 °C; ν_{max} (KBr) 1216 (C=S), 3444 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.70 (d, 1H, *J*= 7.9 Hz, ArH), 7.28 (t, 1H, *J*= 8.1 Hz, ArH), 7.47-7.54 (m, 6H, ArH), 7.76 (d, 1H, *J*= 8.9 Hz, ArH), 7.84 (d, 1H, *J*= 7.6 Hz, ArH), 8.48 (s, 1H, ArH), 8.58 (s, 1H, ArH), 9.68 (s, 1H, NH), 9.97 (s, 1H, NH), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 55.6, 108.5, 109.4, 114.8, 115.7, 117.3, 119.0, 126.1, 126.6, 128.4, 129.7, 131.7, 132.4, 137.5, 139.3, 140.9, 148.1, 154.4, 157.8, 159.9, 181.0; mass (ES+) *m/z*= 480.0 (M^++1). Anal. Calcd. for $C_{22}H_{18}BrN_5OS$ (Exact mass: 479.0415); C, 55.01; H, 3.78; N, 14.58. Found C, 55.41; H, 3.43; N, 14.46.

***N*-[4-(3-methoxyanilino)quinazolin-6-yl]-*N*'-(2-naphthyl)thiourea (8g):** 53% (0.27g from 0.30g) as a off white solid; R_t=15.32 min.; mp 159-160 °C; ν_{max} (KBr) 1216 (C=S), 3406 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.78 (s, 3H, OCH_3), 6.70 (dd, 1H, J_1= 8.2 Hz, J_2= 2.1

Hz, ArH), 7.28 (t, 1H, *J*= 8.2 Hz, ArH), 7.49-7.59 (m, 6H, ArH), 7.74(d, 1H, *J*= 8.9 Hz, ArH), 7.86-7.98 (m, 3H, ArH), 8.04 (d, 1H, *J*= 8.0 Hz, ArH), 8.47 (d, 1H, *J*= 1.4 Hz, ArH), 8.57 (s, 1H, ArH), 9.68 (s, 1H, NH), 9.93 (s, 1H, NH), 10.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 55.4, 108.3, 109.2, 114.7, 115.5, 119.1, 123.6, 125.9, 126.1, 126.5, 126.6, 127.4, 128.1, 128.5, 129.6, 130.4, 132.8, 134.3, 135.3, 137.8, 140.8, 148.0, 154.3, 157.7, 159.7, 182.4; mass (ES+) *m/z*= 452.1 (M^++1). Anal. Calcd. for $C_{26}H_{21}N_5OS$ (Exact mass: 451.1467); C, 69.16; H, 4.69; N, 15.51. Found C, 69.37; H, 4.78; N, 15.34.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-phenylurea (9a):** 55% (0.37g from 0.45g) as a yellow solid; R_t= 14.58 min; mp 167-168 °C; ν_{max} (KBr) 1216 (C=S), 3411 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (d, 2H, *J*=7.3 Hz, ArH), 7.32-7.44 (m, 3H, ArH), 7.49 (d, 2H, *J*=7.7 Hz, ArH), 7.77-7.90 (m, 3H, ArH), 8.11 (s, 1H, ArH), 8.48 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.84 (s, 1H, NH), 9.95.(s, 1H, NH), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 115.5, 118.7, 120.6, 121.6, 123.4, 124.0, 124.6, 125.2, 128.3, 128.9, 130.5, 132.6, 133.1, 137.8, 139.6, 141.3, 148.0, 154.1, 157.6, 180.9; mass (ES+) *m/z*= 406.1 (M^++1). Anal. Calcd. for $C_{21}H_{16}ClN_5S$ (Exact mass: 405.0815); C, 62.14; H, 3.97; N, 17.25. Found C, 62.34; H, 4.01; N, 16.93.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-(3-fluorophenyl)thiourea (9b):** 65% (0.32g from 0.45g) as an off white solid; R_t=15.71 min; mp 156-157 °C; ν_{max} (KBr) 1217 (C=S), 3455 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.94-6.99 (m, 1H, ArH), 7.16 (dd, 1H, J_1= 7.9 Hz, J_2= 1.2 Hz, ArH), 7.28 (d, 1H, *J*= 8.4 Hz, ArH), 7.32-7.54 (m, 3H, ArH), 7.77-7.88 (m, 3H, ArH), 8.10 (s, 1H, ArH), 8.48 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.83 (s, 1H, NH), 10.08 (s, 1H, NH), 10.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 110.7, 111.2, 111.3, 111.7, 115.5, 118.8,

119.9, 120.6, 121.7, 123.5, 128.4, 130.3, 130.5, 132.5, 133.1, 137.6, 141.2, 141.4, 141.6, 148.1, 154.2, 157.6, 159.8, 164.6, 180.8; mass (ES+) *m/z*= 424.0 (M^++1). Anal. Calcd. for $C_{21}H_{15}ClFN_5S$ (Exact mass: 423.0721); C, 59.50; H, 3.57; N, 16.52. Found C, 59.33; H, 3.73; N, 16.75.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N'*-(3-cyanophenyl)thiourea (9c):** 58% (0.46g from 0.50g) as a yellow solid; mp >250 °C; ν_{max} (KBr) 1216 (C=S), 2234 (CN), 3448 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (d, 1H, *J*= 7.9 Hz, ArH), 7.41 (t, 1H, *J*= 8.8 Hz, ArH), 7.52-7.60 (m, 2H, ArH), 7.81-7.88 (m, 4H, ArH), 8.05 (s, 1H, ArH), 8.10 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.64 (s, 1H, ArH), 9.85 (s, 1H, NH), 10.20 (s, 1H, NH), 10.32 (s, 1H, NH); mass (ES+) *m/z*= 431.1 (M^++1). Anal. Calcd. for $C_{22}H_{15}ClN_6S$ (Exact mass: 430.0767); C, 61.54; H, 3.32; N, 19.78. Found C, 61.32; H, 3.61; N, 19.50.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N'*-(3-chlorophenyl)thiourea (9d):** 53% (0.39g from 0.45g) as a yellow solid; R_t= 15.41 min; mp 190-191 °C; ν_{max} (KBr) 1263 (C=S), 3439 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.17 (t, 2H, *J*= 8.0 Hz, ArH), 7.33-7.43 (m, 3H, ArH), 7.68 (s, 1H, ArH), 7.77-7.87 (m, 3H, ArH), 8.10 (s, 1H, ArH), 8.48 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.84 (s, 1H, NH), 10.04 (s, 1H, NH), 10.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 116.0, 119.2, 121.0, 122.1, 123.2, 123.9, 124.4, 125.2, 128.9, 130.9, 132.8, 133.3, 133.6, 137.9, 141.7, 154.6, 158.0, 181.4; mass (ES+) *m/z*= 440.0 (M^++1). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5S$ (Exact mass: 439.0425); C, 57.28; H, 3.43; N, 15.90. Found C, 57.46; H, 3.20; N, 15.86.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N'*-(4-chlorophenyl)thiourea (9e):** 58% (0.43g from 0.45g) as a yellow solid; R_t= 16.47 min; mp 170-171 °C; ν_{max} (KBr) 1188 (C=S), 3303 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (dd, 1H, J_1= 7.9 Hz, J_2= 1.1 Hz, ArH), 7.38-7.43 (m,

3H, ArH), 7.53 (d, 2H, *J*= 8.8 Hz, ArH), 7.77-7.88 (m, 3H, ArH), 8.11 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.64 (s, 1H, ArH), 9.84 (s, 1H, NH), 9.99.(s, 1H, NH), 10.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 114.2, 117.4, 119.2, 120.3, 122.1, 124.4, 124.9, 127.0, 127.4, 127.8, 129.1, 131.1, 131.8, 136.3, 137.3, 139.9, 146.6, 152.8, 156.2, 179.6; mass (ES+) *m/z*= 440.0 (M^++1). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5S$ (Exact mass: 439.0425); C, 57.28; H, 3.43; N, 15.90. Found C, 57.03; H, 3.78; N, 15.76.

***N*-(4-Bromophenyl)-*N*'-[4-(3-chloroanilino)quinazolin-6-yl] thiourea (9f):** 51% (0.31g from 0.35g) as a yellow solid, mp 151-153 °C; ν_{max} (KBr) 1246 (C=S), 3301 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.16 (d, 1H, *J*= 7.8 Hz, ArH), 7.38-7.51 (m, 5H, ArH), 7.77-7.84 (m, 3H, ArH), 8.10 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.84 (s, 1H, NH), 10.00 (s, 1H, NH), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 115.2, 118.4, 120.2, 121.3, 123.1, 126.1, 128.0, 130.1, 131.3, 132.1, 132.8, 137.2, 138.8, 140.9, 147.7, 153.8, 157.2, 180.6; mass (ES+) *m/z*= 485.9 (M^++2). Anal. Calcd. for $C_{21}H_{15}BrClN_5S$ (Exact mass: 482.9920); C, 52.03; H, 3.12; N, 14.45. Found C, 52.10; H, 2.83; N, 14.66.

***N*-[4-(3-Chloroanilino)quinazolin-6-yl]-*N*'-(2-naphthyl)thiourea (9g):** 52% (0.35g from 0.40g) as an off white solid; R_t= 16.55 min; mp 129-130 °C; ν_{max} (KBr) 1216 (C=S), 3419 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.15 (d, 1H, *J*= 7.7 Hz, ArH), 7.40 (t, 1H, *J*= 8.1 Hz, ArH), 7.51-7.61 (m, 4H, ArH), 7.76 (d, 1H, *J*= 8.8 Hz, ArH), 7.85 (t, 2H, *J*= 6.3 Hz, ArH), 7.95 (t, 2H, *J*= 7.0 Hz, ArH), 8.03 (d, 1H, *J*= 8.1 Hz, ArH), 8.11 (s, 1H, ArH), 8.47 (s, 1H, ArH), 8.62 (s, 1H, ArH), 9.84 (s, 1H, NH), 9.95.(s, 1H, NH), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 115.8, 119.4, 120.9, 122.0, 123.8, 123.9, 126.3, 126.5, 126.9, 127.0, 127.8, 128.5, 128.9, 130.7, 130.9, 133.4, 133.5, 134.7, 135.7, 138.4, 154.5, 158.0, 182.8; mass (ES+) *m/z*=

456.1 (M^++1). Anal. Calcd. for $C_{25}H_{18}ClN_5S$ (Exact mass: 455.0971); C, 65.85; H, 3.98; N, 15.36. Found C, 65.63; H, 4.25; N, 15.15.

***N*-Phenyl-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10a):** 53% (0.19g from 0.25g) as a yellow solid, mp 182-183 °C; ν_{max} (KBr) 1216 (C=S), 3428 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.15 (t, 1H, *J*= 7.2 Hz, ArH), 7.34 (t, 2H, *J*= 7.5 Hz, ArH), 7.43-7.50 (m, 3H, ArH), 7.62 (t, 1H, *J*= 7.7 Hz, ArH), 7.79 (d, 1H, *J*= 8.7 Hz, ArH), 7.88 (d, 1H, *J*= 8.8 Hz, ArH), 8.24 (d, 1H, *J*= 7.7 Hz, ArH), 8.32 (s, 1H, ArH), 8.50 (s, 1H, ArH), 8.64 (s, 1H, ArH), 9.98 (s, 2H, 2 x NH), 10.02 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 115.9, 118.7, 119.1, 120.4, 125.0, 125.6, 126.2, 128.8, 129.3, 129.8, 130.5, 133.1, 138.3, 140.1, 141.0, 154.5, 158.0, 181.3; mass (ES+) *m/z*= 440.1 (M^++1). Anal. Calcd. for $C_{22}H_{16}F_3N_5S$ (Exact mass: 439.1078); C, 60.13; H, 3.67; N, 15.94. Found C, 59.93; H, 3.48; N, 16.25.

***N*-(3-Fluorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10b):** 55% (0.37g from 0.45g) as a white solid; R_t=16.36 min; mp 139-140 °C; ν_{max} (KBr) 1216 (C=S), 3406 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 6.97 (dt, 1H, J_1= 8.0 Hz, J_2= 1.9 Hz, ArH), 7.27-7.55 (m, 4H, ArH), 7.62 (t, 1H, *J*= 8.0 Hz, ArH), 7.80(d, 1H, *J*= 8.9 Hz, ArH), 7.88 (dd, 1H, J_1= 8.8 Hz, J_2= 1.9 Hz, ArH), 8.24 (d, 1H, *J*= 8.1 Hz, ArH), 8.31 (s, 1H, ArH), 8.50 (d, 1H, *J*= 1.5 Hz, ArH), 8.64 (s, 1H, ArH), 9.97 (s, 1H, NH), 10.09 (s, 1H, NH), 10.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 110.7, 111.2, 111.3, 111.7, 115.5, 118.3, 118.8, 119.9, 121.9, 125.8, 127.3, 128.4, 129.3, 130.0, 130.3, 130.5, 132.6, 137.6, 140.5, 141.4, 141.6, 148.1, 154.2, 157.6, 159.8, 164.6, 180.9; mass (ES+) *m/z*= 458.1 (M^++1). Anal. Calcd. for $C_{22}H_{15}F_4N_5S$ (Exact mass: 457.0984); C, 57.76; H, 3.31; N, 15.31. Found C, 57.94; H, 3.66; N, 15.05.

***N*-(3-Cyanophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10c):** 58% (0.44g from 0.50g) as a yellow solid, mp 159-160 °C; ν_{max} (KBr) 1216 (C=S), 2231 (CN), 3448 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.45 (d, 1H, *J*= 7.4 Hz, ArH), 7.51-7.65 (m, 3H, ArH), 7.80-7.89 (m, 2H, ArH), 8.00 (s, 1H, ArH), 8.23 (d, 1H, *J*= 7.8 Hz, ArH), 8.31 (s, 1H, ArH), 8.51 (s, 1H, ArH), 8.64 (s, 1H, ArH), 9.98 (s, 1H, NH), 10.13 (s, 1H, NH), 10.28 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 111.6, 115.6, 118.3, 119.0, 120.2, 122.9, 125.9, 126.5, 127.6, 128.6, 129.4, 129.9, 130.1, 130.2, 132.6, 137.5, 140.6, 140.8, 148.2, 154.3, 157.7, 181.2; mass (ES+) *m/z*= 465.1 (M^{+}+1). Anal. Calcd. for $C_{23}H_{15}F_3N_6S$ (Exact mass: 464.1031); C, 59.48; H, 3.26; N, 18.09. Found C, 59.75; H, 3.57; N, 17.86.

***N*-(3-Chlorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10d):** 47% (0.36g from 0.50g) as a white solid, mp 142-143 °C; R_t= 16.48 min; ν_{max} (KBr) 1197 (C=S), 3332 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.46-7.62 (m, 6H, ArH), 7.79-7.86 (m, 2H, ArH), 8.23 (d, 1H, *J*= 6.4 Hz, ArH), 8.31 (s, 1H, ArH), 8.51 (s, 1H, ArH), 8.65 (s, 1H, ArH), 10.01 (s, 1H, NH), 10.11 (s, 1H, NH), 10.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 116.0, 118.7, 118.8, 119.3, 120.4, 122.4, 126.2, 126.7, 127.8, 129.0, 129.2, 129.6, 129.8, 130.5, 133.1, 138.2, 139.2, 141.1, 148.6, 154.6, 158.1; mass (ES+) *m/z*= 474.1 (M^{+}+1). Anal. Calcd. for $C_{22}H_{15}ClF_3N_5S$ (Exact mass: 473.0689); C, 55.76; H, 3.19; N, 14.78. Found C, 55.95; H, 3.33; N, 14.94.

***N*-(4-Chlorophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10e):** 51% (0.36g from 0.45g) as a yellow solid; R_t= 17.31 min; mp 179-181 °C; ν_{max} (KBr) 1178 (C=S), 3306 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.38-7.46 (m, 3H, ArH), 7.52 (d, 2H, *J*= 8.8 Hz, ArH), 7.62 (t, 1H, *J*= 8.0 Hz, ArH), 7.80 (d, 1H, *J*= 8.9 Hz, ArH), 7.86 (dd, 1H, J_1= 8.9 Hz,

J_2= 1.8 Hz, ArH), 8.23 (d, 1H, *J*= 8.1 Hz, ArH), 8.32 (s, 1H, ArH), 8.51 (d, 1H, *J*= 1.5 Hz, ArH), 8.64 (s, 1H, ArH), 10.00 (s, 1H, NH), 10.04 (s, 1H, NH), 10.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 116.0, 118.7, 118.8, 119.3, 120.4, 122.4, 126.2, 126.7, 127.8, 129.0, 129.2, 129.6, 129.8, 130.5, 133.1, 138.2, 139.2, 141.1, 148.6, 154.6, 158.1; mass (ES+) *m/z*= 474.0 (M^++1). Anal. Calcd. for $C_{22}H_{15}ClF_3N_5S$ (Exact mass: 473.0689); C, 55.76; H, 3.19; N, 14.78. Found C, 55.65; H, 3.36; N, 14.96.

-(4-Bromophenyl)-*N*'-{4-[3-(trifluoromethyl)anilino]quinazolin-6-yl}thiourea (10f): 56% (0.43g from 0.45g) as a white solid, mp 142-143 °C; R_t= 16.52 min; ν_{max} (KBr) 1197 (C=S), 3332 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.46-7.51 (m, 5H, ArH), 7.61 (d, 1H, *J*= 7.2 Hz, ArH), 7.81 (s, 1H, ArH), 7.86 (s, 1H, ArH), 8.23 (d, 1H, *J*= 6.5 Hz, ArH), 8.32 (s, 1H, ArH), 8.51 (s, 1H, ArH), 8.65 (s, 1H, ArH), 9.98 (s, 1H, NH), 10.01 (s, 1H, NH), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 116.0, 117.8, 118.8, 119.3, 120.4, 120.6, 126.3, 126.5, 127.0, 129.0, 130.5, 132.2, 133.1, 138.2, 139.7, 141.1, 148.5, 154.6, 158.1, 181.5; mass (ES+) *m/z*= 519.9 (M^++2). Anal. Calcd. for $C_{22}H_{15}BrF_3N_5S$ (Exact mass: 517.0184); C, 50.98; H, 2.92; N, 13.51. Found C, 50.67; H, 2.83; N, 13.73.

***N*-{4-[3-(Trifluoromethyl)anilino]quinazolin-6-yl}-*N*'-(2-naphthyl)thiourea (10g):** 61% (0.39g from 0.40g) as a white solid, mp 167-168 °C; ν_{max} (KBr) 1164 (C=S), 3401 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 7.45 (d, 1H, *J*= 7.6 Hz, ArH), 7.51-7.65 (m, 5H, ArH), 7.78 (d, 1H, *J*= 8.9 Hz, ArH), 7.86-7.88 (m, 1H, ArH), 7.93-7.97 (m, 2H, ArH), 8.04 (d, 1H, *J*= 8.0 Hz, ArH), 8.24 (d, 1H, *J*= 8.2 Hz, ArH), 8.32 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.98 (s, 1H, NH), 9.99 (s, 1H, NH), 10.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 115.9, 118.7, 119.5, 120.4, 124.0, 126.2, 126.4, 126.6, 127.1, 127.9, 128.7, 129.0, 129.8, 130.5, 130.9,

133.5, 134.8, 135.8, 138.6, 141.1, 148.6, 154.6, 158.1, 182.9; mass (ES+) *m/z*= 490.1 (M^++1). Anal. Calcd. for $C_{26}H_{18}F_3N_5S$ (Exact mass: 489.1235); C, 63.79; H, 3.71; N, 14.31. Found C, 64.09; H, 3.95; N, 14.02.

***N*-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]-*N*'-phenylthiourea (11a):** 57% (0.33g from 0.40g) as a yellow solid; R_t= 15.54 min; mp 169-170 °C; ν_{max} (KBr) 1217 (C=S), 3401 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.97 (d, 1H, *J*= 8.6 Hz, ArH), 7.15 (t, 1H, *J*= 7.2 Hz, ArH), 7.35 (t, 2H, *J*= 7.6 Hz, ArH), 7.41-7.51 (m, 4H, ArH), 7.73 (d, 1H, *J*= 8.8 Hz, ArH), 7.84 (d, 1H, *J*= 8.5 Hz, ArH), 8.45 (s, 1H, ArH), 8.52 (s, 1H, ArH), 9.64 (s, 1H, NH), 9.96 (s, 1H, NH), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 56.4, 56.7, 108.5, 112.7, 115.5, 116.0, 119.4, 124.6, 125.1, 125.7, 128.7, 129.4, 132.8, 133.4, 138.0, 140.2, 146.3, 148.4, 149.3, 155.0, 158.3, 181.4; mass (ES+) *m/z*= 432.1 (M^++1). Anal. Calcd. for $C_{23}H_{21}N_5O_2S$ (Exact mass: 431.1416); C, 64.02; H, 4.91; N, 16.23. Found C, 64.23; H, 4.63; N, 16.54.

***N*-(3-Fluorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]thiourea (11b):** 55% (0.42g from 0.50g) as a yellow solid; R_t= 16.96 min; mp 125-126 °C; ν_{max} (KBr) 1236 (C=S), 3677 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 8.4 Hz, ArH), 7.27-7.44 (m, 4H, ArH), 7.54 (d, 1H, *J*= 11.3 Hz, ArH), 7.73 (d, 1H, *J*= 8.8 Hz, ArH), 7.81 (d, 1H, *J*= 8.8 Hz, ArH), 8.43 (s, 1H, ArH), 8.51 (s, 1H, NH), 9.62 (s, 1H, NH), 10.14 (brs, 2H, 2 x NH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ= 56.4, .56.6, 108.5, 111.2, 111.5, 111.8, 112.0, 112.6, 115.5, 116.0, 119.4, 120.3, 128.7, 130.8, 130.9, 132.7, 133.3, 137.7, 142.0, 146.3, 148.4, 149.2, 155.1, 158.3, 161.0, 164.2, 173.2, 181.3; mass (ES+) *m/z*= 450.1 (M^++1).

Anal. Calcd. for $C_{23}H_{20}FN_5O_2S$ (Exact mass: 449.1322); C, 61.46; H, 4.48; N, 15.58. Found C, 61.35; H, 4.67; N, 15.67.

***N*-(3-Cyanophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]thiourea (11c):** 56% (0.33g from 0.38g) as a yellow solid, mp 178-179 °C; ν_{max} (KBr) 1216 (C=S), 2234 (CN), 3422 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 8.7 Hz, ArH), 7.37 (dd, 1H, J_1= 8.7 Hz, J_2= 2.3 Hz, ArH), 7.41-7.44 (m, 2H, ArH), 7.50 (t, 1H, *J*= 7.9 Hz, ArH), 7.71 (d, 2H, *J*= 8.8 Hz, ArH), 7.83 (dd, 1H, J_1= 8.9 Hz, J_2= 1.8 Hz, ArH), 8.04 (s, 1H, ArH), 8.44 (s, 1H, ArH), 8.47 (d, 1H, *J*=1.7 Hz, ArH), 9.13 (s, 1H, NH), 9.27.(s, 1H, NH), 9.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.4, 56.6, 108.7, 111.7, 112.5, 115.8, 116.4, 119.8, 121.8, 123.9, 126.3, 127.4, 129.1, 131.1, 133.5, 137.9, 141.5, 146.2, 146.6, 149.2, 153.5, 153.9, 158.3; mass (ES+) *m/z*= 457.1 (M^++1). Anal. Calcd. for $C_{24}H_{20}N_6O_2S$ (Exact mass: 456.1368); C, 63.14; H, 4.42; N, 18.41. Found C, 63.45; H, 4.23; N, 18.22.

***N*-(3-Chlorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]thiourea (11d):** 45% (0.70g from 1.00g) as a yellow solid; mp 176-178 °C; ν_{max} (KBr) 1270 (C=S), 3439 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 6H, 2 x OCH_3), 6.96 (d, 1H, *J*= 7.5 Hz, ArH), 7.41-7.43 (m, 4H, ArH), 7.53 (d, 2H, *J*= 7.9 Hz, ArH), 7.70-7.82 (m, 2H, ArH), 8.44 (s, 1H, ArH), 8.51 (s, 1H, ArH), 9.62 (s, 1H, NH), 9.98 (s, 1H, NH), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.4, 56.7, 108.6, 112.7, 115.6, 116.0, 119.5, 126.7, 128.8, 129.2, 129.6, 132.7, 133.4, 137.8, 139.3, 146.3, 148.4, 149.3, 155.1, 158.3, 181.5; mass (ES+) *m/z*= 466 0 (M^++1). Anal. Calcd. for $C_{23}H_{20}ClN_5O_2S$ (Exact mass: 465.1026); C, 59.29; H, 4.33; N, 15.03. Found C, 59.18; H, 4.45; N, 14.95.

***N*-(4-Chlorophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]thiourea (11e):** 45% (0.70g from 1.00g) as a brown solid; R_t= 16.79 min; mp 177-178 °C; ν_{max} (KBr) 1247 (C=S), 3448 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.96 (d, 1H, *J*= 8.6 Hz, ArH), 7.38-7.43 (m, 4H, ArH), 7.52 (d, 2H, *J*= 8.8 Hz, ArH), 7.73 (d, 1H, *J*= 8.8 Hz, ArH), 7.80 (dd, 1H, J_1= 8.9 Hz, J_2= 1.6 Hz, ArH), 8.43 (s, 1H, ArH), 8.51 (s, 1H, ArH), 9.63 (s, 1H, NH), 9.99 (s, 1H, NH), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.4, 56.7, 108.6, 112.7, 115.6, 119.4, 126.7, 128.7, 129.2, 129.6, 137.8, 139.2, 146.3, 149.3, 158.4, 181.5; mass (ES+) *m/z*= 466 0 (M^++1). Anal. Calcd. for $C_{23}H_{20}ClN_5O_2S$ (Exact mass: 465.1026); C, 59.29; H, 4.33; N, 15.03. Found C, 59.65; H, 4.14; N, 15.12.

***N*-(4-Bromophenyl)-*N*'-[4-(3,4-dimethoxyanilino)quinazolin-6-yl]thiourea (11f):** 45% (0.39g from 0.50g) as a brown solid; R_t= 16.79 min; mp 177-178 °C; ν_{max} (KBr) 1216 (C=S), 3423 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.97 (d, 1H, *J*= 8.6 Hz, ArH), 7.40-7.51 (m, 6H, ArH), 7.72 (d, 1H, *J*= 8.8 Hz, ArH), 7.81 (d, 1H, *J*= 8.6 Hz, ArH), 8.44 (s, 1H, ArH), 8.51 (s, 1H, ArH), 9.63 (s, 1H, NH), 10.19 (s, 1H, NH), 10.22 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.0, 56.2, 108.0, 112.2, 115.1, 115.6, 117.0, 118.8, 126.2, 128.2, 131.6, 132.3, 133.1, 137.6, 139.5, 145.8, 147.9, 148.8, 154.6, 157.9, 180.8; mass (ES+) *m/z*= 512 0 (M^++2). Anal. Calcd. for $C_{23}H_{20}BrN_5O_2S$ (Exact mass: 509.0521); C, 54.12; H, 3.95; N, 13.72. Found C, 54.08; H, 3.91; N, 13.68.

***N*-[4-(3,4-Dimethoxyanilino)quinazolin-6-yl]-*N*'-(2-naphthyl)thiourea (11g):** 53% (0.43g from 0.50g) as a yellow solid, mp 129-130 °C; ν_{max} (KBr) 1231 (C=S), 3449 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 6H, 2 x OCH_3), 6.96 (d, 1H, *J*= 8.1, Hz, ArH), 7.40-7.72 (m, 7H, ArH), 7.87-8.05 (m, 4H, ArH), 8.43 (s, 1H, ArH), 8.50 (s, 1H, ArH), 9.62 (s, 1H,

NH), 9.93 (s, 1H, NH), 10.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.0, 56.2, 108.0, 112.2, 115.0, 115.5, 123.6, 126.0, 126.2, 126.6, 127.4, 128.6, 134.4, 135.4, 147.9, 148.9, 157.9, 163.4; mass (ES+) *m/z*= 482.1 (M^++1). Anal. Calcd. for $C_{27}H_{23}N_5O_2S$ (Exact mass: 481.1572); C, 67.34; H, 4.81; N, 14.54. Found C, 67.68; H, 5.14; N, 14.62.

***N*-[4-(4-Methoxyanilino)quinazolin-6-yl]-*N*'-phenylthiourea (12a):** 61% (0.65g from 0.70g) as a yellow solid; R_t= 13.73 min; mp 170-171 °C; ν_{max} (KBr) 1216 (C=S), 3621 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.97 (d, 2H, *J*= 8.9 Hz, ArH), 7.15 (t, 1H, *J*= 7.3 Hz, ArH), 7.35 (t, 2H, *J*= 7.8 Hz, ArH), 7.49 (d, 2H, *J*= 7.6 Hz, ArH), 7.67-7.74 (m, 3H, ArH), 7.83 (d, 1H, *J*= 8.8 Hz, ArH), 8.43 (s, 1H, ArH), 8.49 (s, 1H, ArH), 9.68 (s, 1H, NH), 9.94 (s, 1H, NH), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.0, 114.5, 115.8, 119.2, 124.8, 125.0, 125.6, 128.5, 129.3, 132.6, 132.8, 137.8, 140.1, 148.3, 155.0, 156.6, 158.3, 181.3; mass (ES+) *m/z*= 402.1 (M^++1). Anal. Calcd. for $C_{22}H_{19}N_5OS$ (Exact mass: 401.1310); C, 65.81; H, 4.77; N, 17.44. Found C, 65.74; H, 4.68; N, 17.73.

***N*-(3-Fluorophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]thiourea (12b):** 52% (0.55g from 0.67g) as a white solid; R_t= 14.60 min; mp 132-133 °C; ν_{max} (KBr) 1244 (C=S), 3196 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.77 (s, 3H, OCH_3), 6.97 (d, 3H, *J*= 8.5 Hz, ArH), 7.27-7.39 (m, 2H, ArH), 7.54 (d, 1H, *J*= 10.7 Hz, ArH), 7.67-7.83 (m, 4H, ArH), 8.44 (s, 1H, ArH), 8.49 (s, 1H, ArH), 9.66 (s, 1H, NH), 10.04 (s, 1H, NH), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.0, 111.2, 111.5, 112.0, 114.5, 115.9, 119.4, 119.6, 120.3, 125.1, 128.7, 130.7, 130.8, 132.6, 132.8, 137.6, 141.9, 142.1, 148.3, 155.1, 156.7, 158.4, 181.3; mass (ES+) *m/z*= 420.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}FN_5OS$ (Exact mass: 419.1216); C, 62.99; H, 4.33; N, 16.70. Found C, 62.76; H, 4.64; N, 16.58.

***N*-(3-Cyanophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]thiourea (12c):** 58% (0.46g from 0.50g) as a yellow solid, mp 145-147 °C; ν_{max} (KBr) 1248 (C=S), 2234 (CN), 3324 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.73 (s, 3H, OCH_3), 6.94 (d, 2H, *J*= 8.9 Hz, ArH), 7.48-7.57 (m, 4H, ArH), 7.70-7.75 (m, 2H, ArH), 7.82 (d, 1H, *J*= 8.6 Hz, ArH), 7.94 (s, 1H, ArH), 8.33 (s, 1H, ArH), 8.41 (s, 1H, ArH), 9.71 (s, 1H, NH), 10.11.(s, 1H, NH), 10.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.6, 112.4, 115.2, 116.3, 119.6, 120.0, 126.2, 128.6, 128.9, 129.7, 130.4, 131.2, 132.8, 138.1, 141.6, 148.3, 155.6, 157.5, 159.2, 182.1; mass (ES+) *m/z*= 427.1 (M^++1). Anal. Calcd. for $C_{23}H_{18}N_6OS$ (Exact mass: 426.1263); C, 64.77; H, 4.25; N, 19.70. Found C, 64.86; H, 4.53; N, 19.57.

***N*-(3-Chlorophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]thiourea (12d):** 54% (0.63g from 1.14g) as a yellow solid, mp 138-139 °C; ν_{max} (KBr) 1249 (C=S), 3314 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 8.3 Hz, ArH), 7.18 (d, 1H, *J*= 7.3 Hz, ArH), 7.33-7.40 (m, 2H, ArH), 7.66-7.81 (m, 5H, ArH), 8.43 (s, 1H, ArH), 8.48 (s, 1H, ArH), 9.66 (s, 1H, NH), 10.02.(s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.1, 114.5, 115.9, 119.4, 123.3, 124.4, 125.1, 128.8, 130.8, 132.5, 132.8, 133.3, 137.5, 141.8, 148.4, 155.1, 156.7, 158.4, 181.3; mass (ES+) *m/z*= 436.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}ClN_5OS$ (Exact mass: 435.0921); C, 60.61; H, 4.16; N, 16.07. Found C, 60.96; H, 4.34; N, 15.79.

***N*-(4-Chlorophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]thiourea (12e):** 56% (0.64g from 0.70g) as a yellow solid, mp 189-190 °C; ν_{max} (KBr) 1244 (C=S), 3317 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ= 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 8.3 Hz, ArH), 7.35-7.41 (m, 2H, ArH), 7.47-7.55 (m, 2H, ArH), 7.65-7.83 (m, 4H, ArH), 8.43 (s, 1H, ArH), 8.48 (s, 1H,

ArH), 9.67 (s, 1H, NH), 9.97.(s, 1H, NH), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.4, 108.6, 112.7, 115.6, 116.0, 119.5, 126.7, 128.8, 129.2, 129.6, 132.7, 133.4, 137.8, 139.3, 146.3, 148.4, 149.3, 155.1, 158.3, 181.5; mass (ES+) *m/z*= 436.1 (M^++1). Anal. Calcd. for $C_{22}H_{18}ClN_5OS$ (Exact mass: 435.0921); C, 60.61; H, 4.16; N, 16.07. Found C, 60.96; H, 4.34; N, 15.79.

***N*-(4-Bromophenyl)-*N*'-[4-(4-methoxyanilino)quinazolin-6-yl]thiourea (12f):** 57% (0.72g from 0.70g) as a yellow solid; R_t= 17.26 min; mp 159-161 °C; ν_{max} (KBr) 1242 (C=S), 3347 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 8.8 Hz, ArH), 7.45-7.53 (m, 4H, ArH), 7.65-7.73 (m, 3H, ArH), 7.81 (d, 1H, *J*= 8.2 Hz, ArH), 8.42 (s, 1H, ArH), 8.48 (s, 1H, ArH), 9.68.(s, 1H, NH), 9.96.(s, 1H, NH), 10.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.6, 112.4, 115.2, 116.3, 119.6, 120.0, 126.2, 128.6, 128.9, 129.7, 130.4, 131.2, 132.8, 138.1, 141.6, 148.3, 155.6, 157.5, 159.2, 182.1; mass (ES+) *m/z*= 482.0 (M^++2). Anal. Calcd. for $C_{22}H_{18}BrN_5OS$ (Exact mass: 479.0415); C, 55.01; H, 3.78; N, 14.58. Found C, 55.34; H, 3.96; N, 14.37.

***N*-[4-(4-Methoxyanilino)quinazolin-6-yl]-*N*'-(2-naphthyl)thiourea (12g):** 54% (0.65g from 0.70g) as an off white solid, mp 109-110 °C; ν_{max} (KBr) 1219 (C=S), 3404 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ= 3.76 (s, 3H, OCH_3), 6.96 (d, 2H, *J*= 9.0 Hz, ArH), 7.51-7.61 (m, 4H, ArH), 7.67-7.72 (m, 3H, ArH), 7.88 (dd, 2H, J_1= 9.2 Hz, J_2= 2.3 Hz, ArH), 7.96 (d, 2H, *J*= 8.7 Hz, ArH), 8.03 (d, 1H, *J*= 8.0 Hz, ArH), 8.43 (s, 1H, ArH), 8.47 (s, 1H, ArH), 9.65 (s, 1H, NH), 9.90 (s, 1H, NH), 10.02 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ= 56.0, 114.4, 115.8, 119.6, 123.9, 124.9, 126.3, 126.4, 126.9, 127.0, 127.7, 128.4, 128.9, 130.8, 132.9, 133.0, 134.7, 135.8, 138.0, 148.3, 154.9, 156.5, 158.3, 163.1, 182.8; mass (ES+) *m/z*= 452.1 (M^++1). Anal.

Calcd. for $C_{26}H_{21}N_5OS$ (Exact mass: 451.1467); C, 69.16; H, 4.69; N, 15.51. Found C, 69.34; H, 4.43; N, 15.74.

Materials and Methods

In vitro antimalarial assay

The i*n vitro* antimalarial activity of the compounds was assessed against CQ-sensitive 3D7 strain of *P. falciparum* and compared with that of Chloroquine. Both schizontocidal activities (MIC) and 50% Inhibitory concentration (IC_{50}) were obtained as per the methods mentioned by us earlier.

Cytotoxicity assay

Cytotoxicity of the compounds was carried out using Vero cell line (C1008; Monkey kidney fibroblast) and MTT was used as reagent for the detection of cytotoxicity as mentioned earlier.[1] 50% cytotoxic concentration (CC_{50}) values represented the concentration of compound required to kill 50% of the fibroblast cells.

SI= CC_{50}/IC_{50}

In-vivo antimalarial assay

Swiss mice (25±1 g) of either sex were inoculated with $1x10^6$ *P. yoelii nigeriensis* MDR / *P. yoelii* N67 chloroquine resistant parasitized cells on day zero. A group of five mice was administered aqueous suspension of the test compounds at 50 mg/kg or 100 mg/kg dose from day zero to four *via* oral route; while another five mice were administered the vehicle alone. Thin blood smears from the tail vein of treated as well as control mice were observed on day 4, 7, 14, 21 and 28 days to record the degree of parasitaemia till 28 days or until animals survived.

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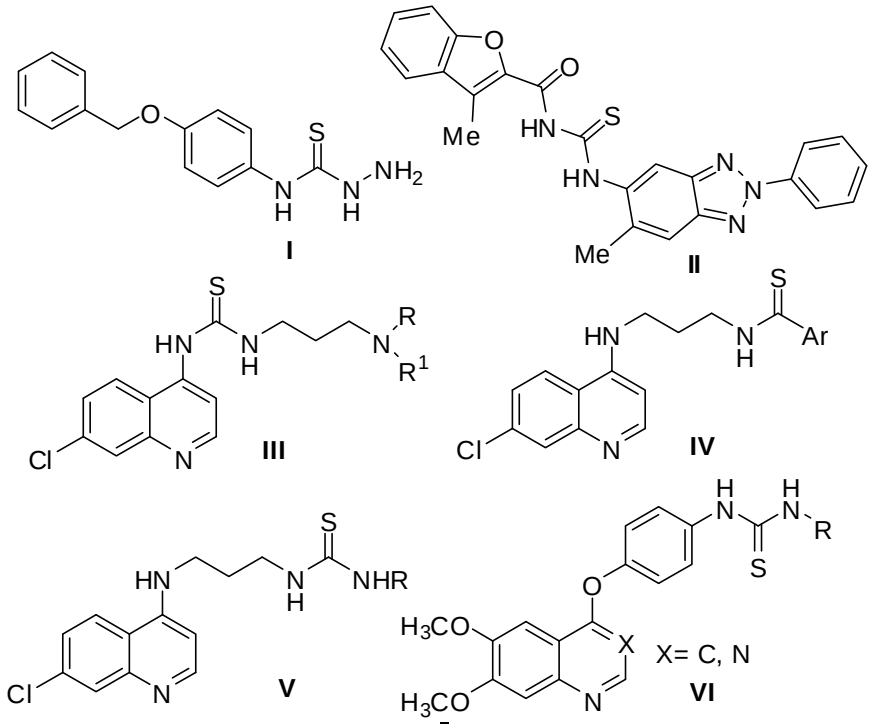
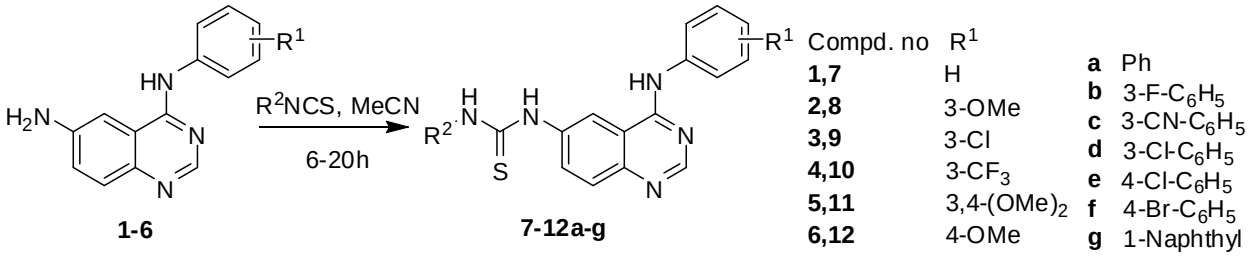


Figure. 1. Structure of a few thiourea derivatives showing antimalarial activity



1-6 **7-12a-g**

Compd. no	R^1
1,7	H
2,8	3-OMe
3,9	3-Cl
4,10	3-CF_3
5,11	3,4-$(OMe)_2$
6,12	4-OMe

a Ph
b 3-F-C_6H_5
c 3-CN-C_6H_5
d 3-Cl-C_6H_5
e 4-Cl-C_6H_5
f 4-Br-C_6H_5
g 1-Naphthyl

Scheme 1

Table 1. Results of the in vitro activity against 3D7 *P.falciparum* and in vivo antimalarial activity against mdr *P.yoelii nigeriensis* in swiss mice

Compd. No	R	R^1	MIC (μg/mL)	IC_{50} (ng/mL)	Selectivity Index	*In vivo* (% Mean Parasitaemia± S.D. on day 4)	*In vivo* (% Mean Parasitaemia± S.D. on day 7)
7a	H	Ph	2	-	-	-	-
7b	H	3-F-C_6H_4	2	792.2	70.3	-	-
7c	H	3-CN-C_6H_4	>10	-	-	-	-
7d	H	3-Cl-C_6H_4	2	813.2	29.0	-	-
7e	H	4-Cl-C_6H_4	2	-	-	-	-
7f	H	4-Br-C_6H_4	10	-	-	-	-
7g	H	1-Naphthyl	2	-	-	-	-
8a	3-OMe	Ph	2	258.2	38.7	-	-
8b	3-OMe	3-F-C_6H_4	1	26.7	510.7	-	-
8c	3-OMe	3-CN-C_6H_4	1	21.0	453.0	-	-
8d	3-OMe	3-Cl-C_6H_4	2	11.5	1615.3	46.54	28.45
8e	3-OMe	4-Cl-C_6H_4	10	-	-	-	-
8f	3-OMe	4-Br-C_6H_4	1	105.8	187.0	100.0	99.9[a]
8g	3-OMe	1-Naphthyl	10	-	-	-	-
9a	3-Cl	Ph	10	-	-	-	-
9b	3-Cl	3-F-C_6H_4	10	-	-	85.71	61.12
9c	3-Cl	3-CN-C_6H_4	>10	-	-	-	-
9d	3-Cl	3-Cl-C_6H_4	2.0	8.8	556.3	77.19	16.10
9e	3-Cl	4-Cl-C_6H_4	10	-	-	-	-
9f	3-Cl	4-Br-C_6H_4	2	526.1	1.0	-	-
9g	3-Cl	1-Naphthyl	10	-	-	-	-

10a	3-CF_3	Ph	2	991.7	69.0	-	-
10b	3-CF_3	3-F-C_6H_4	10	-	-	-	-
10c	3-CF_3	3-CN-C_6H_4	2	443.0	5.5	-	-
10d	3-CF_3	3-Cl-C_6H_4	10	-	-	-	-
10e	3-CF_3	4-Cl-C_6H_4	10	-	-	-	-
10f	3-CF_3	4-Br-C_6H_4	2	39.2	67.1	9.78	died
10g	3-CF_3	1-Naphthyl	10	-	-	-	-
11a	3,4-$(OMe)_2$	Ph	2	303.0	90.0	-	-
11b	3,4-$(OMe)_2$	3-F-C_6H_4	2	385.3	63.7	-	-
11c	3,4-$(OMe)_2$	3-CN-C_6H_4	10	-	-	-	-
11d	3,4-$(OMe)_2$	3-Cl-C_6H_4	10	-	-	-	-
11e	3,4-$(OMe)_2$	4-Cl-C_6H_4	10	-	-	-	-
11f	3,4-$(OMe)_2$	4-Br-C_6H_4	2	682.8	85.7	-	-
11g	3,4-$(OMe)_2$	1-Naphthyl	2	207.2	133.8	-	-
12a	4-OMe	Ph	2	242.6	80.4	-	-
12b	4-OMe	3-F-C_6H_4	2	53.2	206.4	-	-
12c	4-OMe	3-CN-C_6H_4	>10	-	-	-	-
12d	4-OMe	3-Cl-C_6H_4	>10	-	-	-	-
12e	4-OMe	4-Cl-C_6H_4	>10	-	-	-	-
12f	4-OMe	4-Br-C_6H_4	2	50.15	114.9	-	-
12g	4-OMe	1-Naphthyl	10		-	-	-
Control (MDR *P .yoelii nigeriensis*)			-	-	-	55.7±4.64	62.5±3.5[b]

[*]Screened against multidrug resistant *P .yoelii nigeriensis*. [a] 50% survival of mice till 28 days; [b] No survival till 28 days