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Research Paper

Thiazolidinyl-quinazolin-4-one derivatives: Design, Synthesis and *In vitro* evaluation of Antitubercular activities

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Abstract: A series of 2-[(4-oxo-2-phenyl-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazolin-4-one (**7a-v**) derivatives were designed and synthesized. The structures of all the synthesized compounds were characterized by elemental (C, H, and N) and spectral analysis like IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. All the targeted compounds were evaluated for their *in vitro* antitubercular activity against *mycobacterium tuberculosis H37Rv*, *in vitro* antibacterial activity against pathogenic gram positive and gram negative organisms and *in vitro* antifungal activity against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. From the result it was evaluated that those compounds displaying promising antimicrobial activity proved to be better antitubercular. Specially, compound **7m** and **7q** having 2-nitro and 4-chloro derivatives respectively.

Introduction

Nowadays, tuberculosis (TB), a contagious disease transmitted through the air, and caused by the bacterium *Mycobacterium tuberculosis*, is an important world-wide public health problem, which was declared a global health emergency in 1993 by the World Health Organization (WHO). It is estimated that one third of the world's population is infected with mycobacterium tuberculosis that continues to kill more than 1.7 million people every year [1].

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The global emergence of multi-drug-resistant tuberculosis and increased susceptibility of HIV-infected individuals to tuberculosis is emerging as a major infectious disease problem throughout the world [2]. Most of the drug resistant clinical isolates of the tubercle bacillus are resistant to isoniazid which is a first line antituberculous drug [3]. Despite the large number of compounds containing the isoniazid moiety which have already been synthesized and tested, there is still a need for the development of novel, potent, and unique antimicrobial agents of this kind are the preeminent way to overcome microbial

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resistance and develop effective therapies [4].

Thiazolidin-4-one a saturated form of thiazole with carbonyl group on fourth carbon [5] occupy an important place in medicinal chemistry as they show almost all types of biological activities [6-13]. Thiazolidinone-4-one inhibits the bacterial enzyme MurB which is involved in the biosynthesis of peptidoglycan layer of the cell wall, considered as phosphate bioisosteres [14]. The presence of a thiazolidinone ring in penicillin and related derivatives was the first recognition of its occurrence in nature [15]. Thiazolidin-4-one ring also found in naturally occurring actithiazic acid [(–) 2-(5-carboxypentyl) (thiazolidin-4-one)] which has been isolated from *streptomyces* strains and exhibited highly specific *in vitro* activity against *mycobacterium tuberculosis* [16]. It is believed that the presence of N-C-S linkage is responsible for the various biological activities [17].

The molecular manipulation of promising lead compounds is still a major line of approach to new drugs. Molecular manipulation involves the efforts to combine the separate groups of similar activity into one compound, thus making structural changes into the compound leading to changes in the biological activity [18]. Therefore, it was envisaged that chemical entities with isoniazid, quinazolinone and 4-thiazolidinone moieties would result in compounds of interesting biological activities. In order to randomly explore the novel compounds using theory of hybrid pharmacophore in one molecular scaffold [19-24], we have attempted to incorporate all the above three biologically active components together to give a confined structure for evaluating its various biological activities.

Result and Discussion

Chemistry

The synthetic protocol used to synthesize the title compounds is outlined in **Scheme 1.** Compounds **2a/2b**, **3a/3b**, **4a/4b** and **6a-v** were synthesized according to reported procedure [25,26]. Treatment of compounds **6a-v** with mercapto acetic acid in the presence of dry $ZnCl_2$ gives 2-[(4-oxo-2-phenyl-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl] - substituted quinazolin-4-one **7a-v.** The structures assigned to **7a-v** were supported by IR spectra showing absorption bands at 1712-1730 cm^{-1} for (C=O of thiazolidinone), 668-686 cm^{-1} for (C-S-C), 1665-1683 cm^{-1} for (C=O of amide), 3314-3328 cm^{-1} for (NH of amide), 530-560 cm^{-1} for (C-I) and 2947-2968 cm^{-1} for (C-H aliphatic). ^{1}H-NMR of these compounds revealed the presence of singlet at δ 2.76-2.97 ppm for two protons of ($C\underline{H}_2$-S) and singlet at δ 5.86-5.98 ppm for (N-C<u>H</u>-Ar). Further the appearance of singlet at δ 5.33-5.42 ppm for (CH_2-N<u>H</u>) and singlet at δ 2.54-2.70 ppm for ($C\underline{H}_2$-NH) confirming its assigned structure. ^{13}C-spectra of these compounds show the peak at δ 35.10-35.21 ppm for ($\underline{C}H_2$-S) and δ 57.28-57.48 ppm for (N-<u>C</u>H-Ar). Carbonyl carbon of thiazolidinone appears at δ 169.44-169.64 ppm, carbonyl carbon of amide appear at δ 168.39-168.60 ppm. **Figure 1** gives the idea regarding numbering system for ^{13}C-NMR spectra of compounds **7a-v.**

In vitro evaluation of antibacterial and antifungal activities

The MIC (Minimal Inhibition Concentration) of synthesized compounds was carried out by broth dilution method [27]. DMSO was used as the diluents to get desired concentration of drugs to test upon

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standard bacterial strains such as some gram positive bacteria *S. aureus (MTCC 96), S. pyogenus (MTCC 442), B. subtilis (MTCC 441)* and gram negative bacteria *E.coli (MTCC 443), P.aeruginosa (MTCC 1688), Kl. pneumoniae (MTCC109), S. typhi (MTCC 98),* and fungal strain such as *C.albicans (MTCC 227), A.niger (MTCC 282), A.clavatus (MTCC 1323).* Serial dilutions were prepared for the purpose of the primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful (10^6 CFU /ml) of bacteria evenly over a quarter of petri plate with Muller Hinton agar medium suitable for the growth of the test organism and placed for incubation at 37 ± 1 ºC overnight. The lowest concentration of the drugs inhibiting growth of the test bacterium was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was sub cultured and incubated overnight at 37 ± 1 ºC. The amount of growth from the control tube before incubation (which represents the original inoculums) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculums has been killed. Each synthesized drug was diluted obtaining 1000 µg/ml concentration, as a stock solution. In the primary screening 500, 250 and 125 µg/ml of the synthesized drugs was taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 µg/ml concentrations. The highest dilution showing at least 99% inhibition is taken as MIC. The literature survey revealed that substitution at C-2 and N-3 positions of thiazolidinone, presenting diverse degrees of inhibition against gram positive and gram negative bacterial strains and fungal strains [28a]. It has been also known that the introduction of arylidine moieties at different positions of the thiazolidinone ring enhanced the antimicrobial activity. As regards the relationships between the structure and the detected antibacterial activity, the 4-thiazolidinone **7a-v** showed a significant activity and appears to be dependent on the substitution at the benzene ring as well. Also the lipophilicity of the synthesized compounds increased remarkably compared with that of the parent drug, INH. This may render them more capable of penetrating various biomembranes[28b] consequently improving their permeation properties through mycobacterial cell membranes.

From *in vitro* antibacterial activity data, it is confirmed that compounds containing strong electron withdrawing i.e. **7q** (4-chloro) exhibited excellent anti-bacterial activity against almost all the tested microorganisms except *S. aureus,* while compound **7o** (4-nitro) exhibited excellent antibacterial activity against tested all gram positive strains. Introduction of electron withdrawing substituent displayed higher activity compared to electron donating substituent. The evaluation of the *in vitro* antifungal activity demonstrated that compounds **7q** and **7i** exhibited excellent activity against the fungal strain tested. In general, the order of antibacterial activity of the substituent at the aryl ring is 4-Cl>4-NO_2>4-OCH_3>4-OH>4-Br>4-C_2H_5=H>2-NO_2>2-OH>2-Cl>3-NO_2 and also the halogenated (iodo) derivatives are more active than non halogenated derivatives. From antimicrobial activity data it is also confirmed that the

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order of activity of the substituent at the aryl ring is para-isomer>ortho-isomer>meta-isomer. The *in vitro* antibacterial and antifungal screening results are summarized in **Table 1.**

In vitro evaluation of antitubercular activity

Drug susceptibility and determination of MIC of the test compounds against *mycobacterium tuberculosis H37Rv* were performed by L. J. (Lowenstein and Jensen) MIC method [29, 30] for the measurement of MIC. Stock solutions of primary 1000, 500, 250 μg/ml and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25 and 3.25 μg/ml dilutions of each test compound in dimethylsulphoxide (DMSO) were added liquid L. J. Medium and then media were sterilized by inspissations method. A culture of *mycobacterium tuberculosis H37Rv* growing on L. J. Medium was harvested in 0.85% saline in bijou bottles. These tubes were then incubated at 37 ± 1 ºC for 24 h followed by streaking of *mycobacterium tuberculosis H37Rv* ($5x10^4$ bacilli per tube). These tubes were then incubated at 37 ºC. Growth of bacilli was seen after 12 days, 22 days and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *mycobacterium tuberculosis H37Rv*. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. The standard strain *mycobacterium tuberculosis H37Rv* was tested with known drug rifampicin and isoniazid.

The encouraging results from the antibacterial and antifungal studies impelled us to go for preliminary screening of synthesized compounds against *mycobacterium tuberculosis H37Rv* which is summarized in **Table 2**. Compound **7q** and **7m** containing p-chloro and o-nitro substituent showed better activity (50 μg/ml) while, compounds **7d** and **7f** showed good activity (62.5 μg/ml) which is attributed due to the presence of electron withdrawing substituent, where as other compounds displayed moderate to good activity at the concentration of (100-500 μg/ml).

Experimental

All the melting points were taken in open capillaries tube and are uncorrected. The purity of compounds was ascertained by TLC (0.5 mm thickness) using silica gel-G coated aluminium plates (Merck) and spots were visualized by exposing the dry plates in iodine vapors. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. ^1H & ^{13}C NMR spectra were recorded on a Bruker's WM 400 FT MHz NMR instrument using DMSO-d_6 or $CDCl_3$- d_1 as solvent and TMS as internal reference (chemical shifts in δ ppm). IR spectra (ν_{max} in cm^{-1}) were recorded on Shimadzu FTIR spectrophotometer using KBr/Nujol technique. The elemental analysis (C, H, and N) of compounds was performed on Carlo Erba – 1108 elemental analyzer.

Substituted *N*-chloroacetyl anthranilic acid (2a/2b)

N-chloroacetyl anthranilic acid was synthesized using anthranilic acid **1a/1b** (0.01 mol) and chloroacetylchloride (0.02 mol) according to reported procedure [25,26]. The solid thus obtained was recrystallized from ethanol to give the title compound.

2-chloromethyl-3-(*N*-isonicotinamide-yl) -substituted 4*H*-quinazolinone (3a/3b)

N-chloroacetyl anthranilic acid **2a**/ *N*-chloroacetyl, 5-iodo-anthranilic acid **2b** (0.01 mol) was refluxed for 3 h with

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isonicotinic acid hydrazide following the reported procedure [25,26].

2-hydrazinomethyl-3-[*N*-isonicotinamide-yl] - substituted quinazoline-4-one (4a/4b)

Compound **4a/4b** was synthesized according to reported procedure [25,26].

General procedure for the synthesis of 2-benzylidenehydrazinomethyl-3-[*N*-isonicotinamide-yl] - substituted quinazoline-4-one (6a-v)

An equimolar amount of 2-hydrazinomethyl-3-[*N*-isonicotinamide-yl] - substituted quinazoline-4-one **4a/4b** (0.01 mol) and appropriate aromatic aldehyde **5a-k** (0.01 mol) was dissolved in absolute ethanol (50 ml) in the presence of catalytic amount of glacial acetic acid following the procedure [25,26].

General procedure for the synthesis of 2-[(4-oxo-2-phenyl-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl] - substituted quinazolin-4-one (7a-v)

Title compounds **7a-v** was synthesized according to reported procedure [31] by doing minor modification as under.

Thioglycolic acid (0.01 mol) and anhydrous Zinc chloride (0.01 mol) were added to the solution of compound **6a-v** (0.02 mol) in DMF (50 mL) at room temperature and then the reaction mixture was refluxed for 7 to 8 h. The progress and completion of the reaction was checked by TLC. After completion of the reaction, excess of solvent was distilled off to get residue, which was allowed to pour in ice cold water, then filtered and washed with water. The solid, thus, separated out was dried and recrystallized with appropriate solvent to furnish desired compounds **7a-v**. The physical, analytical and spectral data of compounds **7a-v** are as follows,

2-[(4-oxo-2-phenyl-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazolin-4-one (7a)

Yield: 62%; m.p.: 249-251 °C; MS: m/z $[472.13]^+$; FTIR (KBr, ν cm^{-1}): 3325 (NH), 3056 (C-H aromatic), 2947 (C-H aliphatic), 1724 (C=O of thiazolidinone), 1678 (C=O of amide), 1653 (C=O of quinazolinone), 1317 (C=N), 1264 (N-N), 674 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.63 (s, 2H, CH_2), 2.87 (s, 2H, S-CH_2), 5.36 (s, 1H, NH), 5.93 (s, 1H, N-CH-Ar), 6.74-7.95 (m, 13H, Ar-H), 8.72 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.12 (C_{18}), 47.58 (C_{15}), 57.46 (C_{16}), 122.67-133.40 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{23}), 138.23 (C_{24}), 142.68 (C_{14}), 147.83 (C_1), 150.16 (C_{12}-C_{13}), 164.15 (C_8), 167.23 (C_7), 168.54 (C_9), 169.57 (C_{17}); Analysis calculated for $C_{24}H_{20}N_6O_3S$: C, 61.00; H, 4.27; N, 17.79. Found: C, 60.91; H, 4.12; N, 17.68%.

2-[(4-oxo-2-{o-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7b)

Yield: 54%; m.p.: 254-256 °C; MS: m/z $[517.21]^+$; FTIR (KBr, ν cm^{-1}): 3326 (NH), 3048 (C-H aromatic), 2954 (C-H aliphatic), 1720 (C=O of thiazolidinone), 1683 (C=O of amide), 1650 (C=O of quinazolinone), 1523 (NO_2), 1314 (C=N), 1268 (N-N), 675 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.67 (s, 2H, CH_2), 2.76 (s, 2H, S-CH_2), 5.34 (s, 1H, NH), 5.90 (s, 1H, N-CH-Ar), 6.93-8.19 (m, 12H, Ar-H), 8.78 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.18 (C_{18}), 47.60 (C_{15}), 57.34 (C_{16}), 122.36-133.29 (C_2-C_6,C_{10}-C_{11},C_{19},C_{22}-C_{24}), 134.63 (C_{21}), 142.52 (C_{14}), 147.88 (C_1), 148.93 (C_{20}), 150.28 (C_{12}-C_{13}), 164.23 (C_8), 167.19 (C_7), 168.56 (C_9), 169.64 (C_{17}); Analysis calculated for $C_{24}H_{19}N_7O_5S$: C, 55.70; H, 3.70; N, 18.95. Found: C, 55.67; H, 3.44; N, 18.80%.

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2-[(4-oxo-2-{m-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7c)

Yield: 64%; m.p.: 260-262 °C; MS: m/z $[517.13]^+$; FTIR (KBr, ν cm^{-1}): 3314 (NH), 3052 (C-H aromatic), 2953 (C-H aliphatic), 1725 (C=O of thiazolidinone), 1680 (C=O of amide), 1654 (C=O of quinazolinone), 1528 (NO_2), 1320 (C=N), 1263 (N-N), 679 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.65 (s, 2H, CH_2), 2.83 (s, 2H, S-CH_2), 5.41 (s, 1H, NH), 5.92 (s, 1H, N-CH-Ar), 6.78-7.94 (m, 12H, Ar-H), 8.72 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.17 (C_{18}), 47.62 (C_{15}), 57.28 (C_{16}), 122.73-133.40 (C_2-C_6,C_{10}-C_{11},C_{20},C_{21},C_{23}), 135.12 (C_{19}), 139.16 (C_{24}), 142.57 (C_{14}), 147.85 (C_1), 148.16 (C_{22}), 150.09 (C_{12}-C_{13}), 164.20 (C_8), 167.14 (C_7), 168.48 (C_9), 169.61 (C_{17}); Analysis calculated for $C_{24}H_{19}N_7O_5S$: C, 55.70; H, 3.70; N, 18.95. Found: C, 55.67; H, 3.58; N, 18.74%.

2-[(4-oxo-2-{p-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7d)

Yield: 53%; m.p.: 270-272 °C; MS: m/z $[517.36]^+$; FTIR (KBr, ν cm^{-1}): 3324 (NH), 3045 (C-H aromatic), 2950 (C-H aliphatic), 1716 (C=O of thiazolidinone), 1675 (C=O of amide), 1643 (C=O of quinazolinone), 1534 (NO_2), 1324 (C=N), 1255 (N-N), 676 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.70 (s, 2H, CH_2), 2.86 (s, 2H, S-CH_2), 5.37 (s, 1H, NH), 5.89 (s, 1H, N-CH-Ar), 6.94-8.04 (m, 12H, Ar-H), 8.72 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.16 (C_{18}), 47.54 (C_{15}), 57.38 (C_{16}), 122.67-133.47 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{22}), 142.68 (C_{14}), 144.52 (C_{24}), 146.73 (C_{23}), 147.89 (C_1), 150.12 (C_{12}-C_{13}), 164.14 (C_8), 167.17 (C_7), 168.39 (C_9), 169.53 (C_{17}); Analysis calculated for $C_{24}H_{19}N_7O_5S$: C, 55.70; H, 3.70; N, 18.95. Found: C, 55.58; H, 3.68; N, 18.86%.

2-[(4-oxo-2-{o-chlorophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7e)

Yield: 58%; m.p.: 277-279 °C; MS: m/z $[506.15]^+$; FTIR (KBr, ν cm^{-1}): 3320 (NH), 3046 (C-H aromatic), 2963 (C-H aliphatic), 1723 (C=O of thiazolidinone), 1678 (C=O of amide), 1654 (C=O of quinazolinone), 1320 (C=N), 1259 (N-N), 748 (C-Cl), 673 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.61 (s, 2H, CH_2), 2.88 (s, 2H, S-CH_2), 5.34 (s, 1H, NH), 5.98 (s, 1H, N-CH-Ar), 7.08-8.15 (m, 12H, Ar-H), 8.76 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.21 (C_{18}), 47.63 (C_{15}), 57.34 (C_{16}), 122.70-133.42 (C_2-C_6,C_{10}-C_{11},C_{19},C_{21}-C_{23}), 134.36 (C_{20}), 138.65 (C_{24}), 142.56 (C_{14}), 147.80 (C_1), 150.14 (C_{12}-C_{13}), 164.22 (C_8), 167.15 (C_7), 168.60 (C_9), 169.56 (C_{17}); Analysis calculated for $C_{24}H_{19}ClN_6O_3S$: C, 56.86; H, 3.78; N, 16.58. Found: C, 56.71; H, 3.57; N, 16.46%.

2-[(4-oxo-2-{p-chlorophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7f)

Yield: 59%; m.p.: 294-296 °C; MS: m/z $[506.28]^+$; FTIR (KBr, ν cm^{-1}): 3326 (NH), 3053 (C-H aromatic), 2965 (C-H aliphatic), 1725 (C=O of thiazolidinone), 1674 (C=O of amide), 1645 (C=O of quinazolinone), 1321 (C=N), 1256 (N-N), 763 (C-Cl), 675 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.67 (s, 2H, CH_2), 2.91 (s, 2H, S-CH_2), 5.38 (s, 1H, NH), 5.86 (s, 1H, N-CH-Ar), 6.87-7.93 (m, 12H, Ar-H), 8.81 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.14 (C_{18}), 47.58 (C_{15}), 57.42 (C_{16}), 122.69-133.34 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{23}), 136.23 (C_{24}), 142.63 (C_{14}), 147.78 (C_1), 150.20 (C_{12}-C_{13}), 164.18 (C_8), 167.25 (C_7), 168.59 (C_9), 169.54 (C_{17}); Analysis calculated for $C_{24}H_{19}ClN_6O_3S$: C, 56.86; H, 3.78; N, 16.58. Found: C, 56.72; H, 3.68; N, 16.46%.

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2-[(4-oxo-2-{o-hydroxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7g)

Yield: 57%; m.p.: 298-300 °C, MS: m/z $[488.20]^+$; FTIR (KBr, ν cm^{-1}): 3318 (NH), 3064 (OH), 3048 (C-H aromatic), 2959 (C-H aliphatic), 1714 (C=O of thiazolidinone), 1679 (C=O of amide), 1652 (C=O of quinazolinone), 1317 (C=N), 1253 (N-N), 686 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.66 (s, 2H, CH_2), 2.85 (s, 2H, S-CH_2), 5.37 (s, 1H, NH), 5.94 (s, 1H, N-CH-Ar), 6.74-7.85 (m, 12H, Ar-H), 8.76 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.17 (C_{18}), 47.60 (C_{15}), 57.39 (C_{16}), 122.46-133.42 (C_2-C_6,C_{10}-C_{11},C_{19},C_{21}-C_{24}), 142.49 (C_{14}), 147.80 (C_1), 150.16 (C_{12}-C_{13}), 157.64 (C_{20}), 164.21 (C_8), 167.18 (C_7), 168.52 (C_9), 169.50 (C_{17}); Analysis calculated for $C_{24}H_{20}N_6O_4S$: C, 59.01; H, 4.13; N, 17.20. Found: C, 58.81; H, 4.03; N, 17.13%.

2-[(4-oxo-2-{p-hydroxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7h)

Yield: 55%; m.p.: 285-287 °C; MS: m/z $[488.06]^+$; FTIR (KBr, ν cm^{-1}): 3328 (NH), 3068 (OH), 3049 (C-H aromatic), 2963 (C-H aliphatic), 1720 (C=O of thiazolidinone), 1674 (C=O of amide), 1644 (C=O of quinazolinone), 1322 (C=N), 1253 (N-N), 670 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.68 (s, 2H, CH_2), 2.97 (s, 2H, S-CH_2), 5.42 (s, 1H, NH), 5.89 (s, 1H, N-CH-Ar), 6.81-7.98 (m, 12H, Ar-H), 8.73 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.20 (C_{18}), 47.62 (C_{15}), 57.35 (C_{16}), 122.42-133.50 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{22},C_{24}), 142.32 (C_{14}), 147.77 (C_1), 150.23 (C_{12}-C_{13}), 155.68 (C_{23}), 164.23 (C_8), 167.20 (C_7), 168.48 (C_9), 169.54 (C_{17}); Analysis calculated for $C_{24}H_{20}N_6O_4S$: Calcd: C, 59.01; H, 4.13; N, 17.20. Found: C, 58.94; H, 4.02; N, 17.10%.

2-[(4-oxo-2-{p-methoxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7i)

Yield: 61%; m.p.: 283-285 °C; MS: m/z $[502.23]^+$; FTIR (KBr, ν cm^{-1}): 3317 (NH), 3042 (C-H aromatic), 2950 (C-H aliphatic), 2883 (OCH_3), 1721 (C=O of thiazolidinone), 1665 (C=O of amide), 1651 (C=O of quinazolinone), 1315 (C=N), 1257 (N-N), 677 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.58 (s, 2H, CH_2), 2.87 (s, 2H, S-CH_2), 5.33 (s, 1H, NH), 5.96 (s, 1H, N-CH-Ar), 6.86-7.93 (m, 12H, Ar-H), 8.80 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.15 (C_{18}), 47.57 (C_{15}), 56.21 (OCH_3), 57.43 (C_{16}), 122.38-133.50 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{22},C_{24}), 142.51 (C_{14}), 147.82 (C_1), 150.25 (C_{12}-C_{13}), 160.54 (C_{23}), 164.19 (C_8), 167.13 (C_7), 168.54 (C_9), 169.46 (C_{17}); Analysis calculated for $C_{25}H_{22}N_6O_4S$: Calcd: C, 59.75; H, 4.41; N, 16.72. Found: C, 59.68; H, 4.32; N, 16.67%.

2-[(4-oxo-2-{p-ethylphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7j)

Yield: 69%; m.p.: 296-298 °C; MS: m/z $[500.11]^+$; FTIR (KBr, ν cm^{-1}): 3323 (NH), 3046 (C-H aromatic), 2952 (C-H aliphatic), 1719 (C=O of thiazolidinone), 1676 (C=O of amide), 1655 (C=O of quinazolinone), 1314 (C=N), 1264 (N-N), 672 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 1.16 (t, 3H, CH_3, *J=6.7 Hz*), 2.48 (q, 2H, CH_2, *J=6.8 Hz*), 2.54 (s, 2H, CH_2), 2.84 (s, 2H, S-CH_2), 5.38 (s, 1H, NH), 5.93 (s, 1H, N-CH-Ar), 6.97-7.84 (m, 12H, Ar-H), 8.79 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 16.23 (CH_3), 28.54 (CH_2), 35.18 (C_{18}), 47.59 (C_{15}), 57.41 (C_{16}), 122.45-133.48 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{22}), 135.43 (C_{24}), 138.64 (C_{23}), 142.48 (C_{14}), 147.82 (C_1), 150.14 (C_{12}-C_{13}), 164.27 (C_8), 167.23 (C_7), 168.60 (C_9),

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169.44 (C_{17}); Analysis calculated for $C_{26}H_{24}N_6O_3S$: Calcd: C, 62.38; H, 4.83; N, 16.79. Found: C, 62.24; H, 4.72; N, 16.66%.

2-[(4-oxo-2-{p-bromophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazoline-4-one (7k)

Yield: 63%; m.p.: 315-317 °C; MS: m/z $[550.13]^+$; FTIR (KBr, ν cm^{-1}): 3316 (NH), 3048 (C-H aromatic), 2954 (C-H aliphatic), 1712 (C=O of thiazolidinone), 1678 (C=O of amide), 1647 (C=O of quinazolinone), 1320 (C=N), 1263 (N-N), 695 (C-Br), 668 (C-S-C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.69 (s, 2H, CH_2), 2.86 (s, 2H, S-CH_2), 5.40 (s, 1H, NH), 5.95 (s, 1H, N-CH-Ar), 6.82-7.98 (m, 12H, Ar-H), 8.67 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.10 (C_{18}), 47.62 (C_{15}), 57.48 (C_{16}), 122.44-133.35 (C_2-C_6,C_{10}-C_{11},C_{19}-C_{23}), 137.28 (C_{24}), 142.53 (C_{14}), 147.83 (C_1), 150.14 (C_{12}-C_{13}), 157.63 (C_{20}), 164.22 (C_8), 167.15 (C_7), 168.53 (C_9), 169.51 (C_{17}); Analysis calculated for $C_{24}H_{19}BrN_6O_3S$: Calcd: C, 52.28; H, 3.47; N, 15.24. Found: C, 52.13; H, 3.40; N, 15.02%.

2-[(4-oxo-2-phenyl-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazolin-4-one (7l)

Yield: 62%; m.p.: 253-255 °C; MS: m/z $[598.12]^+$; FTIR (KBr, ν cm^{-1}): 3328 (NH), 3053 (C-H aromatic), 2949 (C-H aliphatic), 1721 (C=O of thiazolidinone), 1676 (C=O of amide), 1652 (C=O of quinazolinone), 1318 (C=N), 1265 (N-N), 677 (C-S-C), 530 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.61 (s, 2H, CH_2), 2.89 (s, 2H, S-CH_2), 5.35 (s, 1H, NH), 5.92 (s, 1H, N-CH-Ar), 6.76-7.98 (m, 12H, Ar-H), 8.70 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.14 (C_{18}), 47.59 (C_{15}), 57.45 (C_{16}), 95.73 (C_4), 122.66-133.42 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19}-C_{23}), 138.20 (C_{24}), 142.69 (C_{14}), 147.81 (C_1), 150.18 (C_{12}-C_{13}), 164.17 (C_8), 167.25 (C_7), 168.49 (C_9), 169.58 (C_{17}); Analysis calculated for $C_{24}H_{19}IN_6O_3S$: C, 48.17; H, 3.20; N, 14.04. Found: C, 48.13; H, 3.15; N, 13.94%.

2-[(4-oxo-2-{o-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7m)

Yield: 54%; m.p.: 260-262 °C; MS: m/z $[643.24]^+$; FTIR (KBr, ν cm^{-1}): 3324 (NH), 3050 (C-H aromatic), 2952 (C-H aliphatic), 1718 (C=O of thiazolidinone), 1678 (C=O of amide), 1656 (C=O of quinazolinone), 1523 (NO_2), 1315 (C=N), 1267 (N-N), 673 (C-S-C), 534 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.64 (s, 2H, CH_2), 2.78 (s, 2H, S-CH_2), 5.33 (s, 1H, NH), 5.92 (s, 1H, N-CH-Ar), 6.93-8.19 (m, 11H, Ar-H), 8.79 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.18 (C_{18}), 47.60 (C_{15}), 57.34 (C_{16}), 95.76 (C_4), 122.39-133.26 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19},C_{22}-C_{24}), 134.58 (C_{21}), 142.60 (C_{14}), 147.87 (C_1), 148.89 (C_{20}), 150.30 (C_{12}-C_{13}), 164.22 (C_8), 167.19 (C_7), 168.52 (C_9), 169.53 (C_{17}); Analysis calculated for $C_{25}H_{19}IN_6O_5S$: C, 44.80; H, 2.82; N, 15.24.. Found: C, 44.67; H, 2.74; N, 15.16%.

2-[(4-oxo-2-{m-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7n)

Yield: 64%; m.p.: 265-267 °C; MS: m/z $[643.18]^+$; FTIR (KBr, ν cm^{-1}): 3315 (NH), 3053 (C-H aromatic), 2956 (C-H aliphatic), 1722 (C=O of thiazolidinone), 1682 (C=O of amide), 1655 (C=O of quinazolinone), 1530 (NO_2), 1317 (C=N), 1264 (N-N), 678 (C-S-C), 536 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.67 (s, 2H, CH_2), 2.86 (s, 2H, S-CH_2), 5.40 (s, 1H, NH), 5.91 (s, 1H, N-CH-Ar), 6.74-7.90 (m, 11H, Ar-H), 8.75 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.20 (C_{18}), 47.59 (C_{15}), 57.30 (C_{16}), 95.72 (C_4), 122.73-133.47 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{20},C_{21},C_{23}), 135.14 (C_{19}), 139.23 (C_{24}), 142.54 (C_{14}), 147.76

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(C_1), 148.26 (C_{22}), 150.12 (C_{12}-C_{13}), 164.24 (C_8), 167.14 (C_7), 168.43 (C_9), 169.60 (C_{17}); Analysis calculated for $C_{25}H_{19}IN_6O_5S$: C, 44.80; H, 2.82; N, 15.24. Found: C, 44.76; H, 2.78; N, 15.13%.

2-[(4-oxo-2-{p-nitrophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7o)

Yield: 53%; m.p.: 273-275 °C; MS: m/z $[643.13]^+$; FTIR (KBr, ν cm^{-1}): 3326 (NH), 3048 (C-H aromatic), 2955 (C-H aliphatic), 1721 (C=O of thiazolidinone), 1672 (C=O of amide), 1644 (C=O of quinazolinone), 1537 (NO_2), 1325 (C=N), 1258 (N-N), 670 (C-S-C), 532 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.69 (s, 2H, CH_2), 2.84 (s, 2H, S-CH_2), 5.36 (s, 1H, NH), 5.90 (s, 1H, N-CH-Ar), 6.83-8.21 (m, 11H, Ar-H), 8.74 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.18 (C_{18}), 47.56 (C_{15}), 57.35 (C_{16}), 95.80 (C_4), 122.61-133.40 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19}-C_{22}), 142.60 (C_{14}), 144.58 (C_{24}), 146.71 (C_{23}), 147.83 (C_1), 150.14 (C_{12}-C_{13}), 164.15 (C_8), 167.20 (C_7), 168.45 (C_9), 169.56 (C_{17}); Analysis calculated for $C_{24}H_{18}IN_7O_5S$: C, 44.80; H, 2.82; N, 15.24. Found: C, 44.72; H, 2.68; N, 15.17%.

2-[(4-oxo-2-{o-chlorophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7p)

Yield: 58%; m.p.: 284-286 °C; MS: m/z $[631.78]^+$; FTIR (KBr, ν cm^{-1}): 3324 (NH), 3050 (C-H aromatic), 2964 (C-H aliphatic), 1730 (C=O of thiazolidinone), 1670 (C=O of amide), 1652 (C=O of quinazolinone), 1318 (C=N), 1255 (N-N), 746 (C-Cl), 675 (C-S-C), 540 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.65 (s, 2H, CH_2), 2.84 (s, 2H, S-CH_2), 5.38 (s, 1H, NH), 5.97 (s, 1H, N-CH-Ar), 7.13-8.19 (m, 11H, Ar-H), 8.80 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.20 (C_{18}), 47.65 (C_{15}), 57.30 (C_{16}), 95.74 (C_4), 122.71-133.42 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19},C_{21}-C_{23}), 134.30 (C_{20}), 138.62 (C_{24}), 142.53 (C_{14}), 147.78 (C_1), 150.18 (C_{12}-C_{13}), 164.20 (C_8), 167.16 (C_7), 168.57 (C_9), 169.60 (C_{17}); Analysis calculated for $C_{24}H_{18}ClIN_6O_3S$: C, 45.55; H, 2.87; N, 13.28. Found: C, 45.47; H, 2.85; N, 13.14%.

2-[(4-oxo-2-{p-chlorophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7q)

Yield: 59%; m.p.: 296-298 °C; MS: m/z $[631.84]^+$; (KBr, ν cm^{-1}): 3321 (NH), 3054 (C-H aromatic), 2968 (C-H aliphatic), 1723 (C=O of thiazolidinone), 1673 (C=O of amide), 1648 (C=O of quinazolinone), 1315 (C=N), 1259 (N-N), 760 (C-Cl), 677 (C-S-C), 543 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.68 (s, 2H, CH_2), 2.92 (s, 2H, S-CH_2), 5.40 (s, 1H, NH), 5.86 (s, 1H, N-CH-Ar), 6.84-7.90 (m, 11H, Ar-H), 8.83 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.13 (C_{18}), 47.60 (C_{15}), 57.43 (C_{16}), 95.70 (C_4), 122.70-133.23 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19}-C_{23}), 136.25 (C_{24}), 142.64 (C_{14}), 147.75 (C_1), 150.17 (C_{12}-C_{13}), 164.19 (C_8), 167.24 (C_7), 168.60 (C_9), 169.51 (C_{17}); Analysis calculated for $C_{24}H_{19}ClN_6O_3S$: C, 45.55; H, 2.87; N, 13.28. Found: C, 45.42; H, 2.76; N, 13.11%.

2-[(4-oxo-2-{o-hydroxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7r)

Yield: 57%; m.p.: 299-301 °C; MS: m/z $[614.17]^+$; FTIR (KBr, ν cm^{-1}): 3315 (NH), 3068 (OH), 3034 (C-H aromatic), 2960 (C-H aliphatic), 1723 (C=O of thiazolidinone), 1676 (C=O of amide), 1654 (C=O of quinazolinone), 1318 (C=N), 1255 (N-N), 680 (C-S-C), 546 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.64 (s, 2H, CH_2), 2.82 (s, 2H, S-CH_2), 5.38 (s, 1H, NH), 5.93 (s, 1H, N-CH-Ar), 6.56-7.83 (m, 11H, Ar-H), 8.77 (s, 1H, NH-CO); ^{13}C-NMR (100

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MHz, DMSO-d_6) δ ppm: 35.20 (C_{18}), 47.62 (C_{15}), 57.33 (C_{16}), 95.76 (C_4), 115.58 (C_{22}), 122.24-133.48 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19},C_{21},C_{23},C_{24}), 142.44 (C_{14}), 147.83 (C_1), 150.18 (C_{12}-C_{13}), 157.73 (C_{20}), 164.24 (C_8), 167.18 (C_7), 168.53 (C_9), 169.51 (C_{17}); Analysis calculated for $C_{24}H_{19}IN_6O_4S$: C, 46.92; H, 3.12; N, 13.68. Found: C, 46.85; H, 3.03; N, 13.47%.

2-[(4-oxo-2-{p-hydroxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7s)

Yield: 55%; m.p.: 287-289 °C; MS: m/z $[614.23]^+$; (KBr, ν cm^{-1}): 3318 (NH), 3079 (OH), 3038 (C-H aromatic), 2965 (C-H aliphatic), 1719 (C=O of thiazolidinone), 1678 (C=O of amide), 1648 (C=O of quinazolinone), 1327 (C=N), 1251 (N-N), 674 (C-S-C), 548 (C-I).^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.69 (s, 2H, CH_2), 2.98 (s, 2H, S-CH_2), 5.42 (s, 1H, NH), 5.92 (s, 1H, N-CH-Ar), 6.78-7.95 (m, 11H, Ar-H), 8.74 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.20 (C_{18}), 47.65 (C_{15}), 57.34 (C_{16}), 95.72 (C_4), 115.73 (C_{21},C_{22}), 122.43-133.56 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19},C_{20},C_{24}), 142.33 (C_{14}), 147.75 (C_1), 150.24 (C_{12}-C_{13}), 155.62 (C_{23}), 164.20 (C_8), 167.21 (C_7), 168.47 (C_9), 169.55 (C_{17}); Analysis calculated for $C_{24}H_{19}IN_6O_4S$: Calcd: C, 46.92; H, 3.12; N, 13.68. Found: C, 46.81; H, 3.06; N, 13.49%.

2-[(4-oxo-2-{p-methoxyphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7t)

Yield: 61%; m.p.: 279-281 °C; MS: m/z $[628.19]^+$; (KBr, ν cm^{-1}): 3321 (NH), 3040 (C-H aromatic), 2953 (C-H aliphatic), 2885 (OCH_3), 1724 (C=O of thiazolidinone), 1668 (C=O of amide), 1652 (C=O of quinazolinone), 1319 (C=N), 1258 (N-N), 668 (C-S-C), 552 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.57 (s, 2H, CH_2), 2.88 (s, 2H, S-CH_2), 5.36 (s, 1H, NH), 5.97 (s, 1H, N-CH-Ar), 6.84-7.90 (m, 11H, Ar-H), 8.83 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.16 (C_{18}), 47.53 (C_{15}), 56.24 (OCH_3), 57.44 (C_{16}), 95.67 (C_4), 114.13 (C_{21},C_{22}), 122.40-133.52 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19},C_{20},C_{24}), 142.43 (C_{14}), 147.68 (C_1), 150.24 (C_{12}-C_{13}), 160.57 (C_{23}), 164.22 (C_8), 167.14 (C_7), 168.56 (C_9), 169.49 (C_{17}); Analysis calculated for $C_{25}H_{21}IN_6O_4S$: Calcd: C, 47.78; H, 3.37; N, 13.37. Found: C, 47.69; H, 3.22; N, 13.26%.

2-[(4-oxo-2-{p-ethylphenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7u)

Yield: 69%; m.p.: 316-318 °C; MS: m/z $[500.05]^+$; FTIR (KBr, ν cm^{-1}): 3326 (NH), 3048 (C-H aromatic), 2951 (C-H aliphatic), 1715 (C=O of thiazolidinone), 1674 (C=O of amide), 1653 (C=O of quinazolinone), 1318 (C=N), 1263 (N-N), 670 (C-S-C), 556 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, CH_3, *J=6.8 Hz*), 2.44 (q, 2H, CH_2, *J=6.9 Hz*), 2.55 (s, 2H, CH_2), 2.81 (s, 2H, S-CH_2), 5.37 (s, 1H, NH), 5.96 (s, 1H, N-CH-Ar), 6.80-7.82 (m, 11H, Ar-H), 8.77 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 16.24 (CH_3), 28.56 (CH_2), 35.19 (C_{18}), 47.54 (C_{15}), 57.41 (C_{16}), 95.78 (C_4), 122.43-133.40 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19}-C_{22}), 135.44 (C_{24}), 138.76 (C_{23}), 142.45 (C_{14}), 147.84 (C_1), 150.16 (C_{12}-C_{13}), 164.24 (C_8), 167.27 (C_7), 168.59 (C_9), 169.48 (C_{17}); Analysis calculated for $C_{26}H_{23}IN_6O_3S$: Calcd: C, 49.85; H, 3.70; N, 13.41. Found: C, 49.74; H, 3.57; N, 13.34%.

2-[(4-oxo-2-{p-bromophenyl}-thiazolidin-3-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-6-iodo-quinazoline-4-one (7v)

Yield: 63%; m.p.: 320-322 °C; MS: m/z $[675.89]^+$; FTIR (KBr, ν cm^{-1}): 3319 (NH), 3047 (C-H aromatic), 2956 (C-H aliphatic), 1718 (C=O of thiazolidinone), 1679 (C=O

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of amide), 1650 (C=O of quinazolinone), 1322 (C=N), 1265 (N-N), 694 (C-Br), 670 (C-S-C), 560 (C-I); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.70 (s, 2H, CH_2), 2.84 (s, 2H, S-CH_2), 5.42 (s, 1H, NH), 5.97 (s, 1H, N-CH-Ar), 6.83-7.89 (m, 11H, Ar-H), 8.65 (s, 1H, NH-CO); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 35.12 (C_{18}), 47.64 (C_{15}), 57.47 (C_{16}), 95.82 (C_4), 122.40-133.32 (C_2,C_3,C_5,C_6,C_{10}-C_{11},C_{19}-C_{23}), 137.18 (C_{24}), 142.54 (C_{14}), 147.80 (C_1), 150.18 (C_{12}-C_{13}), 164.27 (C_8), 167.16 (C_7), 168.51 (C_9), 169.57 (C_{17}); Analysis calculated for $C_{24}H_{18}BrIN_6O_3S$: Calcd: C, 42.56; H, 2.68; N, 12.41. Found: C, 42.43; H, 2.57; N, 12.35%.

Conclusion

A series of thiazolidinyl-quinazolin-4-one derivatives were synthesized by using theory of hybrid pharmacophore in one molecular scaffold and assessed for their antimicrobial and antitubercular activities. From SAR study it can be concluded that activity is influenced by the introduction of various substituents on the phenyl ring. The antibacterial activity data indicates that the analogs with electron withdrawing substituents emerged as promising antimicrobials showing better to moderate activity while analogs bearing chloro and methoxy substituent showed better antifungal activities. It was also observed that the promising antimicrobials have proved to be better antitubercular. Specially, compound **7q** and **7m** due to their better activity against *mycobacterium tuberculosis H37Rv* strain are the best choice for the preparation of new derivatives in order to improve antitubercular activity. It can be concluded that this class of compounds certainly holds great promise towards pursuit to discover novel class of antimicrobial and antitubercular agents. Further studies are being conducted to acquire more information about structure–activity relationships.

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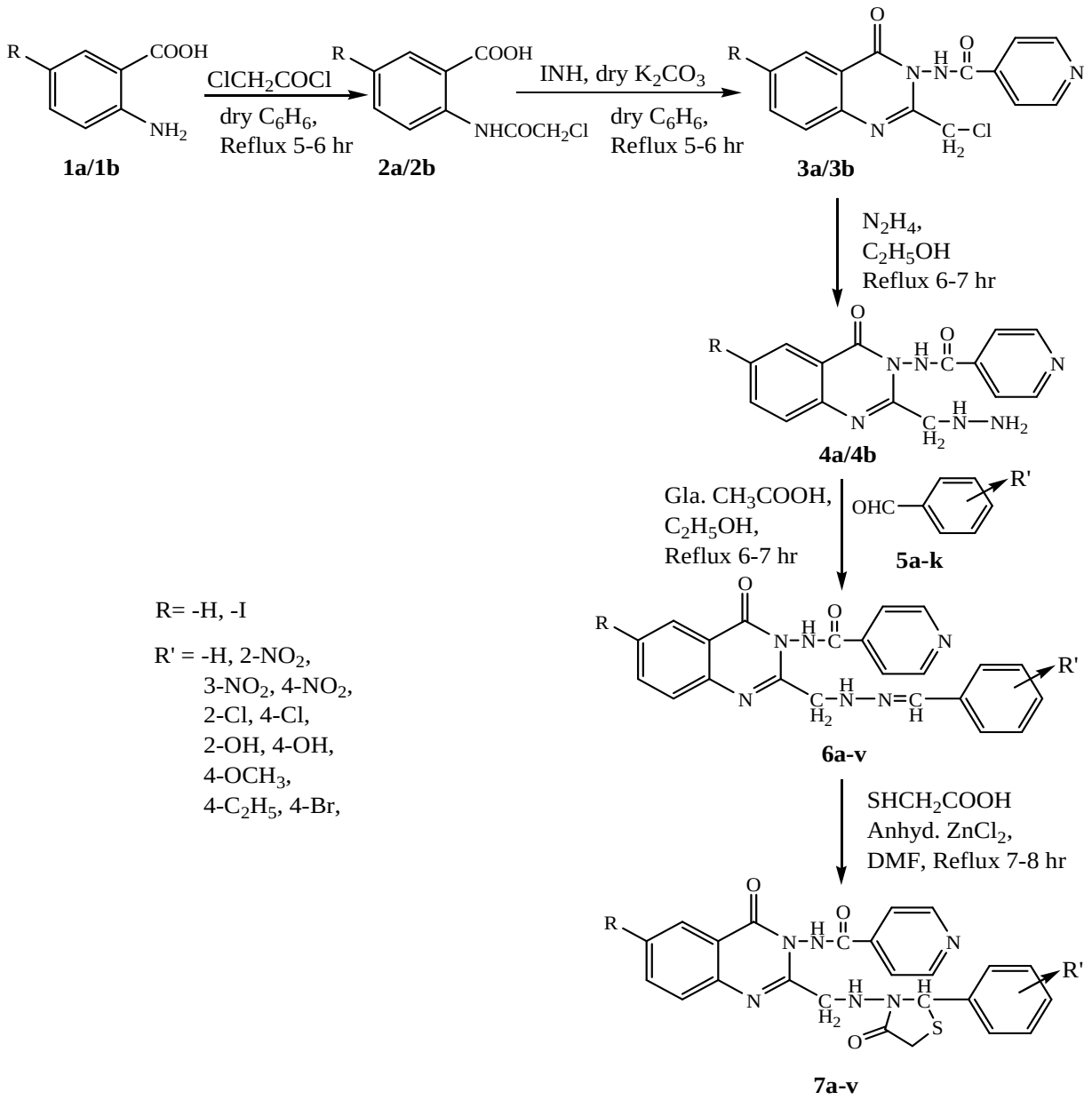
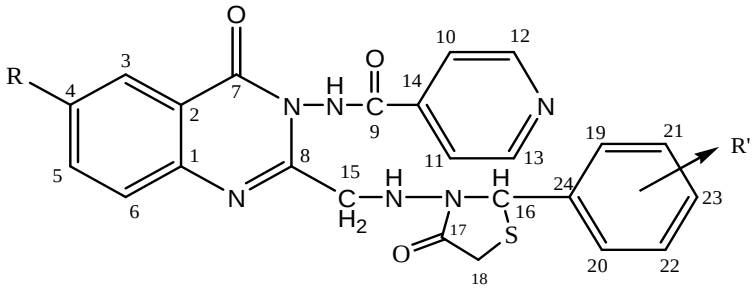


Scheme 1: Synthesis of thiazolidinyl-quinazoline 4-one (**7a-v**)derivatives



7a-v

Figure 1: The numbering system of the compounds **7a-v** for ^{13}C-NMRspectra

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Table 1

In vitro antimicrobial activity data in MIC (µg/ml) of compounds **(7a-v)**

Compound No.	R	R'	*E.c.*	*P.a.*	*Kl.p*	*S.t.*	*S.a.*	*S.p.*	*B.s.*	*C.a.*	*A.n.*	*A.c.*
7a	-H	-H	500	250	250	250	500	250	500	500	500	1000
7b	-H	2-NO_2	250	500	250	250	200	500	200	500	1000	5000
7c	-H	3-NO_2	500	250	250	500	500	500	250	1000	500	1000
7d	-H	4-NO_2	**125**	125	100	100	150	**62.5**	**100**	1000	500	500
7e	-H	2-Cl	250	200	500	250	500	200	500	1000	500	500
7f	-H	4-Cl	100	**100**	**62.5**	**62.5**	100	100	**62.5**	**250**	500	**250**
7g	-H	2-OH	250	250	500	200	250	250	500	1000	>1000	500
7h	-H	4-OH	200	150	200	250	200	150	150	500	500	1000
7i	-H	4-OCH_3	**100**	100	150	200	200	150	200	**250**	**200**	**250**
7j	-H	4-C_2H_5	250	250	500	250	500	200	250	1000	500	500
7k	-H	4-Br	150	200	200	250	**200**	250	150	250	500	500
7l	-I	-H	250	200	150	250	500	500	200	500	1000	1000
7m	-I	2-NO_2	200	250	200	250	125	100	200	250	1000	1000
7n	-I	3-NO_2	200	200	500	500	200	200	250	500	500	500
7o	-I	4-NO_2	100	100	**62.5**	100	**125**	**100**	**62.5**	500	500	**200**
7p	-I	2-Cl	250	500	250	500	500	250	250	500	1000	500
7q	-I	4-Cl	**62.5**	100	**50**	**62.5**	250	**50**	**50**	**200**	**250**	**200**
7r	-I	2-OH	500	250	250	500	200	200	250	500	1000	1000
7s	-I	4-OH	**150**	**62.5**	125	200	150	150	100	500	1000	500
7t	-I	4-OCH_3	**125**	100	100	150	150	125	100	500	**200**	**250**
7u	-I	4-C_2H_5	200	250	250	200	250	250	200	1000	500	1000
7v	-I	4-Br	100	150	200	200	250	200	125	500	**250**	500
Gentamycin		-	0.05	1	0.05	1	0.25	0.5	-	-	-	-
Ampicilin		-	100	100	100	100	250	100	-	-	--	-
Chloramphenicol		-	50	50	50	50	50	50	-	-	-	-
Ciprofloxacin		-	25	25	25	25	50	50	-	-	-	-
Norfloxacin		-	10	10	10	10	10	10	-		-	-
Nystatin		-	-	-	-	-	-	-	--	100	100	100
Greseofulvin		-	-	-	-	-	-	-	-	500	100	100

E.c., *E. coli* (MTCC 443); *P.a.*, *P. aeruginosa* (MTCC 1688); *Kl.p*., *Kl. pneumoniae* (MTCC109); *S.t.*, *S. typhi* (MTCC98); *S.a.*, *S. aureus* (MTCC 96); *S.p.*, *S. pyogenus* (MTCC 442); *B.s.*, *B. subtilis* (MTCC 441); *C.A.*, *C. albicans* (MTCC 227); *A.N.*, *A. niger* (MTCC 282); *A.C.*, *A. clavatus* (MTCC 1323).

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Table 2

In vitro antitubercular activity of compounds **(7a-v)**

Compound No.	*M.Tuberculosis* [µg/ml]	% Inhibition	C log P
7a	250	71	0.699
7b	200	68	0.362
7c	200	64	0.442
7d	**62.5**	**94**	0.442
7e	250	59	1.412
7f	**62.5**	**91**	1.412
7g	200	52	-0.017
7h	250	64	0.032
7i	250	87	0.618
7j	250	24	1.727
7k	100	80	1.562
7l	250	69	1.885
7m	**50**	**93**	1.548
7n	250	64	1.628
7o	200	57	1.628
7p	250	55	2.598
7q	**50**	**94**	2.598
7r	200	50	1.168
7s	250	60	1.218
7t	200	80	1.804
7u	250	30	2.913
7v	100	75	2.748
Rifampicin	40	98	6.044
Isoniazide	0.20	99	-0.60

M.Tuberculosis: *Mycobacterium Tuberculosis H37Rv (MTCC 200)*

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