# Convenient Synthesis of Novel Quinazoline Congeners via Copper Catalyzed C–N/C–S Coupling and Their Biological Evaluation

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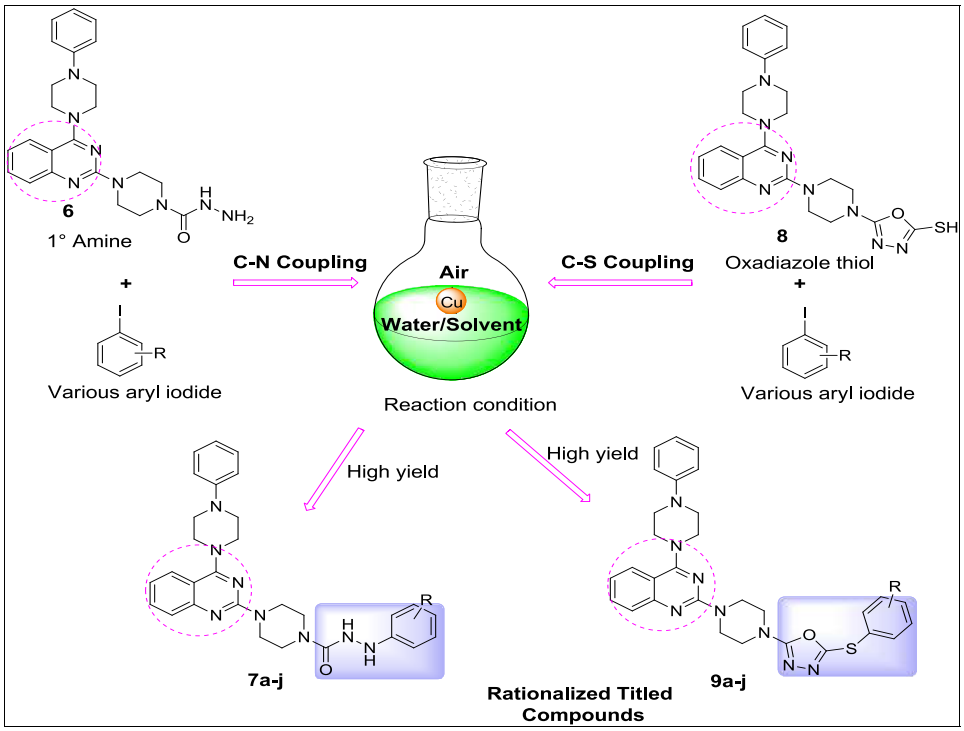



A library of novel quinazoline scaffolds endowed with semicarbazide/oxadiazole thiol motif synthesized via an efficient and sustainable copper catalyzed C–N/C–S coupling is reported, making the presented methodology extremely valuable from economic and environmental point of view. Among the all synthesized compounds screened for *in vitro* antibacterial, antifungal, and anti-TB activity, **7b**, **7c**, **7f**, **9b**, **9c**, **9i,** and **9j** showed excellent inhibitory effect on particular strain of bacteria, fungi, and *M. tuberculosis* H37Rv as well. All the newly synthesized derivatives were well characterized by their IR, $^{1}$H NMR, $^{13}$C NMR, mass spectroscopy as well as elemental analysis.



## INTRODUCTION

A number of reactions comprising copper complexes and its salt to facilitate the cross coupling reaction resulting in to the formation of carbon–heteroatom (C–N, C–S, C–O), C–C, and C-metal bonds have been recommended in the recent decades. Copper catalyzed cross coupling reactions including C–N and C–S bond formation are ubiquitously considered to synthesize a series of novel chemicals [1–4]. Ullmann-type aryl amination reaction has been proved to be an efficient method for the formation of carbon–heteroatom bond, which incorporates the use of inert atmosphere, polar solvent, strong base as well as harsh reaction conditions. Efforts have been made to combat this problem to get a desired product [5–7]. Many chemists have done great efforts to come out or to minimize this problem. To be a part of these efforts, Jiao et al. [8] have developed a method for C–N coupling, which uses a small amount of copper powder, water as solvent, air atmosphere, and ligand free reaction condition. Hua-Jian Xu et al. [9] have also done C–N bond formation using ligand-free CuCl catalyzed reaction condition in aqueous media. Transition metal and ligand free C–O and C–N cross coupling reaction using potassium tert-butoxide as base was reported by S. Yang and co-workers [10]. The copper catalyzed C–S cross coupling formation generally involve harsh reaction conditions, but as a part of the efforts to minimize these problems, a new approach developed by E. Sperottomade et al. [11] described C–S bond formation from aryl iodide and thiophenol using ligand-free air atmospheric CuI catalyzed reaction condition.

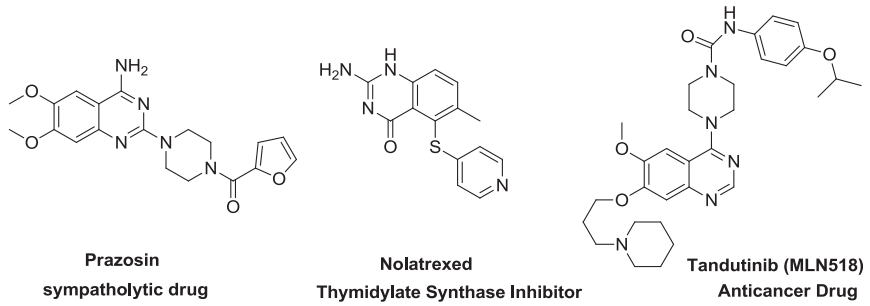



**Figure 1.** Quinazoline Based Drugs.

Multidrug resistant (MDR) attribute in miscellaneous microbes toward traditional standard drugs has been amplified up to alarming level, poses the frightening threat by severe opportunistic microbial infections in recent decades. Such type of phenomenon of infectious microbial flora to resist antimicrobial agents to which it was previously sensitive is known as antimicrobial resistant [12]. In the topical era, some tubercular strains of Mycobacterium tuberculosis cause MDR-TB and extensively drug-resistant (XDR)-TB, which generally affects the lungs [13]. As per World Health Organization, the latest figures on tuberculosis fact sheet for the year 2012 showed 8.6 million people suffered with TB and 1.3 million died from TB [14].

Quinazoline derivatives represent an important group of compounds that have diverse applications in medicinal chemistry by asset of their extensive pharmaceutical characteristics such as antibacterial [15–17], antifungal [18,19], anticancer [20–22], antituberculosis [23], antioxidant [24,25], anti-inflammatory [26], and anticonvulsant. Some quinazoline based drugs, for example., Prazosin, Nolatrexed, and Tandutinib (MLN518) (Fig. 1) have been approved for therapeutic purposes in clinic. Quinazoline based effective antimicrobial agents have been synthesized by many chemists (Fig. 2) [27–29]. Many workers have also prepared the potent chemical congeners based on oxadiazole motif (Fig. 3) [30–33]. Piperazine based entities also known to receive significant attention for their widespread biological activities [34–37]. On the basis of the previously mentioned information, a library of quinazoline scaffolds endowed with oxadiazole and piperazine motifs were rationalized, synthesized, and applied for numerous biological activities against diverse bacterial, fungal as well as mycobacterial strains (Fig. 4).

In this context, our goal was to design and synthesize the novel bioactive heterocycles via copper catalyzed C–N and C–S bond formation with optimized reaction conditions.

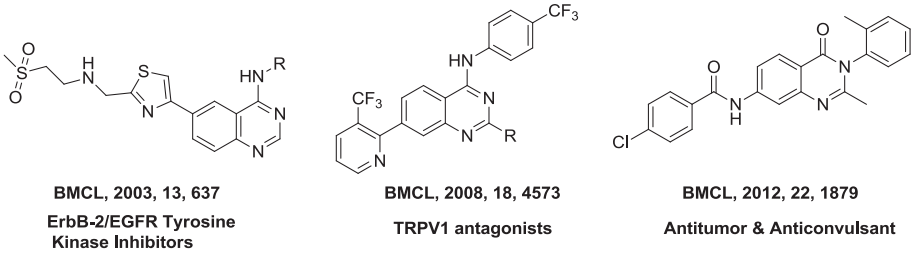



**Figure 2.** Quinazoline Based Active Therapeutic Agents.

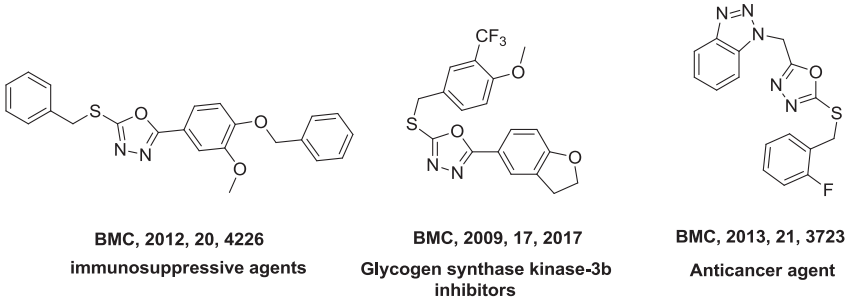



**Figure 3.** Oxadiazole Based Active Medicinal Agents.

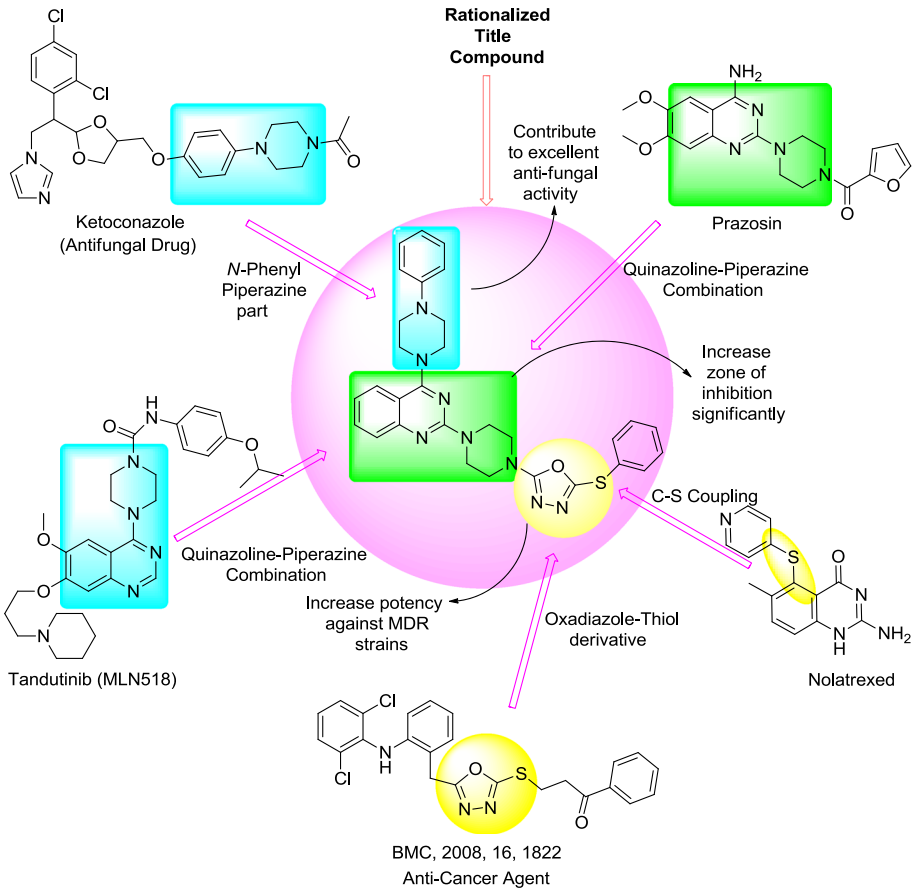


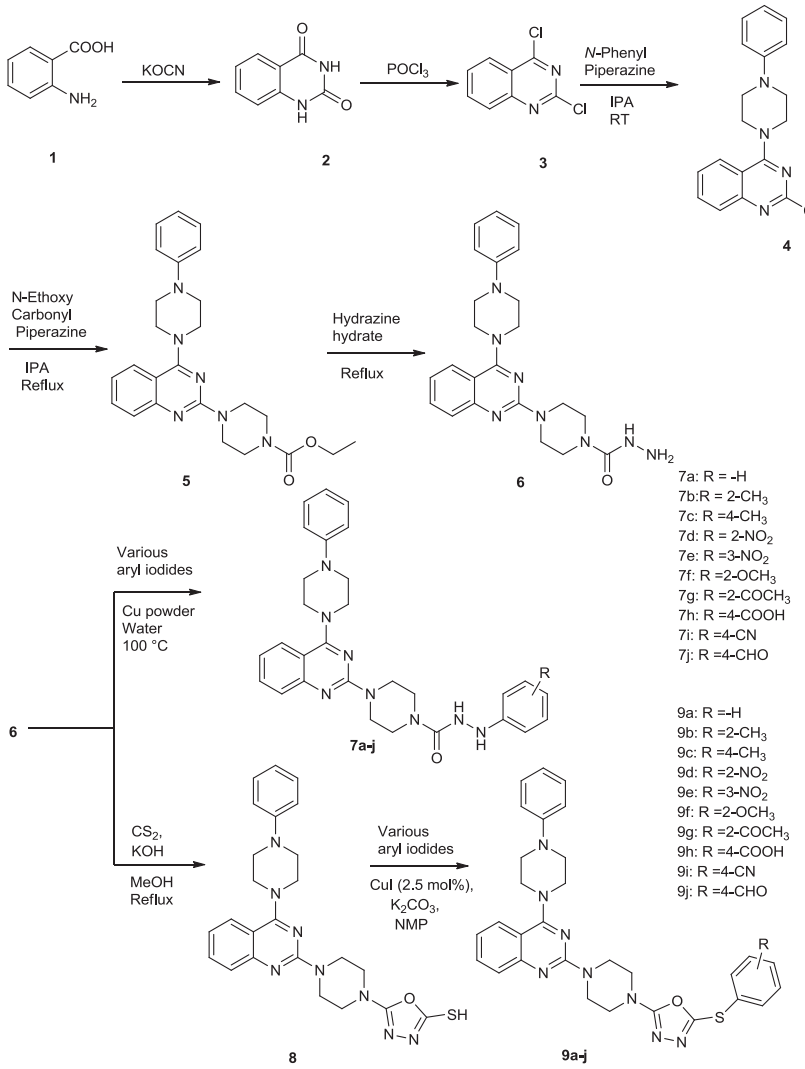

**Figure 4.** Rationale Design of Title Compounds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

## RESULTS AND DISCUSSION

**Chemistry.** Novel quinazoline based congeners endowed with piperazine and oxadiazole thiol derivatives were synthesized via copper catalyzed C–N and C–S cross coupling reaction with economically and environmentally green reaction approach as outlined in Scheme 1. The first step was the preparation of quinazoline-2,4(1*H*,3*H*)-dione (**2**) from anthranilic acid, which was achieved as per the literature. In the second step, compound **2** was treated with phosphorous oxychloride to give 2,4-dichloroquinazoline (**3**) as described in literature. The reactivity of the chloro group at C4 position is higher than the chloro group at C2 position of quinazoline ring, and hence, the substitution reaction will first take place at C4 position of quinazoline ring [38]. The compound **3** was then reacted with *N*-phenylpiperazine in isopropyl alcohol (IPA) at room temperature to yield 2-Chloro-4-(4-phenylpiperazin-1-yl) quinazoline (**4**). In the next step, the formation of compound **5** was achieved by the reaction of **4** with *N*-ethoxy carbonyl piperazine in IPA at reflux temperature. The hydrolysis of compound **5** using hydrazine hydrate was carried out to give carbohydrazide derivative (**6**). Various quinazoline derivatives (**7a–j**) were synthesized by the reaction between **6** and appropriate aryl iodide using copper catalyst, water solvent, ligand free air atmospheric reaction condition. Compound **8** was prepared by the reaction of **6** with carbon disulfide and alcoholic KOH at reflux temperature. Various quinazoline based scaffolds endowed with oxadiazole motif (**9a–j**) were synthesized using CuI catalyst, NMP as solvent, $K_2CO_3$ base and air atmospheric reaction condition.

All the newly synthesized derivatives were well characterized by their IR, $^1$H NMR, $^{13}$C NMR, mass spectroscopy, and elemental analysis. IR spectrum of **4** showed band at 1225 $cm^{-1}$ of C–N stretch aliphatic amine. NMR spectra of **4** indicate the presence of multiplet at 3.79–3.38 $cm^{-1}$, which confirms its formation. The formation of compound **5** was verified by its IR spectra showed characteristic bands at 1743 $cm^{-1}$ for C=O stretch and 1154 $cm^{-1}$ for C–O stretch of ester. The structure of 5 was also confirmed with its $^1$H NMR and $^{13}$C NMR. The configuration of compound **6** was established with its IR spectrum designating the band at 1648 $cm^{-1}$ and the disappearance of the band at 1743 $cm^{-1}$ of ester carbonyl group. The structural presentation of the final analogous (**7a–j**) was corroborated by $^1$H NMR, $^{13}$C NMR, and mass spectroscopy. The structural formula of **8** was authenticated

**Scheme 1.** Schematic diagram for the synthesis of novel quinazoline based derivatives 7a–j and 9a–j.




by its IR spectrum showed band at 2564 $cm^{-1}$ of thiol. The structures of final analogs (**9a–j**) were further validated with their various spectroscopic methods as well as elemental analysis.

**Effect of substituent on the reaction.** The preparation of various derivatives **7a–j** and **9a–j** was achieved under air atmosphere using water or organic solvent. The results showed most of the substrates examined afforded good yields at 100 °C. The reaction time to acquire desired product was maximum of 16 h for each derivative. In the beginning, the electron donating groups ($-CH_3$ or $-OCH_3$) possessing aryl iodide takes up to 10 h for 80% of reaction with compound **6** or **8** (i.e., appearance of compound **6** or **8** on TLC), then the reaction becomes slow and the remaining 20% of reaction with compound **6** or **8** takes up to 5–7 h for the complete conversion into the product. The electron withdrawing group ($-NO_2$, $-COCH_3$, $-COOH$, $-CN$, $-CHO$) containing aryl iodide showed higher reactivity as compared with that of the aryl iodide having electron donating group for both semicarbazide (**6**) and oxadiazole (**8**) motifs. The final analogs endowed with electron withdrawing substituent takes maximum of 12–16 h for their uniform and complete preparation. The reaction of compound **6** or **8** with unsubstituted aryl iodide achieved to gain the desired product was uniformly completed within 15–17 h.

**Biological evaluation.** All currently synthesized quinazoline based amide and 1,3,4-oxadiazole thiol derivatives were screened for their *in vitro* antimicrobial activity against five bacterial strains (*Staphylococcus aureus* MTCC 96, *Bacillus subtilis* MTCC 441, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 741, and *Klebsiella pneumoniae* MTCC 109) and four fungal strains (*Aspergillus niger* MTCC 282, *Aspergillus fumigates* MTCC 343, *Aspergillus clavatus* MTCC 1323, and *Candida albicans* MTCC 183) using

**Table 1**

*In-vitro* anti-bacterial activity of newly synthesized compounds **7a–j** and **9a–j.**

| | | | Zone of Inhibition in mm (MIC in μg/mL) | | | | |
|---|---|---|---|---|---|---|---|
| Entry | R | Log P | *S.a* | *B.s* | *E.c* | *P.a* | *K.p* |
| **7a** | -H | 5.26 | 12 (100) | 29 (200) | 13 (12.5) | 24 (100) | 06 (200) |
| **7b** | 2-$CH_3$ | 5.75 | 17 (6.25) | 25 (100) | 10 (200) | 31 (6.25) | 09 (200) |
| **7c** | 4-$CH_3$ | 5.75 | 16 (25) | 35 (3.12) | 19 (100) | 20 (100) | 11 (50) |
| **7d** | 2-$NO_2$ | 3.63 | 05 (100) | 15 (100) | 14 (25) | 23 (200) | 10 (100) |
| **7e** | 3-$NO_2$ | 3.63 | 09 (50) | 19 (50) | 13 (100) | 17 (100) | 06 (12.5) |
| **7f** | 2-$OCH_3$ | 5.13 | 14 (20) | 24 (100) | 20 (50) | 16 (50) | 18 (12.5) |
| **7g** | 2-$COCH_3$ | 4.57 | 10 (100) | 22 (12.5) | 16 (200) | 22 (200) | 10 (50) |
| **7h** | 4-COOH | 4.82 | 13 (25) | 29 (50) | 22 (100) | 27 (12.5) | 12 (100) |
| **7i** | 4-CN | 5.29 | 16 (100) | 21 (100) | 27 (6.25) | 20 (100) | 03 (200) |
| **7j** | 4-CHO | 5.01 | 10 (200) | 20 (25) | 23 (200) | 15 (100) | 04 (100) |
| **9a** | -H | 8.17 | 18 (50) | 19 (25) | 19 (100) | 19 (50) | 08 (50) |
| **9b** | 2-$CH_3$ | 8.66 | 22 (6.25) | 31 (100) | 16 (25) | 33 (6.25) | 12 (100) |
| **9c** | 4-$CH_3$ | 8.66 | 21 (3.12) | 30 (100) | 21 (50) | 28 (50) | 11 (100) |
| **9d** | 2-$NO_2$ | — | 15 (25) | 17 (50) | 20 (100) | 24 (100) | 08 (25) |
| **9e** | 3-$NO_2$ | — | 13 (50) | 10 (50) | 16 (200) | 30 (200) | 10 (50) |
| **9f** | 2-$OCH_3$ | 8.05 | 19 (12.5) | 26 (100) | 12 (100) | 22 (50) | 13 (50) |
| **9g** | 2-$COCH_3$ | 7.48 | 16 (50) | 20 (200) | 15 (50) | 15 (12.5) | 17 (12.5) |
| **9h** | 4-COOH | 7.73 | 18 (100) | 21 (100) | 13 (12.5) | 10 (100) | 15 (200) |
| **9i** | 4-CN | 8.21 | 20 (25) | 36 (3.12) | 22 (50) | 18 (12.5) | 11 (50) |
| **9j** | 4-CHO | 7.92 | 17 (200) | 32 (50) | 28 (6.25) | 23 (50) | 09 (100) |
| Cip. | — | — | 22 (6.25) | 38 (0.06) | 27 (6.25) | 32 (6.25) | 19 (12.5) |
| DMSO | — | — | — | — | — | — | — |

Log P was calculated using the ChemDraw Ultra, version 12.0 (PerkinElmer, Waltham, MA).
MIC, minimum inhibitory concentration; *S.a Staphylococcus aureus; B.c, Bacillus subtilis; E.c Escherichia coli; P.a, Pseudomonas aeruginosa; K.p, Klebsiella pneumoniae;* Cip, Ciprofloxacin.

**Table 2**

*In-vitro* anti-fungal activity of newly synthesized compounds **7a–j** and **9a–j.**

| | | | Zone of Inhibition in mm (MIC in μg/mL) | | | |
|---|---|---|---|---|---|---|
| Entry | R | Log P | *A.n* | *A.f* | *A.c* | *C.a* |
| **7a** | -H | 5.26 | 18 (50) | 21 (50) | 25 (200) | 32 (1.56) |
| **7b** | 2-$CH_3$ | 5.75 | 12 (100) | 29 (0.78) | 17 (50) | 23 (25) |
| **7c** | 4-$CH_3$ | 5.75 | 28 (3.12) | 20 (100) | 22 (100) | 21 (100) |
| **7d** | 2-$NO_2$ | 3.63 | 21 (200) | 15 (12.5) | 24 (50) | 07 (50) |
| **7e** | 3-$NO_2$ | 3.63 | 20 (25) | 19 (50) | 10 (25) | 16 (12.5) |
| **7f** | 2-$OCH_3$ | 5.13 | 16 (100) | 14 (100) | 29 (1.56) | 24 (200) |
| **7g** | 2-$COCH_3$ | 4.57 | 10 (50) | 17 (25) | 13 (100) | 11 (100) |
| **7h** | 4-COOH | 4.82 | 13 (12.5) | 20 (200) | 17 (200) | 19 (50) |
| **7i** | 4-CN | 5.29 | 19 (100) | 11 (100) | 20 (25) | 10 (100) |
| **7j** | 4-CHO | 5.01 | 17 (50) | 05 (100) | 15 (50) | 21 (12.5) |
| **9a** | -H | 8.17 | 15 (200) | 16 (25) | 24 (12.5) | 20 (3.12) |
| **9b** | 2-$CH_3$ | 8.66 | 32 (3.12) | 09 (100) | 16 (12.5) | 13 (25) |
| **9c** | 4-$CH_3$ | 8.66 | 08 (100) | 27 (1.56) | 11 (100) | 24 (50) |
| **9d** | 2-$NO_2$ | — | 10 (200) | 10 (100) | 18 (200) | 20 (12.5) |
| **9e** | 3-$NO_2$ | — | 11 (50) | 12 (200) | 13 (50) | 18 (100) |
| **9f** | 2-$OCH_3$ | 8.05 | 13 (100) | 20 (50) | 31 (1.56) | 11 (25) |
| **9g** | 2-$COCH_3$ | 7.48 | 22 (12.5) | 17 (100) | 21 (100) | 08 (100) |
| **9h** | 4-COOH | 7.73 | 17 (50) | 18 (12.5) | 17 (50) | 03 (50) |
| **9i** | 4-CN | 8.21 | 27 (6.25) | 06 (100) | 16 (200) | 14 (3.12) |
| **9j** | 4-CHO | 7.92 | 24 (50) | 07 (50) | 24 (12.5) | 33 (0.78) |
| Ket. | — | — | 30 (≤3) | 29 (≤1) | 31 (≤1) | 33 (≤1) |
| DMSO | — | — | — | — | — | — |

Log P was calculated using the ChemDraw Ultra, version 12.0.
MIC, minimum inhibitory concentration; *A.n, Aspergillus niger; A.f, Aspergillus fumigates; A.c, Aspergillus clavatus; C.a, Candida albicans;* Ket. Ketoconazole.

broth dilution technique. Ciprofloxacin and ketoconazole were used as standard control drugs for antibacterial and antifungal activity, respectively. Furthermore, all the newly synthesized derivatives were evaluated for their *in vitro* antimycobacterial activity (against *Mycobacterium tuberculosis* H37Rv) using BACTEC Mycobacteria Growth Indicator Tube (MGIT) method as well as Lowenstein–Jensen minimum inhibitory concentration (MIC) method using Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide as standard control drugs.

***In vitro* antibacterial activity.** Investigation on antibacterial screening data (Table 1) showed some of the compounds were found to exhibit good to moderate activity against specific bacterial strain. Among which, the electron donating methyl group containing final derivatives **7b** and **7c** showed higher efficacy against *P. aeruginosa* MTCC 741 and *B. subtilis* MTCC 441 at MIC 6.25 μg/mL and 3.12 μg/mL, respectively. The final congener **7f** having methoxy group gave equipotent activity compare to standard drug against the bacterial strain *K. pneumoniae* MTCC 109 at MIC 12.5 μg/mL. The compound **7i** owning 4-cyano phenyl part showed higher potency against *E. coli* MTCC 739 at MIC 6.25 μg/mL. Final quinazoline derivatives endowed with oxadiazole residue also exhibited very good activity against various bacterial species, out of them, electron donating methyl group at ortho position to phenyl ring possessing moiety **9b** showed superior inhibitory effect on both *S. aureus* MTCC 96 at MIC 6.25 μg/mL and *Pseudomonas aeruginosa* MTCC 741 (both equipotent to standard control drug). The final synthesized scaffold **9c** was also found to exhibit excellent inhibition profile against bacterial strain *S. aureus* MTCC 96 at MIC 3.12 μg/mL. The compound **9g** having acetyl group showed equipotent activity against *K. pneumoniae* MTCC 109 at MIC 12.5 μg/mL. Final scaffolds **9i** and **9j** possessing cyano and aldehyde group, respectively, displayed very good efficiency against the bacterial strains *B. subtilis* MTCC 441 at MIC 3.12 μg/mL and *E. coli* MTCC 739 at MIC 6.25 μg/mL, respectively.

***In vitro* antifungal activity.** The antifungal screening records (Table 2) demonstrate that the compounds bearing electron donating group proved to be highly potent for the specific fungal strain. Out of which, compounds **7b** and **7c** containing methyl group showed superior antifungal activity against *A. niger* MTCC 282 at MIC 3.12 μg/mL and *A. fumigates* MTCC 343 at MIC 0.78 μg/mL, respectively. Final analogs **7a** with unsubstituted phenyl ring displayed good potency against *C. albicans* MTCC 183 at MIC 1.56 μg/mL. At the same

**Table 3**

*In-vitro* anti-tuberculosis activity of newly synthesized compounds **7a–j** and **9a–j.**

| | | | BACTEC MGIT method[a] | | L–J MIC method[a] | |
|---|---|---|---|---|---|---|
| Entry | R | Log P | MIC (μg/mL) | % Inhibition | MIC (μg/mL) | % Inhibition |
| **7a** | -H | 5.26 | >6.25 | — | 100 | 90 |
| **7b** | 2-$CH_3$ | 5.75 | >6.25 | — | 200 | 89 |
| **7c** | 4-$CH_3$ | 5.75 | >6.25 | — | 50 | 92 |
| **7d** | 2-$NO_2$ | 3.63 | >6.25 | — | 12.5 | 93 |
| **7e** | 3-$NO_2$ | 3.63 | >6.25 | — | 50 | 92 |
| **7f** | 2-$OCH_3$ | 5.13 | >6.25 | — | 25 | 95 |
| **7g** | 2-$COCH_3$ | 4.57 | >6.25 | — | 6.25 | 99 |
| **7h** | 4-COOH | 4.82 | >6.25 | — | 100 | 90 |
| **7i** | 4-CN | 5.29 | >6.25 | — | 12.5 | 93 |
| **7j** | 4-CHO | 5.01 | >6.25 | — | 50 | 92 |
| **9a** | -H | 8.17 | >6.25 | — | 50 | 91 |
| **9b** | 2-$CH_3$ | 8.66 | >6.25 | — | 6.25 | 99 |
| **9c** | 4-$CH_3$ | 8.66 | >6.25 | — | 6.25 | 99 |
| **9d** | 2-$NO_2$ | — | >6.25 | — | 12.5 | 92 |
| **9e** | 3-$NO_2$ | — | >6.25 | — | 25 | 93 |
| **9f** | 2-$OCH_3$ | 8.05 | >6.25 | — | 100 | 91 |
| **9g** | 2-$COCH_3$ | 7.48 | >6.25 | — | 200 | 85 |
| **9h** | 4-COOH | 7.73 | >6.25 | — | 100 | 91 |
| **9i** | 4-CN | 8.21 | >6.25 | — | 12.5 | 93 |
| **9j** | 4-CHO | 7.92 | >6.25 | — | 25 | 91 |
| Isoniazid | — | — | 0.25 | 99 | — | — |
| Rifampicin | — | — | 0.21 | 99 | — | — |
| Ethambutol | — | — | 3.12 | 99 | — | — |
| Pyrazinamide | — | — | 3.12 | 99 | — | — |

L–J MIC, Lowenstein–Jensen minimum inhibitory concentration.
[a]Each value is the mean of three independent experiment.

MIC value, compound **7f** showed better activity against *A. clavatus* MTCC 1323. The compounds **9b** and **9c** with oxadiazole and methyl group part were found to possess excellent inhibitory profile against *A. niger* MTCC 282 at MIC 3.12 μg/mL and *A. fumigates* MTCC 343 at MIC 1.56 μg/mL, respectively. The methoxy group and oxadiazole containing moiety **9f** gave finer inhibitory effect on *A. clavatus* MTCC 1323 at MIC 1.56 μg/mL. Compounds **9i** and **9j** having cyano and aldehyde group, respectively, demonstrated higher antifungal potency against *A. niger* MTCC 282 at MIC 6.25 μg/mL and *C. albicans* MTCC 183 at MIC 0.78 μg/mL, respectively.

***In vitro* antituberculosis activity.** *In vitro* anti-TB activity (Table 3) was performed for the all novel synthesized derivatives against the tubercular strain *M. tuberculosis* H37Rv. Initially, all the derivatives were screened for their anti-TB efficacy using BACTEC MGIT method [39] at MIC 6.25 μg/mL. But at this concentration level, none of the compound was found active. Therefore all the novel congeners were evaluated for anti-TB activity using Lowenstein–Jensen MIC method [40]. Among the all scaffolds, **7g** owing acetyl group exhibited superior inhibition on the mentioned mycobacterial strain. Furthermore, the compounds **9b** and **9c** possessing methyl group were found to be highly active against *M. tuberculosis* H37Rv at MIC 6.25 μg/mL.

## CONCLUSION

The present work mainly targeted to the synthesis of lnovel quinazoline scaffolds endowed with semicarbazide/oxadiazole motif in high yield with a wide range of medicinal applications via transition metal catalyzed C–N/C–S couplings with optimized reaction condition and economically and environmentally beneficial point of view. From the previously mentioned results, it can also be said that many of the synthesized derivatives showed good to moderate activity against particular microbial strain including bacteria, fungi, and mycobacterial. Among the all synthesized derivatives, the compounds possessing electron donating group (methyl/methoxy/cyano) and electron withdrawing group (aldehyde) along with semicarbazide/oxadiazole motif, that is, **7b**, **7c**, **7f**, **9b**, **9c**, **9i,** and **9j** were proved to be highly potent against particular bacterial, fungal and *M. tuberculosis* H37Rv strain as well.

## EXPERIMENTAL

**Material and methods.** All the chemicals and solvents used for the synthesis work acquired from commercial sources were of analytical grade and were used without further purification. Melting points were determined by using open capillary tubes and are uncorrected. TLC was checked on E-Merck (Merck KGaA, Darmstadt, Germany) pre-coated 60 F254 plates, and the spots were rendered visible by exposing to UV light or iodine. IR spectrums were recorded on SHIMADZU HYPER IR (SHIMADZU, Columbia, MD). NMR spectra were recorded by 400 MHz Bruker Avance (Bruker, Billerica, MA) instrument using TMS as internal standard (Chemical Shift in δ, ppm) and DMSO-*d6* as a solvent. Spectra were taken with a resonant frequency of 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ NMR. The splitting patterns are designated as follows; s, singlet; d, doublet; dd, doublet of doublets; and m, multiplet. Elemental analysis was done on "Heraeus Rapid Analyser". The mass spectra were recorded on Joel SX-102 (EI) (AB SCIEX, Framingham, MA) model with 60 eV ionizing energy.

***Synthesis of quinazoline-2,4(1H,3H)-dione (2).*** A mixture of anthranilic acid (5 g, 0.03646 mol), warm water (50 mL), and glacial acetic acid (0.04740 mol) was stirred and allowed to cool to room temperature. A freshly prepared solution of potassium cyanate (0.04740 mol) in water (50 mL) was then added dropwise with stirring over a period of 15–20 min.. The resulting pasty mixture was stirred for 20 min., and then flaked sodium hydroxide (1.0938 mol) was added slowly in small portions. During this addition, the temperature of the reaction mixture was kept below 40 °C. A clear solution was obtained, but in a short time a fine granular precipitates were obtained. The precipitates were dissolved in hot water, and then reprecipitated using diluted $H_2SO_4$. The solid was filtered and washed with water, and then dried, to give the title compound.

Yield: 70%; mp: >300 [41].

***Synthesis of 2,4-dichloroquinazoline (3).*** A mixture of 2 (8 g, 0.04934 mol) and phosphorus oxychloride (47 mL, 0.4934 mol) was stirred and cooled to 0–5 °C. To this mixture, *N,N*-dimethylaniline (0.1040 mol) was added dropwise. After the completion of addition, the reaction mixture was refluxed for 4 h. The progress of the reaction was monitored by TLC using hexane : ethyl acetate (2 : 3) as eluent. After the completion of reaction, the reaction mass was cooled up to room temperature and then poured into crushed ice. The resulting mass was filtered and washed with water to give the title compound [42].

Yield: 61%; mp: 116–117 °C.

***2-Chloro-4-(4-phenylpiperazin-1-yl)quinazoline (4).*** A solution of *N*-phenyl piperazine (2.85 g, 0.01758 mol) in IPA (10 mL) was added dropwise to the solution of **3** in IPA (10 mL) and stirred at room temperature for 18 h. After the completion of reaction, the reaction mass was dumped into crushed ice, filtered, washed with water and then dried to give crude compound. It was then recrystallized from ethanol to get the pure title compound (**4**).

Yield: 67%; IR (KBr) $cm^{-1}$: 1225 (C–N aliphatic amine); $^{1}H$ NMR (400 MHz, DMSO) δ 8.02–7.32 (m, 4H, Ar–H), 7.27–6.67 (m, 5H, Ar–H), 3.79–3.38 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 164.25 (quinazoline ring C–C=N at C4 position), 159.62 (quinazoline C–Cl at C2 position), 156.37 (quinazoline ring C=C–N), 151.07 (Ar–C), 131.82, 129.39, 128.73, 127.72, 126.63, 125.42, 124.61, 123.09 (10C Ar–C), 50.07, 49.33 (4C of piperazine); MS (m/z): 325.1 [$M^+$].

***Ethyl 4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carboxylate (5).*** A mixture of **4** (2 g, 6.16 mmol) and *N*-ethoxy carbonyl piperazine (6.16 mmol) in IPA (20 mL) was refluxed for 7 h. After the completion of reaction, the reaction mixture was cooled up to room temperature and then poured into

crushed ice. The resulting solid mass was filtered, washed with water and then dried to get the title compound.

Yield: 60%; IR (KBr) $cm^{-1}$: 2953 (aromatic C–H), 1743 (C=O ester), 1251 (C–N aliphatic amine), 1154 (C–O ester); $^1H$ NMR (400 MHz, DMSO) δ 8.10–7.46 (m, 4H, Ar–H), 7.34–6.72 (m, 5H, Ar–H), 4.51 (q, 2H, $J = 6.4$ Hz, $–CH_2–$), 3.83–3.61 (m, 8H, piperazine), 3.56-3.39 (m, 8H, piperazine), 1.53 (t, 3H, $J = 6.2$ Hz, $–CH_3$); $^{13}C$ NMR (100 MHz, DMSO) δ 166.30 (quinazoline ring N=C–N C2 position), 164.72 (quinazoline C4 position), 158.82 (ester C=O), 154.43 (quinazoline ring C=C–N), 150.18 (Ar–C), 130.19, 129.36, 127.95, 125.78, 124.46, 123.39, 122.03, 121.14 (10C Ar–C), 65.35 ($–O–CH_2–CH_3$), 49.53, 48.77, 47.64, 46.21 (8C of piperazine), 16.67 ($–O–CH_2–CH_3$); MS (m/z): 447.7 [$M^+$].

***4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (6).*** A mixture of compound **5** (5 g, 0.0112 mol) and hydrazine hydrate (0.03361 mol) in ethanol (50 mL) was refluxed for 16 h. After the completion of reaction, the reaction mixture was cooled up to room temperature and then dumped into crushed ice. The pH of solution was adjusted to neutral by adding diluted HCl to get the desired product.

Yield: 58%; IR (KBr) $cm^{-1}$: 3364 (–NH stretch, sharp band), 2974 (aromatic C–H stretch), 1648 (C=O stretch amide), 1239 (C–N stretch aliphatic amine); $^1H$ NMR (400 MHz, DMSO) δ 7.84 (s, 1H, –NH– of amide group), 7.72–7.43 (m, 4H, Ar–H of quinazoline ring), 7.40–7.24 (m, 5H, Ar–H), 5.03 (s, 2H, $–NH_2$), 3.74–3.60 (m, 8H, piperazine), 3.52–3.34 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 165.58 (quinazoline ring N=C–N C2 position), 162.21 ((quinazoline C4 position), 157.72 (ester C=O), 155.06 (quinazoline ring C=C–N), 149.91 (Ar–C), 128.82, 127.75, 126.46, 125.49, 124.17, 122.20, 121.31, 119.86 (10C Ar–C), 47.75, 46.59, 45.27, 44.48 (8C of piperazine); MS (m/z): 433.3 [$M^+$].

***General procedure for the synthesis of compounds 7a–j.*** To a stirred mixture of **6** (5 g, 1.15 mmol) and appropriate aryl iodide (1.15 mmol) in water (50 mL), copper powder (0.11 mmol) was added. The reaction mixture was then heated at 100 °C for 16 h. After the reaction was completed, the reaction mixture was cooled to room temperature and then the product was extracted with ethyl acetate (50 mL). The organic layer was separated and then the aqueous layer was again extracted with ethyl acetate (3×50 mL). The organic layers were combined, dried with sodium sulfate and evaporated to dryness to give crude product, which was purified using column chromatography (eluent hexane : ethyl acetate) to get the pure product.

***N'-Phenyl-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl) piperazine-1-carbohydrazide (7a).*** Yield: 74%; mp 154–156 °C; IR (KBr) $cm^{-1}$: 3323 (–NH), 2978 (aromatic C–H); $^1H$ NMR (400 MHz, DMSO) δ 8.57 (s, 1H, –NH– of amide group), 7.85–7.57 (m, 4H, Ar–H of quinazoline ring), 7.50–7.39 (m, 5H, Ar–H), 7.14-6.55 (m, 5H, Ar–H), 5.45 (s, 1H, –NH linked to phenyl ring), 3.67–3.59 (m, 8H, piperazine), 3.44–3.29 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 163.08 (quinazoline ring N=C–N C2 position), 162.84 (quinazoline C4 position), 160.02 (amide C=O), 158.16 (quinazoline ring C=C–N), 154.82 (Ar–C), 150.68 (Ar–C), 130.63, 129.12, 128.63, 126.94, 125.15, 124.21, 123.24, 122.19, 121.53, 120.20, 119.32 (15 Ar–C), 49.23, 47.58, 46.82, 46.27 (8C of piperazine); MS (m/z): 509.8 [$M^+$]. *Anal.* Calcd. for $C_{29}H_{32}N_8O$: C, 68.48; H, 6.34; N, 22.03. Found: C, 68.64; H, 6.32; N, 21.97.

***4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)-N'-(o-tolyl) piperazine-1-carbohydrazide (7b).*** Yield: 71%; mp 201–204 °C; IR (KBr) $cm^{-1}$: 3314 (–NH), 2905 (aromatic C-H); $^1H$ NMR (400 MHz, DMSO) δ 8.68 (s, 1H, –NH– of amide group), 7.78–7.50 (m, 4H, Ar–H of quinazoline ring), 7.45–7.34 (m, 4H, Ar–H), 7.23–6.49 (m, 5H, Ar–H), 5.54 (s, 1H, –NH linked to phenyl ring), 3.73–3.58 (m, 8H, piperazine), 3.54–3.24 (m, 8H, piperazine), 2.35 (s, 3H, $Ar–CH_3$); $^{13}C$ NMR (100 MHz, DMSO) δ 162.28 (quinazoline ring N=C–N C2 position), 161.15 (quinazoline C4 position), 160.10 (amide C=O), 158.16 (quinazoline ring C=C–N), 150.57 (Ar–C), 149.62 (Ar–C), 129.24, 128.72, 127.46, 126.44, 125.19, 124.87, 122.28, 123.49, 122.37, 121.61, 120.38, 119.47, 118.34 (15 Ar–C), 48.33, 47.15, 46.32, 45.48 (8C of piperazine), 18.54 ($Ar–CH_3$); MS (m/z): 523.5 [$M^+$]. *Anal.* Calcd. for $C_{30}H_{34}N_8O$: C, 68.94; H, 6.56; N, 21.44. Found: C, 68.75; H, 6.54; N, 21.38.

***4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)-N'-(p-tolyl) piperazine-1-carbohydrazide (7c).*** Yield: 66%; mp 142–145 °C; IR (KBr) $cm^{-1}$: 3326 (–NH), 2986 (aromatic C-H); $^1H$ NMR (400 MHz, DMSO) δ 8.75 (s, 1H, –NH– of amide group), 7.84–7.61 (m, 4H, Ar–H of quinazoline ring), 7.57–7.38 (m, 4H, Ar–H), 7.30–6.35 (m, 5H, Ar–H), 5.67 (s, 1H, –NH linked to phenyl ring), 3.78–3.52 (m, 8H, piperazine), 3.50–3.27 (m, 8H, piperazine), 2.31 (s, 3H, $Ar–CH_3$); $^{13}C$ NMR (100 MHz, DMSO) δ 164.28 (quinazoline ring N=C–N C2 position), 163.49 (quinazoline C4 position), 161.57 (amide C=O), 159.36 (quinazoline ring C=C–N), 151.31 (Ar–C), 148.16 (Ar-C), 130.28, 129.82, 128.27, 126.67, 125.51, 124.63, 123.42, 122.53, 121.90, 120.13, (15 Ar–C), 50.23, 49.38, 48.52, 47.33 (8C of piperazine), 20.44 ($Ar–CH_3$); MS (m/z): 523.7 [$M^+$]. *Anal.* Calcd. for $C_{30}H_{34}N_8O$: C, 68.94; H, 6.56; N, 21.44. Found: C, 68.84; H, 6.58; N, 21.41.

***N'-(2-Nitrophenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7d).*** Yield: 81%; mp 189–193 °C; IR (KBr) $cm^{-1}$: 3356 (–NH), 2974 (aromatic C–H), 1540 (N–O), 1351 (N–O); $^1H$ NMR (400 MHz, DMSO) δ 8.92 (s, 1H, –NH– of amide group), 8.06–7.66 (m, 4H, Ar–H), 7.62–7.25 (m, 4H, Ar–H), 7.18–6.59 (m, 5H, Ar–H), 5.63 (s, 1H, –NH linked to phenyl ring), 3.61–3.43 (m, 8H, piperazine), 3.36–3.22 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 160.10 (quinazoline ring N=C–N C2 position), 158.82 (quinazoline C4 position), 158.56 (amide C=O), 157.72 (quinazoline ring C=C–N), 150.22 (Ar–C), 148.35 (Ar–C), 130.29, 129.64, 128.59, 127.60, 126.94, 125.63, 124.43, 123.66, 122.47, 121.21, 120.65, 119.46, 118.57 (15 Ar–C), 48.37, 47.10, 46.72, 46.12 (8C of piperazine); MS (m/z): 554.7 [$M^+$]. *Anal.* Calcd. for $C_{29}H_{31}N_9O_3$: C, 62.92; H, 5.64; N, 22.77. Found: C, 62.79; H, 5.63; N, 22.79.

***N'-(3-Nitrophenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7e).*** Yield: 75%; mp 164–165 °C; IR (KBr) $cm^{-1}$: 3373 (–NH), 2964 (aromatic C–H), 1571 (N-O), 1367 (N–O); $^1H$ NMR (400 MHz, DMSO) δ 8.89 (s, 1H, –NH– of amide group), 8.10–7.74 (m, 4H, Ar–H), 7.70–7.34 (m, 4H, Ar–H), 7.30-6.63 (m, 5H, Ar–H), 5.57 (s, 1H, –NH linked to phenyl ring), 3.67–3.40 (m, 8H, piperazine), 3.34–3.21 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 163.27 (quinazoline ring N=C–N C2 position), 162.23 (quinazoline C4 position), 160.77 (amide C=O), 158.47 (quinazoline ring C=C–N), 151.14 (Ar–C), 150.27 (Ar–C), 130.88, 129.31, 128.29, 127.21, 126.45, 125.52, 124.28, 123.60, 122.11, 121.43, 120.24, 119.23, 118.10 (15 Ar–C), 49.27, 48.39, 47.43, 46.31 (8C of piperazine); MS (m/z): 554.6 [$M^+$]. *Anal.*

Calcd. for $C_{29}H_{31}N_9O_3$: C, 62.92; H, 5.64; N, 22.77. Found: C, 62.74; H, 5.63; N, 22.72.

***N'-(2-Methoxyphenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7f).*** Yield: 70%; mp 225–229 °C; IR (KBr) $cm^{-1}$: 3348 (-NH), 2977 (aromatic C–H), 1164 (O-C); $^1H$ NMR (400 MHz, DMSO, ppm): δ 8.86 (s, 1H, –NH– of amide group), 7.81–7.60 (m, 4H, Ar–H of quinazoline ring), 7.52–7.46 (m, 4H, Ar–H), 7.40–6.37 (m, 5H, Ar-H), 4.15 (s, 1H, –NH linked to phenyl ring), 3.92 (s, 3H, Ar–$OCH_3$), 3.67–3.43 (m, 8H, piperazine), 3.37–3.13 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 161.30 (quinazoline ring N=C–N C2 position), 162.22 (quinazoline C4 position), 161.27 (amide C=O), 159.23 (quinazoline ring C=C–N), 149.53 (Ar–C), 148.58 (Ar–C), 129.24, 128.41, 127.27, 126.16, 125.40, 124.34, 123.57, 122.29, 121.20, 120.52, 119.26, 118.07, 117.17 (15 Ar–C), 54.22 (Ar–$OCH_3$), 47.34, 46.61, 45.25, 44.43 (8C of piperazine); MS (m/z): 539.1 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{34}N_8O_2$: C, 66.89; H, 6.36; N, 20.80. Found: C, 67.00; H, 6.38; N, 20.74.

***N'-(2-Acetylphenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7g).*** Yield: 84%; mp 164–167 °C; IR (KBr) $cm^{-1}$: 3360 (–NH), 2981 (aromatic C–H), 1732 (C=O acetyl); $^1H$ NMR (400 MHz, DMSO) δ 10.25 (s, 1H, –NH– of amide group), 8.24–7.76 (m, 4H, Ar–H), 7.70–7.54 (m, 4H, Ar–H), 7.48–6.73 (m, 5H, Ar–H), 4.26 (s, 1H, –NH linked to phenyl ring), 3.86–3.57 (m, 8H, piperazine), 3.51–3.29 (m, 8H, piperazine), 2.61 (s, 3H, Ar–$COCH_3$); $^{13}C$ NMR (100 MHz, DMSO) δ 203.64 (acetyl C=O), 162.28 (quinazoline ring N=C–N C2 position), 161.47 (quinazoline C4 position), 166.53 (amide C=O), 160.25 (quinazoline ring C=C–N), 150.13 (Ar–C), 148.29 (Ar–C), 130.81, 129.52, 128.33, 127.26, 126.45, 125.85, 124.74, 123.63, 122.58, 121.67, 120.90, 119.36, 118.82 (15 Ar–C), 49.61, 48.23, 47.37, 46.67 (8C of piperazine), 27.53 (Ar O=C–$CH_3$); MS (m/z): 551.2 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{34}N_8O_2$: C, 67.62; H, 6.22; N, 20.35. Found: C, 67.46; H, 6.21; N, 20.39.

***4-(2-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbonyl)hydrazinyl)benzoic acid (7h).*** Yield: 73%; mp 256–259 °C; IR (KBr) $cm^{-1}$: 3356 (O–H of carboxylic acid, broad band), 3347 (–NH), 2952 (aromatic C–H), 1191 (C–O of acid); $^1H$ NMR (400 MHz, DMSO) δ 11.2 (s, 1H, Ar–COOH), 8.60 (s, 1H, –NH– of amide group), 8.16–7.73 (m, 4H, Ar–H), 7.64-7.51 (m, 4H, Ar–H), 7.42–6.69 (m, 5H, Ar–H), 5.62 (s, 1H, –NH linked to phenyl ring), 3.96–3.63 (m, 8H, piperazine), 3.57–3.33 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 169.91 (Ar–COOH), 165.22 (quinazoline ring N=C–N C2 position), 163.04 (quinazoline C4 position), 162.31 (amide C=O), 158.37 (quinazoline ring C=C–N), 152.20 (Ar–C), 149.87 (Ar–C), 131.23, 130.38, 129.36, 128.57, 127.25, 126.61, 125.62, 124.43, 123.48, 122.69, 121.26 (15 Ar–C), 49.62, 48.85, 47.90, 46.63 (8C of piperazine); MS (m/z): 553.3 [$M^+$]. *Anal*. Calcd for $C_{30}H_{32}N_8O_3$: C, 65.20; H, 5.84; N, 20.28. Found: C, 65.03; H, 5.82; N, 20.23.

***N'-(4-Cyanophenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7i).*** Yield: 82%; mp 147-151 °C; IR (KBr) $cm^{-1}$: 3357 (–NH), 2964 (aromatic C–H), 2242 (CN); $^1H$ NMR (400 MHz, DMSO) δ 8.53 (s, 1H, –NH– of amide group), 7.75–7.53 (m, 4H, Ar–H), 7.42–7.26 (m, 4H, Ar–H), 7.19-6.45 (m, 5H, Ar–H), 5.02 (s, 1H, –NH linked to phenyl ring), 3.84–3.53 (m, 8H, piperazine), 3.43–3.27 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 167.73 (quinazoline ring N=C–N C2 position), 164.17 (quinazoline C4 position), 163.34 (amide C=O), 157.24 (quinazoline ring C=C–N), 155.57 (Ar–C), 152.07 (Ar–C), 130.27, 129.61, 128.72, 127.53, 126.18, 125.37, 124.46, 123.53, 122.27, 121.29, 120.23 (15 Ar–C), 118.27 (Ar–CN), 48.27, 47.29, 46.38, 45.57 (8C of piperazine); MS (m/z): 534.9 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{31}N_9O$: C, 67.52; H, 5.86; N, 23.62. Found: C, 67.59; H, 5.87; N, 23.55.

***N'-(4-Formylphenyl)-4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl)piperazine-1-carbohydrazide (7j).*** Yield: 80%; mp 247–250 °C; IR (KBr) $cm^{-1}$: 3367 (–NH), 2973 (aromatic C–H), 1738 (C=O of aldehyde); $^1H$ NMR (400 MHz, DMSO) δ 9.95 (s, 1H, Ar–CHO), 8.74 (s, 1H, –NH– of amide group), 8.12-7.62 (m, 4H, Ar–H), 7.57–7.40 (m, 4H, Ar–H), 7.37–6.73 (m, 5H, Ar–H), 5.62 (s, 1H, –NH linked to phenyl ring), 3.98–3.64 (m, 8H, piperazine), 3.60–3.28 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 194.43 (Ar–CHO), 165.20 (quinazoline ring N=C–N C2 position), 163.49 (quinazoline C4 position), 161.07 (amide C=O), 160.23 (quinazoline ring C=C–N), 158.81 (Ar–C), 151.67 (Ar–C), 131.59, 130.46, 129.92, 128.31, 127.73, 126.42, 125.50, 124.31, 123.63, 122.37, 121.17 (15 Ar–C), 49.92, 48.83, 47.54, 46.61 (8C of piperazine); MS (m/z): 537.5 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{32}N_8O_2$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.00; H, 5.99; N, 20.94.

***Synthesis of 5-(4-(4-(4-phenylpiperazin-1-yl)quinazolin-2-yl) piperazin-1-yl)-1,3,4-oxadiazole-2-thiol (8).*** A mixture of **6** (5 g, 1.15 mmol), carbon disulfide (0.0012 mol) and alcoholic KOH (10 mL) in methanol (50 mL) was refluxed for 6 h. After the reaction was completed, the reaction mass was then cooled to room temperature and then dumped into crushed ice, which was acidified using conc. HCl to give solid crude product. Furthermore, it was purified by recrystallization from methanol.

Yield: 59%; IR (KBr) $cm^{-1}$: 2564 (oxadiazole –SH), 2981 (aromatic C–H); $^1H$ NMR (400 MHz, DMSO) δ 7.83–7.44 (m, 4H), 7.36–7.14 (m, 5H, Ar–H), 3.72–3.60 (m, 8H, piperazine), 3.57–3.34 (m, 8H, piperazine), 2.85 (s, 1H, oxadiazole–SH); $^{13}C$ NMR (100 MHz, DMSO) δ 190.35 (oxadiazole C–SH), 170.05 (quinazoline ring N=C–N C2 position), 166.64 (quinazoline C4 position), 153.68 (quinazoline ring C=C–N), 152.26 (oxadiazole C–N piperazine), 152.89 (Ar–C), 140.28, 137.71, 135.54, 132.49, 130.27, 129.93, 127.18, 124.46 (10 Ar–C), 50.09, 49.38, 48.86, 47.72 (8C of piperazine); MS (m/z): 475.2 [$M^+$].

***General method for the synthesis of 9a–j.*** To a stirred mixture of **8** (5 g, 0.0105 mol), appropriate aryl iodide (0.0105 mol), and potassium carbonate (0.01158 mol) in NMP (10 mL), copper (I) salt (2.5 mol%) was added. The reaction mixture stirred under air atmosphere was then refluxed at 100 °C for 14 h. After the completion of reaction, the reaction mixture was cooled to room temperature, filtered through hyflo powder, and then solvent was removed in vacuo to give crude product, which was purified by column chromatography.

***2-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-5-(phenylthio)-1,3,4-oxadiazole (9a).*** Yield: 78%; mp 137–141 °C; IR (KBr) $cm^{-1}$: 2957 (aromatic C–H), 1627 (C=N oxadiazole ring), 1164 (oxadiazole C–O–C); $^1H$ NMR (400 MHz, DMSO) δ 7.84–7.63 (m, 4H), 7.54–6.81 (m, 5H, Ar–H), 6.72–6.60 (m, 5H, Ar–H), 3.93-3.57 (m, 8H, piperazine), 3.50–3.21 (m, 8H, piperazine); $^{13}C$ NMR (100 MHz, DMSO) δ 175.56 (oxadiazole C–S–Ar), 166.29 (quinazoline ring N=C–N C2 position), 164.23 (quinazoline C4 position), 155.34 (quinazoline ring C=C–N), 154.43 (oxadiazole C–N piperazine), 151.09 (Ar–C), 139.64, 137.43, 136.65, 135.29, 133.61, 131.10, 129.72, 128.54, 127.41, 126.53, 125.72, 124.57 (16 Ar-C), 51.16, 50.09, 49.90, 48.83 (8C of

piperazine); MS (m/z): 551.7 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{30}N_8OS$: C, 65.43; H, 5.49; N, 20.35. Found: C, 65.25; H, 5.47; N, 20.31.

***2-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-5-(o*-tolylthio)-1,3,4-oxadiazole** ***(9b)***. Yield: 75%; mp 226–230 °C; IR (KBr) $cm^{-1}$: 2943 (aromatic C–H), 1637 (C=N oxadiazole ring), 1173 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 7.92–7.71 (m, 4H), 7.62–6.83 (m, 5H, Ar–H), 6.70–6.61 (m, 4H, Ar–H), 3.84–3.59 (m, 8H, piperazine), 3.52–3.33 (m, 8H, piperazine), 2.63 (s, 3H, Ar–$CH_3$); $^{13}$C NMR (100 MHz, DMSO) δ 178.29 (oxadiazole C–S–Ar), 169.37 (quinazoline ring N=C–N C2 position), 165.18 (quinazoline C4 position), 156.73 (quinazoline ring C=C–N), 155.52 (oxadiazole C–N piperazine), 153.75 (Ar–C), 140.36, 136.49, 134.30, 132.27, 130.17, 129.61, 128.26, 127.43, 126.39, 125.04, 124.44, 123.25, 122.27, 121.45 (16 Ar–C), 49.39, 48.21, 47.05, 46.33 (8C of piperazine), 24.21 (Ar–$CH_3$); MS (m/z): 565.3 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{32}N_8OS$: C, 65.93; H, 5.71; N, 19.84. Found: C, 66.05; H, 5.69; N, 19.79.

***2-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-5-(p*-tolylthio)-1,3,4-oxadiazole** ***(9c)***. Yield: 79%; mp 289–294 °C; IR (KBr) $cm^{-1}$: 2986 (aromatic C-H), 1653 (C=N oxadiazole ring), 1167 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 7.83–7.67 (m, 4H, Ar–H), 7.58–6.76 (m, 5H, Ar–H), 6.71–6.53 (m, 4H, Ar–H), 3.93–3.68 (m, 8H, piperazine), 3.60–3.47 (m, 8H, piperazine), 2.76 (s, 3H, Ar–$CH_3$); $^{13}$C NMR (100 MHz, DMSO) δ 174.48 (oxadiazole C–S–Ar), 167.34 (quinazoline ring N=C–N C2 position), 166.29 (quinazoline C4 position), 157.49 (quinazoline ring C=C–N), 155.54 (oxadiazole C–N piperazine), 152.20 (Ar–C), 137.15, 135.24, 134.19, 133.59, 132.07, 130.16, 128.94, 127.04, 126.31, 124.43, 122.63, 120.16 (16 Ar–C), 48.86, 47.27, 46.35, 45.17 (8C of piperazine), 26.49 (Ar–$CH_3$); MS (m/z): 565.6 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{32}N_8OS$: C, 65.93; H, 5.71; N, 19.84. Found: C, 65.76; H, 5.72; N, 19.78.

***2-((2-Nitrophenyl)thio)-5-(4-(4-(4-phenylpiperazin-1-yl) quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazole (9d)***. Yield: 74%; mp 143–147 °C; IR (KBr) $cm^{-1}$: 2950 (aromatic C–H), 1674 (C=N oxadiazole ring), 1567 (N–O of nitro), 1378 (N–O of nitro), 1138 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 8.05–7.73 (m, 4H, Ar–H), 7.64-7.13 (m, 5H, Ar–H), 7.06–6.72 (m, 4H, Ar-H), 3.94–3.69 (m, 8H, piperazine), 3.64–3.33 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 173.22 (oxadiazole C–S–Ar), 166.24 (quinazoline ring N=C–N C2 position), 163.29 (quinazoline C4 position), 157.74 (quinazoline ring C=C–N), 154.21 (oxadiazole C–N piperazine), 151.16 (Ar–C), 146.61 (Ar–C–$NO_2$), 138.24, 135.57, 133.48, 131.08, 128.84, 125.43, 124.47, 122.26, 121.27, 120.16, 119.64, 118.15, 117.09 (15 Ar–C), 48.54, 47.15, 46.22, 45.27 (8C of piperazine); MS (m/z): 596.8 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{29}N_9O_3S$: C, 60.49; H, 4.91; N, 21.16. Found: C, 60.32; H, 4.90; N, 21.19.

***2-((3-Nitrophenyl)thio)-5-(4-(4-(4-phenylpiperazin-1-yl) quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazole (9e)***. Yield: 70%; mp 245–249 °C; IR (KBr) $cm^{-1}$: 2977 (aromatic C–H), 1649 (C=N oxadiazole ring), 1579 (N–O of nitro), 1367 (N–O of nitro), 1174 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 8.10–7.79 (m, 4H, Ar–H), 7.75–7.28 (m, 5H, Ar–H), 7.21–6.83 (m, 4H, Ar-H), 3.87–3.73 (m, 8H, piperazine), 3.68–3.45 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 176.64 (oxadiazole C–S–Ar), 169.24 (quinazoline ring N=C–N C2 position), 165.11 (quinazoline C4 position), 158.26 (quinazoline ring C=C–N), 155.77 (oxadiazole C–N piperazine), 153.59 (Ar–C), 143.24 (Ar–C–$NO_2$), 140.15, 137.19, 136.29, 134.17, 133.07, 131.21, 129.47, 128.42, 124.43, 121.16, 120.06, 119.34, 118.21 (15 Ar-C), 47.13, 46.37, 45.77, 44.81 (8C of piperazine); MS (m/z): 596.6 [$M^+$]. *Anal*. Calcd. for $C_{30}H_{29}N_9O_3S$: C, 60.49; H, 4.91; N, 21.16. Found: C, 60.41; H, 4.90; N, 21.11.

***2-((2-Methoxyphenyl)thio)-5-(4-(4-(4-phenylpiperazin-1-yl) quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazole (9f)***. Yield: 64%; mp 166–169 °C; IR (KBr) $cm^{-1}$: 2969 (aromatic C-H), 1659 (C=N oxadiazole ring), 1561 (N–O of nitro), 1175 (O–C ether); $^1$H NMR (400 MHz, DMSO) δ 8.08–7.83 (m, 4H, Ar–H), 7.81–7.62 (m, 5H, Ar–H), 7.54–6.95 (m, 4H, Ar–H), 4.15 (s, 3H, Ar–$OCH_3$), 3.67–3.52 (m, 8H, piperazine), 3.47–3.32 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 173.23 (oxadiazole C–S–Ar), 165.22 (quinazoline ring N=C–N C2 position), 161.74 (quinazoline C4 position), 153.67 (quinazoline ring C=C–N), 151.13 (oxadiazole C–N piperazine), 150.16 (Ar–C), 139.64, 137.17, 135.46, 133.27, 130.19, 129.77, 127.51, 125.47, 124.72, 123.20, 121.15, 120.48, 119.61, 118.40 (16 Ar–C), 60.14 (Ar–$OCH_3$), 48.13, 47.42, 46.54, 45.27 (8C of piperazine); MS (m/z): 581.5 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{32}N_8O_2S$: C, 64.12; H, 5.55; N, 19.30. Found: C, 64.26; H, 5.54; N, 19.36.

***1-(4-((5-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazol-2-yl)thio)phenyl)ethanone (9g)***. Yield: 69%; mp 257–260 °C; IR (KBr) $cm^{-1}$: 2987 (aromatic C–H), 1734 (C=O acetyl), 1676 (C=N oxadiazole ring), 1226 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 7.79–7.57 (m, 4H, Ar–H), 7.42–6.86 (m, 5H, Ar–H), 6.83–6.62 (m, 4H, Ar–H), 3.85–3.61 (m, 8H, piperazine), 3.53–3.34 (m, 8H, piperazine), 2.28 (s, 3H, Ar–$COCH_3$); $^{13}$C NMR (100 MHz, DMSO) δ 196.80 (–C=O), 171.97 (oxadiazole C–S–Ar), 164.01 (quinazoline ring N=C–N C2 position), 163.13 (quinazoline C4 position), 155.72 (quinazoline ring C=C–N), 151.56 (oxadiazole C–N piperazine), 140.68 (Ar–C), 134.85, 132.18, 129.83, 127.12, 126.88, 126.32, 125.92, 124.93, 123.84 (16 Ar–C), 49.47, 48.12, 47.32, 46.75 (8C of piperazine), 26.58 (acetophenone –$CH_3$); MS (m/z): 551.8 [$M^+$]. *Anal*. Calcd. for $C_{32}H_{32}N_8O_2S$: C, 64.84; H, 5.44; N, 18.91. Found: C, 64.65; H, 5.42; N, 18.88.

***4-((5-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazol-2-yl)thio)benzoic acid (9h)***. Yield: 72%; mp 134–137 °C; IR (KBr) $cm^{-1}$: 2994 (aromatic C–H), 1746 (C=O acetyl), 1684 (C=N oxadiazole ring), 1264 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 11.34 (s, 1H, Ar–COOH), 8.19-7.89 (m, 4H, Ar–H), 7.84–7.63 (m, 5H, Ar–H), 7.58–7.15 (m, 4H, Ar–H), 3.98–3.73 (m, 8H, piperazine), 3.67–3.30 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 179.25 (oxadiazole C–S–Ar), 170.14 (Ar–COOH), 169.41 (quinazoline ring N=C–N C2 position), 164.11 (quinazoline C4 position), 157.72 (quinazoline ring C=C–N), 154.34 (oxadiazole C–N piperazine), 143.28 (Ar–C), 138.24, 135.43, 130.17, 128.60, 127.34, 126.54, 125.30, 124.11, 123.39, 122.46, 121.41, 120.13 (16 Ar-C), 52.24, 51.82, 50.12, 49.65 (8C of piperazine); MS (m/z): 595.7 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{30}N_8O_3S$: C, 62.61; H, 5.08; N, 18.84. Found: C, 62.53; H, 5.09; N, 18.86.

***4-((5-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazol-2-yl)thio)benzonitrile (9i)***. Yield: 78%; mp 212–215 °C; IR (KBr) $cm^{-1}$: 2977 (aromatic C–H), 2257 (CN), 1750 (C=O acetyl), 1649 (C=N oxadiazole ring), 1281 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 7.96–7.74 (m, 4H, Ar-H), 7.68–7.37 (m, 5H, Ar–H), 7.34–6.99 (m, 4H, Ar-H), 3.52–3.40 (m, 8H, piperazine), 3.38–3.19 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 173.26 (oxadiazole C–S–Ar), 172.55

(quinazoline ring N=C–N C2 position), 167.16 (quinazoline C4 position), 165.40 (quinazoline ring C=C–N), 152.27 (oxadiazole C–N piperazine), 145.21 (Ar–C), 132.14, 131.48, 129.96 128.35, 127.30, 125.09, 124.43, 123.53, 122.51, 122.13, 121.53, 121.09 (16 Ar-C), 117.28 (Ar–CN), 49.61, 48.82, 47.14, 46.53 (8C of piperazine); MS (m/z): 576.4 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{29}N_9OS$: C, 64.68; H, 5.08; N, 21.90. Found: C, 64.54; H, 5.07; N, 21.85.

***4-((5-(4-(4-(4-Phenylpiperazin-1-yl)quinazolin-2-yl)piperazin-1-yl)-1,3,4-oxadiazol-2-yl)thio)benzaldehyde (9j).*** Yield: 68%; mp 177–180 °C; IR (KBr) $cm^{-1}$: 2984 (aromatic C–H), 2247 (CN), 1741 (C=O aldehyde), 1687 (C=N oxadiazole ring), 1276 (oxadiazole C–O–C); $^1$H NMR (400 MHz, DMSO) δ 9.81 (s, 1H, Ar–CHO), 8.09–7.84 (m, 4H, Ar-H), 7.73–7.53 (m, 5H, Ar–H), 7.48–7.27 (m, 4H, Ar-H), 3.64–3.43 (m, 8H, piperazine), 3.36–3.29 (m, 8H, piperazine); $^{13}$C NMR (100 MHz, DMSO) δ 198.24 (Ar–CHO), 175.45 (oxadiazole C–S–Ar), 167.44 (quinazoline ring N=C–N C2 position), 165.57 (quinazoline C4 position), 159.64 (quinazoline ring C=C–N), 156.94 (oxadiazole C–N piperazine), 146.39 (Ar–C), 140.03, 136.47, 133.26, 129.56, 128.61, 127.43, 124.53, 122.20, 121.14, 120.49, 119.81, 119.07 (16 Ar-C), 50.14, 49.53, 48.31, 47.34 (8C of piperazine); MS (m/z): 579.9 [$M^+$]. *Anal*. Calcd. for $C_{31}H_{30}N_8O_2S$: C, 64.34; H, 5.23; N, 19.36. Found: C, 64.31; H, 5.19; N, 19.32.

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## DECLARATION OF INTEREST

The authors confirm that this article content has no conflict of interest.

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