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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

$Zn(OTf)_2$-catalyzed three component, one-pot cyclocondensation reaction of some new octahydroquinazolinone derivatives and access their bio-potential

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Abstract An efficient synthesis of some new octahydroquinazolinone derivatives **4a–x** by the cyclocondensation reaction of corresponding 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde **1a–e**, 1,3-dicarbonyl compounds **2a–b**, and substituted urea **3a–c** using zinc triflate as a catalyst in refluxing ethanol in high yield is described. The structures of new compounds have been characterized on the basis of elemental analysis, FT- IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. All the synthesized compounds were evaluated for their antimicrobial activities against various microbes. Minimum inhibitory concentration values of all the 24 synthesized compounds were also determined. Some of the synthesized compounds exhibited excellent antimicrobial activity.

Keywords Octahydroquinazolinone · Zinc triflate · Cyclocondensation · Bio-potential

Introduction

Dihydropyrimidones (DHPMs) are an important class of the compounds and gaining increasingly importance due to their therapeutic and pharmacological properties (Kappe, 1993). In recent years, properly functionalized DHPMs have been developed as calcium channel modulators, antihypertensive agents, α_{1a}-adrenergic antagonists, neuropeptide Y (NPY) antagonists, and compounds that target the mammalian mitotic machinery (Atwal *et al*., 1991; Grover *et al*., 1995; Kappe, 2000). Furthermore, several isolated marine alkaloids with interesting biological activities were also found to contain the DHPMs core (Snider and Shi, 1993). Most notably among them are batzelladine alkaloids, which were found to be potent HIV gp-120-CD_4 inhibitors (Patil *et al*., 1995; Sinder *et al*., 1996). Thus, synthesis of the heterocyclic nucleus contained in such compounds is of much current interest. The classical Biginelli synthesis is a one-pot cyclocondensation of 1,3-dicarbonyl compounds with aldehydes and urea or thiourea in ethanol solution containing catalytic amounts of acid. This method, however, involves long reaction time period, harsh reaction conditions, and unsatisfactory yields, especially in the case of substituted aromatic and aliphatic aldehydes (Folkers *et al*., 1932; Wipf and Cunningham, 1995; Folkers and Johnson, 1934). Therefore, the discovery of milder and practical routes for synthesis of DHPMs by the Biginelli reaction continues to attract the attention of researchers. More recently, strontium(II) nitrate (Chenjiang *et al*., 2006), $Zn(ClO_4)_2{\cdot}6H_2O$ (Bose and Idrees, 2007), tungstate sulfuric acid (Esfahani *et al*., 2008), chloroacetic acid (Yang *et al*., 2007), iodine (Zalavadiya *et al*., 2009), KSF montmorillonite (Bigi *et al*., 1999) have been found to be effective for this transformation. However, many of these one-pot procedures require strong protic or Lewis acids, prolonged reaction time and high temperature. Consequently, there is scope for further improvement toward milder reaction conditions and better yields. In recent years, zinc triflate is a unique Lewis acid that is currently of great research interest (Ishimaru and Kojima, 2000). Octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* (Kidwai *et al*., 2005) and calcium antagonist activity (Yarim *et al*., 2003). Literature survey reveals that number of octahydroquinazolinone

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(Kantevari *et al*., 2006; Lin *et al*., 2007) derivatives have been synthesized by Biginelli reaction conditions using various aldehydes but not a single reference has been found where 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde is used. In view of the above observation and in continuation of our study on biologically active heterocyclic compounds (Patel *et al*., 2005, 2008; Ladani *et al*., 2009), We wish to report here 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde which is biologically active (Nandeshwarappa *et al*., 2006; Nityadevi *et al*., 2004) with a view to obtain more active heterocyclic systems containing two biologically active moieties 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde (Lamani *et al*., 2010) and octahydroquinazolinone (Abdel-Gawad *et al*., 2000; Minu *et al*., 2008).

Results and discussion

Chemistry

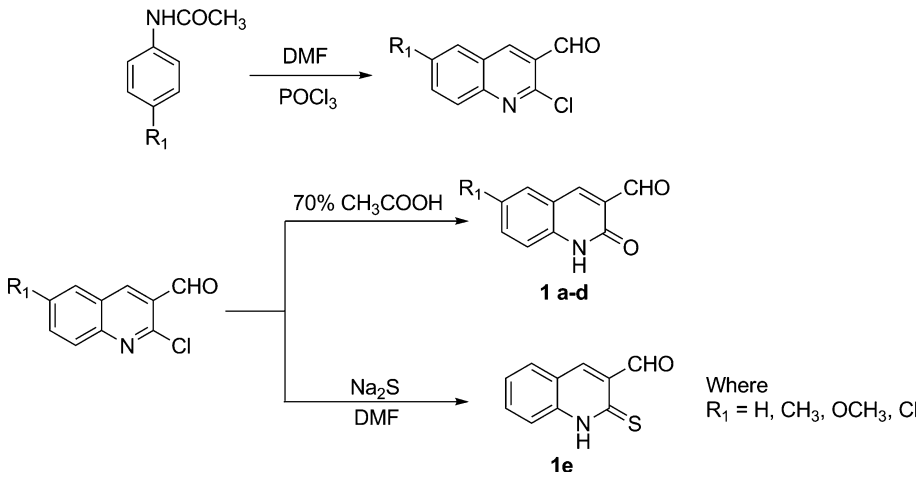
The octahydroquinazolinones **4a–x** were synthesized by zinc triflate catalyzed condensation of 6-(un)sub.2-(thi) oxo-1,2-dihydroquinoline-3-carbaldehyde **1a–e**, cyclohexane-1,3-dione or dimedone **2a–b**, urea or thiourea or phenyl thiourea **3a–c** in ethanol by modification of the Biginelli reaction in good yield (65–85%). The 6-(un)sub.2-(thi)oxo-1,2-dihydroquinoline-3-carbaldehyde **1a–e** were prepared from literature procedure (Sriyastava and Singh, 2005) (Scheme 1).

The structures of compounds **4a–x** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. IR spectra of **4a** exhibited absorptions at 3395, 3206, and 3107 cm^{-1} for (NH), 1711, 1657, and 1644 for (carbonyl group). The ^{1}H NMR of compound **4a** showed singlet at δ 11.86, 9.51, and 7.70 ppm for (NH) proton, it also showed multiplate at δ 1.97–2.58 for ($3CH_2$). Aromatic protons resonate as multiplates at δ 7.04–7.68 ppm. The ^{13}C NMR spectrum of compound **4a** showed signals at δ 21.28, 26.52, 36.79, 48.65 for aliphatic carbon, δ 105.57, 115.26, 119.40, 122.29, 128.61, 130.58, 133.27 for aromatic carbon and carbonyl carbons were observed at δ 156.60, 161.73, and 193.66. The structure was further confirmed by its mass spectral studies. It gave molecular ion peak at *m/z* 310 (M + 1) corresponding to molecular formula $C_{17}H_{15}N_3O_3$ (Scheme 2). Similarly, all these compounds were characterized on the basis of spectral studies. All the compounds were screened for their antibacterial and antifungal activities using gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and griseofulvin as standard drugs. According to the reports by Folkers and Johnson (1933) and Kappe (1997) for Biginelli reaction, the formation of product **4a–x** involves an imine intermediate (**Int-1**), formation of iminium ion (**Int-2**) by protonation of imine intermediate with Lewis acid ($Zn(OTf)_2$), and addition of cyclic β-diketone to the iminium ion (**Int-3**), and subsequent cyclodehydration (Scheme 3).

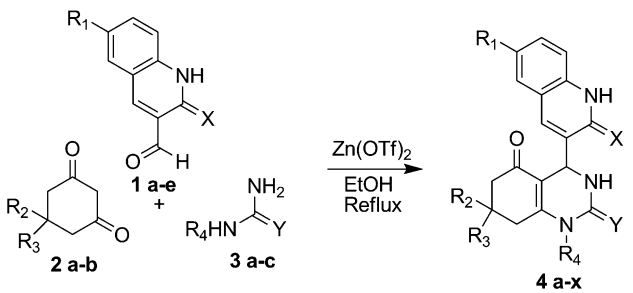
Antimicrobial screening

All the glass apparatus used were sterilized before use. Antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method (NCCLS, 2002). Mueller–Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 108 CFU [colony forming unit] per milliliter by comparing the turbidity. The strains used for the activity were procured from [MTCC—microbial type culture collection] Institute of Microbial Technology, Chandigarh. Each synthesized compound was diluted obtaining 2000 lg/ml concentration, as a stock solution. The results are recorded in the form of primary and secondary screenings. The compounds **4a–x** were screened for their antibacterial

Scheme 1 Synthetic pathway for the intermediates **1a–e**

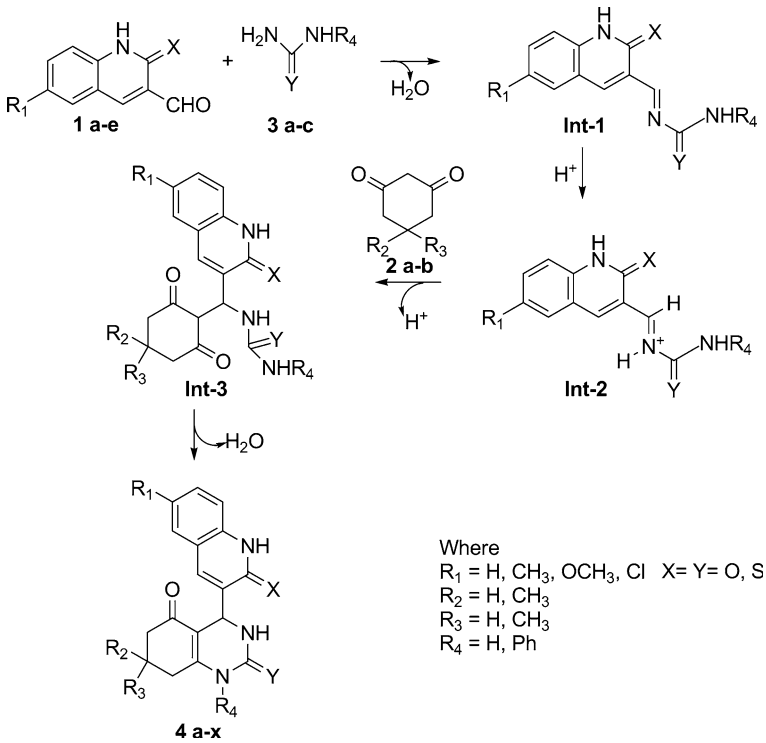


Scheme 2 Synthetic pathway for the compounds **4a–x**



Compd.	R_1	R_2	R_3	R_4	X	Y
4a	H	H	H	H	O	O
4b	CH_3	H	H	H	O	O
4c	OCH_3	H	H	H	O	O
4d	Cl	H	H	H	O	O
4e	H	CH_3	CH_3	H	O	O
4f	CH_3	CH_3	CH_3	H	O	O
4g	OCH_3	CH_3	CH_3	H	O	O
4h	Cl	CH_3	CH_3	H	O	O
4i	H	H	H	H	O	S
4j	CH_3	H	H	H	O	S
4k	OCH_3	H	H	H	O	S
4l	Cl	H	H	H	O	S
4m	H	CH_3	CH_3	H	O	S
4n	CH_3	CH_3	CH_3	H	O	S
4o	OCH_3	CH_3	CH_3	H	O	S
4p	Cl	CH_3	CH_3	H	O	S
4q	H	H	H	H	S	O
4r	H	H	H	H	S	S
4s	H	CH_3	CH_3	H	S	O
4t	H	CH_3	CH_3	H	S	S
4u	H	H	H	Ph	O	S
4v	H	CH_3	CH_3	Ph	O	S
4w	CH_3	H	H	Ph	O	S
4x	CH_3	CH_3	CH_3	Ph	O	S

Scheme 3 Possible mechanism for compounds **4a–x**



activity against *Bacillus subtilis* (MTCC 441), *Clostridium tetani* (MTCC 449), *Streptococcus pneumoniae* (MTCC 1936), *E. coli* (MTCC 443), *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906) as well as for antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227) at concentrations of 1000, 500, and 250 lg/ml as primary screening. DMSO was used as vehicle to get desired concentrations of compounds to test upon microbial strains. The compounds found to be active in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50, 25, 12.5, and 6.25 lg/ml. Ten microliters suspension from each well was further inoculated and growth was noted after 24 and 48 h. The lowest concentration which showed no visible growth (turbidity) after spot subculture was considered as MIC for each compound. The standard drugs used for comparison in this study were ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, and gentamycin for evaluating antibacterial activity and griseofulvin and nystatin for antifungal activity.

From the screening results (Table 1), compound **4k** ($R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$, X = O, Y = S) shows excellent antibacterial activity against *E. coli* when compared with ampicillin and equivalent to chloramphenicol; compounds **4c** ($R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$, X = Y=O), **4e** ($R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = Y=O), **4f** ($R_1 = R_2 = R_3 = CH_3$, $R_4 = H$, X = Y=O), **4g** ($R_1 = OCH_3$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = Y=O), **4h** ($R_1 = Cl$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = Y=O), **4i** ($R_1 = R_2 = R_3 = R_4 = H$, X = O, Y = S), **4l** ($R_1 = Cl$, $R_2 = R_3 = R_4 = H$, X = O, Y = S), and **4t** ($R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = Y=S) show comparable antibacterial activity against *E. coli* when compared with ampicillin; compound **4p** ($R_1 = Cl$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = O, Y = S) shows excellent antibacterial activity against *S. typhi*, *S. pneumoniae*, *V. cholerae*, *B. subtilis* when compared with chloramphenicol and ampicillin; compounds **4t** and **4u** ($R_1 = R_2 = R_3 = H$, $R_4 = Ph$, X = O, Y = S) show excellent antibacterial activity against *S. typhi* when compared with ampicillin; compounds **4d** ($R_1 = Cl$, $R_2 = R_3 = R_4 = H$, X = Y=O) and **4n** ($R_1 = R_2 = R_3 = CH_3$, $R_4 = H$, X = O, Y = S) show excellent antibacterial activity against *V. cholera* when compared with ampicillin; compounds **4a** ($R_1 = R_2 = R_3 = R_4 = H$, X = Y=O), **4b** ($R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, X = Y=O), **4f**, and **4n** show excellent antibacterial activity against *S. pneumoniae* when

Table 1 Antimicrobial activity of compounds **4a–x**

Compounds	Minimum inhibitory concentration (MIC, μg/ml)							
	Gram-negative bacteria			Gram-positive bacteria			Fungi	
	E. coli	*S. typhi*	*V. cholerae*	*S. pneumoniae*	*B. subtilis*	*C. tetani*	*C. albicans*	*A. fumigates*
4a	250	250	500	**100**	**200**	**100**	**500**	>1000
4b	500	500	200	**100**	500	**200**	1000	1000
4c	**100**	250	500	250	**250**	500	**500**	1000
4d	200	250	**100**	500	**250**	500	1000	1000
4e	**100**	250	250	250	500	**200**	**500**	500
4f	**100**	250	1000	**100**	**100**	100	**500**	1000
4g	**100**	150	**50**	250	**250**	**100**	**500**	1000
4h	**100**	200	500	500	**200**	**100**	**500**	>1000
4i	**100**	500	500	200	**200**	**200**	**100**	200
4j	500	500	500	500	500	500	**200**	500
4k	**50**	125	200	200	**200**	**200**	**500**	>1000
4l	**100**	200	250	250	**250**	**250**	**500**	1000
4m	125	150	500	500	500	500	**500**	500
4n	250	150	**100**	**100**	**100**	**100**	>1000	>1000
4o	500	250	200	200	**200**	**200**	**500**	>1000
4p	125	**25**	**50**	**50**	**50**	**250**	**500**	1000
4q	500	200	500	500	500	500	1000	500
4r	250	200	250	500	**250**	**250**	**250**	>1000
4s	500	500	200	250	500	500	**100**	**100**
4t	**100**	**100**	250	500	**250**	**200**	**250**	500
4u	150	**100**	200	150	**250**	**100**	**500**	250
4v	250	200	500	500	500	**250**	**250**	1000
4w	500	250	500	500	500	**250**	1000	500
4x	1000	500	250	1000	**250**	**250**	1000	500
Gentamycin	0.05	5	5	0.5	1	5	–	–
Ampicillin	100	100	100	100	250	250	–	–
Chloramphenicol	50	50	50	50	50	50	–	–
Ciprofloxacin	25	25	25	50	50	100	–	–
Norfloxacin	10	10	10	10	100	50	–	–
Nystatin	–	–	–	–	–	–	100	100
Griseofulvin	–	–	–	–	–	–	500	100

Bold values indicate the values of excellent antimicrobial activity compared to standard drugs used

compared with ampicillin; compounds **4a**, **4c–d**, **4f–i**, **4k, 4l**, **4n**, **4o** ($R_1 = OCH_3$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = O, Y = S), **4r** ($R_1 = R_2 = R_3 = R_4 = H$, X = Y=S), **4t–u**, and **4x** ($R_1 = R_2 = R_3 = CH_3$, $R_4 = Ph$, X = O, Y = S) show excellent antibacterial activity against *B. subtilis* when compared with ampicillin; compounds **4a–b**, **4e**, **4g–i**, **4k–l**, **4n**, **4p**, **4r**, **4t–u**, **4v** ($R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = Ph$, X = O, Y = S), **4w** ($R_1 = CH_3$, $R_2 = R_3 = H$, $R_4 = Ph$, X = O, Y = S), and **4x** show excellent antibacterial activity against *C. tetani* when compared with ampicillin; compound **4g** shows excellent antibacterial activity against *V. cholera* when compared with ampicillin and chloramphenicol. The remaining compounds show moderate to poor activity against all six bacterial species. Antifungal screening data show that compounds **4i** and **4s** ($R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = S, Y = O) show excellent antifungal activity against *C. albicans* when compared with nystatin and griseofulvin; compound **4s** also shows excellent antifungal activity against *A. fumigates* when compared with nystatin and griseofulvin; compounds **4a**, **4c**, **4e–h**, **4j** ($R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, X = O, Y = S), **4k–l**, **4m** ($R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = H$, X = O, Y = S), **4o–p**, **4r**, **4t**, and **4v** show excellent antifungal activity against *C. albicans* when compared with griseofulvin. The remaining compounds of entire series showed only moderate to poor activity against both fungal species.

Structure activity relationship (SAR) study

Analysis of structure–activity relationship shows that the different substituents at positions $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, **X**, and **Y** affect the antimicrobial properties of studied substances. Concerning the quinolone containing octahydroquinazolinone derivatives, substitution at $\mathbf{R_1}$ position of quinolone ring, such as a lipophilic methyl group, does not improve the antimicrobial activity, but hydrophilic methoxy group improves the antimicrobial activity of parent analog **4a** against tested bacterial as well as fungal pathogens. Compounds having electron-withdrawing chlorine group at position $\mathbf{R_1}$ improve the antimicrobial activity, i.e., compound **4p** possessed the highest antimicrobial effectiveness of the tested compounds. The electronic influence on the antimicrobial activity of the selected substituents of **4a–x** can be seen from the favorable effect of electron-withdrawing effect of chlorine (**4d**, **4h**, **4l**, and **4p**) and, conversely, the detrimental action of the electron-donating methyl and methoxy groups.

The structure–activity relationship analysis of the data reported in Table 1 further showed that the replacement of oxygen with sulfur atom at C-2 position of quinolone in compounds **4q**, **4r**, and **4s** (expect compound **4t**) does not improve the antimicrobial effectiveness of the tested compounds. Presence of phenyl group at 1st position of quinazolinone does not improve the antimicrobial activity of parent analog **4a**. Majority of the compounds which showed excellent antimicrobial activity when compared to the standard drug ampicillin are active against *E. coli*, *B. subtilis*, *C. tetani*, and *C. albicans*.

Conclusion

In connection with our on-going study on multi-component synthesis of biologically active heterocyclic compounds, our interests lie in zinc triflate catalyzed reactions at reflux temperature and to access their bio-potential. We now wish to report on a convenient and rapid one-pot three-component synthesis of 7,7-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-diones **(4a–x)** with 5 mol% zinc triflate as a catalyst. These heterocyclic compounds containing both quinazoline and quinoline ring systems are prepared by the reaction of 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde **1a–e**, 1,3-dicarbonyl compounds **2a–b**, and substituted urea **3a–c** in presence of zinc triflate. Zinc triflate may play crucial role in accelerating the dehydrative steps. It can be concluded from antimicrobial screening (Table 1), against panel of human pathogens that most of the synthesized octahydroquinazolinone derivatives were found to be highly active, compared to standard drugs, against bacterial pathogens. Among them, many compounds were found to be the most active against *B. subtilis* and *C. tetani* when compared to rest of the employed species. Antifungal activity of the compounds shows that most of the compounds found to be potent against *C. albicans* when compared to *A. fumigatus*. It is worth mentioning that combination of two biologically active moieties 2-thi(oxo)-1,2-dihydroquinoline-3-carbaldehyde and octahydroquinazolinone profoundly influences the biological activity.

Experimental

Chemistry

General procedures

All the reagents were commercially available and used without further purification. Solvents used were of analytical grade. Melting points were determined by open tube capillary method (using silicon oil 350 cst) and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel, $^{60}F_{254}$, 0.25-mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and

homogeneity of the synthesized compounds; eluent *n*-hexane:ethyl acetate::1:1. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds were within ±0.4% of theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

*General procedure for the synthesis of 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**1a–e**)* 2-(thi)oxo-1,2-dihydroquinoline-3-carbaldehyde **1a–e** were prepared, according to literature procedure (Sriyastava and Singh 2005): dimethylformamide (0.250 mol) was cooled in a three-necked round-bottomed flask at 0°C, to it phosphorous oxychloride (0.70 mol) was added dropwise with stirring at 0–10°C. In this mixture, 4-substituted acetanilide (0.10 mol) was added and the mixture was heated under reflux for 6 h at 75°C. The reaction mass then cooled to room temperature and poured in crushed ice with mechanical stirring. The product isolated was filtered and washed with water till neutral. The solid was crystallized from ethyl acetate to give pure 2-chloro-3-formyl quinoline.

For the synthesis compounds **1(a–d)**, 2-chloro-3-formyl quinolone (0.005 mol) and 70% glacial acetic acid were charged in round-bottomed flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and reflux for 5–6 h. After the completion of reaction (check by TLC), the product was filtered and washed with ethanol. The crude product was purified by leaching in (10:10 v/v) mixture of methanol and chloroform to obtain pure solid sample.

Compound **1e** prepared by stirred 2-chloro-3-formyl quinolone (0.5 mol), sodium sulfide (0.0075 mol) in dimethyl formamide. On completion of reaction (monitored by TLC), the reaction mixture was poured on ice-water and made acidic with acetic acid. The product was filtered off, washed well with water. The crude product was purified by leaching in (10:10 v/v) mixture of methanol and chloroform to obtain pure solid sample (Scheme 1).

*General procedure for the synthesis of 7,7-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**4a–x**)* 2-(thi)oxo-1,2-dihydroquinoline-3-carbaldehyde (0.0025 mol), dimedone or cyclohexane-1,3-dione (0.0025 mol), urea/thiourea/phenylthiourea (0.0025 mol), $Zn(OTf)_2$ (0.0005 mol) and ethanol (15 ml) were charged in 100-ml round-bottomed flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 4–5 h. On completion of reaction, monitored by TLC using 1:1 *n*-hexane/ethyl acetate as eluent, the reaction mixture was cooled to room temperature and solid separated was filtered and washed with mixture of chloroform and methanol (1:1) to obtain the pure compounds **4a–x**. Analytical and spectroscopic characterization data of the synthesized compounds **4a–x** are given below:

4-(2-Oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4a**): yield: 85%; melting range: 281–283°C; IR (KBr): 3395, 3206, 3107 (N–H str.), 1711, 1657, 1644 (–C=O str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.97–2.58 (m, 6H, $3CH_2$), 5.32 (s, 1H, quinazolinone H4), 7.04 (s, 1H, NH), 7.15–7.70 (m, 5H, Ar–H), 9.51 (s, 1H, NH), 11.86 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.28 (CH_2), 26.52 (CH_2), 36.79 ($\underline{C}H_2$–CO), 48.65 (quinazolinone C4), 105.57, 115.26, 119.40, 122.29, 128.61, 130.58, 133.27, 135.49, 138.60, 152.05 (Ar–C), 156.60 (C=O), 161.73 (C=O), 193.66 (C=O); ms: *m/z* 310 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{15}N_3O_3$ (309.33 g/mol): C, 66.01; H, 4.89; N, 13.58%. Found: C, 65.83; H, 4.77; N, 13.74%.

4-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4b**): yield: 82%; melting range: 286–288°C; IR (KBr): 3389, 3209, 3112 (N–H str.), 1705, 1666, 1649 (–C=O str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89–2.51 (m, 6H, $3CH_2$), 2.34 (s, 3H, CH_3), 5.39 (s, 1H, quinazolinone H4), 7.11 (s, 1H, NH), 7.18–7.63 (m, 4H, Ar–H), 9.47 (s, 1H, NH), 11.81 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.78 (CH_3), 21.61 (CH_2), 27.01 (CH_2), 36.21 ($\underline{C}H_2$–CO), 49.07 (quinazolinone C4), 106.08, 115.66, 118.89, 122.87, 129.64, 131.43, 133.71, 135.18, 137.89, 152.57 (Ar–C), 157.06 (C=O), 162.34 (C=O), 194.01 (C=O); ms: *m/z* 324 $[M + 1]^+$; Anal. Calcd. for $C_{18}H_{17}N_3O_3$ (323.35 g/mol): C, 66.86; H, 5.30; N, 13.00%. Found: C, 66.71; H, 5.12; N, 13.19%.

4-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4c**): yield: 79%; melting range: 291–293°C; IR (KBr): 3392, 3209, 3118 (N–H str.), 1719, 1669, 1648 (–C=O str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81–2.43 (m, 6H, $3CH_2$), 3.83 (s, 3H, OCH_3), 5.41 (s, 1H, quinazolinone H4), 7.09 (s, 1H, NH), 7.23–7.51 (m, 4H, Ar–H), 9.41 (s, 1H, NH), 11.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.53 (CH_2), 27.13 (CH_2), 36.29 ($\underline{C}H_2$–CO), 48.93 (quinazolinone C4), 55.81 (OCH_3), 105.97, 115.31, 119.09, 122.75, 129.32, 131.11, 133.44, 134.53, 137.31, 152.65 (Ar–C), 156.95 (C=O), 161.98 (C=O), 194.15 (C=O); ms: *m/z* 340 $[M + 1]^+$; Anal. Calcd. for $C_{18}H_{17}N_3O_4$ (339.35 g/mol): C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.54; H, 4.91; N, 12.58%.

4-(6-Chloro-2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4d**): yield: 83%; melting range: 294–296°C; IR (KBr): 3398, 3214, 3145 (N–H str.), 1703, 1659, 1651 (–C=O str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.75–2.41 (m, 6H, $3CH_2$), 5.33 (s, 1H, quinazolinone H4), 7.15 (s, 1H, NH), 7.27–7.59 (m, 4H, Ar–H), 9.46 (s, 1H, NH), 11.64 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.07 (CH_2), 26.91 (CH_2), 36.78 ($\underline{C}H_2$–CO), 49.11 (quinazolinone C4), 106.08, 115.78, 119.81, 123.04, 129.57, 130.92, 133.76, 134.91, 137.89, 153.01 (Ar–C), 157.11 (C=O), 162.08 (C=O), 194.37 (C=O); ms: *m/z* 344 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$ (343.77 g/mol): C, 59.40; H, 4.10; N, 12.22%. Found: C, 59.18; H, 4.23; N, 12.41%.

7,7-Dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(*1H,6H*)-dione (**4e**): yield: 84%; melting range: 284–286°C; IR (KBr): 3390, 3208, 3114 (N–H str.), 1707, 1666, 1645 (–C=O str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.08–2.43 (m, 4H, $2CH_2$), 5.30 (s, 1H, quinazolinone H4), 7.01 (s, 1H, NH), 7.04–7.68 (m, 5H, Ar–H), 9.47 (s, 1H, NH), 11.82 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.81 (CH_3), 29.04 (CH_3), 32.76 ($\underline{C}(CH_3)_2$), 39.08 (CH_2), 48.66 ($\underline{C}H_2$–CO), 50.12 (quinazolinone C4), 105.61, 115.59, 119.05, 128.11, 131.85, 132.71, 132.93, 136.35, 136.75, 150.54 (10C, Ar–C), 156.58 (C=O), 161.66 (C=O), 193.64 (C=O); ms: *m/z* 338 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{19}N_3O_3$ (337.38 g/mol): C, 67.64; H, 5.68; N, 12.45%. Found: C, 67.85; H, 5.47; N, 12.63%.

7,7-Dimethyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4f**): yield: 81%; melting range: 293–295°C; IR (KBr): 3384, 3212, 3109 (N–H str.), 1701, 1669, 1641 (–C=O str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.07 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.05–2.41 (m, 4H, $2CH_2$), 2.27 (s, 3H, CH_3), 5.37 (s, 1H, quinazolinone H4), 7.07 (s, 1H, NH), 7.11–7.59 (m, 4H, Ar–H), 9.42 (s, 1H, NH), 11.77 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.56 (CH_3), 27.37 (CH_3), 29.53 (CH_3), 32.37 ($\underline{C}(CH_3)_2$), 38.97 (CH_2), 50.61 ($\underline{C}H_2$–CO), 51.22 (quinazolinone C4), 105.93, 115.39, 118.92, 127.90, 131.52, 132.29, 132.73, 136.01, 136.66, 150.61 (Ar–C), 156.27 (C=O), 161.88 (C=O), 193.31 (C=O); ms: *m/z* 352 $[M + 1]^+$; Anal. Calcd. for $C_{20}H_{21}N_3O_3$ (351.41 g/mol): C, 68.36; H, 6.02; N, 11.96%. Found: C, 68.12; H, 5.87; N, 12.19%.

4-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4g**): yield: 78%; melting range: 294–296°C; IR (KBr): 3395, 3213, 3118 (N–H str.), 1714, 1665, 1651 (–C=O str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.05 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.01–2.37 (m, 4H, $2CH_2$), 3.89 (s, 3H, OCH_3), 5.35 (s, 1H, quinazolinone H4), 7.02 (s, 1H, NH), 7.13–7.74 (m, 4H, Ar–H), 9.47 (s, 1H, NH), 11.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.31 (CH_3), 29.87 (CH_3), 32.06 ($\underline{C}(CH_3)_2$), 39.01 (CH_2), 48.45 ($\underline{C}H_2$–CO), 50.29 (quinazolinone C4), 56.92 (OCH_3), 106.08, 115.81, 118.43, 127.67, 131.19, 132.75, 132.89, 136.58, 136.23, 150.46 (Ar–C), 156.98 (C=O), 161.52 (C=O), 193.79 (C=O); ms: *m/z* 368 $[M + 1]^+$; Anal. Calcd. for $C_{20}H_{21}N_3O_4$ (367.41 g/mol): C, 65.38; H, 5.76; N, 11.44%. Found: C, 65.62; H, 5.57; N, 11.26%.

4-(6-Chloro-2-oxo-1,2-dihydroquinolin-3-yl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4h**): yield: 75%; melting range: 296–298°C; IR (KBr): 3398, 3221, 3139 (N–H str.), 1701, 1655, 1648 (–C=O str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.05–2.31 (m, 4H, $2CH_2$), 5.39 (s, 1H, quinazolinone H4), 7.10 (s, 1H, NH), 7.18–7.69 (m, 4H, Ar–H), 9.53 (s, 1H, NH), 11.72 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.13 (CH_3), 29.71 (CH_3), 32.44 ($\underline{C}(CH_3)_2$), 39.57 (CH_2), 48.21 ($\underline{C}H_2$–CO), 50.78 (quinazolinone C4), 106.08, 115.81, 118.43, 127.67, 131.19, 132.75, 132.89, 136.58, 136.23, 150.46 (Ar–C), 156.98 (C=O), 161.52 (C=O), 193.79 (C=O); ms: *m/z* 372 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$ (371.83 g/mol): C, 61.38; H, 4.88; N, 11.30%. Found: C, 61.65; H, 4.71; N, 11.53%.

4-(2-Oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4i**): yield: 81%; melting range: 306–308°C; IR (KBr): 3390, 3201, 3111 (N–H str.), 1657, 1638 (–C=O str.), 1189 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.91–2.53 (m, 6H, $3CH_2$), 5.41 (s, 1H, quinazolinone H4), 7.12–7.71 (m, 5H, Ar–H), 9.08 (s, 1H, NH), 10.91 (s, 1H, NH), 11.89 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.23 (CH_2), 26.41 (CH_2), 36.71 ($\underline{C}H_2$–CO), 48.13 (quinazolinone C4), 105.06, 115.77, 119.87, 122.71, 128.18, 130.07, 132.97, 135.90, 139.01, 153.11 (Ar–C), 156.94 (C=O), 176.03 (C=S), 194.09 (C=O); ms: *m/z* 326 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{15}N_3O_2S$ (325.39 g/mol): C, 62.75; H, 4.65; N, 12.91%. Found: C, 62.49; H, 4.89; N, 13.18%.

4-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4j**): yield: 77%; melting range: 313–315°C; IR (KBr): 3388, 3203, 3114 (N–H str.), 1651, 1644 (–C=O str.), 1183 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.87–2.46 (m, 6H, $3CH_2$), 3.32 (3H, CH_3), 5.33 (s, 1H, quinazolinone H4), 7.04–7.73 (m, 4H, Ar–H), 9.72 (s, 1H, NH), 10.85 (s, 1H, NH), 11.91 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.13 (CH_3), 21.37 (CH_2), 26.43 (CH_2), 36.77 ($\underline{C}H_2$–CO), 48.28 (quinazolinone C4), 105.23, 115.41, 119.73, 122.67, 128.43, 130.18, 133.04, 136.11, 139.13, 153.62 (Ar–C), 156.38 (C=O), 175.94 (C=S), 194.47 (C=O); ms: *m/z* 340 $[M + 1]^+$; Anal. Calcd. for $C_{18}H_{17}N_3O_2S$ (339.42 g/mol): C, 63.70; H, 5.05; N, 12.38%. Found: C, 63.93; H, 5.26; N, 12.14%.

4-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4k**): yield: 75%; melting range: 304–306°C; IR (KBr): 3391, 3207, 3105 (N–H str.), 1656, 1649 (–C=O str.), 1188 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.89–2.49 (m, 6H, $3CH_2$), 3.92 (3H, OCH_3), 5.37 (s, 1H, quinazolinone H4), 7.07–7.75 (m, 4H, Ar–H), 9.67 (s, 1H, NH), 10.79 (s, 1H, NH), 11.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.41 (CH_2), 26.51 (CH_2), 36.92 ($\underline{C}H_2$–CO), 48.18 (quinazolinone C4), 55.61 (3H, OCH_3), 104.97, 115.56, 119.94, 122.81, 128.79, 130.11, 132.95, 136.22, 139.19, 153.92 (Ar–C), 155.87 (C=O), 175.72 (C=S), 194.73 (C=O); ms: *m/z* 356 $[M + 1]^+$; Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.42 g/mol): C, 60.83; H, 4.82; N, 11.82%. Found: C, 60.72; H, 4.98; N, 11.61%.

4-(6-Chloro-2-oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4l**): yield: 77%; melting range: 307–309°C; IR (KBr): 3394, 3211, 3107 (N–H str.), 1658, 1646 (–C=O str.), 1179 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.81–2.44 (m, 6H, $3CH_2$), 5.42 (s, 1H, quinazolinone H4), 7.11–7.69 (m, 4H, Ar–H), 9.64 (s, 1H, NH), 10.73 (s, 1H, NH), 11.85 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.32 (CH_2), 26.43 (CH_2), 36.76 ($\underline{C}H_2$–CO), 48.49 (quinazolinone C4), 104.76, 115.31, 119.82, 122.47, 128.92, 130.34, 132.78, 136.44, 139.25, 154.12 (Ar–C), 155.32 (C=O), 176.02 (C=S), 194.43 (C=O); ms: *m/z* 360 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{14}ClN_3O_2S$ (359.84 g/mol): C, 56.75; H, 3.92; N, 11.68%. Found: C, 56.57; H, 4.05; N, 11.84%.

7,7-Dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4m**): yield: 84%; melting range: 314–316°C; IR (KBr): 3387, 3208, 3102 (N–H str.), 1663, 1661 (–C=O str.), 1193 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.11–2.39 (m, 4H, $2CH_2$), 5.35 (s, 1H, quinazolinone H4), 7.03–7.61 (m, 5H, Ar–H), 9.68 (s, 1H, NH), 9.81 (s, 1H, NH), 11.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.29 (CH_3), 29.78 (CH_3), 32.21 ($\underline{C}(CH_3)_2$), 38.82 (CH_2), 50.43 ($\underline{C}H_2$–CO), 51.22 (quinazolinone C4), 104.91, 115.28, 119.11, 127.72, 131.09, 132.61, 132.39, 136.52, 136.23, 151.04 (Ar–C), 156.88 (C=O), 176.12 (C=S), 194.19 (C=O); ms: *m/z* 354 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353.45 g/mol): C, 64.57; H, 5.42; N, 11.89%. Found: C, 64.43; H, 5.58; N, 11.71%.

7,7-Dimethyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4n**): yield: 65%; melting range: 301–303°C; IR (KBr): 3390, 3211, 3160 (N–H str.), 1655, 1637 (–C=O str.), 1190 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.10- 2.45 (m, 4H, $2CH_2$), 5.32 (s, 1H, quinazolinone H4), 7.19–7.52 (m, 4H, Ar–H), 9.00 (s, 1H, NH), 10.49 (s, 1H, NH), 11.75 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.81 (CH_3), 27.82 (CH_3), 29.06 (CH_3), 32.78 ($\underline{C}(CH_3)_2$), 39.11 (CH_2), 50.14 ($\underline{C}H_2$–CO), 50.40 (quinazolinone C4), 105.67, 115.18, 119.17, 128.03, 131.35, 132.08, 132.46, 136.82, 136.97, 150.53 (Ar–C), 161.11 (C=O), 175.21 (C=S), 193.92 (C=O); ms: *m/z* 368 $[M + 1]^+$; Anal. Calcd. for $C_{20}H_{21}N_3O_2S$ (367.47 g/mol): C, 65.37; H, 5.76; N, 11.43%. Found: C, 65.21; H, 5.93; N, 11.28%.

4-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4o**): yield: 80%; melting range: 319–321°C; IR (KBr): 3394, 3216, 3121 (N–H str.), 1654, 1633 (–C=O str.), 1197 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.08- 2.46 (m, 4H, $2CH_2$), 3.89 (s, 3H, OCH_3), 5.36 (s, 1H, quinazolinone H4), 7.14–7.47 (m, 4H, Ar–H), 9.11 (s, 1H, NH), 10.52 (s, 1H, NH), 11.78 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.78 (CH_3), 29.11 (CH_3), 32.72 ($\underline{C}(CH_3)_2$), 39.09 (CH_2), 50.27 ($\underline{C}H_2$–CO), 50.31 (quinazolinone C4), 55.19 (OCH_3), 105.36, 115.53, 119.29, 128.57, 131.19, 132.22, 132.13, 136.70, 136.43, 150.93 (Ar–C), 161.48 (C=O), 175.44 (C=S), 194.13 (C=O); ms: *m/z* 384 $[M + 1]^+$; Anal. Calcd. for $C_{20}H_{21}N_3O_3S$ (383.47 g/mol): C, 62.64; H, 5.52; N, 10.96%. Found: C, 62.51; H, 5.33; N, 11.12%.

4-(6-Chloro-2-oxo-1,2-dihydroquinolin-3-yl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4p**): yield: 75%; melting range: 312–314°C; IR (KBr): 3390, 3208, 3102 (N–H str.), 1663, 1658 (–C=O str.), 1181 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, CH_3), 1.07 (s. 3H, CH_3), 1.78–2.47 (m, 4H, $2CH_2$), 5.38 (s, 1H, quinazolinone H4), 7.14–7.73 (m, 4H, Ar–H), 9.61 (s, 1H, NH), 10.78 (s, 1H, NH), 11.89 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.56 (CH_3), 29.29 (CH_3), 32.70 ($\underline{C}(CH_3)_2$), 39.51 (CH_2), 49.88 ($\underline{C}H_2$–CO), 51.23 (quinazolinone C4), 105.22, 115.73, 119.24, 122.38, 128.69, 130.81, 132.68, 136.53, 139.67, 154.46 (Ar–C), 155.18 (C=O), 175.92 (C=S), 194.21 (C=O); ms: *m/z* 388 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{18}ClN_3O_2S$ (387.89 g/mol): C, 58.83; H, 4.68; N, 10.83%. Found: C, 58.66; H, 4.54; N, 10.98%.

4-(2-Thioxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4q**): yield: 77%; melting range: 305–307°C; IR (KBr): 3383, 3211, 3108 (N–H str.), 1661, 1653 (–C=O str.), 1176 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.90–2.51 (m, 6H, $3CH_2$), 5.37 (s, 1H, quinazolinone H4), 7.09–7.87 (m, 5H, Ar–H), 9.74 (s, 1H, NH), 10.85 (s, 1H, NH), 11.93 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.42 (CH_2), 26.53 (CH_2), 36.49 ($\underline{C}H_2$–CO), 48.22 (quinazolinone C4), 105.13, 115.71, 119.92, 122.86, 128.24, 130.13, 132.85, 135.80, 139.17, 153.23 (Ar–C), 156.72 (C=O), 188.20 (C=S), 194.14 (C=O); ms: *m/z* 326 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{15}N_3O_2S$ (325.39 g/mol): C, 62.75; H, 4.65; N, 12.91%. Found: C, 62.61; H, 4.77; N, 13.04%.

2-Thioxo-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4r**): yield: 75%; melting range: 316–318°C; IR (KBr): 3379, 3208, 3115 (N–H str.), 1664 (–C=O str.), 1179, 1168 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.86–2.48 (m, 6H, $3CH_2$), 5.42 (s, 1H, quinazolinone H4), 7.07–7.81 (m, 5H, Ar–H), 9.72 (s, 1H, NH), 10.82 (s, 1H, NH), 11.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.31 (CH_2), 26.48 (CH_2), 36.32 ($\underline{C}H_2$–CO), 48.27 (quinazolinone C4), 105.32, 115.54, 119.68, 122.73, 128.37, 130.19, 132.75, 135.69, 139.23, 153.45 (Ar–C), 174.72 (C=S), 188.12 (C=S), 194.31 (C=O); ms: *m/z* 342 $[M + 1]^+$; Anal. Calcd. for $C_{17}H_{15}N_3OS_2$ (341.46 g/mol): C, 59.80; H, 4.43; N, 12.31%. Found: C, 59.62; H, 4.28; N, 12.43%.

7,7-Dimethyl-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4s**): yield: 78%; melting range: 310–312°C; IR (KBr): 3388, 3213, 3110 (N–H str.), 1669, 1651 (–C=O str.), 1172 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.13–2.35 (m, 4H, $2CH_2$), 5.39 (s, 1H, quinazolinone H4), 7.01–7.64 (m, 5H, Ar–H), 9.65 (s, 1H, NH), 9.84 (s, 1H, NH), 11.76 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.33 (CH_3), 29.74 (CH_3), 32.25 ($\underline{C}(CH_3)_2$), 38.91 (CH_2), 50.41 ($\underline{C}H_2$–CO), 51.32 (quinazolinone C4), 105.13, 115.44, 119.21, 127.84, 131.17, 132.70, 132.52, 136.65, 136.19, 151.13 (Ar–C), 156.81 (C=O), 188.53 (C=S), 194.27 (C=O); ms: *m/z* 354 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353.45 g/mol): C, 64.57; H, 5.42; N, 11.89%. Found: C, 64.42; H,5.59; N, 11.70%.

7,7-Dimethyl-2-thioxo-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4t**): yield: 74%; melting range: 322–324°C; IR (KBr): 3382, 3218, 3107 (N–H str.), 1670 (–C=O str.), 1173, 1169 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.11–2.36 (m, 4H, $2CH_2$), 5.34 (s, 1H, quinazolinone H4), 7.08–7.67 (m, 5H, Ar–H), 9.63 (s, 1H, NH), 9.89 (s, 1H, NH), 11.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.41 (CH_3), 29.72 (CH_3), 32.23 ($\underline{C}(CH_3)_2$), 38.87 (CH_2), 50.38 ($\underline{C}H_2$–CO), 51.43 (quinazolinone C4), 105.65, 115.29, 119.76, 127.32, 131.86, 132.57, 132.98, 136.23, 136.45, 151.78 (Ar–C), 176.72 (C=S), 188.49 (C=S), 194.22 (C=O); ms: *m/z* 370 $[M + 1]^+$; Anal. Calcd. for $C_{19}H_{19}N_3OS_2$ (369.51 g/mol): C, 61.76; H, 5.18; N, 11.37%. Found: C, 61.59; H,5.32; N, 11.21%.

4-(2-Oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4u**): yield: 75%; melting range: 303–305°C; IR (KBr): 3353, 3259 (N–H str.), 1701, 1666 (–C=O str.), 1167 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.81–2.43 (m, 6H, $3CH_2$), 5.38 (s, 1H, quinazolinone H4), 7.08–7.67 (m, 10H, Ar–H), 9.85 (s, 1H, NH), 11.79 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.44 (CH_2), 26.62 (CH_2), 36.41 ($\underline{C}H_2$–CO), 51.32 (quinazolinone C4), 105.65, 115.29, 119.76, 127.32, 128.11, 129.31, 129.54, 131.86, 132.57, 132.98, 134.68, 136.42, 136.57, 151.73 (Ar–C), 161.21 (C=O), 177.34 (C=S), 194.43 (C=O); ms: *m/z* 402 $[M + 1]^+$; Anal. Calcd. for $C_{23}H_{19}N_3O_2S$ (401.49 g/mol): C, 68.81; H, 4.77; N, 10.47%. Found: C, 68.62; H,4.93; N, 10.23%.

7,7-Dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4v**): yield: 72%; melting range: 315–317°C; IR (KBr): 3359, 3261 (N–H str.), 1705, 1661 (–C=O str.), 1171 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.82 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.78–2.23 (m, 4H, $2CH_2$), 5.32 (s, 1H, quinazolinone H4), 7.19–7.83 (m, 10H, Ar–H), 9.48 (s, 1H, NH), 11.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.14 (CH_3), 29.21 (CH_3), 32.72 ($\underline{C}(CH_3)_2$), 41.49 (CH_2), 49.51 ($\underline{C}H_2$–CO), 51.12 (quinazolinone C4), 107.93, 115.20, 119.25, 122.43, 128.78, 130.05, 130.94, 131.37, 131.75, 138.49, 138.95, 139.32, 141.09, 151.61 (Ar–C), 161.26 (C=O), 178.42 (C=S), 194.77 (C=O); ms: *m/z* 430 $[M + 1]^+$; Anal. Calcd. for $C_{25}H_{23}N_3O_2S$ (429.54 g/mol): C, 69.91; H, 5.40; N, 9.78%. Found: C, 69.76; H,5.24; N, 9.89%.

4-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-2-thioxo-1,2,3,4,7,8 hexahydroquinazolin-5(6*H*)-one (**4w**): yield: 70%; melting range: 313–315°C; IR (KBr): 3357, 3267 (N–H str.), 1712, 1673 (–C=O str.), 1165 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–2.39 (m, 6H, $3CH_2$), 2.42 (s, 3H, CH_3), 5.41 (s, 1H, quinazolinone H4), 7.03–7.65 (m, 9H, Ar–H), 9.82 (s, 1H, NH), 11.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.81 (CH_3), 21.32 (CH_2), 26.51 (CH_2), 36.47 ($\underline{C}H_2$–CO), 51.45 (quinazolinone C4), 105.56, 115.20, 119.65, 127.41, 128.24, 129.35, 129.76, 131.91, 132.64, 132.95, 134.63, 136.76, 136.94, 151.85 (Ar–C), 155.32 (C=O), 178.19 (C=S), 194.28 (C=O); ms: *m/z* 416 $[M + 1]^+$; Anal. Calcd. for $C_{24}H_{21}N_3O_2S$ (415.52 g/mol): C, 69.38; H, 5.09; N, 10.11%. Found: C, 69.21; H,5.18; N,10.29%.

7,7-Dimethyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**4x**): yield: 71%; melting range: 309–311°C; IR (KBr): 3354, 3264 (N–H str.), 1708, 1669 (–C=O str.), 1176 (–C=S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.79 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.74–2.37 (m, 4H, $2CH_2$), 2.31 (s, 3H, CH_3), 5.39 (s, 1H, quinazolinone H4), 7.05–7.79 (m, 9H, Ar–H), 9.77 (s, 1H, NH), 11.79 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.44 (CH_3), 27.26 (CH_3), 29.71 (CH_3), 32.45 ($\underline{C}(CH_3)_2$), 39.81 (CH_2), 50.56 ($\underline{C}H_2$–CO), 51.57 (quinazolinone C4), 105.37, 115.16, 119.68, 127.25, 128.54, 129.26, 129.87, 131.91, 132.67, 132.94, 134.74, 136.82, 137.13, 151.68 (Ar–C), 155.23 (C=O), 176.57 (C=S), 194.82 (C=O); ms: *m/z* 444 $[M + 1]^+$; Anal. Calcd. for $C_{26}H_{25}N_3O_2S$ (443.57 g/mol): C, 70.40; H, 5.68; N, 9.47%. Found: C, 70.27; H, 5.81; N, 9.30%.

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