An efficient three component one-pot synthesis of some new octahydroquinazolinone derivatives and investigation of their antimicrobial activities

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Abstract

An efficient and convenient procedure has been developed for the synthesis of some new octahydroquinazolinones **5a-p** in good yields. They have been achieved by the reaction between corresponding tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2a-d,** dimedone or cyclohexane-1, 3-dione **3a-b** and (thio) urea **4a-b** in the presence of concentrated HCl in ethanol. The structures of new compounds have been evaluated on the basis of elemental analysis, FT- IR, ^{1}H NMR and ^{13}C NMR spectral data. They have also been screened for their antimicrobial activities.

Keywords: Octahydroquinazolinones, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde, Biginelli reaction, antimicrobial activity

Introduction

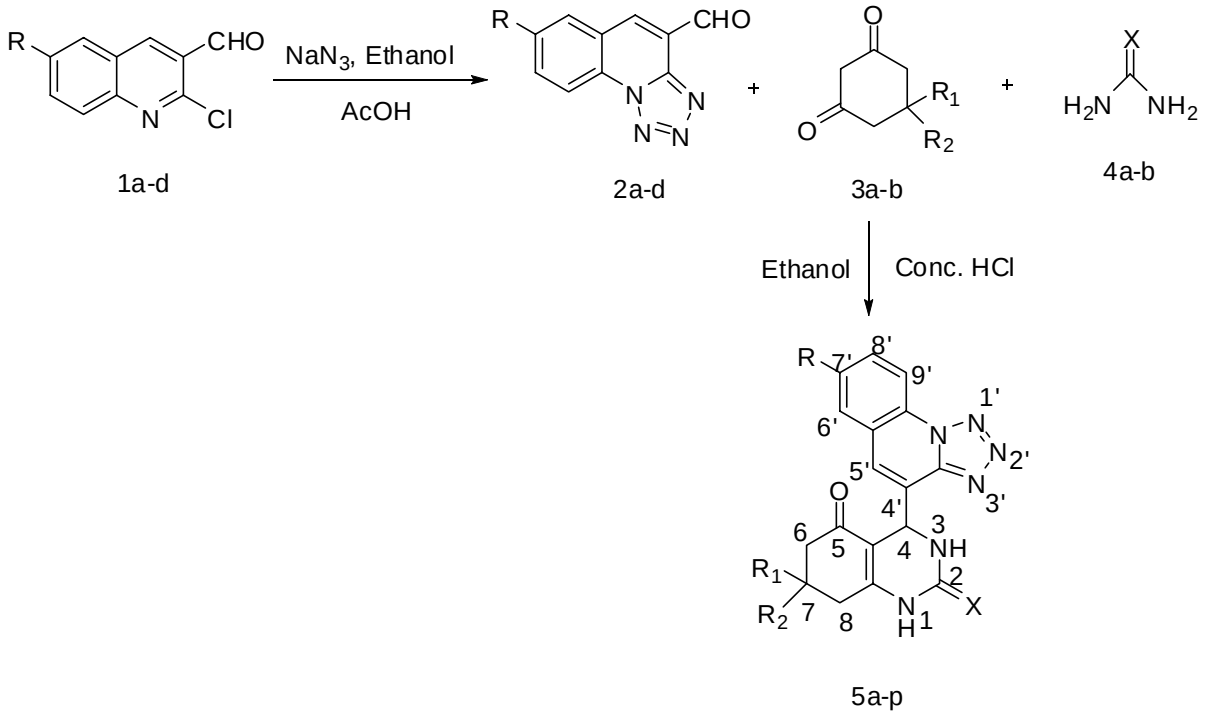
In recent years, dihydropyrimidinones (DHPMs) and their derivatives have occupied an important position in natural and synthetic organic chemistry, due mainly to their wide range of biological activities[1], such as antibacterial, antiviral, antihypertensive, antitumor effects and calcium channel blockers. Scaffold decoration of DHPMs is highly important for creating structural diversity to produce "drug-like" molecules for biological screening. The synthesis of DHPMs was first reported by Biginelli in 1893[2] and has been reviewed recently[3]. Improved procedures and new Biginelli-like scaffolds have been reported over the past decade and a variant of the Beginelli condensation has been described for its application to the total synthesis of bioactive guanidine alkaloids[4]. Basically, these methods are all similar in the use of different Lewis acid catalyst as well as protic acid under classical reflux[5]. Other studies have focused on the use of ionic liquids[6], microwave irradiation[7] and combinatorial chemistry[8]. The use of boron compounds[9], TMSCl[10] and heterogeneous catalysts, such as tangstophosphoric acid[11], Zeolite[12], montmorillonite[13] and ion-exchange resins[14] have been reported. However, to the best of our knowledge, there have been relatively few reports of the synthesis of fused DHPMs from cyclic

β-diketones. More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds using concentrated HCl[15] and H_2SO_4[16] as the catalyst. Octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*[17] and calcium antagonist activity[18-19]. Literature survey reveals that number of octahydroquinazolinone[20] derivatives have been synthesized by Biginelli reaction conditions using various aldehyde but not a single reference have been found where tetrazolo[1,5-*a*]quinoline-4-carbaldehyde is used. In view of the above observation and in continuation of our work on biologically active heterocyclic compounds[21-23], We now wish to report herein this heterocyclic aldehyde which is biologically active[24-25] with a view to obtain more active heterocyclic systems containing two biologically active moieties tetrazoloquinolines[26] and octahydroquinazolinone[27-28].

Results and Discussion

The Octahydroquinazolinone **5a-p** was synthesized by acid catalyzed condensation of 7-(un)sub.tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2a-d,** dimedone or cyclohexane-1,3-dione **3a-b,** (thio)urea **4a-b** in ethanol by a modification of the Biginelli reaction in good yield(60-82%)**.** 7-(un)sub. tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2a-d** was prepared by refluxing 2-chloro-3-formyl quinoline, sodium azide and acetic acid in ethanol for 3-4 hr[29]. The required 2-chloro-3-formyl quinoline was prepared by literature procedure[30]. The structure of compound **2a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectra. IR spectra of **2a** exhibited absorptions at 3000, 3025 cm^{-1} for (aromatic C-H stretching), 1700 cm^{-1} for (carbonyl group) and 1625 cm^{-1} for (C=N stretching). The ^{1}H NMR of compound **2a** showed singlet at δ 10.45 ppm for (CHO) and aromatic protons resonate as multiplets at δ 7.44-8.90 ppm. The ^{13}C NMR spectrum of compound **2a** showed signals at δ 113.74, 118.52, 122.89, 124.77, 125.08, 126.54, 140.43, 145.32 for aromatic carbon, 159.34 for (C=N) and the carbonyl carbon was observed at δ 189.14. The structure of compounds **5a-p** was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. IR spectra of **5a** exhibited absorptions at 3353, 3259 cm^{-1} for (NH) , 3051 cm^{-1} for (aromatic C-H stretching), 1701 & 1666 cm^{-1} for (carbonyl group) and 1646 cm^{-1} for (C=N stretching). The ^{1}H NMR of compound **5a** showed singlet at δ 9.78 and 7.70 ppm for (NH) proton, it also showed singlet at δ 0.81 and 1.01 ppm for (CH_3 of dimedone) and δ 5.47 ppm for(CH) and a multiplet at δ 1.90-2.48 for ($2CH_2$). Aromatic protons resonate as multiplets at δ 7.80-8.62 ppm. The ^{13}C NMR spectrum of compound **5a** showed signals at δ 27.30, 29.18, 32.67, 39.35, 50.29, 52.26 for aliphatic carbon, δ 151.58 (C=N) and δ 103.61, 116.59, 124.05, 128.20, 128.85, 129.77, 130.04, 131.35, 131.75, 146.54 for aromatic carbon and the carbonyl carbon was observed at δ 154.66 and 193.32. The structure was further confirmed by its mass spectral studies. It gave molecular ion peak at *m/z* 363 (M+1) corresponding to molecular formula $C_{19}H_{18}N_6O_2$ (Scheme 1). Similarly, all these compounds were characterized on the basis of spectral studies. All the

compounds were screened for their antibacterial and antifungal activities using ciprofloxacin, ampicillin and griseofulvin as standard drugs.



	R	R_1	R_2	X		R	R_1	R_2	X
5a	H	CH_3	CH_3	O	**5i**	H	CH_3	CH_3	S
5b	CH_3	CH_3	CH_3	O	**5j**	CH_3	CH_3	CH_3	S
5c	OCH_3	CH_3	CH_3	O	**5k**	OCH_3	CH_3	CH_3	S
5d	Cl	CH_3	CH_3	O	**5l**	Cl	CH_3	CH_3	S
5e	H	H	H	O	**5m**	H	H	H	S
5f	CH_3	H	H	O	**5n**	CH_3	H	H	S
5g	OCH_3	H	H	O	**5o**	OCH_3	H	H	S
5h	Cl	H	H	O	**5p**	Cl	H	H	S

Scheme 1. General synthetic procedure of octahydroquinazolinone **5a-p.**

Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity of compounds **5a-p** were carried out against 24 hr old cultures of three bacteria *Escherichia coli* as Gram-negative bacteria and *Bacillus substilis* and *Staphylococcus aureus* as Gram-positive bacteria and two fungi *Aspergillus niger* and *Rhizopus* oryzae by disc-diffusion method[31-32].

Nutrient agar and potato dextrose agars were used to culture the bacteria and fungus respectively. The compounds were tested at a concentration of 1000 μg/mL in DMF solution.

Ciprofloxacin, Ampicillin and Griseofulvin were used as standards for comparison of antibacterial and antifungal activities respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 hr. for bacteria at 35 °C and 48 hr. for fungus at 28 °C. The protocols are summarized in (Table 1).

Table 1. Antimicrobial activity of the compounds **2a-d** & **5a-p**

	Antibacterial activity Zone of inhibition in mm			Antifungal activity Zone of inhibition in mm	
Compd.	*E. coli*	*B. substilis*	*S. aureus*	*R. oryzae*	*A. niger*
2a	+	+	+ +	+ +	+
2b	+	+ +	+	+ +	+
2c	+	+	+	+ +	+
2d	+ +	+	+	+ +	+
5a	+ +	**+ +**	+	+ +	+
5b	+	+ +	+ +	**+ + +**	+
5c	+	+	**+ +**	+ +	**+ +**
5d	+ +	+	+ +	+ +	+
5e	+ +	+	+	+ +	+
5f	+ +	+ +	+	**+ + +**	+
5g	+	**+ +**	+	+ + +	+
5h	+ +	+	+	+ + +	+
5i	+	+	+ +	+ +	+
5j	+	+	+	+ +	+
5k	+	+	+	**+ + +**	**+**
5l	+ +	+	+ +	+ + +	**+**
5m	+	+	**+ + +**	+ + +	+
5n	+	+	+ +	+ +	+
5o	**+ +**	+	+ +	+ + +	+
5p	**+ +**	**-**	+	+ + +	+
Ciprofloxacin	+ + +	+ + +	+ + +	NT	NT
Ampicillin	+ + +	+ + +	+ + +	NT	NT
Griseofulvin	NT	NT	NT	+ + +	+ + +

(-) = Inactive (inhibition zone < 10 mm);
(+) = Slightly active (inhibition zone 10-14 mm);
(+ +) = Moderate activity (inhibition zone 15-19 mm);
(+ + +) = Good activity (inhibition zone ≥ 20 mm);
NT = not tested.
Control (DMF) (-) – No activity.

The antifungal evaluation of the synthesized compounds revealed that among all the compounds **5b, 5f, 5g, 5h, 5k, 5l, 5m, 5o** and **5p** showed good antifungal activity against fungal strain namely *Rhizopus oryzae*. Similarly compound **5a, 5c, 5d, 5e, 5g, 5i, 5j** and **5n** against *Rhizopus oryzae* and compound **5c** against Aspergillus niger showed moderate antifungal activity.

The antibacterial evaluation of the synthesized compounds revealed that among all the compounds **5m** showed good antibacterial activity against bacterial species namely *Staphylococcus aureus*. Compounds **5a, 5d, 5e, 5f, 5h, 5l, 5o** and **5p** showed moderate anti-bacterial activity against Gram-negative bacterial species *Escherichia coli*. Similarly compounds **5a, 5b, 5f** and **5g** against Gram-positive bacterial species *Bacillus substilis* and **5b, 5c, 5d, 5i, 5l, 5n** and **5o** against Gram-positive bacterial species *Staphylococcus aureus* showed moderate antibacterial activity. Compound **5p** is inactive against Gram-positive bacterial species *Bacillus substilis*.

While remaining compounds of the series are slightly active against the Gram-positive, Gram-negative bacterial species and fungal species.

Conclusion

A convenient and efficient method for the direct synthesis of octahydroquinazolinone derivatives over concentrated HCl as the catalyst with good yield has been developed. This successful reaction expands the synthetic scope of the multicomponent Biginelli reaction. Further, the present procedure may be readily amenable to large-scale synthesis and the generation of combinatorial octahydroquinazolinones derivatives. It can be concluded from **Table I** that among all the compounds **5b, 5f, 5g, 5h, 5k, 5l, 5m, 5o** and **5p** showed good antifungal activity against *Rhizopus oryzae* while compound **5a, 5c, 5d, 5e, 5i, 5j** and **5n** against *Rhizopus oryzae* and **5c** against Aspergillus niger showed moderate antifungal activity. Compound **5m** showed good antibacterial activity against *Staphylococcus aureus*. Compounds **5a, 5d, 5e, 5f, 5h, 5l, 5o** and **5p** against *Escherichia coli*, **5a, 5b, 5f** and **5g** against *Bacillus substilis*, **5b, 5c**, **5d, 5i, 5l, 5n** and **5o** against *Staphylococcus aureus* showed moderate antibacterial activity while remaining compounds of the series are slightly active against the Gram-positive, Gram-negative bacterial species and fungal species.

Experimental Section

General Procedures. All the reagents were obtained commercially and used with further purification. All melting points were taken in open capillaries and are uncorrected. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was runned using TLC aluminum sheets silica gel 60 F_{254} (Merck).

Elemental analysis (% C, H, N) was carried out by Perkins Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a shimadzu FTIR 8401 spectrophotometer in KBR. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using solvent peak as internal standard. Mass spectra were scanned on a shimadzu LCMS 2010 spectrometer.

General procedure for 7-(un)substituted-tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (2a-d)

2-chloro-3-formyl quinoline (0.005 moles), sodium azide (0.01 moles), acetic acid (1 mL) and ethanol (10 mL) were charged in R.B. flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 3-4 hr. After the completion of reaction (checked by TLC), the product was filtered and washed with ethanol. The crude product was purified by leaching in volume ratio of chloroform and methanol (10:10 mL) to obtain the pure solid sample**.**

Tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (2a). White solid, (82 %), m.p. 245-246 °C, Anal.Calcd for $C_{10}H_6N_4O$: C 60.60, H 3.05, N 28.27% Found: C 60.70, H 2.93, N 28.38%. IR (KBr, cm^{-1}): 3000, (ArC-H), 1700 (C=O), 1570 (C=C), 1625 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44-8.90 (m, 5H, Ar-H), 10.45 (s, 1H, CHO), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 113.74, 118.52, 122.89, 124.77, 125.08, 126.54, 140.43 (Ar-C), 145.32 (C-N), 159.34 (C=N), 189.14 (C=O).

7-methyltetrazolo[1,5-*a*]quinoline-4-carbaldehyde (2b). White solid, (85 %), m.p. 258-260 °C, Anal.Calcd for $C_{11}H_8N_4O$: C 62.25, H 3.80, N 26.40% Found: C 62.34, H 3.95, N 26.27%. IR (KBr, cm^{-1}): 3020 (ArC-H), 2910 (CH_3), 1710 (C=O), 1580 (C=C), 1620 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.75-8.96 (m, 4H, Ar-H), 10.40 (s, 1H, CHO), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.80 (CH_3), 113.64, 118.37, 122.19, 124.22, 124.90, 126.54, 139.55 (Ar-C), 145.12 (C-N), 159.37 (C=N), 189.14 (C=O).

7-methoxytetrazolo[1,5-*a*]quinoline-4-carbaldehyde (2c). White solid, (80 %), m.p. 236-237 °C, Anal.Calcd for $C_{11}H_8N_4O_2$: C 57.89, H 3.53, N 24.55% Found: C 57.77, H 3.64, N 24.67%. IR (KBr, cm^{-1}): 3015 (ArC-H), 1260 & 1050 (OCH_3), 1690 (C=O), 1590 (C=C), 1610 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.97 (s, 3H, OCH_3), 7.71-8.91 (m, 4H, Ar-H), 10.43 (s, 1H, CHO), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 56.59 (OCH_3), 112.84, 118.48, 122.09, 124.07, 124.88, 126.64, 139.43 (Ar-C), 145.02 (C-N), 159.21 (C=N), 189.04 (C=O).

7-chlorotetrazolo[1,5-*a*]quinoline-4-carbaldehyde (2d). Off-white solid, (75 %), m.p. 220-221 °C, Anal.Calcd for $C_{10}H_5N_4O$: C 51.63, H 2.16, N 24.08% Found: C 51.72, H 2.25, N 23.95%. IR (KBr, cm^{-1}): 2990 (ArC-H), 1695 (C=O), 1585 (C=C), 1615 (C=N), 750 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80-8.81 (m, 4H, Ar-H), 10.52 (s, 1H, CHO), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 114.14, 118.23, 122.79, 124.77, 125.45, 126.28, 140.65 (Ar-C), 145.82 (C-N), 159.25 (C=N), 189.28 (C=O).

General procedure for 7,7-dimethyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5a-p)

Tetrazolo(1,5-a)quinoline-4-carbaldehyde (0.0025 mole), dimedone or cyclohexane-1,3-dione (0.0025 mole), (thio)urea (0.0025 mol), conc.HCl(0.1 mL) and ethanol (15 mL) were charged in

R.B. flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 5 hr. After the completion of reaction (checked by TLC), the product was filtered and washed with ethanol. The crude product was purified by leaching in volume ratio of chloroform and methanol (10:10 mL) to obtain the pure solid sample**.**

7,7-dimethyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5a). White solid, (82 %), m.p. 290-292 °C, Anal.Calcd for $C_{19}H_{18}N_6O_2$: C 62.97, H 5.00, N 23.19% Found: C 63.11, H 4.89, N 23.34%. IR (KBr, cm^{-1}): 3353, 3259 (2NH), 3051 (ArC-H), 1701 (C=O), 1666 (C=O), 1614 (C=C), 1646 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.81 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.90-2.48 (m, 4H, $2CH_2$), 5.74 (s, 1H, CH), 7.70 (s, 1H, NH), 7.80-8.62 (m, 5H, Ar-H), 9.78 (s, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 27.30 (CH_3), 29.18 (CH_3), 32.67 (C), 39.35 (CH_2), 50.29 (CH_2), 52.26 (CH), 103.61, 116.59, 124.05, 128.20, 128.85, 129.77, 130.04, 131.35, 131.75, 146.54 (Ar-C), 151.58 (C=N), 154.66 (C=O), 193.32 (C=O), MS: (M+1) 363.

7,7-dimethyl-4-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5b). White solid, (73 %), m.p. >300 °C, Anal. Calcd. for $C_{20}H_{20}N_6O_2$: C 63.81, H 5.35, N 22.32% Found: C 63.69, H 5.51, N 22.42%. IR (KBr, cm^{-1}): 3310, 3265 (2NH), 3020 (ArC-H), 2920 (CH_3), 1718 (C=O), 1650 (C=O), 1604 (C=C), 1640 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.81 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.88-2.45 (m, 4H, $2CH_2$), 5.70 (s, 1H, CH), 7.77 (s, 1H, NH), 7.60-8.82 (m, 4H, Ar-H), 9.56 (s, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.70 (CH_3), 27.20 (CH_3), 29.20 (CH_3), 32.71 (C), 39.26 (CH_2), 50.80 (CH_2), 52.19 (CH), 104.10, 116.50, 124.00, 128.40, 129.00, 129.90, 130.03, 131.24, 131.55, 146.72 (Ar-C), 151.40 (C=N), 154.18 (C=O), 193.28 (C=O).

7,7-dimethyl-4-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5c). White solid, (64 %), m.p. 298-300 °C, Anal. Calcd. for $C_{20}H_{20}N_6O_3$: C 61.21, H 5.13, N 21.41% Found: C 61.08, H 5.25, N 21.55%. IR (KBr, cm^{-1}): 3431, 3281 (2NH), 3077 (ArC-H), 1721 (C=O), 1627 (C=O), 1524 (C=C), 1579 (C=N), 1236 & 1046 (OCH_3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.81 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 1.92-2.47 (m, 4H, $2CH_2$), 5.73 (s, 1H, CH), 7.72 (s, 1H, NH), 7.50-8.49 (m, 4H, Ar-H), 9.78 (s, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ : 27.39 (CH_3), 29.10 (CH_3), 32.68 (C), 39.35 (CH_2), 50.29 (CH_2), 52.22 (CH), 56.36 (OCH_3), 103.68, 110.17, 118.01, 120.98, 124.23, 125.61, 128.59, 130.92, 145.87, 151.59 (Ar-C), 154.62 (C=N), 159.08 (C=O), 193.31 (C=O).

7,7-dimethyl-4-(7-chlorotetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5d). Off-white solid, (60 %), m.p. >300 °C, Anal. Calcd. for $C_{19}H_{17}ClN_6O_2$: C 57.50, H 4.31, N 21.17% Found: C 57.63, H 4.46, N 21.03%. IR (KBr, cm^{-1}): 3320, 3260 (2NH), 2980 (ArC-H), 1694 (C=O), 1645 (C=O), 1582 (C=C), 1645 (C=N), 745 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.90-2.38 (m, 4H, $2CH_2$), 5.72 (s, 1H, CH), 7.61 (s, 1H, NH), 7.62-7.79 (m, 4H, Ar-H), 9.66 (s, 1H, NH).^{13}C NMR (400 MHz, DMSO-d_6) δ : 27.33 (CH_3), 29.10 (CH_3), 32.49 (C), 39.30 (CH_2), 50.15 (CH_2), 52.34 (CH), 103.48, 116.40, 124.17, 128.14, 128.70, 129.62, 129.94, 131.18, 131.48, 146.12 (Ar-C), 151.27 (C=N), 154.52 (C=O), 193.38 (C=O).

4-(tetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5e). Off-white solid, (80 %), m.p. 283-285 °C, Anal. Calcd. for $C_{17}H_{14}N_6O_2$: C 61.07, H 4.22 , N 25.13% Found: C 61.21, H 4.34, N 25.00%. IR (KBr, cm^{-1}): 3279, 3223 (2NH), 2952 (ArC-H), 1697 (C=O), 1663 (C=O), 1537 (C=C), 1645 (C=N). ^{1}H NMR (400 MHz DMSO-d_6): δ 1.85-2.27 (m, 6H, $3CH_2$), 5.77 (s, 1H, CH), 7.71 (s, 1H, NH), 7.77-8.60 (m, 5H, Ar-H), 9.79 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.17 (CH_2), 26.57 (CH_2), 36.71 (CH_2), 51.57 (CH), 104.82, 116.57, 124.10, 128.22, 128.80, 129.78, 130.08, 130.99, 131.74, 146.66 (Ar-C), 151.52 (C=N), 156.58 (C=O), 193.68 (C=O), MS: (M+1) 335.

4-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5f). Off-white solid, (65 %), m.p. 291-293 °C, Anal. Calcd. for $C_{18}H_{16}N_6O_2$: C 62.06, H 4.62, N 24.12% Found: C 62.16 , H 4.48, N 24.23%. IR (KBr, cm^{-1}) : 3310, 3250 (2NH), 3015 (ArC-H), 2910 (CH_3), 1682 (C=O), 1650 (C=O), 1600 (C=C), 1640 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84-1.94 (m, 6H, $3CH_2$), 3.34 (s, 3H, CH_3), 5.76 (s, 1H, CH), 7.71 (s, 1H, NH), 7.71-8.45 (m, 4H, Ar-H), 9.77 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.18 (CH_2), 21.31 (CH_2), 26.58 (CH_2), 36.71 (CH_3), 51.41 (CH), 104.90, 116.30, 124.12, 127.87, 128.14, 129.38, 130.67, 132.90, 138.54, 146.46 (Ar-C), 151.54 (C=N), 156.59 (C=O), 193.66 (C=O).

4-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5g). White solid, (73 %), m.p. 288-290 °C, Anal. Calcd. for $C_{18}H_{16}N_6O_3$: C 59.36, H 4.42, N 23.06% Found: C 59.27, H 4.58, N 23.18%. IR (KBr, cm^{-1}) : 3280, 3235 (2NH), 2985 (ArC-H), 1668 (C=O), 1640 (C=O), 1590 (C=C), 1642 (C=N), 1245 &1050 (OCH_3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.38 (m, 6H, $3CH_2$), 3.85 (s, 3H, OCH_3), 5.70 (s, 1H, CH), 7.69 (s, 1H, NH), 7.78-8.56 (m, 4H, Ar-H), 9.73 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.18 (CH_2), 22.23 (CH_2), 28.11 (CH_2), 36.25 (CH), 55.81 (OCH_3), 104.78, 116.47, 124.35, 127.90, 128.10, 129.42, 130.50, 132.75, 138.48, 146.28 (Ar-C), 151.70 (C=N), 156.39 (C=O) , 193.56 (C=O).

4-(7-chlorotetrazolo[1,5-*a*]quinolin-4-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*, 6*H*)-dione (5h). Grey solid, (62 %), m.p. 296-298 °C, Anal. Calcd. for $C_{17}H_{13}ClN_6O_2$: C 55.36, H 3.55, N 22.78% Found: C 55.51, H 3.42, N 22.92%. IR (KBr, cm^{-1}) : 3320, 3260 (2NH), 3010 (ArC-H), 1684 (C=O), 1640 (C=O), 1597 (C=C), 1650 (C=N), 750 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.25 (m, 6H, $3CH_2$), 5.60 (s, 1H, CH), 7.75 (s, 1H, NH), 7.68-8.60 (m, 4H, Ar-H), 9.82 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.10 (CH_2), 26.35 (CH_2), 36.61 (CH_2), 51.64 (CH), 104.88, 116.49, 124.17, 128.12, 128.92, 129.75, 130.00, 130.88, 131.86, 146.72 (Ar-C), 151.48 (C=N), 156.46 (C=O) , 193.62 (C=O).

7,7-dimethyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5i). Off-white solid, (79 %), m.p. 299-300 °C, Anal. Calcd. for $C_{19}H_{18}N_6OS$: C 60.30, H 4.79, N 22.20% Found: C 60.44, H 4.95, N 22.04%. IR (KBr, cm^{-1}) : 3292, 3098 (2NH), 3017 (ArC-H), 1712 (C=O), 1623 (C=C), 1671 (C=N), 1191 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.78 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.86-2.38 (m, 4H, $2CH_2$), 5.78 (s, 1H, CH), 9.45 (s, 1H, NH), 7.82-8.57 (m, 5H, Ar-H), 10.76 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 27.30 (CH_3), 29.18 (CH_3), 32.67 (C), 39.15 (CH_2), 50.29 (CH_2), 52.26 (CH),

103.61, 116.59, 124.05, 128.20, 128.85, 129.77, 130.04, 131.35, 131.75, 146.54 (Ar-C), 151.58 (C=N), 175.66 (C=S), 193.32 (C=O).

7,7-dimethyl-4-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5j). White solid, (65 %), m.p. >300 °C, Anal. Calcd. for $C_{20}H_{20}N_6OS$: C 61.20, H 5.13, N 21.41% Found: C 61.05, H 5.24, N 21.58%. IR (KBr, cm^{-1}) : 3180, 3120 (2NH), 3000 (ArC-H), 1650 (C=O), 2930 (CH_3), 1580 (C=C), 1570 (C=N), 1200 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 1.93- 2.47 (m, 4H, $2CH_2$), 5.75 (s, 1H, CH), 9.57 (s, 1H, NH), 7.76-8.45 (m, 4H, Ar-H), 10.79 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.31 (CH_3), 27.28 (CH_3), 29.23 (CH_3), 32.63 (C), 39.12 (CH_2), 50.29 (CH_2), 52.10 (CH), 104.97, 116.34, 123.94, 127.00, 127.95, 129.40, 131.94, 133.19, 138.72, 148.26 (Ar-C), 150.65 (C=N), 175.15 (C=S), 194.06 (C=O).

7,7-dimethyl-4-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5k). Off-white solid, (72 %), m.p. >300 °C, Anal. Calcd. for $C_{20}H_{20}N_6O_2S$: C 58.80, H 4.93, N 20.57% Found C 58.94, H 5.04, N 20.47%. IR (KBr, cm^{-1}) : 3276, 3230 (2NH), 2995 (ArC-H), 1660 (C=O), 1570 (C=C), 1635 (C=N), 1230 &1040 (OCH_3), 1190(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.79 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.80-1.94 (m, 4H, $2CH_2$), 3.92 (s, 3H, OCH_3), 5.76 (s, 1H, CH), 9.45 (s, 1H, NH), 7.78-8.56 (m, 4H, Ar-H), 10.60 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 27.34 (CH_3), 29.28 (CH_3), 33.45 (C), 39.23 (CH_2), 50.60 (CH_2), 52.23 (CH), 55.90 (OCH_3), 105.88, 116.67, 124.65, 127.78, 128.35, 129.43, 130.59, 132.65, 138.58, 146.22 (Ar-C), 151.82 (C=N), 175.44 (C=S), 193.67 (C=O).

7,7-dimethyl-4-(7-chlorotetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5l). Off-white solid, (64 %), m.p. >300 °C, Anal. Calcd. for $C_{19}H_{17}ClN_6OS$: C 55.27, H 4.15, N 20.35% Found C 55.40, H 3.98, N 20.47%. IR (KBr, cm^{-1}): 3247, 3210 (2NH), 3015 (ArC-H), 1668 (C=O), 1587 (C=C), 1640 (C=N), 735 (C-Cl), 1185 (C=S).^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (s, 3H, CH_3), 1.03 (s, 3H, CH_3),1.87-1.98 (m, 4H, $2CH_2$), 5.60 (s, 1H, CH), 9.75 (s, 1H, NH), 7.68-8.60 (m, 4H, Ar-H), 10.82 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 27.30 (CH_3), 29.15 (CH_3), 32.39 (C), 39.20 (CH_2), 50.28 (CH_2), 52.45 (CH), 103.57, 116.39, 124.37, 128.22, 128.75, 129.52, 129.87, 131.20, 131.38, 146.32 (Ar-C), 151.47 (C=N), 175.47 (C=S) , 193.58 (C=O).

4-(tetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5m). White solid, (73 %), m.p. >300 °C, Anal. Calcd. for $C_{17}H_{14}N_6OS$: C 58.27, H 4.02, N 23.98% Found C 58.18, H 4.15, N 24.12%. IR (KBr, cm^{-1}) : 3377, 3152 (2NH), 2984 (ArC-H), 1687 (C=O), 1618 (C=C), 1643 (C=N), 1184 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78-2.12 (m, 6H, $3CH_2$), 5.67 (s, 1H, CH), 9.75 (s, 1H, NH), 7.69-8.58 (m, 5H, Ar-H), 10.65 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.15 (CH_2), 25.57 (CH_2), 35.71 (CH_2), 51.54 (CH), 104.72, 116.59, 124.20, 127.92, 128.70, 129.76, 130.14, 131.09, 131.84, 146.59 (Ar-C), 151.48 (C=N), 175.68 (C=S), 193.78 (C=O).

4-(7-methyltetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5n). White solid, (68 %), m.p. >300 °C, Anal. Calcd. for $C_{18}H_{16}N_6OS$: C 59.32, H 4.42, N 23.06% Found C 59.42, H 4.53, N 22.90%. IR (KBr, cm^{-1}) : 3290, 3210 (2NH), 3008 (ArC-H),

2920 (C-H), 1678 (C=O), 1575 (C=C), 1635 (C=N), 1190 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85-2.20 (m, 6H, 3CH_2), 3.37 (s, 3H, CH_3), 5.74 (s, 1H, CH), 9.73 (s, 1H, NH), 7.71-8.45 (m, 4H, Ar-H), 10.75 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.10 (CH_3), 21.42 (CH_2), 26.59 (CH_2), 36.68 (CH_2), 51.35 (CH), 104.85, 116.20, 124.32, 127.90, 128.34, 129.55, 130.67, 132.70, 138.54, 146.39 (Ar-C), 151.61 (C=N), 175.49 (C=S), 193.73 (C=O).

4-(7-methoxytetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5o). Off-white solid, (66 %), m.p. 287-289 °C, Anal. Calcd. for $C_{18}H_{16}N_6O_2S$: C 56.83, H 4.23, N 22.09% Found C 56.70, H 4.35, N 22.21%. IR (KBr, cm^{-1}) : 3402, 3181 (2NH), 2940 (ArC-H), 1614 (C=C), 1673 (C=O), 1646 (C=N), 1176 (C=S), 1248 &1043 (OCH_3).^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-2.28 (m, 6H, 3CH_2), 3.95 (s, 3H, OCH_3), 5.72 (s, 1H, CH), 9.69 (s, 1H, NH), 7.75-8.65 (m, 4H, Ar-H), 10.73 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.14 (CH_2), 22.13 (CH_2), 28.22 (CH_2), 36.34 (CH), 55.71 (OCH_3), 104.87, 116.54, 124.45, 127.80, 128.36, 129.52, 130.67, 132.65, 138.68, 146.44 (Ar-C), 151.79 (C=N), 175.69 (C=S), 193.56 (C=O).

4-(7-chlorotetrazolo[1,5-*a*]quinolin-4-yl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (5p). Off-white solid, (60 %), m.p. 294-296 °C Anal. Calcd. for $C_{17}H_{13}ClN_6OS$: C 53.05, H 3.40, N 21.83% Found C 53.21, H 3.29, N 21.92%. IR (KBr, cm^{-1}) : 3320, 3250 (2NH), 2998 (ArC-H), 1688 (C=O), 1579 (C=C), 1650 (C=N), 755 (C-Cl), 1178 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-2.14 (m, 6H, 3CH_2), 5.72 (s, 1H, CH), 9.75 (s, 1H, NH), 7.69-8.50 (m, 4H Ar-H), 10.82 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ : 21.15 (CH_2), 26.45 (CH_2), 36.69 (CH_2), 51.55 (CH), 104.98, 116.59, 124.26, 128.26, 128.82, 129.87, 130.20, 130.78, 131.96, 146.86 (Ar-C), 151.68 (C=N), 175.76 (C=S), 193.52 (C=O).

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