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Synthesis of some newer derivatives of substituted quinazolinonyl-2-oxo/thiobarbituric acid as potent anticonvulsant agents

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Abstract—5-{1′-[3″-Aminoacetyl-2″-methyl-6″,8″-dihalosubstitutedquinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-oxo/thiobarbituric acids **3a**–**3h** and 5-{2′-amino-5′-[3″-aminomethylene-2″-methyl-6″,8″-dihalosubstitutedquinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-oxo/thiobarbituric acid **5a**–**5h** were prepared by incorporating 1-[3′-aminoacetyl-2′-methyl-6″,8″-dihalosubstituted-quinazolin-4′(3′H)-onyl]-thiosemicarbazides **2a**–**2d** and 2-amino-5-[3′-aminomethylene-2′-methyl-6′,8′-dihalosubstituted-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazoles **4a-4 h** respectively at 5th position of 2-oxo/thiobarbituric acids (via Mannich reaction). All the newly synthesized compounds were screened for their anti-convulsant activity in MES and PTZ models and were compared with standard drugs phenytoin sodium and sodium valproate. Interestingly, these compounds were found to be devoid of sedative and hypnotic activities when tested. Out of the compounds studied, the most active compound **5h**, that is 5-{2′-amino-5′-[3″-aminomethylene-2″-methyl-6″,8″-dibromoquinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid showed activity (90%) more potent than the standard drug.

1. Introduction

Barbituric acid (2,4,6-trioxohexahydropyrimidine) derivative, phenobarbital[1] and mephobarbital[2] are used for clinical treatment of epilepsy. Further substitution pattern at the 5th position by different alkyl, aryl or heteroaryl moieties plays a pivotal role in barbituric[3–5] and thiobarbituric[6–8] acids. Moreover, quinazolinone[9–11] derivatives substituted by different heterocyclic moieties at the 3rd position have been reported to exhibit anticonvulsant activity. Present series has been synthesized in the light of above discussion in which effort has been made to produce potent and safer anticonvulsant agents by adding two heterocyclic nuclei having anticonvulsant activity, namely barbituric acid and quinazolinone. Furthermore, the currently available anticonvulsant (antiepileptic) drugs are effective in controlling the seizures, but they are associated with severe side effects like sedation, hypnosis and so on, thereby hampering day time work. Research for an ideal anti-epileptic drug which control seizures without causing significant side effects is still the need of the millenium. Therefore, the present project is aimed at synthesizing such compounds which are effective in controlling epilepsy without causing side effects like sedation and hypnosis.

2. Chemistry

Acetylation of 3-amino-2-methyl-6-mono/6,8-dihalosubstitutedquinazolin-4(3H)-ones with ethyl chloroacetate yielded 3-(aminomethylethanoato)-2-methyl-6-mono/6,8-dihalosubstitutedquinazolin-4(3H)-ones **1a**–**1d**, which on reaction with thiosemicarbazide resulted in the formation of 1-[3′-aminoacetyl-2′-methyl-6′-mono/6′,8′-dihalosubstitutedquinazolin-4′(3′H)-onyl] thiosemicarbazides **2a**–**2d**. Compounds **2a**–**2d** on dehydrative cyclization by concentrated H_2SO_4 furnished the thiadiazole **4a**–**4d**. 5-{1′-[3″-Aminoacetyl-2″-methyl-6″-mono/6″, 8″-dihalosubstitutedquinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-oxo/thiobarbituric acids **3a**–**3h** and 5-{2′-amino-5′-[3″-aminoacetyl-2″-methyl-6″-mono/6″,8″-dihalosubstitutedquinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-oxo/thiobarbituric acids **5a**–**5h** were prepared by incorporating compounds **2a**–**2d** and compounds **4a**–**4d**, respectively, at the 5th position of 2-oxo/thiobarbituric acids via Mannich reaction.

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3. Results and discussion

Sedative, hypnotic, anticonvulsant activities and acute toxicity of these new quinazolinonyl and 2-oxo/thiobarbituric acid derivatives **1a–1d**, **2a–2d**, **3a–3 h, 4a–4d** and **5a–5h** are represented in Table 1.

3.1. Anticonvulsant activity (maximum electroshock induced seizures and pentylene tetrazol induced seizure pattern test)

The characteristic feature of the compounds of this series is the incorporation of two heterocyclic moieties, that is quinazolinone and 2-oxo/thiobarbituric acid into a single molecular framework with the aim to develop more potent anticonvulsant agents with minimum or no side effects.

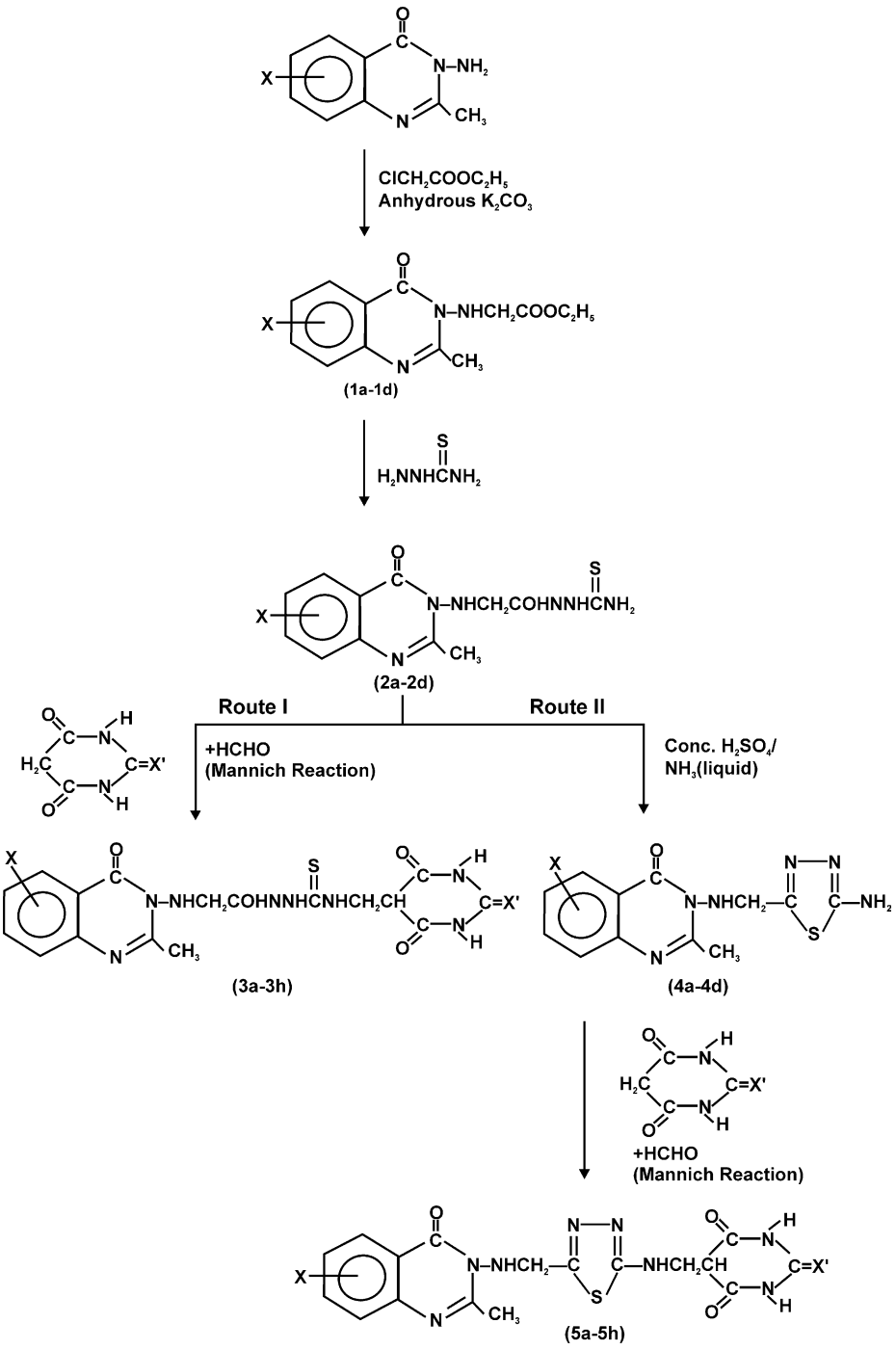
All the four 3-(aminoethylethanoato)-2-methyl-6-mono/6,8-dihalosubstituted-quinazolin-4(3H)-ones **1a–1d** showed 20–30% and 10–30% anticonvulsant activity at a dose of 50 mg/kg ip in maximal electroshock and pentylene tetrazole induced seizures, respectively. Screening of step-2 compounds 1-[3′-aminoacetyl-2′-methyl - 6′ - mono/6′,8′ - dihalosubstitutedquinazolin - 4′(3′H)-onyl]-thiosemicarbazides **2a–2d** revealed that these compounds possess somewhat increase in anticonvulsant activity in both the models (ranging from 30 to 50% and 20 to 50% (MES and PTZ models, respectively) in comparison to step-1 compounds when tested at same dose.

Compounds 5-{1′-[3″-aminoacetyl-2″-methyl-6″-mono/6″,8″-dihalosubstituted-quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-oxo/thiobarbituric acids **3a–3h** showed high percentage protection ranging from 40 to 80% in both MES and PTZ models. The most active compound of **3a–3h** is compound **3h**. This compound was found to be equipotent (80% protection) to phenytoin sodium (standard drug for MES model) and sodium valproate (standard drug for PTZ model) and hence due to its potent nature it was studied in detail at three graded doses (17.5, 25 and 50 mg/kg ip) for its anticonvulsant activity and was found to possess 20, 40, 80% and 20,

Table 1. Sedative, hypnotic, anticonvulsant and toxicity data of compounds **1a–5h** (Scheme 1)

Compd	X	X′	Dose (mg/kg ip)	Sedative activity		Hypnotic activity		Anticonvulsant activity		ALD_{50} (mg/kg ip)
				Locomotor activity square crossed ±SE 0–60	Exploratory movements ±SE 0–60	Pentobarbitone sodium induced sleeping time in min±SE		MES	PTZ	
						Before drug treatment	After drug treatment			
1a	H	—	50	245.0±0.86***	142.6±1.36***	35.6±1.03	34.2±0.06*	20	10	>1000
1b	6-I	—	50	249.1±1.17***	146.0±0.72***	33.7±0.07	34.3±1.27***	20	20	>1000
1c	6-Br	—	50	247.7±0.03***	144.2±1.33***	36.2±1.04	35.2±0.05**	30	20	>1000
1d	6,8-Br_2	—	50	251.0±1.01***	148.1±0.73**	35.4±0.06	34.2±0.08***	30	30	>1000
2a	H	—	50	245.5±0.07***	143.2±0.33***	39.2±1.17	38.4±0.09***	30	20	>1000
2b	6-I	—	50	248.3±1.02***	144.4±1.02***	32.3±0.03	31.2±0.07***	40**	20	>1000
2c	6-Br	—	50	253.0±1.04***	146.2±0.08***	33.3±0.03	34.2±0.23**	50**	30	>1000
2d	6,8-Br_2	—	50	251.0±1.02***	145.6±1.06***	35.2±0.23	36.2±1.22**	40**	40**	>1000
3a	H	O	50	245.3±0.08***	149.2±0.08***	36.1±0.23	36.4±0.73***	40**	40**	>1000
3b	6-I	O	50	246.2±0.66***	147.7±1.23***	32.1±1.11	34.2±0.63***	50**	40**	>1000
3c	6-Br	O	50	247.5±1.05***	143.7±0.73***	38.2±1.12	39.3±1.11***	70***	60**	>1000
3d	6,8-Br_2	O	50	252.0±1.20***	144.8±0.65***	36.4±0.72	38.1±0.71***	70***	70***	>1000
3e	H	S	50	244.6±0.08***	142.9±0.72***	39.4±0.73	39.2±1.32***	60**	50*	>1000
3f	6-I	S	50	246.3±0.07***	144.7±0.53***	37.7±1.24	35.7±0.01***	60**	60**	>1000
3g	6-Br	S	50	249.1±0.62***	144.3±0.13***	31.2±1.11	31.6±0.03***	70***	70***	>1000
3h	6,8-Br_2	S	50	250.2±0.03***	145.0±0.27***	38.1±0.28	37.2±0.24***	80***	80***	>2000
			25					40**	30	
			17.5					20	20	
4a	H	—	50	248.3±1.02***	149.2±1.05***	36.2±1.09	36.1±0.06**	40**	40**	>1000
4b	6-I	—	50	247.6±0.07***	142.1±1.17***	38.2±0.02	38.1±0.01***	50**	40**	>1000
4c	6-Br	—	50	251.2±0.38***	144.7±0.76***	37.1±1.03	38.4±0.03***	50**	50**	>1000
4d	6,8-Br_2	—	50	250.3±1.26***	146.1±1.02***	32.2±0.93	33.1±0.80***	60**	50**	>1000
5a	H	O	50	251.1±0.08***	143.7±1.04***	33.7±1.07	33.9±0.02***	60**	60***	>1000
5b	6-I	O	50	248.2±1.23***	148.2±1.02***	34.9±0.93	35.0±1.07**	70***	70***	>1000
5c	6-Br	O	50	251.2±0.37***	142.3±0.88***	35.3±1.60	35.2±1.01***	60**	70***	>1000
5d	6,8-Br_2	O	50	251.1±0.01***	141.2±0.93***	39.5±0.74	39.9±0.04***	80***	70***	>1000
5e	H	S	50	244.7±1.02***	143.5±0.43***	32.6±1.20	33.1±0.03**	60**	50**	>1000
5f	6-I	S	50	246.3±1.23***	146.1±1.18***	34.8±1.16	35.2±0.60***	80***	70***	>1000
5g	6-Br	S	50	249.2±0.07***	142.0±0.79***	38.2±0.77	38.0±1.20***	80***	80***	>1000
5h	6,8-Br_2	S	50	250.6±1.01***	144.2±0.73***	35.7±0.64	35.1±1.21***	90***	90***	>2000
			25					40**	50**	
			17.5					20	20	
Phenytoin sodium			30	235.3±1.02***	133.8±1.42***	33.3±0.72	39.1±1.63***	80***		
Sodium valproate			80	240.0±1.05***	138.0±0.36***	34.2±1.62	37.7±1.12***		80***	
Propylene glycol			50	248.2±1.23***	145.1±1.04***	34.6±1.32	34.5±2.84	0	0	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



Scheme 1.

30, 80% protection of seizures in MES and PTZ models, respectively.

Further, cyclization of **2a–2d** (via route-11) by concentrated H_2SO_4 and liquid ammonia resulted into the corresponding five-membered ring compounds, that is 2-amino-5-[3′-aminomethylene-2′-methyl-6′-mono/6′,8′-dihalosubstitutedquinazolin-4′(3′H)-onyl]-1,3,4-thiadiazoles **4a–4d** which showed more potent activity (40–60% in MES and 40–50% in PTZ models) than their parent compounds (30–40% and 20–40%, respectively). These compounds **4a–4d** were further incorporated with 2-oxo/thiobarbituric acid via Mannich reaction to yield 5-{2′-amino-5′-[3″-aminomethylene-2″-methyl-6″-mono/6″,8″-dihalosubstitutedquinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-oxo/thiobarbituric acids **5a–5h** which elicited good percentage protection ranging from 60 to 90% in both models, that is MES and PTZ. Out of the eight compounds **5a–5h** the most active compound in **5h**. This compound **5h** along with other promising compound **3h** were studied in details at three graded doses and were found to possess same percentage protection at lower doses of 17.5 and 25 mg/kg ip (20 and 40% protection in MES model, respectively) and different inhibition of seizures at a higher dose at 50 mg/kg ip (80 and 90% inhibition in MES model, respectively).

These compounds **3h** and **5h** were also screened in PTZ model in three graded doses and were found to exhibit protection of 20, 30, 80% and 20, 50, 90%, respectively.

3.2. Sedative and hypnotic activities

Screening of the compounds of this series for sedative and hypnotic activity reveals that almost all the compounds are devoid of sedative and hypnotic activities.

3.3. ALD_{50} studies

The toxicity study of these compounds indicate their good safety margin.

4. Conclusion

From the results of the biological activities we may conclude that the presence of dibromo group at the 6th and 8th positions of quinazolinone nucleus was found to increase the anticonvulsant activity. Moreover, it was found that cyclization of **2a–2d** into corresponding thiadiazole was found to be fruitful as the presence of this five membered ring showed considerable increase in percentage inhibition of seizures. Furthermore, incorporation of 2-oxo/thiobarbituric acid in **2a–2d** and **4a–4d** was found to increase the potency of these compounds and resulted into the formation of **3a–3h** and **5a–5h**, respectively, with high anticonvulsant activity.

Regarding sedative and hypnotic activities it may be concluded that all the compounds of this series are devoid of sedative or hypnotic activities. Regarding acute toxicity studies it may be drawn that all the compounds showed high value of ALD_{50} thus indicating a good safety margin.

5. Experimental

5.1. Chemistry

Melting points were determined in open capillaries with the help of thermonic melting point apparatus and are uncorrected. IR spectra (KBr) are recorded on Backmann Acculab-10-spectrophotometer. ^{1}H NMR spectra were recorded by Bruker WM 400 FT instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shift (δ) are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness. The elemental analysis of the compounds were performed on Heracus Carlo Erba 1108 analyser.

5.1.1. 3-(Aminoethylethanoato)-2-methyl-quinazolin-4(3H)-ones 1a. A mixture of 3-amino-2-methylquinazolin-4(3H)-one (0.1 mol), ethylchloroacetate (0.1 mol) and anhydrous K_2CO_3 (5.0 g) in acetone (80 mL) were refluxed for about 15 h on a steam bath. The acetone was distilled off and the resulting solid thus obtained was poured into water, filtered and the separated solid was washed with petroleum ether (40–60°) and recrystallized from methanol/water to give **1a** (72%), mp 120 °C; IR (KBr) 3344 (NH), 2920 (methyl C–H stretch), 1740 (>C=O), 1680 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30–7.20 (m, 4H, Ar–H), 5.50 (brs, 1H, $NHCH_2$), 4.10 (q, 2H, $J=7$ Hz, $COOCH_2CH_3$) (ppm); MS: M^+ 261. Anal. calcd for $C_{13}H_{15}N_3O_3$; C, 59.77; H, 5.74; N, 16.09. Found: C, 59.75; H, 5.75; N, 16.19.

5.1.2. 3-(Aminoethylethanoato)-6-iodo-2-methyl-quinazolin-4(3H)-ones (1b). 70%, mp 160 °C (methanol); IR (KBr) 3340 (NH), 2925 (methyl C–H stretch), 1738 (>C=O), 1682 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25–7.20 (m, 3H, Ar–H), 5.60 (brs, 1H, $NHCH_2$), 4.15 (q, 2H, $J=7$ Hz, $COOCH_2CH_3$), 3.80 (d, 2H, $NHCH_2$), 2.60 (s, 3H, CH_3), 1.25 (t, 3H, $J=7$ Hz, $COOCH_2CH_3$) (ppm); MS: M^+ 387. Anal. calcd for $C_{13}H_{14}N_3O_3I$; C, 40.31; H, 3.61; N, 10.85. Found: C, 40.28; H, 3.59; N, 10.88.

5.1.3. 3-(Aminoethylethanoato)-6-bromo-2-methyl-quinazolin-4(3H)-ones (1c). 72%, mp 160 °C (methanol/water); IR (KBr) 3345 (NH), 2928 (methyl C–H stretch), 1740 (>C=O), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15–7.10 (m, 3H, Ar-H), 5.45 (brs, 1H, $NHCH_2$), 4.12 (q, 2H, $J=7$ Hz, $COOCH_2CH_3$), 3.76 (d, 2H, $NHCH_2$), 2.58 (s, 3H, CH_3), 1.28 (t, 3H, $J=7$ Hz, $COOCH_2CH_3$) (ppm); MS: M^+ 340. Anal. calcd for $C_{13}H_{14}N_3O_3Br$; C, 45.88; H, 4.11; N, 12.35. Found : C, 45.98; H, 4.11; N, 12.25.

5.1.4. 3-(Aminoethylethanoato)-6,8-dibromo-2-methyl-quinazolin-4(3H)-ones (1d). 73%, mp 195 °C (methanol); IR (KBr) 3348 (NH), 2924 (methyl C–H stretch), 1734 (>C=O), 1686 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00–7.00 (m, 2H, Ar–H), 5.44 (brs, 1H, $NHCH_2$), 4.13 (q, 2H, $J=7$ Hz, $COOCH_2CH_3$), 3.77 (d, 2H, $NHCH_2$), 2.57 (s, 3H, CH_3), 1.26 (t, 3H, $J=7$ Hz, $COOCH_2CH_3$) (ppm); MS : M^+ 419. Anal. calcd for $C_{13}H_{13}N_3O_3Br_2$; C, 37.23; H, 3.10; N, 10.02. Found: C, 37.25; H, 3.09; N, 10.04.

5.1.5. 1-[3′-(Aminoacetyl-2′-methylquinazolin-4′(3′H)-onyl]-thiosemicarbazide (2a). A mixture of 3-(aminoethylethanoato)-2-methylquinazolin-4(3H)-ones (**1a**) (0.07 mol) and thiosemicarbazide (0.07 mol) in methanol (50 mL) were refluxed for 8 h on a steam bath. The excess of solvent was distilled off and the viscous mass poured into ice-cold water was filtered and recrystallized from benzene/petroleum ether to give **2a** (70%), mp 180 °C; IR (KBr) 3400 (NH_2), 3340 (NH), 2918 (methyl C–H stretch), 2853 (CH_2), 1710 (C=O of quinazolinone), 1620 (C=N), 1130 (>C=S); ^{1}H NMR ($CDCl_3$) δ 8.65 (m, 4H, $NHNHCSNH_2$), 8.15–7.10 (m, 4H, Ar-H), 5.45 (brs, 1H, $NHCH_2$), 3.80 (d, 2H, $NHCH_2$), 2.30 (s, 3H, CH_3) (ppm); MS: M^+ 306. Anal. calcd for $C_{12}H_{14}N_6O_2S$; C, 47.05; H, 4.57; N, 27.45. Found : C, 47.15; H, 4.47; N, 27.56.

5.1.6. 1-[3′-(Aminoacetyl-6′-iodo-2′-methyl-quinazolin-4′(3′H)-onyl]-thiosemicarbazide (2b). 73%, mp 140 °C (benzene/water); IR (KBr) 3410 (NH_2), 3342 (NH), 2917 (methyl C–H stretch), 2860 (CH_2), 1712 (C=O of

quinazolinone), 1622 (C=N), 1127 (>C=S); ^{1}H NMR ($CDCl_3$) δ 8.68 (m, 4H, $NHNHCSNH_2$), 8.10–7.15 (m, 3H, Ar–H), 5.45 (brs, 1H, $NHCH_2$), 3.82 (d, 2H, $NHCH_2$), 2.28 (s, 3H, CH_3) (ppm); MS: M^+ 432. Anal. calcd for $C_{12}H_{13}N_6O_2SI$; C, 33.33; H, 3.00; N, 19.44. Found: C, 33.30; H, 3.01; N, 19.42.

5.1.7. 1-[3′-(Aminoacetyl-6′-bromo-2′-methyl-quinazolin-4′(3′H)-onyl]-thiosemicarbazide (2c). 68%, mp 95 °C (benzene/petroleum ether); IR (KBr) 3411 (NH_2), 3345 (NH), 2916 (methyl C–H stretch), 2862 (CH_2), 1715 (C=O of quinazolinone), 1625 (C=N), 1130 (>C=S); ^{1}H NMR ($CDCl_3$) δ 8.65 (m, 4H, $NHNHCSNH_2$), 8.12–7.20 (m, 3H, Ar–H), 5.48 (brs, 1H, $NHCH_2$), 3.80 (d, 2H, $NHCH_2$), 2.26 (s, 3H, CH_3) (ppm); MS: M^+ 385. Anal. calcd for $C_{12}H_{13}N_6OSBr$; C, 37.40; H, 3.37; N, 21.81. Found : C, 37.28; H, 3.19; N, 21.90.

5.1.8. 1-[3′-(Aminoacetyl-6′,8′-dibromo-2′-methyl-quinazolin-4′(3′H)-onyl]-thiosemicarbazide (2d). 70%, mp 165 °C (benzene/petroleum ether); IR (KBr) 3414 (NH_2), 3347 (NH), 2911 (methyl C–H stretch), 2860 (CH_2), 1717 (C=O of quinazolinone), 1624 (C=N), 1128 (>C=S); ^{1}H NMR ($CDCl_3$) δ 8.62 (m, 4H, $NHNHCSNH_2$), 8.00–7.11 (m, 2H, Ar–H), 5.47 (brs, 1H, $NHCH_2$), 3.81 (d, 2H, $NHCH_2$), 2.25 (s, 3H, CH_3) (ppm); MS: M^+ 464. Anal. calcd for $C_{12}H_{12}N_6O_2SBr_2$; C, 31.03; H, 2.58; N, 18.10. Found : C, 31.05; H, 2.60; N, 18.08.

5.1.9. 5 - {1′ - [3″ - Aminoacetyl - 2″ - methyl - quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-barbituric acid (3a). To a solution of barbituric acid (0.01 mol) in methanol (60 mL), formaldehyde (0.02 mol) and 1-[3′-aminoacetyl -2′-methyl-quinazolin-4″(3″H)-onyl]-thiosemicarbazide **2a** were added dropwise and the reaction mixture was refluxed for 4 h. The excess of solvent was distilled off and the solid thus obtained was washed with petroleum ether (40–60 °C) and recrystallized from chloroform to give **3a** (51%), mp 180 °C; IR (KBr) 3320 (NH), 2920 (methyl C–H stretch), 2850 (CH_2), 1690, 1710, 1715 (amidic C=O), 1618 (C=N), 1133 (>C=S); ^{1}H NMR ($CDCl_3$) δ 9.25 (ss, 2H, 2×NHCO), 8.20 (m, 3H, NHNHCSNH), 7.10–8.10 (m, 4H, Ar–H), 5.50 (brs, 1H, $NHCH_2$), 3.90 (s, 2H, CH_2CH), 3.83 (d, 2H, $NHCH_2$), 3.60 (t, 1H, CH_2CH), 2.35 (s, 3H, CH_3) (ppm); MS: M^+ 446. Anal. calcd for $C_{17}H_{18}N_8O_5S$; C, 45.73; H, 4.03; N, 25.11. Found: C, 45.75; H, 4.05; N, 25.09.

5.1.10. 5-{1′-[3″-Aminoacetyl-6″-iodo-2″-methyl-quinazolin - 4″(3″H) - onyl] - thiosemicarbazido} - barbituric acid (3b). 60%, mp 165 °C (methanol/petroleum ether); IR (KBr) 3345 (NH), 2919 (methyl C–H stretch), 2848 (CH_2), 1680, 1700, 1710 (amidic >C=O), 1618 (C=N), 1145 (>C=S) 560 cm^{-1} (C–I); ^{1}H NMR ($CDCl_3$) δ 9.28 (ss, 2H, 2×NHCO), 8.18 (m, 3H, NHNHCSNH), 8.12–7.10 (m, 3H, Ar–H), 5.48 (brs, 1H, $NHCH_2$), 3.91 (s, 2H, CH_2CH), 3.80 (d, 2H, $NHCH_2$), 3.61 (t, 1H, CH_2CH), 2.32 (s, 3H, CH_3) (ppm); MS: M^+ 572. Anal. calcd for $C_{17}H_{17}N_8O_5IS$; C, 35.66; H, 2.97; N, 19.58. Found: C, 35.65; H, 3.00; N, 19.61.

5.1.11. 5-{1′-[3″-Aminoacetyl-6″-bromo-2″-methyl-quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-barbituric acid (3c). 62%, mp 170 °C (DMF); IR (KBr) 3343 (NH), 2916 (methyl C–H stretch), 2847 (CH_2), 1700, 1710, 1715 (amidic >C=O), 1448 (>C=S), 750 (C–Br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.29 (ss, 2H, 2×NHCO), 8.20 (m, 3H, NHNHCSNH), 8.10–7.11 (m, 3H, Ar–H), 5.45 (brs, 1H, $NHCH_2$), 3.90 (s, 2H, CH_2CH), 3.82 (d, 2H, $NHCH_2$), 3.62 (t, 1H, CH_2CH), 2.32 (s, 3H, CH_3) (ppm); MS: M^+ 525. Anal. calcd for $C_{17}H_{17}N_8O_5BrS$; C, 38.85; H, 3.23; N, 21.33. Found: C, 38.84; H, 3.25; N, 21.34.

5.1.12. 5-{1′-[3″-Aminoacetyl-6″,8″-dibromo-2″-methyl-quinazolin - 4″(3″H) - onyl] - thiosemicarbazido} - barbituric acid (3d). 58%, mp 150 °C (Chloroform); IR (KBr) 3345 (NH), 2920 (methyl C–H stretch), 2845 (CH_2), 1690, 1700, 1720 (amidic >C=O), 1650 (C=N), 1150 (>C=S), 810 (C–Br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.26 (ss, 2H, 2×NHCO), 8.20 (m, 3H, NHNHCSNH), 7.80–6.90 (m, 2H, Ar–H), 5.42 (brs, 1H, $NHCH_2$), 3.88 (s, 2H, CH_2CH), 3.83 (d, 2H, $NHCH_2$), 3.59 (t, 1H, CH_2CH), 2.28 (s, 3H, CH_3) (ppm); MS: M^+ 684. Anal. calcd for $C_{17}H_{16}N_8O_5Br_2S$; C, 37.70; H, 2.95; N, 20.70. Found: C, 37.67; H, 2.94; N, 20.69.

5.1.13. 5 - {1′ - [3″ - Aminoacetyl - 2″ - methyl - quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-thiobarbituric acid (3e). 54%, mp 120 °C (benzene/water); IR (KBr) 3343 (NH), 2919 (methyl C–H stretch), 2841 (CH_2), 1700, 1710 (amidic C=O), 1648 (C=N), 1148 (>C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.20 (ss, 2H, 2×NHCO), 8.18 (m, 3H, NHNHCSNH), 8.00–7.10 (m, 4H, Ar–H), 5.41 (brs, 1H, $NHCH_2$), 3.87 (s, 2H, CH_2CH), 3.81 (d, 2H, $NHCH_2$), 3.57 (t, 1H, CH_2CH), 2.27 (s, 3H, CH_3) (ppm); MS: M^+ 462. Anal. calcd for $C_{17}H_{18}N_8O_4S_2$; C, 44.15; H, 3.89; N, 24.24. Found: C, 44.11; H, 3.91; N, 24.21.

5.1.14. 5-{1′-[3″-Aminoacetyl-6″-iodo-2″-methyl-quinazolin - 4″(3″H) - onyl] - thiosemicarbazido} - 2 - thiobarbituric acid (3f). 55%, mp 180 °C (methanol/water); IR (KBr) 3330 (NH), 2915 (methyl C–H stretch), 2848 (CH_2), 1690, 1705 (amidic C=O), 1616 (C=N), 1130 (>C=S), 550 (C–I) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.25 (ss, 2H, 2×NHCO), 8.20 (m, 3H, NHNHCSNH), 8.15–7.20 (m, 3H, Ar–H), 5.46 (brs, 1H, $NHCH_2$), 3.92 (s, 2H, CH_2CH), 3.83 (d, 2H, $NHCH_2$), 3.60 (t, 1H, CH_2CH), 2.32 (s, 3H, CH_3) (ppm); MS: M^+ 588. Anal. calcd for $C_{17}H_{17}N_8O_4IS_2$; C, 34.69; H, 2.89; N, 19.04. Found: C, 34.71; H, 2.87; N, 19.06.

5.1.15. 5-{1′-[3″-Aminoacetyl-6″-bromo-2″-methyl-quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-thiobarbituric acid (3g). 57%, mp 195 °C (methanol/petroleum ether); IR (KBr) 3345 (NH), 2918 (methyl C–H stretch), 2850 (CH_2), 1700, 1715 (amidic C=O), 1446 (>C=S), 745 (C–Br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.30 (ss, 2H, 2×NHCO), 8.10 (m, 3H, NHNHCSNH), 8.05–7.10 (m, 3H, Ar–H), 5.41 (brs, 1H, $NHCH_2$), 3.93 (s, 2H, CH_2CH), 3.82 (d, 2H, $NHCH_2$), 3.65 (t, 1H, CH_2CH), 2.35 (s, 3H, CH_3) (ppm); MS: M^+ 541. Anal. calcd for $C_{17}H_{17}N_8O_4BrS$; C, 37.70; H, 3.14; N, 20.70. Found: C, 37.68; H, 3.16; N, 20.67.

5.1.16. 5-{1′-[3″-Aminoacetyl-6″,8″-bromo-2″-methyl-quinazolin-4″(3″H)-onyl]-thiosemicarbazido}-2-thiobarbituric acid (3h). 52%, mp 160 °C (methanol); IR (KBr) 3347 (NH), 2922 (methyl C–H stretch), 2848 (CH_2), 1690, 1720 (amidic C=O), 1652 (C=N), 1148 (>C=S), 815 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.20 (ss, 2H, 2×NHCO), 8.25 (m, 3H, NHNHCSNH), 7.90–7.00 (m, 2H, Ar–H), 5.45 (brs, 1H, $NHCH_2$), 3.90 (s, 2H, CH_2CH), 3.84 (d, 2H, $NHCH_2$), 3.59 (t, 1H, CH_2CH), 2.30 (s, 3H, CH_3) (ppm); MS: M^+ 620. Anal. calcd for $C_{17}H_{16}N_8O_4Br_2S_2$; C, 32.90; H, 2.58; N, 18.06. Found: C, 32.87; H, 2.60; N, 18.08.

5.1.17. 2-Amino-5-[3′-aminomethylene-2′-methyl-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazole (4a). A mixture of 1-[3′-aminoacetyl-2′-methylquinazolin-4(3H)-onyl]-thiosemicarbazide (0.05 mol) and conc H_2SO_4 (15 mL) were kept overnight at room temperature, poured into ice cold water, neutrallized with liq. ammonia and filtered. The product obtained was recrystallized from methanol/water to give **4a** (65%), mp 170 °C; IR (KBr) 3420 (NH), 3355 (NH_2), 2845 (CH_2), 1720 (C=O), 1610 (C=N), 680 C–S–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (m, 2H, NH_2), 7.10–8.10 (m, 4H, Ar–H), 5.50 (brs, 1H, $NHCH_2$), 4.20 (d, 2H, $NHCH_2$), 2.20 (s, 3H, CH_3) (ppm); MS: M^+ 288. Anal. calcd for $C_{12}H_{12}N_6OS$; C, 50.00; H, 4.16; N, 29.16. Found: C, 50.42; H, 4.35; N, 29.06.

5.1.18. 2-Amino-5-[3′-aminomethylene-6′-iodo-2′-methyl-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazole (4b). 70%, mp 220 °C (methanol); IR (KBr) 3418 (NH), 3358 (NH_2), 2842 (CH_2), 1722 (C=O), 1615 (C=N), 683 (C–S–C), 565 (C–I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (m, 2H, NH_2), 7.05–8.20 (m, 3H, Ar–H), 5.47 (brs, 1H, $NHCH_2$), 4.18 (d, 2H, $NHCH_2$), 2.22 (s, 3H, CH_3) (ppm); MS: M^+ 414. Anal. calcd for $C_{12}H_{11}N_6OSI$; C, 34.78; H, 2.65; N, 22.28. Found: C, 34.80; H, 2.68; N, 22.25.

5.1.19. 2-Amino-5-[3′-aminomethylene-6′-bromo-2′-methyl-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazole (4c). 68%, mp 140 °C (methanol/water); IR (KBr) 3422 (NH), 3361 (NH_2), 2843 (CH_2), 1725 (C=O), 1618 (C=N), 685 (C–S–C), 740 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (m, 2H, NH_2), 7.00–8.00 (m, 3H, Ar–H), 5.50 (brs, 1H, $NHCH_2$), 4.16 (d, 2H, $NHCH_2$), 2.21 (s, 3H, CH_3) (ppm); MS: M^+ 367. Anal. calcd for $C_{12}H_{11}N_6OSBr$; C, 39.23; H, 2.99; N, 22.88. Found: C, 39.00; H, 3.20; N, 22.78.

5.1.20. 2-Amino-5-[3′-aminomethylene-6′,8′-dibromo-2′-methyl-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazole (4d). 69%, mp 180 °C (methanol); IR (KBr) 3423 (NH), 3357 (NH_2), 2845 (CH_2), 1728 (C=O), 1616 (C=N), 687 (C–S–C), 750 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (m, 2H, NH_2), 7.25–8.10 (m, 2H, Ar–H), 5.51 (brs, 1H, $NHCH_2$), 4.15 (d, 2H, $NHCH_2$), 2.24 (s, 3H, CH_3) (ppm); MS: M^+ 446. Anal. calcd for $C_{12}H_{10}N_6OSBr_2$; C, 32.28; H, 2.24; N, 18.83. Found: C, 32.24; H, 2.26; N, 18.85.

5.1.21. 5-{2′-Amino-5′-[3″-aminomethylene-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-barbituric acid (5a). To a solution of barbituric acid (0.01 mol) in methanol formaldehyde (0.02 mol) and 2-amino-5-[3′-aminomethylene-2′-methyl-quinazolin-4′(3′H)-onyl]-1,3,4-thiadiazole (0.02 mol) were added dropwise. The reaction mixture was refluxed on a steam bath for 4 h. The excess of solvent was distilled off. The solid thus obtained was washed with water and recrystallized from acetone to give **5a** (60%), mp 205 °C; IR (KBr) 3410 (NH), 2840 (CH_2), 1710, 1715, 1720 (amidic C=O), 1615 (C=N), 683 (C–S–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.20 (ss, 2H, 2×NHCO), 7.50–8.45 (m, 4H, Ar–H), 5.65 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.25 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.25 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.90 (d, 2H, $NHCH_2$ adjacent to barbituric acid), 2.80 (s, 1H, CH_2CH), 2.23 (s, 3H, CH_3) (ppm); MS: M^+ 428. Anal. calcd for $C_{17}H_{16}N_8O_4S$; C, 47.66; H, 3.73; N, 26.16. Found: C, 47.68; H, 3.75; N, 26.13.

5.1.22. 5-{2′-Amino-5′-[3″-aminomethylene-6″-iodo-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-barbituric acid (5b). 62%, mp 216 °C (methanol); IR (KBr) 3400 (NH), 2842 (CH_2), 1700, 1715, 1725 (amidic C=O), 1620 (C=N), 685 (C–S–C), 560 (C–I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.25 (ss, 2H, 2×NHCO), 7.00–8.10 (m, 3H, Ar–H), 5.62 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.22 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.24 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 3.88 (d, 2H, $NHCH_2$ adjacent to barbituric acid), 2.83 (s, 1H, CH_2CH), 2.25 (s, 3H, CH_3) (ppm); MS: M^+ 554. Anal. calcd for $C_{17}H_{15}N_8O_4IS$; C, 36.82; H, 2.70; N, 20.21. Found: C, 36.80; H, 2.67; N, 20.18.

5.1.23. 5-{2′-Amino-5′-[3″-aminomethylene-6″-bromo-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-barbituric acid (5c). 57%, mp 220 °C (benzene); IR (KBr) 3415 (NH), 2838 (CH_2), 1700, 1710, 1715 (amidic C=O), 1620 (C=N), 685 (C–S–C), 744 (C-Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.26 (ss, 2H, 2×NHCO), 7.40–8.35 (m, 3H, Ar–H), 5.68 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.24 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.22 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.89 (d, 2H, $NHCH_2$ adjacent to barbituric acid), 2.81 (s, 1H, CH_2CH), 2.27 (s, 3H, CH_3) (ppm); MS: M^+ 507. Anal. calcd for $C_{17}H_{15}N_8O_4BrS$; C, 40.23; H, 2.95; N, 22.09. Found: C, 40.25; H, 2.98; N, 22.11.

5.1.24. 5-{2′-Amino-5′-[3″-aminomethylene-6″,8″-dibromo-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-barbituric acid (5d). 56%, mp 195 °C (DMF); IR (KBr) 3412 (NH), 2835 (CH_2), 1680, 1700, 1715 (amidic C=O), 1618 (C=N), 684 (C–S–C), 742 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.28 (ss, 2H, 2×NHCO), 7.45–8.20 (m, 2H, Ar–H), 5.70 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.23 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.20 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.87 (d, 2H, $NHCH_2$ adjacent to barbituric acid), 2.78 (s, 1H, CH_2CH), 2.25 (s, 3H, CH_3) (ppm); MS: M^+ 586. Anal. calcd for $C_{17}H_{14}N_8O_4Br_2S$; C, 34.81; H, 2.38; N, 19.11. Found: C, 34.78; H, 2.41; N, 19.14.

5.1.25. 5-{2′-Amino-5′-[3″-aminomethylene-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thio-

barbituric acid (5e). 58%, mp 210 °C (acetone); IR (KBr) 3420 (NH), 2844 (CH_2), 1680, 1700 (amidic C=O), 1618 (C=N), 687 (C–S–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.21 (ss, 2H, 2×NHCO), 7.45–8.40 (m, 2H, Ar–H), 5.68 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.27 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.28 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.88 (d, 2H, $NHCH_2$ adjacent to 2-thiobarbituric acid), 2.83 (s, 1H, CH_2CH), 2.25 (s, 3H, CH_3) (ppm); MS: M^+ 444. Anal. calcd for $C_{17}H_{16}N_8O_3S_2$; C, 45.94; H, 3.60; N, 25.22. Found: C, 45.97; H, 3.57; N, 25.25.

5.1.26. 5-{2′-Amino-5′-[3″-aminomethylene-2″-methyl-6″-iodoquinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid (5f). 55%, mp 230 °C (methanol); IR (KBr) 3410 (NH), 2845 (CH_2), 1690, 1715 (amidic C=O), 1619 (C=N), 683 (C–S–C), 565 (C–I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.23 (ss, 2H, 2×NHCO), 7.10–8.00 (m, 3H, Ar–H), 5.63 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.23 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.27 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.86 (d, 2H, $NHCH_2$ adjacent to 2-thiobarbituric acid), 2.81 (s, 1H, CH_2CH), 2.27 (s, 3H, CH_3) (ppm); MS: M^+ 570. Anal. calcd for $C_{17}H_{15}N_8O_3S_2$; C, 35.78; H, 2.63; N, 19.64. Found: C, 35.80; H, 2.65; N, 19.67.

5.1.27. 5-{2′-Amino-5′-[3″-aminomethylene-6″-bromo-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid (5g). 60%, mp 245 °C (benzene); IR (KBr) 3418 (NH), 2835 (CH_2), 1705, 1715 (amidic C=O), 1617 (C=N), 686 (C–S–C), 750 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.29 (ss, 2H, 2×NHCO), 7.38–8.30 (m, 3H, Ar–H), 5.66 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.23 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.20 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.87 (d, 2H, $NHCH_2$ adjacent to 2-thiobarbituric acid), 2.80 (s, 1H, CH_2CH), 2.26 (s, 3H, CH_3) (ppm); MS: M^+ 523. Anal. calcd for $C_{17}H_{15}N_8O_3BrS_2$; C, 39.00; H, 2.86; N, 21.41. Found: C, 39.03; H, 2.89; N, 21.39.

5.1.28. 5-{2′-Amino-5′-[3″-aminomethylene-6″,8″-dibromo-2″-methyl-quinazolin-4″(3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid (5h). 54%, mp 240 °C (DMF); IR (KBr) 3415 (NH), 2833 (CH_2), 1685, 1690 (amidic C=O), 1615 (C=N), 685 (C–S–C), 746 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.29 (ss, 2H, 2×NHCO), 7.47–8.10 (m, 2H, Ar–H), 5.68 (brs, 1H, $NHCH_2$ adjacent to quinazolinone), 5.22 (brs, 1H, $NHCH_2$ adjacent to thiadiazole), 4.21 (d, 2H, $NHCH_2$ adjacent to thiadiazole), 3.85 (d, 2H, $NHCH_2$ adjacent to 2-thiobarbituric acid), 2.76 (s, 1H, CH_2CH), 2.27 (s, 3H, CH_3) (ppm); MS: M^+ 602. Anal. calcd for $C_{17}H_{14}N_8O_3Br_2S_2$; C, 33.88; H, 2.32; N, 18.60. Found: C, 33.91; H, 2.36; N, 18.58.

5.2. Pharmacological evaluation

5.2.1. Sedative activity. Locomotor activity. This activity was tested by using chart paper (1 m^2) affixed on a table divided into 16 × 16 cm^2 squares. The experiment was conducted on albino rats by adopting the method of Larsen.[12] Counting the number of squares, which were crossed by each rat in a group for 1 h after test drug treatment, assessed the effect of the test compounds.

Exploratory activity. Hole board test. This was used to study the exploratory behaviour of rats by following the method of Boisser and Summon.[13] In this 0.5 m^2 wooden board with 16 holes (3 cm in diameter) was used and each rat was placed singly on board for a period of 1 h after test drug treatment. The number of exploratory movement performed by each rat was noted in 1 h.

5.2.2. Hypnotic activity. Loss of righting reflexes. For loss of righting reflex, each animal was placed gently on its back on an undulated surface and observed whether it quickly come to its normal posture within 15 s. or not. The animals exhibiting delayed action were discarded. After administration of the test compound, the animals were assessed for the loss of righting reflex Janssen et al.[14]

Effect on Pentobarbitone Sodium induced sleeping time. Group of six albino rats, exhibiting sleeping time (the interval between the loss of righting reflex and the time of regaining it) between 15 and 50 min with pentobarbitone sodium (20 mg/kg ip) were selected out two days prior to the experiment. Test drugs were administered intraperitonealy 20 min prior to pentobarbitone sodium treatment. The animals were injected pentobarbitone sodium (20 mg/kg ip) and sleeping time was noted for each case Swinyard and Castellion.[15]

5.2.3. Anticonvulsant activity. Maximum electroshock seizure (MES) test. This test was performed according to the method of Tomen et al.[16] The group of ten rats was treated with test drugs (50 mg/kg ip) / phenytoin sodium (30 mg/kg ip). After 1 h, they were subjected to the shock of 150 mA by convulsiometer through ear electrodes for 0.2 s. and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

Pentylene tetrazole (PTZ) induced seizures test. This test was performed by following the method of Fischer.[17] The rats were injected with pentylene tetrazol in dose of 70 mg/kg subcutaneously in scruff of neck. After 2–4 min of PTZ injection animals developed sequence of excitement, myoclonic jerks, clonic seizures, one or more maximum tonic seizures. Animals exhibiting these seizures patterns were selected. Standard drug used in this model was sodium valproate (80 mg/kg ip) and was injected 60 min prior to PTZ challenge.

5.2.4. Approximate lethal dose (ALD_{50}). Approximate 50% lethal dose (ALD_{50}) of the compounds were determined in albino mice. The mice of either sex 20–25 g were used. The test compounds were injected intraperitoneally at different dose levels in groups of 10 animals. After 24 h of drug administration, percent

mortality in each group was observed from the data obtained. ALD_{50} was calculated by the method of Smith.[18]

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