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ORIGINAL ARTICLE

1st Nano Update

Synthesis of new azetidinonyl/thiazolidinonyl quinazolinone derivatives as antiparkinsonian agents

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Amantadinylazetidinonyl/thiazolidinonyl quinazolinones;
Antiparkinsonian activity;
Acute toxicity

Abstract Several 3-amantadinyl-2-[(2-substituted benzylidenehydrazinyl)methyl]-quinazolin-4(3H)-ones **(5a–5l)** were prepared by the reaction of 3-amantadinyl-2-hydrazinylmethyl substituted quinazolin-4(3H)-ones (**4a–4b**) with various substituted aromatic aldehydes. Cycloaddition of compounds (**5a–5l**) with thioglycolic acid in the presence of anhydrous zinc chloride yielded 3-amantadinyl-2-[((substitutedphenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-ones (**6a–6l**). Compounds **5a–5l** on further reaction with chloro acetyl chloride in the presence of triethylamine gave 3-amantadinyl-2-[((substitutedphenyl)-3-chloro-2-oxo-azetidin-1-yl)methylamino]-quinazolin-4(3H)-ones (**7a–7l**). The compounds **5a–5l**, **6a–6l** and **7a–7l** were screened for their antiparkinsonian activity. The most active compound was **6g** i.e. 3-amantadinyl-6-bromo-2-[((3,4-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-ones. Structures of the newly synthesized compounds were established on the basis of elemental and spectral (IR, ^{1}H NMR and mass) analysis.

1. Introduction

The deficiency of dopamine in the basal ganglia of parkinsonian patients has been established as a biochemical lesion in all forms of Parkinsonism. The Levodopa (L-DOPA), a precursor of dopamine, acts on the biochemical defects of parkinsonism and is the most effective drug available for treatment of disease. Furthermore, amantadine is another adjustment drug (dopamine facility drug) for the treatment of Parkinsonism (Singer et al., 2006; Luginger et al., 2000; Severy, 1977). Recently various heterocyclic derivatives of quinazolinone have been reported to possess CNS and antiparkinsonian activity, at substitution IInd and IIIrd positions of quinazolinones play a pivotal role in modulating the antiparkinsonian properties. However, five membered thiazolidinone and four membered azetidinones do not appear to have been linked with quinazolinone, so for our study has shown that the

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substitution of amantadinyl at IIIrd position and azetidinone and thiozolidinone moieties at IInd position of quinazolinone yielded better antiparkinsonian agent (Panday et al., 2005; Nathani et al., 1989; Srivastava et al., 1987). These compounds were evaluated for their biological activity. However, abundance of dopa decarboxylase in peripheral tissue has necessitated the use of L-dopa for its entry into brain to liberate dopamine by dopa decarboxylase and thereby maintaining optimal dopamine concentration for desired beneficial effects. In addition, the various side effects associated with L-dopa therapy prompted the synthesis of substituted quinazolinones containing 3,4-dimethoxydopamine moiety in their structure in an attempt to provide preferential transport of these compounds to brain and their possible biotransformation to liberate dopamine and/or dopamine like substances by the action of the drug metabolizing enzyme systems and thus being independent of the use of brain dopa decarboxylase. Furthermore, thiazolidinones and azetidinones of various heterocycles have also been reported to possess antiparkinsonian activity (Kumar et al., 1982; Goel et al., 2005; Srivastava et al., 1990). In the light of the above observations we have synthesized new substituted quinazolinone derivatives by incorporating azetidinones and thiazolidinones moieties with the hope to get better antiparkinsonian agents.

2. Chemistry

The synthetic route of compounds is outlined in Scheme 1. Compounds **1a** and **1b** were synthesized by the reaction of anthranilic acid and 5-bromo anthranilic acid with acidic anhydride, respectively. Compounds **1a**–**1b** on reaction with amantadine yielded substituted 2-methyl benzo [1,3]oxazin-4-ones i.e. compounds **2a**–**2b**. Compounds **2a**–**2b** were reacted with bromine in glacial acetic acid to give 3-amantadinyl-2-bromomethylsubstitutedquinazolinon-4(3H)-ones **3a**–**3b** which on reaction with hydrazine hydrate in methanol yielded 3-amantadinyl-2-(hydrazinylmethyl)substitutedquinazolin-4(3H)-ones **(4a**–**4b)**. Compounds **4a**–**4b** were reacted with various substituted aromatic aldehydes in the presence of 2% NaOH to give 3-amantadinyl-2-[(substitutedbenzylidinehyrazinyl) methyl]substitutedquinazolin-4(3H)-ones i.e. compounds **5a**–**5l**, which on reaction with thioglycolic acid in the presence of anhydrous zinc chloride yielded 3-amantadinyl-2-[((substitutedphenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-ones **6a**–**6l**. Compounds **5a**–**5l** on further reaction with chloroacetyl chloride in the presence of triethylamine yielded 3-amantadinyl-2-[((substitutedphenyl)-3-chloro-2-oxo-azetidin-1-yl)methylamino]-quinazolin-4(3H)-ones **(7a**–**7l)**.

3. Pharmacology

All the newly synthesized compounds were evaluated for their antiparkinsonian activity.

The study was carried out on albino rats weighing 150–200 g and mice 25–30 g of either sex. The animals were fed and allowed water ad libidum. The number of animals in each group was 5. All the compounds were administered in a dose of 100 mg/kg i.p.

3.1. Tremor

This activity was done by the method of Coward and Doggett (1977). Tremors were induced by oxotremorine (OT) (0.5 mg/kg i.p) in mice 45 min after pretreatment with the test compounds. After 5 min of OT injection tremors were assessed visually and scored as: 0 = no tremor; 1 = occasional tremor; 2 = intermittent tremors; 3 = continuous tremors. Each animal of a group was scored and tremor index (mean score for each group) was determined.

3.2. Rigidity

Reserpine (5 mg/kg i.p.) was administered in rats to produce rigidity and after 15 min test compounds were injected. Rigidity was measured 1 h after reserpine administration. To measure rigidity, rats were grasped immediately below forelimbs and slight pressure was applied upward against the hind limbs. The degree of resistance was scored according to(Goldstein et al., 1975): 0 = no resistance; 1 = normal resistance; 2 = complete resistance. A score of 2 was selected as criterion for rigidity and expressed as percentage of animals showing rigidity (score 2) in a group.

3.3. Hypokinesia

This was performed according to the method of Morpugo (1962). It was produced by reserpine (5 mg/kg i.p.) in rats. Locomotor activity was measured after 2 h by placing each group of rats in a photoactometer for 15 min and total counts were recorded. The test compounds were administered 15 min after reserpine administration. The percent increase or decrease in counts was calculated on the basis of counts of untreated groups.

3.3.1. Catatonia

Reserpine (5 mg/kg i.p.) was administered in rats and after 15 min test compounds were administered. Catatonia was observed after 4 h and was scored according to the method of Dews (1953).

3.3.2. Acute toxicity study

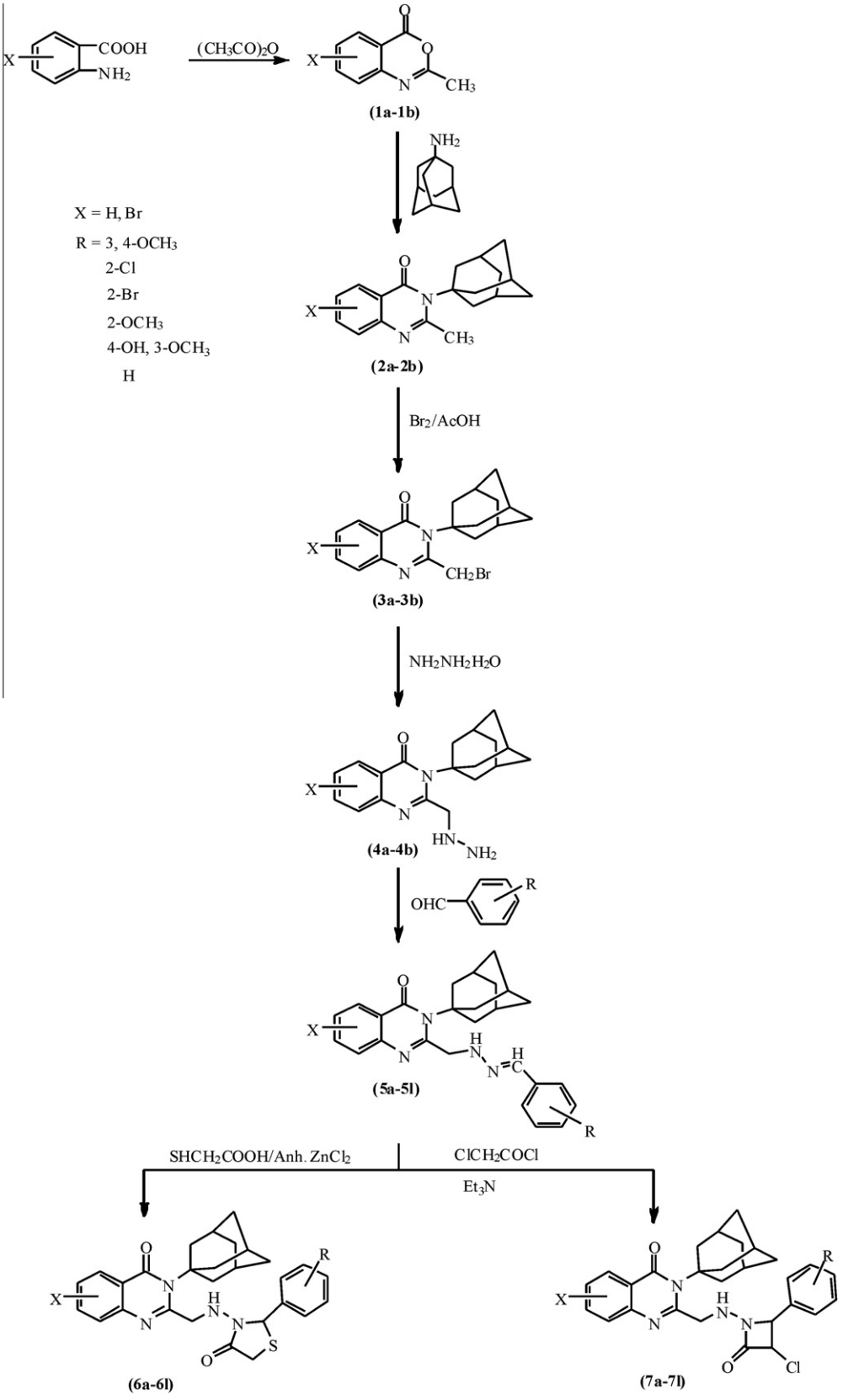
The compounds which showed significant antiparkinsonian activity were investigated for their acute toxicity study in mice (25–30 g) of either sex. The compounds were given orally at graded doses to separated group of six animals. After 24 h of administration, percent mortality in each group was observed from the data obtained. LD_{50} values were calculated by the method Smith (1960).

4. Results and discussion

Compounds **5a**–**5l**, **6a**–**6l** and **7a**–**7l** were screened for their antiparkinsonian activity. Pharmacological data of all the synthesized compounds of this series have been reported in Tables 1–3.

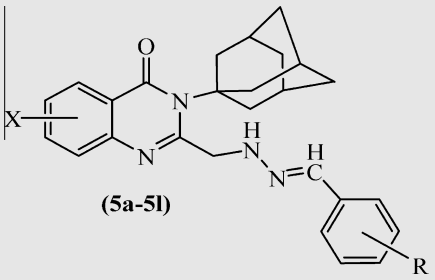
4.1. Antitremor activity

The **6a**–**6l** showed better antitremor activity than L-dopa and **6g** exhibited the most potent activity. Compounds **7g**–**7j** in general showed lesser antitremor activity than thiazolidinones. However, these compounds exhibited almost equipotent activity as L-dopa.


X = H, Br
R = 3, 4-OCH3
2-Cl
2-Br
2-OCH3
4-OH, 3-OCH3
H
(1a-1b)
(2a-2b)
Br2/AcOH
(3a-3b)
NH2NH2H2O
(4a-4b)
(5a-5l)
SHCH2COOH/Anh. ZnCl2
ClCH2COCl
Et3N
(6a-6l)
(7a-7l)

Scheme 1

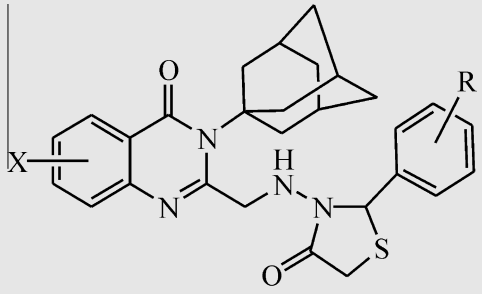
Table 1 Antiparkinsonian activity of compounds **5a**–**5l**.



(5a-5l)

Comp No.	X	R	Oxotremorine induced tremors in mice (0.5 mg/kg)	Reserpine (5 mg/kg induced)			LD_{50} mg/kg i.p.
				Rigidity (%)	Hypokinesia (% counts)	Catatonia (mean scores)	
Control			3.0 ± 0	100	14.06	3.0 ± 0	
L-dopa			2.60 ± 0.24	80	30.39	2.80 ± 0.08	
5a	H	3,4-OCH_3	2.65 ± 0.17	80	25.20	2.24 ± 0.16	>1000
5b	H	2-Cl	2.67 ± 0.28	100	22.10	2.25 ± 0.18	>1000
5c	H	2-Br	2.71 ± 0.13	70	21.08	2.60 ± 0.24	>1000
5d	H	2-OCH_3	2.73 ± 0.17	80	15.20	2.82 ± 0.22	>1000
5e	H	4-OH, 3-OCH_3	2.76 ± 0.21	90	14.70	2.71 ± 0.23	>1000
5f	H	H	2.50 ± 0.26	100	13.50	2.90 ± 0.26	>1000
5g	Br	3,4-OCH_3	2.55 ± 0.25	40	41.70	1.90 ± 0.19	>1000
5h	Br	2-Cl	2.57 ± 0.29	50	39.40	2.43 ± 0.22	>1000
5i	Br	2-Br	2.59 ± 0.25	60	36.50	2.67 ± 0.25	>1000
5j	Br	2-OCH_3	2.61 ± 0.32	80	34.60	2.70 ± 0.23	>1000
5k	Br	4-OH, 3-OCH_3	2.52 ± 0.17	70	32.10	2.90 ± 0.25	>1000
5l	Br	H	2.76 ± 0.30	90	30.20	2.92 ± 0.28	>1000

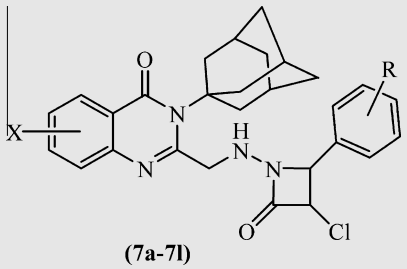
Table 2 Antiparkinsonian activity of compounds **6a**–**6l**.



(6a-6l)

Comp No.	X	R	Oxotremorine induced tremors in mice (0.5 mg/kg)	Reserpine (5 mg/kg induced)			LD_{50} mg/kg i.p.
				Rigidity (%)	Hypokinesia (% counts)	Catatonia (mean scores)	
Control	–	–	3.0 ± 0	100	14.06	3.0 ± 0	
L-dopa	–	–	2.6 ± 0.24	80	30.39	2.8 ± 0.08	
6a	H	3,4-OCH_3	2.32 ± 0.19	40	57.10	1.82 ± 0.17	>1000
6b	H	2-Cl	2.33 ± 0.22	30	56.40	1.86 ± 0.21	>1000
6c	H	2-Br	2.37 ± 0.25	40	54.70	1.95 ± 0.24	>1000
6d	H	2-OCH_3	2.40 ± 0.27	30	52.90	2.10 ± 0.25	>1000
6e	H	4-OH, 3-OCH_3	2.42 ± 0.26	50	51.30	2.60 ± 0.23	>1000
6f	H	H	2.45 ± 0.29	60	49.20	2.80 ± 0.26	>1000
6g	Br	3,4-OCH_3	2.25 ± 0.15	10	82.70	1.30 ± 0.13	>2000
6h	Br	2-Cl	2.27 ± 0.18	20	81.10	1.40 ± 0.17	>1000
6i	Br	2-Br	2.28 ± 0.22	30	77.50	1.90 ± 0.19	>1000
6j	Br	2-OCH_3	2.27 ± 0.26	60	75.30	2.05 ± 0.23	>1000
6k	Br	4-OH, 3-OCH_3	2.29 ± 0.21	100	74.60	2.10 ± 0.26	>1000
6l	Br	H	2.30 ± 0.24	100	73.70	2.21 ± 0.29	>1000

Table 3 Antiparkinsonian activity of compounds **7a**–**7l**.



(7a-7l)

Comp No.	X	R	Oxotremorine induced tremors in mice (0.5 mg/kg)	Reserpine (5 mg/kg induced)			LD_{50} mg/kg i.p.
				Rigidity (%)	Hypokinesia (% counts)	Catatonia (mean scores)	
Control	–	–	3.0 ± 0	100	14.06	3.0 ± 0	
L-dopa	–	–	2.60 ± 0.26	80	30.39	2.80 ± 0.08	
7a	H	3,4-OCH_3	2.52 ± 0.18	30	60.20	1.82 ± 0.23	> 1000
7b	H	2-Cl	2.54 ± 0.22	40	59.10	1.86 ± 0.24	> 1000
7c	H	2-Br	2.53 ± 0.23	50	58.30	1.95 ± 0.27	> 1000
7d	H	2-OCH_3	2.56 ± 0.25	60	56.60	2.10 ± 0.24	> 1000
7e	H	4-OH, 3-OCH_3	2.58 ± 0.26	40	55.40	2.60 ± 0.27	> 1000
7f	H	H	2.59 ± 0.29	80	55.20	2.80 ± 0.29	> 1000
7g	Br	3,4-OCH_3	2.42 ± 0.24	20	64.60	1.30 ± 0.12	> 1000
7h	Br	2-Cl	2.43 ± 0.26	30	63.70	1.40 ± 0.15	> 1000
7i	Br	2-Br	2.46 ± 0.27	40	62.40	1.90 ± 0.16	> 1000
7j	Br	2-OCH_3	2.48 ± 0.29	40	61.30	2.05 ± 0.19	> 1000
7k	Br	4-OH, 3-OCH_3	2.51 ± 0.31	60	63.20	2.10 ± 0.23	> 1000
7l	Br	H	2.49 ± 0.32	60	73.70	2.21 ± 0.26	> 1000

4.2. Antirigidity activity

Compounds **6g**, **6h** and **7g** decreased rigidity by 90%, 80% and 80%, respectively, while L-dopa decreased rigidity up to only 20% at the same dose. Compounds **5a**, **5d**, **5j**, and **7f** were equipotent to L-dopa. Compounds **5c**, **5g**–**5i**, **5k**, **6a**–**6f**, **6i**–**6j**, **7a**–**7e**, **7g**–**7i**, **7k** and **7l**, of this series have shown good antirigidity activity. It can be concluded that thiazolidinone derivatives elicited better antirigidity activity than benzylidenes and azetidinones derivatives.

4.3. Antihypokinetic activity

Compounds **5g**–**5k** showed almost approximately equal antihypokinetic activity as L-dopa, whereas compounds **6a**–**6l** elicited better activity than standard drug. The most active antihypokinetic compound of this series is **6g,** which exhibited 82.70% antihypokinetic activity.

4.4. Anticatatonic activity

Catatonia was significantly decreased by compounds **6g**, **6h**, **7g**, and **7h**. Compounds **5g**, **6i**, and **7i** exhibited good anticatatonic activity.

4.5. Acute toxicity

The newly synthesized compounds were also tested for approximate lethal dose LD_{50} and were found to exhibit a higher value of LD_{50} i.e. more than 1000 mg/kg i.p. except compound **6g,** which exhibited LD_{50} of more than 2000 mg/kg i.p. (maximum dose tested), thus indicating the safer nature of the compounds.

5. Conclusion

Thiazolidinone derivatives showed more potent antiparkinsonian activity than azetidinone derivatives. Moreover, the substitution with 3,4-dimethoxyphenyl group was found to beneficial for antiparkinsonian activity.

6. Experimental protocols

6.1. Chemistry

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in an oven-dried glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate of 0.5 mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions and spots were visualized under iodine chamber. Elemental analysis (C, H, N) of all the compounds was determined through the Perkin–Elmer 2400 elemental analyzer and results were found within ±0.4% of theoretical values. Infra red (IR) spectra were recorded in KBr on the Perkin–Elmer-spectrum RX-I instrument and υ_{max} was recorded in cm^{-1}. ^1H NMR spectra were recorded by the Bruker DR-X-400 FT-NMR instrument using $CDCl_3$ and DMSO-d_6 as

solvents and tetramethysilane (TMS) as an internal reference as δ (ppm).

6.1.1. General procedure for synthesis of 2-methyl-6-substitutedbenzo(1,3)oxazin-4-ones ***(1a–1b)***

These compounds were prepared according to the method of Bogert and Soil (1907). A mixture of unsubstituted/6-bromo-anthranilic acid (1.0 mol) and acetic anhydride (0.02 mol) was refluxed for 2–3 h with occasional stirring. The excess of acetic anhydride was distilled off. On cooling, a solid was separated out which was filtered and washed with appropriate solvent and dried **1a**–**1b**.

*6.1.1.1. 2-Methyl-4H-benzo(1,3)oxazin-4-one (**1a**).* Yield 86% (Methanol): m.p. 79–81 °C; IR (KBr) υ_{max} in cm^{-1} 1701 (C═O), 1610 (C⟷C of aromatic ring), 1570 (C═N), 1302 (C–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 6.65–7.73 (m, 4H, Ar-H), 1.31 (s, 3H, CH_3). MS: $[M]^+$ at m/z 161.16. *Anal.* Calc. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.35; N, 8.65%.

*6.1.1.2. 6-Bromo-2-methyl-4H-benzo(1,3)oxazin-4-one (**1b**).* Yield 83% (Petroleum ether): m.p. 80 °C; IR (KBr) υ_{max} in cm^{-1} 1704 (C═O), 1612 (C⟷C of aromatic ring), 1575 (C═N), 1304 (C–N), 610 (C–Br); ^{1}H NMR ($CDCl_3$) δ in ppm: 6.71–7.65 (m, 3H, Ar-H), 1.30 (s, 3H, CH_3). MS: $[M]^+$ at m/z 240.5. *Anal.* Calc. for $C_9H_6BrNO_2$: C, 45.03; H, 2.52; N, 5.83. Found: C, 45.15; H, 2.55; N, 5.83%.

6.1.2. General procedure for the synthesis of 3-amantadinyl-2-methyl-6-monosubstitutedquinazolin-4(3H)-ones ***2a–2b***

To a solution of compound **1a**–**1b** amantadine (0.02 mol) was added, the mixture was heated on a free flame for 10–20 min in a conical flask. After the disappearance of water droplets in a conical flask it was kept at room temperature. On cooling a jelly like mass was obtained which was dissolved in ethanol, was refluxed and poured into water. The solid thus obtained was filtered, dried and finally recrystallized from the appropriate solvent to obtain compounds **2a**–**2b**.

*6.1.2.1. 3-Amantadinyl-2-methylquinazolin-4(3H)–one (**2a**).* Yield 82% (Methanol): m.p. 205 °C; IR (KBr) υ_{max} in cm^{-1}: 1706 (C═O), 1615 (C⟷C of aromatic ring), 1571 (C═N), 1300 (C–N); ^{1}H NMR (DMSO-d_6) δ in ppm: 6.73–7.70 (m, 4H, Ar-H), 1.27 (s, 3H, CH_3), 1.30 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 294.39. *Anal.* Calc. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.63; H, 7.67; N, 9.44%.

*6.1.2.2. 3-Amantadinyl-6-bromo-2-methylquinazolin-4(3H)-one (**2b**).* Yield 78% (Ethanol): m.p. 201 °C; IR (KBr) υ_{max} in cm^{-1}: 1708 (C═O), 1616 (C⟷C of aromatic ring), 1571 (C═N), 1302 (C–N), 613 (C–Br); ^{1}H NMR ($CDCl_3$) δ in ppm: 1.29 (m, 15H, amantadinyl ring), 6.78–7.37 (m, 3H, Ar-H), 1.32 (s, 3H, CH_3). MS: $[M]^+$ at m/z 373.29. *Anal.* Calc. for $C_{19}H_{21}BrN_2O$: C, 61.13; H, 5.67; N, 7.50. Found: C, 61.22; H, 5.65; N, 7.53%.

6.1.3. General procedure for synthesis of 3-amantadinyl-2-bromomethylsubstitutedquinazolin-4-(3H) ones ***3a–3b***

Bromine (0.4 mol) in acetic acid was added dropwise to the solution of compound **2a**–**ab** in acetic acid (50 mL). The reaction mixture was poured onto crushed ice, then left overnight at room temperature. The precipitate thus obtained was recrystallized with suitable solvents to furnish compounds **3a**–**3b**.

*6.1.3.1. 3-Amantadinyl-2-bromomethylquinazolin-4(3H)-one (**3a**).* Yield 76% (Methanol): m.p. 198 °C; IR (KBr) υ_{max} in cm^{-1}: 1710 (C═O), 1619 (C⟷C of aromatic ring), 1579 (C═N), 1305 (C–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 6.67–7.72 (m, 4H, Ar-H), 1.32 (m, 15H, amantadinyl ring), 1.25 (s, 2H, CH_2). MS: $[M]^+$ at m/z 373.29. *Anal.* Calc. for $C_{19}H_{21}BrN_2O$: C, 61.13; H, 5.67; N, 7.50. Found: C, 61.24; H, 5.58; N, 7.43%.

*6.1.3.2. 3-Amantadinyl-6-bromo-2-(bromomethyl)quinazolin-4(3H)-one (**3b**).* Yield 75% (Methanol): m.p. 201 °C; IR (KBr) υ_{max} in cm^{-1}: 1712 (C═O), 1621 (C⟷C of aromatic ring), 1574 (C═N), 1303 (C–N), 615 (C–Br); ^{1}H NMR (DMSO-d_6) δ in ppm: 6.79–7.92 (m, 3H, Ar-H), 1.31 (s, 2H, CH_2), 1.25 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 452.18. *Anal.* Calc. for $C_{19}H_{20}Br_2N_2O$: C, 50.47; H, 4.46; N, 6.20. Found: C, 50.43; H, 4.45; N, 6.25%.

6.1.4. General procedure for synthesis of 3-amantadinyl-2-(hydrazinylmethyl)substitutedquinazolin-4(3H)-one ***4a–4b***

A compound **3a**–**3b** (0.01 mol) and hydrazine hydrate (0.02 mol) in methanol were refluxed for 10 h. The excess of solvent was distilled off and the reaction mixture was poured onto ice. The solid thus obtained was filtered washed with water dried and recrystallized from appropriate solvents to yield compounds **4a**–**4b**.

*6.1.4.1. 3-Amantadinyl-2-hydrazinylmethylquinazolin-4(3H)-one (**4a**).* Yield 73% (Ethanol): m.p. 195 °C; IR (KBr) υ_{max} in cm^{-1}: 3341 (N–H), 1713 (C═O), 1625 (C⟷C of aromatic ring), 1579 (C═N), 1306 (C–N), 1260 (N–N), 624 (C–Br); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.34 (s, 1H, NH exchangeable with D_2O), 8.15 (s, 2H, NH_2), 6.68–7.67 (m, 4H, Ar-H), 3.28 (d, 2H, J = 9.1 Hz, CH_2NH), 1.34 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 324.42. *Anal.* Calc. for $C_{19}H_{24}N_4O$: C, 70.23; H, 7.46; N, 17.27. Found: C, 70.22; H, 7.45; N, 17.23%.

*6.1.4.2. 3-Amantadinyl-6-bromo-2-hydrazinylmethyl)quinazolin-4(3H)-one (**4b**).* Yield 70% (Ethanol): m.p. 193 °C; IR (KBr) υ_{max} in cm^{-1}: 3345 (N–H), 1710 (C═O), 1617 (C⟷C of aromatic ring), 1581 (C═N), 1304 (C–N), 614 (C–Br); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.12 (s, 1H, NH exchangeable with D_2O), 8.10 (s, 2H, NH_2), 6.62–7.58 (m, 3H, Ar-H), 3.28 (d, 2H, J = 9.1 Hz, CH_2NH), 1.33 (m, 15H, amantadinyl ring), MS: $[M]^+$ at m/z 403.32. *Anal.* Calc. for $C_{19}H_{23}BrN_4O$: C, 56.58; H, 5.75; N, 13.89. Found: C, 56.55; H, 5.78; N, 13.85%.

6.1.5. General procedure for synthesis of 3-amantadinyl-2-[2-(substitutedbenzylidine)hydrazinyl]methylquinazolin-4(3H)-ones ***5a–5l***

A mixture of compound **4a**–**4b** (0.02 mol) and substituted benzaldehydes (0.01 mol) was dissolved in absolute ethanol and (60 mL) in the presence of few drops of glacial acid. The reaction mixture was refluxed for 12 h and poured onto crushed ice and the resultant solid was recrystallized from suitable solvents to yield compounds **5a**–**5l**.

*6.1.5.1.3-Amantadinyl-2-[(2-(3,4-dimethoxybenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5a**)*. Yield 75% (Methanol): m.p. 182 °C; IR (KBr) υ_{max} in cm^{-1}: 3340 (N–H), 1725 (C═O), 1620 (C⟷C of aromatic ring), 1580 (C═N), 1570 (N═CH), 1309 (C–N), 1290 (N–N), 1224 (OCH_3); ^1H NMR (DMSO-d_6) δ in ppm: 8.29 (s, 1H, CH-Ar), 8.13 (s, 1H, NH exchangeable with D_2O), 6.69–7.72 (m, 7H, Ar-H), 3.35 (d, 2H, J = 9.1 Hz, CH_2NH), 3.29 (s, 6H, $2\times OCH_3$), 1.31 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 472.58. *Anal*. Calc. for $C_{28}H_{32}N_4O_3$: C, 71.16; H, 6.83; N, 11.86. Found: C, 71.15; H, 6.85; N, 11.84%.

*6.1.5.2. 3-Amantadinyl-2-[(2-(2-chlorobenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5b**)*. Yield 74% (DMF): m.p. 175 °C; IR (KBr) υ_{max} in cm^{-1}: 3343 (N–H), 1719 (C═O), 1625 (C⟷C of aromatic ring), 1583 (C═N), 1570 (N═CH), 1310 (C–N), 1293 (N–N), 726 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.40 (s, 1H, NH exchangeable with D_2O), 8.30 (s, 1H, CH-Ar), 6.59–7.62 (m, 8H, Ar-H), 3.45 (d, 2H, J = 9.1 Hz, CH_2NH), 1.35 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 446.97. *Anal*. Calc. for $C_{26}H_{27}ClN_4O$: C, 69.87; H, 6.09; N, 12.53. Found: C, 69.85; H, 6.13; N, 12.54%.

*6.1.5.3. 3-Amantadinyl-2-[(2-(2-bromobenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5c**)*. Yield 71% (Ethanol): m.p. 173 °C; IR (KBr) υ_{max} in cm^{-1}: 3346 (N–H), 1716 (C═O), 1624 (C⟷C of aromatic ring), 1585 (C═N), 1574 (N═CH), 1311 (C–N), 1295 (N–N), 612 (C–Br); ^1H NMR (DMSO-d_6) δ in ppm: 8.32 (s, 1H, CH-Ar), 8.20 (s, 1H, NH exchangeable with D_2O), 6.62–7.63 (m, 8H, Ar-H), 3.43 (d, 2H, J = 9.1 Hz, CH_2NH), 1.38 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 491.42. *Anal*. Calc. for $C_{26}H_{27}BrN_4O$: C, 63.55; H, 5.54; N, 11.40. Found: C, 63.52; H, 5.52; N, 11.43%.

*6.1.5.4. 3-Amantadinyl-3-[(2-(2-methoxybenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5d**)*. Yield 68% (DMF): m.p. 167 °C; IR (KBr) υ_{max} in cm^{-1}: 3343 (N–H), 1718 (C═O), 1626 (C⟷C of aromatic ring), 1589 (C═N), 1575 (N═CH), 1311 (C–N), 1293 (N–N), 1226 (OCH_3); ^1H NMR ($CDCl_3$) δ in ppm: 8.45 (s, 1H, NH exchangeable with D_2O), 8.29 (s, 1H, CH-Ar), 6.66–7.72 (m, 8H, Ar-H), 3.46 (s, 3H, OCH_3), 3.43 (d, 2H, J = 9.1 Hz, CH_2NH), 1.30 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 442.24. *Anal*. Calc. for $C_{27}H_{30}N_4O_2$: C, 73.28; H, 6.83; N, 12.66. Found: C, 73.25; H, 6.86; N, 12.63%.

*6.1.5.5. 3-Amantadinyl-2-[(2-(4-hydroxy-3-methoxybenzylidine)hydrazinyl)methyl] quinazolin-4(3H)-one (**5e**)*. Yield 64% (Methanol), m.p. 176 °C; IR (KBr) υ_{max} in cm^{-1}: 3430 (OH), 3345 (N–H), 1718 (C═O), 1622 (C⟷C of aromatic ring), 1588 (C═N), 1579 (N═CH), 1308 (C–N), 1294 (N–N), 1223 (OCH_3); ^1H NMR ($CDCl_3$) δ in ppm: 8.33 (s, 1H, CH-Ar), 8.32 (s, 1H, NH exchangeable with D_2O), 11.15 (s, 1H, OH exchangeable with D_2O), 6.69–7.75 (m, 7H, Ar-H), 3.42 (s, 3H, OCH_3), 3.37 (d, 2H, J = 9.1 Hz, CH_2NH), 1.34 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 458.55. *Anal*. Calc. for $C_{27}H_{30}N_4O_3$: C, 70.72; H, 6.59; N, 12.22. Found: C, 70.76; H, 6.54; N, 12.24%.

*6.1.5.6. 3-Amantadinyl-2-(2-benzylidine)hydrazinyl)methyl] quinazolin-4(3H)-one (**5f**)*. Yield 62% (Acetone): m.p. 171 °C; IR (KBr) υ_{max} in cm^{-1}: 3348 (N–H), 1737 (C═O), 1623 (C⟷C of aromatic ring), 1586 (N═CH), 1582 (C═N), 1307 (C–N), 1291 (N–N); ^1H NMR ($CDCl_3$) δ in ppm: 8.35 (s, 1H, CH-Ar), 8.25 (s, 1H, NH exchangeable with D_2O), 6.65–7.63 (m, 9H, Ar-H), 1.31 (d, 2H, J = 9.2 Hz, CH_2NH), 1.23 (m,15H, amantadinyl ring). MS: $[M]^+$ at m/z 412.53. *Anal*. Calc. for $C_{26}H_{28}N_4O$: C, 75.10; H, 6.84; N, 13.58. Found: C, 75.15; H, 6.91; N, 13.46%.

*6.1.5.7. 3-Amantadinyl-6-bromo-2-[(2-(3,4-dimethoxybenzylidine)hydrazinyl)methyl] quinazolin-4(3H)-one (**5g**)*. Yield 59% (Ethanol): m.p. 169 °C; IR (KBr) υ_{max} in cm^{-1}: 3349 (N–H), 1726 (C═O), 1626 (C⟷C of aromatic ring), 1588 (C═N), 1570 (N═CH), 1312 (C–N), 1291 (N–N), 1224 (OCH_3), 614 (C–Br); ^1H NMR (DMSO-d_6) δ in ppm: 8.34 (s, 1H, CH-Ar), 8.46 (s, 1H, NH exchangeable with D_2O), 6.69–7.72 (m, 6H, Ar-H), 3.47 (d, 2H, J = 9.1 Hz, CH_2NH), 2.29 (s, 6H, $2\times OCH_3$), 1.31 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 551.47. *Anal*. Calc. for $C_{28}H_{31}BrN_4O_3$: C, 60.98; H, 5.67; N, 10.16. Found: C, 60.95; H, 5.65; N, 10.19%.

*6.1.5.8. 3-Amantadinyl-6-bromo-2-[(2-(2-chlorobenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5h**)*. Yield 56% (DMF): m.p. 168 °C; IR (KBr) υ_{max} in cm^{-1}: 3345 (N–H), 1720 (C═O), 1624 (C⟷C of aromatic ring), 1585 (C═N), 1574 (N═CH), 1313 (C–N), 1291 (N–N), 623 (C–Cl), 615 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.46 (s, 1H, NH exchangeable with D_2O), 8.30 (s, 1H, CH-Ar), 6.59–7.62 (m, 7H, Ar-H), 3.44 (d, 2H, J = 9.1 Hz, CH_2NH), 1.35 (m, 15H, amantadinyl ring), MS: $[M]^+$ at m/z 525.87. *Anal*. Calc. for $C_{26}H_{26}BrClN_4O$: C, 59.38; H, 4.98; N, 10.65. Found: C, 59.35; H, 4.95; N, 10.63%.

*6.1.5.9. 3-Amantadinyl-6-bromo-2-[(2-(2-bromobenzylidine)hydrazinyl)methyl] quinazolin-4(3H)-one (**5i**)*. Yield 52% (Acetone): m.p. 165 °C; IR (KBr) υ_{max} in cm^{-1}: 3341 (N–H), 1715 (C═O), 1627(C⟷C of aromatic ring), 1589 (C═N), 1576 (N═CH), 1313 (C–N), 612 (C–Br); ^1H NMR (DMSO-d_6) δ in ppm: 8.32 (s, 1H, CH-Ar), 8.30 (s, 1H, NH exchangeable with D_2O), 6.62–7.63 (m, 7H, Ar-H), 3.45 (d, 2H, J = 9.1 Hz, CH_2NH), 1.38 (m, 15H, amantadinyl ring), MS: $[M]^+$ at m/z 570.32. *Anal*. Calc. for $C_{26}H_{26}Br_2N_4O$: C, 54.76; H, 4.60; N, 9.82. Found: C, 54.78; H, 4.65; N, 9.66%.

*6.1.5.10. 3-Amantadinyl-6-bromo-2-[(2-(2-methoxybenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5j**)*. Yield 56% (Methanol): m.p. 163 °C; IR (KBr) υ_{max} in cm^{-1}: 3342 (N–H), 1629 (C⟷C of aromatic ring), 1720 (C═O), 1590 (C═N), 1578 (N═CH), 1313 (C–N), 1294 (N–N), 1225 (OCH_3), 618 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.45 (s, 1H, NH exchangeable with D_2O), 8.34 (s, 1H, CH-Ar), 6.66–7.72 (m, 7H, Ar-H), 3.50 (d, 2H, J = 9.1 Hz, CH_2NH), 3.30 (s, 3H, OCH_3), 1.30 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 521.45. *Anal*. Calc. for $C_{27}H_{29}BrN_4O_2$: C, 62.19; H, 5.61; N, 10.74. Found: C, 62.15; H, 5.65; N, 10.76%.

*6.1.5.11. 3-Amantadinyl-6-bromo-2-[(2-(4-hydroxy-3-methoxybenzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5k**)*. Yield 53% (Ethanol): m.p. 160 °C; IR (KBr) υ_{max} in cm^{-1}: 3433 (OH), 3342 (N–H), 1721 (C═O), 1624 (C⟷C of aromatic ring), 1589 (C═N), 1580 (N═CH), 1313 (C–N), 1294 (N–N), 1227 (OCH_3), 618 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.48 (s, 1H, NH exchangeable with D_2O), 8.35 (s, 1H,

CH-Ar), 10.95 (s, 1H, OH exchangeable with D_2O), 6.69–7.75 (m, 6H, Ar-H), 3.48 (d, 2H, J = 9.0 Hz, CH_2NH), 3.46 (s, 3H, OCH_3), 1.34 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 537.45. *Anal*. Calc. for $C_{27}H_{29}BrN_4O_3$: C, 60.34; H, 5.44; N, 10.42. Found: C, 60.36; H, 5.46; N, 10.40%.

*6.1.5.12. 3-Amantadinyl-6-bromo-2-[(2-benzylidine)hydrazinyl)methyl]quinazolin-4(3H)-one (**5l**)*. Yield 52% (Ethanol): m.p. 162 °C; IR (KBr) υ_{max} in cm^{-1}: 3350 (N–H), 1722 (C═O), 1627 (C↔C of aromatic ring), 1591 (C═N), 1583 (N═CH), 1312 (C–N), 1290 (N–N); ^1H NMR (DMSO-d_6) δ in ppm: 8.47 (s, 1H, NH exchangeable with D_2O), 6.65–7.63 (m, 8H, Ar-H), 3.51 (d, 2H, J = 9.1 Hz, CH_2NH), 3.36 (s, 1H, CH-Ar), 1.23 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 491.42. *Anal*. Calc. for $C_{26}H_{27}BrN_4O$: C, 63.55; H, 5.54; N, 11.40. Found: C, 63.54; H, 5.59; N, 11.43%.

*6.1.6. General procedure for synthesis of 3-amantadinyl-2-[((substitutedphenyl)-4-oxo-thiazolidin-1-yl) methylamino]quinazolin-4(3H)-ones **6a**–**6l***

To a solution of compound **5a**–**5l** (0.01 mol) and anhydrous $ZnCl_2$ in dry benzene (50 mL), thioglycolic acid (0.02 mol) was added dropwise with stirring at ambient temperature and the reaction mixture was kept for 3 days at room temperature and then refluxed for 14 h. The reaction mixture was filtered. The filtrate was concentrated and poured on crushed ice. The resultant solid was recrystallized from appropriate solvent to yield the desired compounds **6a**–**6l**.

*6.1.6.1. 3-Amantadinyl-2-[((3,4-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6a**)*. Yield 55% (DMF): m.p. 175 °C; IR(KBr) υ_{max} in cm^{-1}: 1768 (C═O), 1626 (C↔C of aromatic ring), 1591 (C═N), 1312 (C–N), 1224 (OCH_3), 674 (C–S–C); ^1H NMR (DMSO-d_6) δ in ppm: 8.48 (s, 1H, NH exchangeable with D_2O), 6.69–7.72 (m, 7H, Ar-H), 5.93 (s, 1H, CH-Ar), 3.53 (s, 2H, CH_2-S), 2.85 (s, 6H, $2\times OCH_3$), 2.52 (d, 2H, J = 9.1 Hz, CH_2NH), 1.17 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 546.68. *Anal*. Calc. for $C_{30}H_{34}N_4O_4S$: C, 65.91; H, 6.27; N, 10.25. Found: C, 65.92; H, 6.25; N, 10.23%.

*6.1.6.2. 3-Amantadinyl-2-[((2-chlorophenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6b**)*. Yield 60% (Ethanol): m.p. 173 °C; IR (KBr) υ_{max} in cm^{-1}: 1772 (C═O), 1625 (C↔C of aromatic ring), 1532 (C═N), 1257 (C–N), 728 (C–Cl), 678 (C–S–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.34 (s, 1H, NH exchangeable with D_2O), 6.65–7.69 (m, 8H, Ar-H), 5.83 (s, 1H, CH-Ar), 3.93 (s, 2H, CH_2-S), 2.87 (d, 2H, J = 9.1 Hz, CH_2NH), 1.17 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 521.07. *Anal*. Calc. for $C_{28}H_{29}ClN_4O_2S$: C, 64.54; H, 5.61; N, 10.75. Found: C, 64.42; H, 5.32; N, 10.43%.

*6.1.6.3. 3-Amantadinyl-2-[((2-bromophenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6c**)*. Yield 64% (Methanol): m.p. 167 °C; IR (KBr) υ_{max} in cm^{-1}: 1772 (C═O), 1627 (C↔C of aromatic ring), 1531 (C═N), 1306 (C–N), 677 (C–S–C), 612 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.23 (s, 1H, NH exchangeable with D_2O), 6.69–7.75 (m, 8H, Ar-H), 5.86 (s, 1H, CH-Ar), 3.60 (s, 2H, CH_2-S), 2.54 (d, 2H, J = 9.1 Hz, CH_2NH), 1.25 (m, 15H amantadinyl ring). MS: $[M]^+$ at m/z 565.52. *Anal*. Calc. for $C_{28}H_{29}BrN_4O_2S$: C, 59.47; H, 5.17; N, 9.91; Found: C, 59.49; H, 5.14; N, 9.93%.

*6.1.6.4. 3-Amantadinyl-2-[((2-methoxyphenyl)-4-oxothiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6d**)*. Yield 58% (Methanol): m.p. 163 °C; IR (KBr) υ_{max} in cm^{-1}: 1773 (C═O), 1626 (C↔C of aromatic ring), 1529 (C═N), 1308 (C–N), 1220 (OCH_3), 676 (C–S–C); ^1H NMR (DMSO-d_6) δ in ppm: 8.35 (s, 1H, NH exchangeable with D_2O), 6.68–7.78 (m, 8H, Ar-H), 5.89 (s, 1H, CH-Ar), 3.65 (s, 2H, CH_2-S), 2.85 (s, 3H, OCH_3), 2.69 (d, 2H, J = 9.2 Hz, CH_2NH), 1.18 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 516.65. *Anal*. Calc. for $C_{29}H_{32}N_4O_3S$: C, 67.42; H, 6.24; N, 10.84. Found: C, 67.42; H, 6.22; N, 10.83%.

*6.1.6.5. 3-Amantadinyl-2-[((4-hydroxy-3-methoxyphenyl)-4-oxo-thiazolidin-3-yl)methyl amino]-quinazolin-4(3H)-one (**6e**)*. Yield 53% (DMF): m.p. 160 °C; IR (KBr) υ_{max} in cm $^{-1}$: 3434 (OH), 1776 (C═O), 1619 (C↔C of aromatic ring), 1532 (C═N), 1313 (C–N), 1228 (OCH_3), 673 (C–S–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.38 (s, 1H, NH exchangeable with D_2O), 11.12 (s, 1H, OH exchangeable with D_2O), 6.75–7.70 (m, 7H, Ar-H), 5.65 (s, 1H, CH-Ar), 3.69 (s, 2H, CH_2-S), 2.83 (s, 3H, OCH_3), 2.68 (d, 2H, J = 9.1 Hz, CH_2NH), 1.18 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 532.65. *Anal*. Calc. for $C_{29}H_{32}N_4O_4S$: C, 65.39; H, 6.06; N, 10.52. Found: C, 65.35; H, 6.08; N, 10.56%.

*6.1.6.6. 3-Amantadinyl-2-[((phenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6f**)*. Yield 51% (Methanol): m.p. 158 °C; IR (KBr) υ_{max} in cm^{-1}: 1777 (C═O), 1622 (C↔C of aromatic ring), 1587 (C═N), 1315 (C–N), 679 (C–S–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.36 (s, 1H, NH exchangeable with D_2O), 6.74–7.72 (m, 9H, Ar-H), 5.62 (s, 1H, CH-Ar), 3.72 (s, 2H, CH_2-S), 2.85 (d, 2H, J = 9.1 Hz, CH_2NH), 1.24 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 486.63. *Anal*. Calc. for $C_{28}H_{30}N_4O_2S$: C, 69.11; H, 6.21; N, 11.51. Found: C, 69.15; H, 6.26; N, 11.54%.

*6.1.6.7. 3-Amantadinyl-6-bromo-2-[((3,4-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl)methyl amino]-quinazolin-4(3H)-one (**6g**)*. Yield 55% (Ethanol): m.p. 155 °C; IR (KBr) υ_{max} in cm^{-1}: 1780 (C═O), 1621 (C↔C of aromatic ring), 1584 (C═N), 1310 (C–N), 1228 (OCH_3), 679 (C–S–C), 617 (C–Br); ^1H NMR ($CDCl_3$). δ in ppm: 8.32 (s, 1H, NH exchangeable with D_2O), 6.65–7.62 (m, 6H, Ar-H), 5.68 (s, 1H, CH-Ar), 3.66 (s, 2H, CH_2-S), 3.40 (s, 6H, $2\times OCH_3$), 2.84 (d, 2H, J = 9.1 Hz, CH_2NH), 1.28 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 625.58. *Anal*. Calc. for $C_{30}H_{33}BrN_4O_4S$: C, 57.60; H, 5.32; N, 8.96. Found: C, 57.62; H, 5.35; N, 8.98%.

*6.1.6.8. 3-Amantadinyl-6-bromo-2-[(2-chlorophenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6h**)*. Yield 58% (Acetone): m.p. 150 °C; IR (KBr) υ_{max} in cm^{-1}: 1771 (C═O), 1621 (C↔C of aromatic ring), 1582 (C═N), 1306 (C–N), 729 (C–Cl), 682 (C–S–C); ^1H NMR (DMSO-d_6) δ in ppm: 8.35 (s, 1H, NH exchangeable with D_2O), 6.67–7.76 (m, 7H, Ar-H), 5.65 (s, 1H, CH-Ar), 3.68 (s, 2H, CH_2-S), 2.87 (d, 2H, J = 9.2 Hz, CH_2NH), 1.32 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 599.97. *Anal*. Calc. for $C_{28}H_{28}BrClN_4O_2S$: C, 56.05; H, 4.70; N, 9.34. Found: C, 55.02; H, 4.73; N, 9.35%.

*6.1.6.9. 3-Amantadinyl-6-bromo-2-[((2-bromophenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6i**).* Yield 64% (Methanol): m.p. 148 °C; IR (KBr) υ_{max} in cm^{-1}: 1776 (C═O), 1623 (C↔C of aromatic ring), 1591 (C═N), 1309 (C–N), 678 (C–S–C), 618 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.39 (s, 1H, NH exchangeable with D_2O), 6.63–7.75 (m, 7H, Ar-H), 5.66 (s, 1H, CH-Ar), 3.65 (s, 2H, CH_2-S), 2.84 (d, 2H, J = 9.1 Hz, CH_2NH), 1.36 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 644.42. *Anal.* Calc. for $C_{28}H_{28}Br_2N_4O_2S$: C, 52.19; H, 4.38; N, 8.69. Found: C, 52.16; H, 4.37; N, 8.65%.

*6.1.6.10. 3-Amantadinyl-6-bromo-2-[((2-methoxyphenyl)-4-oxo-thiazolidin-3-yl)methyl amino]-quinazolin-4(3H)-one (**6j**).* Yield 67% (Ethanol): m.p. 145 °C; IR (KBr) υ_{max} in cm^{-1}: 1777 (C═O), 1629 (C↔C of aromatic ring), 1579 (C═N), 1305 (C–N), 1226 (OCH_3), 675 (C–S–C), 622 (C–Br); ^1H NMR (DMSO-d_6) δ in ppm: 8.40 (s, 1H, NH exchangeable with D_2O), 6.67–7.74 (m, 7H, Ar-H), 5.68 (s, 1H, CH-Ar), 3.68 (s, 2H, CH_2-S), 3.55 (s, 3H, OCH_3), 2.88 (d, 2H, J = 9.1 Hz, CH_2NH), 1.38 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 595.55. *Anal.* Calc. for $C_{29}H_{31}BrN_4O_3S$: C, 58.49; H, 5.25; N, 9.41. Found: C, 58.45; H, 5.17; N, 9.43%.

*6.1.6.11. 3-Amantadinyl-6-bromo-2-[((4-hydroxy-3-methoxy-phenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-one (**6k**).* Yield 53% (Ethanol): m.p. 141 °C; IR (KBr) υ_{max} in cm^{-1}: 3440 (OH), 1773 (C═O), 1625 (C↔C of aromatic ring), 1592 (C═N), 1312 (C–N), 1228 (OCH_3), 680 (C–S–C), 624 (C–Br); ^1H NMR (DMSO-d_6) δ in ppm: 11.16 (s, 1H, OH exchangeable with D_2O), 8.44 (s, 1H, NH exchangeable with D_2O), 6.80–7.79 (m, 6H, Ar-H), 5.68 (s, 1H, CH-Ar), 3.72 (s, 2H, CH_2-S), 3.62 (s, 3H, OCH_3), 2.92 (d, 2H, J = 9.1 Hz, CH_2NH), 1.35 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 611.55. *Anal.* Calc. for $C_{29}H_{31}BrN_4O_4S$: C, 56.96; H, 5.11; N, 9.16. Found: C, 56.94; H, 4.16; N, 9.12%.

*6.1.6.12. 3-Amantadinyl-6-bromo-2-[((phenyl)-4-oxo-thiazolidin-3-ylmethylamino]-quinazolin-4(3H)-one (**6l**).* Yield 61% (Methanol): m.p. 145 °C; IR (KBr) υ_{max} in cm^{-1}: 1772 (C═O), 1628 (C↔C of aromatic ring), 1587 (C═N), 1305 (C–N), 681 (C–S–C), 615 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.47 (s, 1H, NH exchangeable with D_2O), 6.75–7.81 (m, 8H, Ar-H), 5.66 (s, 1H, CH-Ar), 3.70 (s, 2H, CH_2-S), 2.90 (d, 2H, J = 9.1 Hz, CH_2NH), 1.45 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 565.52. *Anal.* Calc. for $C_{28}H_{29}BrN_4O_2S$: C, 59.47; H, 5.17; N, 9.91. Found: C, 59.46; H, 5.15; N, 9.93%.

*6.1.7. General procedure for synthesis of 3-amantadinyl-2-[(substitutedphenyl)-3-chloro-2-oxo-azetidin-1-yl) methylamino]-quinazolin-4(3H)-ones **7a**–**7l***

To a solution of compounds **6a**–**6l** (0.01 mol) and triethylamine (5–6 drops) in dry benzene, mono chloro acetyl chloride (0.15 mol) was added dropwise at 50 °C. The reaction mixture was stirred for 40 min at room temperature and refluxed for 7 h. The reaction mixture was filtered to remove triethylamine hydrogen chloride and the resultant solution was poured onto crushed ice with constant stirring. The solid thus obtained was recrystallized from suitable solvents to yield the desired compounds **7a**–**7l**.

*6.1.7.1. 3-Amantadinyl-2-[((3,4-dimethoxyphenyl)-3-chloro-2-oxo-azetidin-3-yl)methyl amino]-quinazolin-4(3H)-one (**7a**).* Yield 52% (Methanol): m.p. 175 °C; IR (KBr) υ_{max} in cm^{-1}: 1755 (C═O) 1625 (C↔C of aromatic ring), 1575 (C═N), 1322 (C–N), 727 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.35 (s, 1H, NH exchangeable with D_2O), 6.64–7.75 (m, 7H, Ar-H), 5.80 (s, 1H, CH-Ar), 6.42 (d, 1H, J = 6.5 Hz, CHCl), 3.70 (d, 2H, J = 9.1 Hz, CH_2NH), 3.45 (s, 6H, 2 × OCH_3), 1.13 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 549.06. *Anal.* Calc. for $C_{30}H_{33}ClN_4O_4$: C, 65.63; H, 6.06; N, 10.20. Found: C, 65.59; H, 6.12; N, 10.27%.

*6.1.7.2. 3-Amantadinyl-2-[(2-chlorophenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]quinazolin-4(3H)-one (**7b**).* Yield 60% (Acetone): m.p. 173 °C; IR (KBr) υ_{max} in cm^{-1}: 1759 (C═O), 1628 (C↔C of aromatic ring), 1585 (C═N), 1317 (C–N), 727 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.34 (s, 1H, NH exchangeable with D_2O), 6.64–7.75 (m, 8H, Ar-H), 5.75 (s, 1H, CH-Ar), 6.48 (d, 1H, J = 6.4 Hz, CHCl), 3.78 (d, 2H, J = 9.2 Hz, CH_2NH), 1.12 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 523.45. *Anal.* Calc. for $C_{28}H_{28}Cl_2N_4O_2$: C, 64.25; H, 5.39; N, 10.70. Found: C, 64.22; H, 5.35; N, 10.73%.

*6.1.7.3. 3-Amantadinyl-2-[(2-bromophenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]quinazolin-4(3H)-one (**7c**).* Yield 61% (Methanol): m.p. 169 °C; IR (KBr) υ_{max} in cm^{-1}: 1762 (C═O), 1630 (C↔C of aromatic ring), 1583 (C═N), 1315 (C–N), 721 (C–Cl), 616 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.31 (s, 1H, NH exchangeable with D_2O), 6.62–7.72 (m, 8H, Ar-H), 5.78 (s, 1H, CH-Ar), 6.45 (d, 1H, J = 6.5 Hz, CHCl), 3.75 (d, 2H, J = 9.1 Hz, CH_2NH), 1.22 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 567.90. *Anal.* Calc. for $C_{28}H_{28}BrClN_4O_2$: C, 59.22; H, 4.97; N, 9.87. Found: C, 51.22; H, 4.95; N, 8.85%.

*6.1.7.4. 3-Amantadinyl-2-[((2-methoxphenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]quinazolin-4(3H)-one (**7d**).* Yield 64% (Methanol): m.p. 165 °C; IR (KBr) υ_{max} in cm^{-1}: 1767 (C═O), 1622 (C↔C of aromatic ring), 1587 (C═N), 1305 (C–N), 1233 (OCH_3), 728 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.40 (s, 1H, NH exchangeable with D_2O), 6.62–7.73 (m, 8H, Ar-H), 5.98 (s, 1H, CH-Ar), 6.45 (d, 1H, J = 6.5 Hz, CHCl), 3.74 (d, 2H, J = 9.1 Hz, CH_2NH), 3.21 (s, 3H, OCH_3), 1.13 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 519.03. *Anal.* Calc. for $C_{29}H_{31}ClN_4O_3$: C, 67.11; H, 6.02; N, 10.79. Found: C, 66.15; H, 6.05; N, 10.75%.

*6.1.7.5. 3-Amantadinyl-2-[((4-hydroxy3-methoxyphenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]quinazolin-4(3H)-one (**7e**).* Yield 59% (DMF): m.p. 161 °C; IR (KBr) υ_{max} in cm^{-1}: 3422 (OH), 1765 (C═O), 1624 (C↔C of aromatic ring), 1583 (C═N), 1315 (C–N), 1225 (OCH_3), 728 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 11.13 (s, 1H, OH exchangeable with D_2O), 8.38 (s, 1H, NH exchangeable with D_2O), 6.58–7.61 (m, 7H, Ar-H), 5.79 (s, 1H, CH-Ar), 6.41 (d, 1H, J = 6.4 Hz, CHCl), 3.71 (d, 2H, J = 9.0 Hz, CH_2NH), 3.25 (s, 3H, OCH_3), 1.16 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 535.03. *Anal.* Calc. for $C_{29}H_{31}ClN_4O_4$: C, 65.10; H, 5.84; N, 10.47. Found: C, 64.13; H, 5.85; N, 10.55%.

*6.1.7.6. 3-Amantadinyl-2[((phenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7f**).* Yield 57% (Eth-

anol): m.p. 163 °C; IR (KBr) υ_{max} in cm^{-1}: 1762 (C═O), 1625 (C⇿C of aromatic ring), 1584 (C═N), 1318 (C–N), 726 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.35 (s, 1H, NH exchangeable with D_2O), 6.62–7.56 (m, 9H, Ar-H), 5.83 (s, 1H, CH-Ar), 6.46 (d, 1H, $J = 6.5$ Hz, CHCl), 3.69 (d, 2H, $J = 9.1$ Hz, CH_2NH), 1.15 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 489.01. *Anal*. Calc. for $C_{28}H_{29}ClN_4O_2$: C, 78.77; H, 5.98; N, 11.46. Found: C, 78.69; H, 5.86; N, 11.52%.

*6.1.7.7. 3-Amantadinyl-6-bromo-2-[((3,4-dimethoxyphenyl)-3-chloro-2-oxo–azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7g**)*. Yield 55% (Methanol): m.p. 159 °C; IR (KBr) υ_{max} in cm^{-1}: 1726 (C═O), 1635 (C⇿C of aromatic ring), 1575 (C═N), 1323 (C–N), 1226 (OCH_3), 728 (C–Cl), 627 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.44 (s, 1H, NH exchangeable with D_2O), 6.42–7.46 (m, 6H, Ar-H), 5.77 (s, 1H, CH-Ar), 6.43 (d, 1H, $J = 6.5$ Hz, CHCl), 3.73 (d, 2H, $J = 9.1$ Hz, CH_2NH), 3.32 (s, 6H, $2 \times OCH_3$), 1.32 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 627.96. *Anal*. Calc. for $C_{30}H_{32}BrClN_4O_4$: C, 57.38; H, 5.14; N, 8.92. Found: C, 57.35; H, 5.15; N, 8.91%.

*6.1.7.8. 3-Amantadinyl-6-bromo-2-[((2-chlorophenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7h**)*. Yield 54% (Acetone): m.p. 155 °C; IR (KBr) υ_{max} in cm^{-1}: 1723 (C═O), 1614 (C⇿C of aromatic ring), 1582 (C═N), 1316 (C–N), 725 (C–Cl), 623 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.38 (s, 1H, NH exchangeable with D_2O), 6.65–7.46 (m, 7H, Ar-H), 5.80 (s, 1H, CH-Ar), 3.72 (d, 2H, $J = 9.1$ Hz, CH_2NH), 6.45 (d, 1H, $J = 6.5$ Hz, CHCl), 1.19 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 602.35. *Anal*. Calc. for $C_{28}H_{27}BrCl_2N_4O_2$: C, 55.83; H, 4.52; N, 9.30. Found: C, 51.82; H, 4.55; N, 8.31%.

*6.1.7.9. 3-Amantadinyl-6-bromo-2-[(2-bromophenyl)-3-chloro-2-oxo-azetidin-3-ylmethylamino]-quinazolin-4(3H)-one (**7i**)*. Yield 58% (Ethanol): m.p. 149 °C; IR (KBr) υ_{max} in cm^{-1}: 1766 (C═O), 1627 (C⇿C of aromatic ring), 1582 (C═N), 1312 (C–N), 728 (C–Cl), 614 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.37 (s, 1H, NH exchangeable with D_2O), 6.67–7.69 (m, 7H, Ar-H), 5.79 (s, 1H, CH-Ar), 3.68 (d, 2H, $J = 9.2$ Hz, CH_2NH), 6.48 (d, 1H, $J = 6.4$ Hz, CHCl), 1.18 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 646.80. *Anal*. Calc. for $C_{28}H_{27}Br_2ClN_4O_2$: C, 51.99; H, 4.21; N, 8.66. Found: C, 51.92; H, 4.25; N, 8.65%.

*6.1.7.10. 3-Amantadinyl-6-bromo-2-[((2-methoxyphenyl)-3–chloro-2-oxo-azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7j**)*. Yield 54% (DMF): m.p. 152 °C; IR (KBr) υ_{max} in cm^{-1}: 1761 (C═O), 1626 (C⇿C of aromatic ring), 1583 (C═N), 1314 (C–N), 1228 (OCH_3), 727 (C–Cl), 618 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.36 (s, 1H, NH exchangeable with D_2O), 6.62–7.79 (m, 7H, Ar-H), 5.81 (s, 1H, CH-Ar), 6.52 (d, 1H, $J = 6.5$ Hz, CHCl), 3.72 (d, 2H, $J = 9.1$ Hz, CH_2NH), 3.39 (s, 3H, OCH_3), 1.21 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 597.93. *Anal*. Calc. for $C_{29}H_{30}BrClN_4O_3$: C, 58.25; H, 5.06; N, 9.37. Found: C, 58.22; H, 5.13; N, 9.39%.

*6.1.7.11. 3-Amantadinyl-6-bromo-2-[((4-hydroxy3-methoxyphenyl)-3-chloro-2-oxo-azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7k**)*. Yield 51% (Ethanol): m.p. 147 °C; IR (KBr) υ_{max} in cm^{-1}: 3432 (OH), 1765 (C═O), 1626 (C⇿C of aromatic ring), 1580 (C═N), 1310 (C–N), 1234 (OCH_3), 726 (C–Cl), 614 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 11.20 (s, 1H, OH exchangeable with D_2O), 8.37 (s, 1H, NH exchangeable with D_2O), 6.71–7.72 (m, 6H, Ar-H), 5.78 (s, 1H, CH-Ar), 6.43 (d, 1H, $J = 6.5$ Hz, CHCl), 3.73 (d, 2H, $J = 9.1$ Hz, CH_2NH), 3.41 (s, 3H, OCH_3), 1.27 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 613.93. *Anal*. Calc. for $C_{29}H_{30}BrClN_4O_4$: C, 56.73; H, 4.93; N, 9.13. Found: C, 56.72; H, 4.95; N, 9.23%.

*6.1.7.12. 3-Amantadinyl-6-bromo-2-[((phenyl)3-chloro-2-oxo-azetidin-3-yl)methylamino]-quinazolin-4(3H)-one (**7l**)*. Yield 56% (Methanol): m.p. 152 °C; IR (KBr) υ_{max} in cm^{-1}: 1765 (C═O), 1623 (C⇿C of aromatic ring), 1585 (C═N), 1315 (C–N), 725 (C–Cl), 624 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm: 8.34 (s, 1H, NH exchangeable with D_2O), 6.69–7.73 (m, 8H, Ar-H), 5.81 (s, 1H, CH-Ar), 6.42 (d, 1H, $J = 6.5$ Hz, CHCl), 3.71 (d, 2H, $J = 9.2$ Hz, CH_2NH), 1.27 (m, 15H, amantadinyl ring). MS: $[M]^+$ at m/z 567.90. *Anal*. Calc. for $C_{28}H_{28}BrClN_4O_2$: C, 59.22; H, 4.97; N, 9.87. Found: C, 59.25; H, 4.95; N, 9.88%.

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