Full Paper

Synthesis and Evaluation of Novel 4-Substituted Styryl Quinazolines as Potential Antimicrobial Agents

Rahul P. Modh[1], Amit C. Patel[2], Dharmesh H. Mahajan[3], Christophe Pannecouque[4], Erik De Clercq[4], and Kishor H. Chikhalia[1]

[1] Department of Chemistry, Gujarat University, Ahmedabad, Gujarat, India
[2] Department of Chemistry, Veer Narmad South Gujarat University, Surat, Gujarat, India
[3] Department of Chemistry, Uka Tarsadia University, Tarsadi, Gujarat, India
[4] Rega Institute for Medical Research, K.U. Leuven, Leuven, Belgium

In an attempt to afford possible antibacterial and anti-human immunodeficiency virus (HIV) agents, a series of 22 novel styryl quinazoline-based heterocyclic entities were designed and synthesized. Various substituted aryl urea and thiourea cores were incorporated at position 4 of quinazoline, followed by styrylation of position 2, aiming at an augmented biological potential. The synthesized compounds were well characterized through IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. All of the prepared compounds were screened for their *in vitro* anti-HIV activity against the HIV-1 (IIIB) and HIV-2 (ROD) strains. The antibacterial activity was also evaluated against various pathogenic Gram-positive and Gram-negative bacterial strains.

Keywords: Antibacterial / Anti-HIV / Aryl thiourea / Aryl urea / Quinazoline / Styryl

Received: July 15, 2012; Revised: August 19, 2012; Accepted: August 21, 2012

DOI 10.1002/ardp.201200291

Introduction

Major challenges over the next few years will be the development of drugs with significantly improved resistance profiles for chronic infections such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [1]. The optimization of the current anti-HIV drug systems and the development of novel drugs are still provoking issues in HIV chemotherapy [2]. An important component of such regimens will be HIV-1-specific non-nucleoside reverse transcriptase inhibitors (NNRTIs) [3]. Representative candidates of this class are structurally diverse, potent, and highly selective anti-HIV agents that were discovered in the early 1990s by virtual library screening followed by biochemical assays to lead optimization. In this context, some quinazoline analogs of MKC-442 and TNK-561 were synthesized and evaluated [4, 5]. Many known heterocyclic compounds were found to be active against HIV-1. One of the most important features of these compounds seems to be the presence of two aromatic systems bridged with one or multiple atom linkers. In this class, phenyl ethyl thiazolyl thiourea (PETT) [6, 7] analogs having various ethyl thioureas or a condensed system of tetrahydro imidazo benzodiazepine-2(1*H*)-one (TIBO) [8, 9] have been shown to significantly inhibit HIV-1 replication, by interfering with the virus reverse transcriptase enzyme at nanomolar concentrations (Fig. 1).

One of the most repeatedly encountered heterocycles in medicinal chemistry is quinazoline because of its broad range of pharmacological activities. As medicines, many of its derivatives display antifungal [10], antimicrobial [11], anti-HIV, and anti-tobacco mosaic virus (TMV) [12, 13], antitubercular [14], anticancer [15], anti-inflammatory [16], anticonvulsant [17], antidepressant [18], hypolipidemic [19], antiulcer [20], analgesic [21], or immunotropic activities [22]. They are also known to act as thymidylate synthase [23], poly(ADP-ribose) polymerase (PARP) [24], and protein tyrosine kinase inhibitors [25]. As pesticides, they are used as insecticides [26] and fungicides [27].

Correspondence: Prof. Kishor H. Chikhalia, Department of Chemistry, School of Sciences, Gujarat University, Navrangpura, Ahmedabad 380-009, Gujarat, India.
E-mail: chikhalia_kh@yahoo.com
Fax: +91 79 26308545

Additional corresponding author: Rahul P. Modh,
E-mail: rahulmodh@gmail.com

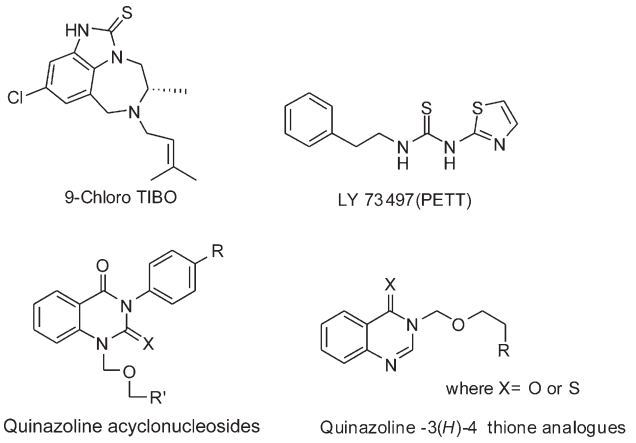


Figure 1. NNRTI derivatives.

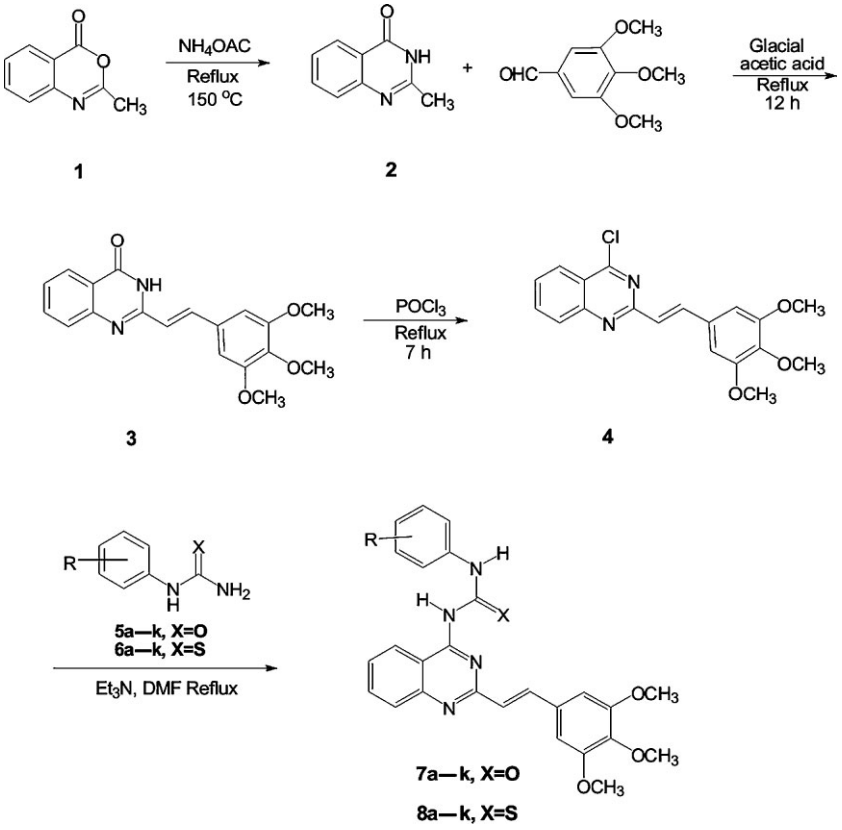
As part of our continuing research program [28–33] in the synthesis of new NNRTIs, we wish to know the key players of effective pharmacophores to obtain higher inhibition of the reverse transcriptase (RT). The target molecule construct contains the quinazoline core linked through a styryl bridge and ureido/thioureido linkages, which we believe to be important key parts to obtain the desired biological response.

Results and discussion

Chemistry

The construction of the quinazoline ring has been extensively described in the literature [34]. The synthesis of the compounds 2-(3,4,5-trimethoxystyryl)-4-(substituted phenyl thioureido/ureido)-quinazoline was accomplished as depicted in Scheme 1. The preparation of the key intermediate 2-methyl quinazoline-4-oxo(3*H*)-benzoxazine (**1**) was achieved as described [35]. The core quinazolinone (**2**) was constructed by fusion addition of ammonium acetate via the precursor 2-methyl quinazoline-4-oxo(3*H*)-benzoxazine (**1**) [36, 37]. Styrylation of 2-methylquinazolin-4(3*H*)-one (**2**) with 3,4,5-trimethoxybenzaldehyde afforded the compound 2-(3,4,5-trimethoxystyryl)-quinazoline-4(3*H*)-one (**3**) [38], which on chlorination with phosphorous oxychloride ($POCl_3$) yielded 2-(3,4,5-trimethoxystyryl)-4-chloro-quinazoline (**4**) [39].

The synthetic pathways employed to achieve compound **4** gave two aromatic systems containing the styryl linker. The chief requirement was to incorporate the ureido and thioureido linkages. To study the quinazoline core connected to the two linkages had already attracted our interest owing to their expected potential biological activities. To the best of our knowledge, only amines [25, 40, 41] have so far been intro-



Scheme 1. Synthesis pathway of the 2-(3,4,5-trimethoxystyryl)-4-(substituted phenyl thioureido/ureido)-quinazolines **7a**–**k** and **8a**–**k**.

duced at position 4 of compound **4**. In this synthetic endeavor, we decided to replace a chloro group with aryl urea (**5a–k**)/thiourea (**6a–k**). We were guided to go for such replacement by the work done for substituted 2,4,6-trichloro *s*-triazine derivatives [42–46] where the third chlorine atom of triazine was replaced by aryl urea/thiourea, assuming their reactivity as a nucleophiles.

Compound **4** was treated with aryl urea **5a–k** and/or thiourea **6a–k** in DMF with a catalytic amount of triethyl amine. The conditions employed in this transformation were found to be considerably effective as the ureido/thioureido group contributed to their weak nucleophilicity. The conversion afforded the title compounds **7a–k** and **8a–k** in moderate to excellent yields.

Anti-HIV activity

The synthesized styryl quinazoline derivatives were evaluated for their anti-HIV activity by determining their ability to inhibit the replication of HIV-1 (III_B) and HIV-2 (ROD) in MT-4 cells in comparison with nevirapine (BIRG587) used as reference drug. The cytotoxicity of the compounds was determined in parallel. The biological evaluation results were interpreted as effective inhibitory concentration (EC_{50}), cytotoxic concentration (CC_{50}), selectivity index (SI, given by the CC_{50}/EC_{50} ratio), and cLog *P* values, which are depicted in Table 1. All the compounds tested for anti-HIV activity failed to show any inhibitory effect on HIV-1 and HIV-2 replication at subtoxic concentrations. In fact, all the compounds proved to be fairly toxic (CC_{50}: 1–4 μg/mL) for the host cells.

Anti-bacterial activity

All the newly synthesized compounds were subjected to *in vitro* antibacterial screening. Compound **7d** with 4-Cl, **7f** with 3-CH_3, and **7g** with 4-CH_3 substitution at the phenyl ureido nucleus exhibited significant antibacterial activity against Gram-positive organisms, while **7c** with 3-Cl displayed moderate inhibition against the *Bacillus subtilis* strain. However growth of *Escherichia coli* was substantially inhibited by compound **7e** with 2-CH_3, **7f** with 3-CH_3, **7h** with 2-OCH_3, and **7i** with 4-OCH_3 substitution, in both Gram-positive and Gram-negative strains. The rest of the compounds showed poor or no activity, even at a concentration of 400 μg/mL. For compounds **8a–k**, with association by aryl thioureido linkage, significant biological response was achieved against *Staphylococcus aureus* (Gram-positive) and *E. coli* (Gram-negative) strains.

Compounds **8e**, **8f**, and **8g** with $-CH_3$ substitution at the phenyl thioureido nucleus exhibited activity at up to 12.5 μg/mL. **8h** with 2-OCH_3 and **8i** with 4-OCH_3 substitution displayed a moderate to good inhibition profile. The remaining compounds were found to be either inactive or only effective at fairly high concentrations (up to 400 μg/mL). The results of the antibacterial assays are summarized in Table 2.

The antibacterial activity results suggest that the attempts to increase the antibacterial activity by introducing substituents at one benzene ring of phenyl urea and phenyl thiourea led to different results, depending on the nature and position of the groups introduced. The antibacterial activity data reveal that electron-donating groups via mesomeric effects (particularly methyl and methoxy) influenced the results towards an enhanced activity. Introduction of an electron-withdrawing group like nitro to the phenyl thioureido and phenyl ureido nucleus furnished compounds with moderate to good activity. The nitro group was found to be not effective in both moieties.

Experimental

Materials and methods

Melting points were recorded on a capillary melting point apparatus and are uncorrected. IR spectra (KBr pellets) in cm^{-1} were recorded on an FT BOMMEN IR spectrophotometer. ^1H NMR spectra were recorded on a Hitachi 300 MHz spectrometer using tetramethyl silane as internal standard (chemical shift in δ ppm). Elemental analyses were carried out on a Heraeus Rapid Analyzer. TLC (silica gel) development was performed on silica gel-coated sheets (Merck Kiesel 60 GF-254, 0.2 mm thickness). All chemicals and solvents were of analytical grade and used as purchased.

*Synthesis of 2-methyl quinazoline-4(3H)-one (**2**)*

A mixture of 2-methyl-4-oxo(3*H*)-benzoxazine (0.1 mol, 16.1 g) and ammonium acetate (0.1 mol, 7.7 g) was refluxed at 150°C for 30 min under nitrogen, cooled to 50°C, and diluted with hot methanol (50.0 mL). The resultant solution was stirred at reflux for 1–2 h, cooled to 25°C, and filtered. The solid was rinsed with methanol and dried. The solid crude was purified by recrystallization from glacial acetic acid. The reaction progress was monitored by TLC using acetone/chloroform (6:4 v/v) as mobile phase. Yield (76%), mp 240–242°C.

*Synthesis of 2-(3,4,5-trimethoxystyryl)-quinazoline-4(3H)-one (**3**)*

A mixture of 2-methyl-quinazoline-4(3*H*)-one (0.1 mol, 16.0 g) and 3,4,5-trimethoxybenzaldehyde (0.1 mol, 19.6 g) in pyridine/DMF (30.0/60.0 mL) was stirred at reflux for 12 h, cooled to 25°C, filtered, and the solid was rinsed with warm methanol and dried. The reaction progress was monitored by TLC using methanol/chloroform (6:4 v/v) as mobile phase. The crude product was purified by recrystallization from absolute alcohol, yielding a white powder (65%), mp 265–268°C.

*Synthesis of 2-(3,4,5-trimethoxystyryl)-4-chloro-quinazoline (**4**)*

A mixture of 2-(3,4,5-trimethoxystyryl)-quinazoline-4(3*H*)-one (0.1 mol, 33.8 g), $POCl_3$ (340 mL), and DMF (0.2 mL) was heated at reflux for 7 h. The excess $POCl_3$ was distilled *in vacuo* and the

Table 1. Anti-HIV-1 and -HIV-2 activity (IC_{50}, in μg/mL) and cytotoxicity of the compounds **7a–k** and **8a–k** in MT-4 cells.

Compound	Strain	EC_{50} (μg/mL)[a]	CC_{50} (μg/mL)[b]	SI[c]	cLog *P*[d]
7a	III_B	>2.13	2.13	<1	4.2619
	ROD	>2.13	2.13	<1	
7b	III_B	>1.69	1.69	<1	4.7173
	ROD	>1.69	1.69	<1	
7c	III_B	>2.08	2.08	<1	5.2773
	ROD	>2.08	2.08	<1	
7d	III_B	>4.97	4.97	<1	5.2773
	ROD	>4.97	4.97	<1	
7e	III_B	>1.89	1.89	<1	4.2009
	ROD	>1.89	1.89	<1	
7f	III_B	>0.96	0.96	<1	4.7609
	ROD	>0.96	0.96	<1	
7g	III_B	>2.75	2.75	<1	4.7609
	ROD	>2.75	2.75	<1	
7h	III_B	>2.03	2.03	<1	4.3645
	ROD	>2.03	2.03	<1	
7i	III_B	>1.88	1.88	<1	4.3645
	ROD	>1.88	1.88	<1	
7j	III_B	>1.17	1.17	<1	4.6529
	ROD	>1.17	1.17	<1	
7k	III_B	>1.72	1.72	<1	4.6529
	ROD	>1.72	1.72	<1	
8a	III_B	>5.66	5.66	<1	4.1123
	ROD	>5.66	5.66	<1	
8b	III_B	>3.85	3.85	<1	4.5677
	ROD	>3.85	3.85	<1	
8c	III_B	>3.25	3.25	<1	5.1277
	ROD	>3.25	3.25	<1	
8d	III_B	>1.73	1.73	<1	5.1277
	ROD	>1.73	1.73	<1	
8e	III_B	>4.05	4.05	<1	4.0513
	ROD	>4.05	4.05	<1	
8f	III_B	>5.46	5.46	<1	4.6113
	ROD	>5.46	5.46	<1	
8g	III_B	>1.70	1.70	<1	4.6113
	ROD	>1.70	1.70	<1	
8h	III_B	>3.42	3.42	<1	4.2149
	ROD	>3.42	3.42	<1	
8i	III_B	>4.43	4.43	<1	4.2149
	ROD	>4.43	4.43	<1	
8j	III_B	>3.07	3.07	<1	4.5033
	ROD	>3.07	3.07	<1	
8k	III_B	>3.87	3.87	<1	4.5033
	ROD	>3.87	3.87	<1	
Nevirapine, BIRG587	III_B	0.00965	>4.00	>415	2.64966
	ROD	0.00965	>4.00		

All data represent mean values for at least two separate experiments.
[a] Concentration required to protect the cells against viral cytopathogenicity by 50% in MT-4 cells.
[b] Concentration that reduces the normal uninfected MT-4 cell viability by 50%.
[c] Selectivity index: ratio CC_{50}/EC_{50}; a higher SI means a more selective compound.
[d] cLog *P* values were calculated by ChemBioDraw 11.0.1 (Cambridge Soft, Cambridge, MA, USA).

residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed several times with cold saturated aqueous Na_2CO_3 and filtered. After evaporation of CH_2Cl_2 *in vacuo*, the final product was separated and further purified by recrystallization from absolute alcohol. This yielded a powder with yellowish color (65%), mp 225–228°C.

*General procedure for the preparation of compounds **7a–k**/**8a–k***

A mixture of 2-(3,4,5-trimethoxystyryl)-4-chloro-quinazoline (0.005 mol) and aryl urea 5**a–k**/aryl thiourea 6**a–k** (0.005 mol) in DMF (50.0 mL) and triethyl amine (2.0 mL) was refluxed on a

Table 2. *In vitro* antibacterial activity (MIC, μg/mL) of compounds **7a–k** and **8a–k**.

Compd. no.	R	MIC (μg/mL)			
		Gram-positive organisms		Gram-negative organisms	
		S. aureus	*B. subtilis*	*E. coli*	*S. typhi*
7a	H	>100	–	50	–
7b	2-Cl	>100	>200	>100	–
7c	3-Cl	50	>100	>200	–
7d	4-Cl	25	50	–	>200
7e	2-CH_3	50	–	25	50
7f	3-CH_3	25	50	25	50
7g	4-CH_3	12.5	25	50	>100
7h	2-OCH_3	50	>100	12.5	25
7i	4-OCH_3	25	50	25	25
7j	3-NO_2	>100	–	>400	>100
7k	4-NO_2	>200	–	>200	>400
8a	H	>100	50	50	–
8b	2-Cl	>100	50	>400	>100
8c	3-Cl	>200	–	>200	50
8d	4-Cl	50	–	>200	50
8e	2-CH_3	12.5	>100	25	>100
8f	3-CH_3	25	50	12.5	50
8g	4-CH_3	50	>100	12.5	50
8h	2-OCH_3	25	50	50	>100
8i	4-OCH_3	25	50	25	>100
8j	3-NO_2	>100	–	>200	–
8k	4-NO_2	>200	>400	>200	>400
Standard drugs	Penicillin	3.12	1.56	6.25	12.5
	Streptomycin	6.25	6.25	10	3.12

heating mantle with stirring for up to 4 h till no starting material was detected by TLC, using the solvent system hexane/ethyl acetate (8:2 v/v). After completion of the reaction, the mass was poured into ice-cold water. The product was filtered and dried. The crude product was purified by recrystallization from absolute alcohol.

*2-(3,4,5-Trimethoxystyryl)-4-(phenyl ureido)-quinazoline (**7a**)*

Yield (59%), mp 129–132°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1622 (C=N str.), 1578 (C=O str. in urea), 3340 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.74 (s, 3H, $-OCH_3$), 3.87 (s, 6H, 2x$-OCH_3$), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.04 (d, 1H, $J = 16$, –CH=CH), 8.84 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.62 (d, 2H, $J = 7$, aromatic), 6.66 (dd, 1H, $J = 7$, 2, Ar–H), 6.76 (dd, 1H, $J = 8$, 2.2, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.12, 56.43, 103.84, 112.74, 115.63, 119.75, 121.62, 124.43, 126.22, 128.86, 129.05, 129.54, 133.43, 133.82, 134.85, 138.46, 149.74, 150.72, 151.90, 169.92, 170.04. MS, *m/z*: $[M+1]^+$ 457.49. Anal. calcd. for $C_{26}H_{24}N_4O_4$: C, 68.41; H, 5.30; N, 12.27. Found C, 68.35; H, 5.29; N, 12.23.

*2-(3,4,5-Trimethoxystyryl)-4-(2-chlorophenyl ureido)-quinazoline (**7b**)*

Yield (64%), mp 152–154°C; IR (KBr) (cm^{-1}): 1733 (C=C str. α, β unsat.), 1621 (C=N str.), 1581 (C=O str. in urea), 3343 (–NH str.), 1542 (–NH def.), 812 (C–O–C assym.), 1241 (C–O–C sym.), 728 (C–Cl str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.73 (s, 3H, -OCH_3), 3.86 (s, 6H, 2x$-OCH_3$), 6.57 (d, 1H, $J = 16$, –CH=CH), 8.00 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.62 (d, 2H, $J = 7$, aromatic), 6.67 (dd, $J = 7.11$, 2.09, 1H, Ar–H), 6.74 (dd, 1H, $J = 8.03$, 2.12, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.14, 56.40, 103.82, 112.72, 115.60, 119.72, 123.01, 125.80, 126.20, 128.83, 129.02, 129.53, 130.50, 133.40, 133.80, 134.83, 138.43, 149.72, 150.70, 151.93, 169.93, 170.02. MS, *m/z*: $[M+1]^+$ 491.14. Anal. calcd. for $C_{26}H_{23}N_4O_4Cl$: C, 63.61; H, 4.72; N, 11.41. Found C, 63.54; H, 4.70; N, 11.37.

*2-(3,4,5-Trimethoxystyryl)-4-(3-chlorophenyl ureido)-quinazoline (**7c**)*

Yield (69%), mp 172–175°C; IR (KBr) (cm^{-1}): 1734 (C=C str. α, β unsat.), 1622 (C=N str.), 1574 (C=O str. in urea), 3341 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.), 732 (C–Cl str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.74 (s, 3H, $-OCH_3$), 3.88 (s, 6H, 2x$-OCH_3$), 6.56 (d, 1H, $J = 16$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 7.18$, 2.21, Ar–H), 6.75 (dd, 1H, $J = 8.11$, 2.09,Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.11, 56.44, 103.83, 112.73, 115.60, 119.73, 122.02, 124.43, 126.24, 128.83, 129.52, 130.42, 133.45, 133.80, 134.52, 137.22, 138.43, 149.73, 150.75, 151.91, 169.94, 170.00. MS, *m/z*: $[M+1]^+$ 491.14. Anal. calcd. for $C_{26}H_{23}N_4O_4Cl$: C, 63.61; H, 4.72; N, 11.41. Found C, 63.59; H, 4.74; N, 11.39.

*2-(3,4,5-Trimethoxystyryl)-4-(4-chlorophenyl ureido)-quinazoline (**7d**)*

Yield (73%), mp 158–160°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1620 (C=N str.), 1572 (C=O str. in urea), 3343 (–NH str.), 1547 (–NH def.), 813 (C–O–C assym.), 1242 (C–O–C sym.), 724 (C–Cl str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.75 (s, 3H, $-OCH_3$), 3.86 (s, 6H, 2x–OCH_3), 6.54 (d, 1H, $J = 15$, –CH=CH), 8.03 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.63 (d, 2H, $J = 7$, aromatic), 6.69 (dd, 1H, $J = 7.32$, 2.18, Ar–H), 6.74 (dd, 1H, $J = 8.34$, 2.12, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.10, 56.40, 103.82, 112.72, 115.62, 119.70, 124.40, 126.20, 128.83, 129.52, 130.40, 133.42, 133.80, 134.52, 138.44, 149.71, 150.75, 151.93, 169.90, 170.02. MS, *m/z*: $[M+1]^+$ 491.14. Anal. calcd. for $C_{26}H_{23}N_4O_4Cl$: C, 63.61; H, 4.72; N, 11.41. Found C, 63.58; H, 4.69; N, 11.36.

*2-(3,4,5-Trimethoxystyryl)-4-(2-methyl phenyl ureido)-quinazoline (**7e**)*

Yield (65%), mp 139–142°C; IR (KBr) (cm^{-1}): 1733 (C=C str. α, β unsat.), 1622 (C=N str.), 1578 (C=O str. in urea), 3340 (–NH str.), 1543 (–NH def.), 811 (C–O–C assym.), 1243 (C–O–C sym.), 1390 (C–CH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.46 (s, 3H, Ar–CH_3), 3.74 (s, 3H, $-OCH_3$), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 14$, –CH=CH), 8.02 (d, 1H, $J = 15$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 7.25$, 2.31, Ar–H), 6.74 (dd, 1H, $J = 8.29$, 2.35, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 18.8, 56.10, 56.42, 103.82, 112.75, 115.61, 119.75, 121.52, 124.43, 126.04, 126.22, 128.82, 129.25, 129.52, 133.41, 133.85, 134.35, 134.71, 138.42, 149.73, 150.72, 151.92, 169.92, 170.04. MS, *m/z*: $[M+1]^+$ 471.20. Anal. calcd. for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91. Found C, 68.95; H, 5.59; N, 11.89.

*2-(3,4,5-Trimethoxystyryl)-4-(3-methyl phenyl ureido)-quinazoline (**7f**)*

Yield (64%), mp 188–190°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1620 (C=N str.), 1583 (C=O str. in urea), 3343 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.), 1394 (C–CH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.42 (s, 3H, Ar–CH_3), 3.76 (s, 3H, $-OCH_3$), 3.86 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.04 (d, 1H, $J = 16$, –CH=CH), 8.84 (s, 1H, –NH), 9.41 (s, 1H, –NH), 6.63 (d, 2H, $J = 7$, aromatic), 6.66 (dd, 1H, $J = 7.45$, 2.34, Ar–H), 6.77 (dd, 1H, $J = 8.39$, 2.19, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 24.32, 56.15, 56.43, 103.82, 112.72, 115.60, 118.62, 119.73, 121.32, 124.63, 126.22, 128.82, 128.94, 129.55, 133.43, 133.82, 135.72, 138.46, 138.63, 149.72, 150.74, 151.94, 169.92, 170.02. MS, *m/z*: $[M+1]^+$ 471.20. Anal. calcd. for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91. Found C, 68.85; H, 5.54; N, 11.87.

*2-(3,4,5-Trimethoxystyryl)-4-(4-methyl phenyl ureido)-quinazoline (**7g**)*

Yield (70%), mp 172–175°C; IR (KBr) (cm^{-1}): 1734 (C=C str. α, β unsat.), 1623 (C=N str.), 1579 (C=O str. in urea), 3341 (–NH str.), 1543 (–NH def.), 812 (C–O–C assym.), 1241 (C–O–C sym.), 1388 (C–CH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.44 (s, 3H, Ar–CH_3), 3.74 (s, 3H, $-OCH_3$), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 7.45$, 2.35, Ar–H), 6.74 (dd, 1H, $J = 8.47$, 2.26, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 24.30, 56.12, 56.42, 103.80, 112.70, 115.62, 119.73, 121.52, 126.22, 128.80, 129.22, 129.52, 132.83, 133.43, 133.82, 134.02, 138.43, 149.72, 150.72, 151.90, 169.90, 170.00. MS, *m/z*: $[M+1]^+$ 471.20. Anal. calcd. for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91. Found C, 68.87; H, 5.58; N, 11.86.

*2-(3,4,5-Trimethoxystyryl)-4-(2-methoxyphenyl ureido)-quinazoline (**7h**)*

Yield (62%), mp 152–155°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1622 (C=N str.), 1573 (C=O str. in urea), 3342 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.76 (s, 3H, $-OCH_3$), 3.87 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 14$, –CH=CH), 8.01 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.43 (s, 1H, –NH), 6.63 (d, 2H, $J = 7$, aromatic), 6.70 (dd, 1H, $J = 7.55$, 2.39, Ar–H), 6.73 (dd, 1H, $J = 8.38$, 2.52, Ar–H), 7.22–7.84 (m, 6H, Ar–H), 3.69 (s, 3H, Ar–OCH_3). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 55.82, 56.12, 56.43, 103.82, 112.72, 114.52, 115.63, 119.72, 121.32, 122.63, 124.23, 125.40, 126.22, 128.82, 129.52, 133.43, 133.82, 138.46, 149.73, 150.72, 151.90, 152.72, 169.92, 170.02. MS, *m/z*: $[M+1]^+$ 486.19. Anal. calcd. for $C_{27}H_{26}N_4O_5$: C, 66.65; H, 5.39; N, 11.52. Found C, 66.55; H, 5.37; N, 11.48.

*2-(3,4,5-Trimethoxystyryl)-4-(4-methoxyphenyl ureido)-quinazoline (**7i**)*

Yield (73%), mp 193–195°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1621 (C=N str.), 1582 (C=O str. in urea), 3340 (–NH str.), 1542 (–NH def.), 813 (C–O–C assym.), 1242 (C–O–C sym.); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.74 (s, 3H, $-OCH_3$), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 7.0$, 2.2, Ar–H), 6.74 (dd, 1H, $J = 8.27$, 2.34, Ar–H), 7.22–7.84 (m, 6H, Ar–H), 3.74 (s, 3H, Ar–OCH_3). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 55.80, 56.10, 56.42, 103.84, 112.74, 114.50, 115.62, 119.72, 122.63, 126.22, 128.12, 128.80, 129.52, 133.40, 133.82, 138.42, 149.70, 150.72, 151.90, 156.22, 169.90, 170.05. MS, *m/z*: $[M+1]^+$ 486.19. Anal. calcd. for $C_{27}H_{26}N_4O_5$: C, 66.65; H, 5.39; N, 11.52. Found C, 66.59; H, 5.41; N, 11.49.

*2-(3,4,5-Trimethoxystyryl)-4-(3-nitrophenyl ureido)-quinazoline (**7j**)*

Yield (62%), mp 164–166°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1620 (C=N str.), 1578 (C=O str. in urea), 3342 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.), 1546 (C–NO_2 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.73 (s, 3H, $-OCH_3$), 3.87 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.03 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.63 (d, 2H, $J = 7$, aromatic), 6.67 (dd, 1H, $J = 7.59$, 2.49, Ar–H), 6.75 (dd, 1H, $J = 8.43$, 2.36, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.12, 56.40, 103.82, 112.72, 114.54, 115.63, 119.53, 119.72, 126.22, 127.73, 128.86, 129.55, 129.94, 133.42, 133.82, 136.72, 138.42, 148.14, 149.74, 150.72, 151.93, 169.92, 170.02. MS, *m/z*: $[M+1]^+$ 502.16. Anal. calcd. for $C_{26}H_{23}N_5O_6$: C, 62.27; H, 4.62; N, 13.97. Found C, 62.20; H, 4.60; N, 13.91.

*2-(3,4,5-Trimethoxystyryl)-4-(4-nitrophenyl ureido)-quinazoline (**7k**)*

Yield (67%), mp 178–181°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1622 (C=N str.), 1579 (C=O str. in urea), 3340 (–NH str.), 1542 (–NH def.), 813 (C–O–C assym.), 1241 (C–O–C sym.), 1542 ($C–NO_2$ str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 3.77 (s, 3H, $–OCH_3$), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 7.50$, 2.42, Ar–H), 6.74 (dd, 1H, $J = 8.38$, 2.46, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.10, 56.42, 103.84, 112.72, 115.63, 119.72, 122.52, 124.12, 126.22, 128.83, 129.52, 133.42, 133.82, 138.42, 141.93, 143.52, 149.74, 150.72, 151.92, 169.94, 170.00. MS, *m/z*: $[M+1]^+$ 502.16. Anal. calcd. for $C_{26}H_{23}N_5O_6$: C, 62.27; H, 4.62; N, 13.97. Found C, 62.19; H, 4.61; N, 13.94.

*2-(3,4,5-Trimethoxystyryl)-4-(phenyl thioureido)-quinazoline (**8a**)*

Yield (74%), mp 122–125°C; IR (KBr) (cm^{-1}): 1730 (C=C str. α, β unsat.), 1620 (C=N str.), 1545 (C=S str. in thiourea), 3340 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 3.74 (s, 3H, $–OCH_3$), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 9.62$, 3.43, Ar–H), 6.74 (dd, 1H, $J = 8.49$, 2.90, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.12, 56.45, 103.82, 112.72, 115.63, 119.72, 124.82, 126.22, 126.54, 128.83, 129.12, 129.52, 133.42, 133.82, 137.02, 138.42, 149.74, 150.72, 169.94, 170.00, 179.82. MS, *m/z*: $[M+1]^+$ 473.16. Anal. calcd. for $C_{20}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86. Found: C, 65.95; H, 5.09; N, 11.81.

*2-(3,4,5-Trimethoxystyryl)-4-(2-chlorophenyl thioureido)-quinazoline (**8b**)*

Yield (68%), mp 148–151°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1622 (C=N str.), 1542 (C=S str. in thiourea), 3342 (–NH str.), 1540 (–NH def.), 811 (C–O–C assym.), 1239 (C–O–C sym.), 725 (C–Cl str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 3.72 (s, 3H, $–OCH_3$), 3.87 (s, 6H, 2x–OCH_3), 6.54 (d, 1H, $J = 15$, –CH=CH), 8.00 (d, 1H, $J = 16$, –CH=CH), 8.87 (s, 1H, –NH), 9.43 (s, 1H, –NH), 6.60 (d, 2H, $J = 7$, aromatic), 6.67 (dd, 1H, $J = 9.55$, 3.34, Ar–H), 6.75 (dd, 1H, $J = 8.68$, 2.34, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.13, 56.42, 103.80, 112.74, 115.61, 119.70, 126.22, 127.24, 127.92, 128.80, 129.12, 129.52, 133.42, 133.82, 135.41, 136.02, 138.42, 149.71, 150.70, 169.92, 170.02, 179.80. MS, *m/z*: $[M+1]^+$ 507.12. Anal. calcd. for $C_{26}H_{23}N_4O_3SCl$: C, 61.59; H, 4.57; N, 11.05. Found: C, 61.49; H, 4.55; N, 11.00.

*2-(3,4,5-Trimethoxystyryl)-4-(3-chlorophenyl thioureido)-quinazoline (**8c**)*

Yield (58%), mp 198–201°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1621 (C=N str.), 1544 (C=S str. in thiourea), 3341 (–NH str.), 1542 (–NH def.), 813 (C–O–C assym.), 1242 (C–O–C sym.); 722 (C–Cl str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 3.73 (s, 3H, $–OCH_3$), 3.89 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.03 (d, 1H, $J = 16$, –CH=CH), 8.83 (s, 1H, –NH), 9.41 (s, 1H, –NH), 6.63 (d, 2H, $J = 7$, aromatic), 6.66 (dd, 1H, $J = 9.42$, 3.44, Ar–H), 6.75 (dd, 1H, $J = 8.35$, 2.56, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.11, 56.43, 103.82, 112.72, 115.61, 119.72, 124.60, 124.82, 126.22, 126.90, 128.82, 129.50, 130.41, 133.42, 133.82, 134.62, 138.42, 149.71, 150.70, 169.92, 170.02, 179.80. MS, *m/z*: $[M+1]^+$ 507.12. Anal. calcd. for $C_{26}H_{23}N_4O_3SCl$: C, 61.59; H, 4.57; N, 11.05. Found C, 61.53; H, 4.59; N, 11.01.

*2-(3,4,5-Trimethoxystyryl)-4-(4-chlorophenyl thioureido)-quinazoline (**8d**)*

Yield (69%), mp 162–165°C; IR (KBr) (cm^{-1}): 1733 (C=C str. α, β unsat.), 1624 (C=N str.), 1546 (C=S str. in thiourea), 3341 (–NH str.), 1547 (–NH def.), 809 (C–O–C assym.), 1243 (C–O–C sym.); 726 (C–Cl str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 3.76 (s, 3H, $–OCH_3$), 3.86 (s, 6H, 2x–OCH_3), 6.58 (d, 1H, $J = 15$, –CH=CH), 8.03 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.43 (s, 1H, –NH), 6.59 (d, 2H, $J = 7$, aromatic), 6.67 (dd, 1H, $J = 9.72$, 3.4, Ar–H), 6.73 (dd, 1H, $J = 8.42$, 2.54, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.12, 56.42, 103.82, 112.73, 115.63, 119.72, 126.22, 127.94, 128.83, 129.12, 129.50, 130.31, 133.42, 135.12, 138.42, 149.74, 150.72, 169.92, 170.00, 179.82. MS, *m/z*: $[M+1]^+$ 507.12. Anal. calcd. for $C_{26}H_{23}N_4O_3SCl$: C, 61.59; H, 4.57; N, 11.05. Found C, 61.51; H, 4.54; N, 11.02.

*2-(3,4,5-Trimethoxystyryl)-4-(2-methyl phenyl thioureido)-quinazoline (**8e**)*

Yield (70%), mp 185–187°C; IR (KBr) (cm^{-1}): 1734 (C=C str. α, β unsat.), 1622 (C=N str.), 1542 (C=S str. in thiourea), 3343 (–NH str.), 1544 (–NH def.), 813 (C–O–C assym.), 1242 (C–O–C sym.), 1393 ($C–CH_3$ str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 2.42 (s, 3H, Ar–CH_3), 3.73 (s, 3H, $–OCH_3$), 3.85 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.04 (d, 1H, $J = 16$, –CH=CH), 8.83 (s, 1H, –NH), 9.41 (s, 1H, –NH), 6.60 (d, 2H, $J = 7$, aromatic), 6.69 (dd, 1H, $J = 9.68$, 3.46, Ar–H), 6.75 (dd, 1H, $J = 8.88$, 2.69, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 19.82, 56.10, 56.41, 103.82, 112.72, 115.60, 119.72, 124.72, 126.10, 126.22, 126.44, 128.83, 129.32, 129.52, 133.42, 133.82, 138.42, 139.21, 149.74, 150.72, 169.94, 170.00, 179.82. MS, *m/z*: $[M+1]^+$ 487.17. Anal. calcd. for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51. Found C, 66.59; H, 5.36; N, 11.46.

*2-(3,4,5-Trimethoxystyryl)-4-(3-methyl phenyl thioureido)-quinazoline (**8f**)*

Yield (63%), mp 178–181°C; IR (KBr) (cm^{-1}): 1735 (C=C str. α, β unsat.), 1621 (C=N str.), 1544 (C=S str. in thiourea), 3342 (–NH str.), 1545 (–NH def.), 811 (C–O–C assym.), 1241 (C–O–C sym.), 1391 ($C–CH_3$ str. in aromatic ring); ^1H NMR (300 MHz; DMSO-d_6; δ ppm): 2.43 (s, 3H, Ar–CH_3), 3.72 (s, 3H, $–OCH_3$), 3.86 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 9.62$, 3.59, Ar–H), 6.74 (dd, 1H, $J = 8.6$, 3.46, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 24.32, 56.09, 56.39, 103.82, 112.72, 115.60, 119.72, 123.52, 125.01, 126.22, 128.83, 129.02, 129.52, 133.42, 133.82, 136.92, 138.42, 138.70, 149.74, 150.72, 169.89, 170.02, 179.80. MS, *m/z*: $[M+1]^+$ 487.17. Anal. calcd. for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51. Found C, 66.53; H, 5.37; N, 11.49.

*2-(3,4,5-Trimethoxystyryl)-4-(4-methyl phenyl thioureido)-quinazoline (**8g**)*

Yield (72%), mp 196–198°C; IR (KBr) (cm^{-1}): 1733 (C=C str. α, β unsat.), 1622 (C=N str.), 1547 (C=S str. in thiourea), 3340 (–NH str.), 1546 (–NH def.), 810 (C–O–C assym.), 1241 (C–O–C sym.), 1389 (C–CH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.43 (s, 3H, Ar–CH_3), 3.74 (s, 3H, –OCH_3), 3.88 (s, 6H, 2x–OCH_3), 6.53 (d, 1H, $J = 15$, –CH=CH), 8.00 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.43 (s, 1H, –NH), 6.60 (d, 2H, $J = 7$, aromatic), 6.65 (dd, 1H, $J = 9.72, 3.58$, Ar–H), 6.75 (dd, 1H, $J = 8.46, 2.52$, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 24.30, 56.11, 56.41, 103.81, 112.72, 115.62, 119.70, 126.22, 126.41, 128.83, 129.32, 129.50, 133.42, 133.82, 134.01, 134.40, 138.42, 149.68, 150.72, 169.90, 170.00, 179.80. MS, *m/z*: $[M+1]^+$ 487.17. Anal. calcd. for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51. Found C, 66.61; H, 5.35; N, 11.48.

*2-(3,4,5-Trimethoxystyryl)-4-(2-methoxyphenyl thioureido)-quinazoline (**8h**)*

Yield (66%), mp 168–171°C; IR (KBr) (cm^{-1}): 1731 (C=C str. α, β unsat.), 1621 (C=N str.), 1546 (C=S str. in thiourea), 3345 (–NH str.), 1541 (–NH def.), 814 (C–O–C assym.), 1244 (C–O–C sym.), 1251 (C–OCH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.67 (s, 3H, Ar–OCH_3), 3.72 (s, 3H, –OCH_3), 3.89 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 9.4, 3.34$, Ar–H), 6.74 (dd, 1H, $J = 8.85, 2.68$, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 55.81, 56.10, 56.41, 103.80, 112.72, 114.62, 115.60, 119.72, 121.42, 125.41, 125.80, 126.22, 127.51, 128.80, 129.52, 133.42, 133.82, 138.42, 149.70, 150.70, 157.61, 169.92, 170.02, 179.82. MS, *m/z*: $[M+1]^+$ 503.17. Anal. calcd. for $C_{27}H_{26}N_4O_4S$: C, 64.52; H, 5.21; N, 11.15. Found C, 64.44; H, 5.19; N, 11.11.

*2-(3,4,5-Trimethoxystyryl)-4-(4-methoxyphenyl thioureido)-quinazoline (**8i**)*

Yield (73%), mp 192–195°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1622 (C=N str.), 1547 (C=S str. in thiourea), 3343 (–NH str.), 1543 (–NH def.), 812 (C–O–C assym.), 1242 (C–O–C sym.), 1250 (C–OCH_3 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.71 (s, 3H, Ar–OCH_3), 3.74 (s, 3H, –OCH_3), 3.87 (s, 6H, 2x–OCH_3), 6.55 (d, 1H, $J = 15$, –CH=CH), 8.00 (d, 1H, $J = 16$, –CH=CH), 8.85 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.62 (d, 2H, $J = 7$, aromatic), 6.67 (dd, $J = 9.72, 3.6$, 1H, Ar–H), 6.75 (dd, 1H, $J = 8.46, 2.58$, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 55.80, 56.10, 56.40, 103.82, 112.72, 114.62, 115.61, 119.70, 126.20, 127.52, 128.80, 129.32, 129.52, 133.40, 133.83, 138.42, 149.70, 150.71, 156.61, 169.92, 170.02, 179.80. MS, *m/z*: $[M+1]^+$ 503.17. Anal. calcd. for $C_{27}H_{26}N_4O_4S$: C, 64.52; H, 5.21; N, 11.15. Found C, 64.44; H, 5.19; N, 11.13.

*2-(3,4,5-Trimethoxystyryl)-4-(3-nitrophenyl thioureido)-quinazoline (**8j**)*

Yield (70%), mp 212–215°C; IR (KBr) (cm^{-1}): 1733 (C=C str. α, β unsat.), 1621 (C=N str.), 1542 (C=S str. in thiourea), 3340 (–NH str.), 1543 (–NH def.), 811 (C–O–C assym.), 1241 (C–O–C sym.), 1542 (C–NO_2 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.70 (s, 3H, –OCH_3), 3.85 (s, 6H, 2x–OCH_3), 6.57 (d, 1H, $J = 15$, –CH=CH), 8.03 (d, 1H, $J = 16$, –CH=CH), 8.87 (s, 1H, –NH), 9.44 (s, 1H, –NH), 6.60 (d, 2H, $J = 7$, aromatic), 6.67 (dd, 1H, $J = 9.69, 3.46$, Ar–H), 6.73 (dd, 1H, $J = 8.38, 2.46$, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.11, 56.42, 103.82, 112.73, 115.61, 119.40, 119.71, 119.92, 126.20, 128.80, 129.52, 130.02, 132.60, 133.41, 133.82, 137.92, 138.42, 148.22, 149.70, 150.71, 169.92, 170.02, 179.80. MS, *m/z*: $[M+1]^+$ 518.14. Anal. calcd. for $C_{26}H_{23}N_5O_5S$: C, 60.34; H, 4.48; N, 13.53. Found C, 60.25; H, 4.46; N, 13.49.

*2-(3,4,5-Trimethoxystyryl)-4-(4-nitrophenyl thioureido)-quinazoline (**8k**)*

Yield (68%), mp 229–233°C; IR (KBr) (cm^{-1}): 1732 (C=C str. α, β unsat.), 1620 (C=N str.), 1545 (C=S str. in thiourea), 3342 (–NH str.), 1545 (–NH def.), 810 (C–O–C assym.), 1240 (C–O–C sym.), 1540 (C–NO_2 str. in aromatic ring); ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 3.73 (s, 3H, –OCH_3), 3.88 (s, 6H, 2x–OCH_3), 6.56 (d, 1H, $J = 15$, –CH=CH), 8.02 (d, 1H, $J = 16$, –CH=CH), 8.86 (s, 1H, –NH), 9.42 (s, 1H, –NH), 6.61 (d, 2H, $J = 7$, aromatic), 6.68 (dd, 1H, $J = 9.59, 3.68$, Ar–H), 6.74 (dd, 1H, $J = 8.52, 2.38$, Ar–H), 7.22–7.84 (m, 6H, Ar–H). ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 56.10, 56.40, 103.80, 112.71, 115.62, 119.71, 124.20, 126.22, 127.41, 128.80, 129.50, 133.40, 133.82, 138.42, 143.12, 143.90, 149.70, 150.71, 169.91, 170.04, 179.82. MS, *m/z*: $[M+1]^+$ 518.14. Anal. calcd. for $C_{26}H_{23}N_5O_5S$: C, 60.34; H, 4.48; N, 13.53. Found C, 60.27; H, 4.44; N, 13.49.

In vitro anti-HIV assay

The evaluation of the antiviral activity of all the synthesized compounds against the HIV-1 strain III_B and the HIV-2 strain ROD in MT-4 cells was performed using the MTT assay method as reported previously [33].

In vitro antibacterial activity

Antibacterial activity was investigated *in vitro* against Gram-positive and Gram-negative bacteria. The standard strains used in these tests were: *S. aureus*, *B. subtilis*, *E. coli*, and *Salmonella typhi*. Standard antibacterial agents such as penicillin and streptomycin were also screened under identical conditions, for comparison. The lowest concentration of the substance that prevents the development of visible growth is considered to be the minimum inhibitory concentration (MIC). The MIC values of the compounds were determined by agar streak dilution method [47] and are presented in Table 2.

The authors are grateful to Prof. (Mrs.) Shobhana K. Menon, Head, Department of Chemistry, Gujarat University, Ahmedabad, India, for her kind cooperation in providing support and research facilities. R.P.M. thanks the UGC, New Delhi, for a BSR-Junior Research Fellowship. One of the authors (A.C.P.) would like to thank Dr. S. Chattopadhyay, Head, Bioorganic Division, B.A.R.C. Mumbai, for spectral analysis.

The authors have declared no conflict of interest.

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