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ORIGINAL ARTICLE

Comparative biological study between quinazolinyl–triazinyl semicarbazide and thiosemicarbazide hybrid derivatives

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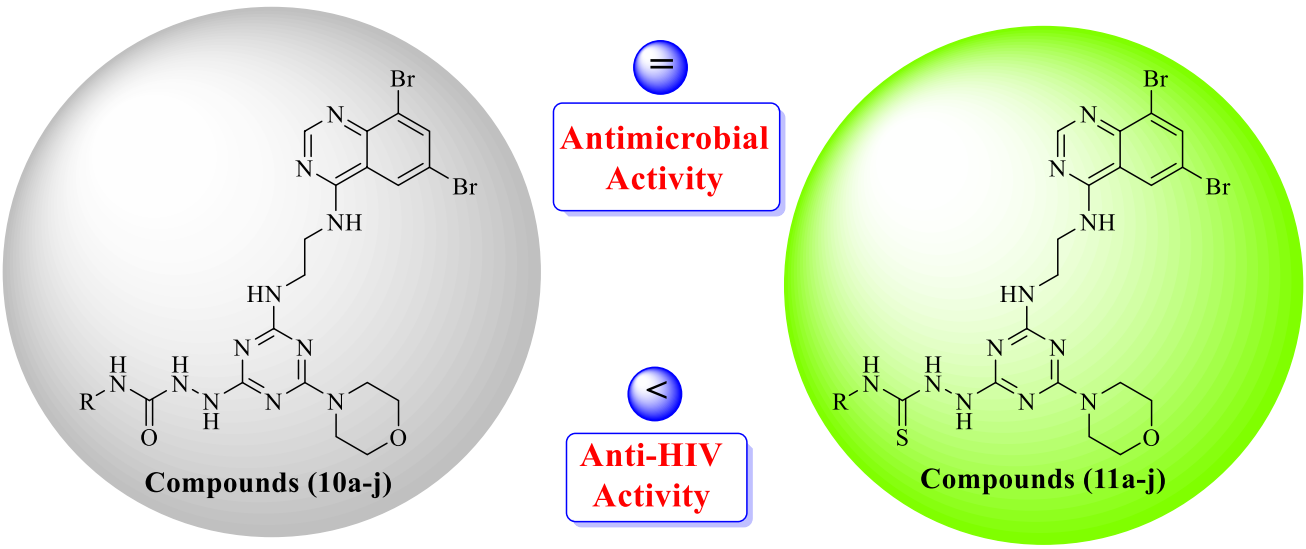
Abstract

Practical synthesis and biological activities of quinazolinyl–triazinyl semicarbazides (**10a–j**) and quinazolinyl–triazinyl thiosemicarbazides (**11a–j**) have been described. The novel semicarbazides and thiosemicarbazides were prepared by condensation of different nucleophiles like isocyanate and isothiocyanate by the displacement of chlorine atoms on the basis of functionality concept on varying conditions. The synthesized quinazolinyl–triazinyl semicarbazide and thiosemicarbazide derivatives were evaluated for their expected antimicrobial activity. All the final synthesized derivatives were characterized by their melting point, mass spectra, ^{1}H NMR and ^{13}C NMR as well as elemental microanalysis. The final analogues were then analyzed for their in vitro antimicrobial activity against bacteria (Gram positive and negative) and fungus using the agar streak dilution method as well as in vitro anti-HIV activity against two types of viral strains, viz. HIV type I (III_B) and type II (ROD) by using MTT assay method. SAR and HOMO–LUMO studies were also carried out for proving the structural biological activity. Among them, compounds **10e**, **10f**, **11h** and **11j** gave best results as their energy gap is very low which makes their activity higher.

Graphical abstract



Keywords Semicarbazides · Thiosemicarbazides · *s*-triazine · Antimicrobial activity · Anti-HIV activity · HOMO–LUMO study

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Extended author information available on the last page of the article

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Introduction

In the present world, the development of the capable and environmental-friendly methods of organic synthesis is one of the main priorities of organic chemists to develop novel heterocyclic compounds in combatting dreadful diseases [1]. Nowadays, both bacterial and fungal infections are serious problem for human as well as for animal body. Thus, researchers have gained advantage from therapeutic substances of synthetic drugs. In contrast, all causative microorganisms have acquired an ability to sustain by developing a great resistance to every synthetic agent administered [2]. In recent times, a number of diseases are being increased by dangerous microorganisms. Therefore, serious research has been made to discover an efficient antimicrobial agent to withstand against these pathogenic microorganisms [3]. Invasive fungal infection has become a growing issue due to the great morbidity and mortality rates in patients who experienced anti-neoplastic chemotherapy, stem cell transplantation and organ transplant or endured human immunodeficiency virus (HIV) infection [4]. Trisubstituted *s*-triazines are one of the oldest classes of organic compounds that continue to be used as important core structure in many chemotherapeutic agents due to their interesting pharmacological properties, including anticancer [5], anti-angiogenesis [6], anti-HIV [7, 8], antimalarial [9] and antimicrobial activities [10, 11]. These compounds have also been used as subunits in the formation of supramolecular structures because they possess good optical and electronic properties and are able to form multiple hydrogen bonds [12]. *s*-Triazine derivatives have also been found to be P13K and mTOR inhibitors as well as efficient corrosion inhibitors for mild steel in acidic solutions [13],

Derivatives of *s*-triazines are found to possess valuable antimicrobial activity against various bacterial and fungal species, and several reported studies by our group have shown our enormous involvement in the discovery of potentially biologically active *s*-triazine derivatives. Chikhalia et al. [14] have designed, synthesized and examined antimicrobial activity of some s-triazine derivatives involving the substitution of 4-hydroxy coumarin (**I**) as well as morpholine (**II**) moieties against various Gram-positive and Gram-negative bacterial and fungal species [15]. Further, Patel et al. [16] explored some triamino-linked triazines (**III**) with remarkable antimicrobial properties. In continuation of our research for novel therapeutically relevant molecules via a suitable structural modification, Patel et al. [17] synthesized some novel s-triazine-based 3,4-dimethoxy phenyl ethyl *s*-triazinyl thioureas analogues (**IV**) and evaluated their anti-HIV activity, and some of the final analogues exhibited excellent IC_{50} level as well as minimum cytotoxicity resulting in derivatives bearing good therapeutic index toward both viral strains HIV-I and HIV-II. In addition, Mahajan et al. [18] further developed 2-(coumarin-4-yloxy)-4,6-(substituted)-*s*-triazine derivatives (**V**) as a potential leading to a novel class of NNRTIs (Fig. 1).

In the consideration of the rising number of application in most recent years, there has been an enormous rise in the attraction among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives. It was recognized that this class of compounds has activity like antibacterial [19], analgesic [20], anticancer [21], antifungal [22], anti-HIV [23], anti-inflammatory [24], antimalarial [25], antioxidant [26], antiviral [27], phosphodiesterase inhibitory agents, sedative–hypnotic agent, and so on. Quinazoline scaffold is a structural backbone for many naturally occurring alkaloids extracted from various plants, animals as well as microorganisms [28]. Chauhan et al. [29] have designed and synthesized a series of new class of hybrid 4-aminoquinoline triazines (**VI**), (**VII**) and screened for their antimalarial activity against CQ (Chloroquine)-sensitive strain 3D7 of *P. falciparum* in an in vitro model and CQ resistance strain N-67 of *P. yoelii* in an in vitro assay. Inspired from these works, we have synthesized quinazoline-based ethylene diamine linkage between *s*-triazine and quinazoline instead of quinoline and checked their antimicrobial and anti-HIV activities (Fig. 2).

From the last five years, the acquired immunodeficiency syndrome (AIDS) has already claimed that 21.7 million people live with HIV and 1.8 million people were newly infected with human immunodeficiency virus (HIV) [30]. Among the NNRTIs (non-nucleoside reverse transcriptase inhibitors), diaryl triazine (DATA) derivatives (Fig. 3) such as **R129385**, **R120393** and **R106168** displayed high potent resistant against wild and NNRTIs have attracted considerable attention over the past few years [31]. In context to the above rationale and in continuation of our ongoing program focused on finding some new leads with anti-HIV activities, a novel hybrid series of DATA molecule with a combination of different pharmacophores such as *s*-triazine, quinazoline, morpholine and thiosemicarbazides have been designed which are structurally related to anti-HIV lead compounds (Fig. 4), i.e., morpholine linked with **DATA-NNRTIs derivatives** [23], **triapine** drug having carbazide moiety and **DPC 961** with quinazoline moiety.

Herein, we synthesized a new class of ethylene diamine-linked quinazoline–triazine–semicarbazide and thiosemicarbazide derivatives starting from the *s*-triazine ring of DATA. Theoretical calculations of DFT at B3LYP level have been carried out to determine the structure–activity relationship.

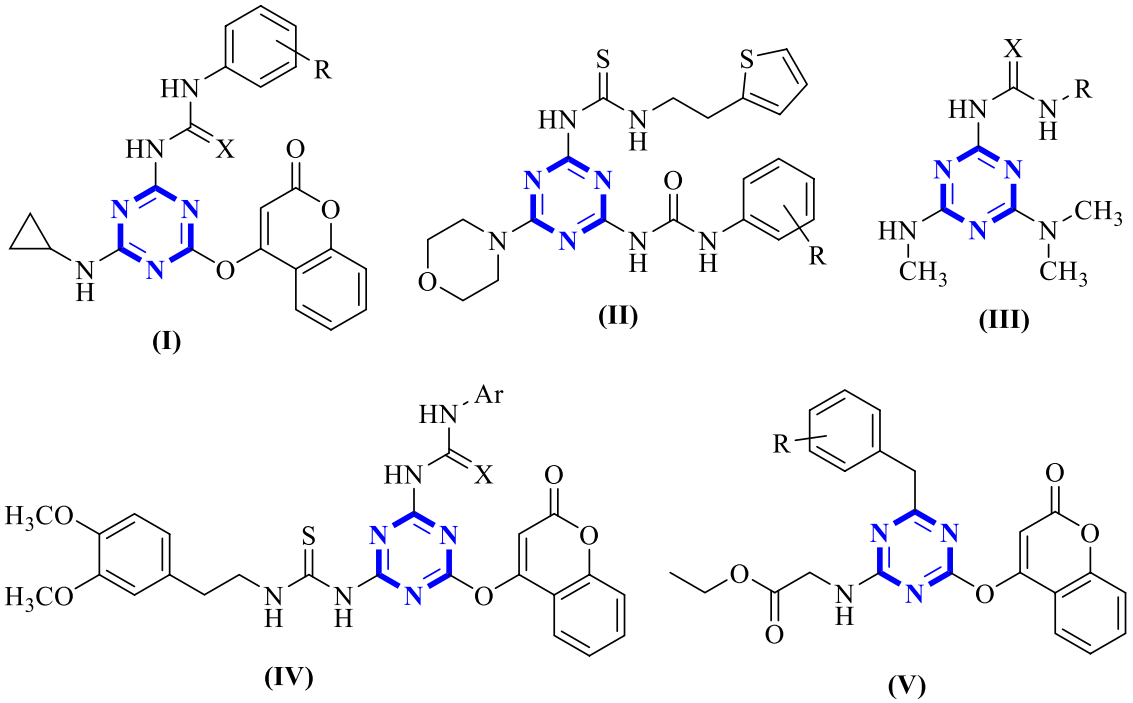


Fig. 1 Our previous work on *s*-triazine moiety

Chemistry

In view of high pharmacological activity profile of quinazoline compounds, we have designed and synthesized this class of compounds. This part deals with the synthesis of novel quinazoline–triazine-based analogues involving semicarbazide and thiosemicarbazide moieties. Different isocyanate and isothiocyanate derivatives were condensed to the hydrazine group to afford semicarbazide and thiosemicarbazide, respectively, which was substituted at the *s*-triazine ring, and the effects of presence/absence of different groups to semicarbazide and thiosemicarbazide on various biological activities of the final analogues have been studied. Based on the synthesized analogues, it was divided into four parts: (Scheme 1).

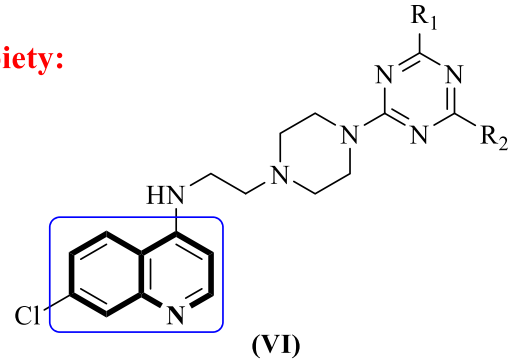
Hence, in the present study, the first step comprises the formation of intermediate **5** in very good yield 80–90%. First of all, in the first part analogues *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine compound **5** were synthesized starting from anthranilic acid **1** via bromination with bromine in glacial acetic acid and refluxed to get compound **2** 3,5-dibromo-2-amino benzoic acid which was further treated with formamide at very high temperature to get compound **3** 6,8-dibromo quinazolin-4(*3H*)-one. Here, in this case formamide acts as a cyclization agent. Compound **3** upon treatment with $POCl_3$ and *N,N′*-dimethylaniline afforded compound **4** 6,8-dibromo-4-chloroquinazoline, which on further treatment with 1,2-diaminoethane gave compound **5** *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine to create the ethylene linkage between final moieties.

In the second part, the generation of triazine analogue 2-(6-chloro-6-hydrazinyl-*s*-triazin-2-yl) morpholine compound **8** was synthesized. Commercially available *s*-triazine compound **6** moiety was condensed with morpholine in the presence of dry acetone at very low temperature (0–5 °C) to get compound **7** 4-(4,6-dichloro-*s*-triazin-2-yl) morpholine which was further treated with hydrazine hydrate in the presence of dry acetone at 35–40 °C temperature to get the final analogue of *s*-triazine 2-(6-chloro-6-hydrazinyl-*s*-triazin-2-yl) morpholine compound **8**.

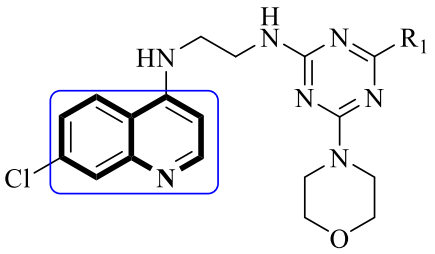
In the third part, the condensation between compound **5** and compound **8** takes place in the presence of acetonitrile at reflux condition to get compound **9** N^1-(6,8-dibromoquinazolin-4-yl)-N^2-(4-hydrazinyl-2-morpholino-*s*-triazin-6-yl) ethane-1,2-diamine which was further divided into two series: In **Series-1** compound **9** was treated with different isocyanates in the presence of ethanol to get the title compounds (**10a–j**) 2-(4-(2-(6,8-dibromoquinazolin-4-yl)amino)

Fig. 2 Ethylene diamine linkage between two different pharmacophores

Previous work on Quinoline moiety:



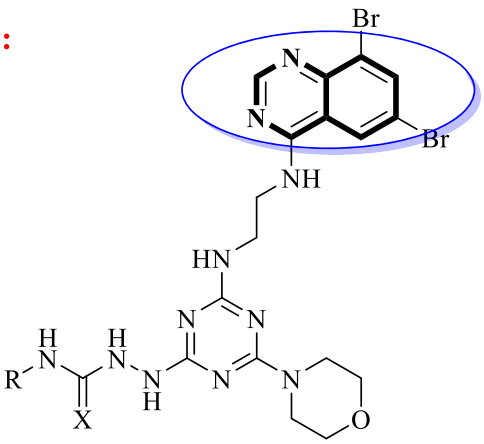
(VI)



(VII)

Where, R_1 & R_2 = Aryl or Alkyl

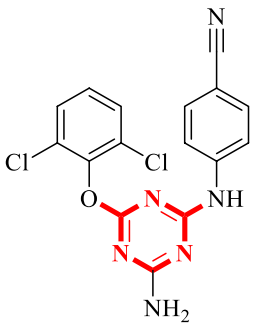
This work on Quinazoline moiety:



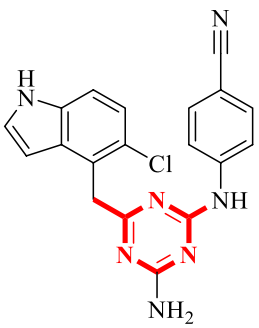
(10a-j) & (11a-j)

Where, X= N or S & R= Aryl or Alkyl

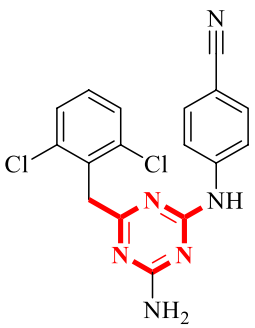
Fig. 3 The structures of some trisubstituted DATA (diaryl triazine) derivatives



R129385



R120393



R106168

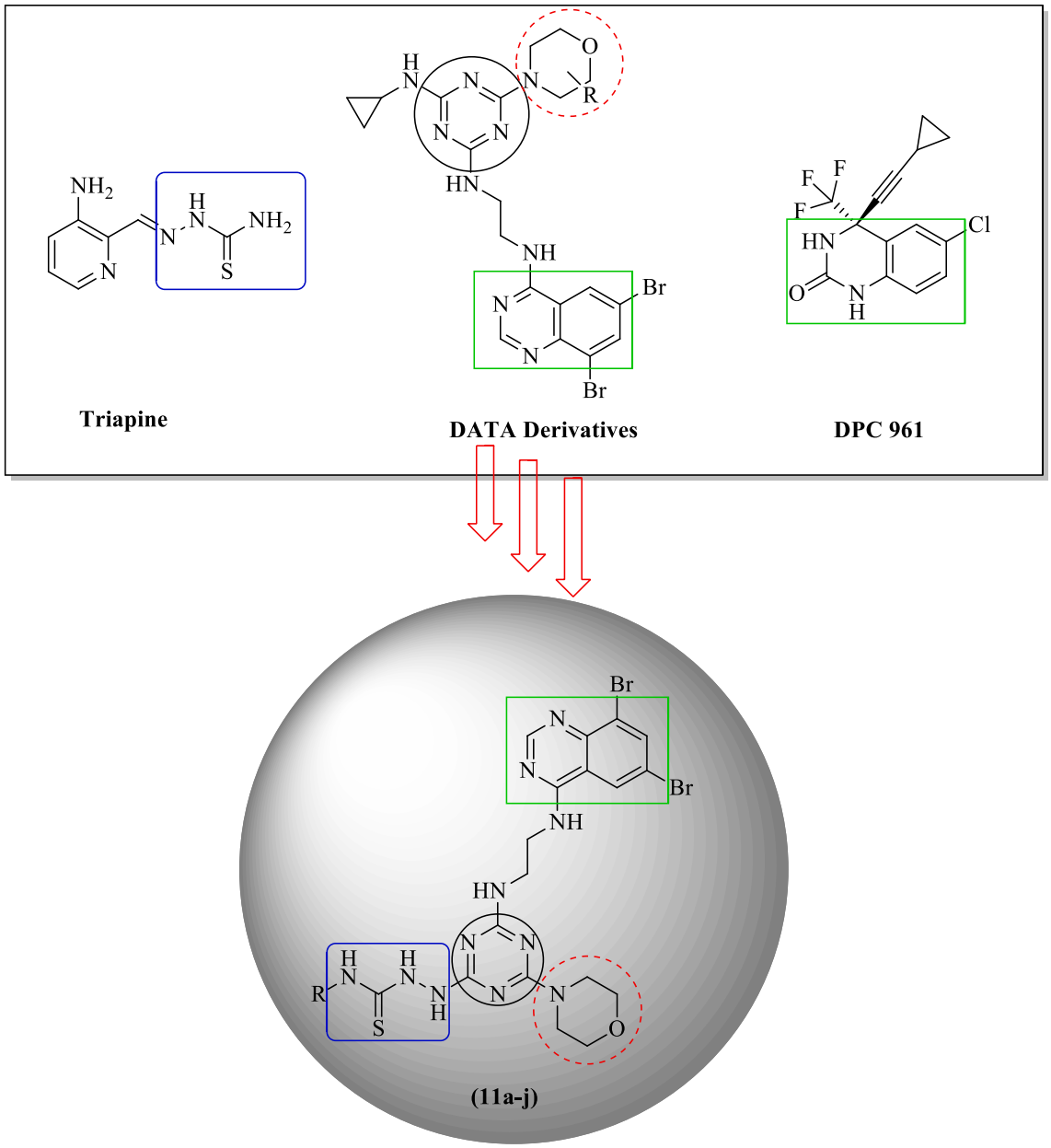
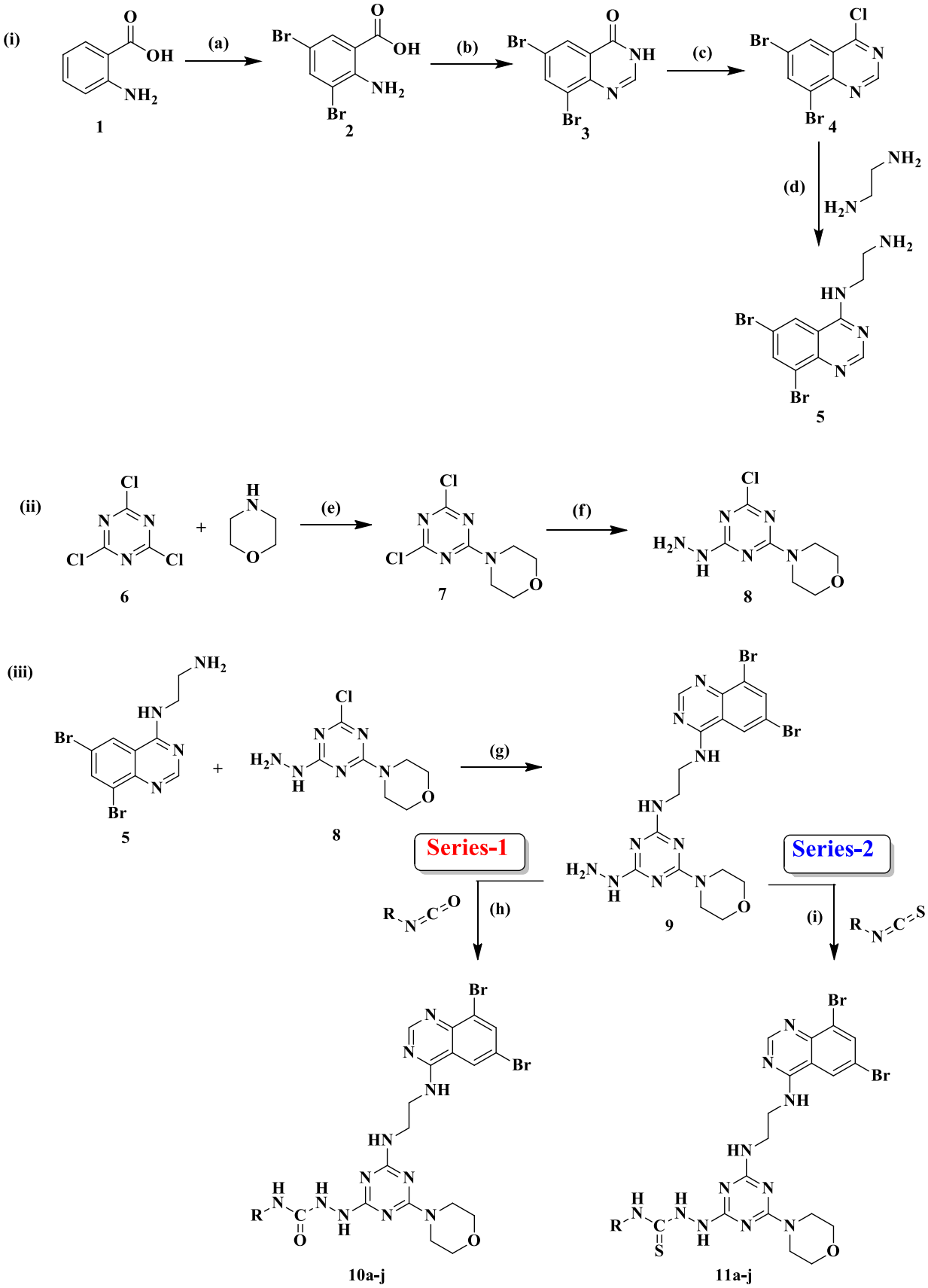


Fig. 4 The design of quinazoline–morpholine–triazine–thiosemicarbazide hybrid derivatives

ethyl) amino)-6-morpholino-*s*-triazine-2-yl)-*N*-substituted hydrazine carboxamides, and in **Series-2**, compound **9** was treated with different isothiocyanates in the presence of ethanol to get the title compounds (**11a**–**j**) 2-(4-(2-(6,8-dibromoquinazolin-4-yl)amino) ethyl) amino)-6-morpholino-*s*-triazin-2-yl)-*N*-substituted hydrazine carbothioamide derivatives.

All the final synthesized derivatives were chemically characterized through melting point, mass spectra, ^{1}H NMR and ^{13}C NMR as well as elemental microanalysis, elucidated in the experimental part. The final analogues were than analyzed for their in vitro antimicrobial activity against bacteria (Gram positive and Gram negative) and fungi using the agar streak dilution method as well as in vitro anti-HIV activity against two types of viral strains viz, HIV type I (III_B) and type II (ROD) using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) assay method. The bioassay results and relative comparison are discussed in the results and discussion part.


(i)
(a)
(b)
(c)
(d)
1
2
3
4
5
(ii)
(e)
(f)
6
7
8
(iii)
(g)
5
8
9
Series-1
Series-2
(h)
(i)
10a-j
11a-j

◂**Scheme 1** Synthetic pathway of compounds (**10a**–**j**) and (**11a**–**j**). Reagents and conditions: (**a**) Br_2, glacial CH_3COOH, 3 h, reflux (**b**) $HCONH_2$, 160 °C, 6 h (**c**) $POCl_3$, *N,N′*-dimethylaniline, 2 h, reflux (**d**) 1,2-diaminoethane, acetonitrile, 8 h, reflux (**e**) morpholine, 0–5 °C, 30 min., acetone (**f**) hydrazine hydrate, acetone, 35–40 °C, 5–6 h (**g**) acetonitrile, 12–20 h (**h**) substituted isocyates, ethanol, 4–6 h (**i**) substituted isothiocyanates, ethanol, 4–6 h

Medicinal chemistry part

In vitro evaluation of antimicrobial activity

In order to study the antimicrobial properties of the novel hybrid quinazolinyl–triazinyl semicarbazide and thiosemicarbazide derivatives, several bacterial (*Staphylococcus aureus* MTCC 96, *Bacillus Cereus* MTCC 430, *Pseudomonas aeniginosa* MTCC 741, *Klebsiella pneumaniae* MTCC 109) and fungal (*Aspergillus clavatus* MTCC 1323 and *Candida albicans* MTCC 183) species were selected and minimum inhibitory concentration (MIC) of the compound was determined by the agar streak dilution method [32]. A stock solution of the tested compound (200 µg/mL) in DMSO was prepared, and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar, i.e., nutrient agar for the evaluation of antibacterial and sabouraud dextrose agar for antifungal activity, respectively. The medium containing the test compound was poured into a petri dish at a depth of 4–5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganisms of approximately 105 CFU/mL was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.125–200 µg/mL in dimethylsulfoxide and incubated at (37 ± 1) °C for 24 h (bacteria) and 48 h (fungi). The lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC values.

In vitro evaluation of anti-HIV assay

The evaluation of the anti-HIV activity of the synthesized compounds against HIV-I strain (III_B) and HIV-II strain (ROD) in MT-4 cells was performed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) assay method as earlier reported [33]. In brief, stock solutions (10 times final concentration) of test compounds were added in 25 µL volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects in mock- and anti-HIV-infected cells at the beginning of each experiment. Serial fivefold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Bechman Instruments, Fullerton, CA). Untreated control HIV- and mock-infected cell samples were included for each sample. HIV-I (III_B) or HIV-II (ROD) stock (50 µL) at 100–300 $CCID_{50}$ (50% Cell Culture infectious dose) for culture medium was added to either the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effects of the test compounds on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells [34] were centrifuged for 5 min at 1000 rpm (220 g), and the supernatant was discarded. The MT-4 cells were resuspended at a final concentration of 6×10^5 cells/mL, and 50 µL volumes were transferred to the microtiter tray wells. After 5 days of incubation at 37 °C following infection, the viability of mock and HIV-infected cells was examined spectrophotometrically by the MTT assay.

The MTT assay is based on the reduction of yellow-colored MTT (Acros Organics, Geel, Belgium) by mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbencies were read in an eight-channel computer-controlled photometer (Safire, Tecan), at two wavelengths (540 and 690 nm). All data were calculated using the median optical density values of three wells. The 50% cytotoxic concentration was defined as the concentration of the test compound that reduced the absorbance (optical density 540) of the mock-infected control sample by 50%. The concentration achieving 50% protection from the cytopathic effect of the virus in infected cells was defined as the 50% effective concentrations. Anti-HIV activity and cytotoxicity of standard drug DDN/DDI were also performed by a similar method in MT-4 cells.

Experimental

Materials and methods

All the chemicals and reagents were of analytical grade of SD Fine-Chem, Aldrich and Merck unless and otherwise specified. All solvents were dried over an appropriate drying agent and purified by standard methods. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. Analytical thin-layer chromatography was performed on Merck precoated aluminum plates 60 F_{254} with a 02 mm layer of silica gel-G, and spots were visualized under UV irradiation. NMR spectra were recorded on a 400 MHz spectrometer (Bruker DRX 400) using DMSO-d_6 as a solvent and TMS as an internal standard, with ^1H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. All ^1H and ^{13}C NMR chemical shifts are quoted in ppm and were calibrated on solvent signals and were conducted at Indian Institute of Science Education and Research, Pune, India. Multiplicities are given as s(singlet), d(doublet), dd(doublet–doublet) t(triplet), q(quartet) and m(multiplet). Elemental analysis (C,

H and N) was performed using a GmbH vario Microcube Elemental Analyzer (Germany).

Synthesis of *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine (compound 5)

This preparation was prepared in the following four steps:

Step-I: Synthesis of 3,5-dibromo-2-amino benzoic acid (compound 2)

A mixture of anthranilic acid compound 1 (50 g, 036 mol) and bromine (27.5 mL, 0.53 mol) in glacial acetic acid (100 mL) was refluxed for 3 h (colorless crystals took place). Progress of the reaction was monitored by TLC using solvent system ethyl acetate/hexane (2:8). After the completion of reaction, it was cooled to 25 °C. Excess of bromine was removed by quenching. The crude product was boiled with distilled water and crystallized from alcohol. Yield 95%; m.p. 234–235 °C.

Step-II: Synthesis of 6,8-dibromo quinazolin-4(*3H*)-one (compound 3)

A mixture of 3,5-dibromo anthranilic acid compound 2 (5.0 g, 0.17 mol) and formamide (15 mL, 0.29 mol) was heated slowly to 160 °C and maintained for 6 h. After the completion of the reaction, the mixture was poured into ice water. Progress of the reaction was monitored by TLC using solvent system ethyl acetate/hexane (2:8). The solid separated was filtered, dried and recrystallized from ethanol to get 6,8-dibromoquinazolin-4(*3H*)-one compound 3. Yield 77%; m.p. 265–267 °C.

Step-III: Synthesis of 6,8-dibromo-4-chloroquinazoline (compound 4)

A mixture of 6,8-dibromoquinazolin-4(*3H*)-one compound 3 (5.0 g, 0.0165 mol) phosphorus oxychloride (10 mL, 0.0348 mol) and *N,N′*-dimethyl aniline (10 mL, 0.0863 mol) was refluxed for 2 h. After the completion of the reaction, the excess $POCl_3$ was removed under reduced pressure; crushed ice (20 g) was added to the reaction mass and neutralized by 1 N NaOH solution. Progress of the reaction was monitored by TLC using solvent system ethyl acetate/hexane (2:8). The separated solid was filtered, dried and crystallized from dichloromethane which afforded 6,8-dibromo-4-chloroquinazoline compound 4. Yield 94%; m.p. 162–163 °C.

Step-IV: Synthesis of *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine (compound 5)

A mixture of 6,8-dibromo-4-chloro quinazoline compound 4 (25 g, 0.0776 mol) and 1,2-diaminoethane (28 g, 25.27 mL, 0.4654 mol, 6 equiv.) was refluxed for 8 h with stirring. After the completion of reaction, it was cooled to room temperature and poured into ice water. Progress of the reaction was monitored by TLC using solvent system ethyl acetate/hexane (4:6). The precipitate formed was filtered, washed with water, dried and crystallized from ethanol which afforded *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine compound 5. Yield 93%; m.p. 128–130 °C.

Synthesis of 2-(6-chloro-6-hydrazinyl-*s*-triazin-2-yl) morpholine (compound 8)

It was prepared into the following two steps:

Step-I: Synthesis of 4-(4,6-dichloro-*s*-triazin-2-yl) morpholine (compound 7)

A mixture of cyanuric chloride compound 6 (25 g, 0.14 mol) in dry acetone (125 mL) was cooled to 0–5 °C, and a solution of morpholine (12.2 g, 0.14 mol) in dry acetone was added dropwise at 0–5 °C within 30 min. The pH was adjusted to neutral by the addition of 10% $NaHCO_3$ solution. After the completion of reaction, it was poured into ice water. Progress of the reaction was monitored by TLC using solvent system toluene/acetone (8:2). The solid was filtered, washed with water, dried and crystallized from chloroform which afforded the product 4-(4,6-dichloro-*s*-triazin-2-yl) morpholine compound 7. Yield 85%; m.p. 150–153 °C.

Step-II: Synthesis of 2-(6-chloro-6-hydrazinyl-*s*-triazin-2-yl) morpholine (compound 8)

A mixture of 4-(4,6-dichloro-*s*-triazin-2-yl)morpholine compound 7(5.0 g, 0.0213 mol) and hydrazine hydrate (0.7 g, 0.0218 mol) in dry acetone (20 mL) was stirred at 35–40 °C for 5–6 h. The pH was adjusted to neutral by 10% K_2CO_3 solution. After the completion of reaction, it was poured into ice water. Progress of the reaction was monitored by TLC using solvent system toluene/acetone (8:2). The solid obtained was filtered, washed with water, dried and recrystallized from chloroform which afforded the 4-(4-chloro-6-hydrazinyl-*s*-triazin-2-yl)morpholine compound 8. Yield 64%; m.p. 203–206 °C.

Condensation between compound 5 and compound 8

Synthesis of N^1-(6,8-dibromoquinazolin-4-yl)-N^2-(4-hydrazinyl-2-morpholino-*s*-triazin-6-yl) ethane-1,2-diamine (compound 9)

A mixture of 4-(4-chloro-6-hydrazinyl-*s*-triazin-2-yl) morpholine compound 8 (1.0 g, 4.34 mol) and *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine compound 5 (1.5 g, 4.34 mol) in dry acetonitrile (10 mL) was refluxed for 12–20 h. The pH was adjusted to neutral by addition of 10% K_2CO_3 solution. After the completion of reaction, it was poured into ice water. Progress of the reaction was monitored by TLC using toluene/acetone (7:3). The product thus obtained was filtered, dried and recrystallized from tetrahydrofuran (THF) which afforded the title compound 9. Yield 72%; m.p. 231–233 °C.

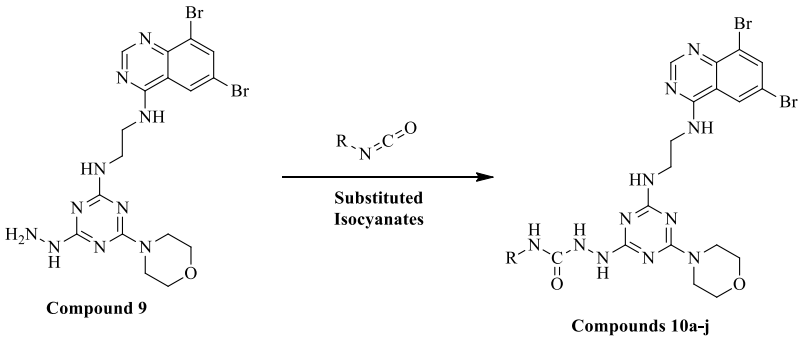
Series-1: General method for the preparation of 2-(4-(2-(6,8-dibromo quinazolin-4-yl) amino)ethylamino)-6-morpholino-1,3,5-triazin-2-yl)-*N*-substituted hydrazine carboxamide (compounds 10a–j)

A mixture of N^1-(6,8-dibromoquinazolin-4-yl)-N^2-(4-hydrazinyl-2-morpholino-*s*-triazin-6-yl) ethane-1,2-diamine compound 9 (1.5 g, 1.85 mol) and substituted isocyanate (1.85 mol) in ethanol (15 mL) was refluxed for 4–6 h. The pH was adjusted to neutral by the addition of 10% K_2CO_3 solution. After the completion of reaction, it was poured into ice water. Progress of the reaction was monitored by TLC using solvent system toluene/acetone (8:2). The product thus obtained was filtered, washed with water, dried and recrystallized from ethanol which afforded the respective compounds (**10a**–**j**).

The physical constant of the synthesized compounds (**10a**–**j**) is tabulated in Table 1.

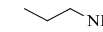
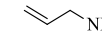
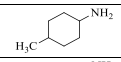
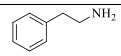
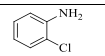
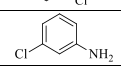
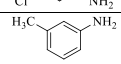
Series-2: General method for the preparation of 2-(4-(2-(6,8-dibromo quinazolin-4-yl) amino)ethylamino)-6-morpholino-1,3,5-triazin-2-yl)-*N*-substituted hydrazine carbothiomide (compounds 11a–j)

A mixture of N^1-(6,8-dibromoquinazolin-4-yl)-N^2-(4-hydrazinyl-2-morpholino-*s*-triazin-6-yl) ethane-1,2-diamine compound 9 (1.5 g, 1.85 mol) and substituted isothiocyanates (1.85 mol) in ethanol (15 mL) was refluxed for 4–6 h. The pH was adjusted to neutral by the addition of 10% K_2CO_3 solution. After the completion of reaction,



Compound 9 — Compounds 10a-j

Table 1 Physical and analytical data of compounds (**10a**–**j**): series-1

Entry	R	Molecular formula	M.W.	% Yield	M.P. (°C)		Elemental analysis		
							% C	% H	% N
10a	S	$C_{20}H_{25}Br_2N_{11}O_2$	611.29	77	238–239	C	39.30	4.12	25.20
						F	39.19	4.13	25.14
10b		$C_{21}H_{27}Br_2N_{11}O_2$	625.32	75	257	C	40.34	4.35	24.64
						F	40.40	4.34	24.58
10c		$C_{21}H_{25}Br_2N_{11}O_2$	623.30	72	268–270	C	40.47	4.04	24.72
						F	40.38	4.05	24.70
10d		$C_{24}H_{31}Br_2N_{11}O_2$	665.38	74	283	C	43.32	4.70	23.16
						F	43.44	4.69	23.11
10e		$C_{24}H_{25}Br_2N_{11}O_2$	659.34	69	269–270	C	43.72	3.82	23.37
						F	43.66	3.83	23.43
10f		$C_{25}H_{33}Br_2N_{11}O_2$	679.41	65	280–282	C	44.20	4.90	22.68
						F	44.07	4.91	22.63
10g		$C_{26}H_{29}Br_2N_{11}O_2$	687.39	73	269	C	45.43	4.25	22.41
						F	45.50	4.24	22.35
10h		$C_{24}H_{24}Br_2ClN_{11}O_2$	693.78	71	290–292	C	41.55	3.49	22.21
						F	41.55	3.50	22.19
10i		$C_{24}H_{24}Br_2ClN_{11}O_2$	693.78	68	252–254	C	41.55	3.49	22.21
						F	41.66	3.48	22.16
10j		$C_{25}H_{27}Br_2N_{11}O_2$	673.36	72	227	C	44.59	4.04	22.88
						F	44.53	4.05	22.94

it was poured into ice water. Progress of the reaction was monitored by TLC using solvent system toluene/acetone (8:2). The product thus obtained was filtered, washed with water, dried and recrystallized from ethanol which afforded the respective compounds (**11a–j**).

The physical constant of the synthesized compounds (**11a–j**) is tabulated in Table 2.

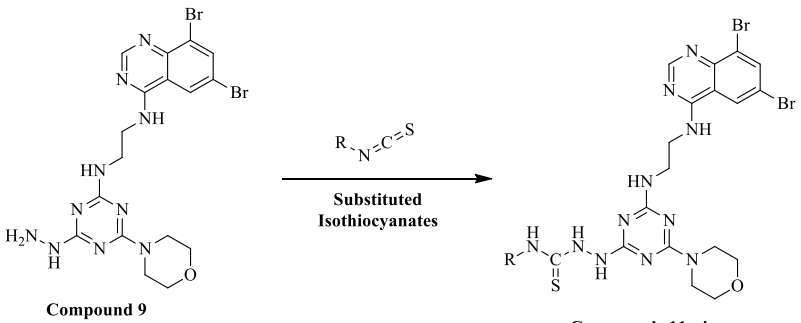
Results and discussion

Structure–activity relationship study

Antimicrobial activity

In vitro antibacterial and antifungal activity of compounds (**10a–j**) and (**11a–j**) are described in Table 3. Out of all 20 compounds, results suggested that alicyclic ring-bearing electron-releasing amino group in the compounds **10f**, **11d** was the most active (MIC 6.25 µg/mL) against Gram-positive *Staphylococcus aureus* strain and Gram-negative *Pseudomonas aeruginosa* strain at 12.5 µg/mL MIC. Compound **10e** bearing aromatic amine and **10h** as well as **10i** containing additional chloro group at ortho and meta position, respectively, endowed with promising antibacterial activity (MIC 12.5 µg/mL). However, these sets of compounds were found comparatively inactive showing MIC varying from 25 to 100, against *Bacillus cereus* strain. **10f** and **10j** compounds with the electron-releasing methyl group at para and meta position of acyclic and aromatic amine ring, respectively, prohibit the growth of *Pseudomonas aeruginosa* Gram-negative strain (MIC 12.5 µg/mL). On the other part, **10a** and **10b** moieties with only alkyl chain amino substitution showed similar efficacy against *Klebsiella pneumoniae* with 12.5 µg/mL MIC, than other aromatic compounds. Furthermore, allylic amino derivatives **11c** and aromatic amine containing electron-withdrawing fluoro in compound **11h** contributed similar efficacy with 12.5 µg/mL MIC value against *Staphylococcus aureus* strain. The result of the compounds exhibited good to moderate activity with 50–100 µg/mL MIC. Among the mentioned set of compounds, compound **11h** and **11i** with electron-snatching fluoro and electron-donating methyl group at para position, respectively, showed the best inhibition profile of 25 µg/mL MIC against *Bacillus cereus* strain whereas remaining were inactive. Compound **11b** with alicyclic, compound **11f** and

Table 2 Physical and analytical data of compounds (**11a–j**): series-2



Compound 9

Compounds 11a-j

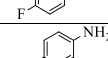
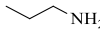
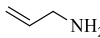
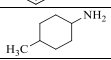
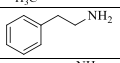
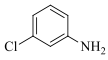
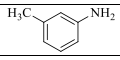
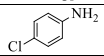
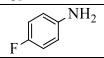
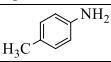
Entry	R	Molecular formula	M.W.	% Yield	M.P. (°C)	Elemental analysis			
							% C	% H	% N
11a		$C_{20}H_{25}Br_2N_{11}OS$	627.36	78	240–242	C	38.29	4.02	24.56
						F	38.20	4.01	24.49
11b		$C_{21}H_{27}Br_2N_{11}OS$	641.39	80	218–219	C	39.32	4.24	24.02
						F	39.22	4.25	24.06
11c		$C_{21}H_{25}Br_2N_{11}OS$	639.37	82	257–258	C	39.45	3.94	24.10
						F	39.51	3.93	24.04
11d		$C_{24}H_{31}Br_2N_{11}OS$	681.45	75	179–181	C	42.30	4.59	22.61
						F	42.43	4.64	22.55
11e		$C_{24}H_{25}Br_2N_{11}OS$	675.40	79	211–212	C	42.68	3.73	22.81
						F	42.75	3.72	22.75
11f		$C_{24}H_{24}Br_2ClN_{11}OS$	709.85	73	278–280	C	40.61	3.41	21.71
						F	40.70	3.40	21.67
11g		$C_{24}H_{24}Br_2ClN_{11}OS$	709.85	79	251–253	C	40.61	3.41	21.71
						F	40.50	3.41	21.65
11h		$C_{24}H_{24}Br_2FN_{11}OS$	693.39	77	250–252	C	41.57	3.49	22.22
						F	41.47	3.50	22.20
11i		$C_{25}H_{27}Br_2N_{11}OS$	689.43	71	278–279	C	43.55	3.95	22.35
						F	43.49	4.03	22.41
11j		$C_{25}H_{27}Br_2N_{11}OS$	689.43	75	256–258	C	43.55	3.95	22.35
						F	43.47	3.89	22.37

Table 3 In vitro antibacterial and antifungal activity in MIC (μg/mL) of compounds (**10a–j**) and (**11a–j**)

Entry	R	Gram +Ve		Gram –Ve		Fungal strains	
		Staphylococcus aureus	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Aspergillus clavatus*	*Candida albicans*
		MTCC 96	MTCC 430	MTCC 741	MTCC 109	MTCC 1323	MTCC 183
10a		100	100	50	12.5	100	100
10b		100	100	100	12.5	100	100
10c		25	50	50	100	100	100
10d		100	50	100	25	50	50
10e		12.5	100	25	100	12.5	25
10f		6.25	100	12.5	100	100	100
10g		100	100	50	100	100	50
10h		12.5	25	100	100	100	100
10i		12.5	25	50	50	50	25
10j		100	100	12.5	100	100	100
11a		100	100	50	100	100	100
11b		100	100	12.5	100	100	100
11c		12.5	50	50	50	100	100
11d		6.25	50	12.5	100	50	50
11e		100	100	25	50	100	100
11f		50	100	12.5	12.5	100	100
11g		100	100	12.5	100	100	50
11h		12.5	25	100	12.5	100	100
11i		50	25	12.5	50	12.5	25
11j		100	100	100	100	100	100
Ciprofloxacin†		3.125	3.125	3.125	3.125	–	–
Ketoconazole†		–	–	–	–	3.125	3.125
DMSO (Control)		–	–	–	–	–	–

**MIC* minimum inhibitory concentration

†*Standard*

11 g with electron-withdrawing chloro group and electron-donating methyl functionalization on compound **11i** showed the lowest MIC value 12.5 μg/mL than other compounds against Gram-negative *Pseudomonas aeruginosa* strain. Halo substituted compounds **11f** and **11h** having chloro and fluoro group, respectively, were endowed with good activity, i.e., MIC 12.5 μg/mL against Gram-negative *Klebsiella pneumonia* bacteria.

In terms of antifungal activity, compound **10e** having substituted aromatic amine moiety showed the best activity against *Aspergillus clavatus* strain with 12.5 μg/mL MIC value which is found to be the highest activity from a set of compounds (**10a–j**). With MIC values ranging from 25 to 100 μg/mL, these compounds tend to be less affective toward *Candida albicans* fungal strain. Compound **11i** with para substituted methyl group existed proper efficacy to inhibit the growth of *Aspergillus clavatus* fungal strain (MIC 12.5 μg/mL). The same compound **11i** also showed the best antifungal activity against *Candida albicans* strain with slight increase MIC 25 μg/mL. Rest of the compounds has effect to a less extent to prevent the mentioned fungal strain growth with MIC value ranging from 50 to 100 μg/mL.

Anti-HIV activity

In this part, ten quinazoline–triazine–semicarbazide derivatives (**10a–j**) and ten quinazoline–triazine–thiosemicarbazide (**11a–j**) derivatives were prepared and evaluated

Table 4 Anti-HIV-1 (III_B) and HIV-2 (ROD) activity[d] (IC_{50} in µg/mL) with cytotoxicity of compounds (**10a–j**) and (**11a–j**) in MT-4 cells

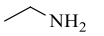
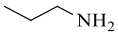
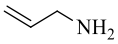
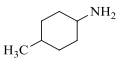
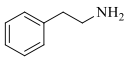
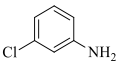
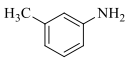
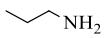
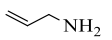
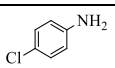
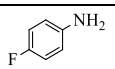
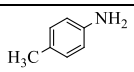
Entry	R	Strains	IC_{50} (µg/mL)[a]	CC_{50} (µg/mL)[b]	SI[C]
10a		III_B	> 106	> 106	< 1
		ROD	> or = 106	> or = 106	< 1
10b		III_B	> 92.7	> 92.7	< 1
		ROD	> or = 92.7	> or = 92.7	< 1
10c		III_B	> 51.98	> 51.98	< 1
		ROD	51.98	51.98	< 1
10d		III_B	> 112.25	> 112.25	< 1
		ROD	112.25	112.25	< 1
10e		III_B	> 33.65	> 33.65	< 1
		ROD	33.65	33.65	< 1
10f		III_B	> 89.5	> 89.5	< 1
		ROD	> or = 89.5	> or = 89.5	< 1
10g		III_B	> 96.2	> 96.2	< 1
		ROD	> or = 96.2	> or = 96.2	< 1
10h		III_B	> 102	> 102	< 1
		ROD	> or = 102	> or = 102	< 1
10i		III_B	> 36.45	> 36.45	< 1
		ROD	36.45	36.45	< 1
10j		III_B	> 106	> 106	< 1
		ROD	106	> 106	< 1
11a		III_B	> 112.95	> 112.95	< 1
		ROD	112.95	112.95	< 1
11b		III_B	> 92.3	> 92.3	< 1
		ROD	> or = 92.3	> or = 92.3	< 1
11c		III_B	> 72.40	> 72.40	< 1
		ROD	72.40	72.40	< 1
11d		III_B	> 69.68	> 69.68	< 1
		ROD	69.68	69.68	< 1
11e		III_B	> 106	> 106	< 1
		ROD	> or = 106	> or = 106	< 1
11f		III_B	> 88.2	> 88.2	< 1
		ROD	> or = 88.2	> or = 88.2	< 1
11g		III_B	> 125	> 125	< 1
		ROD	> 125	> 125	< 1
11h		III_B	> 49.13	> 49.13	< 1
		ROD	49.13	49.13	< 1
11i		III_B	> 70.63	> 70.63	< 1
		ROD	70.63	70.63	< 1
11j		III_B	> 93.8	> 93.8	< 1
		ROD	> or = 93.8	> or = 93.8	< 1
DDN/ DDI	2',3'-Dideoxyinosine	III_B	4.35	> 50	> 12
		ROD	6.96	> 50	> 7
DDN/ DDC	2',3'-Dideoxycytidine	III_B	0.11	0.03	> 180
		ROD	0.11	0.01	> 189
DDN/ AZT	Azidothymidine	III_B	0.0049	0.0074	> 5083
		ROD	0.0061	0.010	> 4115

Table 4 (continued)

[a]Concentration required to protect the cell against viral cytopathogenicity by 50% in MT-4 cells
[b]Concentration that reduces the normal uninfected MT-4 cells viability by 50%
[c]Selectivity index: ratio CC_{50}/IC_{50}, a higher SI means more selective compound
[d]All data represent mean values for at least two separate experiments
Each value is the mean of three independent experiments

for their anti-HIV activity against HIV-1 (III_B) and HIV-2 (ROD) cell cultures. The antiviral screening (HIV-1 and HIV-2) results of the novel synthesized compounds (**10a–j**) and (**11a–j**) are tabulated in Table 4. The results of the antiviral screening reveals that compounds **10a** with ethyl, **10h** with 2-chlorophenyl and **10j** with 3-methylphenyl to semicarbazide were not active as their IC_{50} and CC_{50} values are higher than 100 µg/mL, while compounds **10e** with no substitution and **10i** with 3-chloro at phenyl ring to semicarbazide appeared with IC_{50} 33.65 and 36.45 µg/mL, respectively, which were lowest IC_{50} in this set of compounds against both HIV-1 and HIV-2 viruses. On the other part, from the results it is worth to note that analogue **11h** with fluoro atom at para position to phenyl was only the most potent analogues among all the ten quinazoline–triazine–thiosemicarbazide derivatives studied with 49.13 µg/mL of IC_{50}. Compounds **11a** with ethyl, **11e** with only phenyl and **11g** with 4-chlorophenyl to thiosemicarbazide were not active as their IC_{50} and CC_{50} values are higher than 100 µg/mL (i.e., IC_{50} 112.95, 106 and 125 µg/mL, respectively).

It can be also stated that in all the final analogues among them, compounds (**10a–j**) have not shown selectivity toward any type of the HIV viral strains studied and compounds (**11a–j**) have shown good selectivity toward any type of the HIV viral strains studied. On the basis of SAR studies, it can be concluded that the compounds (**10a–j**) of this series are not active or poorly active because they do not fit into the RT enzyme active site as known in the case of thiosemicarbazide derivatives mentioned in the earlier part. The analogues bearing thiosemicarbazide systems were more active in terms of (IC_{50} µg/Ml) than those involving semicarbazide motifs, with selectivity index below one, which is shown in Fig. 5.

HOMO–LUMO study

To correlate the experimental results, quantum chemical indices such as HOMO (highest occupied molecular orbital) energies, LUMO (lowest unoccupied molecular orbital) energies, HOMO and LUMO energies gap were calculated for compounds **10e**, **10f**, **11h** and **11i** according to the literature methodology [35]. The good agreement reported between this demonstrates the validity of DFT method, which provides a convenient theoretical framework. Results are summarized in Table 5, and the HOMO and LUMO populations are plotted and shown in Fig. 6. Positive and negative phases are represented in red and light green color, respectively. These frontier molecular orbitals (FMO) can afford important insight into chemical properties. They determine the way that how molecule interacts with other species like bacteria and fungi [36]. Thus, the HOMO and LUMO energies are associated, respectively, with the electron-donating and electron-accepting abilities of a

Table 5 Energy gap (LUMO–HOMO) of the compounds (**10e**, **10f**, **11h** and **11i**)

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	Energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$ (eV)
10e	− 5.820	− 1.113	4.707
10f	− 5.895	− 1.240	4.655
11h	− 1.225	− 0.851	0.374
11i	− 1.240	− 0.883	0.357

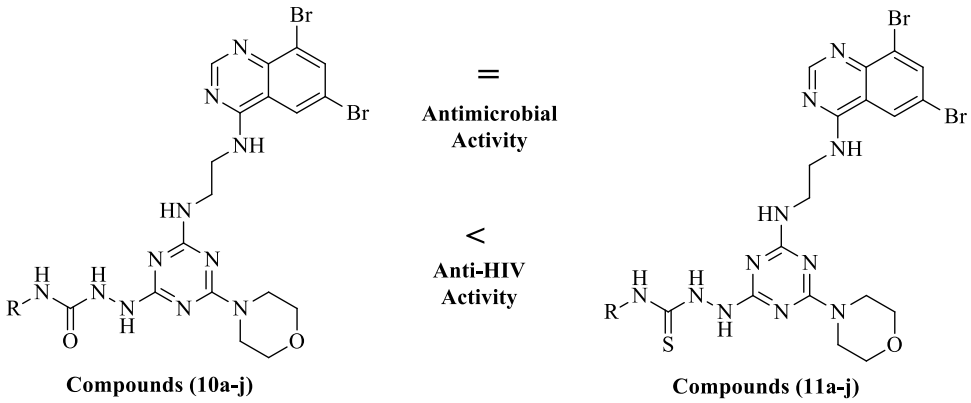


Fig. 5 Comparative SAR study between the final analogues (**10a–j**) and (**11a–j**)

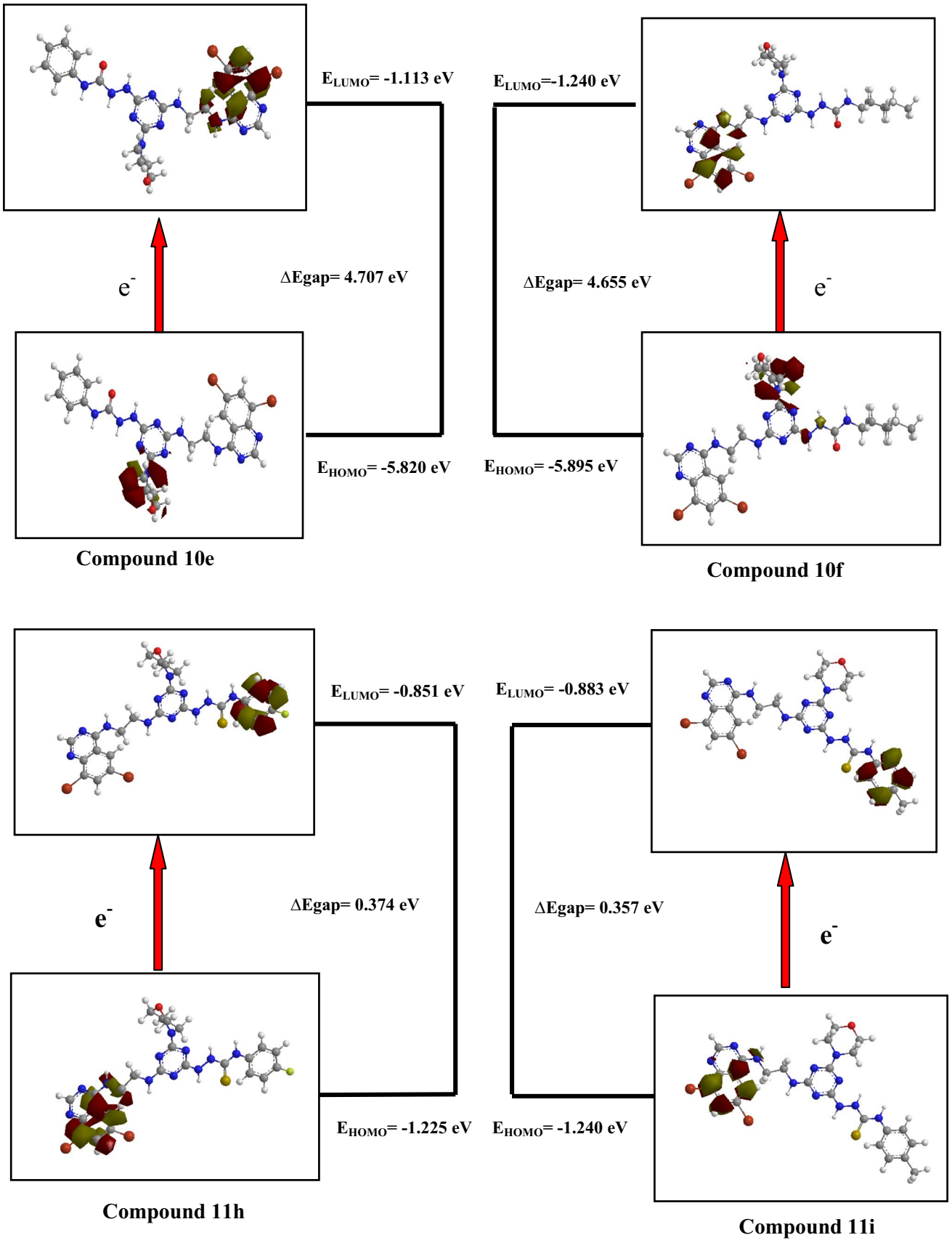


Fig. 6 HOMO-LUMO plot of compounds **10e**, **10f**, **11h** and **11i**

molecule [37]. The calculated HOMO and LUMO energies show that charge transfer occurs within the molecule. Therefore, the high value of HOMO energy indicates a tendency to donate electrons to appropriate acceptor molecules with low energy and empty molecular orbital. Also, the lower value of LUMO energy indicates that this compound would also accept electrons. Several studies reported correlation between HOMO–LUMO energies and antimicrobial activity [38, 39]. This is due to the change in partial charge and to the change in total dipole moment.

In the case of compounds **10e** and **10f**, HOMO is located over the N-atom of morpholine and LUMO is located over quinazoline ring at all C-atoms. So, the HOMO → LUMO transition implies an electron density transfer to the quinazoline ring from the N-atom of morpholine analogue and in the case of **11h** and **11j** compounds HOMO is located over quinazoline and ethylene diamine linkage and LUMO is located over the substituted amine chain of thiosemicarbazide. So, the HOMO → LUMO transition implies an electron density transfer to the substituted thiosemicarbazide's aromatic ring from the quinazoline and ethylene diamine linkage analogues. The energy of the HOMO directly relates to the ionization potential, while the energy of the LUMO directly relates to the electron affinity.

Conclusion

Synthesis, characterization and biological activity of quinazoline–triazine derivatives bearing ethylene diamine linkage endowed with semicarbazides and thiosemicarbazides have been carried out in sequential steps. Out of twenty derivatives screened, compounds **10e** having cyclic ring, **10f** having alicyclic ring, compounds **11d** with acyclic ring bearing electron-releasing amino group, **11h** with cyclic ring bearing electron-withdrawing group fluorine and **11i** with cyclic ring bearing electron-donating methyl group in semicarbazides and thiosemicarbazides, respectively, exhibited promising in vitro antibacterial activity inhibitory effects. Compound **11i** with a para substituted methyl group exhibited good in vitro antifungal activity in thiosemicarbazide derivatives. On the other part, compounds **10a** and **10b** moieties with only alkyl chain amino substitution showed similar efficacy. From the bioassay results presented in these two parts, it can be stated that semicarbazide and thiosemicarbazide motif to the *s*-triazine nucleus showed equipotent activity against both bacterial and fungal strains when compare to each other. In the case of anti-HIV activity compounds **10e** with no substitution and **10i** with 3-chloro at phenyl ring to semicarbazide appeared with the better activity in both, HIV-1 and HIV-2 viral strains. On the other part, compound **11a** with fluoro atom at para position to phenyl of thiosemicarbazide was the most potent analogues. From the results it is worth to note that analogue **11h** with fluoro atom at para position to phenyl was only the most potent analogues among all the ten quinazoline–triazine–thiosemicarbazide derivatives studied with 49.13 μg/mL of IC_{50}. The analogues bearing thiosemicarbazide systems were more active in terms of IC_{50} (μg/mL) than those involving semicarbazide motifs with selectivity index below one. Based on the computational study of DFT calculations of HOMO–LUMO energies gap, it is concluded that lower the value of energy gap the better the biological activity against various strains, i.e., **10e**, **10f**, **11h** and **11j**. Therefore, the lowest energy gap values of **11h** and **11j** (0.374 and 0.357, respectively) compounds reveal that compounds (**11a–j**) having thiosemicarbazide group show best anti-HIV activity compared to compounds (**10a–j**) having semicarbazide group. So, it is worth needed to design more compounds having thiosemicarbazide moiety on another analogues with anticipation of betterment in biological activity profile in the field of medicinal chemistry.

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