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Synthesis, anti-HIV activity, molecular modeling study and QSAR of new designed 2-(2-arylidenehydrazinyl)-4-arylthiazoles

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ABSTRACT

Taking into consideration the eminence of 1,3-thiazoles in medicinal chemistry and in a view of procuring more pronounced biological contour, the synthesis of 2-(2-arylidenehydrazinyl)-4-arylthiazoles **6**–**43** was made possible by the cyclization reaction of thiosemicarbazones and α-bromoacetophenones. The thiosemicarbazones **5a-m** were in turn synthesized from substituted benzaldehydes or acetophenones and thiosemicarbazide. Optimization of the reaction conditions was carried out in order to attain the target molecules in good yields. All the new compounds were evaluated *in vitro* for their antiviral activity against the replication of HIV-1 and HIV-2 in MT4 cells using a MTT assay. Screening results indicated that compounds **32**–**34** are the only compounds in the series inhibiting HIV-1 and HIV-2 replication in cell cultures with IC_{50} of >2.71, >2.19 and > 1.71 μM, respectively. The molecular docking of compounds **32** and **34** with some amino acids of human immunodeficiency virus reverse transcriptase (HIV RT) were also studied. The preliminary quantum structure-activity relationship (QSAR) among the newly synthesized congeners was obtained by two methods, Multiple Linear Regression (MRL) and Genetic Function Approximation (GFA).

1. Introduction

Thiazoles have exhibited a broad spectrum of pharmacological activities as drugs for the treatment of a large number of diseases including viral [1], tumor [2–5], tubercular [6], alzheimer's [7], diabetes [8], leukemia [9], microbial [10], HIV, HCV, HAV and HSV [11,12]. Some of the approved drugs having thiazole backbone are dasatinib (anticancer) [13], ritonavir (anti-HIV-1) [14] (**1**, Fig. 1), nizatidine (anti-ulcer) [15] and fentiazac (anti-inflammatory) [16]. In addition, numerous 1,3-thiazole analogues exhibit remarkable anti-HIV activity [17–19] (*e.g*: **2**, IC_{50} HIV RT = 0.016 nM, Fig. 1) [20], besides many other pharmacological activities such as anti-cancer [21,22], urokinase inhibitors [23], anti-allergic [24], anti-oxidant [25], anti-inflammatory [26], analgesic [27], and anti-convulsant [28]. Thiazole-containing drug molecules are currently being used in the treatment of various central nervous system disorders [29]. Recently, Chimenti et al. [30] reported the synthesis and pharmacological activity of cyclopentylidene-[4-(4′-chlorophenyl)thiazol-2-yl]hydrazine (CPTH2, **3**, Fig. 1) as a selective inhibitor of histone acetyltransferase Gcn5P (HAT), both *in vitro* and *in vivo* (IC_{50} = 0.80 μM). Deregulated HAT and histone deacetylase (HDAC) activity plays a role in the development of a range of cancers. Consequently, inhibitors of these enzymes have potential as anti-cancer agents.

Considering the pharmacological significance of thiazole derivatives and in continuation of our attempts to develop new potent HIV-1 NNRTIs [31–35] herein we report the synthesis of a new series of 2-(2-arylidenehydrazinyl)-4-arylthiazoles and their efficacy as anti-HIV agents together with the quantum structure-activity relationship (QSAR) and molecular docking studies.

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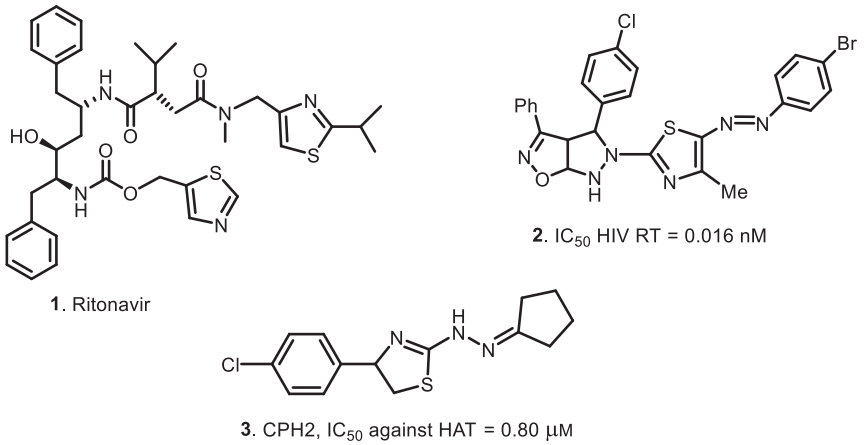


Fig. 1. Some thiazole derivatives as potentially active anti-HIV and anticancer agents.

2. Experimental section

Gallenkamp melting point apparatus MP-D (Northampton, UK) was used for the determination of melting points. The melting points were measured using open capillaries and are uncorrected. The IR spectra were recorded on Thermo Scientific (Waltham, USA) model Nicolet-6700 spectrophotometer and the strongest IR bands are listed. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker (Switzerland), Avance 300 MHz spectrophotometer. All the reactions were monitored using thin layer chromatography (TLC) plates $60F_{254}$ purchased from Merck (Germany), using *n*-hexane: ethyl acetate 3:2 as eluent.

2.1. General procedure for the synthesis of thiosemicarbazones (*5a-m*)

The respective substituted aldehyde or acetophenone (10.00 mol) was dissolved in MeOH (20 mL) followed by addition of 2–3 drops of HOAc as a catalyst. The reaction mixture was stirred under reflux for 15 min. To this solution, equimolar thiosemicarbazide was added and the mixture was heated under reflux for 5–6 h, while the reaction progress was monitored using TLC. The mixture was cooled to ambient temperature, the precipitated product filtered, washed with water followed by MeOH and dried. Recrystallization from MeOH or EtOH afforded the desired thiosemicarbazone.

2.2. General procedure for the synthesis of 2-(2-arylidenehydrazinyl)-4-arylthiazoles (*6–43*)

Phenacyl bromide analogue (1.00 mmol) was dissolved in a mixture of MeOH-EtOH (20 mL) and the solution was stirred with heating at 50–60 °C for 20 min. Equimolar amount of thiosemicarbazone **5a-m** (1.00 mmol) was added, the reaction mixture heated under reflux for 5–6 h and monitored using TLC. After the completion of reaction, the precipitated product was filtered or alternatively the solvent was evaporated to get the crude product. The product was recrystallized from MeOH or EtOH to give the desired product.

3. Biological activity assays

3.1. In vitro anti-HIV assay

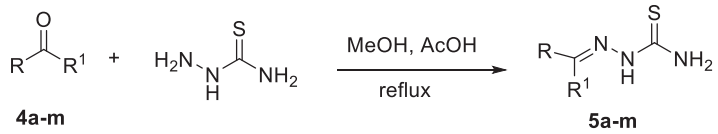
Evaluation of the antiviral activity of **6–43** against HIV-1 strain (III_B) and HIV-2 strain (ROD) in MT-4 cells was performed using an MTT assay as described previously [36]. In brief, stock solutions (10-times final concentration) of test compounds were added in 25-μL volumes to two series of triplicate wells to allow simultaneous evaluation of their effects on mock and HIV-infected cells at the beginning of each experiment. Serial five-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman instruments). Untreated control, HIV- and mock-infected cell samples were included for each sample. HIV-1 (III_B) [37] or HIV-2 (ROD) [38] stock (50 μL) at 100–300 CCID50 (50% cell culture infectious dose) or culture medium was added to either of the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells [39] were centrifuged for 5 min at 1000 rpm (Minifuge T, rotor 2250; Heraeus, Germany), and the supernatant was discarded. The MT-4 cells were resuspended at 6 × 105 cells per mL, and volumes of 50 μL were transferred to the microtiter tray wells. Five days after infection, the viability of the mock- and HIV-infected cells was examined spectrophotometrically.

4. Results and discussion

4.1. Chemistry

The synthesis of 2-(2-arylidenehydrazinyl)-4-arylthiazoles was achieved in two steps by reacting aldehydes/acetophenones with thiosemicarbazide using acetic acid as a catalyst according to a reported procedure [40] to afford thiosemicarbazones **5a-m** (Scheme 1) followed by their treatment with α-bromoacetophenones to result in the synthesis of target molecules, 2-(2-arylidenehydrazinyl)-4-arylthiazoles **6–43** (Scheme 2).

The structures of compounds **5a-m** were ingrained using IR, ^{1}H and ^{13}C NMR spectroscopy. The IR spectra depicted absorption bands in the range of 1507-1450 cm^{-1} assigned to newly formed C=N bond. The N-H stretching absorptions were detected in the region of 3500-3100 cm^{-1}, whereas the absorption bands from 1380 to 1340 cm^{-1} were assigned to C=S functionality. In the ^{1}H NMR spectra of **5a-m**, the singlet in the region δ 7.95–8.42 ppm was assigned to the azomethine proton (-*H*C=N) and affirmed the formation of thiosemicarbazones. The broad singlet in the region δ 10.10–11.71 ppm corresponded to N-H proton, while the two broad singlets in the region δ 7.77–8.43 ppm were ascribed to NH_2 protons. Majority of the target compounds were witnessed to be

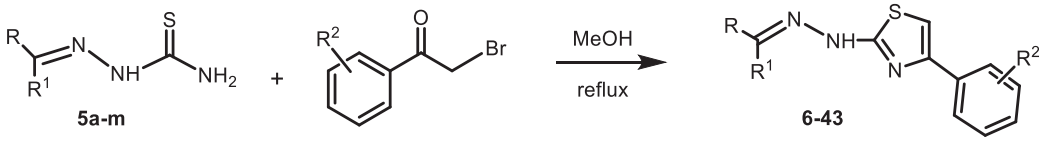


4a-m

5a-m

	R	R^1
4a, 5a	2-OH-C_6H_4	H
4b, 5b	4-OMe-C_6H_4	H
4c, 5c	4-NO_2-C_6H_5	H
4d, 5d	4-Me-C_6H_4	H
4e, 5e	4-Br-biphenyl	CH_3
4f, 5f	4-Imidazolphenyl	CH_3
4g, 5g	3,4-Cl-C_6H_3	CH_3
4h, 5h	3,4-methylenedioxyphenyl	CH_3
4i, 5i	3,4,5-OMe-C_6H_2	CH_3
4j, 5j	2-furyl	H
4k, 5k	2-pyridyl	H
4l, 5l	3-pyridyl	H
4m, 5m	4-pyridyl	CH_3

Scheme 1. Synthesis of thiosemicarbazones (**5a-m**).



5a-m

6-43

	R	R^1	R^2
6	2-OH-C_6H_4	H	4-Br
7	2-OH-C_6H_4	H	4-Cl
8	2-OH-C_6H_4	H	4-CN
9	2-OH-C_6H_4	H	4-NO_2
10	4-OMe-C_6H_4	H	4-Cl
11	4-NO_2-C_6H_4	H	4-CN
12	4-NO_2-C_6H_4	H	4-NO_2
13	4-Me-C_6H_4	H	4-Br
14	4-Br-biphenyl	CH_3	4-Cl
15	4-Br-biphenyl	CH_3	4-NO_2
16	4-Imidazolphenyl	CH_3	4-Br
17	4-Imidazolphenyl	CH_3	4-Cl
18	4-Imidazolphenyl	CH_3	4-CN
19	4-Imidazolphenyl	CH_3	4-NO_2
20	3,4-Cl-C_6H_3	CH_3	4-Br
21	3,4-Cl-C_6H_3	CH_3	4-CN
22	3,4-Cl-C_6H_3	CH_3	4-NO_2
23	3,4-methylenedioxyphenyl	CH_3	4-Br
24	3,4-methylenedioxyphenyl	CH_3	4-Cl
25	3,4-methylenedioxyphenyl	CH_3	4-CN
26	3,4-methylenedioxyphenyl	CH_3	4-NO_2
27	3,4,5-OMe-C_6H_2	CH_3	4-Cl
28	furyl	H	H
29	furyl	H	4-Cl
30	furyl	H	4-CN
31	2-pyridyl	H	H
32	2-pyridyl	H	4-Br
33	2-pyridyl	H	4-Cl
34	2-pyridyl	H	4-CN
35	2-pyridyl	H	4-NO_2
36	3-pyridyl	H	H
37	3-pyridyl	H	4-Br
38	3-pyridyl	H	4-CN
39	3-pyridyl	H	4-NO_2
40	4-pyridyl	H	4-Br
41	4-pyridyl	H	4-Cl
42	4-pyridyl	H	4-CN
43	4-pyridyl	H	4-NO_2

Scheme 2. Synthesis of 2-(2-arylidenehydrazinyl)-4-arylthiazoles (**6**–**43**).

amorphous and were attained in moderate to very good yields (65–90%).

Next, treatment of the thiosemicarbazones **5a-m** with phenacylbromides in MeOH and catalytic amount of HOAc gave 2-(2-arylidenehydrazinyl)-4-arylthiazole analogues **6**–**43** in 64–95% yield (Scheme 2).

The structures of thiazoles **6**–**43** were confirmed from their IR, ^{1}H, and ^{13}C NMR spectra, which showed rather similar patterns of the proton and carbon signals of thiazole scaffold. The IR spectra were characterized by the presence of only one absorption band for NH stretching vibrations in the range 3250–3500 cm^{-1}. The absorption band in the range of 1498–1604 cm^{-1} was attributed to C=N functionality of the thiazole backbone and imine residue, while the absorptions in the range 1591–1638 cm^{-1} was assigned to C=C streching vibrations. In ^{1}H NMR spectra, a singlet in the range δ 6.92–8.15 ppm was assigned to H-5 of the thiazole ring, meanwhile NH proton appeared in the range of δ 10.10–13.00 ppm as a broad singlet. The azomethine (-*HC*=N) proton in compounds **6**–**43** appeared as a singlet in the region of δ 7.39–8.19 ppm. The aromatic and pyridine protons as well as the other substituents have also been fully assigned (*cf.* Experimental section). In the ^{13}C NMR spectra, the low field resonances in the regions δ 166.5–173.8 ppm were assigned to C-2 of the thiazole moiety. C-4 and C-5 of the thiazole backbone resonated in the regions δ 141.9–150.1 and 101.8–110.8 ppm, respectively, while azomethine carbon (HC=N) in compounds **6**–**13** and **14**–**43** resonated in the region δ 135.1–143.4 ppm. The carbon atom of the azomethine group (MeC=N) in thiazoles **14**–**27** appeared in the region δ 170.0–173.8 ppm together with C-2 of the thiazole ring. Compounds **16**–**19** showed resonances in the regions δ 132.2–135.7 and

139.1–141.1 ppm assigned to C-2‴ and C-4‴ of the imidazole moiety, respectively, while C-5‴ of the same group appeared in the region of δ 120.9–121.6 ppm. The carbon atom of 3,4-methylenedioxy (residue (OCH_2O) in compounds **23**–**26** appeared in the region δ 105.5–105.9 ppm. The other substituents and aromatic carbons were also fully analysed (*cf.* Experimental section).

4.2. In vitro anti-HIV activity

Compounds **6**–**43** were evaluated for their inhibitory activity against HIV-1 (strain III_B) and HIV-2 (strain ROD) and monitored by the inhibition of the virus-induced cytopathic effect in the human T-lymphocyte (MT-4) cells, using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [36]. The results are summarized in Table 1, in which the data for nevirapin, (BOE/BIRG587) [41] and azidothymidine (AZT) (DDN/AZT) [42] are included for comparison purpose. Compounds-induced cytotoxicity was also measured in MT-4 cells, parallel with the antiviral activity. Of the title compounds tested, compounds **32** ($IC_{50} > 2.71$ μM), **33** ($IC_{50} > 2.91$ μM), and **34** ($IC_{50} > 1.71$ μM), were found to be the active compounds which inhibited HIV-1 ad HIV-2 replication in cell culture, however, no selectivity was observed ($SI < 1$).

With respect to structure-activity relationship studies, D'Cruz et al. [43,44], and Sudbeck et al. [45] have reported that the molecule containing an intramolecular hydrogen bonding would lock the molecule into a more rigid conformation and impart a more compact molecular shape. The presence of this hydrogen bond is consistent with modeling studies undertaken to predict how the inhibitor could bind to the non-nucleoside inhibitors' (NNI) binding site of HIV RT, as shown in the anti-HIV drug trovidrine [46], PHI236 [44], and our target molecule **34** (Fig. 2). Such compact conformation would allow these molecules to more easily fit into the pocket of the reverse transcriptase binding site. Accordingly, the combined three portions (2-pyridyl moiety, hydrazono group as a spacer, and thiazole scaffold) of compounds **32**–**34** are considered as the optimal substituents that would give rise to the optimal activity. After proceeding with docking studies, it was observed that compounds **34** is well tolerated in the hydrophobic region of HIV RT and showed higher activity than those of **32** and **33** analogues. In conclusion, compound **34** was found to be a potent agent against HIV and identified as a new candidate to act as a NNRTI; it might be considered a promising agent for further structural modifications and pharmacological evaluation.

4.3. Molecular modeling analysis

The molecular docking was performed using the Molecular Operating Environment 2016 (MOE 2016) software and the docking results were also shown by MOE [47]. Molecular docking analysis of the new analogues is based on the modeling study, which was performed to understand the binding mode of these analogues with HIV-RT binding pocket (NNIBP) (PDB ID: 3DLG) [48]. The molecular binding simulation results of the most active compounds in this study, **32** and **34**, with HIV-1 RT are displayed in Fig. 3, panels A and B.

According to the HIV-1 RT docking results, it was observed that compound **32** was able to display one π-cationic interaction between the thiazolyl ring of the molecule and the Leu100 of the active site. Moreover, it was found that compound **34** binds to RT with only one H-bond between its thiazole NH and Lys101. As shown in Fig. 3, the aromatic ring of compound **32** and 2-pyridine ring of compound **34** fitted into an arene-rich subpocket surrounded by the aromatic side chains of Tyr318 and His235 residues. Overall, the combination of hydrophobic interaction and $\pi-$

Table 1
In vitro anti-HIV-1[a] and HIV-2[b] activity of 2-(2-arylidenehydrazinyl)-4-arylthiazoles **6**–**43**.

Compd.	Virus strain	av. IC_{50} (μM)[c]	av. CC_{50} (μM)[d]	SI[e]
6	III_B	>48.70	48.70	<1
	ROD	>48.70	48.70	<1
7	III_B	>101.62	101.62	<1
	ROD	>101.62	101.62	<1
8	III_B	>103.84	103.84	<1
	ROD	>103.84	103.84	<1
9	III_B	>125.00	125.00	<1
	ROD	>125.00	125.00	<1
10	III_B	>125.00	125.00	<1
	ROD	>125.00	125.00	<1
11	III_B	>10.55	10.55	<1
	ROD	>10.55	10.55	<1
12	III_B	>73.58	73.58	<1
	ROD	>73.58	73.58	<1
13	III_B	>125.00	125.00	<1
	ROD	>125.00	125.00	<1
14	III_B	>10.23	10.23	<1
	ROD	>10.23	10.23	<1
15	III_B	>66.15	66.15	<1
	ROD	>66.15	66.15	<1
16	III_B	>87.33	87.33	<1
	ROD	>87.33	87.33	<1
17	III_B	>92.25	92.25	<1
	ROD	>92.25	92.25	<1
18	III_B	>73.95	73.95	<1
	ROD	>73.95	73.95	<1
19	III_B	>38.90	38.90	<1
	ROD	>38.90	38.90	<1
20	III_B	>13.05	13.05	<1
	ROD	>13.05	13.05	<1
21	III_B	>17.10	17.10	<1
	ROD	>17.10	17.10	<1
22	III_B	>14.07	14.07	<1
	ROD	>14.07	14.07	<1
23	III_B	>41.93	41.93	<1
	ROD	>41.93	41.93	<1
24	III_B	>21.83	21.83	<1
	ROD	>21.83	21.83	<1
25	III_B	>68.28	68.28	<1
	ROD	>68.28	68.28	<1
26	III_B	>97.20	97.20	<1
	ROD	>97.20	97.20	<1
27	III_B	>16.39	16.39	<1
	ROD	>16.39	16.39	<1
28	III_B	>11.30	11.30	<1
	ROD	>11.30	11.30	<1
29	III_B	>27.90	27.90	<1
	ROD	>27.90	27.90	<1
30	III_B	>10.04	10.04	<1
	ROD	>10.04	10.04	<1
31	III_B	>2.97	2.97	<1
	ROD	>2.97	2.97	<1
32	III_B	>2.71	2.71	<1
	ROD	>2.71	2.71	<1
33	III_B	>2.19	2.19	<1
	ROD	>2.19	2.19	<1
34	III_B	>1.71	1.71	<1
	ROD	>1.71	1.71	<1
35	III_B	>17.30	17.30	<1
	ROD	>17.30	17.30	<1
36	III_B	>11.60	11.60	<1
	ROD	>11.60	11.60	<1
37	III_B	>23.39	23.39	<1
	ROD	>23.39	23.39	<1
38	III_B	>7.73	7.73	<1
	ROD	>7.73	7.73	<1
39	III_B	>62.40	62.40	<1
	ROD	>62.40	62.40	<1
40	III_B	>125.00	125.00	<1
	ROD	>125.00	125.00	<1
41	III_B	>125.00	125.00	<1
	ROD	>125.00	125.00	<1
42	III_B	>53.10	53.10	<1

Table 1 (*continued*)

Compd.	Virus strain	av. IC_{50} (μM)[c]	av. CC_{50} (μM)[d]	SI[e]
	ROD	>53.10	53.10	<1
43	III_B	>75.60	75.60	<1
	ROD	>75.60	75.60	<1
Nevirapin	III_B	0.05	>4.00	>80
	ROD	4.00	>4.00	<1
AZT	III_B	0.0019	>25	>13144
3 TC	ROD	0.0018	>25	>14245
	III_B	0.51	>20	>39
	ROD	2.02	>20	>10

[a] Anti-HIV-1 activity measured against strain III_B.
[b] anti-HIV-2 activity measured against strain ROD.
[c] Compound concentration required to achieve 50% protection of MT-4 cells from HIV-1 and 2-induced cytopathogenic effect.
[d] Average CC_{50}: compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e] SI: selectivity index (CC_{50}/IC_{50}). All data represents the mean values of at least two separate experiments.

π stacking appears to govern the binding of compounds **32** and **34** with HIV RT.

4.4. Quantitative structure-activity relationship

QSAR plays a crucial role in drug development as it analyzes the properties of the drug. It is a mathematical model that links the structural features of the compounds (*i.e.* molecular descriptors) to their quantity showing specific biological or chemical activity [49]. It gives description of how biological activity can vary as a function of molecular descriptors derived from the chemical structure of a set of molecules using regression models. Hence, a model containing those calculated descriptors can be used to predict responses of the new compounds. The molecular descriptors for the compounds are calculated and used to build QSAR Model. The QSAR models were developed using different statistical methods like stepwise multiple linear regression, genetic function approximation [50] and genetic partial least squares with descriptors of different categories (quantum chemical, physicochemical, spatial and substituent constants). In this study, the QSAR models were built by means of Multiple Linear Regressions (MLR) and Genetic Function Approximation (GFA) techniques embedded in Material Studio, a modeling and simulation software using the experimentally obtained biological activities as the dependent variables and the computed molecular descriptors as independent variables.

4.4.1. Multiple-linear regressions (MLR)

The MLR model was employed to derive the quantitative structure-activity relationship models for differently substituted 31 thiazole derivatives and as a training set has been developed for the prediction of their pIC_{50} against HIV activity, using selected quantum chemical descriptors (Table 2, Supplementary Material).

The activity data [IC_{50} (μM)] was converted to the logarithmic scale pIC_{50} [-log IC_{50} (M)] and then used for the subsequent quantitative structure activity relationship analyses as the response variables.

With the selected descriptors, we have built a linear model using the set data of 31 substituted thiazole analogues and the following equation was obtained:

Model 1:

pIC_{50} = - 0.096429907 [HOMO*Hydrogen bond donor] - 0.001357558 [Dipole z*Octupole xxx] - 0.008655028 [Quadrupole xx*AlogP + 0.000019295 [Octupole xxx*Octupole yyy] + 2.081215644.

S value = 0.55697600, *F* value = 29.85550000, Regression coefficient, $R = 0.906206$, $R^2 = 0.82121$, Cross validation, $R^2(CV) = 0.633876$.

Compounds **22** and **35** are outliers and, therefore, were excluded.

4.4.2. Genetic function approximation (GFA)

The Genetic Function Approximation (GFA) algorithm has a number of important advantages over other standard regression analysis techniques [51], since it forms multiple models instead of a single model. It uses a genetic algorithm to perform a search over the space of possible QSAR/QSPR models using the LOF score to estimate the fitness of each model. Genetic Function Approximation has the advantage of producing more than one combination of descriptors using lack of fit function to eliminate over fitting, while Multi-linear regression Approach (MLR) provides the user with the choice of multi equation. A set data of 31 substituted thiazole analogues with selected descriptors has been chosen to study their QSAR using GFA method to generate a linear model 2 with the equation obtained for calculating predictive anti-HIV activity as shown in Table 3 (Supplementary Material).

Model 2.

pIC_{50} = - 0.051946360 Quadrupole xy + 0.006543703 Octutpole yyy - 0.000066911 Heat of Formation +0.004242579 Quadrupole yz - 0.003485987 * (ramp(- 26.839130145 - Quadrupole xy))^2 - 0.000066774 * (ramp(83.535618337 − Octupole xyz))^2 + 5.125958689.

Friedman L.O.F. = 0.703197, R^2=0.912995, Adjusted $R^2 = 0.89291700$, Cross validated $R^2 = 0.86083700$, Significant regression: Yes, Significance-of-regression *F* value = 45.472389.

Compounds **22**, **33**, **35**, and **39**–**41** are outliers and were excluded.

To determine which QSAR model better describes our data, we evaluated several statistical parameters, such as the fraction of variance (R^2), the correlation coefficient (R) and the Friedman's lack-offit (LOF). Among the QSAR models, we found the best correlation between independent and dependent variables with model 2. In the GFA analysis, the Friedman's lack-offit (LOF), *F* and R^2 scores evaluate the QSAR model. Thus, the lower the LOF, the less likely it is that the GFA model will fit the data. The significant regression is given by the *F* test, the higher the value, the better is the model. In addition, the high value of the correlation coefficient,

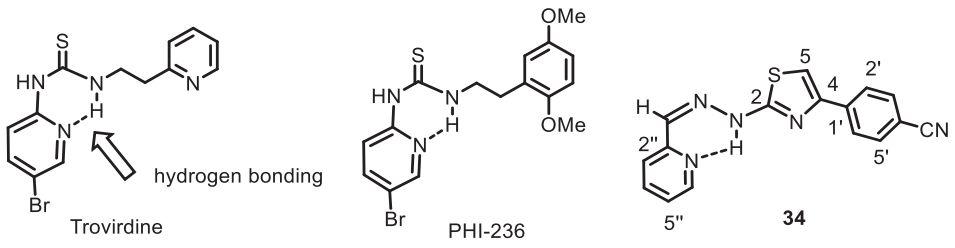


Fig. 2. Rational design of trovirdine, PHI236 and thiazole **34**. 2-Pyridine group is capable of forming an intramolecular H-bonded heterocyclic ring with NH of hydrazono group, and enhance anti-HIV activity.

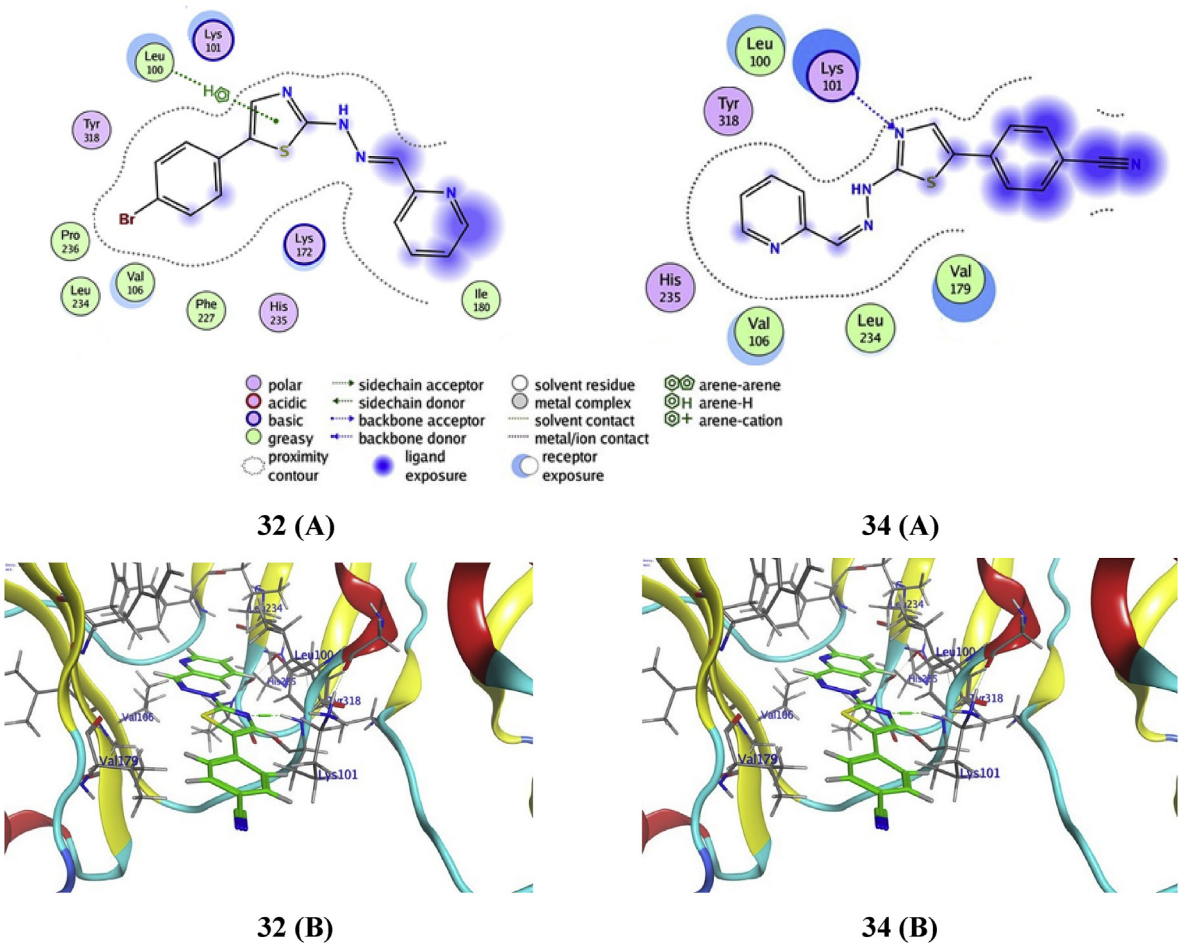


Fig. 3. The binding mode of compounds **32** and **34** with HIV RT (PDB ID: 3DLG). Panels A and B represent the 2D and 3D binding modes of the ligands with essential active site amino acids of HIV-RT, respectively.

R^2 (0.912995), indicated that the model was satisfactory.

In conclusion, the proposed model 2 has good stability, robustness and predictability when verified by internal and external validation. The binding scores for the tested compounds were congruent with their anti-HIV activity. A good correlation between the predicted and the experimentally observed inhibitory activities (pIC_{50}) (Table 3) of the most thiazole analogues suggested that the identified binding conformations of these inhibitors are reliable. The results of docking studies provided an insight into the pharmacophoric structural requirements for HIV RT inhibitory activity of this class of molecules.

5. Conclusion

We have described herein the synthesis and evaluation of anti-HIV-1 and HIV-2 activities of new 2-(2-arylidenehydrazinyl)-4-arylthiazole derivatives **6**–**43**. Compounds **32**–**34** showed significant inhibition of HIV-1 and HIV-2 replication in cell cultures with IC_{50} of >2.71, >2.19 and > 1.71 μM, respectively. The HIV-1 RT docking results revealed that compound **34** binds to RT with a H-bond between its thiazole NH and Lys101. This analogue could be a promising candidate which may be a useful lead in HIV inhibition studies. QSAR studies have given significant information of the biological activity by using MLR and GFA methods, since their models showed a good correlation between the predicted and the experimentally observed inhibitory activities (pIC_{50}).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2019.07.113.

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