European Journal of Medicinal Chemistry 55 (2012) 195–204

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

One pot efficient diversity oriented synthesis of polyfunctional styryl thiazolopyrimidines and their bio-evaluation as antimalarial and anti-HIV agents

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ARTICLE INFO

Article history:
Received 30 March 2012
Received in revised form
11 July 2012
Accepted 14 July 2012
Available online 23 July 2012

Keywords:
Thiazolopyrimidine
Anti-HIV agents
Antimalarial agents
P. falciparum, Styryl thiazolopyrimidine

ABSTRACT

An efficient one pot synthesis of a series of pluripotent (*E*)-1-(3-methyl-5-aryl-7-styryl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)-3-arylprop-2-en-1-ones is reported. It involves reaction of 5-acetyl-6-methyl-4-aryl-dihydropyrimidine-2-thiones, propargyl bromide and aromatic aldehydes in presence of ethanolic KOH. The newly synthesized compounds were evaluated for antimalarial activity against *Plasmodium falciparum* and as HIV-RT inhibitors. Most of the compound displayed potent antimalarial activity with $IC_{50} < 2$ μg/mL. Compounds **6**, **11** and **20** showed better activity against *P. falciparum* K1 strains in comparison to standard drug chloroquine. Compounds **6**, **11**, and **16** exhibited 73.44, 66.92, and 70.81% HIV-RT inhibition at 100 μg/mL.

1. Introduction

In the last two decades C–C bond formation has been increasingly achieved by the addition of carbon centered radicals to carbon–carbon multiple bonds. It is known that the addition of heterosubstituted radicals to styryl sulfimides [1] and styryl triflone [2] results in styryl heterocycles. Traditionally, styryl heterocycles are prepared by Horner–Wadsworth–Emmons reaction of the alkyl(diphenyl)phosphine oxide with a carbonyl compounds [3]. The aldol reactions of 2-methyl azaarenes with aromatic aldehydes in the presence of strong acid or base [4–8], have also been exploited to get alkenyl azaarenes with only low *E*/*Z* selectivity. Very recently a catalyst free benzylic C–H bond olefination of azaarenes with *N*-sulphonyl aldimines have been reported to afford *E*-alkenyl azaarenes stereoselectively involving addition elimination reactions [9]. The alkenyl azaarenes, in general, have been used as antagonist, antiproliferative, antiviral, and antimicrobial agents and also for other important biological activities [10–16]. The bicyclic heterocycles, with condensed thiazole and pyrimidine skeleton, the thienopyrimidines and thiazolopyrimidines have received considerable attention recently due to their wide application in medicinal chemistry. A diverse range of pharmacological activities such as anti-HIV [17], antibacterial [18], anti-inflammatory [19,20], antihypertensive [20], antimicrobial [21], antioxidant, antitumor [22], anti-HSV-1 [23] and herbicidal [24] are associated with these structural prototypes. They are also known to inhibit the CDC25BP phosphates [25], and *IspF* (2-methylerythritol 2,4-cyclodiphosphate synthase) proteins of *Mycobacterium tuberculosis*, *Plasmodium falciparum*, and *Arabidopsis thaliana* [26]. Styryl compounds both of synthetic and natural origin have tremendous potential both in organic synthesis as synthon and in medicinal chemistry as chemotherapeutic agents. Styryl heterocycles are also known as anti-HIV agents [27], while the styryl ketones (chalcones), such as Licochalcone A (**A**), 5-prenylbutein (**B**), and compound **C** are well known for their antimalarial activities [28–30] (Fig. 1).

Currently we have been involved in design and development of new chemotherapeutic agents using many heterocyclic and non-heterocyclic scaffolds [31–36]. In view of the above we were prompted to synthesise hybrid molecules with thiazolopyrimidine, enone and styryl moieties and evaluate their biological activities. In this context we have developed an efficient one pot protocol for the

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http://dx.doi.org/10.1016/j.ejmech.2012.07.018

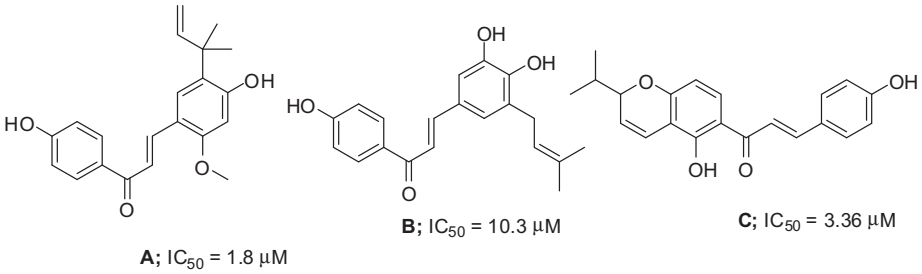


Fig. 1. Naturally occurring chalcones having antimalarial activity.

synthesis thiazolopyrimidines with enone and styryl functionalities (Fig. 2) and evaluate their antimalarial and HIV-RT inhibitory activities in the first instance.

2. Results and discussion

2.1. Chemistry

The retro synthesis of targeted styryl thiazolopyrimidines is shown in Fig. 3. 5-Acetyl-6-methyl-4-phenyl-dihydropyrimidine-2-thiones [37], obtained through Biginelli reaction of acetyl acetone, thiourea and aromatic aldehyde, on reaction with propargyl bromide under basic condition may lead to respective thiazolopyrimidines via allene mediated cycloaddition as recently reported [38]. The latter on reaction with two equivalents of aromatic aldehydes will give rise to the required thiazolopyrimidines with styryl and cinnamoyl moieties.

To optimize the reaction condition for the synthesis of targeted compounds, we have chosen a model reaction of 5-acetyl-6-methyl-4-phenyl-dihydropyrimidine-2-thione (**1a**) with propargyl bromide and benzaldehyde under basic condition. The reaction was carried out under three different conditions and the results are summarized in Fig. 4. In method **I**, dihydropyrimidinethione **1a** (1.0 equiv.) was reacted with propargyl bromide (1.0 equiv.) in ethanol in presence of NaOEt at 80 °C to give the thiazolopyrimidine (**2a**), which was isolated, characterised and reported earlier by our group [38]. The intermediate compound **2a** (1.0 equiv.) was then reacted with benzaldehyde (2.1 equiv.) in presence of KOH (2.5 equiv.) in ethanol to give the required compound **3** in 75% yield. The method **II** consists in reaction of dihydropyrimidine-2-thione **1a** (1.0 equiv.) with propargyl bromide (1.0 equiv.) and benzaldehyde (2.1 equiv.) in presence of KOH (5.0 equiv.) in ethanol to give the required compound **3** in 60% yield. The method **III** involves a reaction of dihydropyrimidine-2-thione **1a** (1.0 equiv.) with propargyl bromide (1.0 equiv.) in presence of KOH (5.0 equiv.) in ethanol at 30 °C to give the intermediate **2a** within 5 min, followed by addition of benzaldehyde (2.1 equiv.) and reaction was shifted now to oil bath at 80 °C to give the required product **3** in 70% yield. Thus method **III** proved to be most efficient as the isolation of intermediate formed during reaction is not required. This method was adopted as a general method for the synthesis of other compounds of the series.

Similarly condensation of different dihydropyrimidine-2-thiones (**1a**–**1d**) prepared earlier [34] with one equivalent of propargyl bromide and two equivalents of selected aromatic aldehydes by method **III**, led to the formation of respective styryl thiazolopyrimidines **4**–**25** in very good yields (Scheme 1).

All the synthesized compounds were fully characterized by their IR, ESI-MS, NMR and elemental analyses (experimental section). In IR spectra the compounds in general, displayed absorption bands at around 1630 and 2932 $cm^{-1}$for the carbonyl and CH-stretching frequencies. All the compounds in MS spectra showed $[M+H]^+$ corresponding to their molecular formulae. In NMR (^1H and ^{13}C) spectral data of the compounds all the proton and carbon signals

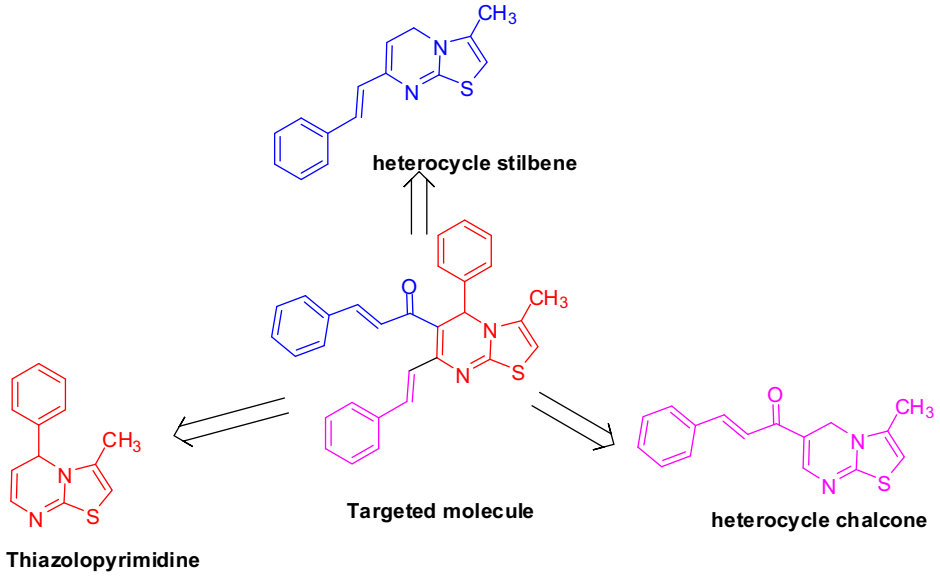


Fig. 2. Targeted hybrid thiazolopyrimidines with heterocycle chalcone, thiazolopyrimidine and heterocycle stilbene moieties.

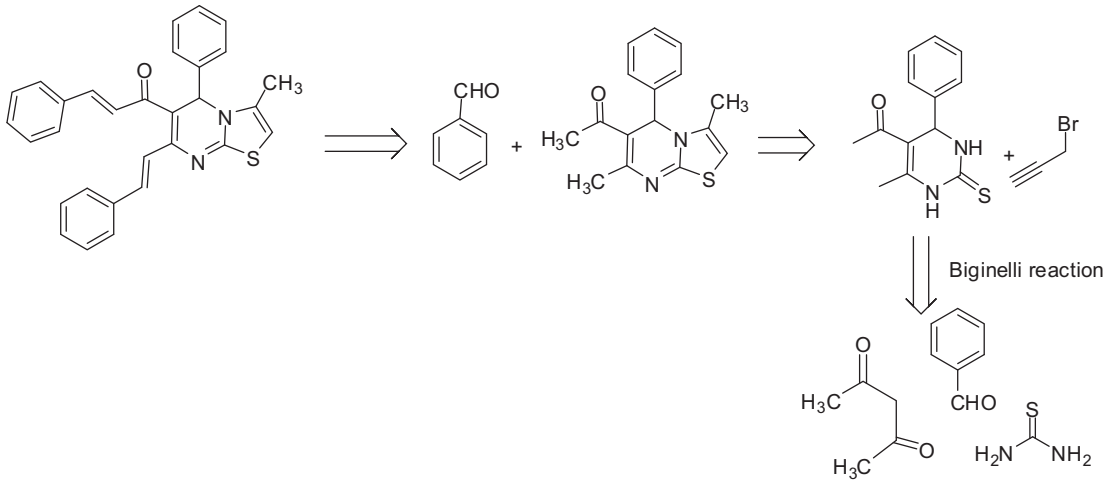


Fig. 3. Retro synthesis of targeted styryl thiazolopyrimidines.

were observed at their usual chemical shift. Other compounds of the series follow the same pattern. The chemical shift assignments in one of the prototype compound **21** was carried out using correlation spectroscopy (COSY), hetero nuclear single quantum coherence spectroscopy (HSQC), hetero nuclear multiple bond correlation spectroscopy (HMBC) and nuclear over hauser spectroscopy (NOESY). All the important correlations are given in Fig. 5.

It was observed that the two olefenic protons (H-3′ and H-2″) appeared as doublet at 7.89 and 8.05 ppm with coupling constant $^{3}J_{H3'-H2'} = 15.62$ and $^{3}J_{H2''-H1''} = 15.50$ respectively, which suggest an *E* geometry of the olefinic bonds. The protons of CH_3 show nOe correlation with H2, H5 and *Ar1*-H2,6; whereas H-5 is showing nOe correlation with *Ar1*-H2,6 and it led us to assign the chemical shift values of H5 and H2 protons. The signals for H1″ and H2′ show nOe

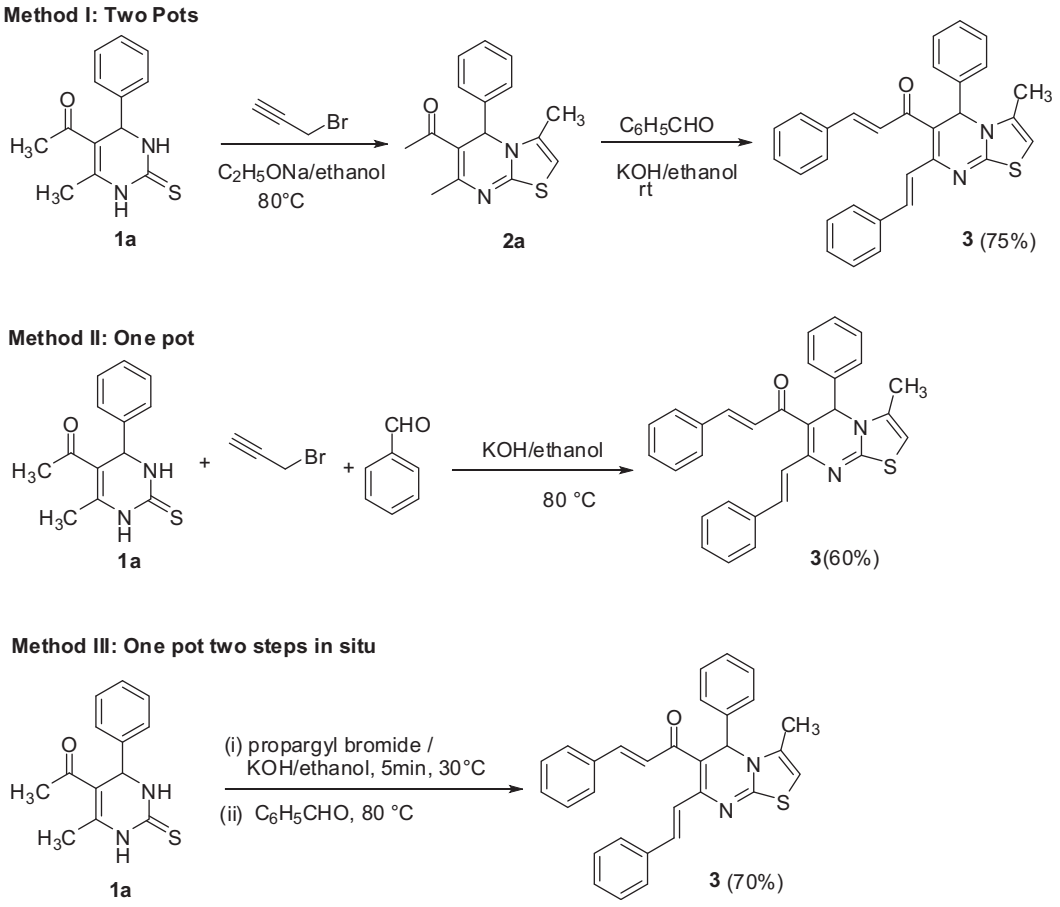
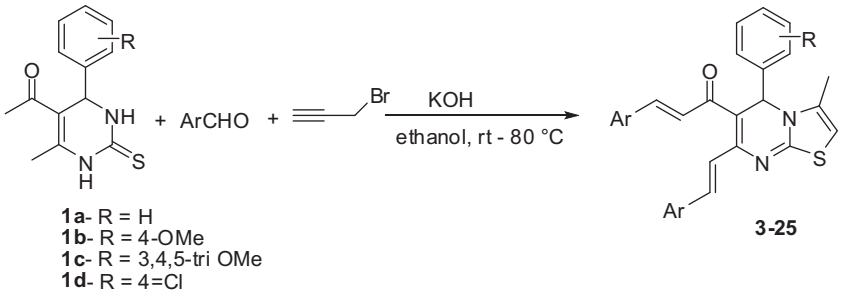


Fig. 4. Synthesis of the compound **3** with the three different methods.



Scheme 1. Synthesis of (*E*)-1-(3-methyl-5-aryl-7-styryl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)-3-arylprop-2-en-1-one) derivatives (**3**–**25**).

correlation with *Ar3*-H6 and *Ar2*-H6 respectively and nOe peak between H5 and *Ar1*-H2,6, facilitated to differentiate the protons of the three aromatic ring *Ar1*, *Ar2* and *Ar3* for the protons and carbons. Further, H5, H2′ and H3′ showed HMBC correlation with C1′ (C═O) assisting the assignment of olefinic protons of H2′, H3′ and H1″, H2″. The HMBC long range correlations between *Ar2*-H6 ↔ *Ar2*-C2 ↔ H3′, *Ar2*-H5 ↔ *Ar2*-C1 ↔ H2′, *Ar1*-H3, 5 ↔ *Ar1*-C1 ↔ H5, *Ar1*-H2,6 ↔ *Ar1*-C4, led us to assign the chemical shifts (Table A, Supplementary information) and establish the structure of the molecule.

2.2. Biology

2.2.1. Antimalarial activity

All the newly synthesized compounds were evaluated for their antimalarial activity against two different strains of *P. falciparum* i.e. 3D7 (chloroquine sensitive) and K1 (chloroquine resistant) employing the method reported earlier [39]. The antimalarial activities of the compounds are depicted in Table 1. As evident from the results almost all the compounds except compounds **4**, **7**, **10**, and **25** are potent antimalarial with $IC_{50} < 2$ μg/mL against either of the two Plasmodium strains. Chloroquine was taken as standard whose IC_{50} value was found to be 0.006 and 0.6 μg/mL against 3D7 and K1 strains respectively. Among the active compounds, the

Table 1
Antimalarial activity and cytotoxicity of the synthesised compounds (**3**–**25**).

Compound no.	IC_{50} against *P. falciparum* (3D7) μg/mL	IC_{50} against *P. falciparum* (K1) μg/mL	CC_{50} against Vero cells, μg/mL	SI for 3D7	SI for K1
3	0.57	0.79	195.47	342.93	247.43
4	5.15	2.71	252.48	49.03	93.17
5	0.79	1.2	285.95	361.96	238.29
6	0.56	0.36	206.01	367.88	572.25
7	5.38	2.50	282.32	52.48	112.93
8	2.68	1.59	306.12	114.22	192.53
9	2.19	<0.76	358.19	163.56	>471.31
10	24.52	4.30	>500μg	>20.39	>116.28
11	0.5	<0.3	260.47	520.94	>868.23
12	5.07	1.09	496.72	97.97	455.71
13	2.11	0.85	210.89	99.95	248.11
14	5.3	1.49	272.51	51.42	182.89
15	5.15	1.09	260.83	50.65	239.29
16	3.94	1.14	417.64	106.00	205.73
17	5.17	2.03	235.14	45.48	115.83
18	6.82	<0.76	166.67	24.44	>219.3
19	1.57	0.71	347.86	221.57	489.94
20	0.5	0.27	319.65	639.3	1183.89
21	5.9	2.79	429.75	72.84	154.03
22	2.25	<0.76	317.30	141.02	>417.5
23	0.85	0.6	309.03	363.57	515.05
24	1.27	1.22	419.75	330.51	344.06
25	6.97	19.55	>500	>71.74	>25.56
Chloroquine	0.006 μg/mL	0.6 μg/mL			

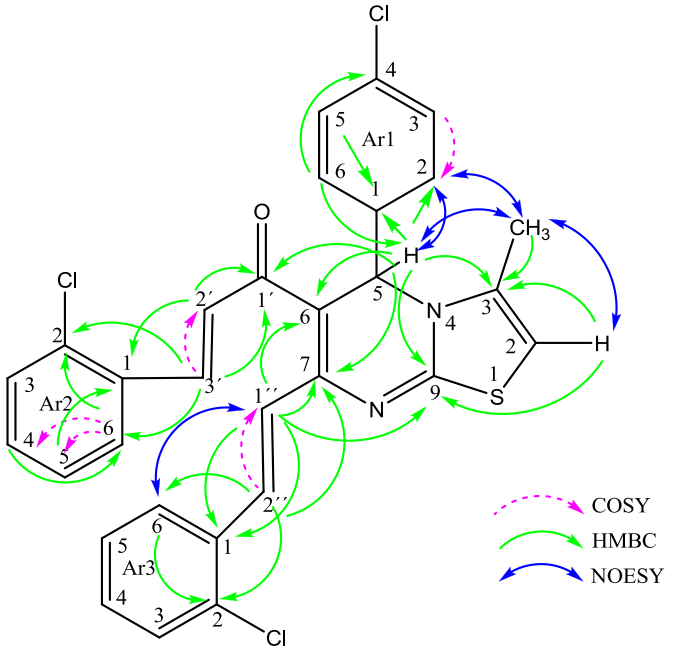


Fig. 5. Important HMBC, COSY and nOe correlations of compound no **21**.

compounds **6** ($IC_{50} = 0.36$ μg/mL), **11** ($IC_{50} < 0.3$ μg/mL), and **20** ($IC_{50} = 0.27$ μg/mL) were found to be more potent than the standard antimalarial agent chloroquine against K1 strains of *P. falciparum*. The cytotoxicity of these compounds were evaluated against the vero cell lines of monkey. Their CC_{50} values ranged from 166.67 to 500 μg/mL. Based on IC_{50} and CC_{50} values selective indices (SI) (IC_{50}/CC_{50}) of these compounds were calculated and found to be in the range of 20.39–1183.89. Compound **20** was found to be the best compound with $IC_{50} = 0.27$ μg/mL and SI = 1183.89 against *P. falciparum* K1 strains.

A closure look into the structure activity relationship indicates that out of all the compounds, compounds having benzyloxy phenyl or 3,4-methylenedioxy phenyl as 5-phenyl substitutents in thizolopyrimidines (compounds **10**, **12**, **16** and **25**) do not show any significant activity against 3D7 strains but 3,4-methylenedioxy phenyl substituted compounds(**12** and **16**) showed significant activity against K1 strain. In general compounds having OMe substituent in either of the phenyl rings (**9**, **11**, **13**–**16**, **18** and **19**) were found to show potent activity against K1 strain and activity increases by increasing the number of OMe group. Furthermore compounds with 3,4,5 trimethoxysubstituted phenyl ring displayed very good activity against 3D7 strain as well (**11**, **19**). If the aromatic rings in the enone and styryl moieties are phenyl and the 5-phenyl has substitutents the activity follows the order

Cl > H > OMe (**20** > **3** > **13**). The effect of nature and position of the halogen substituents in the two phenyl rings of the stilbene and propenone moieties was found to be F > Cl > Br and *o*− > *m*− > *p*−. Further, an interesting observation is observed that when the value of R changes from H to Cl the effect of the position of the halogens on the activity was found to be the just reversed and become *p*− > *m*− > *o*−. Changing the Ar with heteroaromatic (compound **17**) did not offer any significant improvement in the activity.

2.2.2. Anti-HIV-1 evaluation

All the newly synthesized compounds (**3**–**25**) were also evaluated for their reverse transcriptase inhibitory activity at two different concentrations 10 and 100 μg/mL and the results are shown in Table 2.

At 10 μg/mL only one compound i.e. compound **16** showed significant (58%) RT inhibition. However, at 100 μg/mL RT inhibition ranges from 11 to 73%. Among all the compounds screened, three compounds **6** (73.44%), **11** (66.92%) and **16** (70.81%) showed very good RT inhibitory activities. Other compounds of the series showed moderate to good inhibitory activity. Nevirapine a non-nucleoside reverse transcriptase (NNRT) inhibitor clinically used drug, showed 97.9% inhibition at 10 μg/mL concentration.

A closure look into structure activity relationship indicates that in general compounds having 4-chloro substituent in the phenyl ring are least active in comparison to the other compounds. The effect of substituent in the 5-phenyl ring on RT inhibition follows activity order as H > OMe > Cl (**3** > **13** > **20**). Further, increasing the number of OMe substitutents in either of the aromatic rings results in enhancement of enzyme inhibitory activities. Compound **9** with one OMe substituent on phenyl ring showed 33% RT inhibition while compound **11** with increased number of methoxy substituent led to strong inhibition (66%) of RT. Similar observation was made for compounds **18** and **19**. The halogen substituents in the two phenyl rings of the stilbene and propenone moieties effect the inhibition in the order F > Br > Cl. The position of the halogen substituents on the phenyl rings has significant effect on the RT inhibitory activity and follows the pattern of *o*− > *m*− > *p*−. Further replacement of the aromatic ring in the enone and stilbene moiety with heteroaromatic (17) did not offer any significant improvement in the activity.

Table 2
% HIV-1 RT inhibition activity of different styryl thiazolopyrimidine (**3**–**25**).

Compound no.	% Inhibition at 10 μg/mL	% Inhibition at 100 μg/mL
3	42.26	49.63
4	42.58	53.39
5	15.39	54.50
6	38.91	73.44
7	39.76	55.44
8	30.04	59.25
9	40.57	32.73
10	47.71	56.30
11	5.69	66.92
12	Nd	Nd
13	39.35	48.59
14	31.23	50.89
15	9.22	41.40
16	58.78	70.81
17	47.71	54.39
18	48.40	55.92
19	30.07	51.33
20	23.57	30.55
21	17.96	26.12
22	13.23	16.57
23	10.62	11.41
24	17.80	26.47
25	17.64	18.56
Nevirapine	97.91	

3. Conclusion

In conclusion, a series of novel pluripotent (*E*)-1-(3-methyl-5-aryl-7-styryl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)-3-phenylprop-2-en-1-ones have been synthesized from 5-acetyl-6-methyl-4-aryl dihydropyrimidine-2-thiones in very good yields. The compounds were evaluated for their antimalarial and HIV-RT inhibitory activities. A number of compounds showed significant to moderate antimalarial and HIV-RT inhibitory activities. Three compounds **6**, **11**, and **20** were found to more potent than the standard drug Chloroquine against K1 strains of *P. falciparum.* These compounds with three different pharmcophores have potential to be exploited for explorations in medicinal chemistry.

4. Experimental

4.1. Chemistry

Commercially available reagent grade chemicals and solvents were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, spraying a 20% $KMnO_4$ aq. solution or exposure to I_2 vapours. Column chromatography was performed on silica gel (60–120 mesh E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. The ^1H (400 and 300 MHz) and ^{13}C NMR (100 and 50 MHz) spectra were recorded on a Bruker Avance-400, Bruker DRX-300 and Bruker DRX-200 in DMSO, CD_3OD and $CDCl_3$. Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference, unless otherwise stated: s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), bs (broad singlet); *J* in hertz. ESI mass spectra were performed using Quattro II (Micromass). Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

*4.1.1. Typical procedure for the synthesis of compounds (**3**–**25**)*

To a magnetically stirred solution of 5-acetyl-6-methyl-4-aryldihydropyrimidine-2-thione (**1a**–**1d**) (1.0 equiv.) at 25 °C in ethanol as solvent, propargyl bromide (1.0 equiv.) and KOH (5.0 equiv.) is added, the solution colour changes to yellow which is marked by the formation of product i.e. thiazolopyrimidine. After 5 min aromatic aldehyde (2.1 equiv.) is added to the same pot and now the reaction is shifted to an oil bath at 80 °C. The reaction mixture turned to red colour after sometime. The reaction mixture was stirred at the same temperature for further half an hour. The ethanol is evaporated under reduced pressure to give a crude mass which was chromatographed over silica gel (60–120 mesh) using ethylacetate: hexane as eluent to give the desired products.

*4.1.1.1. (E)-1-(3-Methyl-5-phenyl-7-styryl-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-phenylprop-2-en-1-one (**3**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and benzaldehyde (0.9 mL, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 160–165 °C; yield (1.30 g, 70%) ; IR (KBr) ν_{max} cm^{-1}: 2926 (CH stretching), 1720 (C=O stretching), 1625 (C=N stretching), 696 (CH_2–S stretch); ESMS: $m/z = 461$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (d, 1H, $J = 15.42$ Hz, H2″), 7.54–7.47 (m, 5H, ArH, H3′), 7.42–7.38 (m, 4H, ArH), 7.33–7.20 (m, 9H, ArH, H1″, H2′), 6.38 (s, 1H, H5), 6.05 (s, 1H, H2), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.5, 166.5, 151.4, 142.4, 139.6, 136.8, 136.4, 136.0, 135.4, 129.6, 128.8, 128.7, 128.1, 128.0, 127.8, 127.4, 126.2, 125.7, 111.9, 101.1,$

57.5, 14.2. Anal. calcd. for $C_{30}H_{24}N_2OS$: C, 78.23; H, 5.25; N, 6.08; found: C, 78.20; H, 5.29; N, 6.04.

*4.1.1.2. (E)-3-(4-Chlorophenyl)-1-(7-(4-chlorostyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**4**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 4-chlorobenzaldehyde (1.19 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 184–188 °C; yield (1.45 g, 68%); IR (KBr) ν_{max} cm^{-1}: 2924 (CH stretching), 1630 (-C=O stretching), 1564 (-C=N stretching), 700 (CH–S stretch); ESMS: $m/z = 530$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, 1H, $J = 15.42$ Hz, H2″), 7.49–7.35 (m, 7H, ArH, H3′), 7.35–7.24 (m, 9H, ArH, H1″, H2′), 6.37 (s, 1H, H5), 6.12(s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.4$, 167.1, 152.0, 142.3, 138.3, 136.2, 135.6, 135.4, 134.9, 134.7, 133.9, 129.1, 129.0, 128.9, 128.5, 128.4, 128.2, 126.6, 126.2, 111.8, 101.2, 57.5, 13.9. Anal. calcd. for $C_{30}H_{22}N_2Cl_2OS$: C, 68.05; H, 4.19; N, 5.29; found: C, 68.01; H, 4.24; N, 5.31.

*4.1.1.3. (E)-3-(3-Chlorophenyl)-1-(7-(3-chlorostyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**5**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.06 mmol), KOH (1.12 g, 20.0 mmol) and 3-chlorobenzaldehyde (1.19 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 142–145 °C; yield (1.54 g, 72%); IR (KBr) ν_{max} cm^{-1}: 2925 (CH stretching), 1635 (-C=O stretching), 1566 (-C=N- stretch), 681 (CH–S stretch); ESMS: $m/z = 530$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, 1H, $J = 15.45$ Hz, H2″), 7.45–7.37 (m, 6H, ArH, H3′), 7.34–7.31 (m, 4H, ArH), 7.28–7.18 (m, 6H, ArH, H1″, H2′), 6.39 (s, 1H, H5), 6.12 (s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.3$, 167.2, 152.1, 142.3, 138.2, 138.1, 137.3, 136.2, 135.4, 134.9, 130.1, 130.0, 129.6, 129.2, 128.9, 128.8, 128.2, 127.7, 127.5, 127.2, 126.2, 125.7, 125.3, 111.9, 101.4, 57.5, 14.0. Anal. calcd. for $C_{30}H_{22}Cl_2N_2OS$: C, 68.05; H, 4.19; N, 5.29; found: C, 68.00; H, 4.23; N, 5.26.

*4.1.1.4. (E)-3-(2-Chlorophenyl)-1-(7-(2-chlorostyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**6**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 2-chlorobenzaldehyde (1.19 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 158–160 °C; yield (1.52 g, 71%); IR (KBr) ν_{max} cm^{-1} : 2925 (CH stretching), 1600 (-C=O stretching), 1564 (-C=N- stretch), 692 (CH–S stretch); ESMS: $m/z = 530$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$ (d, 1H, $J = 15.45$ Hz, H2″), 7.93 (d, 1H, $J = 15.45$ Hz, H3′), 7.54–7.49 (m, 5H, ArH, H1″, H2′), 7.35–7.26 (m, 6H, ArH), 7.23–7.17 (m, 2H, ArH), 7.12–7.07 (m, 2H, ArH), 6.39 (s, 1H, H5), 6.12 (s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz $CDCl_3$): $\delta = 187.3$, 167.1, 152.1, 142.3, 136.1, 135.5, 135.0, 134.4, 133.6, 132.7, 130.5, 130.1, 129.7, 128.9, 128.2, 127.3, 127.1, 126.9, 126.3, 112.0, 101.6, 57.6, 13.9. Anal. calcd. for $C_{30}H_{22}Cl_2N_2OS$: C, 68.05; H, 4.19; N, 5.29; found: C, 68.01; H, 4.21; N, 5.30.

*4.1.1.5. (E)-3-(4-Bromophenyl)-1-(7-(4-bromostyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**7**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 4-bromobenzaldehyde (1.57 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 165–168 °C; yield (1.75 g, 70%); IR (KBr) ν_{max} cm^{-1}: 2932 (CH stretching), 1627 (-C=O stretching), 1560 (C=N stretch), 703 (CH–S stretch); ESMS: $m/z = 619$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, 1H, $J = 15.48$ Hz, H2″), 7.47–7.39 (m, 7H, ArH, H3′), 7.36–7.31 (m, 6H, ArH), 7.28–7.25 (m, 3H, ArH, H1″, H2′), 6.37 (s, 1H, H5), 6.11 (s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.4$, 167.1, 152.0, 142.3, 138.4, 136.2, 135.5, 134.4, 132.1, 131.9, 129.1, 128.9, 128.8, 128.7, 128.4, 128.2, 126.7, 126.2, 123.9, 123.0, 111.9, 101.2, 57.5, 13.9. Anal. calcd. for $C_{30}H_{22}Br_2N_2OS$: C, 58.27; H, 3.59; N, 4.53; found: C, 58.22; H, 3.69; N, 4.50.

*4.1.1.6. (E)-3-(4-Fluorophenyl)-1-(7-(4-fluorostyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**8**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 4-fluorobenzaldehyde (1.05 mL, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 153–156 °C; yield (1.4 g, 71%); IR (KBr) ν_{max} cm^{-1}: 2932 (CH stretching), 1627 (-C=O stretching), 1560 (-C=N- stretch), 703 (CH–S stretch); ESMS: $m/z = 497$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, 1H, $J = 15.48$ Hz, H2″), 7.50–7.40 (m, 6H, ArH, H3′), 7.30–7.22 (m, 6H, ArH, H1″), 7.03–6.94 (m, 4H, ArH, H2′), 6.38 (s, 1H, H5), 6.10 (s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.5$, 167.0, 152.0, 142.4, 138.2, 136.1, 135.4, 132.6, 131.7, 129.6, 129.4, 129.1, 128.9, 128.8, 128.1, 127.8, 126.2, 125.9, 116.1, 115.7, 111.7, 101.0, 57.5, 13.9. Anal. calcd. for $C_{30}H_{22}F_2N_2OS$: C; 72.56; H, 4.47; N, 5.64; found: C, 72.53; H, 452; N, 5.60.

*4.1.1.7. (E)-3-(4-Methoxyphenyl)-1-(7-(4-methoxystyryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**9**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 4-methoxybenzaldehyde (1.16 mL, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 100–113 °C; yield (1.45 g, 69%); IR (KBr) ν_{max} cm^{-1} : 2934 (CH stretching), 1640 (-C=O stretching), 1605 (-C=N- stretch), 688 (CH-S stretch); ESMS: $m/z = 521$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): 7.68 (d, 1H, $J = 15.48$ Hz, H2″), 7.54–7.41 (m, 6H, ArH, H3′), 7.30–7.23 (m, 6H, ArH, H2′), 6.85–6.80 (m, 4H, ArH, H1″), 6.38 (s, 1H, H5), 6.06 (s, 1H, H2), 3.82 (s, 6H, OCH_3), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.9$, 166.8, 160.9, 160.3, 142.6, 139.2, 136.1, 129.4, 128.9, 128.7, 128.3, 127.9, 126.3, 125.9, 124.1, 119.9, 114.2, 111.4, 101.0, 57.5, 55.3, 13.9. Anal. calcd. for $C_{32}H_{28}N_2O_3S$: C, 73.82; H, 5.42; N, 5.38; found: C, 73.80; H, 5.49; N, 5.35.

*4.1.1.8. (E)-3-(4-(Benzyloxy)phenyl)-1-(7-(4-(benzyloxy)styryl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**10**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 4-benzyloxybenzaldehyde (1.80 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 190–193 °C; yield (1.85 g, 68%) ; IR (KBr) ν_{max} cm^{-1} : 2934 (CH stretching), 1640 (-C=O stretching), 1605 (-C=N- stretch), 688 (CH–S stretch); ESMS: $m/z = 673$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.68$ (d, 1H, $J = 15.45$ Hz, H2″), 7.54–7.33 (m, 16H, ArH, H3′), 7.30–7.23 (m, 6H, ArH, H2′), 6.92–6.88 (m, 4H, ArH, H1″), 6.38 (s, 1H, H5), 6.06 (s, 1H, H2), 5.08 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2), 2.14 (s, 3H, CH_3) ; Anal. calcd. for $C_{44}H_{36}N_2O_3S$: C, 78.54; H, 5.39; N, 4.16; found: C, 78.50; H, 5.42; N, 4.13.

*4.1.1.9. (E)-1-(3-Methyl-5-phenyl-7-(3,4,5-trimethoxystyryl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**11**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 3,4,5-trimethoxybenzaldehyde (1.67 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 180–182 °C; yield (1.82 g in 70%); IR (KBr) ν_{max} cm^{-1}: 2929 (CH stretching), 1631 (-C=O stretching), 1581 (-C=N- stretch), 697 (CH–S stretch); ESMS: $m/z = 641$ $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 15.42$ Hz, 1H, H2″), 7.43 (d, $J = 7.44$ Hz, 2H, ArH), 7.38 (s, 1H, ArH,), 7.33–7.28 (m, 5H, ArH, H2′, H1″, H3′), 6.72 (d, $J = 1.95$ Hz, 4H, ArH,), 6.40 (s, 1H, H5), 6.11 (s, 1H, H2), 3.85 (s, 6H,

OCH_3), 3.65 (s, 6H, OCH_3), 3.62 (s, 6H, OCH_3), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.5, 167.1, 153.4, 153.3, 152.3, 142.4, 139.0, 138.9, 136.3, 136.2, 132.0, 131.0, 128.8, 128.1, 128.0, 126.2, 111.6, 104.7, 60.8, 57.4, 55.8, 55.7, 13.9$. Anal. calcd. for $C_{36}H_{36}N_2O_7S$: C, 67.48; H, 5.66; N, 4.37; found: C, 67.45; H, 5.71; N, 4.35.

*4.1.1.10. (E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(7-((E)-2-(benzo[d][1,3] dioxol-5-yl)vinyl)-3-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**12**).* It was obtained by the reaction of **1a** (1.0 g, 4.0 mmol), propargyl bromide (0.5 mL, 4.0 mmol), KOH (1.12 g, 20.0 mmol) and 3,4-methylenedioxybenzaldehyde (1.28 g, 8.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 156–160 °C; yield (1.45 g, 65%) ; IR (KBr) ν_{max} cm^{-1}: 2900 (CH stretching), 1730 (C=O stretching), 1598 (C=N stretch), 696 (CH–S stretch); ESMS: $m/z = 549$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): 7.47 (d, 1H, $J = 15.66$ Hz, H2″), 7.40 (d, $J = 6.99$ Hz, 2H, ArH), 7.32–7.24 (m, 4H, ArH, H3′) 7.18–7.11 (m, 2H, ArH, H1″), 7.05–6.98 (m, 4H, ArH, H2′), 6.78–6.73 (m, 2H, ArH,), 6.38 (s, 1H, H5), 6.16 (s, 1H, H2), 5.97 (s, 2H, OCH_2), 5.95 (s, 2H, OCH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.8, 148.5, 148.2, 136.1, 130.9, 128.8, 128.1, 126.2, 123.9, 123.1, 111.5, 108.5, 106.5, 101.3, 101.2, 57.6, 13.9$. Anal. calcd. for $C_{32}H_{24}N_2O_5S$: C, 70.06; H, 4.41; N, 5.11; found: C, 70.03; H, 4.46; N, 5.10.

*4.1.1.11. (E)-1-(5-(4-Methoxyphenyl)-3-methyl-7-styryl-5H-thiazolo [3,2-a]pyrimidin-6-yl)-3-phenylprop-2-en-1-one (**13**).* It was obtained by the reaction of **1b** (1.0 g, 3.6 mmol), propargyl bromide (0.43 mL, 3.6 mmol), KOH (1.0 g, 18.0 mmol) and benzaldehyde (0.80 mL, 7.6 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 138–140 °C; yield (1.26 g in 71%); IR (KBr) ν_{max} cm^{-1}: 2930 (CH stretching), 1722 (-C=O stretching), 1574 (-C=N stretch), 686 (CH–S stretch); ESMS: $m/z = 491$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): 7.72 (d, $J = 15.45$ Hz, 1H, H2″), 7.56–7.45 (m, 6H, ArH, H3′), 7.39–7.26 (m, 9H, ArH, H1″, H2′), 6.83 (d, $J = 8.61$, 2H, ArH), 6.31 (s, 1H, H5), 6.07 (s, 1H, H2), 3.76 (s, 3H, CH_3), 2.16 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.9, 166.7, 159.3, 151.6, 139.7, 136.7, 136.4, 136.1, 135.4, 129.7, 128.9, 128.8, 128.7, 128.0, 127.8, 127.7, 127.5, 125.9, 114.1, 112.2, 101.1, 57.2, 55.2, 14.0$. Anal. calcd. for $C_{31}H_{26}N_2O_2S$; C, 75.89; H, 5.34; N, 5.71; found: C, 75.85; H, 5.38; N, 5.70.

*4.1.1.12. (E)-3-(4-Chlorophenyl)-1-(7-(4-chlorostyryl)-5-(4-methoxyphenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**14**).* It was obtained by the reaction of **1b** (1.0 g, 3.6 mmol), propargyl bromide (0.43 mL, 3.6 mmol), KOH (1.0 g, 18.0 mmol) and 4-chlorobenzaldehyde (1.06 g, 7.6 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 165–168 °C; yield (1.39 g, 69%); IR (KBr) ν_{max} cm^{-1}: 2923 (CH stretching), 1723 (-C=O stretching), 1595 (-C=N stretch), 682 (CH–S stretch); ESMS: $m/z = 560$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): 7.69 (d, $J = 14.61$ Hz, 1H, H2″), 7.48–7.35 (m, 5H, ArH, H3′), 7.32–7.24 (m, 8H, ArH, H1″, H2′), 6.83 (d, $J = 8.31$, 2H, ArH), 6.30 (s, 1H, H5), 6.12 (s, 1H, H2), 3.76 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3); Anal. calcd. for $C_{31}H_{24}Cl_2N_2O_2S$: C, 66.55; H, 4.32; N, 5.01; found: C, 66.50; H, 4.34; N, 5.05.

*4.1.1.13. (E)-3-(4-Fluorophenyl)-1-(7-(4-fluorostyryl)-5-(4-methoxyphenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**15**).* It was obtained by the reaction of **1b** (1.0 g, 3.6 mmol), propargyl bromide (0.43 mL, 3.6 mmol), KOH (1.0 g, 18.0 mmol) and 4-fluorobenzaldehyde (0.94 mL, 7.6 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 159–162 °C; yield (1.42 g, 75%) ; IR (KBr) ν_{max} cm^{-1}: 2931 (CH stretching), 1700 (-C=O stretching), 1567 (-C=N stretch), 677 (CH–S stretch); ESMS: $m/z = 526$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$) = 7.66 (d, $J = 15.45$ Hz, 1H, H2″), 7.50–7.45 (m, 5H, ArH, H3′), 7.36–7.16 (m, 4H, ArH, H1″, H2′), 7.03–6.94 (m, 3H, ArH), 6.83 (d, $J = 8.61$, 2H, ArH), 6.30 (s, 1H, H5), 6.08 (s, 1H, H2), 3.76 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.7, 159.4, 138.4, 136.2, 135.5, 134.8, 131.6, 129.6, 129.4, 129.1, 128.9, 127.6, 125.6, 116.0, 115.7, 114.7, 114.1, 112.0, 101.4, 57.2, 55.2, 14.7$. Anal. calcd. for $C_{31}H_{24}F_2N_2O_2S$; C, 70.71; H, 4.59; N, 5.32; found: C, 70.70; H, 4.64; N, 5.30.

*4.1.1.14. (E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(7-((E)-2-(benzo[d][1,3] dioxol-5-yl)vinyl)-5-(4-methoxyphenyl)-3-methyl-5H-thiazolo[3,2-a] pyrimidin-6-yl)prop-2-en-1-one (**16**).* It was obtained by the reaction of **1b** (1.0 g, 3.6 mmol), propargyl bromide (0.43 mL, 3.6 mmol), KOH (1.0 g, 18.0 mmol) and 3,4-methylenedioxybenzaldehyde (1.14 g, 7.6 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 185–189 °C; yield (1.36 g, 65%) ; IR (KBr) ν_{max} cm^{-1}: 2922 (CH stretching), 1714 (-C=O stretching), 1560 (-C=N stretch), 680 (CH–S stretch); ESMS: $m/z = 579$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 15.05$ Hz, 1H, H2″), 7.45 (d, $J = 15.42$ Hz, 1H, H3′), 7.33–7.28 (m, 2H, ArH, H1″), 7.21–7.11 (m, 2H, ArH, H2′), 7.02–6.97 (m, 4H, ArH), 6.81–6.72 (m, 4H, ArH), 6.28 (s, 1H, H5); 6.06 (s,1H); 2.15 (s, 3H, CH_3). Anal. calcd. for $C_{33}H_{26}N_2O_6S$; C, 68.50; H, 4.53; N, 4.84; found: C, 68.55; H, 4.58; N, 4.80.

*4.1.1.15. (E)-1-(5-(4-Methoxyphenyl)-3-methyl-7-((E)-2-(thiophen-2-yl)vinyl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-(thiophen-2-yl)prop-2-en-1-one (**17**).* It was obtained by the reaction of **1b** (1.0 g, 3.6 mmol), propargyl bromide (0.43 mL, 3.6 mmol), KOH (1.0 g, 18.0 mmol) and thiophene-2-carboxaldehyde(0.71 mL, 7.6 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 143–145 °C; yield (1.27 g, 70%) ; IR (KBr) ν_{max} cm^{-1}: 2937 (CH stretching), 1623 (-C=O stretching), 1513 (-C=N stretch), 700 (CH–S stretch); ESMS: $m/z = 503$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 14.53$ Hz, 1H, H2″), 7.70 (d, $J = 15.09$ Hz, 1H, H3′), 7.34–7.28 (m, 3H, ArH, H1″), 7.24–7.20 (m, 3H, ArH, H2′), 7.17–7.13 (m, 2H, ArH), 7.04–7.00 (m, 2H, ArH), 6.82 (d, $J = 8.58$ Hz, 2H, ArH), 6.28 (s, 1H, H5); 6.08 (s,1H, H2); 3.76 (s, 3H, OCH_3); 2.15 (s, 3H, CH_3); anal. calcd. for $C_{27}H_{22}N_2O_2S_3$: C, 64.51; H, 4.41; N, 5.57; found: C, 64.45; H, 4.47; N, 5.53

*4.1.1.16. (E)-1-(3-Methyl-5-(3,4,5-trimethoxyphenyl)-7-(3,4,5-trimethoxystyryl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (**18**).* It was obtained by the reaction of **1c** (1 g, 2.9 mmol), propargyl bromide (0.35 mL, 2.9 mmol), KOH (0.83 g, 14.5 mmol) and 3,4,5-trimethoxybenzaldehyde (1.22 mL, 6.2 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 182–184 °C; yield (1.27 g, 69%); IR (KBr) ν_{max} cm^{-1}: 2939 (CH stretching), 1630 (-C=O stretching), 1581 (-C=N stretch), 700 (CH–S stretch); ESMS: $m/z = 731$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (d, $J = 15.39$ Hz, 1H, H2″), 7.41 (d, $J = 15.63$ Hz, 1H, H3′), 7.30–7.24 (m, 2H, H2′ , H2″), 6.70 (d, $J = 1.65$ Hz, 4H, ArH), 6.59 (s, 2H, ArH), 6.30 (s, 1H, H5), 6.12 (s, 1H, H2), 3.82–3.77 (m, 15H, OCH_3), 3.63 (s, 6H, OCH_3), 3.59 (s, 6H, OCH_3), 2.16 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.3, 166.8, 153.4, 152.1, 139.8, 139.1, 138.7, 137.8, 136.4, 131.8, 130.9, 128.8, 128.0, 128.0, 125.9, 111.6, 104.7, 104.2, 103.0, 96.1, 65.9, 60.7, 57.1, 55.9, 55.7, 13.9$. Anal. calcd. for $C_{39}H_{42}N_2O_{10}S$: C, 64.09; H, 5.79; N, 3.83; found: C, 64.06; H, 5.81; N, 3.81; O, 21.94; S, 4.31.

*4.1.1.17. (E)-3-(4-Methoxyphenyl)-1-(7-(4-methoxystyryl)-3-methyl-5-(3,4,5-trimethoxyphenyl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**19**).* It was obtained by the reaction of **1c** (1.0 g, 2.9 mmol), propargyl bromide (0.35 mL, 2.9 mmol), KOH (0.83 g, 14.5 mmol) and 4-methoxybenzaldehyde (0.85 mL, 6.2 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 148–150 °C; yield (1.27 g, 69%) ; IR (KBr) ν_{max} cm^{-1}: 2922 (CH stretching), 1629 (-C=O stretching), 1508 (-C=N- stretch), 768 (CH–S stretch); ESMS: $m/z = 611$ $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 15.08$ Hz, 1H, H2″), 7.52–7.42 (m, 5H, ArH,

H3′), 7.28–7.22 (m, 2H, ArH, H1″), 6.84–6.78 (m, 4H, ArH), 6.59 (s, 2H, ArH), 6.29 (s, 1H, H5), 6.07 (s, 1H, H2), 3.82–3.78 (m, 15H, $OCH_3\times5$), 2.17 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.8$, 166.5, 160.9, 160.3, 153.3, 152.0, 139.1, 138.0, 137.6, 136.2, 136.1, 129.4, 129.2, 128.8, 128.2, 126.0, 123.9, 114.2, 111.3, 103.0, 100.4, 60.5, 57.3, 55.9, 55.1, 13.9. Anal. calcd. for $C_{35}H_{34}N_2O_6S$: C, 68.83; H, 5.61; N, 4.59; found: C, 68.80; H, 5.67; N, 4.64.

*4.1.1.18. (E)-1-(5-(4-Chlorophenyl)-3-methyl-7-styryl-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-phenylprop-2-en-1-one (**20**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and benzaldehyde (0.79 mL, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 204–205 °C; yield (1.21 g, 69%); IR (KBr) ν_{max} cm^{-1}: 2970 (CH stretching), 1623 (-C=O stretching), 1563 (-C=N- stretch), 687 (CH–S stretch); ESMS: $m/z = 496$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 15.18$ Hz, 1H, H2″), 7.59–7.48 (m, 5H, ArH, H3′), 7.43–7.38 (m, 2H, ArH, H1″), 7.35–7.24 (m, 10H, ArH, H2′), 6.35 (s, 1H, H5), 6.12 (s, 1H, H2), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.6$, 167.0 (C9), 152.4, 141.0, 139.7, 137.0, 136.3, 135.9, 135.4, 133.9, 129.7, 128.9, 128.8, 127.8, 127.7, 127.5, 126.0, 111.3, 101.3, 56.9(C5), 13.9(CH_3). Anal. calcd. for $C_{30}H_{23}ClN_2OS$: C, 72.79; H, 4.68; N, 5.66; found: C, 72.75; H, 4.73; N, 5.70.

*4.1.1.19. (E)-3-(2-Chlorophenyl)-1-(5-(4-chlorophenyl)-7-(2-chlorostyryl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**21**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and 2-chlorobenzaldehyde (0.84 mL, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 185–186 °C; yield (1.21 g, 70%); IR (KBr) ν_{max} cm^{-1}: 2921 (CH stretching), 1707 (-C=O stretching), 1567 (-C=N- stretch), 673 (CH–S stretch); ESMS: $m/z = 564$ $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.05$ (d, $J = 15.50$ Hz, 1H, H-2″), 7.89 (d, $J = 15.62$ Hz, 1H, H-3′), 7.51–7.47 (m, 2H, Ar–H), 7.38–7.35 (m, 5H, Ar–H, H-1″), 7.30–7.25 (m, 3H, H-2′, Ar–H), 7.23–7.16 (m, 2H, Ar–H), 7.10–7.04 (m, 2H, Ar–H), 6.34 (s, 1H, H-5), 6.13 (s, 1H, H-2), 2.13 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 187.5$, 167.3, 152.6, 141.1, 136.1, 135.9, 135.3, 134.7, 134.6, 134.3, 133.8, 133.2, 130.6, 130.5, 130.4, 130.3, 129.9, 129.2, 128.9, 128.0, 127.5, 127.3, 127.1, 127.0, 111.8, 101.9, 57.3, 14.1. Anal. calcd. for $C_{30}H_{21}Cl_3N_2OS$: 63.90; H, 3.75; N, 4.97; found: 63.88; H, 3.77; N, 4.95.

*4.1.1.20. (E)-3-(3-Chlorophenyl)-1-(5-(4-chlorophenyl)-7-(3-chlorostyryl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**22**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and 3-chlorobenzaldehyde (0.85 mL, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 175–176 °C; yield (1.42 g, 71%) ; IR (KBr) ν_{max} cm^{-1} : 2921 (CH stretching), 1707 (-C=O stretching), 1567 (-C=N- stretch), 673 (CH–S stretch); ESMS: $m/z = 564$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 15.43$ Hz, 1H, H2″), 7.46–7.41 (m, 3H, ArH, H3′), 7.36–7.30 (m, 6H, ArH, H1″), 7.29–7.21 (m, 6H, ArH, H2′), 6.36 (s, 1H, H5), 6.17 (s, 1H, H2), 2.15 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.1$, 167.0, 152.0, 140.7, 138.2, 138.1, 137.2, 136.0, 135.8, 134.9, 134.8, 134.1, 130.1, 129.6, 129.0, 128.9, 127.7, 127.5, 127.2, 125.7, 125.3, 111.5, 101.7, 96.1, 56.9, 13.9. Anal. calcd. for $C_{30}H_{21}Cl_3N_2OS$: C, 63.90; H, 3.75; N, 4.97; found: 63.86; H, 3.80; N, 4.99.

*4.1.1.21. (E)-3-(4-Chlorophenyl)-1-(5-(4-chlorophenyl)-7-(4-chlorostyryl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**23**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and 4-chlorobenzaldehyde (1.05 g, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 197–198 °C; yield (1.34 g, 67%); IR (KBr) ν_{max} cm^{-1}: 2967 (CH stretching), 1720 (-C=O stretching), 1565 (-C=N- stretch), 676 (CH–S stretch); ESMS: $m/z = 564$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 15.51$ Hz, 1H, H2″), 7.51–7.41 (m, 3H, ArH, H3′), 7.38–7.35 (m, 3H, ArH), 7.33–7.22 (m, 9H, ArH, H1″), 6.33 (s, 1H, H5), 6.14 (s, 1H, H2), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.2$, 140.7, 138.4, 136.0, 135.8, 134.9, 134.7, 134.0, 129.1, 129.0, 128.9, 128.5, 128.1, 127.7, 126.3, 124.0, 123.2, 111.4, 101.7, 56.9, 13.9. Anal. calcd. for $C_{30}H_{21}Cl_3N_2OS$: C, 63.90; H, 3.75; N, 4.97; found: 63.87; H, 3.77; N, 4.91.

*4.1.1.22. (E)-3-(4-Bromophenyl)-1-(7-(4-bromostyryl)-5-(4-chlorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**24**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and 4-bromobenzaldehyde (1.38 g, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 199–200 °C; yield (1.51 g, 65%); IR (KBr) ν_{max} cm^{-1}: 2964 (CH stretching), 1628 (-C=O stretching), 1566 (-C=N- stretch), 678 (CH–S stretch); ESMS: $m/z = 653$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 15.65$ Hz, 1H, H2″), 7.49 (d, $J = 5.61$ Hz, 1H, ArH), 7.43–7.39 (m, 4H, ArH, H3′), 7.36–7.30 (m, 7H, ArH, H1″), 7.27–7.23 (m, 3H, ArH, H2′), 6.33 (s, 1H, H5), 6.14 (s, 1H, H2), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.2$, 167.0, 152.2, 140.7, 138.5, 136.0, 135.9, 135.1, 134.2, 134.0, 132.1, 132.0, 131.7, 129.1, 129.0, 128.7, 128.2, 127.7, 126.4, 124.0, 123.2, 111.4, 101.6, 56.9, 13.9. Anal. calcd. for $C_{30}H_{21}Br_2ClN_2OS$: C, 55.19; H, 3.24; N, 4.29; found: C, 55.15; H, 3.27; N, 4.28.

*4.1.1.23. (E)-3-(4-(Benzyloxy)phenyl)-1-(7-(4-(benzyloxy)styryl)-5-(4-chlorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)prop-2-en-1-one (**25**).* It was obtained by the reaction of **1d** (1.0 g, 3.5 mmol), propargyl bromide (0.42 mL, 3.5 mmol), KOH (0.99 g, 17.5 mmol) and 4-benzyloxybenzaldehyde (1.58 g, 7.4 mmol) and ethanol (20 mL) as solvent as described above as red solid, mp = 170–171 °C; yield (1.71 g, 68%); IR (KBr) ν_{max} cm^{-1}: 2925 (CH stretching), 1633 (-C=O stretching), 1507 (-C=N- stretch), 615 (CH–S stretch); ESMS: $m/z = 708$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 15.39$, 1H, H2″), 7.51–7.31 (m, 16H, ArH, H3′), 7.28–7.16 (m, 6H, ArH), 6.91–6.87 (m, 3H, H2″, H2′, H1″), 6.33 (s, 1H, H5), 6.07 (s, 1H, H2), 5.08 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 187.5$, 166.6, 160.1, 159.6, 152.2, 141.1, 139.3, 136.6, 136.5, 135.8, 133.8, 129.4, ,128.9, 128.5, 128.0, 127.7, 127.4, 125.8, 123.9, 115.1, 111.1, 69.9, 56.8, 13.9. Anal. calcd. for $C_{44}H_{35}ClN_2O_3S$: C, 74.72; H, 4.99; N, 3.96; found: C, 74.70; H, 5.01; N, 3.93.

4.1.2. 2D NMR studies

The **2D** NMR Studies of compound **21** were carried out on a Bruker Avance-400 MHz (300 K) in $CDCl_3$ solvent with TMS as an internal standard. ^{13}C NMR spectra were recorded with complete proton decoupling. The assignment was carried out with the help of COSY, NOESY, HSQC and HMBC experiments. 2D-NOESY was used to fix the spatial correlations which helped in assignment. All the spectra were recorded in phase sensitive mode except for COSY which is in magnitude mode. The spectra were acquired with 2*256 FID for NOESY and HMBC, 256 Fids for HSQC and 128 Fids for COSY containing 4–16 transients for all the experiments with a recycle delay of 1.5 s.

4.2. Biology

4.2.1. Antimalarial assay

Antimalarial assay for synthetic compounds was carried out against CQ sensitive 3D7 as well as CQ resistant K1clone of *P. falciparum* [39]. Parasite culture was maintained *in vitro* in RPMI-1640 (HEPES modification) medium supplemented with 0.5% AlbuMaxII, 0.2% glucose, 0.2% $NaHCO_3$ and additionally 15 μM

hypoxanthine, incubated at 37 °C with 5% CO_2 and daily change of medium. Parasite growth rate and stage was determined by the examination of a giemsa's stained thin smear of the parasitized RBCs.

Stock solution of synthesized compounds were prepared at 10mg/mL in DMSO and stored at 0 °C until use. Two fold serial dilutions of these compounds as well as standard drug chloroquine (50 μL per well) were prepared in 96 well microtiter plates. Infected erythrocytes (50 μL per well with 4% haematocrit and 1% parasitaemea) were added to these wells. Plates were incubated in CO_2 incubator maintained at 37 °C and 5% CO_2. After 72 h incubation, 100 μL lytic buffer (20 mM Tris pH 7.5, 5 mM EDTA, 0.008% saponin, and 0.08% Triton X-100) containing SYBR green (2X), was added to each well and incubated for 4 h at room temp in dark. Plates were read under fluorescence reader at ex.485 nm, em. 535 nm. IC_{50} values were determined on the basis of DNA content of the parasite relative to controls using MS-EXEL.

4.2.2. Cytotoxicity assay

Cytotoxic assay was carried out against monkey kidney cell line C1008 (Vero cells) [40]. Cells were cultivated in 25 cm^2 tissue culture flask supplemented with MEM-medium and 15%FBS provided with 5% CO_2 at 37 °C. For the cytotoxicity assay, cells were washed with PBS, trypsinized with 0.25% trypsin and a cell suspension was made in culture medium. Cells were counted in Neubaur chamber and appropriate dilution was made (1×10^5 cells/mL). Vero cell suspension (100 μL) was added to the 96 well microtiter plates and allowed to adhere overnight. Serial dilutions of test compounds were prepared in these plates and adhered Vero cells were incubated with these compounds for 72 h. Cell viability marker resazurin was added in wells and after 4 h, these plates were read under florescence reader. Cytotoxic concentration (CC_{50}) was determined using MS-EXEL.

Selectivity index was calculated using formula:

$$\text{Selective index} = \frac{\text{Median cytotoxic concentration} \quad (CC_{50})}{\text{Median inhibitory concentration} \quad (IC_{50})}$$

4.2.3. RT assay: determination of reverse transcriptase inhibition

The compounds for anti-HIV-1 RT activity was measured by using non radioactive colorimetric ELISA RT Assay kit (Roche) [41], and the procedure for assaying RT inhibition was performed as described elsewhere [42–44]. The detection and quantification of synthesized DNA as a parameter for RT activity that incorporate digoxigenin and biotin-labelled dUTP in DNA strand. The synthesized DNA strand is separated from free biotin-labelled dUTP by streptovidin coated plates. The peroxidase conjugated anti-DIG-POD antibodies bind to the digoxigenin-labelled DNA that is incorporated in synthesized DNA. Further, the peroxidase substrate ABTS is added. The peroxidase enzyme catalyzes the cleavage of the substrate, producing a coloured reaction product.

Briefly, the reaction mixture consists of 20 μl each of template/primer complex with dNTPs, reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors to make a total volume of 60 μl was incubated at 37 °C for 1 h. As a negative control, 20 μL lysis buffer with no RT was used. The activity of compounds was measured at two concentrations, 10 μg/mL and 100 μg/mL. Nevirapine was used as a positive compound. The reaction mix was transferred in streptavidine-coated microtiter plate (MTP) and incubation for 1 h at 37 °C. After incubation, plates were washed five times with 250 μL washing buffer to remove the unbound dNTPs and added 200 μL of anti-dioxigenin-peroxidase (Anti-DIG-POD, 200 mU/mL) diluted in conjugate dilution buffer. After 1 h, plates were washed again, 200 μL ABTS substrate solution/well was added, and incubated at room temperature until sufficient colour was developed. Optical density (OD) was measured by ELISA reader at 405 nm (reference wavelength: 490 nm). The resulting colour intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by using the formula shown below.

$$\%\ \text{RT inhibition} = 100 - \frac{(\text{OD 405 nm with inhibitor})}{(\text{OD 405 nm without inhibitor})} \times 100$$

Acknowledgments

Authors thank, CSIR network project "SPLENDID" and DRDO New Delhi for financial assistance. Seerat and Anindra are thankful to CSIR New Delhi for their SRF. We are also thankful to SAIF Division, CDRI for providing the spectral data and microanalyses. This is a CDRI communication No. 8286.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejmech.2012.07.018.

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