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RESEARCH ARTICLE

Synthesis and anti-HIV-1 screening of novel *N*′-(1-(aryl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides

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Abstract A novel series of *N*′-(1-(aryl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides was synthesized. The synthesis was carried out by thermal method as well as ultrasonic bath to reduce reaction time and to enhance product yields. The synthesized compounds were characterized by spectroscopic techniques like NMR, infrared and EIMS. The structure of compound **5w** was elucidated by X-ray crystallography. The titled compounds were evaluated for anti-human immunodeficiency virus type 1 (anti-HIV-1) and cytotoxic activities. Biological studies indicated that amongst these compounds, **5a**, **b**, **j**, **h** and **i** showed the activity with median effective concentration (EC_{50}) values less than 20 μM. Compound **5i** exhibited the most potent anti-HIV-1 activity (EC_{50} = 3.2 μM) while **5h** showed anti-HIV-1 activity (EC_{50} = 3.8 μM) with no toxicity at all in primary human lymphocytes, CEM and VERO cells.

Keywords Pyrazolobenzothiazine · Hydrazides · Cytotoxic activity · Anti-HIV-1 activity

This work is dedicated to Dr. Hamid Latif Siddiqui, our honourable teacher (SA and MA), our friend and colleague (MZ, MP and RFS) who passed away on 26 July 2012.

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Introduction

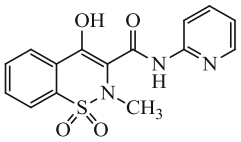
Human immunodeficiency virus type 1 (HIV-1) is a retrovirus belonging to the family *Lentiviridae*. It replicates over a RNA–cDNA intermediate through the virally encoded reverse transcriptase (RT) enzyme. Potent anti-HIV agents, e.g. guanosine analogue carbovir (Vince and Hua 1990) and its prodrug abacavir (Daluge 1991) have a skeletal structure of carbocyclic nucleosides. At present nucleoside RT inhibitors (NRTIs; De Clercq 2001) represent the backbone of combinatorial regimens for the treatment of HIV infections. These inhibitors are usually combined with protease inhibitors and non-NRTI, integrase, or entry/fusion inhibitors for the treatment of infection. Despite the effectiveness of this combinatorial psychotherapy, a long-term use of these drugs results in the assortment of viral resistance mutants (Turner et al. 2004). Moreover, the infected individuals with resistant strains of HIV-1, have significantly been increased (Mocroft et al. 2002; Little et al. 2002; Tamalet et al. 2003). Consequently, the discovery of novel anti-HIV drugs with anti-viral activity against drug-resistant strains of HIV-1 is critical.

Oxicams are 1,2-benzothiazine-3-carboxamides 1,1-dioxides and are recognized as second generation of non-steroidal anti-inflammatory drugs (Olkkola et al. 1994). Oxicams include piroxicam, meloxicam, isoxicam and ampiroxicam, etc. Heterocyclic ring systems such as pyrimidine, piperazine and piperidine are acting as a template in various anti-HIV drugs that are available in the market. Benzothiazine derivatives have been reported for a wide range of biological activities like anti-inflammatory (Suh et al. 1987; Lomabardino et al. 1971), anti-malarial (Barazarte et al. 2009), anti-depressants (Lopatina et al. 1982), anti-bacterial (Hogale and Uthale 1990), anti-allergic (Ikeda et al. 1992), and anti-thrombotic agents (Constantine 1967). A great deal of research work has been performed on potentially biologically active benzothiazine derivatives.

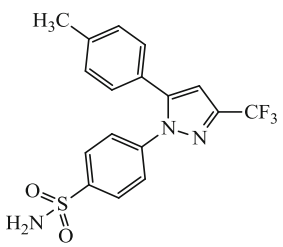
From medicinal point of view, pyrazole is characterized as one of the most significant class of heterocyclic compounds. They possess a wide range of pharmaceutical applications like anti-bacterial (Akbas et al. 2005; Akbas and Berber 2005), anti-viral (Baraldi et al. 1998), herbicidal (Mahajan et al. 1991), anti-fungal (Iovu et al. 2003) and anti-tumor activity (Hall et al. 2008). Some of pyrazole derivatives have therapeutic potential of hypoglycaemic (Smith et al. 2001), anti-inflammatory (Silverstein et al. 2000), anti-arrhythmic and sedative (Cottineau et al. 2002). Celecoxib (Fig. 1), a pyrazole based drug is an important selective COX-2 enzyme inhibitor (Talley et al. 1995; Silverstein et al. 2000).

Keeping in view the pharmacological importance of these two pharmacophores, i.e., pyrazole and 1,2-benzothiazine (Fig. 1), we have incorporated both heterocyclic nuclei into one therapeutic unit as pyrazolobenzothiazine. Some derivatives of this ring system are recently reported as inhibitors of HCV replication (Maria et al. 2013). While continuing our research on pyrazolobenzothiazines, we have explored pyrazolo[4,3-*c*][1,2]benzothiazine,2,4-dihydro-3,4-dimethyl-, 5,5-dioxide derivatives (Ahmad et al. 2010a), *N*′-arylmethylidene-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2] benzothiazin-2(4*H*)-yl)acetohydrazides (Ahmad et al. 2010d), *N*-(substituted-2-chloroquinolin-3-yl)methylidene-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazides 1,1-dioxides (Ahmad et al. 2012) and *N*-substituted benzyl/phenyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides (Ahmad et al. 2013) as anti-oxidants and anti-microbial agents. In the present study, we synthesized novel *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenyl benzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides and have evaluated them for anti-HIV-1 activity and cytotoxicity (Scheme 1).

In this work, we have incorporated a range of substituted heterocyclic moieties in the final compounds to discuss the effect of particular heterocycle. Structure–activity relationship (SAR) is established by incorporating a versatile range of substituted thiophenes as well as other heterocyclic moieties like thiazole, furan and pyridine. Moreover, an aldimine was prepared by using thiophen-2-carboxaldehyde to determine the role of methyl group at N=CCH$_3$ in the biological activity. The synthetic procedures were optimized by conduction of chemical reactions in an ultrasonic bath to increase the yield and minimize the reaction time period.



(**Piroxicam**)



(**Celecoxib**)

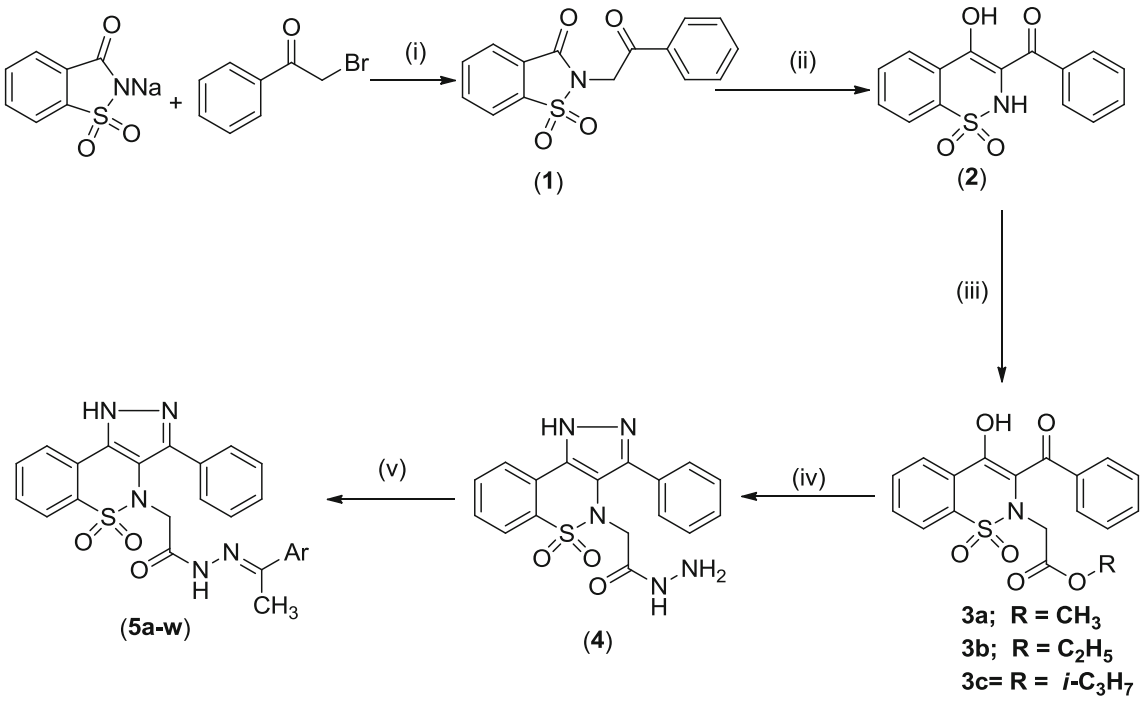
Fig. 1 Potent anti-inflammatory drugs based on benzothiazine and pyrazole pharmacophores, respectively

Materials and methods

All the chemicals were purchased from E. Merck, Sigma/Aldrich or Fluka and were used without purification. General melting points were obtained on Gallenkamp melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded in KBr pellets on Perkin Elmer infrared spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on Brucker/XWIN NMR (300 and 400 MHz) and TMS was used as internal standard (chemical shifts, δ in ppm). Mass spectra were recorded on a Jeol MS Route instrument. Ultrasonic mediated reactions were carried out in Clifton Ultrasonic Bath (29 T2A, 300 W, DU-4) made by Nickel Electro Ltd. X-ray crystallography was carried out on Bruker Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation and the data were corrected for Lorentz and polarization effects and for absorption using multi-scan method.

Synthesis of 2-(2-oxo-2-phenylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (*N*-phenacyl saccharin) (**1**)

Phenacyl bromide (0.222 mol) was added to anhydrous sodium saccharine (45.55 g, 0.222 mol) using DMF (20 mL) as reaction medium. The reaction mixture was irradiated under microwave of 30 W for 25 min and was monitored with TLC as compared to our previously reported method where it completed in 3 h (Ahmad et al. 2010b). Then, the reaction mixture was cooled to room temperature



Scheme 1 Synthetic route for novel series of *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides (**5a**–**w**)

and poured on crushed ice. Resulted white precipitates were filtered, washed with water and re-crystallized by ethanol. Yield: 87 %; FT-IR (KBr) ν_{max}: 1715, 1345, 1165 cm^{-1}; ^1H NMR: (DMSO-d_6, 400 MHz) δ: 5.15 (2H, s, *N*–CH_2), 7.47 (2H, t, $J = 7.4$ Hz, Ar–*H*), 7.59 (1H, t, $J = 7.4$ Hz, Ar–*H*), 7.81–7.90 (2H, m, Ar–*H*), 7.92 (1H, d, $J = 6.6$ Hz, Ar–*H*), 7.94 (2H, d, $J = 6.8$ Hz, Ar–*H*), 8.07 (1H, d, $J = 7.8$ Hz, Ar–*H*); MS: ES−; 301.1 (M^+), +ES; 324.04 (M^++Na^+).

Synthesis of 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2**)

Compound (**2**) was prepared according to the literature method (Ahmad et al. 2010c). Fresh sodium methoxide was first prepared by refluxing the sodium metal (10.68 g, 0.464 mol) in 60 mL of freshly dried methanol under inert atmosphere maintained by N_2 gas. Subsequently, *N*-phenacyl saccharin (**1**) (10.0 g, 0.232 mmol) was added to the sodium methoxide in refluxing methanol. The colour of the reaction mixture was immediately turned to orange red. The mixture was further refluxed for 20 min and then cooled to room temperature, poured to ice cold 10 % HCl solution. The resulted white precipitates were filtered, washed with distilled water and dried (caution; inert atmosphere must be maintained in the vessel, otherwise traces of moisture could cause the drastic decrease in yield). White crystalline solid. Yield: 82 %; mp 156 °C; FT-IR (KBr) cm^{-1}: 3457, 3215, 1625, 1358, 1157; ^1H NMR: (DMSO-d_6) (400 MHz) δ: 5.79 (1H, s, SO_2NH), 7.61 (1H, t, $J = 7.8$ Hz, Ar–*H*), 7.71 (1H, d, $J = 7.8$ Hz, Ar–*H*), 7.95–7.99 (5H, m, Ar–*H*), 8.15 (2H, t, $J = 4.6$ Hz, Ar–*H*), 14.67 (1H, s, O–H); MS *m*/*z*: ES−; 301.07 (M^+), +ES; 302.06 (M^++H^+).

General procedure for the synthesis of alkyl [4-hydroxy-1,1-dioxido-3-(phenylcarbonyl)-2*H*-1,2-benzothiazin-2-yl]acetate (**3**)

3-Benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2**) (6.0 g, 0.020 mol) and anhydrous potassium carbonate (3.31 g, 0.024 mol) and methyl chloroacetate (2.60 g, 0.024 mol) were mixed in acetonitrile (50 mL). The mixture was allowed to reflux for 8 h during which the completion of reaction was monitored by TLC. The solvent was removed under vacuum. The contents of the flask were poured in cold water and neutralized by dil. HCl to get the dirty yellow crystalline product.

3a

Mp 165 °C; FT-IR (KBr) cm^{-1}: 1756, 1328, 1181; ^1H NMR (DMSO-d_6) (400 MHz) δ: 3.25 (3H, s, O–CH_3), 3.96 (2H, s, *N*–CH_2), 7.63 (1H, t, $J = 7.8$ Hz, Ar–H), 7.78 (1H, d, $J = 8.4$ Hz, Ar–*H*), 7.89–7.97 (5H, m, Ar–*H*), 8.16 (2H, t, $J = 4.8$ Hz, Ar–*H*), 14.68 (1H, s, O–H); MS *m/z*: ES−; 373.09 (M^+), +ES; 374.09 ($M^+ + H^+$).

3b

Dirty yellow crystalline; ^1H NMR (DMSO-d_6) (300 MHz) δ: 0.9 (3H, t, $J = 8.4$ Hz, C–CH_3), 2.98 (2H, q, $J = 8.4$ Hz, O–CH_2), 3.96 (2H, s, *N*–CH_2), 7.63 (1H, t, $J = 7.8$ Hz, Ar–H), 7.78 (1H, d, $J = 8.4$ Hz, Ar–*H*), 7.89–7.97 (5H, m, Ar–*H*), 8.16 (2H, t, $J = 4.8$ Hz, Ar–*H*), 14.68 (1H, s, O–H); ^{13}C NMR: 13.43, 39.75, 51.92, 60.72, 115.93, 122.20, 127.18, 128.23, 128.61, 129.18, 128.69, 132.99, 133.05, 134.00, 135.23, 138.17, 166.80, 167.17, 190.02; MS *m/z*: ES−; 387.09 (M^+), +ES; 410.09 ($M^+ + Na^+$); HR/MS (ES−) 386.0700 ($C_{19}H_{17}NO_6S$).

3c

Light yellow crystalline; ^1H NMR (DMSO-d_6) (300 MHz) δ: 1.34 (6H, d, $J = 8.4$ Hz, C–CH_3), 3.97 (2H, s, *N*–CH_2), 4.11 (1H, m, O–CH), 7.67 (1H, t, $J = 8.1$ Hz, Ar–H), 7.79 (1H, d, $J = 8.4$ Hz, Ar–*H*), 7.87–7.99 (5H, m, Ar–*H*), 8.17 (2H, t, $J = 7.8$ Hz, Ar–*H*), 14.67 (1H, s, O–H); ^{13}C NMR: 23.43, 51.91, 69.72, 117.86, 122.20, 126.77, 127.18, 128.23, 128.61, 129.08, 128.59, 132.99, 133.15, 134.04, 135.33, 139.17, 161.80, 169.17, 191.02; MS *m/z*: ES−; 400.09 (M^+), +ES; 401.01 ($M^+ + H^+$); HR/MS (ES−) 400.0910 ($C_{20}H_{19}NO_6S$).

Synthesis of 2-(5,5-dioxido-3-phenylpyrazolo[4,3-*c*][1,2]benzothiazin-4(1*H*)-yl)acetohydrazide (**4**)

A mixture of methyl [4-hydroxy-1,1-dioxido-3-(phenylcarbonyl)-2*H*-1,2-benzothiazin-2-yl]acetate (**3**) (5.0 g, 13.4 mmol) and hydrazine monohydrate (4.9 mL, 99 mmol) in 50 mL ethanol was refluxed for 4 h. Then the unreacted hydrazine monohydrate and ethanol was removed under vacuum. The crude product then dissolved in ice cold water and neutralized with dil. HCl. The resulted precipitates were filtered, recrystallized with ethanol and dried. Light dirty yellow powder; mp 192–193 °C; FT-IR (KBr) cm^{-1}: 3368, 1675, 1337, 1165; ^1H NMR: (DMSO-d_6) (400 MHz) δ: 4.16 (2H, s, *N*–CH_2), 4.52 (2H, d, $J = 10.4$ Hz, NH_2), 7.60 (3H, d, $J = 8.4$ Hz, Ar–*H*), 7.77–7.89 (4H, m, Ar–*H*), 7.98–8.05 (1H, dd, $J_1 = 7.8$ Hz, $J_2 = 18.4$ Hz, Ar–*H*), 8.96 (1H, s, NH), 14.27 (1H, s, N–H); MS *m/z*: 369.1 (ES−), 392.10 (ES+, $M^+ + Na^+$).

General procedure for the synthesis of *N*′-(1-(substituted-thiophen-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazide (**5a**–**w**)

2-(5,5-Dioxido-3-phenylpyrazolo[4,3-*c*][1,2]benzothiazin-4(1*H*)-yl)acetohydrazide (**4**) (0.5 g, 1.355 mmol), heterocyclic aromatic ketones (1.355 mmol) were dissolved in ethanol. 0.3 mL of glacial acetic acid was added in the reaction mixture and the mixture was allowed to reflux for 0.5–1 h; during the time period, the reaction was monitored by TLC. The resulted precipitates were filtered and washed with hot methanol and dried.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(thiophen-2-yl)ethylidene)acetohydrazide (**5a**)*

White powder; yield: 92 %; mp 260 °C; FT-IR (KBr) cm^{-1}: 3648, 3309, 3178, 3075, 1671, 1594, 1326, 1156; ^1H NMR (DMSO-d_6) (300 MHz) δ: 2.06 (3H, s, C–CH_3), 4.61 (2H, s, *N*–CH_2), 6.98–7.01 (2H, q, $J = 5.7$ Hz, Ar–*H*), 7.28–7.36 (2H, dd, $J_1 = 3.0$ Hz, $J_2 = 18.0$ Hz, Ar–*H*), 7.49 (2H, d, $J = 5.1$ Hz, Ar–*H*), 7.55–7.65 (3H, m, Ar–*H*), 7.77–7.91 (2H, m, Ar–*H*), 8.04 (1H, s, Ar–*H*), 10.46 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 14.32, 51.21, 119.07, 121.90, 122.11, 123.17, 125.99, 126.18, 127.23, 127.44, 128.21, 128.94, 129.18, 132.07, 132.17, 133.09, 134.44, 139.55, 142.83, 142.94, 148.95, 162.76, 167.75; MS *m/z*: 477.1 (M^+); anal. calcd. for $C_{23}H_{19}N_5O_3S_2$: C, 57.85; H, 4.01; N, 14.66. Found: C, 57.81; H, 4.09; N, 14.73.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(3-methylthiophen-2-yl)ethylidene)acetohydrazide (**5b**)*

White powder; yield: 94 %; mp 252 °C; FT-IR (KBr) cm^{-1}: 3678, 3263, 2936, 1694, 1604, 1312, 1151; ^1H NMR (DMSO-d_6) (300 MHz) δ: 2.06 (3H, s, C–CH_3), 2.25 (3H, s, C–CH_3), 4.61 (2H, s, *N*–CH_2), 6.90 (2H, d, $J = 5.10$ Hz, Ar–*H*), 7.41 (1H, d, $J = 5.10$ Hz, Ar–*H*), 7.46–7.54 (2H, m, Ar–*H*), 7.61–7.81 (4H, m, Ar–*H*), 8.04–8.07 (2H, m, Ar–*H*), 10.37 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 16.45, 51.76, 119.07, 121.90, 122.21, 123.10, 125.03, 125.52, 126.00, 127.26, 128.22, 128.93, 129.19, 131.92, 132.13, 132.46, 134.75, 135.30, 136.38, 139.59, 145.27, 149.79, 162.67, 167.87; MS *m/z*: 491.1 (M^+); anal. calcd. for $C_{24}H_{21}N_5O_3S_2$: C, 58.64; H, 4.31; N, 14.25. Found: C, 58.57; H, 4.28; N, 14.36.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(thiophen-3-yl)ethylidene)acetohydrazide (**5c**)*

Off white powder; yield: 91 %; mp 267 °C; FT-IR (KBr) cm^{-1}: 3644, 3314, 2986, 1676, 1576, 1328, 1157; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.02 (3H, s, C–CH_3), 4.67 (2H, s, *N*–CH_2), 7.18 (1H, d, $J = 4.8$ Hz, Ar–*H*), 7.44–7.46 (3H, dd, $J_1 = 3.0$ Hz, $J_2 = 5.10$ Hz, Ar–*H*), 7.54 (1H, d, $J = 7.5$ Hz, Ar–*H*), 7.69 (1H, s, Ar–*H*), 7.84 (4H, d, $J = 7.5$ Hz, Ar–*H*), 8.05 (2H, d, $J = 7.5$ Hz, Ar–*H*), 10.34 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 14.61, 51.29, 119.16, 122.13, 122.46, 123.16, 125.10, 125.59, 126.25, 128.03, 128.30, 128.94, 129.17, 132.04, 133.06, 134.46, 139.53, 140.67, 141.75, 145.30, 149.19, 162.92, 168.11; MS *m/z*: 471.0 (M^+); anal. calcd. for $C_{23}H_{19}N_5O_3S_2$: C, 57.85; H, 4.01; N, 14.66. Found: C, 57.89; H, 4.07; N, 14.57.

*N′-(1-(2,5-dimethylthiophen-3-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5d**)*

White powder; yield: 90 %; mp 220 °C; FT-IR (KBr) cm^{-1}: 3649, 3329, 2921, 1688, 1596, 1324, 1154; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 1.95 (3H, s, C–CH_3), 2.08 (3H, s, C–CH_3), 2.30 (3H, s, C–CH_3), 4.59 (2H, s, *N*–CH_2), 6.74 (1H, s, Ar–*H*), 7.44–7.54 (2H, m, Ar–*H*), 7.61–7.81 (5H, m, Ar–*H*), 8.03 (2H, d, $J = 7.5$ Hz, Ar–*H*), 10.25 (1H, s, NH), 13.76 (1H, s, NH); ^{13}C NMR: 14.54, 15.46, 15.86, 51.81, 119.13, 121.07, 121.97, 123.03, 125.06, 125.52, 125.98, 126.05, 126.22, 127.36, 128.41, 128.69, 129.09, 131.88, 132.07, 133.97, 134.46, 135.12, 146.95, 162.69, 167.88; MS *m/z*: 505.1 (M^+); anal. calcd. for $C_{25}H_{23}N_5O_3S_2$: C, 59.39; H, 4.59; N, 13.85. Found: C, 59.48; H, 4.67; N, 13.77.

*N′-(1-(3-chlorothiophen-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5e**)*

White powder; yield: 92 %; mp 264 °C; FT-IR (KBr) cm^{-1}: 3608, 3257, 2916, 1703, 1604, 1319, 1157; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.13 (3H, s, C–CH_3), 4.62 (2H, s, *N*–CH_2), 7.02 (2H, d, $J = 5.10$ Hz, Ar–*H*), 7.44 (1H, d, $J = 8.4$ Hz, Ar–*H*), 7.52 (1H, t, $J = 7.5$ Hz, Ar–*H*), 7.60 (2H, d, $J = 5.4$ Hz, Ar–*H*), 7.82 (3H, t, $J = 8.4$ Hz, Ar–*H*), 7.99–8.08 (2H, dd, $J_1 = 7.8$ Hz, $J_2 = 18.3$ Hz, Ar–*H*), 10.61 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 15.48, 51.52, 119.04, 122.04, 122.12, 122.36, 123.16, 123.86, 125.99, 126.19, 126.93, 127.25, 128.28, 128.94, 129.19, 132.04, 133.10, 134.63, 139.56, 142.93, 147.58, 163.03, 168.16; MS *m/z*: 511.0 (M^+); anal. calcd. for $C_{23}H_{18}ClN_5O_3S_2$: C, 53.95; H, 3.54; N, 13.68. Found: C, 53.88; H, 3.41; N, 13.74.

*N′-(1-(3-bromothiophen-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5f**)*

White powder; yield: 93 %; mp 257 °C; FT-IR (KBr) cm^{-1}: 3668, 3257, 2919, 1700, 1603, 1318, 1156; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.13 (3H, s, C–CH_3), 4.65 (2H, s, *N*–CH_2), 7.08 (2H, d, $J = 5.4$ Hz, Ar–*H*), 7.54 (2H, t, $J = 4.8$ Hz, Ar–*H*), 7.60 (2H, d, $J = 5.4$ Hz, Ar–*H*), 7.812 (3H, d, $J = 5.8$ Hz, Ar–*H*), 8.05 (2H, d, $J = 6.2$ Hz, Ar–*H*), 10.57 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 16.04, 51.91, 107.90, 122.04, 122.18, 122.44, 123.10, 126.09, 126.66, 127,11, 127.60, 128.31, 128.96, 129.16, 132.00, 132.44, 134.63, 136.12, 139.56, 142.95, 147.59, 163.06, 168.24; MS *m/z*: 556.9 (M^+), 558.2 (M^++2); anal. calcd. for $C_{23}H_{18}BrN_5O_3S_2$: C, 49.64; H, 3.26; N, 12.59. Found: C, 49.69; H, 3.19; N, 12.71.

*N′-(1-(5-chlorothiophen-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5g**)*

Off white powder; yield: 94 %; mp >280 °C; FT-IR (KBr) cm^{-1}: 3670, 3312, 2956, 1677, 1605, 1326, 1160; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.00 (3H, s, C–CH_3), 4.59 (2H, s, *N*–CH_2), 7.01 (2H, d, $J = 3.9$ Hz, Ar–*H*), 7.16–7.24 (2H, dd, $J_1 = 3.9$ Hz, $J_2 = 21$ Hz, Ar–*H*), 7.46 (1H, d, $J = 7.2$ Hz, Ar–*H*), 7.56 (1H, t, $J = 7.4$ Hz, Ar–*H*), 7.82 (3H, q, $J = 7.0$ Hz, Ar–*H*), 8.06 (2H, d, $J = 7.8$ Hz, Ar–*H*), 10.54 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 12.76, 51.78, 122.12, 122.42, 123.16, 126.01, 126.84, 127.27, 127.55, 128.34, 128.96, 129.22, 130.29, 130.62, 132.06, 132.21, 134.48, 135.98, 141.99, 144.29, 148.04, 162.88, 167.86; MS *m/z*: 511.0 (M^+); anal. calcd. for $C_{23}H_{18}ClN_5O_3S_2$: C, 53.95; H, 3.54; N, 13.68. Found: C, 53.86; H, 3.63; N, 13.77.

*N′-(1-(2-amino-4-methylthiazol-5-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5h**)*

Bright yellow powder; yield: 89 %; mp 234 °C; FT-IR (KBr) cm^{-1}: 3680, 3324, 3006, 1676, 1587, 1327, 1153; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.01 (3H, s, C–CH_3), 2.62 (3H, s, C–CH_3), 4.61 (2H, s, *N*–CH_2), 7.16 (2H, s, NH_2), 7.19 (2H, d, $J = 4.8$ Hz, Ar–*H*), 7.40–7.43 (2H, dd, $J_1 = 3.0$ Hz, $J_2 = 5.10$ Hz, Ar–*H*), 7.47–7.51 (1H, dt, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz, $J_3 = 8.7$ Hz, Ar–*H*), 7.54 (1H, d, $J = 7.5$ Hz, Ar–*H*), 7.58–7.64 (1H, dt, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz, $J_3 = 8.7$ Hz, Ar–*H*), 7.85–7.99 (2H, dd, $J_1 = 12.9$ Hz, $J_2 = 21.0$ Hz, Ar–*H*), 10.34 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 14.61, 18.17, 55.95, 120.23, 121.17, 122.22, 123.16, 125.10, 125.59, 129.15, 130.39, 130.82, 132.04, 132.81, 134.98, 135.55, 141.89, 144.19, 148.04, 149.98,

157.56, 170.39, 188.10; MS *m/z*: 507.1 (M^+); anal. calcd. for $C_{23}H_{21}N_7O_3S_2$: C, 54.42; H, 4.17; N, 19.32. Found: C, 54.49; H, 4.10; N, 19.40.

*N′-(1-(2,5-dichlorothiophen-3-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5i**)*

White powder; yield: 91 %; mp 242 °C; FT-IR (KBr) cm^{-1}: 3671, 3344, 3103, 1691, 1609, 1316, 1149; ^{1}H NMR (DMSO-d_6) (300 MHz) δ: 2.00 (3H, s, C–CH_3), 4.64 (2H, s, *N*–CH_2), 7.13 (1H, s, Ar–*H*), 7.44–7.61 (3H, m, Ar–*H*), 7.71–7.96 (4H, m, Ar–*H*), 7.99–8.04 (2H, m, Ar–*H*), 10.52 (1H, s, NH), 13.75 (1H, s, NH); ^{13}C NMR: 13.57, 15.47, 51.74, 119.02, 121.99, 122.30, 123.13, 124.62, 126.02, 126.21, 127.40, 128.04, 128.28, 128.81, 128.97, 129.15, 132.00, 133.04, 134.60, 135.68, 143.13, 162.88, 168.36; MS *m/z*: 546.1 (M^+); anal. calcd. for $C_{23}H_{17}Cl_2N_5O_3S_2$: C, 50.55; H, 3.14; N, 12.82. Found: C, 50.43; H, 3.19; N, 12.91.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(4-methylthiophen-2-yl)ethylidene)acetohydrazide (**5j**)*

Light yellow powder; yield: 90 %; mp 270 °C; FT-IR (KBr) cm^{-1}: 3647, 3308, 2928, 1690, 1592, 1312, 1151; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 2.02 (3H, s, C–CH_3), 2.03 (3H, s, C–CH_3), 4.58 (2H, s, *N*–CH_2), 7.06 (1H, s, Ar–*H*), 7.12 (1H, s, Ar–*H*), 7.55 (2H, t, $J = 7.2$ Hz, Ar–*H*), 7.59 (1H, d, $J = 6.4$ Hz, Ar–*H*), 7.81 (4H, t, $J = 6.8$ Hz, Ar–*H*), 7.99–8.07 (2H, dd, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz, Ar–*H*), 10.43 (1H, s, NH), 13.76 (1H, s, NH); ^{13}C NMR: 15.29, 51.84, 119.14, 122.42, 123.17, 123.32, 123.79, 126.18, 127.26, 128.28, 128.94, 129.17, 129.33, 129.98, 132.07, 133.08, 134.43, 137.27, 139.54, 142.50, 144.86, 148.89, 162.72, 167.73; MS *m/z*: 491.1 (M^+); anal. calcd. for $C_{24}H_{21}N_5O_3S_2$: C, 58.64; H, 4.31; N, 14.25. Found: C, 58.69; H, 4.39; N, 14.17.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(2-oxo-2H-chromen-3-yl)ethylidene)acetohydrazide (**5k**)*

Creamy off white powder; yield: 90 %; mp 208 °C; FT-IR (KBr) cm^{-1}: 3665, 3314, 3015, 1691, 1589, 1321, 1155; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 1.99 (3H, s, C–CH_3), 4.65 (2H, s, *N*–CH_2), 7.315 (2H, d, $J = 7.6$ Hz, Ar–*H*), 7.41 (2H, d, $J = 8.4$ Hz, Ar–*H*), 7.62 (3H, t, $J = 8.4$ Hz, Ar–*H*), 7.74 (2H, t, $J = 8.0$ Hz, Ar–*H*), 7.85 (3H, d, $J = 8.2$ Hz, Ar–*H*), 8.00 (1H, s, Ar–*H*), 8.05 (1H, d, $J = 7.6$ Hz, Ar–*H*), 10.59 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 15.31, 51.52, 115.88, 118.64, 122.43, 123.14, 124.67, 126.05, 128.56, 129.00, 128.94, 129.17, 132.32, 132.58, 132.87, 133.64, 134.70, 135.15, 135.86, 137.56, 140.96, 141.40, 146.69, 150.31, 153.25, 158.78, 163.43, 168.35; MS *m/z*: 539.1 (M^+); anal. calcd. for $C_{28}H_{21}N_5O_5S$: C, 62.33; H, 3.92; N, 12.98. Found: C, 62.41; H, 3.99; N, 12.89.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(naphthalen-2-yl)ethylidene)acetohydrazide (**5l**)*

Light yellow powder; yield: 90 %; mp 279 °C; FT-IR (KBr) cm^{-1}: 3655, 3311, 3155, 3021, 1681, 1587, 1321, 1154; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 2.17 (3H, s, C–CH_3), 4.78 (2H, s, *N*–CH_2), 7.51–7.53 (4H, dd, $J_1 = 5.7$ Hz, $J_2 = 18.6$ Hz, Ar–*H*), 7.57 (2H, d, $J = 7.6$ Hz, Ar–*H*),7.81 (2H, t, $J = 6.9$ Hz, Ar–*H*), 7.86 (2H, d, $J = 7.6$ Hz, Ar–*H*), 7.91 (2H, t, $J = 7.2$ Hz, Ar–*H*), 8.07 (2H, d, $J = 8.0$ Hz, Ar–*H*), 8.11–8.15 (2H, m, Ar–*H*), 10.53 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 13.07, 18.50, 51.45, 119.17, 122.15, 122.46, 123.06, 123.48, 123.85, 125.96, 126.37, 126.74, 127.39, 127.63, 128.39, 128.99, 129.18, 132.08, 132.58, 133.09, 134.51, 134.85, 135.17, 139.54, 141.57, 148.18, 151.73, 163.26, 168.34; MS *m/z*: 521.1 (M^+); anal. calcd. for $C_{29}H_{23}N_5O_3S$: C, 66.78; H, 4.44; N, 13.43. Found: C, 66.70; H, 4.56; N, 13.37.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(5-methylthiophen-2-yl)ethylidene)acetohydrazide (**5m**)*

Light yellow powder; yield: 91 %; mp 280 °C; FT-IR (KBr) cm^{-1}: 3618, 3268, 2926, 1692, 1601, 1317, 1153; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 2.00 (3H, s, C–CH_3), 2.34 (3H, s, C–CH_3), 4.58 (2H, s, *N*–CH_2), 6.68 (1H, s, Ar–*H*), 7.07–7.15 (2H, dd, $J_1 = 2.7$ Hz, $J_2 = 20.4$ Hz, Ar–*H*), 7.46–7.61 (3H, m, Ar–*H*), 7.79–7.88 (3H, m, Ar–*H*), 7.99–8.07 (2H, dd, $J_1 = 5.7$ Hz, $J_2 = 18.6$ Hz, Ar–*H*), 10.39 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 13.20, 15.12, 51.18, 122.16, 122.48, 123.16, 123.32, 125.73, 125.97, 126.28, 127.35, 128.05, 128.94, 129.22, 129.73, 132.08, 133.11, 139.52, 140.56, 142.03, 145.03, 149.04, 162.63, 167.72; MS *m/z*: 491.1 (M^+); anal. calcd. for $C_{24}H_{21}N_5O_3S_2$: C, 58.64; H, 4.31; N, 14.25. Found: C, 58.78; H, 4.25; N, 14.37.

*N′-(1-(benzofuran-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5n**)*

Light yellow powder; yield: 89 %; mp 281 °C; FT-IR (KBr) cm^{-1}: 3633, 3301, 2924, 1692, 1596, 1314, 1160; ^{1}H

NMR (DMSO-d_6) (400 MHz) δ: 2.09 (3H, s, C–CH_3), 4.69 (2H, s, *N*–CH_2), 7.11 (1H, d, $J = 9.2$ Hz, Ar–*H*), 7.25 (1H, s, Ar–*H*), 7.54 (3H, d, $J = 8.4$ Hz, Ar–*H*), 7.62 (3H, t, $J = 7.2$ Hz, Ar–*H*), 7.81–7.86 (4H, m, Ar–*H*), 7.91 (1H, d, $J = 7.6$ Hz, Ar–*H*), 8.07 (1H, d, $J = 7.6$ Hz, Ar–*H*), 10.66 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 12.88, 51.42, 106.51, 111.18, 121.53, 122.99, 123.21, 125.56, 126.05, 127.31, 127.79, 127.91,128.12, 128.93, 129.13, 132.18, 133.05, 133.89, 1356.67, 140.41, 143.20, 153.17, 153.39, 154.33, 163.32, 168.28; MS *m/z*: 511.2 (M^+); anal. calcd. for $C_{27}H_{21}N_5O_4S$: C, 63.39; H, 4.14; N, 13.69. Found: C, 63.51; H, 4.02; N, 13.80.

*N′-(1-(1H-pyrrol-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5o**)*

Greyish green powder; yield: 91 %; mp 255 °C; FT-IR (KBr) cm^{-1}: 3649, 3298, 3090, 2921, 1694, 1601, 1318, 1149; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 1.05 (3H, s, C–CH_3), 4.68 (2H, s, *N*–CH_2), 6.80 (1H, d, $J = 3.6$ Hz, Ar–*H*), 6.93 (2H, t, $J = 7.6$ Hz, Ar–*H*), 7.07 (1H, t, $J = 3.2$ Hz, Ar–*H*), 7.10–7.17 (3H, dd, $J_1 = 7.2$ Hz, $J_2 = 18.8$ Hz, Ar–*H*), 7.69–7.76 (2H, m, Ar–*H*), 7.89 (1H, t, $J = 7.6$ Hz, Ar–*H*), 7.99 (1H, d, $J = 8.0$ Hz, Ar–*H*), 8.09–8.11 (1H, d, $J = 7.6$ Hz, Ar–*H*), 10.51 (1H, s, NH), 11.31 (1H, s, NH), 13.72 (1H, s, NH); ^{13}C NMR: 18.16, 54.64, 105.02, 108.39, 110.49, 112.87, 116.31, 118.96, 121.22, 123.71, 124.51, 125.26, 126.05, 128.02, 129.39, 131.46, 132.29, 133.91, 137.57, 139.17, 139.89, 151.85, 168.10; MS *m/z*: 460.1 (M^+); anal. calcd. for $C_{23}H_{20}N_6O_3S$: C, 59.99; H, 4.38; N, 18.25. Found: C, 60.08; H, 4.26; N, 18.29.

*N′-(1-(5-bromothiophen-2-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5p**)*

Off white powder; yield: 94 %; mp 278 °C; FT-IR (KBr) cm^{-1}: 3639, 3278, 2916, 1702, 1601, 1318, 1156; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 2.07 (3H, s, C–CH_3), 4.60 (2H, s, *N*–CH_2), 7.11–7.18 (2H, m, Ar–*H*), 7.46–7.61 (2H, m, Ar–*H*), 7.76 (1H, d, $J = 7.6$ Hz, Ar–*H*), 7.81 (3H, t, $J = 7.6$ Hz, Ar–*H*), 7.88 (1H, d, $J = 7.2$ Hz, Ar–*H*), 7.98–8.06 (2H, dd, $J_1 = 7.6$ Hz, $J_2 = 18.4$ Hz, Ar–*H*), 10.53 (1H, s, NH), 13.77 (1H, s, NH); ^{13}C NMR: 12.90, 51.01, 118.97, 122.11, 122.42, 123.17, 126.02, 127.27, 127.64, 128.33, 128.97, 129.21, 130.75, 132.05, 132.95, 133.15, 134.49, 139.50, 144.21, 144.66, 147.98, 162.86, 167.87; MS *m/z*: 556.9 (M^+), 558.2 (M^++2); anal. calcd. for $C_{23}H_{18}BrN_5O_3S_2$: C, 49.64; H, 3.26; N, 12.59. Found: C, 49.76; H, 3.33; N, 12.41.

*N′-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5q**)*

Off white powder; yield: 90 %; mp 253 °C; FT-IR (KBr) cm^{-1}: 3655, 3307, 3097, 2918, 1697, 1601, 1319, 1160; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 1.97 (3H, s, C–CH_3), 4.24 (4H, s, C–CH_2), 4.66 (2H, s, *N*–CH_2), 6.75 (2H, d, $J = 8.4$ Hz, Ar–*H*), 6.90 (1H, t, $J = 8.4$ Hz, Ar–*H*), 7.54 (2H, t, $J = 8.0$ Hz, Ar–*H*), 7.59 (2H, d, $J = 7.6$ Hz, Ar–*H*), 7.79 (1H, s, Ar–*H*), 7.81–7.89 (2H, dd, $J_1 = 7.6$ Hz, $J_2 = 15.6$ Hz, Ar–*H*), 7.98–8.06 (2H, dd, $J_1 = 8.0$ Hz, $J_2 = 17.2$ Hz, Ar–*H*), 10.34 (1H, s, NH), 13.76 (1H, s, NH); ^{13}C NMR: 13.19, 51.32, 63.91, 64.17, 114.75, 116.67, 119.06, 123.83, 126.04, 127.25, 128.05, 128.34, 128.99, 129.15, 130.84, 132.08, 132.77, 133.10, 134.34, 139.49, 141.79, 142.92, 144.36, 147.96, 151.63, 162.95, 168.08; MS *m/z*: 529.1 (M^+); anal. calcd. for $C_{27}H_{23}N_5O_5S$: C, 61.24; H, 4.38; N, 13.22. Found: C, 61.36; H, 4.30; N, 13.28.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(5-nitrothiophen-2-yl)ethylidene)acetohydrazide (**5r**)*

Orange yellow powder; yield: 91 %; mp 250 °C; FT-IR (KBr) cm^{-1}: 3647, 3288, 2918, 1699, 1597, 1315, 1154; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 2.07 (3H, s, C–CH_3), 4.66 (2H, s, *N*–CH_2), 7.36–7.43 (2H, dd, $J_1 = 4.0$ Hz, $J_2 = 18.4$ Hz, Ar–*H*), 7.54 (3H, t, $J = 7.6$ Hz, Ar–*H*), 7.74 (1H, d, $J = 4.4$ Hz, Ar–*H*), 7.81 (3H, d, $J = 8.0$ Hz, Ar–*H*), 8.00–8.07 (2H, dd, $J_1 = 4.4$ Hz, $J_2 = 12.4$ Hz, Ar–*H*), 10.84 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 12.88, 51.01, 118.93, 122.18, 123.21, 123.75, 126.04, 126.81, 127.19, 127.96, 128.40, 128.90, 129.18, 130.19, 132.17, 133.20, 134.33, 139.42, 143.36, 146.62, 150.22, 163.44, 168.24; MS *m/z*: 522.1 (M^+); anal. calcd. for $C_{23}H_{18}N_6O_5S_2$: C, 52.86; H, 3.47; N, 16.08. Found: C, 52.80; H, 3.58; N, 16.02.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(5-methylfuran-2-yl)ethylidene)acetohydrazide (**5s**)*

Off white powder; yield: 90 %; mp 200 °C; FT-IR (KBr) cm^{-1}: 3668, 3336, 2957, 1689, 1594, 1322, 1151; ^{1}H NMR (DMSO-d_6) (400 MHz) δ: 1.92 (3H, s, C–CH_3), 2.24 (3H, s, C–CH_3), 4.59 (2H, s, *N*–CH_2), 6.11 (1H, d, $J = 2.4$ Hz, Ar–*H*), 6.56–6.67 (1H, m, Ar–*H*), 7.54 (2H, t, $J = 8.0$ Hz, Ar–*H*), 7.59 (1H, d, $J = 6.8$ Hz, Ar–*H*), 7.82 (4H, q, $J = 8.4$ Hz, Ar–*H*), 8.05 (2H, d, $J = 7.6$ Hz, Ar–*H*), 10.33 (1H, s, NH), 13.76 (1H, s, NH); ^{13}C NMR: 13.18, 13.77, 52.00, 108.55, 112.41, 113.31, 114.98, 119.75, 122.69,

123.68, 126.04, 126.50, 127.79, 129.46, 132.64, 133.17, 139.56, 141.19, 144.33, 150.24, 153.88, 154.17, 163.38, 168.41; MS *m/z*: 475.1 (M^+); anal. calcd. for $C_{24}H_{21}N_5O_4S$: C, 60.62; H, 4.45; N, 14.73. Found: C, 60.50; H, 4.40; N, 14.79.

*N′-(1-(2,5-dimethylfuran-3-yl)ethylidene)-2-(5,5-dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)acetohydrazide (**5t**)*

Light yellow powder; yield: 90 %; mp 250 °C; FT-IR (KBr) cm^{-1}: 3658, 3301, 2917, 1689, 1594, 1327, 1156; ^1H NMR (DMSO-d_6) (400 MHz) δ: 1.88 (3H, s, C–CH_3), 2.07 (3H, s, C–CH_3), 2.16 (3H, s, C–CH_3), 4.58 (2H, s, *N*–CH_2), 6.06 (1H, s, Ar–*H*), 7.55 (2H, t, $J = 7.2$ Hz, Ar–*H*), 7.59 (1H, d, $J = 7.6$ Hz, Ar–*H*), 7.80 (4H, q, $J = 6.4$ Hz, Ar–*H*), 8.04–8.06 (2H, dd, $J_1 = 7.6$ Hz, $J_2 = 15.6$ Hz, Ar–*H*), 10.20 (1H, s, NH), 13.75 (1H, s, NH); ^{13}C NMR: 12.84, 14.03, 14.96, 51.68, 106.07, 119.06, 119.60, 121.86, 122.20, 122.94, 123.10, 125.98, 126.19, 127.28, 128.04, 128.21, 129.22, 131.88, 132.93, 134.80, 139.57, 145.39, 146.37, 148.67, 167.72; MS *m/z*: 489.1 (M^+); anal. calcd. for $C_{25}H_{23}N_5O_4S$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.39; H, 4.81; N, 14.23.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(thiazol-2-yl)ethylidene)acetohydrazide (**5u**)*

Light yellow powder; yield: 92 %; mp 246 °C; FT-IR (KBr) cm^{-1}: 3626, 3278, 2918, 1698, 1599, 1311, 1154; ^1H NMR (DMSO-d_6) (400 MHz) δ: 2.15 (3H, s, C–CH_3), 4.66 (2H, s, *N*–CH_2), 7.42–7.61 (2H, m, Ar–*H*), 7.69 (3H, d, $J = 5.2$ Hz, Ar–*H*), 7.80 (4H, t, $J = 9.6$ Hz, Ar–*H*), 8.07 (2H, d, $J = 7.6$ Hz, Ar–*H*), 10.82 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 12.75, 51.04, 118.99, 122.16, 122.46, 123.21, 123.81, 126.01, 127.24, 128.97, 129.20, 131.46, 132.18, 133.18, 134.34, 139.49, 143.10, 144.77, 147.94, 163.37, 166.90, 168.04; MS *m/z*: 478.1 (M^+); anal. calcd. for $C_{22}H_{18}N_6O_3S_2$: C, 55.22; H, 3.79; N, 17.56. Found: C, 55.33; H, 3.67; N, 17.67.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(1-(pyridin-4-yl)ethylidene)acetohydrazide (**5v**)*

White powder; yield: 91 %; mp 260 °C; FT-IR (KBr) cm^{-1}: 3633, 3308, 2978, 1694, 1596, 1317, 1153; ^1H NMR (DMSO-d_6) (400 MHz) δ: 2.04 (3H, s, C–CH_3), 4.75 (2H, s, *N*–CH_2), 7.34–7.54 (4H, m, Ar–*H*), 7.69–7.93 (5H, m, Ar–*H*), 7.99–8.05 (2H, m, Ar–*H*), 8.50–8.52 (2H, dd, $J_1 = 0.9$ Hz, $J_2 = 3.6$ Hz, Ar–*H*), 10.68 (1H, s, NH), 13.78 (1H, s, NH); ^{13}C NMR: 12.73, 51.21, 119.97, 120.29, 121.78, 122.29, 122.96, 123.14, 123.83, 125.98, 126.14, 127.38, 128.01, 128.48, 129.08, 131.88, 132.14, 134.80, 139.57, 144.41, 146.11, 149.75, 163.56, 168.61; MS *m/z*: 472.1 (M^+); anal. calcd. for $C_{24}H_{20}N_6O_3S$: C, 61.00; H, 4.27; N, 17.79. Found: C, 61.13; H, 4.35; N, 17.65.

*2-(5,5-Dioxido-3-phenylbenzo[e]pyrazolo[4,3-c][1,2]thiazin-4(1H)-yl)-N′-(thiophen-2-ylmethylene)acetohydrazide (**5w**)*

Dirty green powder; yield: 94 %; mp 246 °C; FT-IR (KBr) cm^{-1}: 3642, 3312, 3128, 1697, 1589, 1328, 1159; ^1H NMR (DMSO-d_6) (400 MHz) δ: 4.57 (2H, s, *N*–CH_2), 7.03–7.05 (2H, dd, $J_1 = 2.7$ Hz, $J_2 = 3.9$ Hz, Ar–*H*), 7.28–7.34 (1H, dd, $J_1 = 2.4$ Hz, $J_2 = 5.6$ Hz, Ar–*H*), 7.56 (4H, t, $J = 5.8$ Hz, Ar–*H*), 7.83 (3H, q, $J = 8.0$ Hz, Ar–*H*), 7.94 (1H, s, N=CH), 8.05–8.10 (2H, m, Ar–*H*), 11.14 (1H, s, NH), 13.76 (1H, s, NH); ^{13}C NMR: 50.64, 121.78, 122.23, 123.22, 126.06, 127.26, 127.74, 128.52, 128.94, 129.18, 130.37, 130.97, 132.23, 133.17, 133.48, 134.25, 138.32, 138.95, 142.08, 146.11, 162.40, 166.98; MS *m/z*: 463.0 (M^+); anal. calcd. for $C_{22}H_{17}N_5O_3S_2$: C, 57.00; H, 3.70; N, 15.11. Found: C, 57.10; H, 3.61; N, 15.20.

X-ray crystallographic studies

A colorless plate crystal of $C_{22}H_{17}N_5O_3S_2$ (**5w**) was coated with Paratone 8277 oil (Exxon) and mounted on a glass fiber. All measurements were made on a Bruker APEX2 CCD installed on a Nonius Kappa Goniometer diffractometer with graphite monochromated Mo-Kα radiation. Details of crystal data and structure refinement have been provided in Table 1. The data were collected (Otwinowski and Minor 1997) using ω and φ scans. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method (Hooft 1998). The structure was solved by the direct methods using SHELXS (Sheldrick 2008). The H-atoms were included at geometrically idealized positions and were not refined. The final cycle of full-matrix least-squares refinement using the structure was solved by the direct methods using SHELXS (Sheldrick 2008). The H-atoms were included at geometrically idealized positions and were not refined. The final cycle of full-matrix least-squares refinement using SHELXL (Sheldrick 2008) converged with unweighted and weighted agreement factors, $R = 0.068$ and $wR = 0.138$ (all data), respectively, and goodness-of-fit, $S = 1.08$. The weighting scheme was based on counting statistics and the final difference Fourier map was essentially featureless. The figure was plotted with the aid of ORTEP-3 for Windows (Farrugia 1997). Selected bond lengths (Å) and angles (°) for **5w** have been listed in Table 2.

Table 1 Crystal data and structure refinement for **5w**

Parameters	Values	Parameters	Values
CCDC No.	881049	θ range for data collection	3.13–27.13°
Empirical formula	$C_{22}H_{19}N_5O_4S_2$	Index ranges	$-10 \leq h \leq 10, -12 \leq k \leq 12, -18 \leq l \leq 18$
Formula weight	481.54	Reflections collected	8695
Temperature	173(2) K	Independent reflections	4811 [$R_{(int)} = 0.048$]
Wavelength	0.71073 Å	Completeness to $\theta = 27.13°$	96.6 %
Crystal system	Triclinic	Absorption correction	Multi-scan
Space group	*P*-1	Max. and min. transmission	0.989 and 0.968
Unit cell dimensions	$a = 8.148(3)$ Å, $\alpha = 91.57(2)°$	Refinement method	Full-matrix least-squares on F^2
	$b = 10.102(5)$ Å, $\beta = 90.05(2)°$		
	$c = 14.579(7)$ Å, $\gamma = 110.52(2)°$		
Volume	1123.4(9) Å^3	Data/restraints/parameters	4811/3/304
Z	2	Goodness-of-fit on F^2	1.08
Density (calculated)	1.424 Mg/m^3	Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.068$, $wR_2 = 0.121$
Absorption coefficient	0.277 mm^{-1}	*R* indices (all data)	$R_1 = 0.096$, $wR_2 = 0.138$
F(000)	500	Largest diff. peak and hole	0.35 and −0.41 e/Å^3
Crystal size	0.12 × 0.10 × 0.04 mm^3		

Anti-HIV-1 assay

The anti-HIV-1 assay was conducted in activated primary human peripheral blood mononuclear (PBM) cells as described by Schinazi et al. (1990) with modifications. Briefly, the percent of control was calculated and then determined the median effective concentration (EC_{50}) by concentration response curve using the median effective method of Belen'kii and Schinazi (1994) (Belen'kii, and Schinazi). The results are expressed in Table 5.

Cytotoxic assay

Primary human PBM, CEM, and VERO cells were cultured in 96-well plates (5×10^4 cells/well) along with increasing concentrations of the test compounds (Stuyver et al. 2002). Cell viability was measured after 5-day incubation period using the Cell Titer 96 Aqueous One Solution cell proliferation assay (Promega, Madison, WI) by incubating in an incubator at 37 °C with 5 % CO_2 for primary human PBM cells. The results are mentioned in Table 5.

Results and discussion

Chemistry

2-(2-Oxo-2-phenylethyl)-1,2-benzisothiazol-3(2*H*)-one1,1-dioxide(*N*-phenacyl saccharin) (**1**) was prepared by *N*-alkylation of commercially available sodium salt of saccharine with appropriate aryl halide in DMF. For the optimization of the reaction conditions to get the highest yields in short time periods, the reaction were performed under microwave irradiation as compared to the our previously reported thermal method (Ahmad et al. 2010b). The spectroscopic data showed that stretching frequencies in IR spectra were observed for compound (**1**) at 1,715 cm^{-1} (C=O), 1,345 and 1,165 (SO_2NH). In the ^{1}H NMR, *N*–CH_2 group appeared as singlet at 5.15 ppm for *N*-phenacyl saccharin (**1**).

3-Benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2**) was prepared by the ring expansion of 2-(2-oxo-2-phenylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (**1**) which was prepared according to the reported method (Ahmad et al. 2010c). The product was confirmed by the presence of IR peaks for OH and NH groups at 3,457 and 3,215 cm^{-1}, respectively. In the ^{1}H NMR, enolic OH was observed at δ value of 14.67 ppm and SO_2NH as a broad singlet at 5.79 ppm. *N*-alkylation of 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2**) with variety of alkyl chloroacetates was carried out in the presence of K_2CO_3 and acetonitrile. In the ^{1}H NMR of **3**, methoxy and *N*-CH_2 groups appeared at δ values 3.25 and 3.96 ppm, respectively. Alkyl [4-hydroxy-1,1-dioxido-3-(phenylcarbonyl)-2*H*-1,2-benzothiazin-2-yl]acetate (**3**) on reaction with hydrazine monohydrate resulted in the formation of hydrazide functionality as well as pyrazole ring to give the pyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide derivative (**4**). Compound **4** is a structural hybrid of benzothiazine and pyrazole nuclei and both represent medicinally important molecules. The pyrazolobenzothiazine ring system that was developed here has a great potential for bioactive

Table 2 Selected bond lengths (Å) and angles (°) for **5w**

Bond lengths (Å)		Bond angles (°)	
S(1)–O(1)	1.426(3)	O(1)–S(1)–O(2)	118.72(15)
S(1)–O(2)	1.432(2)	O(1)–S(1)–N(1)	107.45(16)
S(1)–N(1)	1.641(3)	O(2)–S(1)–N(1)	107.40(15)
S(1)–C(1)	1.759(3)	O(1)–S(1)–C(1)	107.98(16)
S(2)–C(22)	1.711(4)	O(2)–S(1)–C(1)	109.87(16)
S(2)–C(19)	1.726(4)	N(1)–S(1)–C(1)	104.49(15)
O(3)–C(17)	1.231(4)	C(22)–S(2)–C(19)	91.09(19)
N(1)–C(8)	1.415(4)	C(8)–N(1)–C(16)	121.1(3)
N(1)–C(16)	1.458(4)	C(8)–N(1)–S(1)	114.5(2)
N(2)–C(7)	1.348(4)	C(16)–N(1)–S(1)	119.6(2)
N(2)–N(3)	1.350(4)	C(7)–N(2)–N(3)	109.1(3)
N(3)–C(9)	1.356(4)	N(2)–N(3)–C(9)	109.2(3)
N(4)–C(17)	1.342(4)	C(17)–N(4)–N(5)	118.3(3)
N(4)–N(5)	1.381(4)	C(18)–N(5)–N(4)	117.8(3)
N(5)–C(18)	1.271(4)		

molecules and could be used as a template for novel drugs. The presence of hydrazide moiety in compound **4** was confirmed by the appearance of peaks at 4.52 and 8.96 ppm for NH_2 and NH, respectively. On the other hand, peak at δ value 14.27 ppm (NH) confirmed the formation of pyrazole ring. Finally, *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides (**5a**–**w**) were prepared by the reaction of 2-(5,5-dioxido-3-phenylpyrazolo[4,3-*c*][1,2]benzothiazin-4(2*H*)-yl) acetohydrazide (**4**) with a series of substituted heterocyclic ketones in alcoholic media by using thermal method as well as in ultrasonic bath (Scheme 1). The data presented in the Table 3 revealed that reactions in ultrasonic bath completed in shorter time periods i.e., 10–17 min and enhanced yields, i.e., 89–95 % as compared to the thermal method.

The targeted compounds were well characterized by spectroscopic techniques, like vibrational stretching frequency of imine linkage (–C=N) in IR spectra appeared at frequency range of 1,576–1,604 cm^{-1}. ^1H NMR data revealed the formation of products by the appearance of singlet peaks at 4.58–4.62 and 10.20–11.14 ppm for the protons of *N*–CH_2 and NH protons, respectively. On the other hand, peak in the range of 13.78–14.27 ppm indicated the presence of N–H proton for pyrazole ring system. In their ^{13}C NMR spectra, carbon of carbonyl group was appeared around 167.71–188.10 ppm, while that of imine linkage (–C=N) observed around 151–162 ppm. Finally,

Table 3 Synthesis of *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides (**5a**–**w**)

Sr. nos.	Products	Ar	Thermal method		Ultrasonic bath	
			Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)
1	**5a**	Thiophen-2-yl	36	83	14	92
2	**5b**	3-Methylthiophen-2-yl	35	87	12	94
3	**5c**	Thiophen-3-yl	40	85	14	91
4	**5d**	2,5-Dimethylthiophen-3-yl	52	88	15	90
5	**5e**	3-Chlorothiophen-2-yl	57	89	14	92
6	**5f**	3-Bromothiophen-2-yl	50	87	16	93
7	**5g**	5-Chlorothiophen-2-yl	51	88	15	94
8	**5h**	5-Acetyl-2amino-4-methylthiazole	57	84	14	89
9	**5i**	2,5-Dichlorothiophen-3-yl	51	87	14	91
10	**5j**	4-Methylthiophen-2-yl	45	89	13	90
11	**5k**	Coumarin-3-yl	53	85	15	90
12	**5l**	Naphthalen-2-yl	50	86	17	90
13	**5m**	5-Methylthiophen-2-yl	35	88	10	91
14	**5n**	Benz[*b*]furan-2-yl	50	82	13	89
15	**5o**	Pyrrole-2-yl	48	84	14	91
16	**5p**	5-Bromothiophen-2-yl	47	85	13	94
17	**5q**	1,4-Benzodioxane-6-yl	55	81	14	90
18	**5r**	5-Nitrothiophen-2-yl	50	83	16	91
19	**5s**	5-Methylfuran-2-yl	41	87	15	90
20	**5t**	2,5-Dimethylfuran-3-yl	50	85	13	90
21	**5u**	Thiazolo-2-yl	55	83	14	92
22	**5v**	Pyridino-4-yl	54	85	16	91
23	**5w**	Thiophen-2-yl	51	87	15	94

the respective molecular ion peaks in MS spectra confirmed the targeted compounds.

X-ray crystallographic studies

The molecular structure of compound **5w** is shown in Fig. 2 and the crystal data and structure refinement parameters are listed in Table 1. The heterocyclic thiazine ring in **5w** (Fig. 2) adopts a half chair conformation with atoms N1 and S1 displaced by 0.555(6) and 0.140(7) Å, respectively, on the opposite sides from the mean plane formed by the remaining ring atoms. The benzene rings (C1–C6) and (C10–C15) are oriented with respect to the essentially planar pyrazolyl ring (N2/N2/C7–C8) at dihedral angles 18.78(19) and 34.81(12)°, respectively. The five-membered ring (S2/C19–C22) is essentially planar (RMSD 0.0006 Å) and the side chain (O3/N4/N5/C17/C18) which is fully extended, is oriented at 4.4(3)° with respect to its mean-plane. While the molecular structure of the compound **5w** is consolidated by intramolecular interactions: O–H···O, and C–H···S, the crystal packing is stabilized by strong intermolecular N–H···O and O–H···N hydrogen bonds (Table 4).

Pharmacology

Anti-HIV-1 activity

The activities of the title pyrazolobenzothiazine based acetohydrazides against HIV-1, were established by determining their ability to prevent the virus production in activated primary human PBM cells as described by Schinazi et al. (1990). The results detected for the targeted

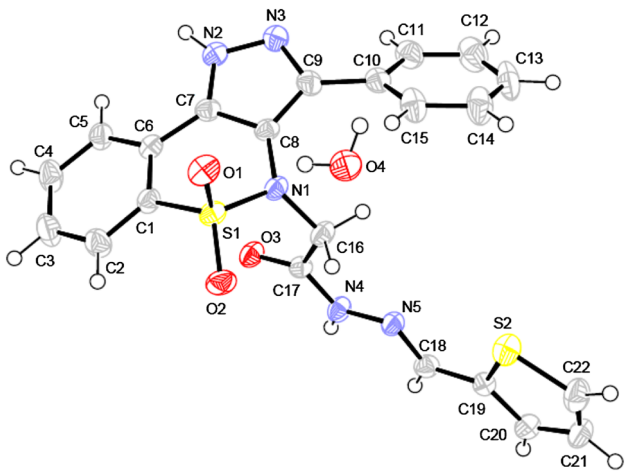


Fig. 2 ORTEP-3 drawing of 2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)-*N*′-(thiophen-2-ylmethylene)acetohydrazide (**5w**)

compounds of this novel series are reported in Table 5. 3′-Azido-3′-deoxythymidine (AZT), one of the active anti-HIV NRTIs was used as a positive reference standard. Among the *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazide derivatives (**5a**–**w**), it is evident that the unsubstituted thiophenyl acetohydrazides (**5a** and **c**) demonstrated anti-HIV-1 activity with EC_{50} of 11.2 and 24.3 μM, respectively. SAR revealed that electron withdrawing substituents enhanced the activity e.g., 3-Cl group (**5e**) (EC_{50} of 17.4 μM) while 2,5-dichloro substitution in compound **5i** considerably enhanced the activity and thus, **5i** appeared as the most potent anti-HIV-1 agent among the series with an EC_{50} of 3.2 μM. Among the methylthiophen-2-yl substituted compounds, the following order was observed; 3-Me > 5-Me > 4-Me with an EC_{50} of 11.2, 12.3 and 13.3 μM, respectively.

Coumarin-4-yl containing compound (**5k**) exhibits anti-HIV-1 activity with an EC_{50} of 22.9 μM, while compound **5h** bearing 2-amino-4-methylthiazole-5-yl moiety showed good activity with an EC_{50} of 3.8 μM. Whereas, compounds substituted with 5-methylfuran-2-yl (**5s**), benzofuran (**5n**) and pyridino-4-yl (**5v**) were found to be inactive when tested up to 100 μM. For comparative studies, we also synthesized acetohydrazide with thiophen-2-carboxaldehyde (**5w**) to evaluate the role of methyl group at $N{=}CCH_3$ and it was observed that **5w** exhibited no anti-HIV-1 activity as compared to corresponding ketimines (**5a** and **c**).

Cytotoxic activity

All the final compounds were tested for their cytotoxicity in primary human PBM, CEM, and VERO cells as described by Stuyver et al. (2002). The results of cell-based assays are expressed as IC_{50} (median inhibitory concentration) and are summarized in Table 5. Among the *N*′-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides (**5a**–**w**), it was found that compounds bearing unsubstituted thiophenyl moieties (**5a**, **c** and **w**) showed no toxicity in primary human PBM and VERO cells. Among halogen substituted compounds, compound **5e** (bearing 3-Cl group) was non-toxic in primary human PBM and VERO cells, whereas all the rest halogen substituted compounds were cytotoxic in all the three cell system used.

Moreover, among compounds having methyl substituted thiophenyl moieties, 3-methylthiophen-2-yl substituted compound exhibited no cytotoxicity in primary human PBM and VERO cells. Acetohydrazide with other heterocyclic systems e.g., coumairn-4-yl (**5k**), 1,4-benzodioxane-6-yl (**5q**) were also non-toxic to primary human PBM and VERO cells, while 2-amino-4-methylthiazole-5-yl (**5h**)

Table 4 Hydrogen bonds for **5w** (Å and °)

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠(DHA)
N(2)–H(2N)···O(4)#1	0.88	2.02	2.811(4)	149.1
N(4)–H(4N)···O(3)#2	0.88	1.93	2.807(4)	174.4
O(4)–H(4BO)···N(3)#3	0.82	1.997(5)	2.815(4)	175(3)
O(4)–H(4AO)···O(1)	0.82	2.255(9)	3.062(4)	168(4)
O(4)–H(4AO)···S(1)	0.82	3.00(3)	3.678(3)	142(3)

Symmetry transformations used to generate equivalent atoms: #1 $x + 1, y, z$; #2 $-x + 1, -y + 1, -z$; #3 $-x + 1, -y + 1, -z + 1$

Table 5 Anti-HIV-1 and cytotoxic activity of *N′*-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazide (**5a**–**w**)

Anti-HIV-1 activity in human PBM cells (μM)			Cytotoxicity (IC_{50}, μM)		
Codes	EC_{50}	EC_{90}	PBM	CEM	VERO
5a	11.2	45.2	88.0	23.3	77.2
5b	11.6	>100	56.2	13.1	75.3
5c	24.3	89.3	73.2	10.7	78.7
5d	>100	>100	36.5	17.6	44.4
5e	17.4	61.2	69.1	16.8	>100
5f	>100	>100	42.8	19.6	>100
5g	>100	>100	13.9	8.4	57.4
5h	3.8	>100	>100	>100	>100
5i	3.2	38.8	12.2	14.4	38.8
5j	13.3	>100	≥100	18.3	6.0
5k	22.9	85.6	82.7	27.8	>100
5l	>100	>100	12.2	24.2	<1
5m	12.3	>100	62.3	13.8	30.6
5n	79.0	>100	>100	22.4	23.0
5o	>100	>100	41.4	20.0	22.3
5p	>100	>100	10.5	<1	18.1
5q	>100	>100	67.1	23.9	>100
5r	>100	>100	85.0	5.0	43.6
5s	75.7	>100	53.8	15.4	>100
5t	>100	>100	17.3	9.9	41.4
5u	>100	>100	15.7	8.2	43.1
5v	80.5	>100	75.6	34.5	84.1
5w	70.2	>100	30.6	13.9	41.8
AZT	0.00037	0.014	>100	14.3	56.0

EC_{50} median effective (anti-viral) concentrations, *IC_{50}* inhibitory (cytotoxic) concentrations

showed no toxicity in primary human PBM, CEM and VERO cells.

Conclusion

A number of compounds in the series *N′*-(1-arylethylidene)-2-(5,5-dioxido-3-phenylbenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-4(1*H*)-yl)acetohydrazides (**5a**–**w**) exhibited modest anti-HIV-1 activity. 2-Amino-4-methylthiazole-5-yl substituted acetohydrazide (**5h**) with an EC_{50} of 3.8 μM was the most potent anti-HIV-1 inhibitor which also demonstrated no toxicity in primary human PBM, CEM and VERO cells whereas, compound **5i** exhibited the most significant anti-HIV-1 activity ($EC_{50} = 3.2$ μM) but was toxic in primary human PBM, CEM and VERO cells. Compound **5h** is the excellent discovery among the titled compounds as it bears significant anti-HIV potential ($EC_{50} = 3.8$ μM) and is significantly non-toxic in primary human PBM, CEM and VERO cells as well ($EC_{50} > 100$ μM). The data presented in this manuscript suggests that pyrazolobenzothiazine ring system could be used as a template for the generation of novel anti-HIV agents.

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Conflict of Interest The authors declare no conflicts of interest.

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