

# Design, Synthesis and Evaluation of Some Novel 1-phenyl-3-(5-phenyl-1H-imidazol-1-yl) Thiourea Derivatives as Anti-HIV Agents.

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## ABSTRACT

**Objective:** In the present study, a series of nineteen compound of 1-phenyl-3-(5-phenyl-1H-imidazol-1-yl) thiourea derivatives (5a-9b) were designed, synthesized, characterized by physicochemical and spectral data (IR, <sup>1</sup>H NMR, and mass spectroscopy) and evaluated for their Anti-HIV activity with the aim to develop novel substituted imidazole derivatives with broad-spectrum chemotherapeutic properties. **Methods:** Compounds (5a-9b) were designed by using Glide 5.0 to carry out binding mode analysis of N-substituted imidazoles against reverse transcriptase enzyme of wild type as well as resistant strains of HIV-1 virus with PDB ID: 1RT2, synthesized by reacting various substituted anilines and substituted phenacyl bromides in four steps and evaluated their anti HIV activity as well as cytotoxicity assay through MTT colorimetric measure. **Results:** Compounds 6a, 6b, 6c, 6d, 7c, 9a and 9b being the most active exhibited therapeutic index that were >22.4, 31.1, 30.5, 51.5, 34.6, 30.5 and 85.6 compared to Zidovudine (AZT) having therapeutic index (TI) 514342.6. Compound **9b** showed the highest docking score -12.47 in the active site of the HIV protein of 1RT2 as well better *in vitro* anti-HIV activity.

**Key words:** Molecular docking, Imidazole derivatives, Reverse transcription, Non-nucleoside reverse transcriptase inhibitors (NNRTI), Anti-HIV.

## INTRODUCTION

Since the leap forward of HIV as the infective operators of AIDS (HIV) in the late 1980's, a lot of progression has been made in creating restorative specialists to control viral levels in pompous people.<sup>1,2</sup> As indicated by UNAIDS report 2016 United Nations Political Declaration on HIV and AIDS rush the fight against HIV and to end up to the AIDS as endemic by 2030, In last two years the most extreme number of individuals living with HIV, achieving around 17.0 million individuals which is more than the 15 million by 2015 as per United Nations General Assembly in 2011.<sup>3</sup> Reverse transcriptase (RT) is a key protein which contributes a crucial and multidimensional significance in the replication of the human immunodeficiency virus (HIV-1) and in this manner considered

as an eye-getting objective for the advancement of new medications disclosure and improvement valuable in AIDS treatment.<sup>4</sup> The primary action against HIV drugs allowed by the USA and Europe were nucleoside turn around transcriptase inhibitors (NRTIs) which rival ordinary nucleoside substrates for reconciliation into the viral genome, along these lines they carries on like chain eliminators.<sup>5</sup> Dissimilar to nucleoside and nucleotide subsidiaries, Non-nucleoside invert transcriptase inhibitors (NNRTIs) tie in a noncompetitive way with a particular specific 'pocket' of the HIV-1 RT changing with various capacity and fondness of their capacities.<sup>6,7</sup> X-beam crystallographic systems and their investigations of Non-nucleoside reverse transcriptase inhibitors

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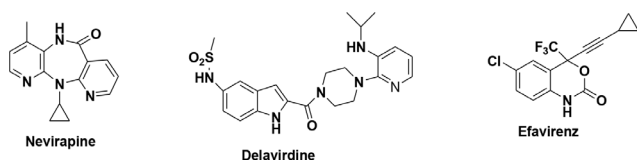
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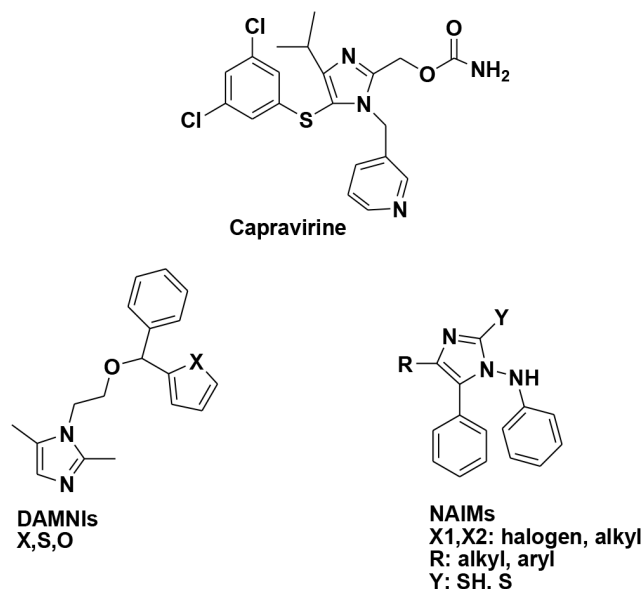
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and turn around transcriptase buildings have demonstrated that the NNRTIs are masterminded in conformational structure 'butterfly-like' shape and p-electron contributor site of fragrant side chain of the blended compound ties with restricting pocket of protein deposits.<sup>8</sup> For the most part, three Non-nucleoside Reverse transcriptase inhibitors in particular Nevirapine, Delavirdine and Efavirenz are as of now easily available which are utilized as a part of clinical practices. Nucleoside reverse transcriptase (RT) inhibitors (N[t]RTIs), Non-nucleoside RT inhibitors (NNRTIs), Protease inhibitors (PIs) and Integrase inhibitors has a place with various class of inhibitors which are focused at viral compounds; a combination inhibitor, which keeps the combination of the infection envelope with the host-cell film; and a CCR5 inhibitor, which hinders the association of the infection with one of its receptors on the host cell.<sup>9</sup>



### Some established structure of non-nucleoside reverse transcriptase inhibitors.

Imidazoles have been known as anti-HIV agents, one of the examples being capravirine.<sup>10</sup>



### Structural formula of some clinically established imidazole drugs.

Prior works in our research facility have distinguished different imidazole subsidiaries showing expansive range chemotherapeutic properties.<sup>11,12</sup> Capravirine (some time ago known as S-1153 and AG-1549) is a standout amongst the most encouraging non-nucleoside inhibitors

of HIV-1 reverse transcriptase right now being worked on as potentially hostile to HIV drugs.<sup>13</sup>

In any case, the utility of Capravirine has been confined because of vasculitis (an irritation in veins) in creatures that are being treated with high measurements of capravirine.<sup>14</sup>

Silvestri *et al.*<sup>15</sup> and De Martino *et al.*<sup>16</sup> incorporated various 1-2(diarylmethoxy) ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogs as novel HIV-1 turn around transcriptase (RT) inhibitory specialists dynamic at submicromolar fixation, with the racemic 1-2-[(thiophen-2-yl)phenylmethoxy]ethyl]-2-methyl-5-nitroimidazole being the most dynamic among every one of the analogs. In continuation of our push to create imidazoles as wide range chemotherapeutic operators and empowered by Martino *et al.*<sup>17</sup> We attempted the present investigation to integrate and assess novel imidazoles subsidiaries that could keep down HIV replication and go about as strong hostile to HIV drugs and furthermore hinder sharp microorganisms effectively.

Floresta *et al.* investigated the hypothesis that pseudouridine isoxazolidinyl nucleoside analogues could act as potential inhibitors of the pseudouridine 5'-mono-phosphate glycosidase.<sup>18</sup> while Bkhaitan *et al.* series a derivatives of phosphonated carbocyclic 2'-oxa-3'-aza nucleosides were synthesized via 1,3 dipolar cycloaddition and evaluated for their *in vitro* antiproliferative activity against the growth of cancer cell lines (MCF-7, A2780, HCT116) and normal non-transformed fibroblast (MRC5) using MTT assay.<sup>19,20</sup>

## EXPERIMENTAL

### MATERIALS

Every Chemical reagents were bought from commercial distributors like Sigma Aldrich, Merck India Ltd., and Rankem chemicals. All reagents were guaranteed reagent (GR) or analytical reagent (AR) grade and utilized without cleaning. The accurateness and closeness of the compound were checked by the TLC performed on Merck silica gel G aluminum sheets utilizing n-Hexane: Ethyl acetic acid derivation (7:3) as eluent. Iodine chamber and Shimadzu (UV-254) spectrometer were utilized for vizualization of TLC spots. Ashless Whatmann No.1 channel paper was 254 utilized for vacuum filtration. Melting points were determined on an Opti-melting point automatic apparatus and were uncorrected. IR spectra (KBr disc/or pellets) were recorded on SHIAMADZU FT-IR 8400 and were reported in  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR spectra were recorded at 400 MHz with BRUKER Advance Digital Spectrophotometer. Chemical shifts are expressed in  $\delta$ -values

(ppm) relative to TMS as an internal standard, using  $\text{CDCl}_3$  as solvent.

## METHODS

### Computational Docking Study by Glide 5.0 (Schrodinger Inc; USA)

Docking study was performed for all designed compounds (5a-9b) by glide 5.0 version (ref. schrodinger Inc USA schrodinger LLC New York 2008) installed in a single machine running on a 3.4 GHz Pentium 4 processor with 1 GB RAM and 160 GB hard disk with red hat linux enterprise version 8.5 as operating system.

### Protein Structure Preparation

The X-beam crystallographic structure of HIV-1 RT complexed with TNK-651 (PDB ID: 1RT2), was acquired from Brookhaven Protein Data Bank (RCSB). (ref. <http://www.rcsb.org/pdb>) for glide docking studies, chain A was held and all water particles, and additionally chain B, were evacuated and missing hydrogen molecule was added and the structure was improved since TNK crystallized ligand in the catalyst HIV-1 RT complexed with TNK-651.

### Ligand Structure Preparation

All the composed substituted imidazole compound utilized as a part of docking study were set up with a glide in maestro 8.5 version of Schrodinger Inc. these structures were geometrically advanced possibilities for liquid simulations<sub>2005</sub> (OPLS<sub>2005</sub>) constrain field. Partial atomic charges were figured utilizing the OPLS<sub>2005</sub> force field.

### Receptor Grid Generation

Shape and properties of receptor were spoken to on a network by various arrangements of fields that give dynamically more precise scoring of ligand postures. Pick the ligand atom and that was prohibited from receptor framework age. After that scaling of van der Waals radii of non-polar molecules which gave better association amongst receptor and ligand. Scaling of other connection can likewise demonstrate adaptability of parts of the receptor. Proper technique to decide how nearly ligand bound with the receptor amid docking method.

### Docking study

In this examination, docking of TNK 651 was removed from protein 1RT2 and performed to dock with arranged individual proteins so as to dock with arranged particular proteins to check unwavering quality and reproducibility of docking convention for our investigation. A decent

communication was found between ligand their specific receptor. SH imidazole ring with carbonyl gathering of lysine and 'N' heteroatom of imidazole with hydrogen security that was 1.909 Å<sup>0</sup> and 2.262 Å<sup>0</sup> separately.

## METHODS OF SYNTHESIS

### General procedure

#### 1) Synthesis of ammonium phenyl carbamodithioate.

General substituted anilines were added to the mixture of carbon-di-sulphide (0.071 mole) and conc. Ammonia (0.52 mole) drop wise with vigorous stirring for 60 min. A milky homogenous mixture was formed initially. Kept on at ice bath for 2 h to get a solid mass. A precipitate was formed as powder, filtered the content and washed with ether solution and dried.

#### 2) Conversion of ammonium phenyl carbamodithioate to methyl phenyl carbamodithioate

Ammonium phenyl carbamodithioate was dissolved in 10 ml of methanol with cooling in an ice bath. Methyl iodide (0.01 mole) was added to solution and stirred vigorously at temperature 0-4 °C for 3 h.

#### 3) Conversion of methyl phenyl carbamodithioate to phenyl thiosemicarbazide

Intermediate as methyl phenyl carbamodithioate was dissolved in 15 ml of methanol at 60°C. 85% hydrazine hydrate (0.025 mole) was added to the solution and stirred continuously for 2 h. A solution mixture was cooled at room temperature to yield crystalline mass which was filtered with methanol (3x5 mL).

#### 4) Synthesis of para substituted phenyl-2-mercapto-1H-imidazol-1-yl-3-phenyl thiourea

To a solution of para substituted phenacyl bromide (0.002 mole) in glacial acetic acid (10 ml), Potassium thiocyanate (0.002 mole) was added with continuous stirring at temperature of 60°C. the reaction mixture was then stirred for 30 min at same temperature. Intermediate as phenyl thio semicarbazide was added to reaction mixture and stirring was continued at 60°C for 1 h. The reaction mixture then refluxed for 6 h. After refluxing was complete, 30 ml of water was added to reaction mixture which yielded a gummy mass. It was washed with ether (25x10 mL) and product was precipitated out as an amorphous powder and recrystallized from ethanol-water mixture.

#### 1-(5-(4-chlorophenyl)-2-mercapto-1H-imidazol-1-yl)-3-o-tolylthiourea (5a)

Yield: 80%, M.P. 78-80°C, IR (KBr,  $\text{cm}^{-1}$ ): 3058 (N-H stretching), 2957 (C-H stretch  $\text{CH}_3$  group) 1599 (C=S stretching), 1314 (C-N stretching)  $\text{cm}^{-1}$ , NMR (DMSO,

400 MHz): 2.29 (s; 3H; CH<sub>3</sub>) 3.95 (s; 1H; SH), 6.29 (s; 1H; NH-Ar), 7.38-7.55 (m; 8H; Ar-H), 8.01 (s;1H;=CH), 4.70 (s;1H; NH-imidazole), EI MS: 374.04 [M + 1], Analysis calculated for C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S<sub>2</sub>: C, 54.46; H, 4.03; N, 14.94, Cl, 9.46, S, 17.11

**1-(5-(4-bromophenyl)-2-mercapto-1H-imidazol-1-yl)-3-o-tolylthiourea (5b)**

Yield: 68%, M.P. 80-82°C, IR (KBr, cm<sup>-1</sup>): 3012 (N-H stretching), 2123 (C-H stretch CH<sub>3</sub> group) 1602 (C=S stretching), 1321 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.25 (s; 3H; CH<sub>3</sub>) 1.28 (s; 1H; SH), 5.93 (s; 1H; NH-Ar), 7.84-6.89 (m; 8H; Ar-H), 6.30 (s;1H;=CH), 5.32 (s;1H; NH-imidazole), 419.99 [M + 1], Analysis calculated for C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S<sub>2</sub>: C, 48.69; H, 3.61; N, 13.36, Br, 19.05, S, 15.29.

**1-(2-mercapto-5-p-tolyl-1H-imidazol-1-yl)-3-o-tolylthiourea (5c)**

Yield: 72%, M.P. 60-62°C, IR (KBr, cm<sup>-1</sup>): 3076 (N-H stretching), 2024 (C-H stretch CH<sub>3</sub> group) 1564 (C=S stretching), 1330 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.35 (s; 3H; CH<sub>3</sub>) 2.61 (s; 1H; SH), 6.30 (s; 1H; NH-Ar), 7.49-7.15 (m; 8H; Ar-H), 6.88 (s;1H;=CH), 5.96 (s;1H; NH-imidazole), 354.10 [M + 1], Analysis calculated for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>S<sub>2</sub>: C, 60.99; H, 5.12; N, 15.80, S, 18.09.

**1-(2-mercapto-5-(4-methoxyphenyl)-1H-imidazol-1-yl)-3-o-tolylthiourea (5d)**

Yield: 64%, M.P. 72-74°C, IR (KBr, cm<sup>-1</sup>): 3082 (N-H stretching), 2042 (C-H stretch CH<sub>3</sub> group) 1620 (C=S stretching), 1280 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.19 (s; 3H; CH<sub>3</sub>) 1.25 (s; 1H; SH), 6.23 (s; 1H; NH-Ar), 7.83-6.82 (m; 8H; Ar-H), 5.96 (s;1H;=CH), 3.82 (s;1H; NH-imidazole), 370.09 [M + 1], Analysis calculated for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>OS<sub>2</sub>: C, 58.35; H, 4.90; N, 15.12, O, 4.32; S, 17.31.

**1-(5-(4-methoxy phenyl) -2-mercapto-1H-imidazol-1-yl)-3-o-tolylthiourea (5e)**

Yield: 82%, M.P. 102-104°C, IR (KBr, cm<sup>-1</sup>): 3078 (N-H stretching), 2152 (C-H stretch CH<sub>3</sub> group) 1608 (C=S stretching), 1192 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.33 (s; 3H; CH<sub>3</sub>) 1.42 (s; 1H; SH), 8.02 (s; 1H; NH-Ar), 7.99-7.15 (m; 8H; Ar-H), 7.13 (s;1H;=CH), 4.61 (s;1H; NH-imidazole), 416.11 [M + 1], Analysis calculated for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>S<sub>2</sub>: C, 66.32; H, 4.84; N, 13.45, S, 15.40.

**1-(4-chlorophenyl)-3-(5-(4-chlorophenyl)-2-mercapto-1H-imidazol-1-yl) thiourea (6a)**

Yield: 68%, M.P. 72-74°C, IR (KBr, cm<sup>-1</sup>): 3028 (N-H stretching), 2012 (C-H stretch CH<sub>3</sub> group) 1564 (C=S stretching), 1290 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.62 (s; 1H; SH), 5.32 (s; 1H; NH-Ar),

7.93-7.02 (m; 8H; Ar-H), 6.24 (s;1H;=CH), 3.97 (s;1H; NH-imidazole), 393.11[M + 1], Analysis calculated for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>4</sub>S<sub>2</sub>: C, 48.61; H, 3.06; N, 14.17, S, 16.22; Cl, 17.94.

**1-(5-(4-bromophenyl)-2-mercapto-1H-imidazol-1-yl)-3-(4-chloro phenyl) thiourea (6b)**

Yield: 54%, M.P. 70-72°C, IR (KBr, cm<sup>-1</sup>): 3078 (N-H stretching), 2024 (C-H stretch CH<sub>3</sub> group) 1582 (C=S stretching), 1264 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.20 (s; 1H; SH), 6.27 (s; 1H; NH-Ar), 7.64-7.21 (m; 8H; Ar-H), 6.24 (s;1H;=CH), 2.29 (s;1H; NH-imidazole), 437.94 [M + 1], Analysis calculated for C<sub>16</sub>H<sub>12</sub>BrClN<sub>4</sub>S<sub>2</sub>: C, 43.70; H, 2.75; N, 12.74, S, 14.58, Cl, 8.06; Br, 18.17.

**1-(4-chlorophenyl)-3-(2-mercapto-5-p-tolyl-1H-imidazol-1-yl) thiourea (6c)**

Yield: 62%, M.P. 78-80°C, IR (KBr, cm<sup>-1</sup>): 3012 (N-H stretching), 2028 (C-H stretch CH<sub>3</sub> group), 1602 (C=S stretching), 1282 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.20 (s; 1H; SH), 6.27 (s; 1H; NH-Ar), 7.64-7.21 (m; 8H; Ar-H), 6.24 (s;1H;=CH), 2.29 (s;1H; NH-imidazole), 437.94 [M + 1], Analysis calculated for C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S<sub>2</sub>: C, 54.46; H, 4.03; N, 14.94, S, 54.46, Cl, 9.46.

**1-(4-chlorophenyl)-3-(2-mercapto-5-(4-methoxy phenyl)-1H-imidazol-1-yl)thiourea (6d)**

Yield: 68%, M.P. 68-70°C, IR (KBr, cm<sup>-1</sup>): 3042 (N-H stretching), 2112 (C-H stretch CH<sub>3</sub> group), 1546 (C=S stretching), 1260 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 2.32 (s; 1H; SH), 6.20 (s; 1H; NH-Ar), 8.01-7.08 (m; 8H; Ar-H), 6.96 (s;1H;=CH), 3.87 (s;1H; NH-imidazole), 374.04 [M + 1], Analysis calculated for C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>OS<sub>2</sub>: C, 52.23; H, 3.87; N, 14.33, O, 4.09; S, 16.41, Cl, 9.07.

**1-(4-bromophenyl)-3-(5-(4-chlorophenyl)-2-mercapto-1H-imidazol-1-yl) thiourea (7a)**

Yield: 72%, M.P. 98-100°C, IR (KBr, cm<sup>-1</sup>): 3086 (N-H stretching), 2048 (C-H stretch CH<sub>3</sub> group) 1580 (C=S stretching), 1256 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 1.44 (s; 1H; SH), 6.25 (s; 1H; NH-Ar), 7.74-7.01 (m; 8H; Ar-H), 7.92 (s;1H;=CH), 4.55 (s;1H; NH-imidazole), 439.06 [M + 1], Analysis calculated for C<sub>16</sub>H<sub>12</sub>BrClN<sub>4</sub>S<sub>2</sub>: C, 43.70; H, 2.75; N, 12.74; S, 16.41; Cl, 9.07; Br, 18.17.

**1-(4-bromophenyl)-3-(5-(4-bromophenyl)-2-mercapto-1H-imidazol-1-yl) thiourea (7b)**

Yield: 58%, M.P. 80-82°C, IR (KBr, cm<sup>-1</sup>): 3054 (N-H stretching), 2066 (C-H stretch CH<sub>3</sub> group) 1542 (C=S stretching), 1260 (C-N stretching) cm<sup>-1</sup>, NMR (DMSO, 400 MHz): 1.22 (s; 1H; SH), 3.49 (s; 1H; NH-Ar), 7.84-6.91 (m; 8H; Ar-H), 4.69 (s;1H;=CH), 2.68 (s;1H;

NH-imidazole), 483.88 [M + 1], Analysis calculated for  $C_{16}H_{12}Br_2N_4S_2$ : C, 39.69; H, 2.50; N, 11.57; S, 13.24; Br, 33.00.

**1-(4-bromophenyl)-3-(2-mercapto-5-p-tolyl-1H-imidazol-1-yl) thiourea (7c)**

Yield: 66%, M.P. 76-78°C, IR (KBr,  $cm^{-1}$ ): 3072 (N-H stretching), 2084 (C-H stretch  $CH_3$  group) 1560 (C=S stretching), 1248 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 2.43 (s, 3H,  $CH_3$ ), 2.08 (s; 1H; SH), 4.81 (s; 1H; NH-Ar), 7.93-7.04 (m; 8H; Ar-H), 7.99 (s; 1H; =CH), 2.28 (s; 1H; NH-imidazole), 419.99 [M + 1], Analysis calculated for  $C_{17}H_{15}BrN_4S_2$ : C, 48.69; H, 3.61; N, 13.36; S, 15.29; Br, 19.05.

**1-(4-bromophenyl)-3-(2-mercapto-5-(4-methoxyphenyl)-1H-imidazol-1-yl) thiourea (7d)**

Yield: 52%, M.P. 60-62°C, IR (KBr,  $cm^{-1}$ ): 3084 (N-H stretching), 2052 (C-H stretch  $CH_3$  group) 1522 (C=S stretching), 1208 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 3.83 (s, 3H,  $CH_3$ ), 1.28 (s; 1H; SH), 4.69 (s; 1H; NH-Ar), 7.93-6.87 (m; 8H; Ar-H), 6.88 (s; 1H; =CH), 2.32 (s; 1H; NH-imidazole), 433.99 [M + 1], Analysis calculated for  $C_{17}H_{15}BrN_4OS_2$ : C, 46.90; H, 3.47; N, 12.87; S, 14.73; O, 3.67; Br, 18.35.

**1-(5-(4-chlorophenyl)-2-mercapto-1H-imidazol-1-yl)-3-(2, 4-dimethyl phenyl)thiourea (8a)**

Yield: 58%, M.P. 71-73°C, IR (KBr,  $cm^{-1}$ ): 3064 (N-H stretching), 2042 (C-H stretch  $CH_3$  group) 1558 (C=S stretching), 1224 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 2.32 (s; 6H;  $CH_3$ ), 3.99 (s; 1H; SH), 9.87 (s; 1H; NH-Ar), 7.93-7.10 (m; 8H; Ar-H), 388.06 [M + 1], Analysis calculated for  $C_{18}H_{17}ClN_4S_2$ : C, 55.59; H, 4.41; N, 14.41; S, 16.49; Cl, 9.12.

**1-(5-(4-bromophenyl)-2-mercapto-1H-imidazol-1-yl)-3-(2, 4-dimethylphenyl) thiourea (8b)**

Yield: 66%, M.P. 68-70°C, IR (KBr,  $cm^{-1}$ ): 3042 (N-H stretching), 2012 (C-H stretch  $CH_3$  group) 1612 (C=S stretching), 1204 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 2.41-2.05 (s; 6H;  $CH_3$ ), 1.97 (s; 1H; SH), 6.70 (s; 1H; NH-Ar), 7.84-7.06 (m; 8H; Ar-H), 7.02 (s; 1H; =CH), 2.61 (s; 1H; NH-imidazole), 432.01 [M + 1], Analysis calculated for  $C_{18}H_{17}BrN_4S_2$ : C, 49.88; H, 3.95; N, 12.93; S, 14.80; Br, 18.44.

**1-(2-mercapto-5-p-tolyl-1H-imidazol-1-yl)-3-(2, 4-dimethylphenyl) thiourea (8c)**

Yield: 72%, M.P. 55-58°C, IR (KBr,  $cm^{-1}$ ): 3072 (N-H stretching), 2052 (C-H stretch  $CH_3$  group) 1562 (C=S stretching), 1236 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 2.39-2.05 (s; 6H;  $CH_3$ ), 0.88 (s; 1H; SH), 4.75 (s; 1H; NH-Ar), 7.22-6.97 (m; 8H; Ar-H), 7.42 (s; 1H; =CH), 2.39 (s; 1H; NH-imidazole), 388.06 [M + 1],

Analysis calculated for  $C_{19}H_{20}N_4S_2$ : C, 61.92; H, 5.47; N, 15.20; S, 17.40.

**1-(2-mercapto-5-(4-methoxyphenyl)-1H-imidazol-1-yl)-3-(2,4-dimethylphenyl)thiourea (8d)**

Yield: 72%, M.P. 70-72°C, IR (KBr,  $cm^{-1}$ ): 3066 (N-H stretching), 2028 (C-H stretch  $CH_3$  group) 1586 (C=S stretching), 1202 (C-N stretching)  $cm^{-1}$ , NMR (DMSO, 400 MHz): 3.85 (d; 3H,  $OCH_3$ ), 2.34-2.04 (s; 6H;  $CH_3$ ), 2.59 (s; 1H; SH), 6.58 (s; 1H; NH-Ar), 7.55-6.88 (m; 8H; Ar-H), 7.97 (s; 1H; =CH), 3.90 (s; 1H; NH-imidazole), 384.06 [M + 1], Analysis calculated for  $C_{19}H_{20}N_4OS_2$ : C, 59.35; H, 5.24; N, 14.57; S, 16.68; O, 4.16.

**1-(5-(4-chlorophenyl)-2-mercapto-1H-imidazol-1-yl)-3-(naphthalen-5-yl) thiourea (9a)**

Yield: 58%, M.P. 63-65°C, IR (KBr,  $cm^{-1}$ ): 2984.78 (NH stretching), 2846.63  $cm^{-1}$  (symmetrical C-H stretching of methyl group), 2368.83 (S-H stretching), 1637.74 (C=S stretching), 1584.24  $cm^{-1}$  (N-H aromatic bending vibration), 1474.10  $cm^{-1}$  (C-N stretching of aromatic amine), 872.74  $cm^{-1}$  (C=S group attached to N atom), NMR (DMSO, 400 MHz): 2.32 (s; 1H; SH), 6.30 (s; 1H; NH-Ar), 8.01-6.77 (m; 8H; Ar-H), 7.25 (s; 1H; =CH), 4.73 (s; 1H; NH-imidazole), 410.04 [M + 1], Analysis calculated for  $C_{20}H_{15}ClN_4S_2$ : C, 58.45; H, 3.68; N, 13.63; S, 15.61; Cl, 8.63.

**1-(5-(4-bromophenyl)-2-mercapto-1H-imidazol-1-yl)-3-(naphthalen-5-yl) thiourea (9b)**

Yield: 51%, M.P. 67-69°C, IR (KBr,  $cm^{-1}$ ): 2959.39 (NH stretching), 2712.62  $cm^{-1}$  (symmetrical C-H stretching of methyl group), 2348.72 (S-H stretching), 1653.47 (C=S stretching), 1526.83  $cm^{-1}$  (N-H aromatic bending vibration), 1439.14  $cm^{-1}$  (C-N stretching of aromatic amine), 874.39  $cm^{-1}$  (C=S group attached to N atom), NMR (DMSO, 400 MHz): 2.14 (s; 1H; SH), 6.29 (s; 1H; NH-Ar), 7.91-7.38 (m; 8H; Ar-H), 6.94 (s; 1H; =CH), 4.71 (s; 1H; NH-imidazole), 455.9 [M + 1], Analysis calculated for  $C_{20}H_{15}BrN_4S_2$ : C, 52.75; H, 3.32; N, 12.30; S, 14.08; Br, 17.55.

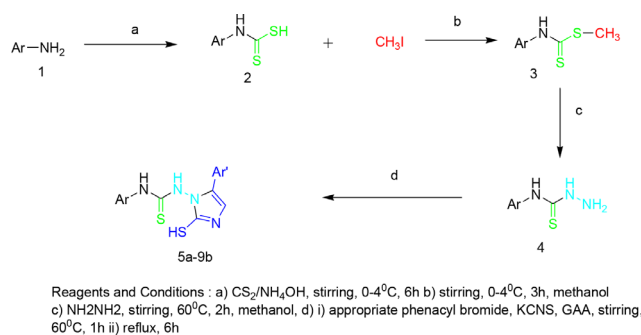
## ANTI-HIV ACTIVITY

### Sample and chemicals

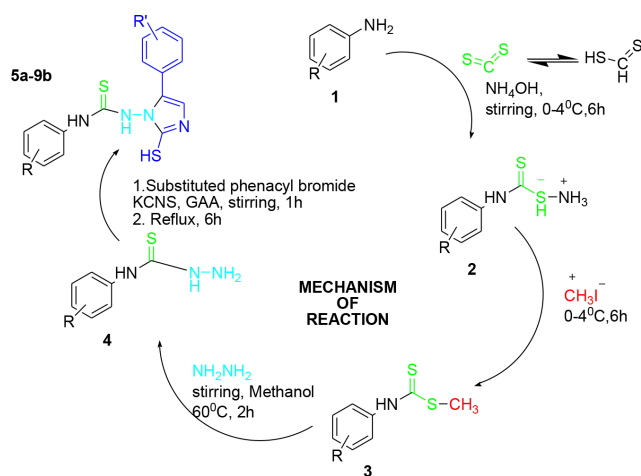
All testing tests were given by Dr. Swastika Ganguly (Department of Pharmaceutical Science and Technology, Birla Institute of Technology, Mesra, India). All examples were broken down in DMSO. AZT was bought from USP and broken down in sans serum RPMI-1640 medium.

### Reagents

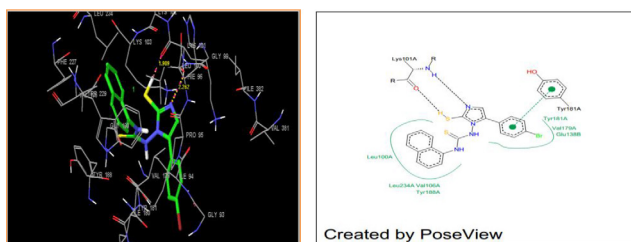
HEPES (N (2-Hydroxyethyl) piperazine-N'- (2-ethanesulfonic corrosive), MTT (3,(4,5-dimethylthiazol-2-yl)



**Reaction scheme: General reaction procedure of synthesized compound (5a-9b).**



**General Mechanism of Reaction of synthesized compound.**



**Molecular model of imidazole A series (9b) in the NNRTI of HIV-1 RT (PDB code 1RT2). Active site amino acid residues are represented as lines while the inhibitor is shown as ball and stick model with the atoms colored as carbon: green, hydrogen: cyan, nitrogen: blue, and oxygen: red. Hydrogen bond interactions are represented by pink dotted lines. (SH)<sub>IMIDAZOLE RING</sub> — CO<sub>LYS101</sub> = 1.909 Å° and N of imidazole ring — NH<sub>LYS101</sub> = 2.262 Å° Put the distance of H bond interactions as shown in sample here (Glide XP Score-12.47) b. Schematic (2D) representation of interactions of compound 9b in the binding pocket of the protein.**

- 2,5-diphenyl tetrazolium bromide), DMF (N, N<sup>2</sup>-Dimethyl formamine), Penicillin, Streptomycin sulfate, Glutamine were obtained from Sigma; 2-ME (2-Mercaptoethanol) was bought from Bio-Rad. RPMI-1640 and fetal ox-like serum (FBS) were bought from Gibco.

## Cells and viruses

C8166 cell and HIV-1IIB were benevolently given by Medical Research Council, AIDS Regent Project. The cells were kept up at 37°C out of 5% CO<sub>2</sub> in RPMI-1640 medium supplemented with 10% warmth inactivating FBS (Gibco). HIV-1IIB was set up from the supernatants of H9/HIV-1IIB cells. The half HIV-1 tissue culture irresistible dosage (TCID<sub>50</sub>) in C8166 cells was resolved and computed by Reed and Muench strategy. Infection stocks were put away in little aliquots at - 70°C. The titer of infection stock was 1.0×10<sup>8</sup> TCID<sub>50</sub> per ml.

## Cytotoxic assay

The cell poisonous quality of mixes on C8166 was evaluated by MTT colorimetric measure. Quickly, 100 μl of 4X10<sup>5</sup> cells were plated into 96 well plates. 100 μl of different groupings of mixes were included and brooded at 37°C out of a humidified air of 5% CO<sub>2</sub> for 72 h. Dispose of 100 μl supernatant, MTT reagent was included and hatched for 4 h, 100μl half DMF-15% SDS was included. After the formazan was broken down totally, the plates were investigated by a Bio-Tek ELx 800 ELISA peruser at 570 nm/630 nm. half cytotoxicity focus (CC<sub>50</sub>) was computed.

## Inhibition of syncytia formation

The hindrance impact of tests on intense HIV-1 contamination was estimated by the syncytia development test. In the nearness or nonappearance of different groupings of tests, 4×10<sup>4</sup> C8166 cells were tainted with HIV-1 at a variety of contamination (MOI) of 0.04, and refined in 96-well plates at 37°C of every 5% CO<sub>2</sub> for 3 days. EFV was utilized as a positive control. At 3 days post-contamination, Cytopathic effect (CPE) was estimated by checking the quantity of syncytia (multinucleated giant cell) in each well of 96-well plates under a transformed magnifying instrument (100×). The inhibitory level of syncytia arrangement was ascertained by the level of syncytia number in the treated example contrasted with that in tainted control. 50% effective concentration (EC<sub>50</sub>) was calculated.

## Formula

As per the technique portrayed by Reed and Munch, half cytotoxic focus (CC<sub>50</sub>) and half viable fixation (EC<sub>50</sub>) was resolved from measurement reaction bend. Therapeutic index (TI) of anti-HIV activity is CC<sub>50</sub>/EC<sub>50</sub>.

$$\text{Cell viability (\% of control)} = \frac{\text{Cell viability (\% of control)}}{\text{Odcctl} - \text{Odblk}} \times 100$$

$$\text{CPE inhibition (\%)} = \frac{1 - \text{CPE}_{\text{test}}}{\text{CPE}_{\text{ctrl}}} \times 100$$

## RESULTS AND DISCUSSION

### Chemistry

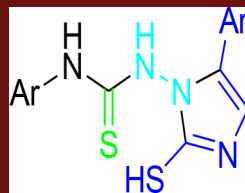
A small library of nineteen imidazole analogs (5a-9b) were synthesized following the reaction outlined in Scheme 1. The synthesis of the compounds were carried out in 4 steps.

First ammonium phenyl carbamodithioate (2) was synthesized. Ammonium phenyl carbamodithioate was dissolved in 10 ml of methanol with cooling in an ice bath. Methyl iodide was added to solution and stirred vigorously at temperature 0-4°C for 3 h. Intermediate as methyl phenyl carbamodithioate (3) was dissolved in 15 ml of methanol at 60°C. 85% hydrazine hydrate was added to the solution and stirred continuously for 2 h a phenyl thiosemicarbazide was formed. (4) To a solution of para substituted phenacyl bromide in glacial acetic acid, Potassium thiocyanate was added with continuous stirring at temperature of 60°C. the reaction mixture was then stirred for 30 min at same temperature. Intermediate as phenyl thio semicarbazide was added to reaction mixture and stirring was continued at 60°C for 1 h. The reaction mixture then refluxed for 6 h. After refluxing was complete, 30 ml of water was added to reaction mixture which yielded a gummy mass. It was washed with ether and product was precipitated out as an amorphous powder and recrystallized from ethanol-water mixture.

A product para substituted phenyl-2-mercapto-1-H-imidazol-1-yl-3-phenyl thiourea derivatives have been synthesized. (5a-9b). The substitution of Ar and Ar' are shown in Table 1.

The IR (KBr) range of all the blended mixes showed fundamentally the same as frequencies demonstrating the nearness of thiourea structures for the title mixes. The IR spectra of the blended mixes contained the thiocarbonyl extending (C=S) band 1731-1600 cm<sup>-1</sup>. Likewise, N-H extending band was seen in the middle of 3200-3000 cm<sup>-1</sup>. The C-H band in IR spectra of the considerable number of mixes showed up at 2100–2000 cm<sup>-1</sup> and C-N assimilation ranges from 1300-1200 cm<sup>-1</sup>. The 1H-NMR range of the title mixes (5a-9b) were recorded in Deuterated CDCl<sub>3</sub> arrangement and are in whole accord with the anticipated reverberation motions as far as synthetic movements and integrations. 1H-NMR range of the title mixes (5a-9b) demonstrated an expansive singlet of 1 proton appointed to SH proton at δ 1.20-2.20. Contingent upon the idea of the

Table 1: Substituents of Ar and Ar'.



General structure of Imidazole derivatives

S.No.	Ar	Ar'
5a	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>
5b	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-Br C <sub>6</sub> H <sub>4</sub>
5c	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
5d	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
5e	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-C <sub>6</sub> H <sub>4</sub> C <sub>6</sub> H <sub>4</sub>
6a	4-Cl C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>
6b	4-Cl C <sub>6</sub> H <sub>4</sub>	4-Br C <sub>6</sub> H <sub>4</sub>
6c	4-Cl C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
6d	4-Cl C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
7a	4-Br C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>
7b	4-Br C <sub>6</sub> H <sub>4</sub>	4-Br C <sub>6</sub> H <sub>4</sub>
7c	4-Br C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
7d	4-Br C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
8a	2,4-DI- CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>
8b	2,4-DI- CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	4-Br C <sub>6</sub> H <sub>4</sub>
8c	2,4-DI- CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
8d	2,4-DI- CH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>
9a	α-naphthyl amine	4-Cl C <sub>6</sub> H <sub>4</sub>
9b	α-naphthyl amine	4-Br C <sub>6</sub> H <sub>4</sub>

substituent's and substitution designs on the N - phenyl ring, the sweet-smelling protons of specific mixes (5a-9b) were seen in particular synthetic movements with expected part designs as doublets, triplets, or multiplets incorporating more than one proton because of the nearby concoction shifts going from δ 5.530 - 8.020. In the aliphatic area, an expansive singlet of 3 protons relegated to the methyl or methoxyl proton of - CH<sub>3</sub> or OCH<sub>3</sub> ranges δ 2.20-2.86 was watched for the mixes. The basic affirmations of these mixes were dictated by utilizing ESI-MS.

### Anti-HIV activity

All the compounds were screened for their *in vitro* Anti-HIV activity. The results are given in Table 2.

Among all the series of compounds 5a-9b. Compounds 5a, 6a, 6b, 6c, 6d, 7c, 9a and 9b showed a significant degree of anti-HIV activity compared to zidovudine (AZT), with compounds 6a, 6b, 6c, 6d being the most active because of chlorine as substituent showed therapeutic index were >22.4, 31.1, 30.5 and 51.5, compound 9a and 9b shows maximum activity against of therapeutic

**Table 2: The summary of cytotoxicity and Anti-HIV-1 activities of compound.**

Compounds	Experiment	Method	CC50 ( $\mu\text{M}$ )	EC50 ( $\mu\text{M}$ )	Therapeutic Index (TI)
5a	Cytotoxicity assay	MTT	59.23	-	17.8
	Inhibition of syncytium formation	CPE	-	3.37	
5b	Cytotoxicity Assay	MTT	27.14	-	8.1
	Inhibition of syncytium formation	CPE	-	3.39	
5c	Cytotoxicity Assay	MTT	109.83	-	8.02
	Inhibition of syncytium formation	CPE	-	13.7	
5d	Cytotoxicity Assay	MTT	20.91	-	5.5
	Inhibition of syncytium formation	CPE	-	3.77	
5e	Cytotoxicity Assay	MTT	65.78	-	7.8
	Inhibition of syncytium formation	CPE	-	8.45	
6a	Cytotoxicity Assay	MTT	>200	-	>22.4
	Inhibition of syncytium formation	CPE	-	8.92	
6b	Cytotoxicity Assay	MTT	80.00	-	31.1
	Inhibition of syncytium formation	CPE	-	2.57	
6c	Cytotoxicity Assay	MTT	104.63	-	30.5
	Inhibition of syncytium formation	CPE	-	3.43	
6d	Cytotoxicity Assay	MTT	100.9	-	51.5
	Inhibition of syncytium formation	CPE	-	1.96	
7a	Cytotoxicity Assay	MTT	7.00	-	15.7
	Inhibition of syncytium formation	CPE	-	4.97	
7b	Cytotoxicity Assay	MTT	88.11	-	6.8
	Inhibition of syncytium formation	CPE	-	13	
7c	Cytotoxicity Assay	MTT	117.39	-	34.6
	Inhibition of syncytium formation	CPE	-	3.39	
7d	Cytotoxicity Assay	MTT	25.14	-	11.4
	Inhibition of syncytium formation	CPE	-	2.2	
8a	Cytotoxicity Assay	MTT	25.21	-	9.1
	Inhibition of syncytium formation	CPE	-	2.77	
8b	Cytotoxicity Assay	MTT	19.91	-	1.6
	Inhibition of syncytium formation	CPE	-	12.43	
8c	Cytotoxicity Assay	MTT	31.69	-	2.7
	Inhibition of syncytium formation	CPE	-	11.75	
8d	Cytotoxicity Assay	MTT	42.03	-	2.8
	Inhibition of syncytium formation	CPE	-	15.09	
9a	Cytotoxicity Assay	MTT	104.63	-	30.5
	Inhibition of syncytium formation	CPE	-	3.43	
9b	Cytotoxicity Assay	MTT	48.79	-	85.6
	Inhibition of syncytium formation	CPE	-	0.57	
AZT	Cytotoxicity Assay	MTT	1291.00	-	514342.6
	Inhibition of syncytium formation	CPE	-	0.00251	



index 30.5 and 85.6 respectively. Compound 7c and 5a also showed remarkable significant activity and their therapeutic index were 34.6 and 17.8. while cytotoxicity concentration ( $CC_{50}$ ) in  $\mu\text{M}$  by MTT method of compound 5c, 6a, 6c, 6d, 7c, 9a and 9b were found to be 109.83, >200, 104.63, 100.9, 117.39, 104.63 and 48.79 which were found to be less toxic than standard zidovudine (AZT) that is ( $CC_{50}$ =1291.00  $\mu\text{g}/\text{mL}$ ), compound 5a, 5e, 6b and 7b showed a moderate toxicity that were 59.23, 65.78, 80.00, and 88.11 and compound 5b, 5d, 7a, 7d, 8a, 8b, 8c and 8d showed a least cytotoxicity that were 27.14, 20.91, 7.00, 25.14, 25.21, 19.91, 31.69 and 42.03. The effective concentration of synthesized compounds 5a-9b, compound 5a, 5b, 5d, 6b, 6c, 6d, 7a, 7c, 7d, 8a, 9a and 9b were found to be very effective among all and that were 3.37, 3.39, 3.77, 2.57, 4.97, 3.39, 2.2, 2.77, 3.43 and 0.57 respectively which were less than standard zidovudine (AZT) that is ( $EC_{50}$ =0.00251 $\mu\text{g}/\text{mL}$ ). As a control, AZT has the best anti-HIV activity ( $EC_{50}$ =0.00251 $\mu\text{g}/\text{mL}$ ) *in vitro*, and the  $CC_{50}$  of is 1291.00 $\mu\text{g}/\text{mL}$ , its therapeutic index is 514342.6.

### Docking studies

The imidazole scaffold is favorably embedded in the hydrophobic pocket surrounded by the side chains of Leu 101A, Tyr 101A and Val 106A. The compound also shows one H-bond interaction between the hydrophilic spacer group  $\text{SH}_{\text{IMIDAZOLE RING}} \cdots \text{CO}_{\text{LYS101}} = 1.909 \text{ \AA}$  and N of imidazole ring  $\text{NH}_{\text{LYS101}} = 2.262 \text{ \AA}$ . These interactions may be responsible for the binding affinity of the molecule as indicated by the docking scores  $-12.47$  comparable and more than the docking score  $-12.04$  of the reference ligand Tnk 651. The summary of docked compound with 1RT2 protein is given below in Table 3.

### CONCLUSION

A small library of seventeen imidazole analogs (5a-9b) have been synthesized and their structures have been characterized by IR, NMR and mass spectroscopy. All the newly synthesized compounds were evaluated for their anti-HIV activities. The cellular toxicity of compounds on C8166 was assessed by MTT colorimetric assay while inhibition effect of samples on acute HIV-1 infection was measured by the syncytia formation assay. It can be concluded that incorporation of hydrophobic electron releasing /electron withdrawing groups in the in both the aryl moieties attached to the aryl/heteroaryl pharmacophore was a required feature for high antibacterial and antifungal activities. This study encourages us to consider a new molecular skeleton of para substituted

**Table 3: The summary of docking score on 1RT2 receptor.**

Compound Code	R	R'	Dock score on 1RT2
5a	2-CH <sub>3</sub>	Cl	-10.14
5b	2-CH <sub>3</sub>	Br	-11.66
5c	2-CH <sub>3</sub>	CH <sub>3</sub>	-8.25
5d	2-CH <sub>3</sub>	CH <sub>3</sub> O	-9.02
5e	2-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	-8.99
6a	4-Cl	Cl	-11.11
6b	4-Cl	Br	-10.54
6c	4-Cl	CH <sub>3</sub>	-8.69
6d	4-Cl	CH <sub>3</sub> O	-9.06
7a	4-Br	Cl	-11.34
7b	4-Br	Br	-11.99
7c	4-Br	CH <sub>3</sub>	-9.90
7d	4-Br	CH <sub>3</sub> O	-8.78
8a	2,4-Di Me	Cl	-10.85
8b	2,4-Di Me	Br	-11.68
8c	2,4-Di Me	CH <sub>3</sub>	-9.80
8d	2,4-Di Me	CH <sub>3</sub> O	-10.01
9a	$\alpha$ -naphthyl	Cl	-11.77
9b	$\alpha$ -naphthyl	Br	<b>-12.47</b>
<b>Standard</b>	Tnk 651		-12.04

phenyl-2-mercapto-1-H-imidazol-1-yl-3-phenyl thiourea which may be identified as a potential scaffold for the development of broad-spectrum chemotherapeutic agents. It can be concluded that these series of imidazoles might be useful as starting moieties that can be further exploited synthetically for the discovery of analogues with more potent anti-HIV activity with broad-spectrum chemotherapeutic properties.

### ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

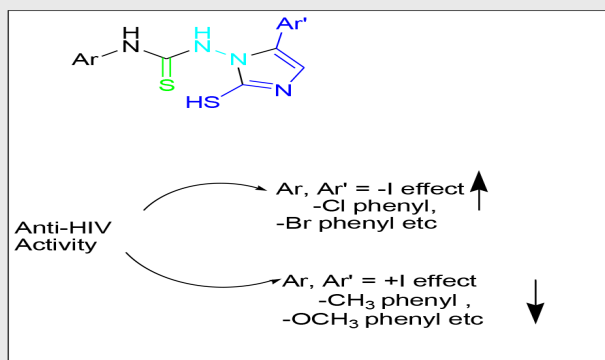
## ABBREVIATIONS

**1RT2:** Reverse transcriptase enzyme, **AZT:** Zidovudine, **NNRTI:** Non-nucleoside reverse transcriptase inhibitors, **HIV:** human immunodeficiency virus, **GAA:** Glacial acetic acid, **FT-IR:** Fourier Transform Infrared; **<sup>1</sup>H NMR:** Proton Nuclear Magnetic Resonance; **ESI Mass:** Electrospray Ionization Mass Spectrometry; **TLC:** Thin-layer chromatography; **DMSO:** Dimethyl sulfoxide; **TMS:** Tetramethylsilane.

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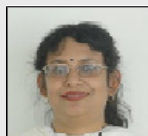
## PICTORIAL ABSTRACT



## SUMMARY

A Novel library of nineteen substituted imidazole analogs have been synthesized and their structures have been characterized by IR, NMR and Mass spectroscopy. All the recently synthesized compounds were assessed for their Anti-HIV activity as well as cytotoxicity assay through MTT colorimetric measure. Maximum number of compounds showed a significant degree of anti-HIV activity compared to zidovudine (AZT).

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