**S1. HIV-1 RT wt inhibition by A15 compound** 

RNA dependent DNA polymerase activity (●) and DNA polymerase independent RNase H activity (o) were measured in presence of The results from three independent experiments (biological replicates) are shown as percentage of control. Error bars represent the standard deviation.

**S2. Effect of MgCl2 on the spectrum of absorbance of A15 compound.**

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Chelation of Mg2+ UV/vis spectrum was measured with 100 µM of compound alone (unbroken line) or in the presence of 6 mM MgCl2 (dotted line)

**S3. Scheme 1. Synthesis of pyrazole derivatives A1-A18**a

aReaction conditions: i) EtOH, r.t.; ii) DMF, r.t.; iii) CH2Cl2, TEA, r.t.

**Scheme 2. Synthesis of pyrrolecarbothioamides B1-20**a



aReaction conditions: i) CH2Cl2, TEA, r.t.

**S4. *General procedure for synthesis of cyanoacetamidrazones* 10-17**

A solution of 3-amino-3-ethoxypropenenitrile **1** (1,1 g, 10 mmoles) and the appropriate hydrazine **2-9** (10 mmoles) in anhydrous ethanol was heated at 70 °C for 5 min and then left overnight at room temperature. The formed precipitate was filtered off, washed with diethyl ether and recrystallized from the indicated solvent.

*3.1.2.1. N1-(4-Methoxyphenylacetyl)-2-cyanoacetamidrazone* (**11**). Obtained starting from 4-(methoxyphenylacetyl)hydrazine (**3**) in 85% yield. M. p. 130-132 °C (acetonitrile). IR (Nujol) 3420, 3180, 2250, 1650, 1595. 1H-NMR: 3.49 (s, 2H, CH2), 3.73 (s, 1H, CH), 3.77 (s, 3H, CH3), 6.58 (s, 2H, NH2), 6.94 (d, J= 8.5 Hz, 2H, Ar), 9.64 (s, 1H, NH), 9.77 (s, 1H, NH). Anal. Calcd. for C12H14N4O2 %C 58.53, %H 5.73, %N 22.75. Found %C 58.48, %H 5.72, %N 22.79.

*3.1.2.2. N1-(2,4-Dichlorophenylacetyl)-2-cyanoacetamidrazone* (**14**). Obtained starting from 2,4-(dichlorophenylacetyl)hydrazine (**6**) in 91% yield. M. p. 163-164 °C (acetonitrile). IR (Nujol) 3413, 3217, 3047, 2261, 1658, 1637, 1610. 1H-NMR: 3.48 (s, 2H, CH2), 3.72 (s, 1H, CH), 6.74 (s, 2H, NH2), 7.13 (d, J= 8.1 Hz, 2H, Ar), 7.27 (d, J= 8.1 Hz, 2H, Ar), 7.70 (s, 1H, Ar), 9.52 (s, 1H, NH), 9.91 (s, 1H, NH). Anal. Calcd. for C11H10Cl2N4O %C 46.34, %H 3.54, %N 19.65. Found %C 46.39, %H 3.53, %N 19.67.

*3.1.3. General procedure for the synthesis of propenethioamides* **18-35**

A mixture of amidrazone **10-17** (5 mmoles) and isothiocyanate (5 mmoles) in dry dimethylformamide (10 mL) was stirred at room temperature. After 24 hours water (30 mL) was added and the resulting precipitate was filtered, washed with ethyl acetate (3 x 10 mL) and dried to give compounds **18-35** in analytical pure form without additional purification by recrystallization or chromatography.

*3.1.3.1. 3-Amino-3-(2-(2-(4-nitrophenyl)acetyl)hydrazine-2-((phenylamino)thioxamethyl)-2-propenenitrile* (**20**).Obtained from cyanoacetamidrazone **12** and phenylisothiocyanate. Yield 96%. M.p. 204-205 °C. IR 3250, 3238, 2188, 1686, 1615. 1H-NMR: 3.45 (s, 2H, CH2), 7.18-7.46 (m, 11H, Ar and NH2), 9.42, 10.18, 10.33 (s, 3H, NH). Anal. Calcd. for C18H16N6O3S (396.42) %C 54.54, %H 4.07, %N 21.20. Found %C 54.48, %H 4.06, %N 21.16.

*3.1.3.2. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((2,4-dichlorophenylamino)thioxamethyl)-2-propenenitrile* (**23**) Obtained from cyanoacetamidrazone **13** and 2,4-dichlorophenylisothiocyanate. Yield 91%. M.p. 211-212 °C. IR 3344, 3226, 3127, 2185, 1881, 1623. 1H-NMR: 3.42 (s, 2H, CH2), 6.98-7.51 (m, 8H, Ar and NH2), 8.01 (s, 1H, Ar), 9.34, 10.22, 10.41 (s, 3H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.49, %H 3.11, %N 15.37.

*3.1.3.3. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((3-chlorophenylamino)thioxamethyl)-2-propenenitrile* (**24**). Obtained from cyanoacetamidrazone **13** and 3-chlorophenylisothiocyanate. Yield 95%. M.p. 176-177°C. IR 3330, 3258, 3137, 3073, 2187, 1705, 1624. 1H-NMR: 3.44 (s, 2H, CH2), 6.46-7.48 (m, 10H, Ar and NH2), 8.98, 9.80, 10.18 (s, 3H, NH). Anal. Calcd. for C18H15Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.49, %H 3.61, %N 16.63.

*3.1.3.4. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((4-chlorophenylamino)thioxamethyl)-2-propenenitrile* (**25**). Obtained from cyanoacetamidrazone **13** and 4-chlorophenylisothiocyanate. Yield 97%. M.p. 193-194 °C. IR 3331, 3266, 3176, 3064, 2188, 1704, 1622. 1H-NMR: 3.45 (s, 2H, CH2), 6.72-7.36 (m, 10H, Ar and NH2), 9.25, 9.97, 10.41 (s, 3H, NH). Anal. Calcd. for C18H15Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.50, %H 3.59, %N 16.70.

*3.1.3.5. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((3,4-dichlorophenylamino)thioxamethyl)-2-propenenitrile* (**27**). Obtained from cyanoacetamidrazone **13** and 3,4-dichlorophenylisothiocyanate. Yield 88%. M.p. 205-206 °C. IR 3338, 3267, 3185, 3075, 2188, 1706, 1625. 1H-NMR: 3.46 (s, 2H, CH2), 6.57-7.38 (m, 9H, Ar and NH2), 9.00, 10.31, 10.45 (s, 3H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.58, %H 3.11, %N 15.45.

*3.1.3.6. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((2,5-dichlorophenylamino)thioxamethyl)-2-propenenitrile* (**28**). Obtained from cyanoacetamidrazone **13** and 2,5-dichlorophenylisothiocyanate. Yield 84%. M.p. 190-191°C. IR 3345, 3260, 2175, 1679, 1622. 1H-NMR: 3.43 (s, 2H, CH2), 6.73-7.44 (m, 9H, Ar and NH2), 8.97, 10.44, 10.68 (s, 3H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.59, %H 3.12, %N 15.37.

*3.1.3.7. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((4-fluorophenylamino)thioxamethyl)-2-propenenitrile* (**29**). Obtained from cyanoacetamidrazone **13** and 4-fluorophenylisothiocyanate. Yield 92%. M.p. 150-151 °C. IR 3570, 3254, 2188, 1704, 1621. 1H-NMR: 3.46 (s, 2H, CH2), 6.49-7.49 (m, 10H, Ar and NH2), 8.88, 10.03, 10.45 (s, 3H, NH). Anal. Calcd. for C18H15ClFN5OS (403.86) %C 53.53, %H 3.74, %N 17.34. Found %C 53.48, %H 3.75, %N 17.38.

*3.1.3.8. 3-Amino-3-(2-(2-(4-chlorophenyl)acetyl)hydrazine-2-((4-methoxyphenylamino)thioxamethyl)-2-propenenitrile* (**30**). Obtained from cyanoacetamidrazone **13** and 4-methoxyphenylisothiocyanate. Yield 80%. M.p. 137-139 °C. IR 3570, 3330, 3255, 3230, 2190, 1642, 1613. 1H-NMR: 3.45 (s, 2H, CH2), 3.84 (s, 3H, CH3), 6.40-7.29 (m, 10H, Ar and NH2), 9.01, 10.12, 10.32 (s, 3H, NH). Anal. Calcd. for C19H18ClN5O2S (415.90) %C 54.87, %H 4.36, %N 16.84. Found %C 54.92, %H 4.37, %N 16.80.

*3.1.3.9. 3-Amino-3-(2-(2-(2,4-dichlorophenyl)acetyl)hydrazine-2-((phenylamino)thioxamethyl)-2-propenenitrile* (**33**). Obtained from cyanoacetamidrazone **14** and phenylisothiocyanate. Yield 93%. M.p. 184-185 °C. IR 3362, 3220, 2188, 1692, 1620. 1H-NMR: 3.45 (s, 2H, CH2), 3.84 (s, 3H, CH3), 6.92-7.63 (m, 9H, Ar and NH2), 7.71 (s, 1H, Ar), 9.07, 10.14, 10.40 (s, 3H, NH). Anal. Calcd. for C19H18Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.38, %H 3.61, %N 16.70.

*3.1.4. Synthesis of pyrazoles* **A1-3, A5-18**

A solution of propenethioamide **18-30** (1 mmol) and triethylamine (0.14 mL, 1 mmol) in dichoromethane (20 mL) was stirred at room temperature for 48 hours. Then the solution was concentrated in vacuo, the residue was ice added, and the formed precipitate was filtered, dried and recrystallized from the appropriate solvent to give the title compounds.

*3.1.4.1. 2,4-Diamino-1-(2-(4-methoxyphenyl)acetyl)-N-phenyl-1H-pyrazole-4-carbothioamide* (**A2**)

Obtained from propenethioamide **19**. Yield 78% (MeCN). M.p. 166-167 °C. IR 3418, 3244, 1713, 1610. 1H-NMR: 3.93 (s, 3H, CH3), 4.30 (s, 2H, CH2), 5.71 (s, 2H, NH2), 6.68-7.44 (m, 9H, Ar), 8.31 (s, 2H, NH2), 10.50 (s, 1H, NH). Anal. Calcd. forC19H19N5OS (381.45) %C 59.82, %H 5.02, %N 18.36. Found %C 59.89, %H 5.01, %N 18.40.

*3.1.4.2. 2,4-Diamino-1-(2-(4-nitrophenyl)acetyl)-N-phenyl-1H-pyrazole-4-carbothioamide* (**A3**)

Obtained from propenethioamide **20**. Yield 90%. M.p. 115-116 °C (2-PrOH). IR 3250, 3230, 1685, 1605. 1H-NMR: 4.25 (s, 2H, CH2), 5.70 (s, 2H, NH2), 6.72-7.17 (m, 5H, Ar), 7.68 (d, *J* = 8.0 Hz, 2H, Ar), 8.05 (d, *J* = 8.0 Hz, 2H, Ar), 8.43 (s, 2H, NH2), 10.48 (s, 1H, NH). Anal. Calcd. for C18H16N6O3S (396.42) %C 54.54, %H 4.07, %N 21.20. Found %C 54.58, %H 4.06, %N 21.24.

*3.1.4.3. 2,4-Diamino-1-(2-(2,4-dichlorophenyl)acetyl)-N-phenyl-1H-pyrazole-4-carbothioamide* (**A6**). Obtained from propenethioamide **23**. Yield 75%. M.p. 168-170 °C (MeCN). IR 3410, 3286, 3155, 1714, 1610. 1H-NMR: 4.24 (s, 2H, CH2), 5.70 (s, 2H, NH2), 6.74-7.39 (m, 7H, Ar), 7.68 (s, 1H, Ar), 8.37 (s, 2H, NH2), 10.61 (s, 1H, NH). Anal. Calcd. for C18H15Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.49, %H 3.62, %N 16.69.

*3.1.4.4. 2,4-Diamino-N-(3-chlorophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A7**) Obtained from propenethioamide **24**. Yield 88%. M.p. 205-206 °C (EtOH). IR 3416, 3295, 3245, 1714, 1700, 1615. 1H-NMR: 4.28 (s, 2H, CH2), 5.72 (s, 2H, NH2), 6.38-7.51 (m, 8H, Ar), 8.40 (s, 2H, NH2), 10.54 (s, 1H, NH). Anal. Calcd. for C18H15Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.39, %H 3.58, %N 16.70.

*3.1.4.5. 2,4-Diamino-N-(4-chlorophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A8**) Obtained from propenethioamide **25**. Yield 92%. M.p. 194-195 °C (EtOH). IR 3388, 3210, 3196, 1704, 1609. 1H-NMR: 4.26 (s, 2H, CH2), 5.70 (s, 2H, NH2), 6.68-7.40 (m, 8H, Ar), 8.38 (s, 2H, NH2), 10.48 (s, 1H, NH). Anal. Calcd. for C18H15Cl2N5OS (420.32) %C 51.44, %H 3.60, %N 16.66. Found %C 51.49, %H 3.59, %N 16.63.

*3.1.4.6. 2,4-Diamino-N-(2,4-dichlorophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A9**) Obtained from propenethioamide **26**. Yield 80%. M.p. 176-177 °C (MeCN). IR 3369, 3281, 3178, 1703, 1617. 1H-NMR: 4.28 (s, 2H, CH2), 5.74 (s, 2H, NH2), 7.13-7.43 (m, 6H, Ar) 7.98 (s, 1H, Ar), 8.41 (s, 2H, NH2), 10.60 (s, 1H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.48, %H 3.09, %N 15.35.

*3.1.4.7. 2,4-Diamino-N-(3,4-dichlorophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A10**) Obtained from propenethioamide **27**. Yield 85%. M.p. 203-204 °C (EtOH). IR 3413, 3298, 3241, 1707, 1613. 1H-NMR: 4.28 (s, 2H, CH2), 5.75 (s, 2H, NH2), 6.62-7.41 (m, 7H, Ar) 8.39 (s, 2H, NH2), 10.59 (s, 1H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.49, %H 3.12, %N 15.45.

*3.1.4.8. 2,4-Diamino-N-(2,5-dichlorophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A11**) Obtained from propenethioamide **28**. Yield 84%. M.p. 194-195 °C (EtOH). IR 3420, 3311, 3247, 1713, 1686, 1614. 1H-NMR: 4.30 (s, 2H, CH2), 5.77 (s, 2H, NH2), 6.80 (s, 1H, Ar), 7.10-7.49 (m, 6H, Ar) 8.44 (s, 2H, NH2), 10.61 (s, 1H, NH). Anal. Calcd. for C18H14Cl3N5OS (454.76) %C 47.54, %H 3.10, %N 15.40. Found %C 47.59, %H 3.11, %N 15.36.

*3.1.4.8. 2,4-Diamino-N-(4-fluororophenyl)-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A12**). Obtained from propenethioamide **29**. Yield 89%. M.p. 204-205 °C (MeCN). IR 3405, 3247, 3077, 1725, 1607. 1H-NMR: 4.29 (s, 2H, CH2), 5.76 (s, 2H, NH2), 6.94-7.42 (m, 9H, Ar) 8.46 (s, 2H, NH2), 10.52 (s, 1H, NH). Anal. Calcd. for C18H15ClFN5OS (403.86) %C 53.53, %H 3.74, %N 17.34. Found %C 53.58, %H 3.72, %N 17.37.

*3.1.4.9. 2,4-Diamino-1-(2-(4-chlorophenyl)acetyl)-N-(4-methoxyphenyl)-1H-pyrazole-4-carbothioamide* (**A13**). Obtained from propenethioamide **30**. Yield 82%. M.p. 124-125 °C (2-PrOH). IR 3414, 3253, 1712, 1698, 1609. 1H-NMR: 3.77 (s, 3H, CH3), 4.30 (s, 2H, CH2), 5.76 (s, 2H, NH2), 6.94-7.42 (m, 9H, Ar) 8.46 (s, 2H, NH2), 10.52 (s, 1H, NH). Anal. Calcd. for C19H18ClN5O*2*S %C 54.87, %H 4.36, %N 16.84. Found %C 54.91, %H 4.34, %N 16.86.

415.90

*3.1.4.10. 3,5-Diamino-N-benzyl-1-(2-(4-chlorophenyl)acetyl)-1H-pyrazole-4-carbothioamide* (**A16**)

Obtained from propenethioamide **33**. Yield 90%. M.p. 128-130°C (2-PrOH). IR 3440, 3357, 3220, 3042, 1677, 1640, 1609. 1H-NMR: 3.92 (s, 2H, CH2), 4.30 (s, 2H, CH2), 5.78 (s, 2H, NH2), 7.21-7.46 (m, 9H, Ar) 8.39 (s, 2H, NH2), 10.48 (s, 1H, NH). Anal. Calcd. for C19H18ClN5OS (399.90) %C 57.07, %H 4.54, %N 17.51. Found %C 57.01, %H 4.55, %N 17.56.

*3.1.5. 3-Amino-3-((5-methylpyridin-2-yl)amino)-2-((phenylamino)thioxamethyl)-2-propenitrile* (**36**). A solution of 3-amino-3-ethoxypropenenitrile (1.10 g, 10 mmoles) and 2-amino-5-methylpyridine (0.11g, 10 mmoles) in anhydrous acetonitrile was stirred at room temperature. After 24 hours phenyl isothiocyanate (1.35 g, 10 mmoles) was added and the stirring was continued for 6 hours. The formed precipitated was collected by filtration and recrystallized from MeCN. Yield 90%. M.p. 158-160 °C. IR 3390, 3190, 3127, 3030, 1605. 1H-NMR: 2.26 (s, 3H, CH3), 6.75 (d, J=4.9 Hz, 1H, Py), 7.03 (s, 2H, NH2), 7.17, 7.34, 7.65 (m, 6H, Ar and Py), 8.14 (d, J= 7.8 Hz, 2H, Py), 8.13 (m, 1H, Py), 10.76 (s, 1H, NH), 13.90 (s, 1H, NH). Anal. Calcd. for C16H15N5S %C 62.11, %H 4.89, %N 22.64. Found %C 62.16, %H 4.88, %N 22.67.

*3.1.6. Synthesis of pyrrole-3-carbothiamide derivatives* **B1-20**

A solution of propenethioamide (1 mmol), the appropriate bromoketone (1 mmol) and triethylamine (0.14 mL, 1 mmol) in dichoromethane (10 mL) was stirred at room temperature for 24 hours. The solvent was removed in vacuo, the residue was washed with water, filtered and recrystallized from the appropriate solvent to give compound **B1-20**.

*3.1.6.1. 4-Amino-5-(4-bromobenzoyl)-N-phenyl-2-(p-tolylamino)-1H-pyrrole-3-carbothioamide* **(B4)**. Obtained from propenethioamide **34** and 4’-bromophenacyl bromide **41**. Yield 78%. M.p. 218-220 °C (MeCN). IR (Nujol): 3450, 3390, 3250, 3140, 3060, 1620, 1580. 1H-NMR: 2.24 (s, 3H, CH3), 7.03 (m, 7H, Ar) 7.04 (d, J= 7.8 Hz, 2H, Ar), 7.23 (d, J= 7.8 Hz, 2H, Ar), 7.54 (d, J= 7.8 Hz, 2H, Ar), 7.44 (d, J= 8.3 Hz, 2H, Ar), 7.54 (d, J= 7.8 Hz, 2H, Ar), 8.24 (s, 2H, NH2), 11.10 (br s, 1H, NH). Anal. Calcd. for C25H21BrN4OS %C 59.41, %H 4.19, %N 11.08. Found %C 59.37, %H 4.18, %N 11.06.

*3.1.6.2. 4-Amino-5-(4-bromobenzoyl)-2-((4-methoxyphenyl)amino)-N-phenyl-1H-pyrrole-3-carbothioamide* **(B11)**. Obtained from propenethioamide **33** and 4’-bromophenacyl bromide **41**. Yield 82%. M.p. 216-218 °C (EtOH). IR (Nujol): 3450, 3380, 3240, 3115, 3060, 1620, 1585. 1H-NMR: 3.36 (s, 3H, CH3), 7.07 (m, 8H, Ar), 7.11 (m, 3H, Ar), 7.32 (m, 2H, Ar), 7.51 (m, 2H, Ar), 8.32 (s, 2H, NH2), 10.99 (br s, 1H, NH). Anal. Calcd. for C25H21BrN4O2S %C 57.59, %H 4.06, %N 10.74. Found %C 57.63, %H 4.08, %N 10.70.

*3.1.6.3. 4-Amino-5-benzoyl-2-((5-methylpyridin-2-yl)amino)-N-phenyl-1H-pyrrole-3-carbothioamide* **(B20)**. Obtained from propenethioamide **36** and phenacyl bromide **38**. Yield 68%. M.p. 152-154 °C (MeCN). IR (Nujol): 3350, 3060, 1625, 1590. 1H-NMR: 2.27 (s, 3H, CH3), 6.54 (s, 2H, NH2), 6.75 (s, 1H, NH), 7.02 (m, 10H, Ar), 7.48 (d, J= 7.8 Hz, 2H, Py), 8.13 (d, J= 4.9 Hz, 1H, Py), 10.03 (br s, 1H, NH), 12.82 (br s, 1H, NH). Anal. Calcd. for C24H21N5OS %C 67.43, %H 4.95, %N 16.38. Found %C 67.37, %H 4.96, %N 16.41.