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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, in-vitro reverse transcriptase inhibitory activity and docking study of some new imidazol-5-one analogs

Santosh N. Mokale · Deepak K. Lokwani · Devanand B. Shinde

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Abstract Non-nucleoside reverse transcriptase inhibitors have a definitive role and most commonly used in treatment of HIV-1 infection. A new series of 4-ethylidene/substituted-benzylidene-1-(4-hydroxy/chloro-6-methylpyrimidin-2-yl)-2-ethyl/phenyl-1H-imidazol-5(4H)-one were designed, synthesized, and evaluated for HIV-1 reverse transcriptase (RT) inhibitory activity. The results of in-vitro HIV-1 RT assay showed that some of the new compounds, such as **4c**, **4d**, **4e**, **5a,** and **5e** effectively inhibit HIV-1 RT activity. 1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(furan-2-ylmethylene)-2-methyl-1H-imidazol-5(4H)-one (**5e**) exerted most potent in-vitro HIV-1 RT inhibitory activity, among the group of compounds. Molecular docking studies were carried out to explore the binding affinity of imidazole-5-one analogs in active site of HIV-1 RT enzyme.

Keywords Imidazol-5-one · HIV-1 RT · Docking · NNRTI · Glide

Introduction

Human immunodeficiency virus type-1 (HIV-1) is responsible for human acquired immunodeficiency syndrome (AIDS), one of the most urgent world health threats. The successful replication of HIV-1 requires viral genome reverse transcription to generate proviral DNA which then subsequently integrated into the human genome as a provirus. Two types of drugs that inhibit HIV-1 reverse transcriptase (RT) activity are nucleoside and non-nucleoside inhibitors. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric inhibitors which bind to the viral enzyme RT by interacting with specific allosteric non-substrate binding pocket site (non-nucleoside binding pocket-NNBP), blocking its mechanism, and making it unable to produce viral DNA (Balzarini, 2004). NNRTIs are highly specific inhibitors of HIV-1, they are not active against other retroviruses (Balzarini and De Clercq, 1998). This specificity results in high selectivity indexes (ratio of in-vitro cytotoxicity over antiviral activity) for this class of compounds.

Several NNRTIs have been approved for clinical use by the Food and Drug Administration as anti-AIDS drugs, which include nevirapine, delavirdine, efavirenz, and etravirine (Pauwels, 2004). However, in view of the increasing incidence of resistance to the current drug regimens and frequency of adverse events, there is the need of development of new, selective, and potent NNRTIs. This makes HIV-1 RT as a good target to test the drug lead exploration strategies.

The NNRTIs appear very diverse in structure and they have some common features, such as a central heterocyclic moiety (body) surrounded by two bulky hydrophobic groups (wings). The overall structure may be seen as a butterfly with hydrophilic center and two hydrophobic outskirts. It was suggested from literature that a heteroaryl system would be preferred as one of the wings for better HIV-1 RT inhibitory activity (Rao *et al.,* 2004a, b; Rawal *et al.,* 2007). By considering above idea, we reported in our previous study, the new RT inhibitors having imidazole ring as central moiety with methylpyridine and substituted

S. N. Mokale
Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad, Maharashtra, India
e-mail: santoshmokale@rediffmail.com

D. K. Lokwani · D. B. Shinde (✉)
Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India
e-mail: dbsdeepak10@rediffmail.com

D. K. Lokwani
e-mail: dklokwani@gmail.com

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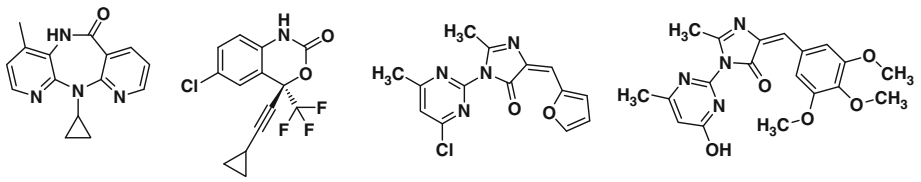
Fig. 1 Chemical structure of compounds



Nevirapine **Efavirenz** **5e** **4e**

ethylidene/benzylidene as two hydrophobic groups (Mokale *et al*., 2012). In present work, we designed and synthesized new compounds by replacing methylpyridine ring with 4-substituted-6-methylpyrimidine as one of new hydrophobic wings for NNRTI (Fig. 1). The most effective HIV-1 RT inhibitors were further subjected to docking studies to investigate their possible binding interactions with HIV-1 RT enzyme.

Experimental

All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Melting points were determined on SRS OPTI-MELT and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE III 400 spectrometer (400 MHz) with TMS as internal standard and DMSO as a solvent. Mass spectra were recorded on Time of flight mass spectrometer. FT-IR spectra were recorded on JASCO FT-IR 4000 using KBr powder.

Synthesis of acetyl glycine (**1**) from glycine

Glycine (0.5 mol) and water (150 ml) were taken in 500 ml conical flask. The mixture was stirred vigorously until solid dissolved completely. To this solution, acetic anhydride (1 mol) was added in one portion and again stirred vigorously for 15–20 min. The resultant mixture was cooled in a refrigerator overnight. The precipitate was collected by filtration, washed with ice-cold water and dry at 100 °C. The crude product was recrystallized from 40 ml of boiling water.

Yield: 65.21 %; M.P: 206 °C.

Synthesis of benzoyl glycine (**2**) from glycine

Glycine (1 mol) was taken in a conical flask and it was dissolved in 750 ml of 10 % sodium hydroxide solution. To this solution, benzoyl chloride (1.15 mol) was added in five portions with stirring until benzoyl chloride reacted completely. The solution was transferred to beaker containing crushed ice and conical flask was rinsed with little water. The concentrated hydrochloric acid was added to above mixture slowly with stirring until the mixture became acidic. The crystalline precipitate of benzoyl glycine was filtered and washed with carbon tetrachloride and cold water. The solid product was collected, dried and recrystallized from boiling water.

Yield: 94.51 %; M.P: 86 °C.

General procedure for synthesis of 4-(substituted ethylidene/benzylidene)-2-methyloxazol-5-ones (**3a**–**j**) from acetyl glycine

A mixture of aldehyde (1 mol), acetyl glycine (**1**, 1 mol), acetic anhydride (3 mol) and anhydrous potassium acetate (1 mol) was placed in a 500 ml RBF. The mixture was heated on an electric hot plate with constant shaking till the mixture liquefied. Then the content of RBF was further heated on water bath for 2 h. To this, 100 ml of ethanol was added slowly and mixture was allowed to stand overnight. The residue was separated by filtration, and then it was washed with 25 ml of ice-cold alcohol and 25 ml of boiling water. The crude product was collected, dried and recrystallized using suitable solvent.

General procedure for synthesis of 4-(substituted ethylidene/benzylidene)-2-phenyloxazole-5-ones (**3k**–**t**) from benzoyl glycine

A mixture of aldehyde (1 mol), benzoyl glycine (**2**, 1 mol), acetic anhydride (3 mol), and anhydrous potassium acetate (1 mol) was placed in a 500 ml RBF. The mixture was heated on an electric hot plate with constant shaking till it liquefied. Then the content of RBF was further heated on water bath for 2 h. To this 100 ml of ethanol was added slowly and the mixture was allowed to stand overnight. The crystalline product was separated by filtration, washed with 25 ml of ice-cold alcohol, then with 25 ml of boiling water and recrystallized using suitable solvent.

General procedure for synthesis of 4-ethylidene/substituted benzylidene-2-methyl/phenyl-1-(4-chloro-6-methylpyrimidin-2-yl)-1H-imidazol-5-one (**4a**–**5t**)

A mixture of 4-substituted ethylidene/benzylidene-2-methyl/phenyl-1,3-oxazol-5-one (1 mol), 2-amino-6-methylpyrimidin-4-ol or 4-chloro-6-methylpyrimidin-2-amine (1 mol), 25 ml glacial acetic acid or 25 ml pyridine, and potassium

acetate (1 mol) was placed in a 250 ml RBF equipped with a reflux condenser and it was heated on heating mantel. The completion of reaction was monitor on TLC plate. After the completion of reaction, the reaction mixture was poured into ice. The precipitate was collected and recrystallized from suitable solvent.

The spectral characterizations of synthesized derivatives are given below.

*4-(4-Chlorobenzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4a**)*

% Yield: 67; MW: 328.75; MF: $C_{16}H_{13}ClN_4O_2$; MP: 180; IR (KBr): 3389, 3056, 2878, 1730, 1638, 1575, 1454, 876, 658 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 10.9 (*s*, 1H, OH), 8.2–7.3 (*m*, 5H, Ar–H), 5.8 (*s*, 1H, –C=CH–), 2.5–2.2 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 173.1 (C, C=O), 164.2 (C, CN_3), 161.2 (C, CN_2), 160.5 (C, C–OH), 159.3 (C, C-5), 133.1 (C, C–Cl), 132.5 (C, C-1′) 130.3 (C, CN), 129.3 (CH, C-2′, C-6′), 128.1 (CH, C-3′, C-5′), 116.2 (CH, C-8), 103.5 (CH, C-4), 24.2 (CH_3), 23.5 (CH_3); MS: *m*/*z* 329 (M+1).

*4-Benzylidene-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4b**)*

% Yield: 45; MW: 294.30; MF: $C_{16}H_{14}N_4O_2$; MP: 210–212; IR (KBr): 3401, 3057, 2877, 1730, 1638, 1575, 1454, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.1 (*s*, 1H, OH), 8.0–7.1 (*m*, 6H, Ar–H), 5.7 (*s*, 1H, –C=CH–), 2.5–2.2 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 169.1 (C, C=O), 164.6 (C, CN_3), 161.6 (C, CN_2), 160.1 (C, C–OH), 159.8 (C, C-5), 131.9 (C, C-1′) 130.1 (C, CN), 128.9 (CH, C-2′, C-6′), 127.5 (CH, C-3′, C-5′), 126.8 (CH, C-4′), 115.7 (CH, C-8), 103.1 (CH, C-4), 23.1 (CH_3), 22.8 (CH_3); MS: *m*/*z* 295 (M+1).

*1-(4-Hydroxy-6-methylpyrimidin-2-yl)-4-(2-hydroxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**4c**)*

% Yield: 51; MW: 310.30; MF: $C_{16}H_{14}N_4O_3$; MP: 190–192; IR (KBr): 3563, 3052, 2959, 1734, 1650, 1602, 1443, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.9 (*s*, 1H, OH), 7.9–7.2 (*m*, 6H, Ar–H), 5.8 (*s*, 1H, –C=CH–), 5.1 (*s*, 1H, OH), 2.5–2.2 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 171.3 (C, C=O), 162.9 (C, CN_3), 160.8 (C, CN_2),159.8 (C, C–OH), 157.7 (C, C-5), 151.1 (C, C–OH), 130.5 (C, CN), 129.1 (C, C-1′), 128.3 (CH, C-4′), 127.6 (CH, C-2′), 126.2 (CH, C-3′), 121.3 (CH, C-5′), 114.9 (CH, C-8), 102.9 (CH, C-4), 24.1 (CH_3), 23.2 (CH_3); MS: *m*/*z* 311 (M+1).

*4-(Furan-2-ylmethylene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4d**)*

% Yield: 49; MW: 284.27; MF: $C_{14}H_{12}N_4O_3$; MP: 170–172; IR (KBr): 3487, 3057, 2877, 1730, 1638, 1575, 1454, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.2 (*s*, 1H, OH), 8.4–7.6 (*m*, 4H, Ar–OH), 6.8 (*s*, 1H, –C=CH–), 2.6–2.3 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 168.9 (C, C=O), 161.3 (C, CN_3), 160.5 (C, CN_2), 157.2 (C, C–OH), 155.3 (C, C-5), 150.1 (C, C-1′), 142.3 (CH, C-2′), 131.1 (C, CN), 116.2 (CH, C-8), 113.2 (CH, C-3′), 109.2 (CH, C-4′), 103.4 (CH, C-4), 24.6 (CH_3), 23.8 (CH_3); MS: *m*/*z* 285 (M+1).

*1-(4-Hydroxy-6-methylpyrimidin-2-yl)-2-methyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (**4e**)*

% Yield: 65; MW: 384.38; MF: $C_{19}H_{20}N_4O_5$; MP: 290–292; IR (KBr): 3390, 3050, 2959, 1744, 1658, 1612, 1447, 1386, 875 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.1 (*s*, 1H, OH), 8.1–7.4 (*m*, 3H, Ar–H), 6.4 (*s*, 1H, –C=CH–), 3.8 (*s*, 9H, OCH_3), 2.3–2.1 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 172.2 (C, C=O), 163.3 (C, CN_3), 160.1 (C, CN_2), 156.8 (C, C–OH), 155.8 (C, C-5), 154.1 (C, C-3′, C-5′), 140.1 (C, C-4′), 132.1 (C, CN), 130.4 (C, C-1′), 120.2 (CH, C-2′, C-6′), 117.0 (CH, C-8), 103.5 (CH, C-4), 60.3 (OCH_3), 56.2 (OCH_3), 24.5 (CH3), 23.3 (CH_3); MS: *m*/*z* 385 (M+1).

*4-(2,4-Dichlorobenzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4f**)*

% Yield: 66; MW: 363.19; MF: $C_{16}H_{12}N_4O_2$; MP: 236–238; IR (KBr): 3391, 3042, 2897, 1735, 1638, 1575, 1454, 864, 762, 658 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 10.9 (*s*, 1H, OH), 7.8–7.2 (*m*, 4H, Ar–H), 5.8 (*s*, 1H, –C=CH–), 2.7–2.3 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 171.8 (C, C=O), 164.1 (C, CN_3), 162.3 (C, CN_2), 155.1 (C, C–OH), 154.3 (C, C-5), 136.3 (C, C–Cl), 133.5 (C, C-1′), 129.6 (C, C–Cl), 128.6 (CH, C-6′), 127.9 (CH, C-3′), 127.0 (C, CN), 125.9 (CH, C-5′), 116.2 (CH, C-8), 102.4 (CH, C-4), 23.9 (CH_3), 22.5 (CH_3); MS: *m*/*z* 363 (M+1).

*4-(4-(Dimethyl amino) benzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4g**)*

% Yield: 67; MW: 337.37; MF: $C_{18}H_{19}N_5O_2$; MP: 310–312; IR (KBr): 3410, 3052, 2959, 1734, 1650, 1602,

1443, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.8 (*s*, 1H, OH), 8.0–7.2 (*m*, 5H, Ar–H), 6.1 (*s*, 1H, –C=CH–), 3.2 (*s*, 6H, CH_3), 2.1–2.2 (*m*, 6H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.1 (C, C=O), 166.3 (C, CN_3), 160.5 (C, CN_2), 156.5 (C, C–OH), 153.2 (C, C-5), 151.2 (C, C-4′), 134.2 (C, CN), 130.3 (C, C-1′), 126.8 (CH, C-2′ C-6′), 125.6 (CH, C-3′, C-5′), 114.1 (CH, C-8), 102.3 (CH, C-4), 41.2 (CH_3, $N(CH_3)_2$), 24.9 (CH_3), 23.1 (CH_3); MS: *m/z* 338 (M+1).

*4-((1H-Indol-3-yl)methylene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4h**)*

% Yield: 56; MW: 333.34; MF: $C_{18}H_{15}N_5O_2$; MP: 190–192; IR (KBr): 3425, 3353, 3053, 2972, 1750, 1662, 1618, 1444, 1380, 868 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.1 (*s*, 1H, OH), 10.1 (*s*, 1H, OH), 7.8–7.0 (*m*, 5H, Ar–H), 5.6 (*s*, 1H, –C=CH–), 2.4–2.2 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 167.1 (C, C=O), 165.2 (C, CN_3), 162.6 (C, CN_2), 154.5 (C, C–OH), 151.3 (C, C-5), 133.2 (C, CN), 132.1 (C, C-3′), 131.5 (CH, C-2′), 128.3 (C, C-8′), 125.0 (C, C-1′), 124.2 (CH, C-4′), 123.9 (CH, C-7′), 121.2 (CH, C-5′, C-6′), 113.4 (CH, C-8), 102.1 (CH, C-4), 25.1 (CH_3), 23.5 (CH_3); MS: *m/z* 334 (M+1).

*4-Ethylidene-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**4i**)*

% Yield: 45; MW: 232.23; MF: $C_{11}H_{12}N_4O_2$; MP: 194–198; IR (KBr): 3389, 2984, 2877, 1735, 1632, 1585, 1441, 884 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.3 (*s*, 1H, OH), 6.8 (*s*, 1H, Ar–H), 5.8 (*s*, 1H, –C=CH–), 2.5–2.2 (*m*, 9H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 169.1 (C, C=O), 164.3 (C, CN_3), 162.9 (C, CN_2), 153.5 (C, C–OH), 150.2 (C, C-5), 131.5 (C, CN), 112.1 (CH, C-8), 101.3 (CH, C-4), 23.9 (CH_3), 22.5 (CH_3), 10.2 (CH_3); MS: *m/z* 333 (M+1).

*1-(4-Hydroxy-6-methylpyrimidin-2-yl)-4-(4-methoxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**4j**)*

% Yield: 68; MW: 324.33; MF: $C_{17}H_{16}ClN_4O_3$, IR (KBr): 3405, 3052, 2959, 1734, 1650, 1602, 1443, 1381, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.3 (*s*, 1H, OH), 8.1–7.3 (*m*, 5H, Ar–H), 5.9 (*s*, 1H, –C=CH–), 3.5 (*s*, 3H, OCH_3), 2.5–2.2 (*m*, 6H, CH_3); ^{13}C NMR (DMSO, 400 MHz): δ = 171.3 (C, C=O), 163.3 (C, CN_3), 162.2 (C, CN_2), 158.2 (C, C-4′), 152.2 (C, C–OH), 149.9 (C, C-5), 133.1 (C, CN), 126.8 (C, C-1′), 125.3 (CH, C-2′, C-6′), 113.2 (C, C-3′, C-5′), 111.5 (CH, C-8), 101.6 (CH, C-4), 56.3 (OCH_3), 24.2 (CH_3), 23.3 (CH_3); MS: *m/z* 325 (M+1).

*4-Benzylidene-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one (**4k**)*

% Yield: 56; MW: 356.37; MF: $C_{21}H_{16}N_4O_2$; MP: 180–182; IR (KBr): 3381, 3050, 1790, 1651, 1596, 1489, 886 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.3 (*s*, 1H), 7.8–7.2 (*m*, 11H), 5.6 (*s*, 1H), 2.2 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 169.6 (C, C=O), 161.3 (C, CN_3), 160.2 (C, CN_2), 151.3 (C, C–OH), 150.3 (C, C-5), 134.0 (C, C-1′), 133.1 (C, CN), 132.3 (C, C1″), 128.4 (CH, C-3″, C-5″), 128.2 (CH, C-3′, C-5′), 128.0 (CH, C-2′, C-6′), 127.8 (CH, C-2″, C-6″), 127.3 (CH, C-4′), 126.9 (CH, C-4″), 113.2 (CH, C-8), 102.1 (CH, C-4), 23.3 (CH_3); MS: *m/z* 357 (M+1).

*4-(4-Chlorobenzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one (**4l**)*

% Yield: 69; MW: 390.82; MF: $C_{21}H_{15}ClN_4O_2$; MP: 202–204; IR (KBr): 3426, 3063, 2986, 1754, 1582, 1651, 1446, 865 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.2 (*s*, 1H), 7.8–7.3 (*m*, 10H), 5.4 (*s*, 1H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 168.9 (C, C=O), 161.5 (C, CN_3), 160.6 (C, CN_2), 150.9 (C, C–OH), 149.8 (C, C-5), 134.2 (C, C-1′), 133.9 (C, CN), 133.5 (C, C–Cl), 132.1 (C, C-1″), 129.1 (CH, C-3″, C-5″), 128.9 (CH, C-3′, C-5′), 127.5 (CH, C-2′, C-6′), 126.8 (CH, C-2″, C-6″), 126.1 (CH, C-4″), 112.5 (CH, C-8), 101.8 (CH, C-4), 23.5 (CH_3); MS: *m/z* 391 (M+1).

*4-(2,4-Dichlorobenzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one (**4m**)*

% Yield: 68; MW: 425.26; MF: $C_{21}H_{14}Cl_2N_4O_2$; MP: 178–180; IR (KBr):3391, 3063, 2986, 1754, 1582, 1651, 1446, 865 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 11.5 (*s*, 1H), 7.9–7.1 (*m*, 9H), 5.3 (*s*, 1H), 2.4 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 169.3 (C, C=O), 164.1 (C, CN_3), 162.1 (C, CN_2), 155.1 (C, C–OH), 152.3 (C, C-5), 136 (C, C–Cl), 134.8 (C, C-1′), 134.1 (C, CN), 133.1 (C, C–Cl), 132.6 (C, C-1″), 128.6 (CH, C-3″, C-5″), 127.9 (CH, C-3′, C-5′), 127.1 (CH, C-6′), 126.5 (CH, C-2″, C-6″), 125.8 (CH, C-4″), 113.1 (CH, C-8), 102.2 (CH, C-4), 24.1 (CH_3); MS: *m/z* 426 (M+1).

*4-(4-(Dimethyl amino) benzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one (**4n**)*

% Yield: 61; MW: 399.44; MF: $C_{23}H_{21}N_5O_2$; MP: 250; IR (KBr): 3385, 3052, 2920, 1725,1606,1648,1449,891 cm^{-1};

^{1}H NMR (DMSO, 400 MHz): δ 11.3 (*s*, 1H), 8.1–7.5 (*m*, 10H), 5.4 (*s*, 1H), 3.2 (*s*, 6H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 169.1 (C, C=O), 163.9 (C, CN_3), 160.5 (C, CN_2), 154.6 (C, C–OH), 151.4 (C, C-5), 150.1 (C, C–C4′), 134.2 (C, C-1′), 131.3 (C, CN), 130.6 (C, C-1″), 128.1 (CH, C-3″, C-5″), 127.7 (CH, C-3′, C-5′), 126.3 (CH, C-2′, C-6′), 125.5 (CH, C-2″, C-6″), 124.7 (CH, C-4″), 114.2 (CH, C-8), 101.6 (CH, C-4), 41.1 (-N(CH_3)$_2$), 25.1 (CH_3); MS: *m/z* 400 (M+1).

1-(4-Hydroxy-6-methylpyrimidin-2-yl)-4-(2-hydroxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(4o)***

% Yield: 56; MW: 327.37; MF: $C_{21}H_{16}N_4O_3$; MP: 204–206; IR (KBr): 3563, 3055, 2962, 1746, 1650, 1604, 1443, 878 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ11.5 (*s*, 1H), 7.6–6.9 (*m*, 10H), 5.8 (*s*, 1H), 5.3 (*s*, 1H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.3 (C, C=O), 164.3 (C, CN_3), 160.1 (C, CN_2), 157.8 (C, C–OH), 157.1 (C, C-2′), 152.3 (C, C-5), 132.8 (C, C-1′), 130.2 (C, CN), 129.5 (C, C-1″), 128.5 (CH, C-3″, C-5″), 128.0 (CH, C-4′), 127.2 (CH, C-6′), 126.1 (CH, C-2″, C-6″), 123.9 (CH, C-4″), 122.3 (CH, C-5′), 121.9 (CH C-3′), 112.5 (CH, C-8), 101.1 (CH, C-4), 24.1 (CH_3); MS: *m/z* 373 (M+1).

4-(Furan-2-ylmethylene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one ***(4p)***

% Yield: 51; MW: 346.33; MF: $C_{19}H_{14}N_4O_3$; MP: 200–202; IR (KBr): 3399, 3055, 2962, 1746, 1650, 1604, 1443, 878 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 11.1 (*s*, 1H), 8.2–7.3 (*m*, 9H), 5.4 (*s*, 1H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 169.3 (C, C=O), 164.1 (C, CN_3), 160.6 (C, CN_2), 157.2 (C, C–OH), 151.2 (C, C-5), 150.9 (C, C-1′), 143.2 (CH, C-2′), 132.2 (C, CN), 130.2 (C, C-1″), 128.3 (CH, C-3″, C-5″), 127.6 (CH, C-2″, C-6″), 124.9 (CH, C-4″), 112.1 (CH, C-3′), 111.1 (CH, C-8), 108.2 (CH, C-4′), 100.2 (CH, C-4), 23.5 (CH_3); MS: *m/z* 347 (M+1).

4-(4-Hydroxy-3-methoxybenzylidene)-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one ***(4q)***

% Yield: 54; MW: 402.40; MF: $C_{22}H_{18}N_4O_4$; MP: 196–198; IR (KBr): 3563, 3052, 1734, 1650, 1602, 1443, 1381, 884 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 11.5 (*s*, 1H), 7.8–7.4 (*m*, 9H), 5.9 (*s*, 1H), 5.2 (*s*, 1H), 3.4 (*s* 3H), 2.2 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.2 (C, C=O), 162.3 (C, CN_3), 160.1 (C, CN_2), 158.6 (C, C–OH), 152.5 (C, C-5), 147.1 (C, C-3′), 144.2 (C, C–C4′), 134.3 (C, C-1″), 133.2 (C, C-1′), 131.8 (C, CN), 130.3 (CH, C-4″), 128.5 (CH, C-3″, C-5″), 127.2 (CH, C-2″, C-6″), 123.2 (CH, C-6′), 122.1 (C, C-2′), 119.9 (C, C-5′), 113.2 (CH, C-8), 101.3 (CH, C-4), 60.3 (OCH_3), 24.2 (CH_3); MS: *m/z* 403 (M+1).

4-Ethylidene-1-(4-hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one ***(4r)***

% Yield: 53; MW: 294.30; MF: $C_{16}H_{14}N_4O_2$; MP: 140; IR (KBr): 3405, 2984, 2877, 1735, 1632, 1585, 1441, 884 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 11.4 (*s*, 1H), 7.8–7.3 (*m*, 6H), 5.6 (*s*, 1H), 2.4–2.2 (*s*, 6H); ^{13}C NMR (DMSO, 400 MHz): δ = 169.1 (C, C=O), 163.2 (C, CN_3), 162.1 (C, CN_2), 159.2 (C, C–OH), 152.9 (C, C-5), 134.8 (C, C-1″), 130.3 (C, CN), 129.7 (CH, C-4″), 128.1 (CH, C-3″, C-5″), 126.9 (CH, C-2″, C-6″), 111.8 (CH, C-8), 100.1 (CH, C-4), 25.1 (CH_3), 9.7 (CH_3); MS: *m/z* 294 (M+1).

1-(4-Hydroxy-6-methylpyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one ***(4s)***

% Yield: 68; MW: 446.45; MF: $C_{24}H_{22}N_3O_5$; MP: 118–120; IR (KBr): 3394, 3004, 2959, 1715, 1603, 1650, 1443, 888 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 11.5 (*s*, 1H), 7.9–7.2 (*m*, 8H), 5.4 (*s*, 1H), 3.9 (*s*, 9H), 2.2 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.1 (C, C=O), 162.9 (C, CN_3), 160.2 (C, CN_2), 158.6 (C, C–OH), 153.6 (C, C-5), 152.1 (C, C-3′, C-5′), 139.2 (C, C-4′), 134.1 (C, C-1″), 130.8 (C, CN), 130.1 (C, C-1′), 129.6 (CH, C-4″), 127.8 (CH, C-3″, C-5″), 126.8 (CH, C-2″, C-6″), 103.2 (CH, C-2′, C-6′), 112.1 (CH, C-8), 103.1 (CH, C-4), 60.1 (OCH_3), 56.3 (OCH_3), 23.5 (CH_3); MS: *m/z* 447 (M+1).

1-(4-Hydroxy-6-methylpyrimidin-2-yl)-4-(4-methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(4t)***

% Yield: 65; MW: 386.40; MF: $C_{22}H_{18}N_4O_3$; MP: 138–140; IR (KBr): 3417, 3023, 2917, 1730, 1575, 1646, 1447, 863 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 11.3 (*s*, 1H), 7.7–7.1 (*m*, 10H), 5.3 (*s*, 1H), 3.8 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.3 (C, C=O), 163.3 (C, CN_3), 162.3 (C, CN_2), 158.1 (C, C–OH), 157.3 (C, C-4′), 152.8 (C, C-5), 134.8 (C, C-1″), 130.2 (CH, C-2′, C-6′), 129.3 (CH, C-2″, C-6″), 129.0 (CH, C-4″), 128.6 (CH, C-3″, C-5″), 128.1 (C, C-1′), 115.2 (CH, C-3′, C-5′), 113.0 (CH, C-8), 101.3 (CH, C-4), 56.3 (OCH_3), 24.2 (CH_3); MS: *m/z* 387 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-chlorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**5a**)*

% Yield: 61; MW: 347.19; MF: $C_{16}H_{12}Cl_2N_4O$; MP: 210–212; IR (KBr): 3053, 2878, 1730, 1638, 1575, 1454, 876, 658 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.5–7.7 (*m*, 6H), 2.8 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 172.6 (C, C=O), 165.1 (C, CN_3), 162.1 (C, CN_2), 161.3 (C, C–Cl), 159.8 (C, C-5), 134.2 (C, C–Cl), 133.5 (C, C-1′) 131.3 (C, CN), 129.2 (CH, C-2′, C-6′), 128.6 (CH, C-3′, C-5′), 115.2 (CH, C-8), 103.2 (CH, C-4), 24.2 (CH_3), 22.5 (CH_3); MS: *m*/*z* 348 (M+1).

*4-Benzylidene-1-(4-chloro-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one (**5b**)*

% Yield: 64; MW: 312.75; MF: $C_{16}H_{13}ClN_4O$; MP: 204–208; IR (KBr): 3057, 2877, 1730, 1638, 1575, 1454, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.4–7.5 (*m*, 7H), 2.8 (*s*, 3H), 2.2 (*s*, 3H); MS: *m*/*z* 314 (M+1); ^{13}C NMR (DMSO, 400 MHz): δ = 170.2 (C, C=O), 165.6 (C, CN_3), 162.3 (C, CN_2), 161.5 (C, Cl), 160.1 (C, C-5), 132.9 (C, C-1′) 131.0 (C, CN), 127.9 (CH, C-2′, C-6′), 127.0 (CH, C-3′, C-5′), 126.1 (CH, C-4′), 115.1 (CH, C-8), 103.5 (CH, C-4), 23.5 (CH_3), 22.6 (CH_3); MS: *m*/*z* 348 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-methoxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**5c**)*

% Yield: 67; MW: 342.78; MF: $C_{17}H_{15}ClN_4O_2$; MP: 178–180; IR (KBr): 3052, 2959, 1734, 1650, 1602, 1443, 1381, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.1–7.3 (*m*, 6H), 3.5 (*s*, 3H), 2.7 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 172.5 (C, C=O), 164.1 (C, CN_3), 163.1 (C, CN_2), 160.2 (C, Cl), 159.1 (C, C-4′), 150.1 (C, C-5), 134.2 (C, CN), 127.3 (C, C-1′), 125.2 (CH, C-2′, C-6′), 114.5 (C, C-3′, C-5′), 112.6 (CH, C-8), 102.8 (CH, C-4), 57.1 (OCH_3), 24.9 (CH_3), 23.1 (CH_3); MS: *m*/*z* 344 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(2-hydroxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**5d**)*

% Yield: 58; MW: 328.75; MF: $C_{16}H_{13}ClN_4O_2$; MP: 210-212; IR (KBr): 3563, 3052, 2959, 1734, 1650, 1602, 1443, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.4–7.3 (*m*, 6H), 5.8 (*s*, 1H), 2.9 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 173.1 (C, C=O), 163.1 (C, CN_3), 162.1 (C, CN_2),160.8 (C, Cl), 157.9 (C, C-5), 152.3 (C, C–OH), 129.9 (C, CN), 129.0 (C, C-1′), 128.8 (CH, C-4′), 128.0 (CH, C-2′), 127.1 (CH, C-3′), 120.5 (CH, C-5′), 116.1 (CH, C-8), 104.0 (CH, C-4), 24.3 (CH_3), 22.9 (CH_3); MS: *m*/*z* 330 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(furan-2-ylmethylene)-2-methyl-1H-imidazol-5(4H)-one (**5e**)*

% Yield: 59; MW: 328.75; MF: $C_{14}H_{11}ClN_4O_2$; MP: 280; IR (KBr): 3057, 2877, 1730, 1638, 1575, 1454, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 7.8–6.3 (*m*, 5H), 2.8 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.8 (C, C=O), 163.1 (C, CN_3), 161.2 (C, CN_2), 160.2 (C, C–Cl), 154.2 (C, C-5), 151.2 (C, C-1′), 141.5 (CH, C-2′), 131.6 (C, CN), 116.1 (CH, C-8), 114.5 (CH, C-3′), 112.1 (CH, C-4′), 103.6 (CH, C-4), 23.9 (CH_3), 23.1 (CH_3); MS: *m*/*z* 303 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-2-methyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (**5f**)*

% Yield: 68; MW: 402.83; MF: $C_{19}H_{19}ClN_4O_4$; MP: 165; IR (KBr): 3050, 2959, 1744, 1658, 1612, 1447, 1386, 875 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 7.8 (*m*, 1H), 6.9–6.3 (*m*, 3H), 3.8 (*s*, 9H), 2.9 (*s*, 3H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.9 (C, C=O), 162.9 (C, CN_3), 161.0 (C, CN_2), 160.5 (C, Cl), 154.9 (C, C-5), 153.5 (C, C-3′, C-5′), 139.5 (C, C-4′), 131.8 (C, CN), 130.2 (C, C-1′), 119.5 (CH, C-2′, C-6′), 117.5 (CH, C-8), 102.1 (CH, C-4), 60.6 (OCH_3), 55.8 (OCH_3), 23.9 (CH3), 22.5 (CH_3); MS: *m*/*z* 403 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(2,4-dichlorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**5g**)*

% Yield: 62; MW: 381.64; MF: $C_{16}H_{11}Cl_3N_4O$; MP: 220–223; IR (KBr): 3042, 2897, 1735, 1638, 1575, 1454, 864, 762, 658 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 7.6 (*m*, 1H), 7.0–6.5 (*m*, 4H), 2.6 (*s*, 3H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 172.1 (C, C=O), 164.5 (C, CN_3), 161.0 (C, CN_2), 160.1 (C, Cl), 153.2 (C, C-5), 137.1 (C, C–Cl), 134.1 (C, C-1′), 128.9 (C, C–Cl), 128.0 (CH, C-6′), 127.2 (CH, C-3′), 126.1 (C, CN), 125.5 (CH, C-5′), 115.9 (CH, C-8), 103.1 (CH, C-4), 23.2 (CH_3), 22.1 (CH_3); MS: *m*/*z* 382 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-(dimethylamino)benzylidene)-2-methyl-1H-imidazol-5(4H)-one (**5h**)*

% Yield: 71; MW: 355.82; MF: $C_{18}H_{18}ClN_5O$; MP: 148–150; IR (KBr): 3052, 2959, 1734, 1650, 1602, 1443, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.2–7.3 (*m*, 6H), 3.1 (*s*, 6H), 2.7 (*s*, 3H), 2.2 (*s*, 3H); ^{13}C NMR (DMSO,

400 MHz): δ = 171.9 (C, C=O), 165.1 (C, CN_3), 162.1 (C, CN_2), 161.5 (C, Cl), 154.1 (C, C-5), 152.1 (C, C-4′), 135.6 (C, CN), 131.2 (C, C-1′), 127.1 (CH, C-2′ C-6′), 126.6 (CH, C-3′, C-5′), 115.5 (CH, C-8), 102.8 (CH, C-4), 40.9 (CH_3, $N(CH_3)_2$), 23.6 (CH_3), 22.4 (CH_3); MS: *m/z* 356 (M+1).

4-((1H-indol-3-yl)methylene)-1-(4-chloro-6-methylpyrimidin-2-yl)-2-methyl-1H-imidazol-5(4H)-one ***(5i)***

% Yield: 60; MW: 351.79; MF: $C_{18}H_{14}ClN_5O$; MP: 186–190; IR (KBr): 3353, 3053, 2972, 1750, 1662, 1618, 1444, 1380, 868 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 10.2 (*s*, 1H), 8.3–7.4 (*m*, 7H), 2.6 (*s*, 3H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.2 (C, C=O), 165.0 (C, CN_3), 162.2 (C, CN_2), 160.1 (C, Cl), 152.3 (C, C-5), 134.1 (C, CN), 131.9 (C, C-3′), 130.6 (CH, C-2′), 128.8 (C, C-8′), 126.1 (C, C-1′), 125.1 (CH, C-4′), 123.1 (CH, C-7′), 122.1 (CH, C-5′, C-6′), 115.1 (CH, C-8), 101.8 (CH, C-4), 24.7 (CH_3), 23.6 (CH_3); MS: *m/z* 352 (M+1).

1-(4-Chloro-6-methylpyrimidin-2-yl)-4-ethylidene-2-methyl-1H-imidazol-5(4H)-one ***(5j)***

% Yield: 55; MW: 250.68; MF: $C_{11}H_{11}ClN_4O$; MP: 255–257; IR (KBr): 2984, 2877, 1735, 1632, 1585, 1441, 884 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 6.96–6.15 (*m*, 2H), 2.52 (*d*, 3H), 2.5 (*s*, 3H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.5 (C, C=O), 164.1 (C, CN_3), 162.0 (C, CN_2), 161.1 (C, Cl), 151.1 (C, C-5), 130.1 (C, CN), 111.5 (CH, C-8), 100.9 (CH, C-4), 23.4 (CH_3), 22.1 (CH_3), 9.6 (CH_3); MS: *m/z* 251 (M+1).

4-Benzylidene-1-(4-chloro-6-methylpyrimidin-2-yl)-2-phenyl-1H-imidazol-5(4H)-one ***(5k)***

% Yield: 70; MW: 374.82; MF: $C_{21}H_{15}ClN_4O$; MP: 202–204; IR (KBr): 3050, 1790, 1651, 1596, 1489, 886 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 7.25–7.65 (*m*, 11H), 6.8 (*s*, 1H), 2.5 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 172.1 (C, C=O), 162.1 (C, CN_3), 161.9 (C, CN_2), 159.9 (C, Cl), 149.8 (C, C-5), 134.5 (C, C-1′), 132.6 (C, CN), 131.8 (C, C1″), 128.1 (CH, C-3″, C-5″), 127.5 (CH, C-3′, C-5′), 126.8 (CH, C-2′, C-6′), 126.1 (CH, C-2″, C-6″), 125.5 (CH, C-4′), 124.3 (CH, C-4″), 114.5 (CH, C-8), 103.4 (CH, C-4), 23.4 (CH_3); MS: *m/z* 375 (M+1).

1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-chlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(5l)***

% Yield: 72; MW: 409.26; MF: $C_{21}H_{14}Cl_2N_4O$; MP: 222–224; IR (KBr): 3063, 2986, 1754, 1582, 1651, 1446, 865 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 7.10–7.45 (*m*, 10H), 6.7 (*s*, 1H), 2.2 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.0 (C, C=O), 163.5 (C, CN_3), 162.6 (C, CN_2), 160.9 (C, Cl), 148.4 (C, C-5), 132.1 (C, C-1′), 131.2 (C, CN), 130.4 (C, C–Cl), 129.6 (C, C-1″), 128.4 (CH, C-3″, C-5″), 128.0 (CH, C-3′, C-5′), 127.1 (CH, C-2′, C-6′), 126.2 (CH, C-2″, C-6″), 125.1 (CH, C-4″), 113.1 (CH, C-8), 102.5 (CH, C-4), 22.5 (CH_3); MS: *m/z* 410 (M+1).

1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(2,4-dichlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(5m)***

% Yield: 76; MW: 443.71; MF: $C_{21}H_{13}Cl_3N_4O$; MP: 218–220; IR (KBr): 3063, 2986, 1754, 1582, 1651, 1446, 865 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.5–7.6 (*m*, 9H), 6.7 (*s*, 1H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 170.8 (C, C=O), 163.8 (C, CN_3), 162.4 (C, CN_2), 161.1 (C, Cl), 154.1 (C, C-5), 135.8 (C, C–Cl), 134.4 (C, C-1′), 133.2 (C, CN), 132.8 (C, C–Cl), 132.0 (C, C-1″), 128.1 (CH, C-3″, C-5″), 127.1 (CH, C-3′, C-5′), 126.3 (CH, C-6′), 125.8 (CH, C-2″, C-6″), 124.6 (CH, C-4″), 114.6 (CH, C-8), 102.8 (CH, C-4), 24.5 (CH_3); MS: *m/z* 444 (M+1).

1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-(dimethylamino)benzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(5n)***

% Yield: 67; MW: 417.89; MF: $C_{23}H_{20}ClN_5O_2$; MP: 265–267; IR (KBr): 3052, 2920, 1725,1606,1648,1449, 891 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.5–7.65 (*m*, 8H), 6.8–6.65 (*m*, 3H), 3. 1 (*s*, 6H), 2.4 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 172.1 (C, C=O), 163.2 (C, CN_3), 162.1 (C, CN_2), 161.2 (C, Cl), 152.1 (C, C-5), 151.2 (C, C–C4′), 133.1 (C, C-1′), 131.6 (C, CN), 130.9 (C, C-1″), 128.6 (CH, C-3″, C-5″), 128.0 (CH, C-3′, C-5″), 127.1 (CH, C-2′, C-6′), 126.1 (CH, C-2″, C-6″), 124.9 (CH, C-4″), 114.1 (CH, C-8), 101.2 (CH, C-4), 42.0 (-$N(CH_3)_2$), 24.2 (CH_3); MS: *m/z* 418 (M+1).

1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(2-hydroxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one ***(5o)***

% Yield: 69; MW: 390.82; MF: $C_{21}H_{15}ClN_4O_2$; MP: 240; IR (KBr): 3563, 3055, 2962, 1746, 1650, 1604, 1443, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.1–7.5 (*m*, 8H), 6.8–6.65 (*m*, 3H), 5. 8 (*s*, 1H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.2 (C, C=O), 164.5 (C, CN_3), 162.3 (C, CN_2), 160.8 (C, Cl), 157.5 (C, C-2′), 151.9 (C, C-5), 133.1 (C, C-1′), 131.5 (C, CN), 130.5 (C, C-1″), 128.9 (CH, C-3″, C-5″), 127.5 (CH, C-4′), 126.2 (CH,

C-6′), 125.6 (CH, C-2″, C-6″), 124.2 (CH, C-4″), 121.5 (CH, C-5′), 120.6 (CH C-3′), 113.3 (CH, C-8), 102.4 (CH, C-4), 23.5 (CH_3); M.S: *m/z* 391 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(furan-2-ylmethylene)-2-phenyl-1H-imidazol-5(4H)-one (**5p**)*

% Yield: 62; MW: 364.78; MF: $C_{19}H_{13}ClN_4O_2$; MP: 240–242; IR (KBr): 3055, 2962, 1746, 1650, 1604, 1443, 878 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.2–7.5 (*m*, 7H), 7.1–6.7 (*m*, 3H), 2.1 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.2 (C, C=O), 164.5 (C, CN_3), 161.6 (C, CN_2), 160.1 (C, Cl), 152.6 (C, C-5), 151.0 (C, C-1′), 145.1 (CH, C-2′), 133.8 (C, CN), 131.6 (C, C-1″), 129.1 (CH, C-3″, C-5″), 128.1 (CH, C-2″, C-6″), 125.0 (CH, C-4″), 114.5 (CH, C-3′), 110.6 (CH, C-8), 109.1 (CH, C-4′), 99.5 (CH, C-4), 22.9 (CH_3);M.S: *m/z* 365 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(3-hydroxy-4-methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (**5q**)*

% Yield: 70; MW: 402.40; MF: $C_{22}H_{17}ClN_4O_3$; MP: 260–262; IR (KBr): 3563, 3052, 1734, 1650, 1602, 1443, 1381, 884 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.6–7.5 (*m*, 10H), 5. 6 (*s*, 1H), 3.6 (*s*, 3H) 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.2 (C, C=O), 162.8 (C, CN_3), 162.1 (C, CN_2), 161.1 (C, C–OH), 153.1 (C, C-5), 148.0 (C, C-3′), 146.1 (C, C–C4′), 133.1 (C, C-1″), 132.7 (C, C-1′), 131.9 (C, CN), 131.2 (CH, C-4″), 129.1 (CH, C-3″, C-5″), 128.1 (CH, C-2″, C-6″), 122.4 (CH, C-6′), 120.1 (C, C-2′), 119.2 (C, C-5′), 113.8 (CH, C-8), 101.4 (CH, C-4), 60.5 (OCH_3), 23.1 (CH_3); MS: *m/z* 421 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-ethylidene-2-phenyl-1H-imidazol-5(4H)-one (**5r**)*

% Yield: 60; MW: 312.75; MF: $C_{16}H_{13}ClN_4O$; MP: 248–250; IR (KBr): 2984, 2877, 1735, 1632, 1585, 1441, 884 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.2–7.5 (*m*, 5H), 6.86.65 (*m*, 2H), 2.6 (*s*, 3H), 2.3 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.8 (C, C=O), 162.1 (C, CN_3), 161.0 (C, CN_2), 159.1 (C, Cl), 156.1 (C, C-5), 133.5 (C, C-1″), 129.3 (C, CN), 128.7 (CH, C-4″), 127.0 (CH, C-3″, C-5″), 125.9 (CH, C-2″, C-6″), 112.6 (CH, C-8), 100.5 (CH, C-4), 24.6 (CH_3), 10.1 (CH_3); MS: *m/z* 313 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (**5s**)*

% Yield: 71; MW: 464.90; MF: $C_{24}H_{22}ClN_4O_4$; MP: 284-286; IR (KBr): 3004, 2959, 1715, 1603, 1650, 1443, 888 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.4–7.65 (*m*, 6H), 6.7–6.5 (*m*, 3H), 3. 6 (*s*, 9H) 2.4 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 171.2 (C, C=O), 163.5 (C, CN_3), 161.5 (C, CN_2), 159.8 (C, Cl), 152.8 (C, C-5), 152.0 (C, C-3′, C-5′), 140.1 (C, C-4′), 135.1 (C, C-1″), 132.4 (C, CN), 131.1 (C, C-1′), 130.1 (CH, C-4″), 127.5 (CH, C-3″, C-5″), 126.4 (CH, C-2″, C-6″), 103.1 (CH, C-2′, C-6′), 112.8 (CH, C-8), 102.4 (CH, C-4), 61.5 (OCH_3), 55.8 (OCH_3), 23.6 (CH_3); MS: *m/z* 465 (M+1).

*1-(4-Chloro-6-methylpyrimidin-2-yl)-4-(4-methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (**5t**)*

% Yield: 70; MW: 404.84; MF: $C_{22}H_{17}ClN_4O_2$; MP: 158–160; IR (KBr): 3023, 2917, 1730, 1575, 1646, 1447, 863 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 8.3–7.3 (*m*, 8H), 6.9–6.5 (*m*, 3H), 3. 7 (*s*, 3H) 2.2 (*s*, 3H); ^{13}C NMR (DMSO, 400 MHz): δ = 173.1 (C, C=O), 164.1 (C, CN_3), 162.5 (C, CN_2), 160.5 (C, Cl), 157.9 (C, C-4″), 151.4 (C, C-5), 135.3 (C, C-1″), 131.3 (CH, C-2′, C-6′), 130.2 (CH, C-2″, C-6″), 129.8 (CH, C-4″), 129.1 (CH, C-3″, C-5″), 128.0 (C, C-1′), 114.9 (CH, C-3′, C-5′), 113.3 (CH, C-8), 101.4 (CH, C-4), 57.3 (OCH_3), 24.5 (CH_3); MS: *m/z* 405 (M+1).

In vitro anti-HIV activity

The 20 μg/ml of finely powdered test compounds (**4a**–**t**) in DMSO was used for in-vitro assay. The HIV-1 RT inhibition assay was performed by using RT assay kit (Roche) and carried out as described in kit protocol. Briefly, the reaction mixture was set with template primer complex, dNTPs and RT enzyme in the lysis buffer with or without inhibitors. After 1 h incubation at 37 °C, the reaction mixture was transferred to streptavidine-coated microtitre plate (MTP). The biotin-labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and anti-DIG-POD was added to the MTP. The DIG-labeled dNTPs incorporated in the template were bound to anti-DIG-POD antibody. The unbound anti-DIG-POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyzed by a peroxide enzyme. The absorbance of the sample was determined at optical density (OD), 405 nm using micro titer plate ELISA reader. The % inhibition was calculated using following formula.

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

Docking methodology

Molecular docking studies were performed using Glide v5.6 (Schrödinger, LLC). The coordinate for RT enzyme was taken from RCSB Protein Data Bank (PDB Id. 1FKP) and prepared for docking using protein preparation wizard. Water molecules in the enzyme structure were removed and termini were capped by adding ACE and NMA residue. The bond orders and formal charges were added for heterogroups and the hydrogens were added to all atoms. The side chains that were not close to the binding cavity and not participate in salt bridges, were neutralized. After preparation, the structure was refined to optimize the hydrogen bond network using OPLS_2005 force field. This helps in reorientation of side chain hydroxyl group. The minimization was terminated when the energy converged or the RMSD reached a maximum cutoff of 0.30 Å. Grid was then defined around active site of enzyme by centering on ligand using default box size. The extra precision (XP) docking mode of Glide was used for docking of compounds, optimized by Ligprep, on generated grid of protein structure (Friesner *et al*., 2006).

Result and discussion

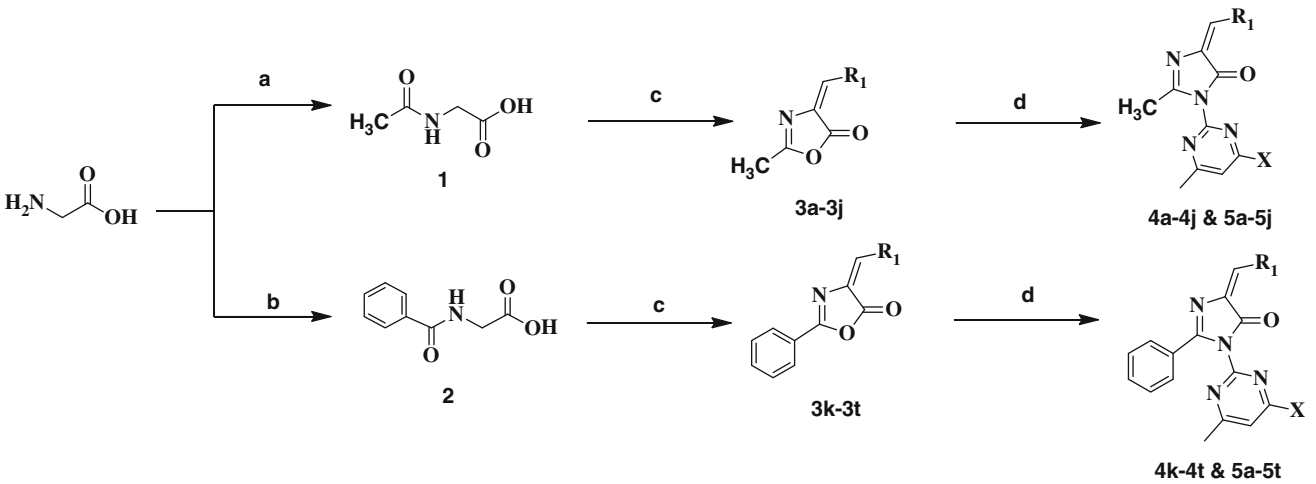
Chemistry

The synthesis of target compounds **4a**–**t** and **5a**–**t** is outlined in Scheme 1. Acetyl glycine was used to synthesize intermediates **3a**–**j.** Glycine on reaction with acetic anhydride gave acetyl glycine (**1**) which further subjected to cyclocondensation with aliphatic or aromatic aldehydes in the presence of acetic anhydride and anhydrous potassium acetate to give 4-(substituted ethylidene/benzylidene)-2-methyloxazol-5-ones (**3a**–**j**). Benzoyl glycine was used to synthesize the intermediates **3k**–**t**. Benzoyl glycine (**2**) was first synthesized from glycine by reacting with benzoyl chloride in alkaline condition and further subjected to cyclocondensation with aliphatic or aromatic aldehydes in the presence of acetic anhydride and anhydrous potassium acetate to get 4-(substituted ethylidene/benzylidene)-2-phenyloxazole-5-ones (Furnis *et al*., 2005) (**3k**–**t**).

The target compounds 4-substituted ethylidene/benzylidene-1-(4-hydroxy/chloro-6-methylpyrimidin-2-yl)-2-methyl/phenyl-1H-imidazol-5(4H)-ones (**4a**–**t** and **5a**–**t**) were obtained by reacting 4-substituted ethylidene/benzylidene-2-methyl/phenyl oxazol-5-ones (**3a**–**t**) with 2-amino-6-methylpyrimidin-4-ol or 4-chloro-6-methylpyrimidin-2-amine.

Biological screening

A group of imidazole-5-one derivatives along with methylpyrimidine ring was prepared to investigate the effect of substitution at R and R_1 position of imidazole ring on HIV-1 RT activity. All title compounds (**4a**–**5t**) were tested for antiviral activity against HIV-1 RT using in-vitro RT assay. It was observed that most of the newly synthesized compounds such as **4c**, **4d**, **4e**, **4h**, **5a**, **5e**, **5f** and **5j** possess notable HIV-1 RT inhibitory activity (Table 1). Among them, the compounds **4c**, **4d, 4e**, **5a** and **5e** in which 2-hydroxyphenyl, furan-2-yl, 3,4,5-trimethoxyphenyl, 4-chlorophenyl, and furan-2-yl groups substituted at R_1 position, respectively, showed significantly more HIV-1 RT inhibitory activity. The compounds bearing bulky substituents along with electron withdrawing groups at R_1 position of imidazole-5-one ring showed higher HIV-1 RT inhibitory activity (compounds **4c**,



Scheme 1 The scheme for synthesis of final compounds (**4a**–**5t**) reagents and condition: *a* water, *b* 10 % NaOH, *c* substituted aldehyde (R_1CHO), potassium acetate, acetic anhydride, *d* AcOH, 2-amino-6-methylpyrimidin-4-ol or 4-chloro-6-methylpyrimidin-2-amine

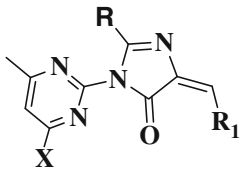
4d, **4e**, **5a** and **5e**). However as bulkiness at R_1 position of imidazole-5-one ring decreased, the HIV-1 RT inhibitory activity was also decreased (compounds **4i**, **4r** and **5r**). Thus, it can be said that RT inhibitory activity of compounds is sensitive to the size and nature of substituent at their R_1 position. The compounds **4a–4j** and **5a–5j** in which methyl group is substituted at R position of imidazole-5-one ring showed higher HIV-1 RT inhibitory activity than the compounds **4k–4t** and **5k–5t** possessing phenyl group at R position. Thus, it is suggested that compounds with less hydrophobic group at R position on the imidazole-5-one ring would be better for the HIV-1 RT inhibitory activity.

Docking studies

To rationalize most relevant SAR and to predict the binding affinity of synthesized compounds, the docking studies were carried out on X-ray coordinates of HIV-1 RT enzyme (PDB Id 1FKP). The accuracy of a docking procedure was first evaluated by comparing binding conformation of co-crystalized inhibitor predicted by extra precision (XP) Glide docking mode and experimental binding mode as determined by X-ray crystallography. The root mean square deviations of 1.28 and 0.26 Å were found for flexible and rigid docking, respectively, which suggests the reliability of docking procedure.

Docking score (G-score) of all compounds against HIV-1 RT enzyme is shown in Table 1. The most of compounds showed good correlation of virtual docking score with their experimental activity. All docked compounds adopted a similar conformation and position in the active binding site of HIV-1 RT structure. For most of compounds, the ligand–enzyme complex was primarily stabilized by hydrophobic interactions and specific polar hydrogen bonds. The side chain, 4-hydroxy/chloro-6-methylpyrimidine ring (One of the wing of butterfly shape) of imidazole-5-ones analogs pointed toward hydrophobic pocket was formed by Leu 100, Val 106, Leu 234, and Tyr 318 amino acid residues.

Table 1 In vitro HIV-RT inhibition data of compounds **4a–t** and **5a–t**



4a–t X = OH; **5a–5t** X = Cl; **4a–j** and **5a–j** R = CH3; **4k–t** and **5k–t** R = C6H5

Comp.	R_1	% Inhibition[a]	G-score	Comp.	R_1	% Inhibition[a]	G-score
4a	–4-ClC_6H_4	60.77	−7.50	**5a**	–4-ClC_6H_4	72.84	−8.15
4b	–C_6H_5	65.86	−6.94	**5b**	–C_6H_5	61.71	−6.45
4c	–2-OHC_6H_4	71.15	−9.15	**5c**	–4-$OCH_3C_6H_4$	56.05	−8.01
4d	–2-furon	83.03	−9.88	**5d**	–2-OHC_6H_4	65.67	−6.94
4e	–3,4, 5-tri-$OCH_3C_6H_2$	71.33	−9.10	**5e**	–2-Furon	86.24	−9.56
4f	–2,4-di-ClC_6H_3	56.24	−7.12	**5f**	–3,4,5-tri-$OCH_3C_6H_2$	67.56	−7.65
4g	–4-$N(CH_3)_2$–C_6H_4	65.86	−8.32	**5g**	–2,4-di-ClC_6H_3	60.77	−6.68
4h	–3-Indole	67.94	−8.50	**5h**	4-$N(CH_3)_2$–C_6H_4	66.81	−7.21
4i	–CH_3	53.60	−6.42	**5i**	–3-Indole	58.88	−5.95
4j	–4-$OCH_3C_6H_4$	51.60	−6.75	**5j**	–CH_3	67.56	−6.51
4k	–C_6H_5	47.75	−5.80	**5k**	–C_6H_5	52.28	5.24
4l	–4-ClC_6H_4	60.58	−6.80	**5l**	–4-ClC_6H_4	52.09	−6.02
4m	–2,4-di-ClC_6H_3	48.69	−6.01	**5m**	–2,4-di-ClC_6H_3	54.16	−5.29
4n	–4-$N(CH_3)_2$–C_6H_4	49.45	−6.15	**5n**	–4-$N(CH_3)_2$–C_6H_4	52.47	−5.65
4o	–2-OHC_6H_4	51.26	−5.80	**5o**	–2-OHC_6H_4	46.43	−6.13
4p	–2-Furon	49.12	−7.49	**5p**	–2-Furon	53.03	−6.78
4q	–3-OCH_3, 4-OH–C_6H_3	54.54	−6.81	**5q**	–3-OCH_3, 4-OH–C_6H_3	42.47	−5.18
4r	–CH_3	50.58	−7.15	**5r**	–CH_3	43.22	−6.95
4s	–3,4,5-tri-$OCH_3C_6H_2$	57	−6.20	**5s**	–3,4,5-tri-$OCH_3C_6H_2$	30.96	−5.80
4t	–4-$OCH_3C_6H_4$	56.24	−5.40	**5t**	–4-$OCH_3C_6H_4$	33.41	−5.65
Nevirapine	–	99.97	−11.50				

[a] Data are indicated as percentage of inhibition at 20 μg/ml

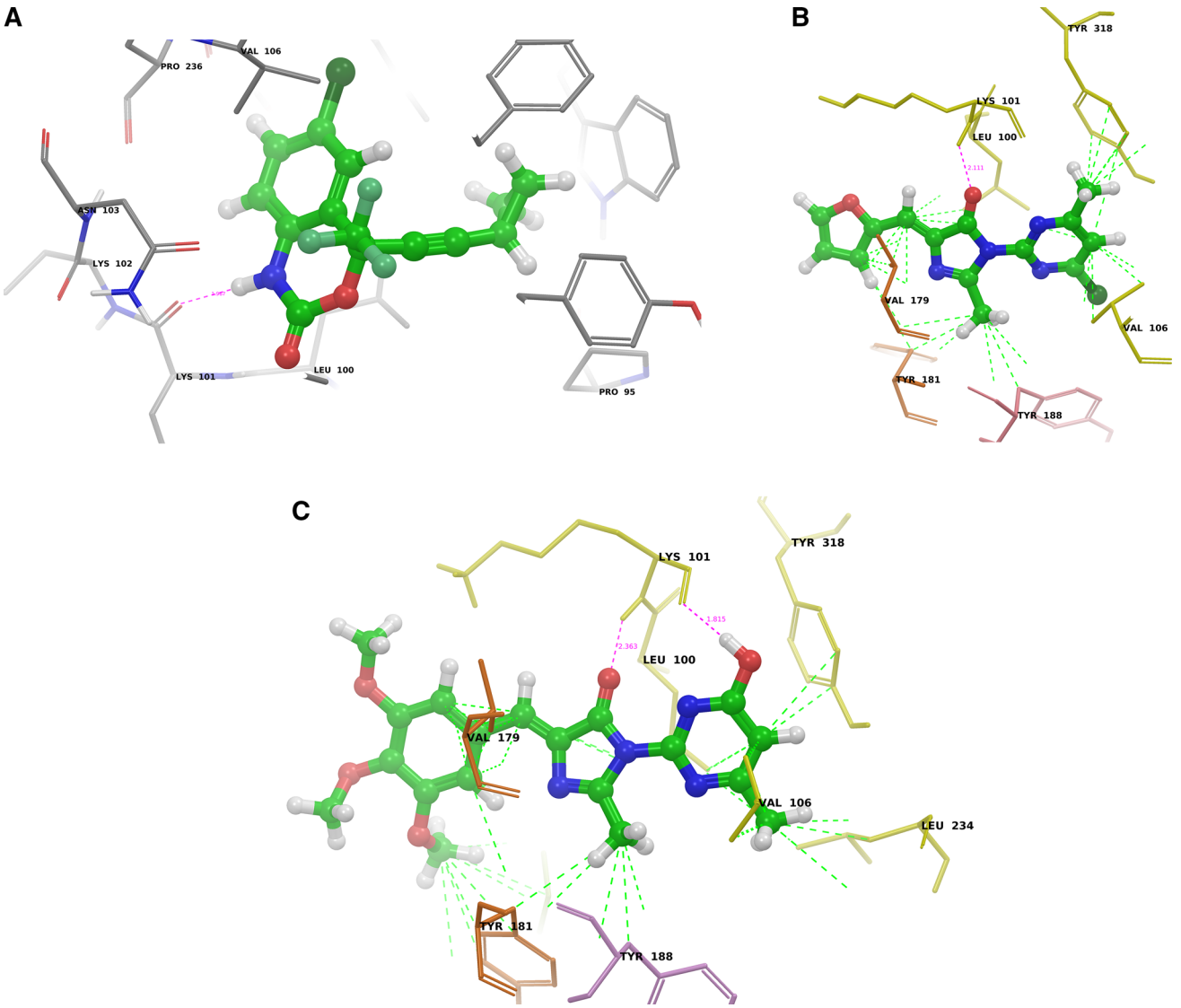


Fig. 2 Docking poses of compounds at active binding site of RT enzyme. **a** Efavirenz, **b** compound **5e** and **c** compound **4e**. Hydrogen bond with amino acid residues is shown in *pink dotted lines*. Hydrophobic interaction with amino acid residues is shown in *green dotted lines*

Whereas another side chain at position R_1 (furan-2-yl and 3,4,5-trimethoxyphenyl for **5e** and **4e**, respectively) showed hydrophobic interaction with Tyr 181, Pro95, and Val 179 amino acid residues (Fig. 2). The methyl group is substituted at R position on the imidazole-5-one ring also showed some hydrophobic interactions with Tyr 181 and Tyr 188. Thus, this may be reason that the replacement of this methyl group by bulky phenyl ring in compounds **4k–t** and **5k–t** showed the less activity as compared to compounds **4a–j** and **5a–j.** This may be due to phenyl ring that occupies the larger space and reduces the possibility of hydrophobic interaction with Tyr 181 and Tyr 188. The compound **5e** and **4e** showed strong hydrogen bond with Lys 101, similar to reference compounds Efavirenz (Fig. 2a). It was observed that –C=O group of imidazole ring in all docked compound formed the hydrogen bond with –NH Lys 101. Moreover, this hydrogen bond between –C=O group of imidazole and –NH of Lys 101 was found in hydrophobic space of enzyme which increases the affinity of the compounds toward the enzyme. This indicates the importance of –C=O group of central imidazole ring for anti-HIV-1 RT activity (Fig. 3). Although there is very little difference in HIV-1 RT inhibitory activity of compounds bearing hydroxyl or chloro groups at X position on pyrimidine ring, but docking study revealed that both groups play a different important role for stabilization of imidiazole-5-ones-RT complex. The –OH group of pyrimidine ring formed hydrogen bond with –C=O groups of Lys 101, whereas substitution of –Cl group at -X position of pyrimidine ring supports the stabilization of complex by forming hydrophobic interaction with surrounding amino acid residues.

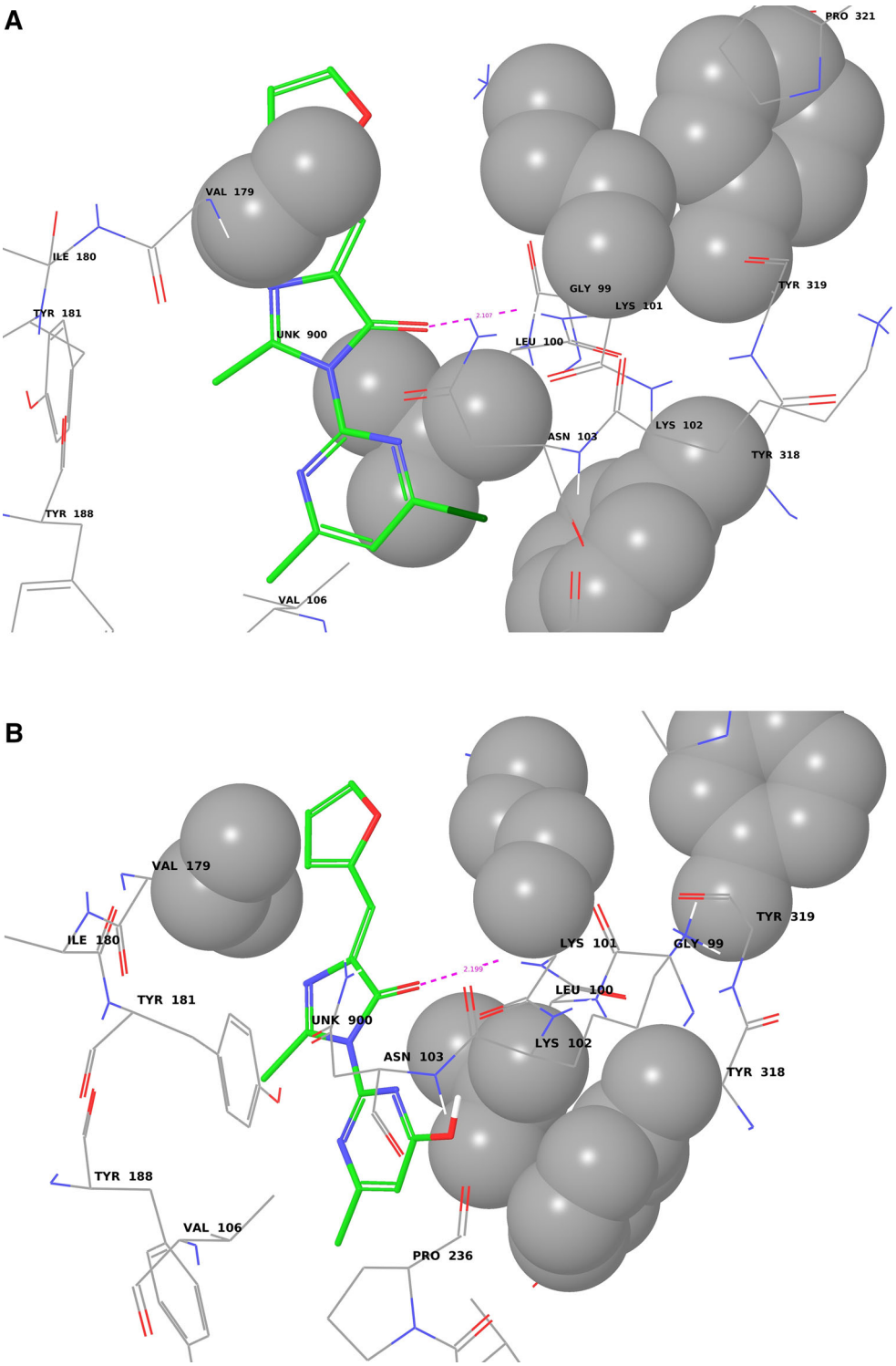


Fig. 3 Docking pose of **a** compounds **5e** and **b** compound **4e** at active binding site of RT enzyme showing the hydrogen bond in hydrophobic space. Hydrogen bond with amino acid is shown in *pink dotted lines*. The *gray color balls* indicate the hydrophobic amino acid resides

Conclusion

We have designed and synthesized the new series of 4-substituted ethylidene/benzylidene-1-(4-hydroxy/chloro-6-methylpyrimidin-2-yl)-2-methyl/phenyl-1H-imidazol-5(4H)-ones as HIV-1 RT inhibitors. It has been observed from in-vitro screening that the most of compounds exhibit RT inhibitory activity. Among the compounds, **4c**, **4d**, **4e**, **5a** and **5e** showed more significant RT inhibitory activity. The substitution pattern around imidazole ring showed the requirement of small hydrophobic groups at R position and bulky groups at R_1 position on imidazole-5-one ring. The

molecular docking studies showed the potential binding mode of synthesized imidazole-5-one analogs in the allosteric binding site of HIV-1 RT. The imidazole-5-one ring formed important hydrogen bond with Lys 101, and thus crucial for HIV-1 RT inhibition. The 4-hydroxy/chloro-6-methylpyrimidin-2-yl and bulky substitution at R_1 position of imidazole-5-one ring stabilize the ligand–enzyme by forming the hydrophobic interactions with HIV-1 RT enzyme. The overall SAR exploration helped us for the new rational design, and thus further structure modifications on the R and R_1 position of imidazole-5-one ring and pyrimidine ring are underway.

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