Design, Synthesis and Docking Studies of Novel 1, 2, 3-Triazolyl Phenylthiazole Analogs as Potent Anti-HIV-1 NNRT Inhibitors

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Abstract

In an attempt to design and synthesize a new class of anti-HIV-1 RTIs i.e., 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine derivatives, substituted 2-amino-4-phenylthiazoles were alkylated with propargyl bromide to obtain dialkyne 2-amino-4-phenylthiazoles. This dialkyne 2-amino-4-phenylthiazole was reacted with ary1 azides to generate small library of 15 compounds (4a-o) by click chemistry. The obtained derivatives were studied as anti-HIV-1 NNRT Inhibitors. All synthesized compounds of 1,2,3-triazolopyrrophenylthiazole series were be docked into the non-nucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT and highly inhibiting derivatives studied for in vitro anti-HIV-1 assay.

Keywords: 4-(Phenyl)-N, N-bis((1-phenyl-1H-1,2,3-triazol-4-yl) methyl)thiazol-2-amine; Dialkyne 2-amino-4-phenylthiazole; Anti-HIV-1 NNRTI

Introduction

Reverse transcriptase inhibitors (RTIs) are a class of antiretroviral drugs used to treat HIV infection or AIDS, and in some cases hepatitis B. RTIs inhibit activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses. When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus. RTIs block reverse transcriptase’s enzymatic function and prevent completion of synthesis of the double stranded viral DNA, thus preventing HIV from multiplying.

A similar process occurs with other types of viruses. The hepatitis B virus, for example, carries its genetic material in the form of DNA, and employs a RNA dependent DNA polymerase to replicate. Some of the same compounds used as RTIs can also block HBV replication; When used in this way they are referred to as polymerase inhibitors. HIV only contains RNA and so needs to change its RNA into DNA to be able to integrate with our DNA for replication. To do this it has to first change its RNA to DNA. HIV uses a compound called reverse transcriptase to convert its RNA to DNA. Reverse transcriptase enzyme is not found in human cell without HIV, so that RT is the main target for the Anti-HIV drug synthesis.

RTIs come in three forms: Nucleoside analog reverse transcriptase inhibitors (NARTIs or NRTIs) Nucleotide analog reverse transcriptase inhibitors (NiARTIs or NiRTIs) and Nonnucleoside Reverse transcriptase inhibitors (NNRTIs). The mode of action of NRTIs and NiRTIs is essentially the same; They are analogues of the naturally occurring deoxynucleotides needed to synthesize the viral DNA and they compete with the natural deoxynucleotides for incorporation into the growing viral DNA chain. NRTI working different ways but one of the main ways is to compete with reverse transcriptase for their interaction site with HIV genetic material while NNRTIs work by sitting in a binding site in the virus structure.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are the third class of antiretroviral drugs that were developed. In all cases, patents remain in force until beyond 2007.

The 2-amino-1,3-thiazoles are biologically important compounds with a wide range of medicinal and biological applications including antibacterial, antifungal, anti-HIV, anti-hypertension, anti-inflammatory, anticancer, anticonvulsant, and antidepressant [1-6]. Some 2-amino-1,3-thiazole derivatives have been reported as ligands of thrombopoietin [7,8], neuropetide Y5 [9] and adenosine receptors [10,11] and as inhibitors of several physiological important enzymes like cyclindependent kinase [12], poly (ADP-Ribose) polymerase [13], urokinase [14] etc. Thiazole is also considered as a heterocyclic bioisostere of the phenol moiety in the extensively used anti-parkinsonian agent pramipexol [15] and in morphinan derivatives [16,17]. Due to their broad utility in the pharmaceutical industry, the development of methods that give quick access to diverse 2-amino-1,3-thiazole libraries would provide additional lead molecules for drug discovery.

However, 1,2,3-triazole ring is not found in any marketed drugs. The click chemistry improved by Sharpless et al. is an admirable approach for regioselective synthesis of 1, 2, 3-triazole ring system in presence of various functional groups. Genuine efforts have been made to integrate 1, 2, 3-triazole in existing drugs, still more research is needed to find lead molecule [18]. 1,2,3-triazole structural moiety is present in several compounds showing various biological activities including anti-HIV [19], anti-bacterial [20], anti-allergic [21], anti-convulsant [22], b-lactamase inhibitory [23], and anti-tuberculosis activities [24], 1,2,3-triazole has been comprehensively studied due to its important applications in industrially interesting materials, such as dyes, anticorrosive agents, photo stabilizers, photographic materials, and agrochemicals [18]. Therefore, we found it interesting to design new molecules within the scope of synthetic procedure using
phenylthiazole scaffold followed by suitable modification to generate diversified compounds for anti-HIV activity. In this study, we exploited click chemistry for synthesis of diversified phenylthiazole compounds mainly for the two reasons; first, it can tolerate wide range of functional groups and easy to do eco-friendly reactions at room temperature either in water or mixture of water and organic solvents; secondly, this approach will generate compounds having 1,2,3-triazole functionality rather than 1,2,4-triazole. These compounds can be studied for anti-HIV-1 RT activities.

The study of new hybrid systems in which 1,2,3-triazole and 2-amino-4-phenyl-1,3-thiazole are combined comprises an unfamiliar field of research. These findings have encouraged us to investigate the potential synergistic effect of 1,2,3-triazole and 2-amino-4-phenyl-1,3-thiazole scaffolds. Herein, for the first time, we report the hybridization of these two pharmacophores and their anti-HIV-1 NNRTI activity. It has been hope that combination of these active groups in the new molecular design would lead to better anti-HIV-1 agents. In this communication, we report the synthesis of newly designed 4-(phenyl)-N,N-bis((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine derivatives starting from dialkynyl substituted 2-amino-4-phenylthiazole derivatives which has been synthesized from substituted 2-amino-4-phenyl-1,3-thiazole and propargyl bromide.

Experimental

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 × 20 cm, Silica gel 60 F254, Merck grade was used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. The NMR spectra were recorded on Bruker Advance spectrometer at 300 MHz and Jeol JNM ECX spectrometer at 300 MHz using TMS as an internal standard. The chemical shifts values are recorded on δ-scale in DMSO solvent. Mass spectra were taken on Polaris-Q Thermo scientific GC-MS.

General procedure for synthesis of dialkynyl substituted 2-amino-4-phenylthiazoles derivatives (2a, 2b)

A mixture of aniline (0.5 mmol), allyl bromide (1.5 mmol), potassium carbonate (2 mmol), ethanol (2 mL), and water (1 mL) was added to a 50 mL round flask ask and stirred at 105 °C for 2 h. The reaction mixture was condensed by evaporation of solvents under reduced pressure and was washed with saturated sodium carbonate solution. After evaporation of the solvent, the crude product was purified by column chromatography using hexane and dichloromethane (65:35) as eluent.

 Elemental Analysis: C_{11}H_{27}N_{2}OS: C, 66.64; H, 5.59; N, 19.43; Found C, 66.60; H, 5.55; N, 19.39.

4-(4-chlorophenyl)-N,N-di(prop-2-ynyl) thiazol-2-amine (2b): Yellow solid; M.P. (180°C); 1H NMR (300 MHz, CDCl3): δ 2.51 (t, 2H), 4.46 (d, 4H), 7.14 (s, 1H), 7.32 (m, 2H), 7.64 (m, 2H); 13C-NMR (300MHz,CDCl3): δ 153.20, 149.00, 136.21, 131.40, 126.21, 115.80, 111.82, 78.44, 73.72, 40.22; GC-MS: m/z 286.03 (M+); Elemental Analysis: C_{11}H_{27}ClN_{2}S: C, 62.82; H, 3.87; N, 9.77; Found C, 62.80; H, 3.84; Cl, 12.33, N, 9.73.

General procedure for the synthesis of 4-(phenyl)-N,N-bis((1-phenyl-1H-1, 2, 3-triazol-4-yl) methyl) thiazol-2-amine derivatives (4a-o)

The synthesis of various azides was carried out according to the literature procedure [26]. Briefly, aniline (1 eq. 5 mmol) was dissolved in 6N HCl solution (20 ml) at room temperature and cooled up to 0°C, followed by addition of a solution of NaN3 (1 eq. 5 mmol). The reaction mixture was stirred for 10 min at 0-5°C. Sodium azide (1.2 eq. 6 mmol) was added and mixture was further stirred at room temperature for 2 h. The reaction was worked up by dilution with ethyl acetate. The organic layer was washed with brine solution and dried over sodium sulfate. After evaporation of the solvent, the crude product (2 a-t) was pure enough for further reactions. To this diaalkynyl substituted 2-amino-4-phenylthiazole (2a, b) (1 mmol) suspended in N,N′-dimethylformamide (10 ml). Sodium ascorbate (0.3 mmol, in water) was added, followed by copper (II) sulfatepentahydrate (0.03 mmol, in water). The heterogeneous mixture was stirred vigorously over 24-48 hrs, and the completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water, cooled in ice, and the precipitate was collected by filtration [27].

N,N-bis((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-methoxyphenyl)thiazol-2-amine (4b): White solid; M.P. (135 °C); 1H NMR (300 MHz, DMSO): δ 3.66 (s, 3H), 5.12 (s, 2H),7.12 (s, 1H), 7.30 (t, 1H), 7.42 (t, 2H), 7.53 (t, 2H), 7.80 (t, 2H), 8.51 (s, 1H); 13C-NMR (300MHz, DMSO): δ 167.45, 161.26, 155.05, 152.58, 143.58, 131.26, 131.26, 124.23, 126.03, 123.42, 121.66, 119.24, 115.33, 112.41, 105.33, 55.68, 45.92; GC-MS: m/z 589.5 (M+); Elemental Analysis: C_{22}H_{22}ClN_{2}OS: C, 75.05; H, 3.76; N, 19.07; Found C, 75.05; H, 3.76; N, 19.07.

N,N-bis((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-methoxyphenyl)thiazol-2-amine (4g): White solid; M.P. (122 °C); 1H NMR (300 MHz, DMSO): δ 3.75 (s, 3H), 5.02 (s, 2H), 7.12 (s, 1H), 7.30 (t, 1H), 7.40 (t, 2H), 7.57 (t, 2H), 7.80 (t, 2H), 8.60 (s,1H); 13C-NMR (300MHz, DMSO): δ 167.45, 161.26, 155.05, 152.58, 143.70, 131.32, 131.13, 126.29, 126.19, 124.40, 120.81, 119.23, 115.59, 112.64, 105.09, 55.33, 45.92; GC-MS: m/z 556.16 (M+); Elemental Analysis: C_{13}H_{16}F_{2}N_{2}OS: C, 60.42; H, 3.98; N, 20.13; Found C,60.40; H, 3.95; N, 20.09.

4-(4-methoxyphenyl)-N,N-bis((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl) thiazol-2-amine (4h): White solid; M.P. (176°C); 1H NMR (300 MHz, DMSO): δ 2.13 (s, 3H), 3.65 (s, 4H), 4.99 (s, 2H), 7.08 (t, 1H), 7.31 (d, 2H), 7.54 (q, 2H), 7.77 (d, 1H), 8.72 (s,1H); 13C-NMR (300MHz, DMSO): δ 161.17, 150.71, 152.51, 145.22, 134.72, 131.24, 129.01, 126.41, 125.98,121.59, 119.18, 100.58, 56.41, 42.95, 28.42; GC-MS: m/z 576.24 (M+); Elemental Analysis: C_{17}H_{2}N_{2}OS: C,66.64; H, 5.59; N,19.43; Found C, 66.60; H, 5.55; N,19.39.

4-(4-chlorophenyl)-N,N-bis((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine (4i): White solid; M.P. (142°C):
The coordinates of the non-nucleoside binding site were taken from the intermolecular interaction between the ligand and the targeted enzyme. Structure-based docking studies were carried out to investigate the interaction mode with RT, using Glide (Glide 5.8, Schrödinger, 2012) conformations of our newly synthesized compounds and their modeling study was performed to examine the possible binding molecules from Indolyl and chromenyl xanthenone series was carried out with enzyme reverse transcriptase PDB ID: 2ZD1. The ligands were prepared by using LigPrep (LigPrep 2.5, Schrödinger, 2012) [30]. The protein was refined using the protein preparation wizard present in Maestro 9.3 (Maestro 9.3, Schrödinger, 2012) [31]. All the water molecules were deleted. H atoms were added to the protein, including the protons necessary to define the correct ionization and tautomeric states of the amino acid residues. Prime interface module incorporated in Maestro was used to add the missing residues of the side chain. Each structure minimization was carried out with the impact refinement module, using the OPLS-2005 force field to alleviate steric clashes potentially existing in the structures. Minimization was terminated when the energy converged or the root mean square deviation reached a maximum cutoff of 0.30 Å. To find out active site grid was prepared using grid generation panel of glide with the default settings. Grid is defined for the binding site of native ligand on the receptor. The ligand was selected to define the position and size of the active site (Friessner et al.; Halgren et al.) [32,33]. Glide XP docking was used for docking purposes.

Results and Discussion

Chemistry

Various 4-(phenyl)-N,N-bis((1-phenyl 1H-1, 2, 3-triazol-4-yl)methyl)thiazole-2-amine derivatives were generated by reacting 2-amino-4-phenylthiazole with propargyl bromide in presence of base K2CO3 in dry acetone which yielded 2a (major) and 2a (minor). The compound 2a containing propargyl group at 2-position was used as substrate to further generate small 1,4-disubstituted 1,2,3-triazole library of 15 compounds (4a-o) by reacting various substituted aromatic azides using click chemistry as outlined in Scheme 1. The detailed general synthesis procedure of the compounds is mentioned in the experimental section. Exploration of the substrate scope for the synthesis of 4-(phenyl)-N,N-bis((1-phenyl 1H-1, 2, 3-triazol-4-yl)methyl)thiazole-2-amine derivatives was carried out by using grid generation panel of glide with the default settings. Grid is defined for the binding site of native ligand on the receptor. The ligand was selected to define the position and size of the active site (Friessner et al.; Halgren et al.) [32,33]. Glide XP docking was used for docking purposes.
Molecular docking

Docking score of compound 4k and 4h was found to be good around -11.126 and -11.125 respectively (Table 2). All molecules from 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine series were be docked into the non-nucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT. As illustrated in Figure 1b, 1a and native ligand TMC 278 in Figure 1c and 2c, the 1-phenyl-1H-1,2,3-triazol-4-yl)methyl and 4-phenyl-thiazolyl moiety of compound 4k and 4h of 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine series interacts through hydrophobic interactions into the hydrophobic binding pocket, surrounded by the aromatic portion of Trp 181, Tyr 188, Phe227, Trp 229, Val 106, Pro 226, Pro 225, Pro 233, Lbu 234, Pro95, Val 381and Ile 382. From the two dimensional Figure 1 (1a and 1b) and three dimensional view Figure 2 (2a and 2b), it is observed that Lys 101 and Lys 102 is juxtaposed for better interaction with the 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine series.

The methoxy and chlorophenyl-thiazolyl nucleus moiety at of compounds 4d and 4k makes π–π interaction into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of Trp229 and Tyr 181 residue. The N-aryl substituted triazolyl ring of the compound 4k and 4h makes π-cation interaction with into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of lys103 residue. Triazolyl ring of compound 4h form the hydrogen bond interactions with the backbone N–H of Lys101 residue. The decrease in activity of compounds 4l and 4f of 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine series was due to lack of π–π interaction of the methoxy and chlorophenyl-thiazolyl nucleus into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of Trp229 and Tyr 181 residue and nonexistence of π-cation interaction with the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of lys103 residue (Figure 3), instead it is showing π-π stacking of triazolyl ring with amino acid Trp 229 and Tyr 181.

Docking score of compound 4k, 4h, 4f and 4l was found to be around -11.126, -11.126, -8.189 and -7.698 respectively, (Table 2) while of native ligand was found to be -13.413 which confirms that 4k and 4h compounds might have potent RT inhibition activity. Further, in silico binding studies suggested that inhibitors possessing π–π interaction of the phenyl-thiazolyl nucleus into the hydrophobic binding pocket,

4-(y)methyl)thiazol-2-amine derivatives is as shown in Table 1. All synthesized compounds (4a–o) were characterized by GC-MS, 1H and 13C NMR. The conversion of the aldehyde group of 2a,b into the triazole ring of the product 4a–o can be confirmed by melting points and 1H and 13C NMR. A difference in the melting point, the high solubilities of 2a,b in CDCl3 and in DMSO, while the product 4a–o is soluble only in DMSO, the 1H NMR spectra of 4a–o, the NH, protons of 2-aminophenythiazole moiety disappeared by alkylation using propargylbromide. In 1H-NMR of compound 2,a the protons attached to N-CH3 and acetylene proton occurred at δ 3.82-4.46 and 2.31-2.35 respectively. The carbons attached to N-CH3 and acetylene occurred at 40.22-39.22 and 73.42-73.72, 77.44-78.44 respectively. Mass spectra of 2,a,b were corresponding to their molecular weight. In addition, of aromatic azides to 2a and 2b, some direct C-H correlations were observed, confirming that the signals of the triazolyl chain N-aryl substituted thiazolyl nucleus into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of Trp229 and Tyr 181 residue. The N-aryl substituted triazolyl ring of the compound 4k and 4h makes π–π interaction into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of lys103 residue. Triazolyl ring of compound 4h form the hydrogen bond interactions with the backbone N–H of Lys101 residue. The decrease in activity of compounds 4l and 4f of 4-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine series was due to lack of π–π interaction of the methoxy and chlorophenyl-thiazolyl nucleus into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of Trp229 and Tyr 181 residue and nonexistence of π-cation interaction with the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of lys103 residue (Figure 3), instead it is showing π–π stacking of triazolyl ring with amino acid Trp 229 and Tyr 181.

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Figure 1: Two-dimensional view of the binding interaction of the most active compounds, 4h (1a), 4k (1b) with active site of HIV-1 reverse transcriptase (RT) in complex with TMC278 and native ligand TMC 278 (2c) with HIV-1 reverse transcriptase (RT). Abbreviations: VAL, valine; LEU, leucine; GLY, glycine; ASP, aspartate; SER, serine; ALA, alanine; LYS, lysine; ILE, isoleucine; HIE, histidine epsilon H; MET, methionine; THR, threonine.

Figure 2: Three dimensional view of the binding interaction of the most active compounds, 4h (2a), 4k (2b) with active site of HIV-1 reverse transcriptase (RT) in complex with TMC278 and native ligand TMC278 (3c) with HIV-1 reverse transcriptase (RT).
surrounded by the aromatic side chains of portion of Trp 229 and Tyr 181 residue and π-cation interaction with the aromatic side chains of portion of lys103 residue improves the inhibitor selectivity for RT and thus helps in further drug design attempts to obtain potent 1,2,3, triazolyl-phenylthiazole derivatives.

In vitro anti-HIV

According to the docking study of synthesized compounds, some of it showed the high inhibition activity and some with low activity. From the above conclusion, we studied in vitro anti-HIV assay for particular compounds to verify their activity. The HIV-RT inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol (Roche Kit) [34]. The compounds presented in this study namely 24-(phenyl)-N,N-bis((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thiazol-2-amine derivatives (4k, 4h, 4o, 4f, 4l) were evaluated for anti-HIV-1 activity by using enzymatic (RT) and cell based assays. The HIV-1 RT inhibition activity range for these compounds showed from 64–92% inhibition at 100 μg/ml concentrations. The compounds 4k and 4h showed highest inhibitory activity both in docking as well cell based study (91.45%, 90.0%) respectively, whereas the control NNRTI marketed drug nevirapine showed 99.15% inhibition at 100 μg/ml concentration. The enzyme assay results demonstrated that the compound 4k and 4h were more potent than remaining derivatives comparing against reverse transcriptase enzyme. Subsequently, the inhibitory activity of HIV-1 viral replication was also assessed by cell-based assay. The results are summarized in Table 3 along with standard nevirapine as reference drug. In the cell based assay, the compounds 4k and 4h were the most potent inhibitors of HIV-1 replication against HIV-1 IIIB (EC50 =0.65 and 0.93 μg/ml respectively; the selectivity index (SI)=62.00 and 41.82 respectively; CC50 with HIV-1 IIIB=40.3 and 38.9 μg/ml respectively) and HIV-1 ADA5 (EC50 =1.02 and 0.25 μg/ml;the selectivity index (SI)=40.98 and 180.8 respectively; CC50=41.08;

| Compound | R     | Anti-HIV-1 activity | % Inhibition (HIV-RT kit assay) |
|----------|-------|---------------------|---------------------------------|
|          |       | EC50 (μg/ml) | CC50 (μg/ml) | SI | HIV-1 IIB | ADAS | HIV-1 IIB | ADAS | HIV-1 IIB | ADAS |
| 4k       | 4-Br  | 0.65          | 40.3          | 40.98 | 91.45 | 62   | 40.98   | 91.45 |
| 4h       | 3,4-CH3 | 0.93          | 39.8          | 45.2   | 41.82   | 180.8   | 90.40   |
| 4o       | 3,4-CH3 | 0.7           | 37.78         | 46.66   | 53.97   | 161.58   | 86.67   |
| 4f       | 4-NO2  | 1.32          | 50.78         | 48.3   | 38.46   | 39.53   | 66.88   |
| 4l       | 3-NO2  | 0.98          | 3.42          | 5.5                | 3.48       | 6.79       | 64.71   |
| Nevirapine|       | 0.05          | 76.12         | 1522.51 | 99.15 | 76.12     | 1522.51 | 99.15   |

*Data represent the mean of two and three independent assays for EC50 and CC50, respectively; EC50 is the 50% effective concentration required to reduce HIV-1 induced cytopathic effect of HIV-1 IIB and HIV-1 ADAS; The CC50 is the 50% cytotoxic concentration for HIV-1 IIB and HIV-1 ADAS; Selectivity index ratio CC50/EC50

Table 3: Anti-HIV-1 activity, cytotoxicity and selectivity index in HIV-1 IIB, ADAS and HIV-1 RT kit assay for compounds.
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References

Vidyapeeth Deemed University, Pune for biological evolution. The spectral data is highly appreciated and also Poona College of Pharmacy, Bharati necessary facilities and Vishnu Chemical Laboratory, Hyderabad for providing ADA5. The decrease in activity of compound 4f and 4l 1,2,3-triazolophenythiazole due to lack of π- cation interaction with lys103. This study suggested that inhibitors’ possessing π-cation interaction with lys103 and π-π interaction with the aromatic side chains of Trp 229 and Tyr 181 improves the inhibitor selectivity for RT.

Supporting Information

It includes docking score table and full characterization of synthesized compounds.

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Keunzel J, de Grote M, et al. (2001) Thiazole and thiadiazole analogues as a novel class of adenosine receptor antagonists. Journal of Medicinal Chemistry. 44: 749-762.

19. Zapata J, Berendsen HC, et al. (2002) The critical role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

20. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

21. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

22. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

23. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

24. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

25. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

26. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

27. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

28. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

29. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

30. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

31. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

32. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

33. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

34. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

35. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

36. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

37. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

38. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

39. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

40. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

41. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

42. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

43. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

44. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

45. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

46. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

47. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

48. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

49. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.

50. van Kerk et al. (2001) The role of π-π stacking in protein-DNA recognition. Biochemistry 41: 12211-12221.
33. Halgren TA, Murphy RB, Friesner RA, Beard HS, Frye LL, et al. (2004) Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. Journal of Medicinal Chemistry 47: 1750-1759.

34. Reverse Transcriptase Assay, Colorimetric Kit, Roche Diagnostics GmbH, Roche Applied Science, Sandhofer Strasses 116, D-68305 Mannheim, Germany.