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Original article

Investigation of novel bis-thiadiazole bearing schiff base derivatives as effective inhibitors of thymidine phosphorylase: Synthesis, in vitro bioactivity and molecular docking study

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ABSTRACT

Thymidine phosphorylase (TP) is an angiogenic enzyme. It is crucial for the development, invasion and metastasis of tumors as well as angiogenesis. In our current research, we examine how structurally changing bis-thiadiazole bearing bis-schiff bases affects their ability to inhibit TP. Through the oxidative cyclization of pyridine-based bis-thiosemicarbazone with iodine, a series of fourteen analogs of bis-thiadiazole-based bis-imines with pyridine moiety were developed. Newly synthesized scaffolds were assessed in vitro for their thymidine phosphorylase inhibitory potential and showed moderate to good inhibition profile. Eleven scaffolds such as **4a-4d**,**4f-4 h** and **4j-4 m** were discovered to be more effective than standard drug at inhibiting the thymidine phosphorylase enzyme with IC_{50} values of 1.16 ± 1.20, 1.77 ± 1.10, 2.48 ± 1.30, 12.54 ± 1.60, 14.63 ± 1.70, 15.53 ± 1.80, 17.47 ± 1.70, 18.98 ± 1.70, 19.53 ± 1.50, 22.73 ± 2.40 and 24.87 ± 2.80 respectively, while remaining three analogs such as **4n, 4i** and **4e**were found to be more potent, but they were less potent than the standard drug. All analogs underwent SAR studies based on the pattern of substitutions around the aryl part of the bis-thiadiazole skeleton. The most active analogs in the synthesized series were then molecular docking study performed to investigate their interactions of active part of enzyme. The results showed that remarkable interactions were exhibited by these analogs with the targeted enzymes active sites. Furthermore, to confirm the structure of synthesized analogs by employing spectroscopic tools such as HREI-MS and NMR.

1. Introduction

By working in the pyrimidine salvage routes, human thymidine phosphorylase restores bases for the repairing and replication process of DNA (Friedkin& Roberts, 1954). Inorganic based enzymes contain the phosphate which catalyzes the phosphorolysis resulting in the development of thymine and 2-deoxy-D-ribose-1-phosphate. Deoxyribosyl transferase activity is another feature of hTP. This enzyme catalyzes and transfers of the deoxyribose from pyrimidine to produce new pyrimidine nucleosides (Schwartz

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1319-0164/

1971; Iltzsch et al., 1985). The proteins aregliostatin and endothelial cell platelet-derived factor have been linked, and it has been shown that they share an amino acid sequence with hTP. Gliostatin is to regulate glial cell growth, but has been PD-ECGF demonstrated to promote angiogenesis (Moghaddam& Bicknell, 1992; usuki et al., 1992; Asai et al., 1992). Due to the higher levels of *h*TP expression present in different tumor types is crucial in the cancer's development. The has been discovered generally in tissues enzyme that have been put to chemotherapeutic and radioactive, the existence of a range of microenvironments and inflammatory cytokines of circumstances of stressful such as hypoxia and low pH (Brown et al., 2000). Elevations of hTP level are largely associated with cancer aggressiveness and a bad prognosis due to its pro-angiogenic and anti-apoptotic characteristics (Moghaddam et al., 1995; Matsuura et al., 1999; Ikeda et al., 2003). The enzymatic process catalyzed by hTP formed products that have been found to be associated with the pro tumor signaling pathway. N-glycosidic bond ruptures and in the results the production of 2DDR-1P, which undergoes non-enzymatic dephosphorylation to become 2-deoxy-D-ribose. As 2DDR exits the cell its angiogenic and anti-apoptotic properties become apparent (Haraguchi et al., 1994; Liekens et al., 2002, Miyadera et al., 1995). Through empowering the downstream integrin signaling network, this drug change the motility of endothelial cells. By enhancing the constructing and/or release of different angiogenic features like interleukins, vascular endothelial growth factor and matrix metallic-proteases, the tumor microenvironment also expedites angiogenesis and cancer dissemination (Hotchkiss et al., 2003; Bijnsdorp et al., 2011; Takubo et al., 2013).Additionally, linked to the resistance of several tumor cell types to hypoxia-induced apoptosis are hTP and 2DDR. Two different forms of caspase (3 and 9) activate the methods by which hTP or 2DDR reduced hypoxia induced pro apoptotic signals, the decline in mitochondrial transmembrane potential, the release of mitochondrial cytochrome *C*, the down regulation of BCl2 and the up regulation of HIF-1 (Ikeda et al., 2002; Jeung et al., 2005; 2006).

Based on their outstanding chemistry and diverse biological characteristics, heterocyclic molecules are particularly interesting to medicinal chemists. Even though heterocyclic ring systems have seen considerable advancements in research, work is still being done to find new heterocyclic compounds with strong bioactivities. The 1,3,4-thiadiazole scaffold has garnered particular interest due of the various and inherent biological responses it exhibits (Holla et al., 2002). Due to its extensive spectrum of pharmacological profile, the 1,3,4-thiadiazole, a privileged structure, holds a prominent position in medicinal chemistry (Taha et al., 2017). It also serves as a major motif in heterocyclic chemistry. Recent studies have reported the numerous biological profile of thiadiazole derivatives including antifungal (Liu et al., 2013), antibacterial (Xu et al., 2012), antiviral (Dong et al., 2016), anti-inflammatory (Palaska et al., 2002), antimicrobial (Farshori et al., 2010), anti-anxiety (Harfenist et al., 1996), anticancer (Yang et al., 2012), anticonvulsant (Jatav et al., 2008), anti-tubercular (Orcu et al., 2004), anti-thymidine phosphorylase (Shehzad et al., 2015) and anti-depressant (Siddidui et al., 2011) activities.

Due to their intriguing bioactivity, heterocyclic scaffolds with schiff base skeleton having imines (azomethine) functional moiety displayed diverse spectrum of biological characteristics. Furthermore, heterocyclic derivative-containing Schiff bases were said to have a wide range of therapeutic and biological potentials including antitumor agents (Zhou et al., 2007), antimicrobial (Prakash et al., 2013), anti-helminthic (Revanasiddappa et al., 2013), antiviral (Kumar et al., 2010) and anti-urease (Ahmad et al., 2023; Ahmad et al., 2022) (Fig. 1).

Keeping in mind, diverse biological applications of pyridine-based analogs (El-Naggar et al., 2018; Baraei et al., 2021) and scaffolds bearing thiadiazole skeleton in their core structure (Farooqi et al., 2021; Javid et al., 2018; Alomari et al., 2021; Khan et al., 2023), herein this study we had reported the novel analogs based on pyridine bearing bis-thiadiazole moieties and then evaluated for their enzymatic potentials to explore the lead candidates (Fig. 2).

2. Results

2.1. Chemistry

In this research work newly bis-thiadiazole analogs based bis-imines (**4a-n**) from pyridine were developed. In order to synthesize (2E,2′E)-2,2′-(pyridine-2,6-diylbis(methanylylidene))bis(hydrazine-1-carbothioamide) as an intermediate (**2**), pyridine-2,6-dicarbaldehyde (**1**) was mixed with hydrazinecarbothioamide (two molar), which was then refluxed in MeOH along with addition of CH_3COOH as a catalyst. This reaction was then allowed to run on reflux for 6 h. Further, (2E,2′E)-2,2′-(pyridine-2,6-diylbis(methanylylidene))bis(hydrazine-1-carbothioamide) substrate underwent oxidative cyclization with I_2 and K_2CO_3 using 1,4-dioxane to afford 5,5′-(pyridine-2,6-diyl)bis(1,3,4-thiadiazol-2-amine) as substrate (**3**) (Aliabadi et al., 2017). In the last step, intermediate (**3**) was put in stirring and reflux with the different benzaldehyde derivatives in methanol and a catalytic amount of CH_3COOH. The targeted (1E,1′E)-N,N'-(pyridine-2,6-diylbis(1,3,4-thiadiazole-5,2-diyl))bis(1-phenylmethanimine) derivatives (**4a-n**) were afforded by heating the residue for 7 h. After the completion of reaction, the solvent was evaporated to leave the desired compounds in solid form. These solid residues were cleaned, recrystallized and dried to afforded the pure (1E,1′E)-N,N'-(pyridine-2,6-diylbis(1,3,4-thiadiazole-5,2-diyl))bis(1-phenylmethanimine) (**4a–n**). Several spectroscopic methods, including ^{1}NMR, ^{13}CNMR, and HR-EIMS were used to confirm structure of synthesized analogs (scheme 1). As for ^{1}H NMR spectrum of compound 4i, two singlets were appeared one for two chemically equivalent proton of schiff base-H (HC = N) resonating at 8.02 chemical shift values and other for six chemically equivalent dimethylamino protons (-N$(CH_3)_2$ appearing at chemical shift values of 2.95. Additionally, the chemical was designed in symmetry, and just one half of the molecule's spectrum was detected. The four protons of two dimethylamino-substituted aryl rings that are meta- to -N$(CH_3)_2$ group are chemically equivalent and linked to their surrounding *ortho*-protons, giving doublet resonating at chemical shift values of 7.95 with J = 7.9 Hz suggesting that *ortho*-coupling take place. Like this, the four protons that are ortho- to dimethylamino groups are chemically similar, connected to protons in their surrounding molecules, and resonate as a doublet with chemical shift values of 7.84 and J = 7.4 Hz. Additionally, triplet was appeared for pyridine proton at 7.45 with J = 7.0 Hz as this pyridine proton coupled to *ortho*-protons in its neighboring position. Further, the other two protons of pyridine resonate as doublet appearing at chemical shift of 7.39 having coupling constant values of 6.7 Hz showing that *ortho*-coupling take place.

2.2. In vitro thymidine phosphorylase activity

Using 7-deazaxanthine as a reference compound, the inhibitory profile of fourteen produced analogs of pyridine including bis-thiadiazole and possessing bis-imines moiety was evaluated. Based on the pattern of substitution(s) around the aryl component, SAR studies were conducted on all newly generated scaffolds. Based on the results of SAR studies, it was discovered that inhibition profile of the target enzyme appears to be actively influenced by pyridine, bis-thiadiazole, bis-schiff base as well as aromatic parts of the residue and substitutions around structures (Fig. 3).

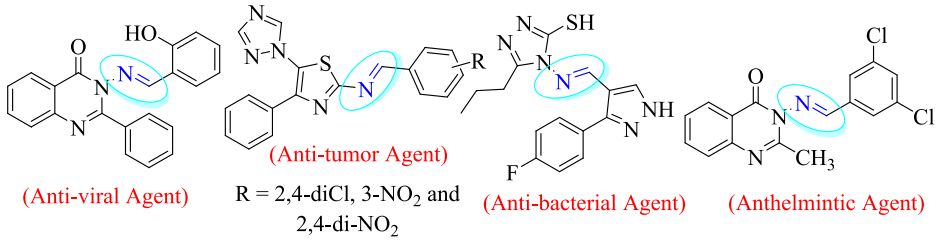


Fig. 1. Heterocyclic compounds with schiff base skeleton and its biological applications.

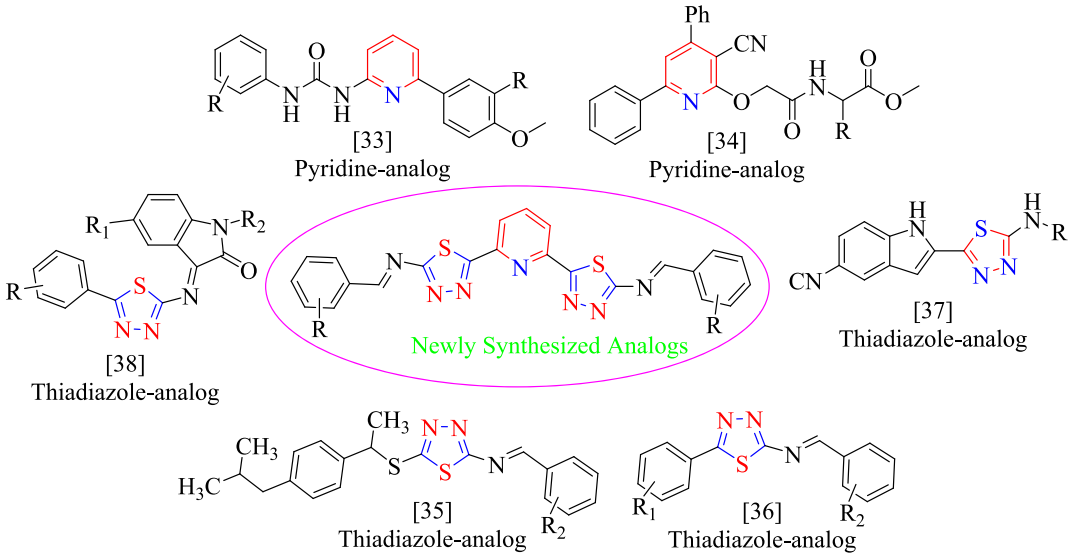
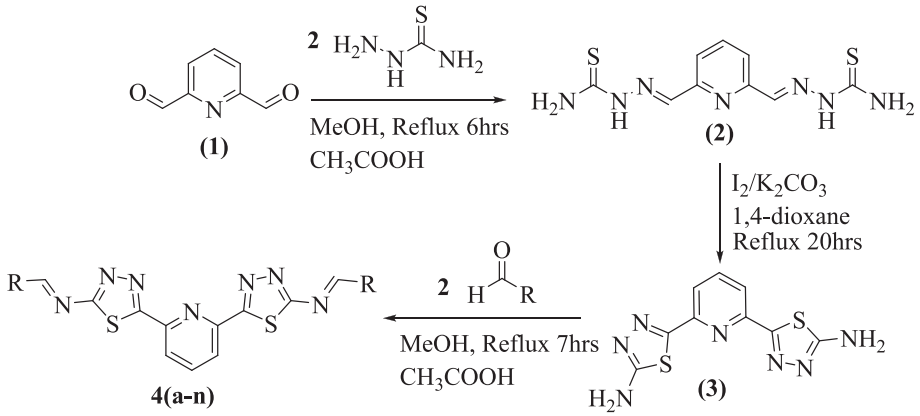


Fig. 2. Rationale study of the current work.



Scheme 1. Preparation of bis-imines based bis-thiadiazole analogs.

3. Discussions

3.1. Structure-activity relationship (SAR) analysis

Analog **4c** bearing 3-nitro & 5-trifluoro moieties at aryl part was identified as the highly potent analogs against the target enzyme and shown many folds more potency when compared to as standard drug. Similarly analog **4 k** which is structurally identical to that of analog **4c** but had different position of tri-fluoro methyl moiety at aryl part of bis-thiadiazole skeleton. Analog **4 k** bearing trifluoro methyl moiety at *ortho*- and $-NO_2$ moiety at position-5 of same aryl part showed less inhibitory potential when compared to its counterpart 4c although both these scaffolds had same nature of substituents. These most active scaffolds enhanced the enzymatic activity might be strong EW nature of attached substituent(s) like $-NO_2$ & $-CF_3$ which interacts with the catalytic cavity of targeted enzyme in better way and hence improved the activity. On the other hand, analogs **4n** (*para*-toluene moiety at aryl part) and **4e** (*para*-phenyl ring at aryl part) were recognized as the less potent and shown fewer inhibition properties than the standard drug.

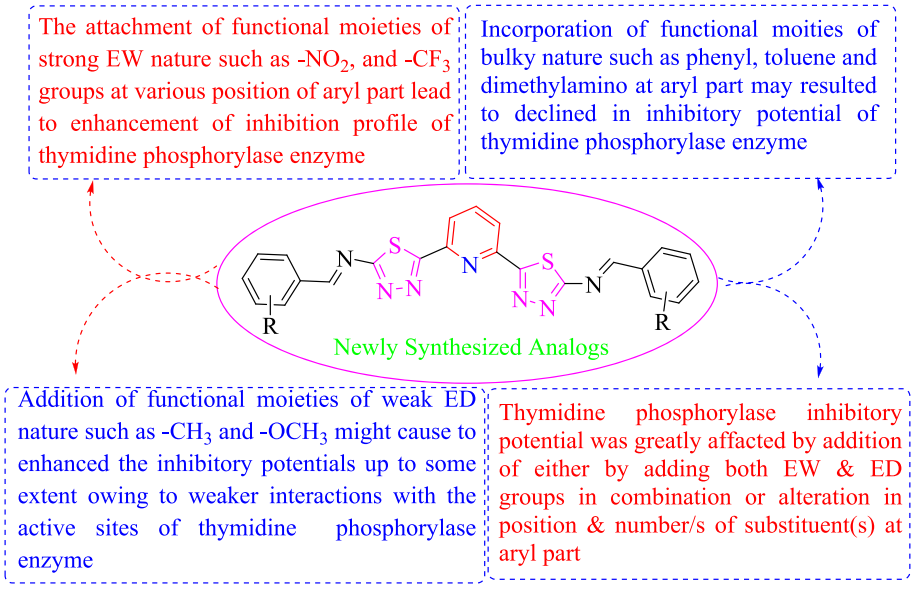


Fig. 3. SAR studies summary showing disturbing or enhancing the enzymatic activities.

The less potency of these analogs might due to large size functional moiety attached substituent which causes crowdness and not allowing the functional moieties of analogs (**4e**&**4n**) to interact with active part of thymidine phosphorylase (Table 1).

The **4 l** analog containing 3-hydroxy & 5-nitro functional analogs at aromatic region of bis-thiadiazole skeleton found to be third most active scaffold and displayed few folds more potency when associated to regular drug. This analog **4 l** showed somewhat less inhibitory potential in comparison to analog 4c that bears $-CF_3$ instead moiety group of –OH at 3-position of aryl part. The lower inhibitory potential of analog **4 l** than analog **4c** might be due to better provided interactions by $-CF_3$ moiety group than –OH with the thymidine phosphorylase active pockets. The analog **4b** showed better inhibition profile of thymidine phosphorylase enzyme. Nevertheless, the inhibition properties possessed by analog **4b** was increased by substituting *para*-CH_3 group with Cl group as in the case of compound **4a** indication that introduction of EW nature functional moiety might responsible for the enhancement of inhibition profile against thymidine phosphorylase enzyme. Additionally, by substituting the 2-NO_2 moiety with a $-CH_3$ group, just in case of compound **4 m**, which has di-CH_3 groups at the 2,4-position of the aryl part of the bis-thiadiazole skeleton, the inhibition profile of analog **4b** was dramatically decrease (Table 1).

By comparing scaffold **4j** bearing di-OCH_3 groups at 2,4-position of aryl part with analog 4 m that holds di-CH_3 moieties, the analog **4j** displayed better inhibitory potential than scaffold 4 m. This indicates that compounds bearing di–OCH_3 functional moieties showed better inhibitory potential when compared to analogs having di-CH_3 groups. Additionally, compound **4j** showed less potency in comparison to analog **4f** that holds di-Cl moieties at 2,4-position of aryl part of bis-thiadiazole skeleton. The di-Cl groups withdraw the electronic density and gain stability through with strong the sites active interactions of the phosphorylase thymidine enzyme. Moreover, the inhibition profile of the analog **4f** was resulted to decline by changing *ortho*-Cl with moiety group $-CH_3$ as in compound **4 h** which had *ortho*-CH_3 & 4-Cl groups at aryl part of bis-thiadiazole skeleton (Table 1).

On the basis of observation, it was note that inhibition profile of the derivatives and get altered by bringing substitution(s) of different nature of groups around the bis-thiadiazole unit. Moreover, it was also observed that the inhibition profile was also affected either by changing the position of substituent(s) at aryl part or incorporation of functional moieties in greater number/s (Table 1).

3.2. In silico studies

To comprehend the binding method of interactions of produced analogs with the active cavity of amino acids of the targeted thymidine phosphorylase enzyme, a molecular docking research was done against the two most active analogs of the synthesized bis-thiadiazole series, **4c** and **4 k**. The most potent analog-4c (that hold 2-NO_2& 3-CF_3 at aryl part) have found to show maximum numbers of important bindings with the active part of amino acids of targeted enzyme such asVal96 (CHB), Phe95 (pi-alkyl), Arg91 (halogen (fluorine) & pi-alkyl), (halogen (fluorine), His94 Phe200 (CHB &pi-pi stacking), Val201 (pi-alkyl & pi-sigma), Phe91 (pi-alkyl), Thr204 (CHB), Glu595 (pi-anion), Ser597 (CHB) and Thr205 (halogen (fluorine)). This analog-4c enhanced the inhibitory potentials against targeted enzyme owing to important interactions possess by stronger electron withdrawing (EW) groups such as $-NO_2$ and $-CF_3$ moieties (Fig. 4). However, changing the position of these EW groups around aryl ring considerably affect the inhibitory potential as in analog-4 k although this analog was emerged as second most active among the synthesized series.

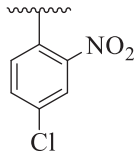
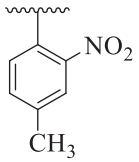
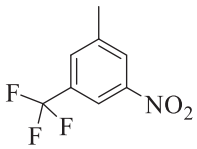
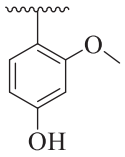
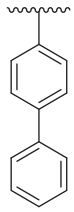
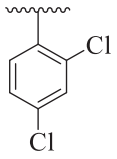
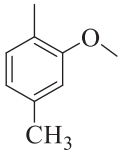
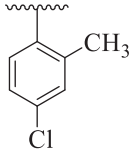
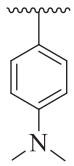
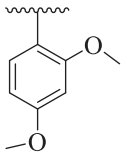
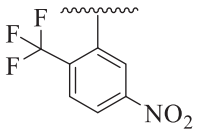
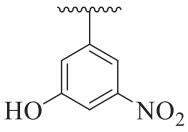
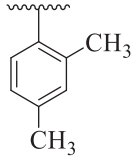
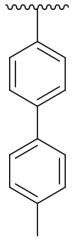
The second most potent analog-4 k bearing same substituent(s) as in analog-4c but had different position around aryl ring of bis-thiadiazole skeleton, adopted numerous key interactions with the target enzyme active locations. These interactions with the targeted enzyme active hole including Tyr205 (halogen (fluorine), Tyr508 & Arg600 (CHB), Thr204 (CHB), Glu595 (pi-anion), Val201 (pi-sigma), Phe200 (pi-pi stacking), Val96 (pi-alkyl & CHB), Phe51 (pi-alkyl), Arg91 (pi-alkyl & halogen (fluorine), Phe95 (pi-alkyl) and His94 (halogen (fluorine)) interactions which enhanced the inhibition profile of this analog against enzyme (Fig. 5).

4. Experimental

4.1. General information

All necessary reagents, solvent and chemicals were acquired from Sigma-Aldrich and Alfa Aesar and were employed without further purification. NMR on a Bruker Advance operating at

Table 1
Effect of varied substitutions on inhibitory potential against targeted enzyme.

S.NO	R	IC_{50} ± SEM[a] [μM]	S.NO	R	IC_{50} ± SEM[a] [μM]
4a		12.54 ± 1.60	**4b**		15.53 ± 1.80
4c		1.16 ± 1.20	**4d**		17.47 ± 1.70
4e		32.38 ± 4.50	**4f**		14.63 ± 1.70
4 g		22.73 ± 2.40	**4 h**		18.98 ± 1.70
4i		30.58 ± 3.10	**4j**		19.53 ± 1.50
4 k		1.77 ± 1.10	**4 l**		2.48 ± 1.30
4 *m*		24.87 ± 2.80	**4*n***		35.78 ± 5.80
Standard 7-Deazaxanthine[d]					25.78 ± 1.90 **μM**

600 MHz (for proton) and 150 MHz (for 13C) spectrometer was used to corroborate the precise structures of newly afforded scaffolds. Tetramethylsilane was utilized as the internal standard after the compounds were solubilized in dimethyl sulfoxide (DMSO d_6). The ^{13}C signals were assigned using the distortion less enhancement by polarization transfer (DEPT) experiment. The HRMS spectra were captured using HRMS (ESI) with electrospray ionization.

4.2. Procedure adopted for affording bis-thiadiazole-bearing bis-imines scaffolds (4a-n)

4.2.1. Synthesis of (2E,2′E)-2,2′-(pyridine-2,6-diylbis (methanylylidene))bis(hydrazine-1-carbothioamide) (2)

Pyridine-2,6-dicarbaldehyde (**1**, 1 equivalent) and hydrazinecarbothioamide (2 equivalent) were mixed in methanol (10 mL) and then adding CH_3COOH (few drops as catalyst). The resulting residues was refluxed and stirred for 6 h at refluxing temperature. Upon completion, the reaction residue was filtered, dried and stored for further reaction.

*4.2.2. Synthesis of 5,5′-(pyridine-2,6-diyl)bis(1,3,4-thiadiazol-2-amine) (**3**)*

Molecular iodine (1 equivalent) was taken in round bottom flask using 1,4-dixoane (10 mL) as solvent, then (*2E,2′E*)-2,2′-(pyridine-2,6-diylbis(methanylylidene))bis(hydrazine-1-carbothioamide) (**2**, 1 equivalent) and potassium carbonate (catalyst) were added to reaction mixture and stirred under refluxed 20 h. The solvent was extracted under decreased pressure after being cooled to 25 °C. The product (**3**) so obtained was precipitated, filtered,

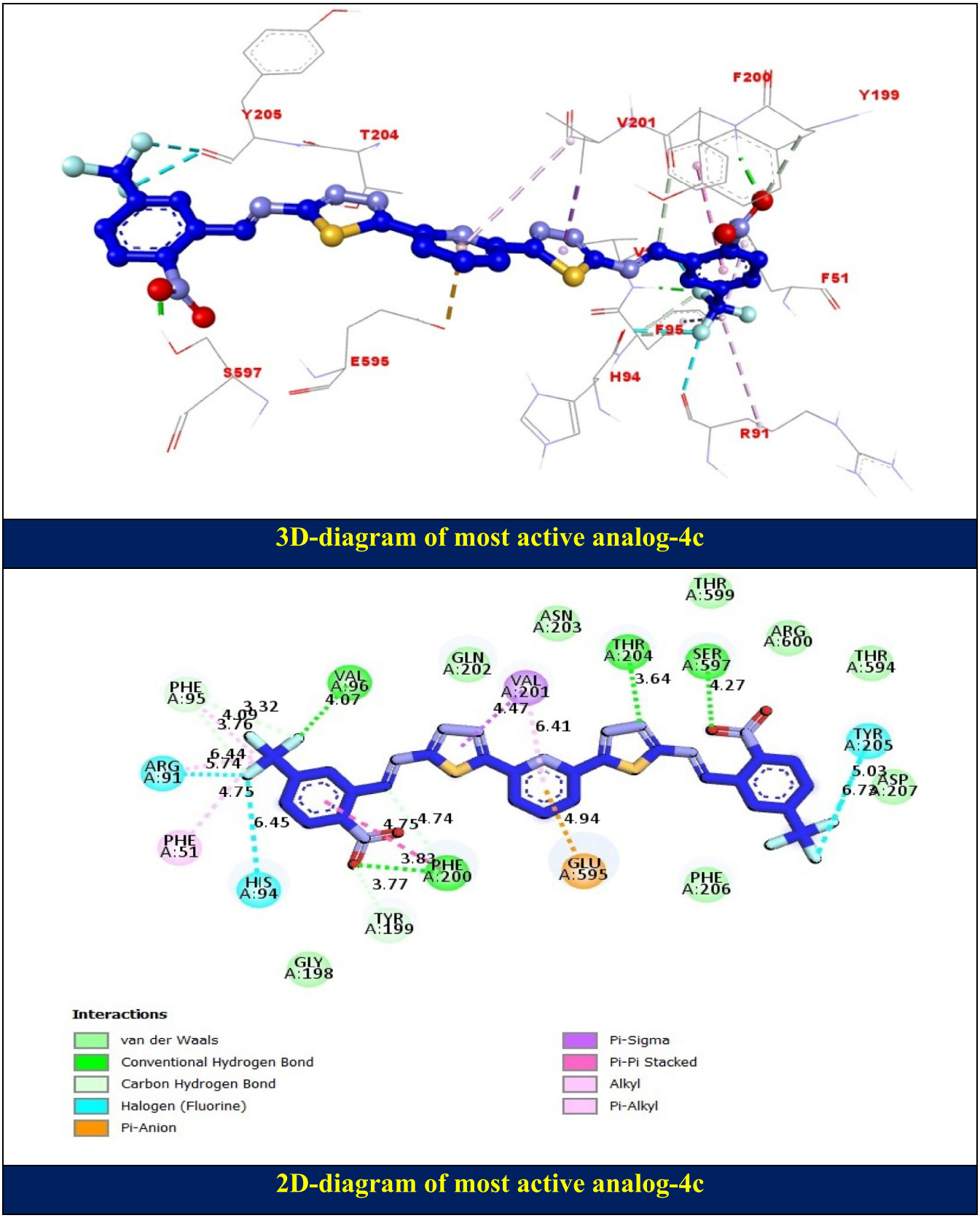


Fig. 4. Represent PLI profile of most potent analog-**4c** against targeted enzyme and its 3D (top) and 2D (bottom) diagram.

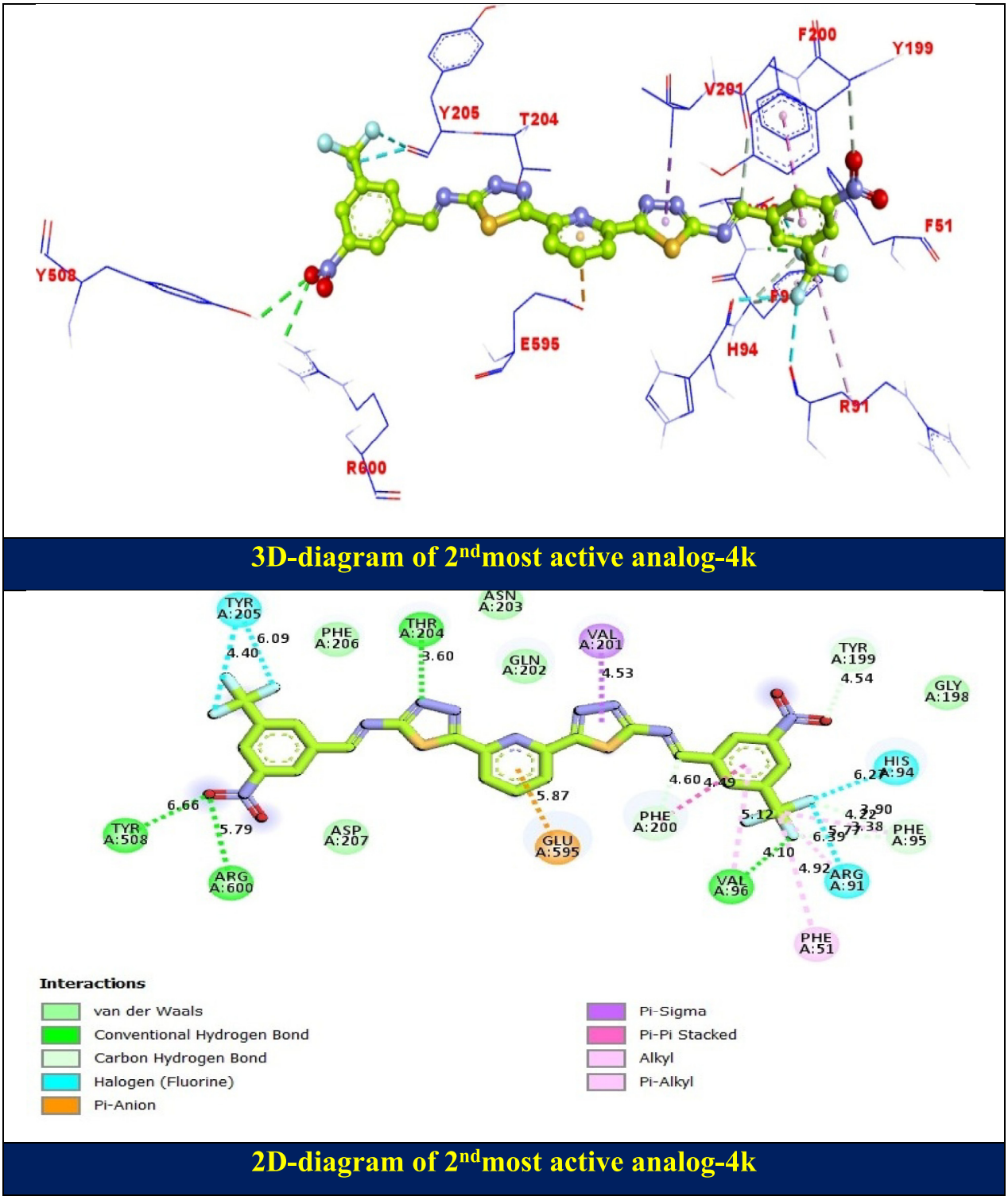


Fig. 5. Represent PLI profile of 2nd most potent analog-**4 k** against targeted enzyme and its 3D (top) and 2D (bottom) diagram.

washed, dried and preserved for next reaction (Aliabadi et al., 2017).

4.2.3. Synthesis of substituted (1E,1′E)-N,N′-(pyridine-2,6-diylbis (1,3,4-thiadiazole-5,2-diyl))bis(1-phenylmethanimine) (4a-n)

The targeted scaffolds (**4a-n)** were finally afforded by stirring 5,5′-(pyridine-2,6-diyl)bis(1,3,4-thiadiazol-2-amine) (**3,** 1 equivalent) and diverse substituted benzaldehyde (2 equivalent) in MeOH (10 mL) for 7 h catalyzed using 3–5 drops of acetic acid. As the reaction was completed, the different substituted (1E,1′E)-N,N′-(pyridine-2,6-diylbis(1,3,4-thiadiazole-5,2-diyl))bis(1-phenylmethanimine) (**4a-n**) products were precipitated in cold water, filtered, washed and dried (scheme 1).

4.3. Spectral analysis

Spectral data were also placed in the supplementary information.

4.4. Assay protocol for thymidine phosphorylase inhibition

This was performed according to the reported work (Hussain et al., 2023).

4.5. Assay protocol for molecular docking

It has also done by follow the literature known protocol (Khan et al., 2022; Khan et al., 2023; Adalat, 2023).

5. Conclusion

Finally, a simple technique was employed to create pyridine-derived bis-thiadiazole containing bis-imine moieties, which was then tested under the positive influence of a reference medication against the desired thymidine phosphorylase enzyme. Several spectroscopic methods, including HREI-MS, ^{13}C NMR, and ^{1}H NMR, were used to determine the exact structures of the synthesized analogs. All the synthesized compounds demonstrated significant inhibitory capabilities exhibiting IC_{50} values in the range of 1.16 ± 1.20 to 35.78 ± 5.80 μM when associated to typical drug (IC_{50} = 25.78 ± 1.90 μM**).** Structure-activity relationship (SAR) revealed that compounds having substituents either of strong associating nature like (–OH) or strong EW nature (–NO_2 & CF_3) has significant impact on inhibitory potentials. Specifically, compounds **4c** (IC_{50} = 1.16 ± 1.20 μM), **4 k** (IC_{50} = 1.77 ± 1.10 μM) & **4 l** (IC_{50} = 2.48 ± 1.30 μM) were emerged as remarkable inhibitors of targeted enzyme, even manifolds more active than standard drug. The active analogs showed several important interactions including HB, pi-pi alkyl and pi-pi T shaped etc. with the thymidine phosphorylase active pockets when put on to in silico studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101823.

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