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Synthesis, Characterization, Molecular Docking Studies and Biological Evaluation of Thiazole Schiff Base Analogs

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In this work, potentially safe few Schiff base compounds containing a thiazole moiety were synthesized and characterized. Three thiazole derivatives (**2a-c**) were successfully synthesized through a two-step reaction involving substituted benzaldehyde, thiosemicarbazide and 1,3-dichloroacetone. The elucidation of the synthesized compounds was accomplished by using spectral studies. Antimicrobial activities demonstrated that some compounds exhibited moderate effectiveness against microbes, compared to the standard antibiotic's ceftriaxone and amphotericin B, using the disc diffusion technique. In the DPPH free radical scavenging assay, all compounds displayed promising antioxidant effectiveness. Moreover, the molecular docking studies showed that thiazole Schiff base analogs effectively bind to potential receptor binding sites.

Keywords: Schiff base, Thiazole, Antimicrobial activity, Antioxidant activity, Molecular docking.

INTRODUCTION

The global concern towards the treatment of infectious diseases caused by different pathogens has increased due to the extensive utilization of antibiotics and the rapid development of multidrug resistance in microorganisms [1]. This drives researchers globally to develop new and potent antibacterial compounds. The most widely used antibiotics including penicillin, amphotericin B and fluconazole were found to be resistant to a variety of microorganisms [2]. The development of novel and highly potent antimicrobial medications is desperately needed to address this issue. These five-membered heterocyclic compounds, which contain electron-rich S and N atoms and a thiazole scaffold, are an important class of pharmacophore in the synthetic medicinal domain [3]. Their low toxicity allows them to exhibit a broad range of bioactivities. It is found in a wide range of commercially available drugs such as abafungin (antifungal drug), sulfathiazol (antimicrobial drug), ritonavir (antiretroviral drug) and tiazofurin (antineoplastic drug) [4-6]. They exhibit wide range of bioactivities such as antibacterial [7], antifungal [8], anti-HIV [9], antihypertension [10], anticancer [11], anti-inflammatory [12] and antioxidant [13] activities.

Schiff bases have gained importance in pharmaceutical fields due to wide range of bioactivities such as analgesic, anti-inammatory, antimicrobial, anticonvulsant, antitubercular, anti-cancer, antioxidant, anthelmintic activities, *etc*. [14-18]. Reactive oxygen species (ROS) induced by the presence of free radicals leads to damage to cell membranes, membrane lipids and nucleic acids. It causes several fatal diseases like cancer, diabetes, cataracts, heart diseases and arteriosclerosis [19]. Free radicals are also responsible for autoimmune, cardiovascular neurodegenerative, inflammatory and Alzheimer's disease [20,21]. Antioxidants are administrated to neutralize free radicals to give protection to the tissue from various fatal diseases [22]. Antioxidant therapy is now acknowledged as a safe and effective treatment to lower the risk of neurological and cardiovascular disorders, as well as cancer [23]. It has been revealed that the thiazole Schiff bases may function as antioxidants [24]. The current study aimed to synthesize new Schiff bases containing heterocyclic thiazole derivatives, taking into account the

biological significance of thiazoles as a core structure of several drugs and their ability to prevent ROS formation. The Agar disc diffusion method was used to assess the synthesized derivatives' *in vitro* antimicrobial activities against strains of fungi, bacteria and Gram-positive and Gram-negative bacteria after synthesis. The DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging assay was utilized to investigate antioxidant activities. Molecular docking experiments were also conducted to elucidate the interaction mechanisms between the produced chemicals and the specific target proteins.

EXPERIMENTAL

The melting points the synthesized thiazole Schiff Base analogs' are uncorrected and were measured using an SMP10 device. A Bruker 400 MHz NMR spectrometer was used to analyze the ^{1}H and ^{13}C NMR spectra. Samples were run as KBr pellets on a Shimadzu IR Tracer-100 infrared spectrometer. Reagents were procured from Sigma-Aldrich, USA and used without further purification.

General procedure for the synthesis of benzaldehyde thiosemicarbazones (1a-c): A solution containing thiosemicarbazide and substituted benzaldehydes was heated in ethanol and allowed to react at 80 ºC with constant stirring. The progress of the reaction was checked using TLC. After completion, the reaction mixture was cooled, filtered and the resulting crude products were purified by recrystallization in ethyl alcohol, resulting in the formation of substituted benzaldehyde thiosemicarbazones (**1a-c**, **Scheme-I**).

2-(4-Nitrobenzylidene)hydrazine carbothioamide (1a): Yield: 72%, m.p.: 251 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3441 (NH_2), 3363 (NH), 1577 (C=N), 1527 (C=C Ar), 1340 (C=S); ^{1}H NMR ($CDCl_3$, δ ppm): 4.88 (1H, s, N-NH), 8.00 (1H, d, *J* = 8.8 Hz, Ar-H), 8.02 (1H, d, *J* = 8.8 Hz, Ar-H), 8.07 (1H, s, CH=N), 8.27 (1H, d, *J* = 8.8 Hz, Ar-H), 8.30 (1H, d, *J* = 8.8 Hz, Ar-H), ^{13}C NMR ($CDCl_3$, δ ppm): 123.5, 127.7, 140.3, 140.4, 148.3, 178.5.

2-(2-Nitrobenzylidene)hydrazine carbothioamide (1b): Yield: 84%, m.p.: 202-203 ºC; FT-IR (KBr, ν_{max}, cm^{-1}):3491 (NH_2), 3269 (NH), 1614 (C=N), 1529 (C=C Ar), 1334 (C=S); ^{1}H NMR ($CDCl_3$, δ ppm): 4.87 (1H, s, N-NH), 6.18 (1H, t, *J* = 2.8 Hz, Ar-H), 6.45 (1H, dd, *J* = 4.8, 1.2 Hz, Ar-H), 6.92 (1H, t, Ar-H), 7.82 (1H, s, CH=N), 7.82 (1H, d, *J* = 4.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, δ ppm):109.7, 113.8, 121.8, 127.1, 135.7, 177.3.

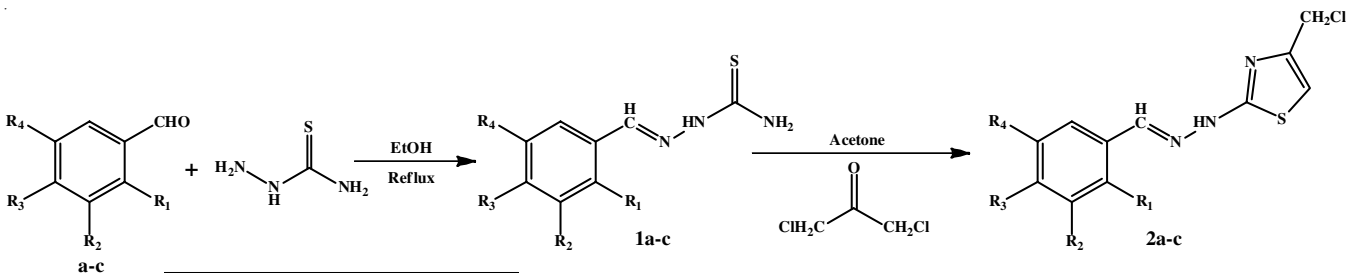
2-(2-Hydroxy-5-bromobenzylidene)hydrazine carbothioamide (1c): Yield: 92%, m.p.: 253-254 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3455 (NH_2), 3250 (NH), 1610 (C=N), 1545 (C=C Ar), 1351 (C=S); ^{1}H NMR ($CDCl_3$, δ ppm): 3.37 (1H, s, N-NH), 6.83 (1H, d, *J* = 8.8 Hz, Ar-H), 7.35 (1H, dd, *J* = 8.8, 2.4 Hz, Ar-H), 8.20 (1H, d, *J* = 1.6 Hz, Ar-H), 8.29 (1H, s, CH=N), 10.24 (1H, s, OH).^{13}C NMR ($CDCl_3$, δ ppm): 111.5, 118.6, 123.3, 128.7, 133.6, 137.8,156.0, 178.3.

General procedure for the synthesis of 2-{2-[(aryl)-methylidene]hydrazin-1-yl}-1,3-thiazoles (2a-c): Substituted benzaldehyde thiosemicarbazones and 1,3-dichloroacetone was refluxed in acetone at 60 ºC with continuous stirring. The progress of the reaction was checked using TLC. Once the reaction was complete, the reaction mixture was cooled, filtered and the crude solid obtained was purified by recrystallization in ethanol, resulting in the formation of the final products **2a-c** (**Scheme-I**).

2-(2-(4-Nitrobenzylidene)hydrazineyl)-4-(chloromethyl)-1,3-thiazole (2a): Yield: 75%, m.p.: 240-241 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3423 (NH), 1614 (C=N), 1514 (C=C Ar), 1430 (CH_2), 844 (C-Cl), 740 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 4.73 (2H, s, thiazole-CH_2), 4.90 (1H, s, N-NH),7.25 (1H, s, thiazole-H), 8.07 (1H, d, *J* = 8.8 Hz, Ar-H), 8.09 (1H, d, *J* = 8.8 Hz, Ar-H), 8.34 (1H, s, CH=N),8.36 (1H, d, *J* = 8.4 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, δ ppm): 36.1, 109.4, 123.7, 128.3, 138.4, 138.7, 147.8, 149.2, 165.4.

2-(2-(2-Nitrobenzylidene)hydrazineyl)-4-(chloromethyl)-1,3-thiazole (2b): Yield: 68%, m.p.: 267-268 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3423 (NH), 1610 (C=N), 1552 (C=C Ar), 1418 (CH_2), 779 (C-Cl), 705 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 4.73 (1H, s, thiazole-CH_2), 4.90 (2H, s, N-NH), 7.25 (2H, s, CH=N), 8.07 (1H, d, *J* = 8.8 Hz, Ar-H), 8.09 (1H, d, *J* = 8.8 Hz, Ar-H), 8.36 (1H, t, *J* = 8.4 Hz, Ar-H), 8.38 (1H, t, *J* = 8.4 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, δ ppm): 36.1, 109.3, 115.1, 123.7, 128.3, 138.4, 147.8, 149.2, 177.4, 177.5.

2-(2-(2-Hydroxy-5-bromobenzylidene)hydrazineyl)-4-(chloromethyl)-1,3-thiazole (2c): Yield: 84%, m.p.: 201-202 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3142 (NH), 1625 (C=N), 1476 (C=C Ar), 1371 (CH_2), 818 (C-Cl), 778 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 4.17 (1H, s, N-NH), 4.64 (2H, s, thiazole-CH_2), 6.93 (1H, d, *J* = 8.8 Hz, Ar-H), 6.99 (1H, s, thiazole-H),



Compd.	R_1	R_2	R_3	R_4
a	H	H	NO_2	H
b	H	NO_2	H	H
c	OH	H	H	Br

Scheme-I: Synthesis of thiazole Schiff base analogs

7.37 (1H, dd, *J* = 8.8, 2.4 Hz, Ar-H), 7.75 (1H, d, *J* = 2.4 Hz, Ar-H), 8.29 (1H, s, CH=N), 10.54 (1H, s, OH). ^{13}C NMR ($CDCl_3$, δ ppm): 41.5, 108.8, 111.2, 118.9, 122.9, 128.0, 133.3, 138.8, 146.8, 155.7, 168.6.

Antimicrobial assay: The antimicrobial activity of synthesized compounds was estimated using the agar disk diffusion technique as previously outlined [23]. Mueller-Hinton agar (for bacteria) and potato dextrose agar (for fungi) were prepared as basal media. After incubating the media for 24 h and confirming their lack of contamination, non-contaminated dishes were chosen for the assay. Test organisms were inoculated onto the media with a sterile cotton swab. Disks containing the samples were gently positioned on pre-inoculated agar plates and then incubated at 37 ºC for 24 h (for bacteria) or at 26 ºC for 48 h (for fungi). Dimethyl sulfoxide (DMSO) served as the control in both experiments. Positive controls included ceftriaxone and amphotericin B for antibacterial and antifungal assays, respectively. Each disk held 25 µL of sample solution in DMSO, containing 300 µg of compounds. The antimicrobial and antifungal assay disks contained 10 µL of ceftriaxone/amphotericin B solution in DMSO, respectively, with 50 µg of standard compounds. After incubation, the inhibition zone diameters (mm) were measured using a calibrated scale. The study utilized two Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, two Gram-negative bacteria *Escherichia coli* and *Salmonella typhimurium* and two fungal strains *Trichoderma harzianum* and *Aspergillus niger*.

Antioxidant assay: The newly synthesized derivatives were also assessed for their antioxidant potential using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method [23]. Initially, 6 µg/mL ethanolic solution of DPPH was prepared and allowed to stir for 24 h. The derivatives, dissolved in ethyl alcohol at concentrations ranging from 500 µg/mL to 31.25 µg/mL, were separately added in 100 µL aliquots to 4.0 mL of the DPPH radical solution in individual test tubes. These tubes were then placed in a dark ice-bath. A standard solution of ascorbic acid in ethyl alcohol, prepared at equivalent concentrations, was also included for comparison. Following a brief 10 s centrifugation, each tube was incubated in darkness for 15 min. Subsequently, the absorbance of each solution at 517 nm against a blank was measured using a spectrophotometer.

The inhibition (%) of the radicals was determined using the following equation:

$$\text{Inhibition (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100 \quad (1)$$

where $A_{control}$ = absorbance of DPPH radical and A_{sample} = absorbance of DPPH with sample. The IC_{50} values for ascorbic acid and synthesized compounds were estimated from the concentration-inhibition curves.

Molecular docking studies: Computational molecular docking studies were performed using Gaussian 09, PyRx 0.8, and Pymol software to investigate the interaction between the newly synthesized derivatives and certain target receptors. The structures of synthesized derivatives were optimized through the density functional theory (DFT) method in Gaussian 09, employing the B3LYP/6-31+G(d,p) basis set [23]. These derivatives were docked against protein receptors from *E.Coli* (PDB ID: 1KZN), *S. aureus* (PDB ID: 2BV6) and antifungal receptors (PDB ID: 5JBO) to evaluate their potential antibacterial and antifungal activities, respectively. Ceftriaxone, amphotericin B served as standard compounds for the 2BV6, 1KZN and 5JBO protein receptors, respectively.

RESULTS AND DISCUSSION

In this study, three thiazole Schiff base derivatives were synthesized *via* two step reaction by introducing changes in the substituted phenyl ring. Thiazole Schiff base analogs **2a-c** was synthesized starting with the synthesis of intermediate thiosemicarbazones (**1a-c**) through the reaction between thiosemicarbazides and substituted benzaldehydes. Compounds **2a-c** were synthesized in yields ranging from 68-84% by reacting thiosemicarbazones **1a-c** with 1,3-dichloroacetone (**Scheme-I**). The synthesized Schiff base derivatives were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques. For instance, in compound **2b**, the peaks observed in the IR spectrum at 3423, 1610, 1552, 1418, 779 and 705 cm^{-1} were attributed to NH, C=N, C=C of Ar, CH_2, C-Cl and C–S–C groups, respectively. The ^{1}H NMR spectrum of compound **2b** revealed specific singlets at δ 4.73 ppm for thiazole methylene groups, while aromatic protons were detected between δ 8.07 to δ 8.38 ppm. A singlet at δ 7.25 ppm indicated the presence of –CH=N.

Antimicrobial assay: *In vitro* antimicrobial activities of the synthesized analogs were evaluated using the agar disk diffusion technique against two Gram-positive bacteria, two Gram-negative bacteria and two fungal strains. The zone of inhibition produced by both the standards and synthesized derivatives is shown in Table-1. All the compounds exhibited activity against microorganisms. Compound **2c** demonstrated a zone of inhibition measuring 17.0 ± 2.0 mm against *S. aureus* and 15.0 ± 1.0 mm against *B. subtilis*. Moreover, compound

TABLE-1
In vitro ANTIMICROBIAL DETERMINATION OF SYNTHESIZED COMPOUNDS **2a-c** WITH STANDARDS

Compd.	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*	*S. typhimurium*	*T. harzianum*	*A. niger*
2a	11.0 ± 1.0	15.0 ± 1.0	12.3 ± 1.5	13.0 ± 2.0	6.0 ± 1.0	12.0 ± 1.0
2b	14.0 ± 1.0	11.0 ± 1.0	16.7 ± 0.6	19.3 ± 1.5	22.0 ± 1.0	7.0 ± 01.0
2c	17.0 ± 2.0	14.3 ± 2.5	14.7 ± 0.6	8.0 ± 2.0	8.7 ± 2.0	7.7 ± 1.5
Ceftriaxone	40.3 ± 0.6	20.0 ± 1.0	38.3 ± 0.6	44.3 ± 0.6	–	–
Amphotericin B	–	–	–	–	17.7 ± 0.6	8.3 ± 0.6
DMSO	–	–	–	–	–	–

2b exhibited zone of inhibition 19.3 ± 1.5 mm against *S. typhimurium*. Additionally, compound **2b** exhibited the highest zone of inhibition against *T. harzianum* (22.0 ± 1.0 mm).

Antioxidant assay: The DPPH radical scavenging method was employed to assess the antioxidant effectiveness of the synthesized derivatives, with ascorbic acid serving as reference standard. The IC_{50} values of both ascorbic acid and compounds **2a-c** were determined from concentration-inhibition curves and are presented in Table-2. Ascorbic acid, used as standard, exhibited an IC_{50} value of 27.34 ± 1.86 µg/mL, indicating its antioxidant activity. All the produced compounds exhibited significant antioxidant properties, with their IC_{50} values changing depending on the specific substituents chosen.

TABLE-2
ANTIOXIDANT PROPERTIES OF SYNTHESIZED COMPOUNDS **2a-c**

Compd.	IC_{50} (µg/mL)
2a	81.14 ± 2.92
2b	66.82 ± 3.90
2c	73.64 ± 3.47
Ascorbic acid	27.34 ± 1.86

Molecular docking studies: The synthesized derivatives' structure optimization was achieved through Gaussian 09 software, employing the B3LYP/6-31+G (d,p) basis set within the DFT method and the resulting structures are depicted in Fig. 1. The 2D and 3D depictions of the non-covalent interactions between these derivatives and the target receptors can be found in the Fig. 2 and Table-3, respectively. The poses exhibiting the most negative docking scores were selected for the final analysis and presentation.

Conclusion

In this research, three thiazole Schiff base derivatives (**2a-c**) were successfully synthesized through a two-step reaction method with excellent yields. Spectral analyses confirmed the chemical structures of the synthesized analogues. Evaluation of the *in vitro* antimicrobial activity of these derivatives against several strains revealed the moderate activity compared to standard. All the synthesized compounds showed good anti-oxidant activities in DPPH radical scavenging assay. The experi-mental and *in silico* findings of the study, which might be useful in the future for designing new drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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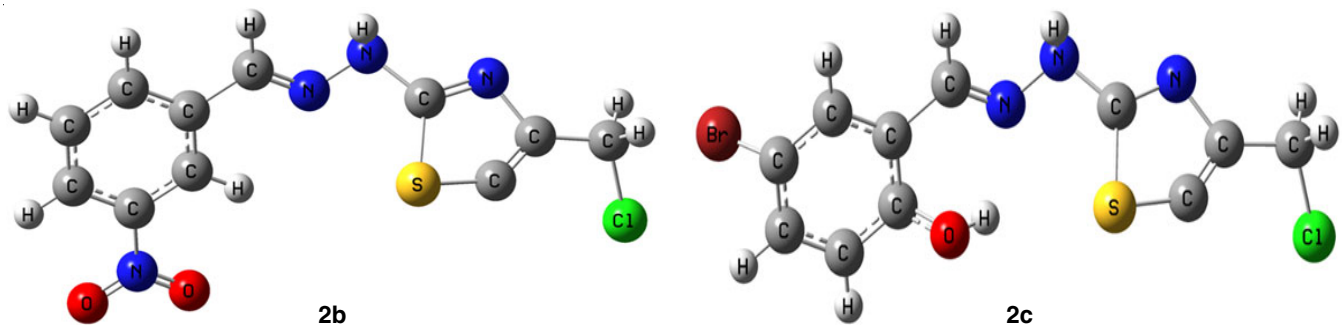

Fig. 1. Optimized molecular structures of the synthesized derivatives **2b** and **2c**

TABLE-3
PROTEIN-LIGAND INTERACTIONS WITH THE BOND DISTANCES OF 1KZN, 2BV6 AND 5JBO PROTEIN RECEPTOR AMINO ACID RESIDUES

Comp.	Protein receptor	Binding energy (Kcal/mol)	Hydrogen bond (Distance: Å)	Hydrophobic (Distance: Å)	Electrostatic (Distance: Å)
2b	1KZN	-7.0	VAL167 (2.86), ASN46 (2.86), GLU50 (2.04)	ARG76 (4.76), PRO79 (4.24), ILE78 (5.26), VAL120 (5.35)	
2c	2BV6	-5.6	VAL116 (2.73)	ALA117 (3.76), VAL116 (4.51), LEU122 (4.88), VAL22 (4.82), ALA119 (5.38), ALA18 (5.43), VAL22 (5.46), VAL116 (4.96), LEU130 (5.27)	
2b's	5JBO	-8.2	TRP442 (2.97), TYR316 (3.81)	TYR316 (4.73), TRP357 (4.63), TRP357 (4.07), TRP434 (4.91), PHE450 (5.74), TRP357 (4.79), TRP357 (4.50)	GLU384 (3.87), GLU441 (3.96)

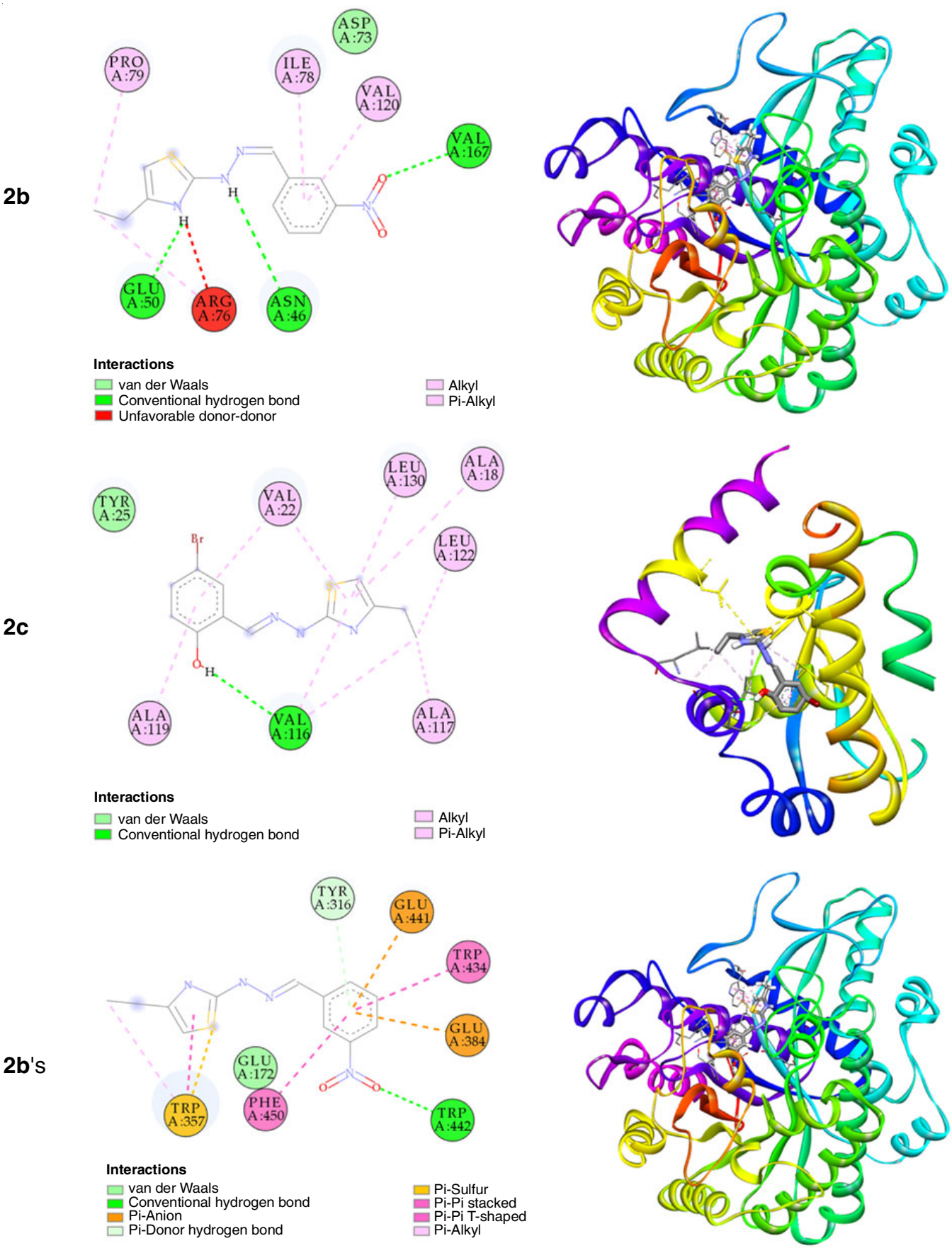

Fig. 2. Studies of **2b**, **2c** and **2b**'s molecular docking against the 2BV6, 1KZN and 5JBO protein receptors, respectively. Sketches of 2D interaction (a), Predictions for 3D docking (b)

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