S-Benzyl-L-cysteine Based Schiff bases Containing Peptide Groups: Design, Synthesis, Characterization, Cyclic Voltammetry, Antimicrobial and Molecular Docking Studies

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Abstract. New Schiff bases, **5a-5d** have been synthesized by the condensation of L-2-amino-3-(benzylthio)-N-(3,4-dimethoxyphenethyl)propanamide (**4**) with substituted aldehydes such as 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, Orthovanillin and 3,5-ditertbutylsalicylaldehyde. The compounds were characterized by elemental and spectroscopic analysis. The antibacterial and antifungal activities of **5a-5d** against pathogenic microbial strains revealed that they showed a considerable growth of inhibition. The *insilico* studies of **5a-5d** within the active site of DNA Gyrase (PDB: 3G75) showed a favorable binding energies (-5.78 to -6.64 kcal/mol). Similarly, molecular docking with N-Myristoyl transferase (PDB: 1IYL) exhibited binding energies between -10.72 and -11.85 kcal/mol. Notably, compounds participated in hydrogen bonding with the target.

Keywords: Schiff base, synthesis, spectroscopy, antimicrobial, molecular docking

1. Introduction

During the last 3 to 4 decades a range of biologically active peptide compounds were identified and studied thoroughly. The search for drug-like target compounds in synthetic organic chemistry entails replacing the natural amino-acid groups in peptides. The design of peptidomimetic compounds, which are anticipated to have the same therapeutic effects as their natural peptide counterparts with the added benefit of metabolic stability, and drug design are two areas in which this research is highly fascinating [1-4].

Many biological activities, which include antibacterial, antiviral, antifungal, anti-malarial, antioxidant, cytotoxic, pesticidal, enzyme inhibitory, and anticancer, inclusive of DNA damage, had been suggested to be displayed with the aid of Schiff bases and their metallic complexes when used therapeutically [5-16].

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The biological activities of Schiff bases generated from physiologically significant molecules, like isatin, 2-azetidinone, and cephalothin, are being studied [17]. Although, amino acid and 2-(3,4-dimethoxyphenyl)ethanamine have been utilized very recently to create Schiff bases [18]. Hence, we have reported herein the synthesis, cyclic voltammetry and molecular docking study of new aminoacid amide based Schiff bases compounds **5a-5d** by using L-2-amino-3-(benzylthio)-N-(3,4-dimethoxyphenethyl)propanamide (**4**) with respective salicylaldehyde derivatives. The compounds were characterized by elemental and spectroscopy studies. Further, the antimicrobial studies of **5a-5d** are asessed [18].

2. Experimental

2.1 Materials and methods

Orthovanillin, substituted salicylaldehydes, boc-L-benzyl cysteine and N, N'-dicyclohexyl carbodiimide (DCC) were purchased from Merck (India) Pvt. Ltd. The reactions were monitored by Merck 60 F_{254} TLC aluminum sheets. Elemental composition was analyzed using a LECO–CHNSO–9320 analyzer, and UV-Visible spectral data were collected with an Agilent Cary-60 spectrophotometer (200-800 nm spectral range). The FT-IR spectra were obtained using Perkin Elmer Frontier MIR/FIR spectrometer (ATR method). The cyclic voltammetry studies were performed by using CHI608E model potentiostat with a standard 3 electrode cell (glassy carbon working electrode, platinum wire counter electrode, and Ag/AgCl reference electrode) in CH_3CN with 0.1M $^tBu_4N(PF_6)$ as supporting electrolyte. ^{1}H- and ^{13}C-NMR spectra were recorded by using Agilent VNMRS-400 and Bruker WM-400 NMR spectrophotometers TMS as an internal standard. The antimicrobial activity was assessed using micro dilution technique. Using Biosolve IT and GOLD 5.1, *Insilico* studies were conducted on all the synthesized Schiff bases.

2.2 Procedure for the preparation of Schiff bases (5a-5d).

A methanol solution of L-2-amino-3-(benzylthio)-N-(3,4-dimethoxyphenethyl)propanamide (**4**) (1.0 mmol) added to respective salicylaldehydes (1.0 mmol), 5-chlorosalicylaldehyde/5-bromosalicylaldehyde/orthovanillin/3,5-ditertbutylsalicylaldehyde, stirred for 2-3 hrs at RT. After completion of the reaction the solvent was removed using a rotary evaporator to yield a yellow compound of **5a-5d**.

5a: Yield: 88%; m.p. 78-80˚C; Elemental Anal. Calcd. (Found) for $C_{27}H_{29}N_2O_4SCl$: C, 63.21 (63.25); H, 5.70 (5.72); N, 5.46 (5.50); UV-vis (λ_{max} nm): 332, 436; FT-IR (ATR, $\bar{\upsilon}$ cm^{-1}): 3385, 2920, 2840, 1657, 1633, 1541, 1511, 1262, 1237, 1141, 1027, 916, 810, 760, 700, 640, 599; ^{1}H NMR (399.82 MHz, $CDCl_3$, δ ppm): 12.152 (s, 1H, O-H), 8.040 (s, 1H, >CH=N), 7.295-7.335 (m, 2H, H21, H25), 7.237-7.278 (m, 3H, H22, H23, H24), 6.932-6.954 (d, 2H, H15, H14), 6.740-6.840 (m, 1H, H17), 6.641-6.652 (m, 3H, H6, H9, H10), 6.019 (s, 1H, NHCO), 3.842-3.857 (m, 1H, CH), 3.806 (s, 6H, OCH_3), 3.637-3.713 (d, 2H, H19), 3.428-3.551 (m, 2H, NCH_2), 3.155-3.198 (dd, 1H, H18), 2.767-2.825 (m, 1H, H18), 2.721-2.755 (t, 2H, H4); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, δ ppm): 168.95 (C2), 166.82 (C11), 158.67 (C13), 148.59 (C7), 147.30 (C8), 137.58 (C20), 132.72 (C5), 130.84 (C12), 130.26 (C15), 128.47 (C17), 128.14 (C25, C21), 126.76 (C22, C24), 123.46 (C23), 120.15 (C6), 118.24 (C14), 111.21 (C10), 110.84 (C9), 76.58 (C1), 55.344 (OCH_3), 55.305 (OCH_3), 40.22 (C3), 36.68 (C4), 35.86 (C18), 34.54 (C19).

5b: Yield: 90%; m.p. 80-82 ˚C; Elemental Anal. calcd. (found) for $C_{27}H_{29}N_2O_4SBr$: C, 58.17 (58.20); H, 5.24 (5.20); N, 5.02 (5.09); UV-vis (λ_{max} nm): 329, 433; FT-IR (ATR, $\bar{\upsilon}$ cm^{-1}): 3343, 2956, 2876, 1647, 1620, 1512, 1437, 1362, 1232, 1156, 1031, 804, 764, 707, 642; ^1H NMR (399.821 MHz, $CDCl_3$, δ ppm): 12.175 (s,1H, OH), 8.037(s,1H, >CH=N), 7.450-7.478 (d, 1H, H23), 7.376-7.382 (d, 1H, H15), 7.260-7.319 (m, 4H, H21, H22, H24, H25), 7.224-7.240 (m,1H, H17), 6.890-6.912 (d, 1H, H14), 6.642-6.654 (m, 3H, H6, H9, H10), 5.998 (bs, 1H, NHCO), 3.847-3.861 (m, 1H, CH), 3.811 (s, 3H, OCH_3), 3.787 (s, 3H, OCH_3), 3.673-3.682 (d, 1H, H19), 3.447-3.537 (m, 2H, NCH_2), 3.159-3.202 (dd, 1H, H18), 2.767-2.824 (dd, 1H, H18), 2.723-2.757 (t, 2H, H4); ^{13}C {^1H} NMR (100, $CDCl_3$, δ ppm): 168.94 (C2), 166.74 (C11), 159.67 (C13), 148.70 (C7), 147.32 (C8), 137.58 (C20), 135.54 (C5), 133.85 (C12), 130.23 (C15), 128.46 (C17), 128.14 (C25,C21), 126.77 (C22, C24), 120.14 (C23), 119.14 (C6), 118.67 (C16), 111.20 (C14), 110.85 (C10), 110.29 (C9), 76.53 (C1), 55.36 (OCH_3), 55.31 (OCH_3), 40.21 (C3), 36.69 (C4), 35.88 (C18), 34.53 (C19).

5c: Yield: 85%; m.p. 79-82 ˚C; Elemental Anal. calcd. (found) for $C_{28}H_{32}N_2O_5S$: C, 66.12 (66.15); H, 6.34 (6.30); N, 5.51 (5.55); UV-vis (λ_{max} nm): 330.3, 440; FT-IR (ATR, $\bar{\upsilon}$ cm^{-1}): 3367, 2994, 2931, 2836, 1667, 1622, 1512, 1460, 1247, 1139, 1025, 765, 698, 628; ^1H NMR (399.821 MHz, $CDCl_3$, δ ppm): 12.630 (s, 1H, OH), 8.170 (s, 1H, >CH=N), 7.267 (bs, 5H, H21, H22, H23 H24, H25), 6.994 (m, 1H, H16), 6.910 (bs, 2H, H15, H17), 6.665 (s, 3H, H6, H9, H10), 6.169 (bs, 1H, NHCO), 3.924 (s, 3H, OCH_3), 3.801 (s, 3H, OCH_3), 3.778 (s, 3H, OCH_3), 3.709 (m, 1H, CH), 3.670 (bs, 2H, H19), 3.424-3.503 (m, 2H, NCH_2), 3.154-3.187 (m, 1H, H18), 2.775-2.832 (m, 2H, H18), 2.724 (t, 2H, H4); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, δ ppm): 169.28 (C2), 168.08 (C11), 150.20 (C13), 148.598 (C14), 147.85 (C7), 147.22 (C8), 137.61 (C20), 130.39 (C5), 128.48 (C12), 128.08 (C15), 126.65 (C25, C21), 123.244 (C22, C24), 120.19 (C23), 118.47 (C6), 117.82 (C16), 114.56 (C17), 111.22 (C10), 110.90 (C9), 76.534 (C1), 55.67 (OCH_3), 55.30 (OCH_3), 55.30 (OCH_3), 40.38 (C3), 36.71 (C4), 35.98 (C18), 34.75 (C19).

5d: Yield: 88%; m.p. 84-85 ˚C; Elemental Anal. calcd. (found) for $C_{35}H_{46}N_2O_4S$: C, 71.15 (71.20); H, 7.85 (7.82); N, 4.74 (4.79); UV-vis (λ_{max} nm): 331, 430; FT-IR (ATR, $\bar{\upsilon}$ cm^{-1}): 3376, 2928, 2839, 1655, 1633, 1534, 1513, 1480, 1258, 1232, 1138, 1023, 831, 809, 763, 704, 633, 598; ^1H NMR (399.821 MHz, $CDCl_3$, δ ppm): 12.668 (s,1H, OH), 8.192 (s, 1H, >CH=N), 7.466-7.471 (d, 1H, H23), 7.275-7.360 (m, 2H, H21, H25), 7.204-7.259 (m, 2H, H22, H24), 7.103-7.108 (d,1H, H15), 6.756- 6.804 (m,1H, H17), 6.659-6.708 (m, 3H, H6, H9, H10), 6.212-6.239 (t, 1H, CONH), 3.838-3.863 (m, 1H, CH), 3.752 (s, 3H, CH_3), 3.723 (s, 3H, OCH_3), 3.688 (s, 2H, H19), 3.407-3.607 (m, 2H, NCH_2), 3.157-3.200 (dd, 1H, H18), 2.796-2.879 (dd, 1H, H18), 2.733-2.767 (t, 2H, H4), 1.391-1.430 (s, 9H, ^{t}Bu), 1.323 (s, 9H, ^{t}Bu); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, δ ppm): 169.59 (C2), 169.26 (C11), 157.21 (C13), 148.65 (C7), 147.26 (C8), 140.50 (C20), 137.66 (C5), 137.11 (C12), 136.49 (C15), 131.39 (C17), 128.52 (C25), 128.06 (C21), 127.83 (C22), 127.36 (C24), 126.62 (C23), 126.39 (C14), 120.36 (C16), 116.99 (C6), 111.76 (C9), 110.80 (C10), 73.27 (C1), 55.44 (OCH_3), 55.29 (OCH_3), 40.34 (C3), 36.66 (C4), 35.95 (C18), 34.69 (C19), 34.33 (^{t}Bu), 33.72 (^{t}Bu), 30.96 (^{t}Bu), 28.95 (^{t}Bu).

2.3 Antimicrobial activity

The antimicrobial activity of **5a-5d** were screened by using agar well diffusion method [19] as per the reported procedure [23] against 4 bacteria (Gram -ve bacteria: *K. aerogenes*, *E. coli*, *P.*

desmolyticum; Gram +ve bacteria: *S. aureus*) and 2 fungi (*A. flavus* and *C. albicans*) and the reulted values were tabulated.

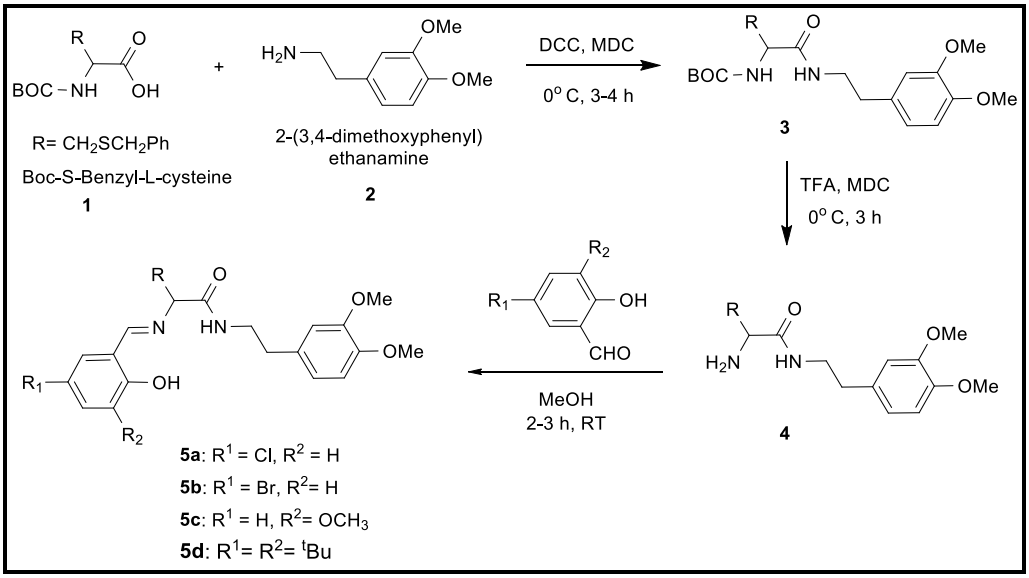
2.4 Molecular docking

The docking calculation of **5a-5d** was carried out using HP Intel® xenon® processor E3-1200v2. Accelrys Discovery studio client 3.5 was used for docking preparation, Biosolve IT and GOLD 5.1 are docking software's used for binding energy calculation.

3. Results and discussion

3.1 Synthesis

The compound **4** was synthesized as per the related reported procedure [20]. The Schiff's bases (**5a-5d**) were obtained by the condensation reaction of compound **4** with various salicylaldehyde derivatives such as 5-chloro salicylaldehyde, 5-bromo salicylaldehyde, and orthovanillin in 1:1 equimolar ratio as given in **Scheme 1**. The Schiff's base (**5a-5d**) are obtained as yellow solid and are freely soluble in $CHCl_3$, C_2H_5OH, CH_3OH, CH_2Cl_2, DMSO and DMF. The compounds were purified by recrystallization by using 1:1 solvent mixture of $CHCl_3$ and n-hexane. The structures of **5a-5d** were represented in **Chart 1**.



Scheme 1 Synthesis of **5a-5d**

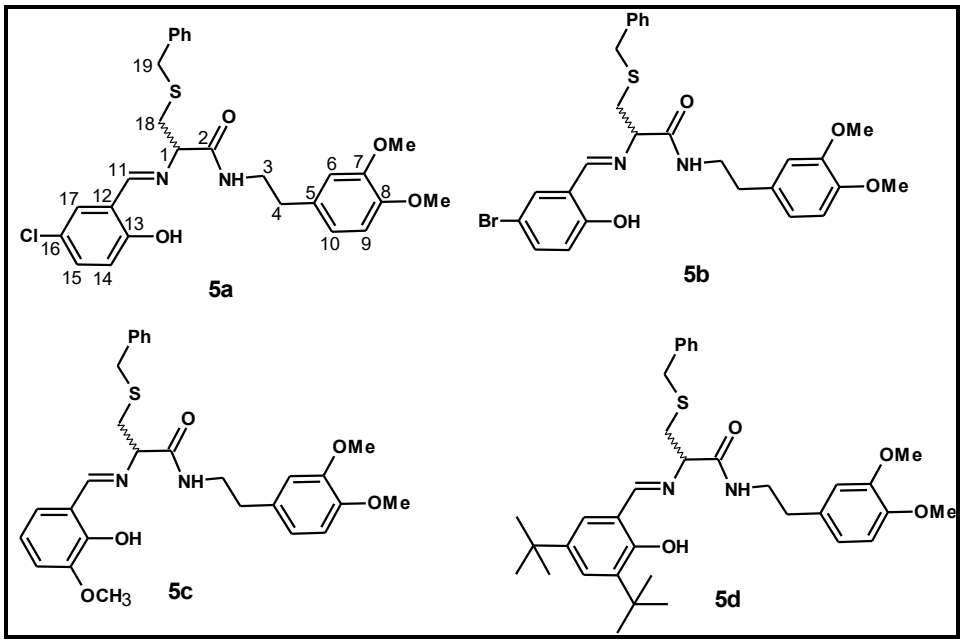


Chart 1. Structure of **5a-5d**

3.2 UV-Visible Spectra

The UV–Visible spectral data of **5a-5d** (2.5×10^{-5} M) have been recorded in DMSO solvent and are shown in **Fig. 1**. The intense absorption bands observed at around λ_{max}, 330 nm due to the n→π* and π→π* transitions within the delocalized π-system. The less intense bands appeared at λ_{max}, 430-435 nm, which were due to the charge transfer transitions within the delocalized π-system.

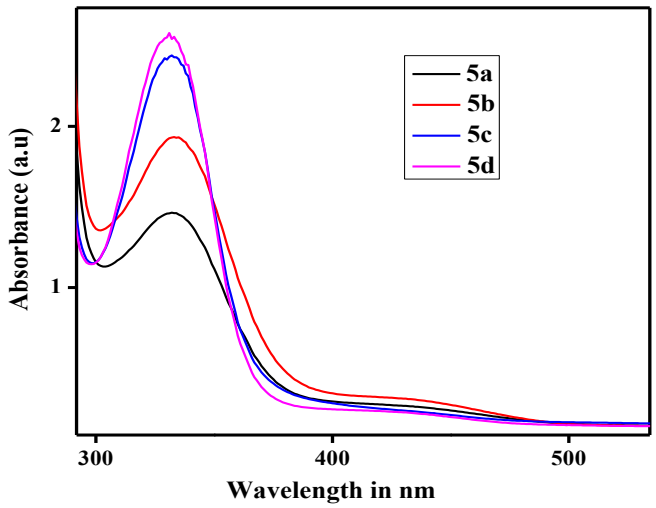
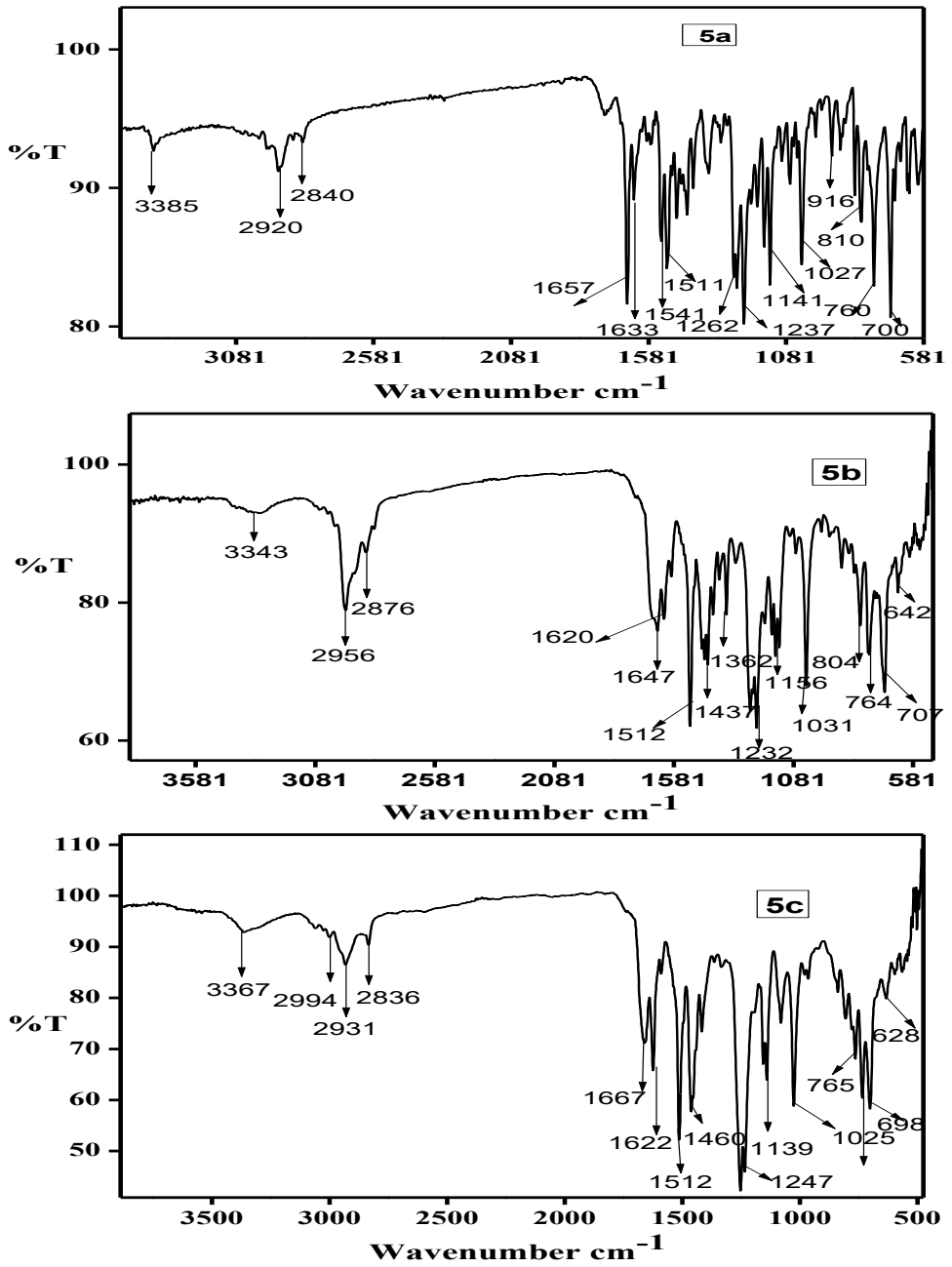


Fig. 1 UV-Visible spectra of the compounds **5a-5d**

3.3 FT-IR Spectroscopy

In FT-IR spectra of **5a-5d** (**Fig. 2**), the N-H and >C=N- stretching bands were observed in the range of ῡ, 3345-3385 cm^{-1} and 1620-1635 cm^{-1} respectively. The amide >C=O stretching bands are observed around ῡ, 1645-1670 cm^{-1} and the band around ῡ, 1230-1260 cm^{-1} appeared due to the C-O stretching. [20,22,23]



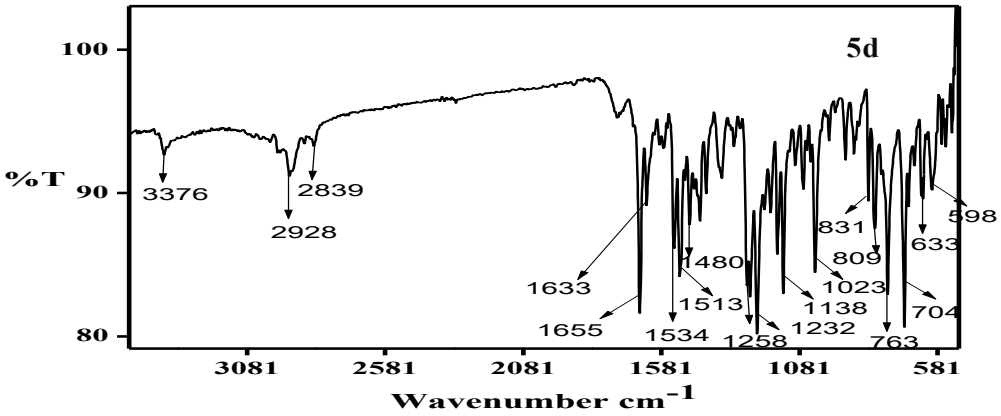
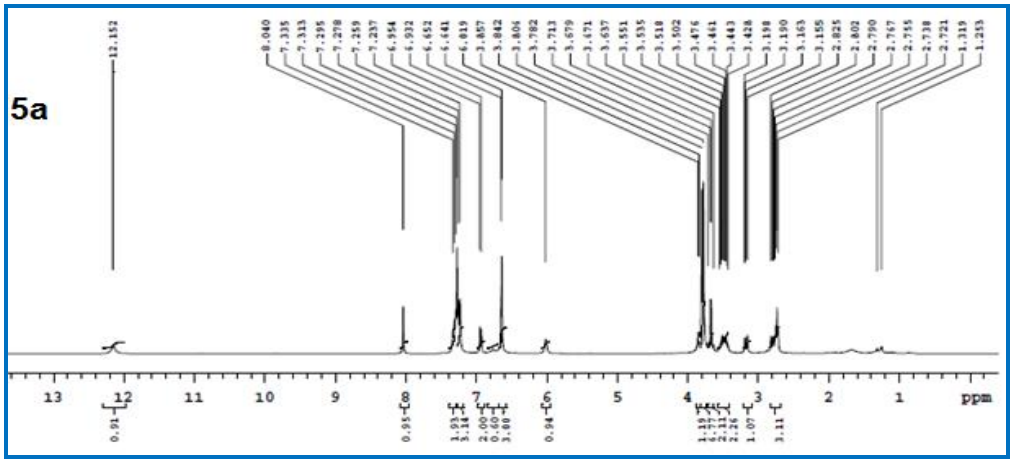


Fig. 2 FT-IR spectra of **5a-5d**

3.4 NMR Spectroscopy

In ^{1}H-NMR spectra of **5a-5d** (**Fig. 3**), the OH peak appeared at around δ, 12-12.5 ppm and found deshielded due to Ar-O-H···N=C< hydrogen bonding interaction. The $ArCH_2$ and CH_2N protons found as triplets at around δ, 2.73-2.77 and 4.64-3.59 ppm respectively. The imine -N=CH- proton found as a singlet at around δ, 7.90-8.35 ppm whereas CO-NH- proton appeared as a triplet at δ, ~6 ppm respectively in **5a-5d**. The peaks for other protons in **5a-5d** found at their characteristic δ ppm.

In ^{13}C-NMR spectra of **5a-5d** (**Fig. 4**), the benzylic carbon (Ar-CH_2) signal was found at δ, ~35 ppm while the N-CH_2 carbon observed at δ, ~40 ppm. The -N=C and CO-N carbon peaks appeared at δ, ~170 ppm and the C-OH carbon found at δ, 150-159 in all **5a-5d**. The H^1 and ^{13}C-NMR spectral data correlated with the respective structure of **5a-5d**.



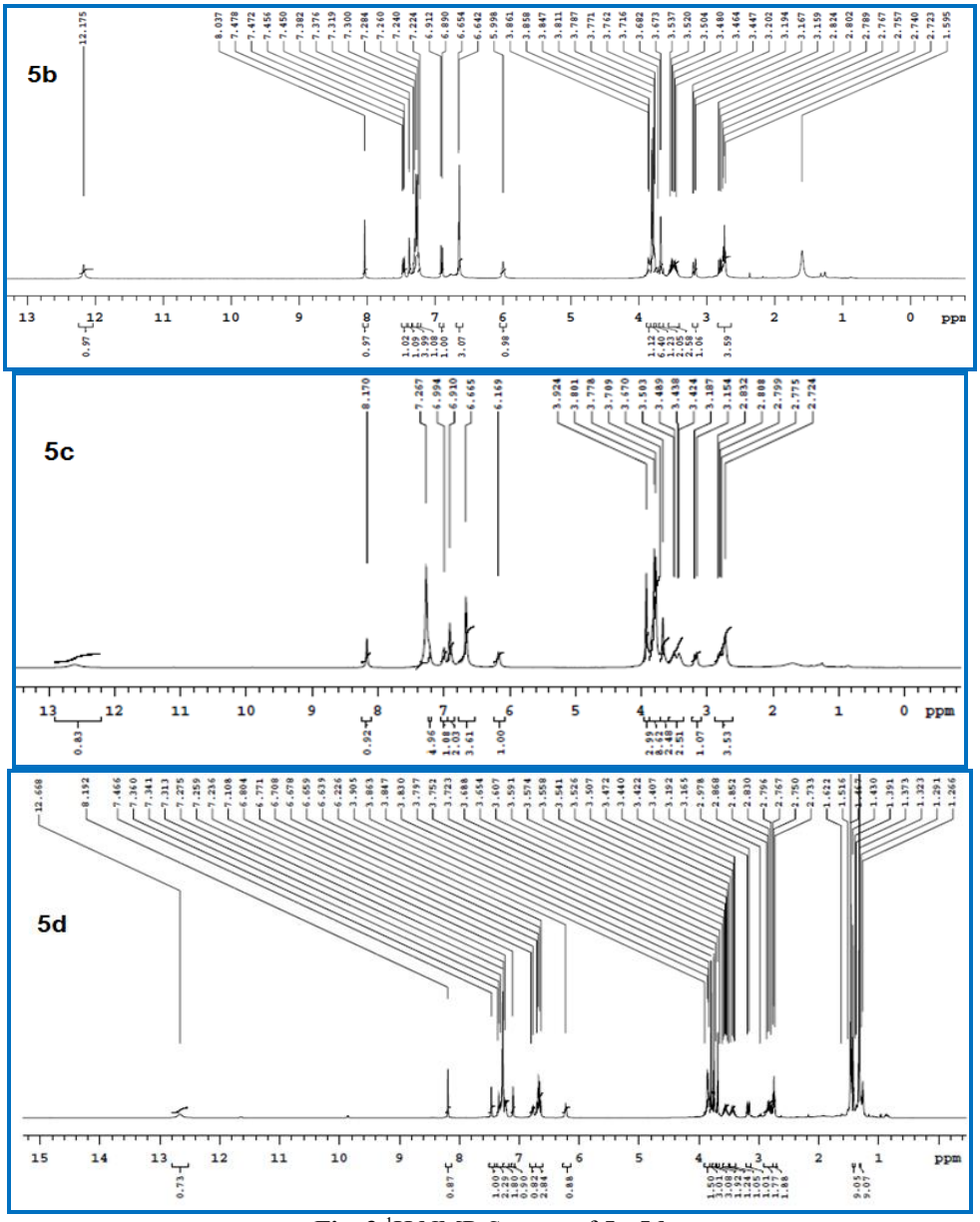


Fig. 3 ^{1}H NMR Spectra of **5a-5d**

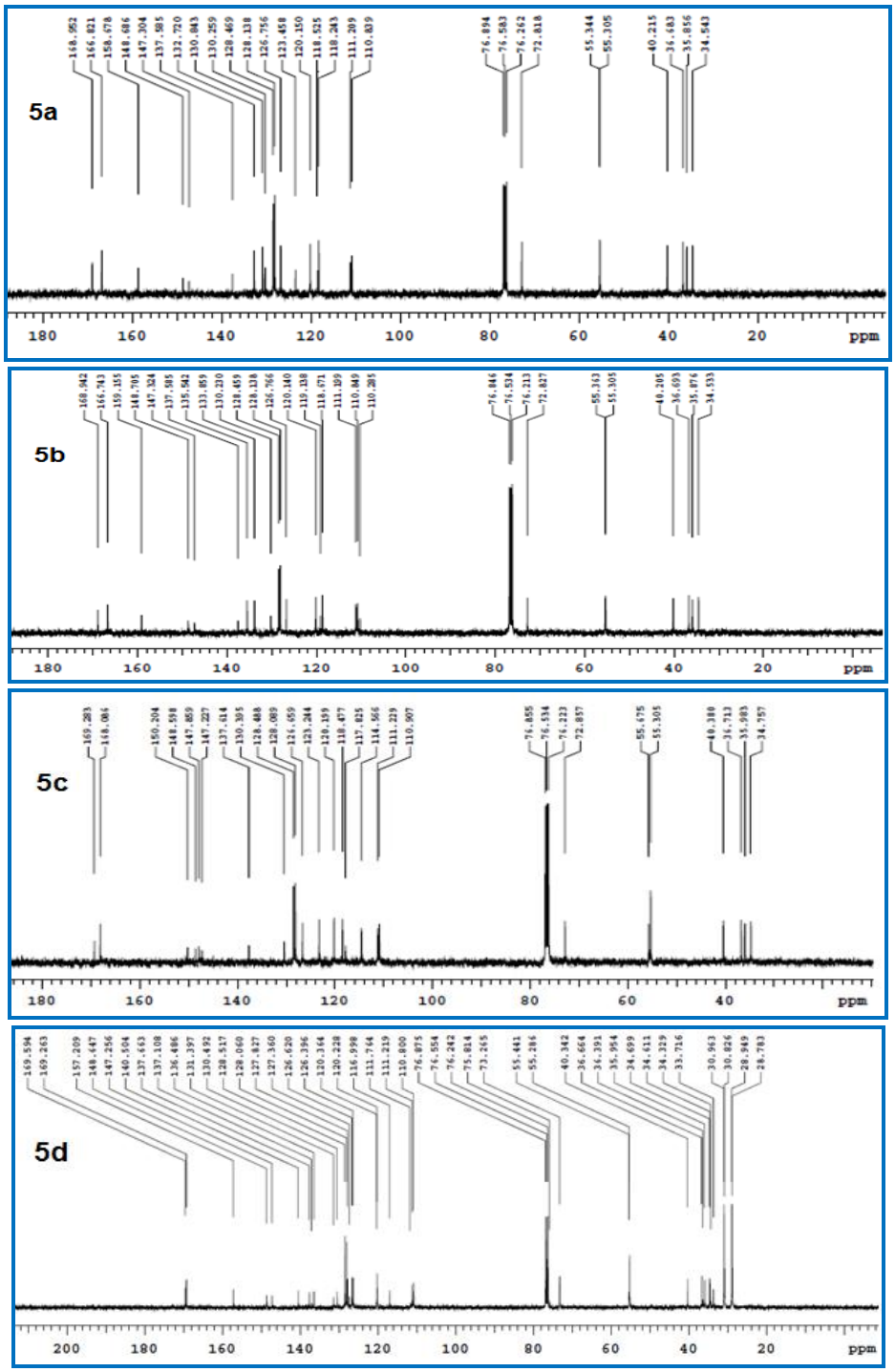


Fig. 4 $^{13}C\{^{1}H\}$ NMR Spectra of **5a-5d**

3.5 Cyclic voltammetry (CV)

The CV of **5a-5d** were studied as per the reported procedure [21]. In **5a-5d** (**Fig. 5**), the two oxidation peaks (Eox) were observed for compounds, **5a** (+0.457V, +0.861V) and **5b** (+0.457V, +0.861V) whereas **5c** (+1.094V) and **5d** (+1.311V) have been showed only one oxidation peak but there was no observable reduction peaks. The energy of HOMO and LUMO were determined based on oxidation potential and band gap respectively, and were calculated corresponding to the onset λ_{max} as given in the **Table 1**.

Table 1. UV-Visible and CV data of **5a-5d**

Compound	5a	5b	5c	5d
λ_{max} (nm)	332.438	332.434	333.435	331.435
E_{ox} (V)	+0.457; +0.861	+0.525; +0.982	+1.094	+1.311
E_{red} (V)	-0.658	-0.619	-0.636	-0.674
E_{HOMO} (eV)	-5.261	-5.382	-5.494	-5.711
E_{LUMO} (eV)	-1.538	-1.662	-1.782	-1.971
E_g (eV)	3.723	3.720	3.712	3.741

E_{HOMO} = - (E_{ox} (Fc/Fc$^+$) + 4.8) eV, Fc/Fc$^+$= 0.4; E_{LUMO}= E_{HOMO} + E_g; Band gap, E_g = 1240/$\lambda_{max.}$

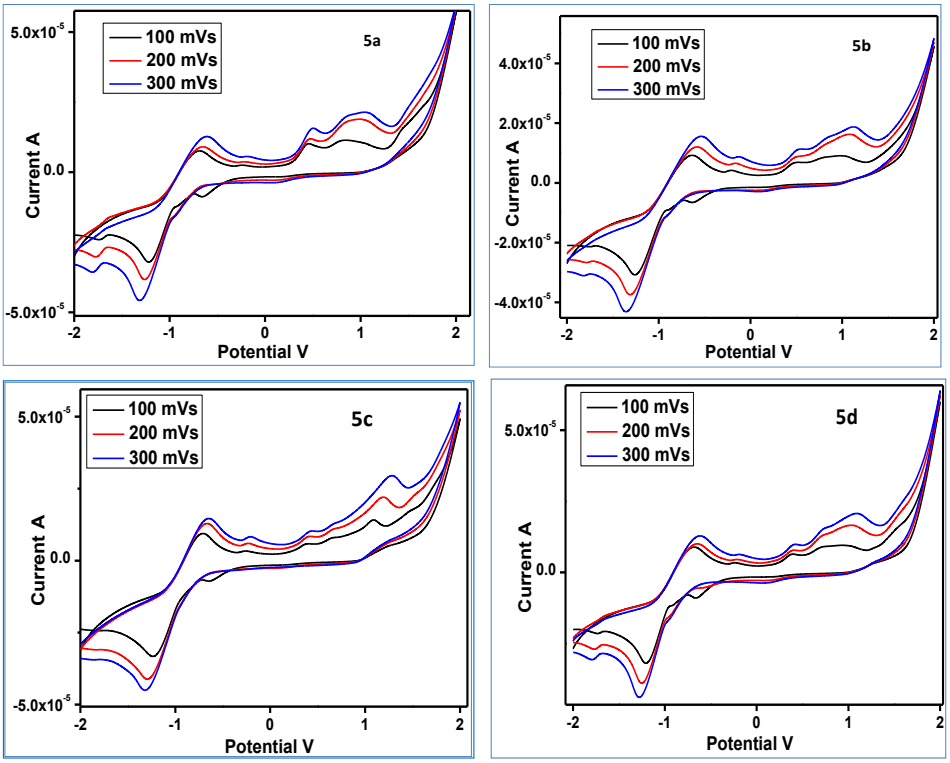


Fig. 5 Cyclic Voltammetry of **5a-5d** scan rate of 100-300 mV/s

3.6 Antimicrobial activity and antifungal activity

The inhibition values of **5a-5d** shown appreciable antibacterial and antifungal activities [22] and corresponding results were tabulated in **Table 2** and **3** and their graphical representations are given in **Fig. 6**.

Table 2 Antibacterial activities of **5a-5d**

Compound	Treatment ($\mu g/\mu L$)	*K.aerogenes* (Mean ± SE)	*E. coli* (Mean ± SE)	*S. aureus* (Mean ± SE)	*P. desmolyticum* (Mean ± SE)
Cipro	5/50	14.67 ± 0.03	11.67 ± 0.05	15.00 ±0.03	13.67 ± 0.03
5a	500/50	1.50 ± 0.03	1.35 ± 0.01	1.25 ± 0.00	1.80± 0.01
	1000/100	2.90 ± 0.23	2.70± 0.17	2.55 ± 0.07	3.00 ± 0.17
5b	500/50	1.60 ± 0.00	1.50 ± 0.00	1.75 ± 0.00	2.10 ± 0.00
	1000/100	2.90 ± 0.09	2.80 ± 0.06	3.10 ± 0.00	3.40 ± 0.17
5c	500/50	1.80 ± 0.02	1.60 ± 0.06	1.90 ± 0.07	2.50 ± 0.00
	1000/100	3.50 ± 0.07	3.20 ± 0.02	3.55 ± 0.07	4.10 ± 0.03
5d		2.10 ± 0.02	2.00 ± 0.02	2.30 ± 0.00	2.60 ± 0.02
		4.20 ± 0.01	4.10 ± 0.01	4.50 ± 0.01	4.70 ± 0.00

Values are the mean ± SE of zone of inhibition in mm, Cipro: Ciprofloxacin

Table 3. Antifungal activities of **5a-5d**

Sample	Treatment ($\mu g/\mu L$)	*A. flavus* (Mean ± SE)	*C. albicans* (Mean ± SE)
Fluconazole	200/50	10.30 ± 0.03	11.60 ± 0.06
5a	250/25	1.80 ± 0.00	1.90 ± 0.03
	500/50	2.40 ± 0.06	2.80 ± 0.03
5b	250/25	1.65 ± 0.03	1.85 ± 0.01
	500/50	2.40 ± 0.03	2.60 ± 0.02
5c	250/25	1.95 ± 0.00	2.00 ± 0.03
	500/50	2.90 ± 0.03	3.00± 0.03
5d	250/25	2.10 ± 0.00	2.80 ± 0.01
	500/50	3.20 ± 0.02	3.50 ± 0.02

Values are the mean ± SE of zone of inhibition in mm

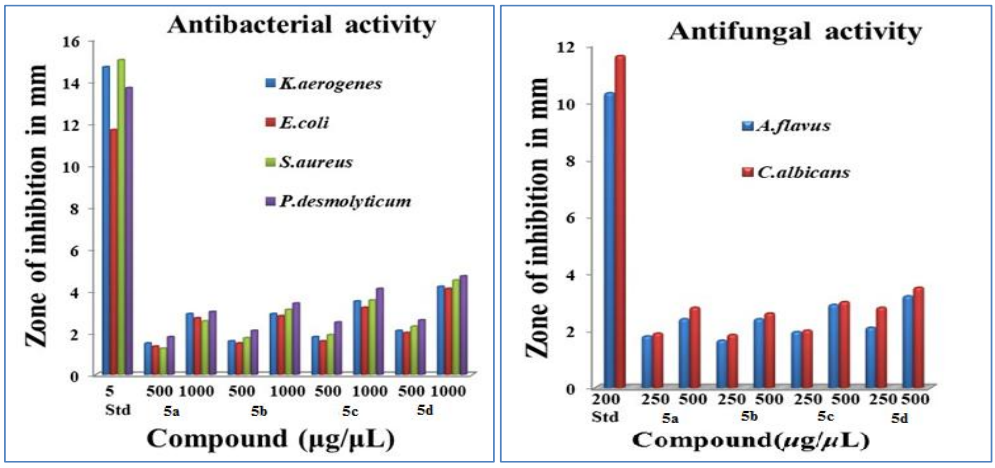


Fig. 6 Antibacterial and Antifungal activity of **5a-5d**

3.7 *Insilico* studies

The **5a-5d** structures were drawn using Chemdraw and optimization was achieved as per the reported method [24,25]. The refined molecules of ligands and protein docked using DS 3.5 which is based on the FlexX docking approach. The interaction modes between the **5a-5d** with protein were studied using Biosolve IT FlexX and the results are tabulated in **Table 4** and **5**. The binding mode analyses of the compounds are given in **Fig. 7**.

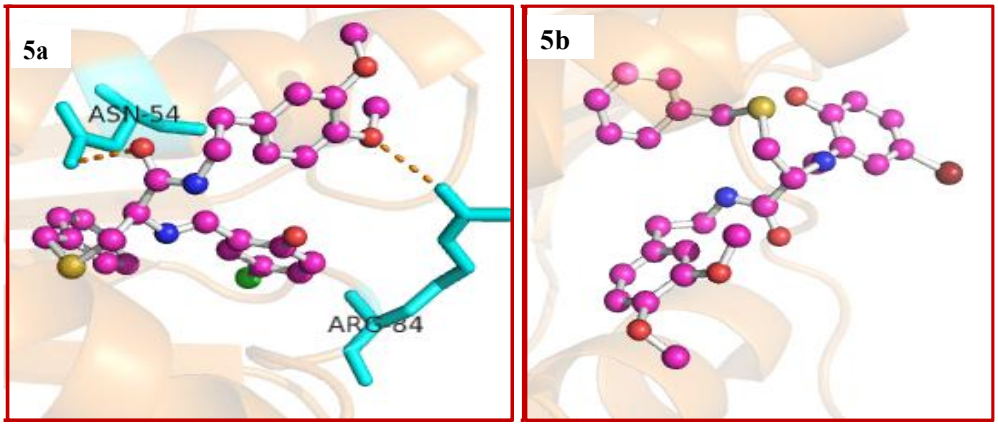
Table 4 Docking results of **5a-5d** against 3G75 target

Comp.	Pose	Binding Energy (delta G)	No. of interactions	H bonding
5a	2	-5.78	2	Asn-392, Tyr-225
5b	8	-6.64	1	Tyr-225
5c	3	-5.9	2	His-227, Asn-392
5d	8	-6.05	0	

Table 5 Docking results of **5a-5d** against 1IYL target

Comp.	Pose	Binding Energy (delta G)	No. of Interactions	H bonding
5a	10	-11.34	2	Asn-392, Tyr-225
5b	4	-10.75	1	Tyr-225
5c	10	-10.72	2	His-227, Asn-392
5d	5	-11.85	0	

The docking of **5a-5d** into the active site of target protein 3G75 and 1IYL revealed that the compounds showing binding energy of -5.78 to -6.64 and -10.72 to -11.85 kcal/mol. The compounds **5a, 5b and 5d** are involved in the hydrogen bonding with target. The binding poses of the compounds with 3G75 and 1IYL are given in **Fig. 7** and **8** respectively.



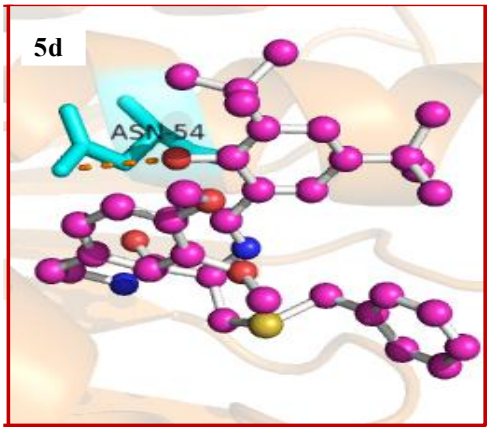


Fig. 7 Binding pose of **5a, 5b and 5d** with DNA gyrase target

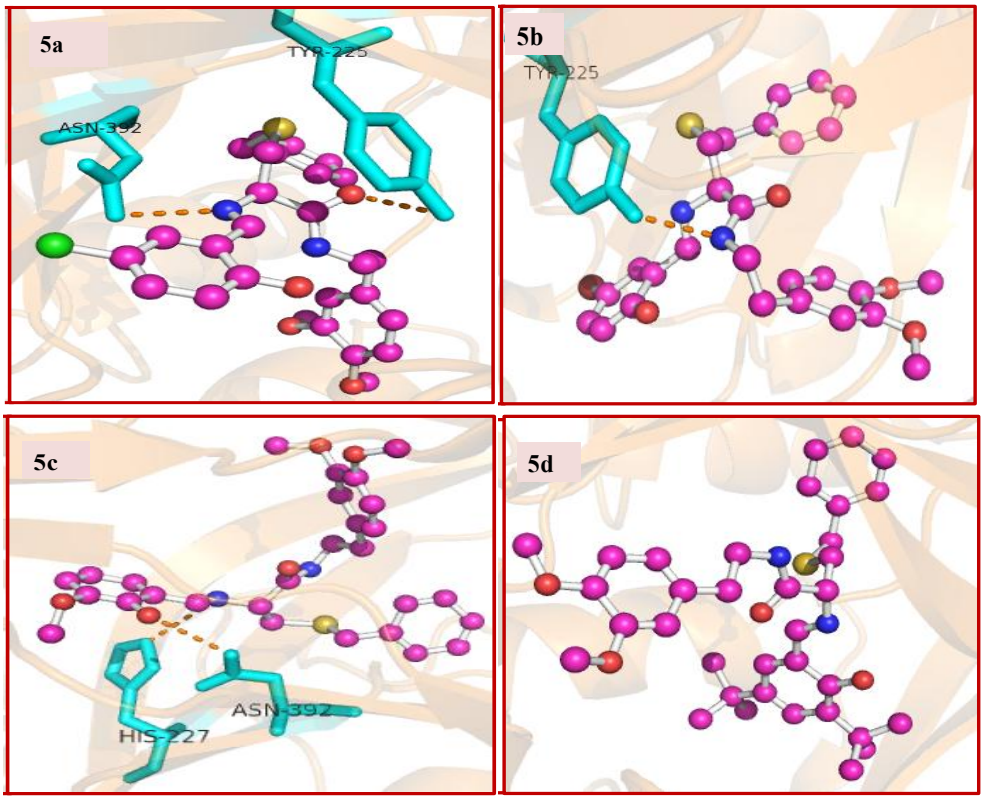


Fig. 8 Binding pose of **5a-5d** with N-myristoyl synthase transferase

4. Conclusion

The *S*-benzyl-L-cysteine based Schiff base compounds, **5a-5d** have been synthesized via condensation of L-2-amino-3-(benzylthio)-N-(3,4-dimethoxyphenethyl)propanamide (**4**) with salicylaldehyde derivatives and characterised by FT-IR, UV–Visible, Cyclic voltammetry, ^{1}H- and ^{13}C{^{1}H}-NMR spectroscopy. Docking simulations of **5a-5d** revealed the favorable binding interactions within the active site of the target protein, with binding energies in the variety of -5.78 to -6.64 kcal/mol. Moreover, docking into the fungal goal protein validated even more potent binding affinities, with energies spanning from -10.72 to -11.85 kcal/mol. Hydrogen bonding analysis suggested that the compounds **5a–5c** form interactions with the goal protein besides **5d.**

Conflicts of Interest

The authors declare that they have no competing interests

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