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Synthesis, characterization, antimicrobial and antioxidant screening of novel oxazepines

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Oxazepines **4a-e** have been synthesized by condensing aromatic aldehydes with sulfamethoxazole in the presence of chloroform and methanol, resulting in the formation of Schiff bases **3a-e**. The Schiff bases have been subsequently condensed with maleic anhydride in dry benzene. The synthesis has been validated through FT-IR, ^{1}H NMR, mass spectrometry and elemental analysis. The compounds of interest have been assessed for their antimicrobial properties against *Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli* and *Staphylococcus aureus* through the Kirby-Bauer disc diffusion technique. Furthermore, the fluorescence method has been employed to screen for antioxidant activity. The pharmacokinetics of the compounds have been evaluated using computational studies conducted through SwissADME. Additionally, molecular docking studies have been performed on thymidylate synthase A, revealing that the compounds exhibit favorable interactions with the target.

Keywords: Oxazepines, Schiff base, Antibacterial, Antioxidant, ADME, Molecular docking

The extensive biological activity of Schiff bases has been evidenced, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral and antipyretic properties[1,2]. Sulfonamides, one of the most prevalent and long-established classes of synthetic antibiotics, prominently feature sulfamethoxazole as a key representative[3]. Sulfamethoxazole is effective not only for respiratory tract infections and urinary tract diseases but also for treating sinusitis. It is commonly utilized alongside other antimicrobials, like trimethoprim, in human medicine[4,5]. Oxazepines possess significant pharmacological, therapeutic and biological applications, highlighting their importance in the field of medicine[6]. Oxazepine derivatives are advantageous in the treatment of anxiety and have been linked to schizophrenia. A combination of pharmaceuticals known as 7-hydroxyamoxapine has been demonstrated to impact the central nervous system (CNS)[7]. Oxazepine derivatives have demonstrated a wide range of biological activities, including antibacterial[8], antifungal[9], hypnotic muscle relaxant[10], antagonistic[11], anti-inflammatory[12], telomerase inhibitors[13] and antiepileptic effects[14]. Fused oxazepines, also referred to as benzoxazepine, exhibit a broad range of bio-medicinal properties, including anti-epileptic[15], antagonist[16], progesterone agonist[17], analgesic[18], anti-histaminic[19], anti-psychotic[20,21], anxiolytics[22], anti-aggregating[23] and tyrosine kinase inhibitory[24] effects on the epidermal growth factor receptor (EGFR). The objective of this investigation is to synthesize and assess the biological activity of the obtained oxazepine derivatives.

Experimental Section

The raw material obtained from BLD Pharmatech (India) Pvt Ltd was used without additional purification. TLC was employed to observe the reaction, which was carried out on silica gel plates. Infrared spectra were obtained and analyzed in the 4000–400 cm^{-1} range using a Shimadzu spectrophotometer with a KBr pellet. ^{1}H NMR spectra were obtained at 25°C utilizing a Bruker Ultra Shield 500 MHz spectrometer in DMSO-d_6, with TMS serving as the internal standard.

General procedure for the synthesis of 4-(substituted benzylidene)-N-(5-methylisooxazol-3-yl) benzenesulfonamide, 3a-e: 0.01 mole (2.5328 g) of sulfamethoxazole **(1)** and aromatic aldehyde **2a-e** 0.01 moles are dissolved in 20 mL chloroform and methanol were mixed in a 1:1 ratio in a 250 mL round-bottom flask and the temperature was increased

to 328-333 K, which was sustained for 4 hours. The reaction mixture was filtered and cooled to a RT. Schiff bases **3a-e** were separated, filtered, dried and recrystallized using ethanol[25,26].

4-(Benzylideneamino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide, 3a: Yield: 81-82%, off white, solid, Mp: 175°C; IR (Bruker) v max cm^{-1}: 3209.19 (-HC=N stretch), 2923.14 (-NH- stretch), 2852.58 (-CH_3 stretch), 1619.07 (aromatic C=N stretch), 1592.78 (aromatic C=C stretch), 1136.37 (-SO_2 stretch), 1090.42 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.38 (s, 3H of –C*H*$_3$), 6.57 (s, 1H of C-*H* of oxazole ring), 6.06-6.58 (m, 9H of C-*H* of both aromatic rings), 7.47 (s, 1H *H*C=N), 10.90 (s, 1H of N*H*). Elemental Analysis Calculated: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.75; H, 4.35; N, 12.28. MS: m/z 342 (M+H); $C_{17}H_{15}N_3O_3S$ requires 341.08.

4-((4-Hydroxybenzylidene)amino)-N-(5-methylisoxazol-3-yl) benzene-sulfonamide, 3b: Yield: 90%, light brown, crystalline solid, Mp 163°C; IR (Bruker) v max cm^{-1}: 3425 (-OH stretch), 3202.41 (-HC=N stretch), 2925 (-NH- stretch), 2850 (-CH_3 stretch), 1668.83 (aromatic C=N stretch), 1593.10 (aromatic C=C stretch), 1152.92 (-SO_2 stretch), 1038.57 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.28 (s, 3H of –C*H*$_3$), 6.94 (s, 1H of C-*H* of oxazole ring), 6.06-7.77 (m, 8H of C-*H* of both aromatic rings), 9.79 (s, 1H *H*C=N), 10.61 (s, 1H of -O*H*), 10.89 (s, 1H of N*H*). Elemental Analysis Calculated: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.08; H, 4.19; N, 11.69. MS: m/z 358 (M+H); $C_{17}H_{15}N_3O_4S$ requires 357.08.

4-((2-Chlorobenzylidene)amino)-N-(5-methylisoxazol-3-yl) benzene-sulfonamide, 3c: Yield: 68%, light yellow, solid, Mp: 153°C; IR (Bruker) v max cm^{-1}: 3078.46 (-HC=N stretch), 2986.32 (-NH-stretch), 2896.05 (-CH_3 stretch), 2848.58 (=N-C-Ar stretch), 1614.37 (aromatic C=N stretch), 1579.60 (aromatic C=C stretch), 1159.37(SO_2 stretch), 1137.78 (aromatic C-H bending). ^{1}H NMR ($CDCl_3$, 500 MHz) (δ in ppm): 2.37 (s, 3H of –C*H*$_3$), 6.24 (s, 1H of C-*H* of oxazole ring), 7.35-8.19 (m, 8H of C-*H* of both aromatic rings), 8.85 (s, 1H *H*C=N), 10.47 (s, 1H of N*H*). Elemental Analysis Calculated: C, 54.33; H, 3.75; N, 11.18. Found: C, 54.28; H, 3.71; N, 11.14. MS: m/z 376 (M+H); $C_{17}H_{14}Cl_1N_3O_3S$ requires 375.04.

4-((4-Fluorobenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzene-sulfonamide, 3d: Yield: 73%, Dark yellow, solid, Mp: 156°C; IR (Bruker) v max cm^{-1}: 3120 (-HC=N stretch), 2979 (-NH-stretch), 2835.73 (-CH_3 stretch), 1609.77 (aromatic C=N stretch), 1571.38 (aromatic C=C stretch), 1159.66 (-SO_2 stretch), 1028.52 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.30 (s, 3H of –C*H*$_3$). 6.06 (s, 1H of C-*H* of oxazole ring), 6.57-7.90 (m, 8H of C-*H* of both aromatic rings), 9.87 (s, 1H of *H*C=N), 10.91 (s, 1H of N*H*). Elemental Analysis Calculated: C, 56.82; H, 3.93; N, 11.69. Found: C, 56.78; H, 3.87; N, 11.56. MS: m/z 360 (M+H); $C_{17}H_{14}F_1N_3O_3S$ requires 359.07.

4-((4-Methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzene-sulfonamide, 3e: Yield: 88%, yellow, solid, Mp: 158°C; IR (Bruker) v max cm^{-1}: 3077.12 (-HC=N stretch), 2975 (-NH- stretch), 2830 (-OCH_3 stretch), 1701.97 (aromatic C=N stretch), 1611.31 (aromatic C=C stretch), 1162.32 (-SO_2 stretch), 1040.24 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.28 (s, 3H of –C*H*$_3$), 3.86 (s, 3H of –C*H*$_3$ of methoxy group), 6.0-6.1 (s, 1H of C-*H* of oxazole ring), 6.57-7.91 (m, 8H of C-*H* of both aromatic rings), 8.31 (s, 1H of *H*C=N), 10.90 (s, 1H of N*H*). Elemental Analysis Calculated: C, 58.21; H, 4.61; N, 11.31. Found: C, 58.17; H, 4.56; N, 11.25. MS: m/z 372 (M+H); $C_{18}H_{17}N_3O_4S$ requires 371.09.

General method for synthesis of 4-(4,7-dioxo-2-substituted benzylidene -4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4a-e

Compounds **3a-e** (0.01 mole) are cyclized with maleic anhydride 0.01 mole in 25 mL dry benzene for 6 hrs at 348-353 K in a one-pot assembly. Filtered out from benzene and separated, title compounds were then dried and recrystallized from ethanol.

4-(4,7-Dioxo-2-phenyl-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4a: Yield: 73.64%, whitish yellow, solid, Mp: 162°C; IR KBr (Bruker) v max cm^{-1}: 3287.79 (-NH- stretch), 2914.98 (-CH- stretch), 2847.73 (-CH_3- stretch), 1702.58 (aromatic C=O stretch), 1185.36 (-SO_2 stretch), 845.73 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 3.39 (s, 3H of –C*H*$_3$), 6.13 (s, 1H of C-*H* of oxazole ring), 6.33 (s, 1H of *H*C-N), 6.47-7.60 (m, 9H of C-*H* of both aromatic rings), 10.68 (s, 1H of C-*H* of oxazepine ring), 11.33 (s, 1H of C-*H* of oxazepine ring),12.68 (s, 1H of N*H*). Elemental Analysis

Calculated: C, 57.40; H, 3.90; N, 9.56. Found: C, 57.33; H, 3.83; N, 9.49. MS: m/z 440 (M+H); $C_{21}H_{17}N_3O_6S$ requires 439.08.

4-(2-(4-Hydroxyphenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4b: Yield: 75.43%, yellow, solid, Mp: 178°C; IR KBr (Bruker) ν max cm^{-1}: 3284.83 (-NH- stretch), 3078.03 (-OH stretch), 2981.21 (-CH- stretch), 1702.23 (aromatic C=O stretch), 1186.44 (-SO_2 stretch), 845.93 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.29 (s, 3H of –C*H*$_3$), 6.12 (s, 1H of C-*H* of oxazole ring), 6.24 (s, 1H of *H*C-N), 6.32-6.34 (d, 2H of C-*H* of oxazepine ring), 6.48-7.83 (m, 8H of C-*H* of both aromatic rings), 10.70 (s, 1H of -O*H*), 11.34 (s, 1H of N*H*). Elemental Analysis Calculated: C, 55.38; H, 3.76; N, 9.23. Found: C, 55.34; H, 3.70; N, 9.16. MS: m/z 456 (M+H); $C_{21}H_{17}N_3O_7S$ requires 455.08.

4-(2-(2-Chlorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4c: Yield: 71.89%, light yellow, solid, Mp: 173°C; IR KBr (Bruker) ν max cm^{-1}: 2980.67 (-NH- stretch), 2878.28 (-CH- stretch), 1771.66 (aromatic C=O stretch), 1435.65 (-CH_3 stretch), 1127.48 (-SO_2 stretch), 817.63 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.39 (s, 3H of –C*H*$_3$), 6.13 (s, 1H of C-*H* of oxazole ring), 6.33 (s, 1H of *H*C-N), 6.47-7.83 (m, 8H of C-*H* of both aromatic rings), 10.67 (s, 1H of C-*H* of oxazepine ring), 11.33 (s, 1H of C-*H* of oxazepine ring), 12.76 (s, 1H of N*H*). Elemental Analysis Calculated: C, 53.23; H, 3.40; N, 8.87. Found: C, 53.19; H, 3.33; N, 8.81. MS: m/z 474 (M+H); $C_{21}H_{16}Cl_1N_3O_6S$ requires 473.04.

4-(2-(4-Fluorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4d: Yield: 77.18%, light yellow, solid, Mp: 168°C; IR KBr (Bruker) ν max cm^{-1}: 3284.32 (-NH- stretch), 3078.27 (-CH- stretch), 2797.03 (-CH_3 stretch), 1701.71 (aromatic C=O stretch), 1186.54 (-SO_2 stretch), 845.46 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 500 MHz) (δ in ppm): 2.29 (s, 3H of –C*H*$_3$), 6.12 (s, 1H of C-*H* of oxazole ring), 6.26 (s, 1H of *H*C-N), 6.33-7.82 (m, 8H of C-*H* of both aromatic rings), 10.67 (s, 1H of C-*H* of oxazepine ring), 11.32 (s, 1H of C-*H* of oxazepine ring), 12.81 (s, 1H of N*H*). Elemental Analysis Calculated: C, 55.14; H, 3.53; N, 9.19. Found: C, 55.09; H, 3.47; N, 9.15. MS: m/z 458 (M+H); $C_{21}H_{16}F_1N_3O_6S$ requires 457.07.

4-(2-(4-Methoxylphenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide, 4e: Yield: 79.96%, orange, crystalline solid, Mp: 169°C; IR KBr (Bruker) ν max cm^{-1}: 2979.69 (-NH- stretch), 2878.89 (-CH- stretch), 2716.89 (-CH_3 stretch), 1669.50 (aromatic C=O stretch), 1152.49 (-SO_2 stretch), 828.82 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6, 400 MHz) (δ in ppm): 2.22 (s, 6H of two –C*H*$_3$), 6.13 (s, 1H of C-*H* of oxazole ring), 6.26 (s, 1H of *H*C-N), 6.33-7.83 (m, 8H of C-*H* of both aromatic rings), 10.70 (s, 1H of C-*H* of oxazepine ring), 11.37 (s, 1H of C-*H* of oxazepine ring), 12.94 (s, 1H of N*H*). Elemental Analysis Calculated: C, 56.29; H, 4.08; N, 8.95. Found: C, 56.21; H, 4.01; N, 8.89. MS: m/z 470 (M+H); $C_{22}H_{19}N_3O_7S$ requires 469.09.

Antioxidant activity

Neutrophils were isolated from human blood following ethical approval and prior consent, demonstrating antioxidant activity. 10^6 cells were incubated with DCF-DA with or without PMA, **4a-e** (1 μgm/mL) for 30 minutes at 310 K in the dark. The fluorescence intensity was measured at an excitation wavelength of 488 nm and an emission wavelength of 520 nm using a fluorescence reader. The mean fluorescence of the untreated cell was normalized to the basal level and the mean stimulation index was calculated[27].

Antibacterial activity

The antibacterial activity of the synthesized compounds was assessed using the Kirby-Bauer agar disc diffusion method[28]. The compounds were assessed for their capacity to hinder bacterial growth against both gram-positive *(Bacillus subtilis, Staphylococcus aureus)* and gram-negative *(Pseudomonas aeruginosa, Escherichia coli)* bacteria. Penicillin served as a widely recognized standard antibiotic. The culture was grown in Petri dishes for approximately 24 hours using nutrient agar. DMSO (Dimethyl sulfoxide) was utilized to dissolve the entire synthesized Schiff base and oxazepines. A blank disk saturated with 10 mg/mL was placed on a Petri plate containing a solid bacterial medium, measuring 10 cm in diameter. Each plate is placed in the incubator at 310 K for duration of 24 hours. The antibacterial potential was assessed by measuring the zone with a standard scale.

Results and Discussion

The synthesis of Schiff bases **3a-e** using various specific aldehydes were validated through FT-IR

spectroscopy. The IR spectrum distinctly displays the characteristic absorption band at (3387-3282 cm^{-1}) corresponding to υ NH stretching of $NHSO_2$, a band for υ C=N stretching in the region of (1606-1641 cm^{-1}) and the absence of primary amine υNH_2 stretching at (3469 cm^{-1}). The ^{1}H NMR spectra for the compounds **3a-e** displayed a broad singlet at (δ 10.46-11.53 ppm) corresponding to the (-N*H*-SO_2) proton. Additionally, the spectrum revealed a signal at (δ 8.16-9.80 ppm) for the imine (C*H*=N) group. The final compounds **4a-e** were synthesized by condensing Schiff base **3a-e** with maleic anhydride in dry benzene, refluxing for 6 hours, as illustrated in Scheme 1. The FT-IR spectroscopy confirmed the presence of targeted oxazepines **4a-e**. The IR spectrum distinctly illustrates the loss of the stretching vibration band of the (C=N) group of the Schiff base within the range of (1606-1641 cm^{-1}) and the emergence of the absorption band of two carbonyl groups of oxazepine ring (C=O) at (1668-1712 cm^{-1}). The ^{1}H NMR spectra of compounds **4a-e** displayed the presence of the C*H*=C*H* signal of oxazepine at (δ 10.03-11.89 ppm).

Antioxidant activity

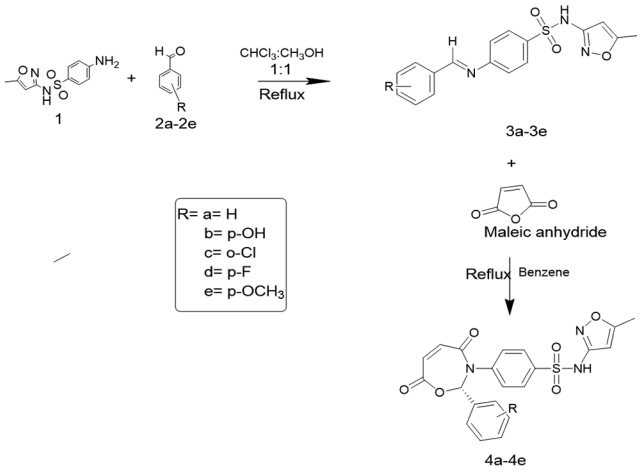
PMAs (phorbol 12-myristate 13-acetate) have the potential to reduce cellular antioxidant activity. The graphical data in Fig. 1 shows that both the individual and the compound reacted with PMA exhibit mean fluorescence intensity for all final compounds. The synthesized compound demonstrates strong antioxidant properties. The fluorescence intensity decreased in the PMA-induced neutrophils.

Antibacterial activity

The findings in Table 1 indicate that compound **3a** demonstrated superior action compared to the common medications amoxicillin and penicillin-G, particularly against *S. aureus* (25±2 mm) and *E. coli* (24±2 mm). Among all strains, compounds **4c–4e** demonstrated competitive potency against *E. coli* and *Pseudomonas aeruginosa* strains, whereas compounds **3c** and **3d** exhibited moderate activity.

ADME studies of synthesized compounds

The SwissADME web server was employed to ascertain the physical properties and absorption, distribution, metabolism and excretion (ADME) of synthesized compounds[29] **4a-e**, with the results presented in Table 2. For each compound, the following five parameters were determined using Lipinski's rule of five: molecular weight (MW) (150 g mol^{-1} < MW < 500 g mol^{-1}), number of hydrogen bond acceptors (nHBA), donors (nHBD), number of rotatable bonds (nRB) and topological polar surface area (TPSA). Lipophilicity (-0.7 < XLOGP3 < 5.0), polarity (20 Å2 < TPSA < 130 Å2), solubility (0 < log S (ESOL) < 6), saturation (0.25 < Fraction Csp3 < 1) and flexibility (0 < number of rotatable bonds < 9) are the criteria considered for calculating the score. **4a-d** meets all these criteria, whereas **4e** has a higher TPSA value. A log S scale was developed to quantify the qualitative solubility of



Scheme 1 — Protocol for the synthesis of sulfamethoxazole containing oxazepine derivatives

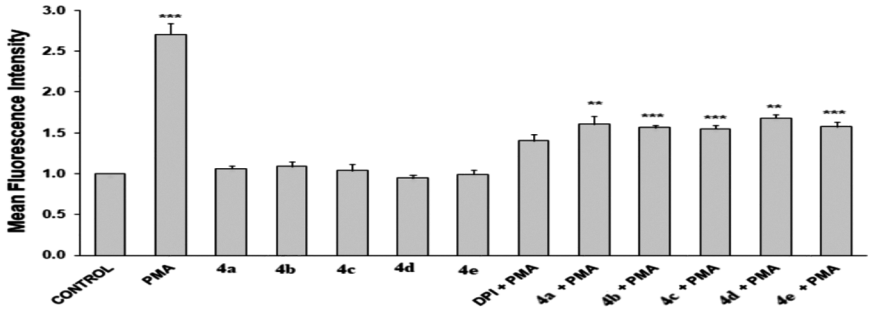


Fig. 1 — Graphical representation of antioxidant activity's result

Table 1 — Antibacterial activity of synthesized compounds

Compd	Inhibition zone in (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	25±2	14±2	24±2	10±2
3b	24±2	10±2	15±2	12±2
3c	22±2	11±2	15±2	12±2
3d	19±2	11±2	20±2	14±2
3e	14±2	18±2	17±2	20±2
4a	11±2	13±2	13±2	11±2
4b	14±2	15±2	13±2	10±2
4c	8±2	11±2	17±2	14±2
4d	14±2	19±2	16±2	14±2
4e	10±2	14±2	17±2	17±2
Penicillin-g (standard)	12±2	12±2	14±2	12±2
Amoxicillin (standard)	14±2	14±2	16±2	14±2

Table 2 — Results of synthesized compounds of Swiss ADME, compared with standard butylated hydroxyl anisole (BHA) and ifofsamide

Compd	Lipinski drug like				Veber drug like		Solubility	Absorption and distribution			
	Molecular Weight	MLogP	H-Bond Acceptors	H-Bond Donors	TPSA	Rotatable bonds	ESOL	WLogP	GI	Pgp substrate	BBB permeant
3a	341.38	1.41	5	1	92.94	5	Soluble	4.42	High	No	No
3b	357.38	0.88	6	2	113.17	5	Soluble	4.13	High	No	No
3c	375.83	1.91	5	1	92.94	5	Moderately soluble	5.08	High	No	No
3d	359.37	1.8	6	1	92.94	5	Moderately soluble	4.98	High	No	No
3e	371.41	1.52	6	1	102.17	6	Moderately soluble	4.43	High	No	No
4a	439.44	1.31	7	1	127.19	5	Moderately soluble	3.11	High	No	No
4b	455.44	0.81	8	2	147.42	5	Moderately soluble	2.82	Low	No	No
4c	473.89	1.8	7	1	127.19	5	Moderately soluble	3.77	High	No	No
4d	457.43	1.69	8	1	127.19	5	Moderately soluble	3.67	High	No	No
4e	469.47	1.43	8	1	136.42	6	Moderately soluble	3.12	Low	No	No
BHA	180.24	2.39	2	1	29.46	2	Soluble	2.7	High	No	Yes
IFOSFAMIDE	261.09	0.97	4	1	51.38	5	Very soluble	1.5	High	No	Yes

Note: MlogP- Topological method implemented, TPSA- Topological polar surface area, ESOL- Estimated aqueous solubility, WlogP- atomistic method implemented, GI- Gastrointestinal absorption, P-gp Glycoprotein substrate, BBB- Blood brain barrier parameter.

drugs that require high solubility in water for the effective delivery of active ingredients. Values below -10 suggest weak solubility; values below -6 indicate moderate solubility; values below -4 reflect extreme solubility; and values below -2 and below 0 signify high solubility.

The brain or intestine estimated permeation approach (BOILED-Egg, Fig. 2) serves as a reliable prediction model for determining lipophilicity and polarity[30]. The white region indicates passive absorption in the stomach, whereas the yellow region illustrates passive permeability in the brain. All compounds exhibit gastrointestinal adsorption. The permeability of the blood-brain barrier to this molecule suggests that harmful toxicants may enter the bloodstream and brain following digestion. The penetration of the blood-brain barrier by the other medication was unforeseen.

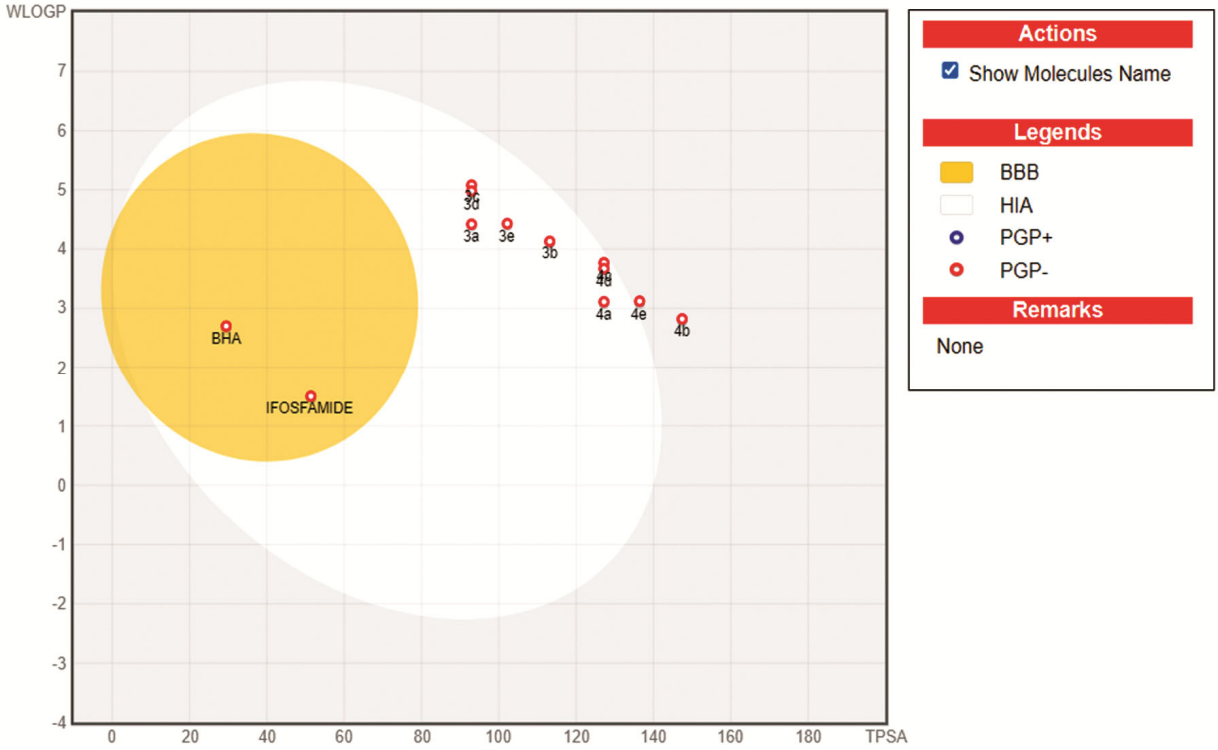


Fig. 2 — BOILED-Egg representation of compounds **3a-e** and **4a-e** with standard BHA and ifofsamide

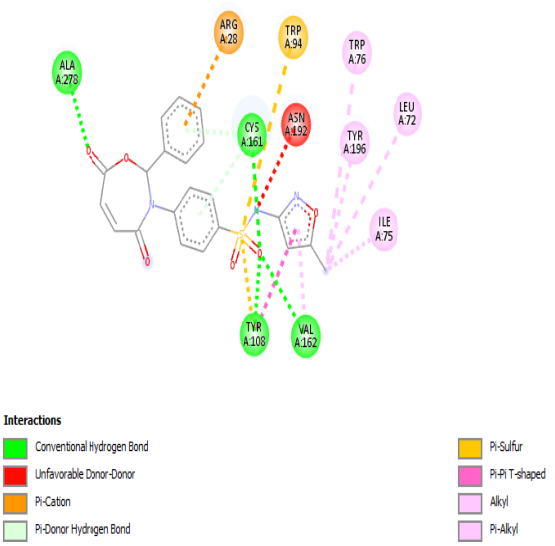
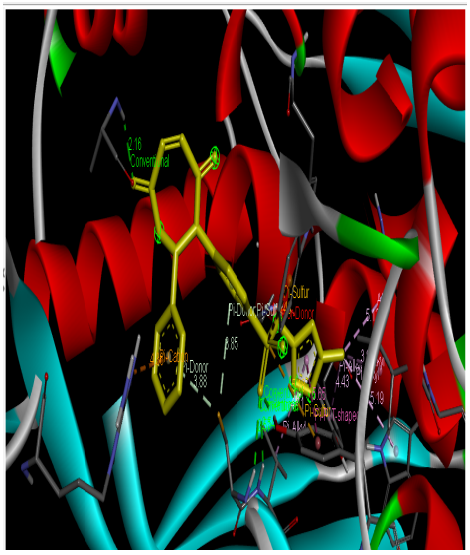
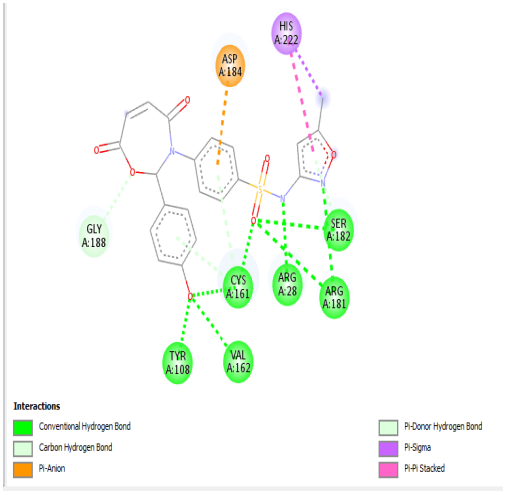
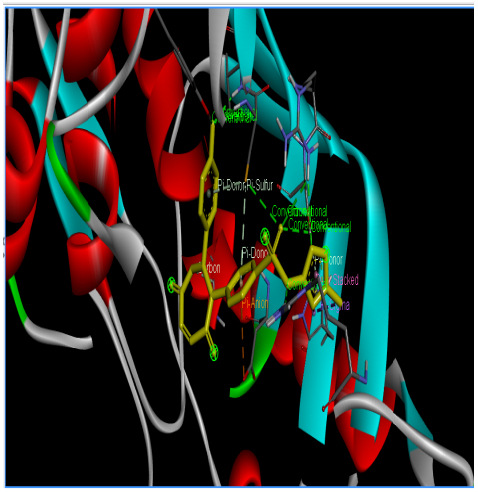
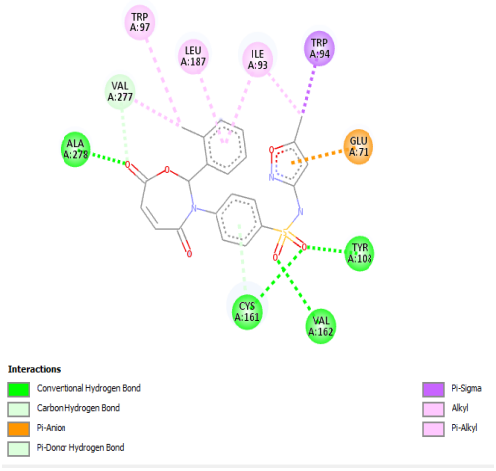
Table 3 — Compounds with Thymidylate synthase A docking binding energies (Kcal.mol^{-1})

Compd	Protein	Binding Energy (Kcal/mole)	Estimated inhibition constant (KI) at 25°C	Protein-ligand interactions
4a	Thymidylate synthase A (1b02)	-10.19	33.89 nM (nanoMolar)	Conventional H-bond:- ALA 278, CYS 161, TYR 108, VAL 162.
4b	Thymidylate synthase A (1b02)	-10.16	35.81 nM (nanoMolar)	Conventional H-bond:- ARG 28, ARG 181, CYS 161, SER 182, TYR 108, VAL 162.
4c	Thymidylate synthase A (1b02)	-9.95	50.97 nM (nanoMolar)	Conventional H-bond:- ALA 278, CYS 161, TYR 108, VAL 162.
4d	Thymidylate synthase A (1b02)	-10.22	32.32 nM (nanoMolar)	Conventional H-bond:- CYS 161, TYR 108, VAL 162.
4e	Thymidylate synthase A (1b02)	-10.33	26.97 nM (nanoMolar)	Conventional H-bond:- CYS 161, TYR 108, VAL 162.
5-Fluorouracil (standard)	Thymidylate synthase A (1b02)	-5.07	192.46 µM (micromolar)	Conventional H-bond:- GLN 166, HIS 143, LYS 170, TRP 167, VAL 169.

Molecular docking

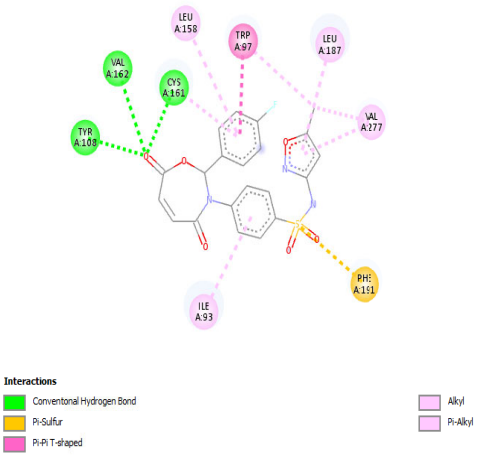
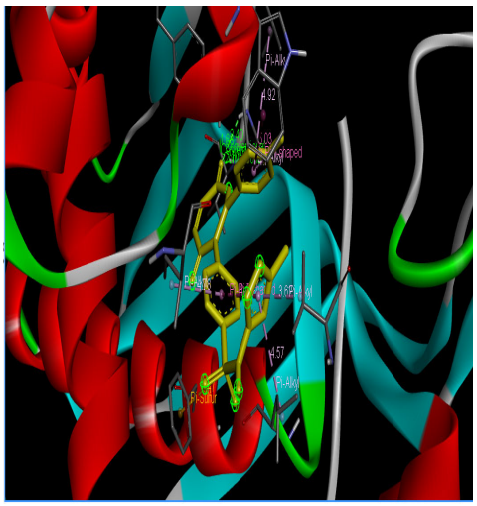
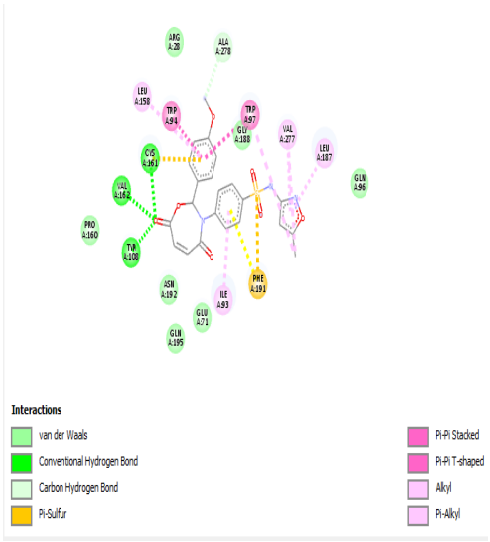
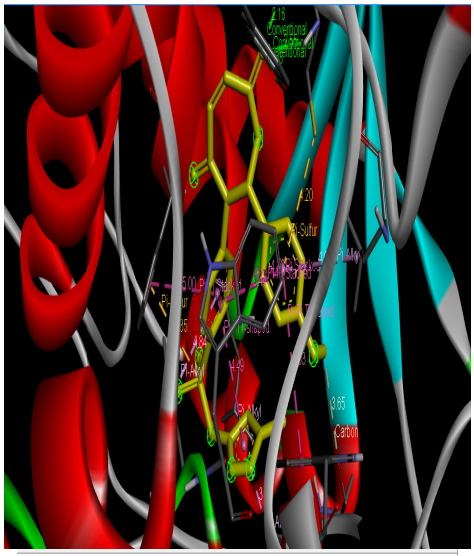
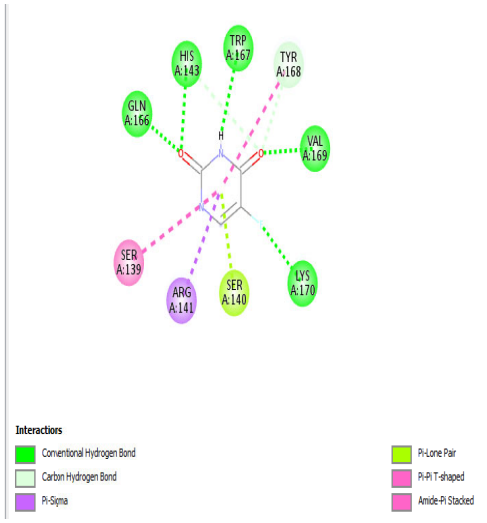
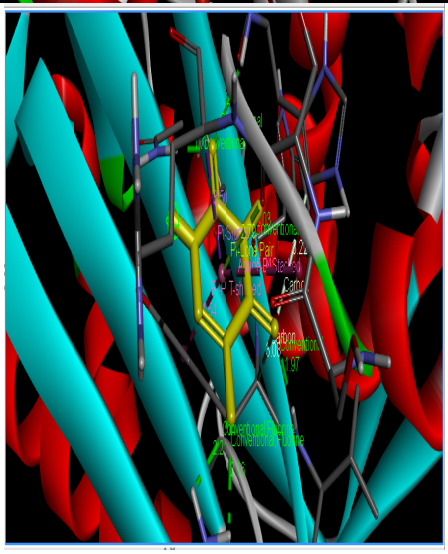
The synthesized final products were analyzed for molecular docking with the AutoDock 1.5.7 software and the visualization of docking interactions was performed using Discovery Studio 2024 Client[31]. The X-ray crystallography structure of Thymidylate synthase A (PDB: 1B02), was obtained from the RCSB Protein Data Bank (PDB) server for docking purposes (Table 3 and Table 4). After downloading the target protein crystal structure that was corrected and optimized by removing unwanted water molecules and co-crystallized ligand. Next, it was energy-minimized using the Discovery studio 2024 client. The Root-Mean-Square Deviation (RMSD) tolerance value was established at 2.0 Å. The process of reductive methylation transforms 2′-deoxyuridine 5′-monophosphate into 2′-deoxythymidine 5′-monophosphate, which is an essential precursor for DNA synthesis and this reaction is facilitated by Thymidylate synthase A (TS, Thy A). When this enzyme is specifically inhibited, bacterial cells perish[32]. Reports indicate that 5-fluorouracil acts as a TS

Table 4 — Final compounds and 5-fluorouracil (standard) docked with thymidylate synthase A, 2D and 3D interactions

Compd	2D and 3D interaction of molecular docking	
4a		
4b		
4c		

(Contd.)

Table 4 — Final compounds and 5-fluorouracil (standard) docked with thymidylate synthase A, 2D and 3D interactions — (Contd.)

Compd	2D and 3D interaction of molecular docking	
4d		
4e		
5-Fluorouracil		

inhibitor by engaging with the active binding site of the protein through several residues[33,34]. Consequently, 5-fluorouracil was chosen as the standard reference.

Conclusions

The synthesized oxazepines **4a-e** were created through the condensation of Schiff base **3a-e** and maleic anhydride, utilizing dry benzene as the solvent, resulting in an excellent yield. The synthesized compounds have been identified and characterized through elemental analyses, FT-IR spectroscopy, physical characteristics, mass spectrometry and ^{1}H NMR spectra. Compounds **3a-e** demonstrated significant inhibitory effects against *Escherichia coli* and *Pseudomonas aeruginosa* (gm^{-ve}), as well as *Bacillus subtilis* and *Staphylococcus aureus* (gm^{+ve}) strains when compared to standard penicillin and amoxicillin while based on the results of the antioxidant assay, we can state that compounds **4a-e** demonstrate strong antioxidant properties. We successfully predicted the ADME of our synthesized compounds using the SwissADME approach. All synthesized compounds exhibit high GI adsorption, with the exception of **4b** and **4e**. An excellent prediction of the inhibition constant and binding energy was provided by the molecular docking of title compounds, which showed their binding affinity to targeted protein Thymidylate synthetase A. The 2D and 3D images presented in Table 4 illustrate the final products, which exhibit the best conformation corresponding to the lowest binding energy. The title compounds present a wide range of possibilities for future lead optimization in drug development.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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