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SYNTHESIS AND BIOLOGICAL EVALUATION OF SCHIFF BASE AND 4-THIAZOLIDINONES OF AMINO SALICYLIC ACID AND THEIR DERIVATIVES AS AN ANTIMICROBIAL AGENT

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ABSTRACT: Schiff base, azetidinone and 4-thiazolidinone derivatives of para aminosalicylic acid were synthesised. It was planned to employ the structure based computer aided drug designing (CADD) to Schiff base, azetidinone and 4-thiazolidinoneof para aminosalicylic acid. Approach was employed to understand the probable binding of para aminosalicylic acid on the active site of AMpC enzyme of HKY28 which will suggest the better insight in the designing of novel analogues of schiff base, azetidinone and 4-thiazolidinone of para amino salicylic acid as a probable antimicrobial agent. Based on the data obtained from ligand-receptor binding studies, the novel molecules were synthesised and evaluated for antimicrobial studies.The synthesised compounds were screened for their *in vitro* antimicrobial activity. The structure of synthesised compounds **Ia-c, IIa, IIIa** have been established on the basis of their spectral (IR, ^{1}H NMR and mass) data. The purity of the synthesised compounds was confirmed by TLC.
Key Words: Para amino salicylic acid, Schiff base, physicochemical properties**.**

INTRODUCTION

Para amino salicylic acid is a second line anti-tubercular[1-3] agent and possesses antibiotic property. There is always need for the safer antibacterial agents and research efforts are going on for developing safer antibacterial agents. Schiff base approach is one of the most promising amongst these[4]. In recent years, there has been an increasing interest in the design and development of Schiff base derivatives.

Employing the structure based CADD techniques, we have evaluated a series of virtual Schiff base, azetidinone, 4-thiazolidinone derivatives of para amino salicylic acid using AMpC enzyme of E.coli, HKY28. Based on docking studies we have taken up the compounds for the synthesis and evaluated for the antibacterial activity against the *E. coli*, *S. aureus,* and antifungal activity of compounds was studied against *C. albicans and A. niger* according to cup-plate method. The synthesised compound found to have better antimicrobial activity than the parent compound. The present studies are the model for the application of structure based computer aided drug designing (CADD) in development of novel molecule.

MATERIALS AND METHODS

Melting points were determined in a DBK programmed melting point apparatus and are uncorrected. The TLC of the compounds was performed on silica gel G coated glass plate with benzene: methanol (9:1) as solvent. Iodine vapour was used as detecting agent. The absorbance maxima (λ max) were recorded on Shimadzu 2401 UV-Visible spectrophotometer. ^{1}H NMR was recorded on AVANCE-300, (300MHz FT NMR), using DMSO. Infrared spectra were recorded on FTIR spectrophotometer 8400 S, Shimadzu Corporation, Tokyo, Japan. Mass spectras was recorded in MICROMASS QUATTO II triple quadrapole mass spectrometer.

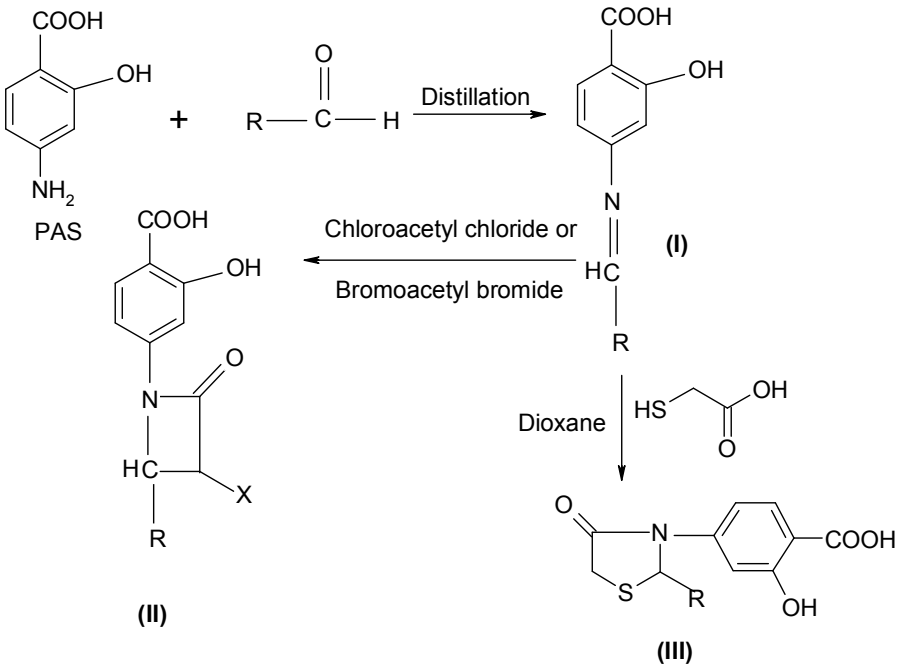
Preparation of Schiff base derivatives of para aminosalicylic acid (Ia-c)[5]

All the Schiff base derivatives of para aminosalicylic acid were synthesised by stirring a methanolic solution of para aminosalicylic acid (1.53 g, 0.01 mol) with corresponding aldehydes (1.22 g, 0.01 mol) in 1:1 stoichiometric ratio at room temperature over 24 h. The precipitate obtained were filtered washed with methanol and dried and were re-crystallized from methanol.

The physicochemical, docking score and spectral data:
Chemical name: 4-(benzylideneamino)-2-hydroxy benzoic acid.
Docking score: -49.426 **Ia**.
Yellow crystals, m.p. 180-185^{O}C, yield 70 %, IR (KBR) cm-^{1}: 1681 (C = O, COOH), 3043 (Ar-C-H str), 3360 (OH str, COOH), 1608(C=N), 1226, 784, 699; ^{1}H NMR δ ppm: 8.9 (S, ArH), 8.0 (m, ArH), 7.0-7.7(m, ArH); MASS m/z: 241 calculated for $C_{14}H_{11}O_3N_1$, found 241.
The physicochemical, docking score and spectral data:
Chemical name: 2-hydroxy-4-(4-methoxybenzylideneamino) benzoic acid.
Docking score: -55.427 **Ib**.
Yellowish white crystals, m.p 130-135 ^{O}C, yield 78 %, IR (KBR) cm-^{1}: 1602(C=N). 3053(Ar-C-H str), 3250 (OH str, COOH), 1602(C=N), 1249, 773, 686; ^{1}H NMR δ ppm: 8.9 (S, ArH), 8.0 (m, ArH), 7.0-7.7 (m, ArH); MASS m/z: 271 calculated for $C_{15}H_{13}O_4N_1$, found 271.
The physicochemical, docking score and spectral data:
Chemical name: 2-hydroxy-4-(hydroxybenzylideneamino) benzoic acid.
Docking score: -51.497 **Ic.**
Yellow crystals, m.p 175-180OC, yield 80 %, IR (KBR) cm-1: 1602(C=N), 1662 (C=O, COOH), 3029 (Ar-C-H str), 1447, 1234,769; 1H NMR δ ppm: 8.9(m, ArH), 8.0 (m, ArH), 7.0-7.7 (m, ArH), 3.7 (s,CH3); MASS m/z: 257 calculated for $C_{14}H_{11}O_4N_1$, found 257.

Synthesis of azetidinones from Ic[6] :
To a mixture of compound **Ic** (0.01 mol) in dioxane (10 ml), trimethylamine (3.49 ml, 0.025 mol), was added chloroacetyl chloride (1.99 ml, 0.025 mol) drop-wise at 5-10^{0}C. The reaction mixture was stirred for 6 h. Then reaction mixture was then poured into crushed ice. The solid separated was dried and re-crystallized from ethanol.
The physicochemical, docking score and spectral data:
Chemical name: 4-(3-chloro-2-(4-methoxyphenyl)-4-oxocyclobutyl)-2-hydroxybenzoic acid. Docking score: -50.548 **IIa**.
Brownish crystals, m.p. 195-200OC, yield 65 %, IR (KBR) cm-1: 1693 (C=O, COOH), 3413 (OH str.), 3101 (Ar-C-H str), 1436, 1242, 827; ^{1}H NMR δ ppm: 8.1 (S,ArH), 7.4-7.8 (m, ArH), 5.0-5.6 (m, ArH); MASS m/z: 333 calculated for $C_{16}H_{12}O_5N_1Cl_1$, found 334.

Synthesis of 4-thiazolidinones from Ic[7] :
To a solution of compound **Ic** (1mmol) in dry dioxane (10 ml) a solution of mercaptoacetic acid (10 mmol) in dry dioxane (10 ml) was added followed by catalytic amount of zinc chloride (15 mg), and reaction mixture was refluxed for 8h, mixture was evaporated electrical water bath. Residue was then treated by solution of bicarbonate to remove excess of mercaptoacetic acid. The compound obtained was re-crystallized by ethanol.
The physicochemical, docking score and spectral data:
Chemical name: 2-hydroxy-4-(2-(4-hydroyphenyl)-4-oxothiazolidin-3-yl) benzoic acid acid. Docking score: -52.458 **IIIa**.
Brownish crystals, m.p. 215-2200C, yield 54 %, %, IR (KBR) cm-1: 1681 (C=O, COOH), 3440 (OH str.), 3226 (Ar-C-H str) 1417, 282, 860. ^{1}H NMR δ ppm: 8.0-8.5 (S, ArH), 7.0-7.8 (m, ArH), 5.0-5.6 (m, ArH); MASS m/z: 330 calculated for $C_{16}H_{12}O_5N_1S_1$, found 330.



Scheme1.: Synthesis of Schiff base, azetidinone and 4-thiazolidinone from para aminosalicylic acid.

Table 1: Various substitutions used and physciochemical data of synthesised Schiff's Base derivatives.

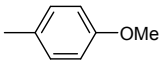
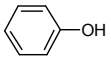
Compound	R	m.p. (^{0}C)	Yield (%)	R_f Value
Ia		**180-185**	**70**	**0.68**
Ib		**130-135**	**78**	**0.71**
Ic		**175-180**	**80**	**0.74**

Table 2: Substitution used and physicochemical data of synthesised Azetidinone derivative.

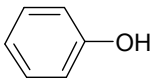
Compound	R	m.p.(^{0}C)	Yield (%)	R_f Value
IIa		**195-200**	**65**	**0.62**

Table 3: Substitution used and Physicochemical data of synthesised 4-thiazolidinone derivative.

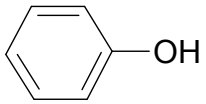
Compound	R	m.p. (^{0}C)	Yield (%)	R_f Value
IIIa		**215-220**	**54**	**0.70**

Table 4: Anti-microbial study at 100 µg/ml concentration of synthesised compound.

Compound	Concentration (µg/ml)	Zone of inhibition in mm diameter against bacteria and fungi			
		S. aureus	***E. coli***	***C. albicans***	***A. niger***
Ia	100	16.2	17.2	16.8	17.2
Ib	100	18.6	18.2	16.4	16
Ic	100	17.4	17.8	24.2	23.8
IIa	100	24.6	24.8	22.2	22
IIIa	100	20.2	22.2	26	25.6
Std 1	100	16.6	17	-	-
Std 2	100	-	-	18	18.4

Docking study:

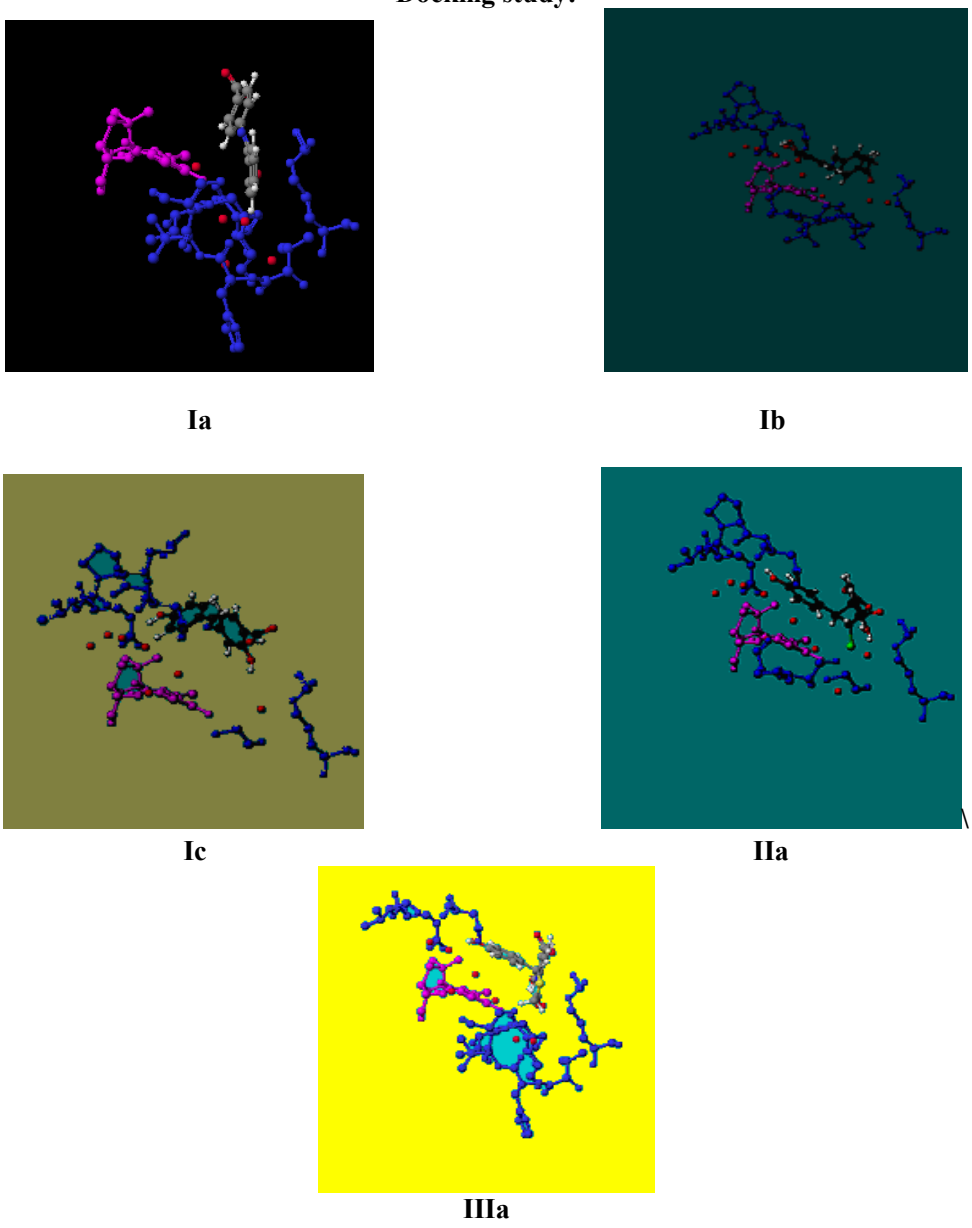


Fig. 1: Docking study of Schiff base, azetidinone and 4-thiazolidinone derivatives of para aminosalicylic acid.

RESULTS AND DISCUSSION

The series of Schiff's bases, Azetidinones, 4-Thiazolidinones derivatives of the para aminosalicylic acid were docked and depending upon the docking score the synthesis of different derivatives were carried out by the procedure reported in the literature.

Thin layer chromatography was performed on pre-coated silica gel G, glass plates using benzene: methanol (9:1) solvent systems to ascertain the purity of these compounds. Melting point, % yield etc. was noted and data is given in Table 1, Table 2 and Table 3 for synthesised compounds. The compounds gave single spots. The structure of synthesised compounds was confirmed by infrared spectroscopy, ^{1}H NMR spectroscopy and mass spectroscopy. Infrared spectroscopy showed the characteristic absorption bands of C=N stretching, C-O stretching and C=O vibration of these compounds.

The ^{1}H NMR spectra of the synthesised compounds show chemical shifts, which are characteristics of the anticipated structure of compounds. The mass spectra of the synthesised compounds showed the parent peak confirming the molecular weight of the compounds. The *in-vitro* antimicrobial study is also carried out. The docking studies Schiff base, azetidinone and 4-thiazolidinone are shown in the Fig. 1. Based on the data obtained from ligand-receptor binding studies, the novel molecules will be synthesised and evaluated for antimicrobial studies.

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