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IN-SILICO PREDCITION OF ADMET PROPERTIES AND SYNTHESIS OF NOVEL ANTIBACTERIAL SCHIFF BASES DERIVED FROM NOVEL SUBSTITUTED 1, 2, 4-TRIAZOLE-3-THIOLE

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ABSTRACT

In the present investigation, an attempt was made to predict pharmacokinetic, toxicity and bioactivity profile of selected substituted 1, 2, 4-triazole-3-thiole by *In-silico* methods before actual synthesis. *In-silico* prediction tools were used for prediction of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties were predicted by using Swiss ADME tool and from the present study, it can be concluded that the useful pharmacokinetics, drug-likeness and medicinal chemistry friendliness of synthesized compounds suggested that these compounds can be a good drug candidate in future and hence selected for study. Thiocarbohydrazide and 3, 5,-dimethoxy benzoic acid were heated above their meting point temperature to get a novel 4-amino-5(3, 5-dimethoxy-phenyl)-4H-1, 2, 4-triazole-3-thiole and a series of Schiff bases were prepared by treating 4-amino-5(3, 5-dimethoxy-phenyl)-4H-1, 2, 4-triazole-3-thiole with corresponding substituted benzaldehydes. The structures of all synthesized compounds were confirmed by elemental analysis, IR, MS and ^{1}H-NMR. All newly synthesized compounds were screened for their antibacterial activity. All compounds exhibited promising activity against human pathogenic bacteria.

Keywords: ADMET prediction, Triazole, Synthesis, Schiff base, Antibacterial, 3, 5-dimethoxy-phenyl moiety

1. INTRODUCTION

Swiss ADME tool allows calculating physicochemical properties; estimate ADMET factors of drug like small molecules to sustain drug discovery process. Physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeness and Medicinal Chemistry could be predicted by software before starting actual study to reduce cost of drug discovery [1].

The 1, 2, 4-triazole moiety possess significant pharmacological activities reported in numerous literature [2-13] Bacterial infections have become an significant problem and foremost cause of morbidity and mortality in immune-compromised persons suffering from cancer, tuberculosis or AIDS and in organ transplant cases. However, their clinical worth has been inadequate by their comparatively high possibility of toxicity, the appearance of drug resistance, pharmacokinetic insufficiency, and insufficiencies in their antibacterial activities. There is still a need for genuinely broad-spectrum and low toxicity antibacterial agents.

Provoked by these interpretation, it was considered to synthesize some new Schiff base 5-aryl- 4H-1,2,4-triazle-3-thiole derivatives with view to explore their potency as better chemotherapeutic agents. All newly synthesized compounds were screened for the antibacterial activity.

2. MATERIAL AND METHODS

2.1. Procedure for prediction of ADME by using Swiss ADME *In-silico* tool

To calculate physicochemical properties, forecast ADMET parameters, drug like small molecules to sustain drug discovery process Swiss ADME tool were used. Physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeness and Medicinal Chemistry of compounds to be synthesize were predicted.

2.2. Synthesis of 4-Amino-5-(3, 5-dimethoxy-phenyl)-4H-[1, 2, 4] triazole-3-thiol (3)

A combination of (0.01 mol) 3,5-dimethoxy benzoic acid and (0.01 mol) Thiocarbohydrazide enclosed in round-bottomed flask was heated on a heating mantle until it

melted. Consistently the mixture was kept at 220-230° C for 15-20 min. The product obtained was neutralized by treating with sodium bicarbonate solution. It was then washed with water and collected by filtration. The solid product was recrystallized from a mixture of dimethylformamide and ethanol**.**

2.3. General procedure for derivative preparation containing Schiff base

To a suspension of substituted (0.2 mol) benzaldehydes in (1 ml) ethanol an equimolar amount of the corresponding amino mercapto triazole (3) was added. The suspension was heated until a clear solution was obtained. Then few drops of concentrated sulphuric acid were added and the solution was heated under reflux for 3-/4 hr on a water-bath. The precipitated solid was filtered off and recrystallized from a mixture of ethanol and dimethylformamide.

Melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBR pallets) were recorded on a Jasco FT-IR 1700 series spectrophotometer. 1H NMR spectra were recorded using DMSO-d6 as solvent and TMS as an internal standard on Bruker NMR spectrometer. Chemical shift values are given in δ scale. The mass spectra were recorded on a LC-MS low resolution mass spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using ethyl acetate and n-heptane as mobile phase.

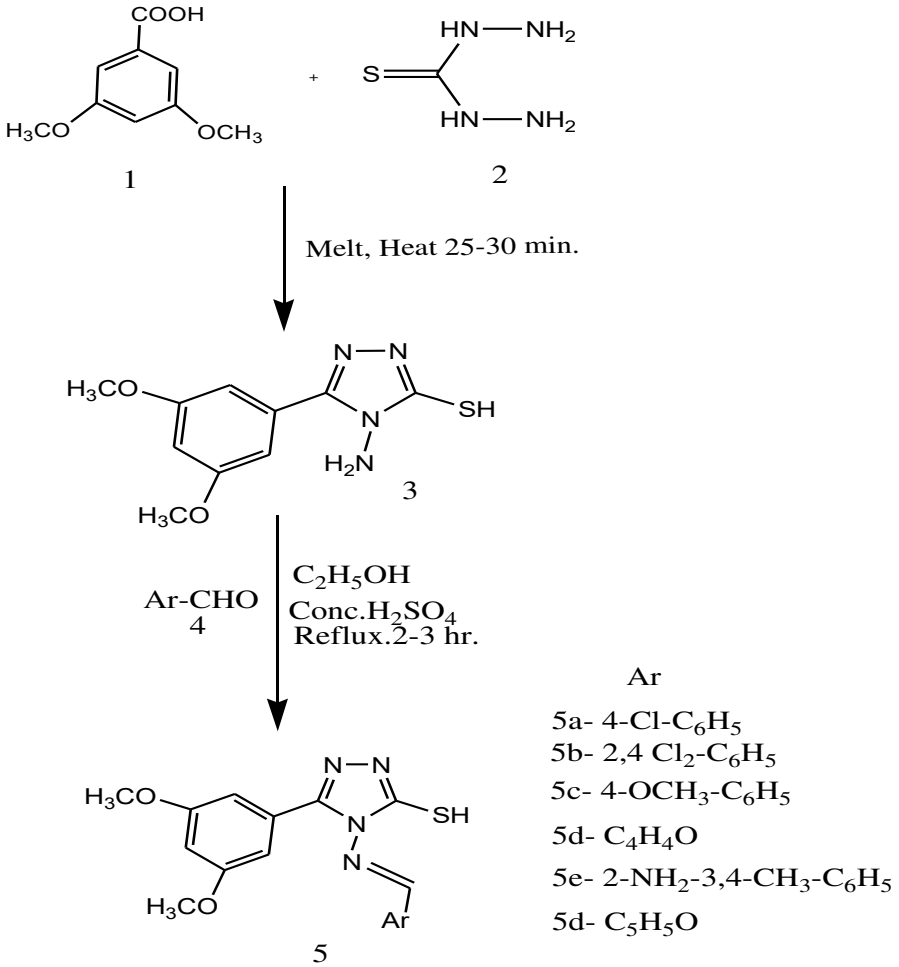

Fig. 1: Scheme for Synthesis of Schiff bases.

2.4. Antibacterial studies

The compounds, 5a-5f were screened against P.aeuroginose, E.coli and S. aureus by cup plate method and serial dilution method [14] DMSO was used as control while drug norfloxacin used as standard, all the synthesized compounds showed varying degree of activity against selected strains at concentrations 100 μg/ml and 150 μg/ml.

3. RESULT AND DISCUSSION

Table 1: Predicted physicochemical properties of compounds

Physicochemical Properties	Predicted Values						Ref.
Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
Molecular weight	374.84 g/mol	409.29 g/mol	370.43 g/mol	330.36 g/mol	383.47 g/mol	344.39 g/mol	[15]
No. of heavy atoms	25	26	26	23	27	24	
Fraction Csp3	0.12	0.12	0.17	0.13	0.21	0.19	
No. rotatable bonds	5	5	6	5	5	5	
No. H-bond acceptors	5	5	6	6	5	6	
No. H-bond donors	0	0	0	0	1	0	
Molar Refractivity	100.14	105.15	101.62	87.39	109.46	92.70	
TPSA	100.33 Å²	100.33 Å²	109.56 Å²	113.47 Å²	126.35 Å²	109.56 Å²	[16]

Table 2: Predicted Lipophilicity of compounds

Lipophilicity	Predicted Values						Reference
Compounds	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
Log $P_{o/w}$ (iLOGP)	3.12	3.17	3.52	3.05	3.35	3.32	[16]
Log $P_{o/w}$ (XLOGP3)	3.88	4.50	3.22	2.65	3.30	2.17	[17]
Log $P_{o/w}$ (WLOGP)	3.79	4.44	3.14	2.73	3.34	2.56	[18]
Log $P_{o/w}$ (MLOGP)	3.41	3.91	2.20	1.65	2.84	1.93	[19]
Log $P_{o/w}$ (SILICOS-IT)	3.79	4.44	3.21	2.55	3.47	2.21	[20]
Consensus Log $P_{o/w}$	3.60	4.09	3.06	2.53	3.26	2.44	Average

Lipophilicity of compounds to be synthesized were below 5 indicating these molecules could be explored as orally active critical importance of this physicochemical property for pharmacokinetics drug discovery.

Table 3: Predicted water solubility of compounds

Water Solubility	Predicted Values						[Ref.]
Compounds	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
Log *S* (ESOL)	-4.78	-5.37	-4.25	-3.74	-4.43	-3.35	[21]
Solubility (mg/ml)	6.20e-03	1.76e-03	2.07e-02	5.98e-02	1.42e-02	1.53e-01	
Class	Moderately soluble	Moderately soluble	Moderately soluble	Soluble	Moderately soluble	Soluble	
Log *S* (Ali)	-5.68	-6.33	-5.19	-4.68	-5.63	-4.10	[22]
Solubility	7.75e-04 mg/ml	1.92e-04 mg/ml	2.37e-03 mg/ml	6.84e-03 mg/ml	9.01e-04 mg/ml	2.71e-02 mg/ml	
Class	Moderately soluble	Poorly soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	
Log *S* (SILICOS-IT)	-6.09	-6.68	-5.61	-4.72	-5.88	-3.39	[20]
Solubility	3.05e-04 mg/ml	8.61e-05 mg/ml	9.20e-04 mg/ml	6.32e-03 mg/ml	5.03e-04 mg/ml	1.40e-01 mg/ml	
Class	Poorly soluble	Poorly soluble	Moderately soluble	Moderately soluble	Moderately soluble	Soluble	

Log S Scale: (Insoluble < -10, Poorly < -6, Moderately < -4, souble < -2, Very <0< Highly)

All predicted values are the decimal logarithm of the molar solubility in water (log *S*). Swiss ADME also provides solubility mg/ml along with qualitative solubility classes. Compounds to be synthesized shows moderate to poor water solubility indicating efforts should be taken to enhance solubility during formulation.

Human gastrointestinal absorption of compounds to be synthesized were found to be high with no blood-brain barrier permeability indicating molecule can absorb from intestine easily with no side effect in brains as it cannot passes through BBB.

The knowledge about compounds being substrate or non-substrate of the permeability glycoprotein provides information about its active efflux through biological membranes like gastrointestinal wall to the lumen or from the brain compounds to be synthesized were not substrate for P-gp

The information concerning interaction of molecules with cytochromes P450 (is critical because it plays important role in drug elimination through metabolic biotransformation. It is therefore of great importance for drug discovery to predict the tendency of the molecule to inhibit CYPs. All compounds to be synthesized were interact with cytochrome P450 isoform indicating these isoforms may be involved in biotransformation of this molecule.

Table 4: Predicted Pharmacokinetics properties of compounds

Pharmacokinetics	Predicted Values						[Ref.]
Compounds	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
GI absorption	High	High	High	High	High	High	[23]
BBB permeant	No	No	No	No	No	No	
P-gp substrate	No	No	No	No	No	No	[24]
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	No	Yes	
CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	

Table 5: Predicted Drug likeness of compounds

Drug likeness	Predicted Values						[Ref.]
Compounds	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	[25,26]
Ghose	Yes	Yes	Yes	Yes	Yes	Yes	[27]
Veber (GSK) filter	Yes	Yes	Yes	Yes	Yes	Yes	[28]
Egan (Pharmacia) filter	Yes	Yes	Yes	Yes	Yes	Yes	[29]
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	[30]

Table 6: Predicted Medicinal Chemistry of compounds

Medicinal Chemistry	Predicted Values						[Ref.]
Compounds	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	
PAINS (Pan Assay Interferance structures)	0 alert	0 alert	0 alert	0 alert	0 alert	0 alert	[31]
Brenk	2 alerts: imine_1, thiol_2	2 alerts: imine_1, thiol_2	2 alerts: imine_1, thiol_2	2 alerts: imine_1, thiol_2	3 alerts: aniline, imine_1, thiol_2	2 alerts: imine_1, thiol_2	[32]
Lead likeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 2 violations: MW>350, XLOGP3>3.5	No; 1 violation: MW>350	Yes	No; 1 violation: MW>350	Yes	[33]
Synthetic accessibility Score (1Easy to 10 difficult)	3.2	3.31	3.37	3.41	3.43	3.91	[34]

Table 7: Characterization data of Schiff bases 5a-5f

Comp.	Ar	Molecular Formula	M.P (°C)	Yield (%)	Analysis (%) Found (calculated)		
					C	H	N
5a	4-Cl-C_6H_5	$C_{17}H_{15}ClN_4O_2S$	212-213	60.19	54.47	4.03	*14.95*
5b	2,4-Cl_2-C_6H_5	$C_{17}H_{14}Cl_2N_4O_2S$	222-223	66.65	49.89	3.45	*13.69*
5c	4-OCH_3-C_6H_5	$C_{17}H_{16}N_4O_3S$	198-201	76.59	58.36	4.90	*15.12*
5d	C_4H_4O	$C_{18}H_{18}N_4O_3S$	188-190	68.40	54.53	4.27	*16.96*
5e	2-NH_2-3,4-CH_3-C_6H_5	$C_{19}H_{21}N_5O_2S$	225-228	50.56	59.51	5.52	*18.26*
5f	*4-OH-C_6H_5*	*$C_{15}H_{14}N_4O_3S$*	*218-219*	*64.99*	*57.29*	*4.52*	*15.72*

Table 8: Characterization data of Schiff bases 5a-5f

Comp.	IR (KBr) υ/ cm^{-1}	^{1}H NMR (δ, DMSO-d_6)	Mass (m/z)
3	1204 (C-O-C), 1647 (C=N), 3295 (N-H), 2960 (CH_3C-H), 1540 (Ar C=C), 1346 (C-N), 1158(C=S).	3.7, bis S, 6H (OCH_3), 5.2, S, 2 H.(NH_2),6.9-7.3, m, 6 H.(Ar-H),13.7, S, 1 H. (SH);	252.1 $[M+H]^+$
5a	1207 (C-O-C), 1647 (C=N), 3346 (N-H), 2956 (CH_3C-H), 1541 (Ar C=C), 1365 (C-N), 1159(C=S), 1051 (C-Cl);	3.8, bis S, 6H. (OCH_3), 6.57-7.8, m, 7 H. (Ar-H), 10.0, S, 1 H. (HC=N), 13.7, S, 1 H. (SH).	375.1 $[M+H]^+$
5b	1204 (C-O-C), 1647 (C=N), 3647 (N-H), 1541 (Ar C=C),1358 (C-N), 1165 (C=S), 1051 (C-Cl).	3.7, bis S, 6H (OCH_3), 6.5-8.1, m, 6 H.(Ar-H), 10.7, S, 1 H.. (HC=N), 13.9, S, 1 H. (SH).	409.1 $[M+H]^+$
5c	1202 (C-O-C), 1647 (C=N), 3295 (N-H), 2959 (CH_3C-H), 1540 (Ar C=C), 1367 (C-N), 1159(C=S).	3.7-3.8, tri S, 9 H. (OCH_3), 6.5-7.8, m, 7 H. (Ar-H), 9.7, S, 1 H. (HC=N), 13.9, S, 1 H (SH).	371.1 $[M+H]^+$
5d	1205 (C-O-C), 1688 (C=N), 3648 (N-H), 2941 (CH_3C-H), 1540 (Ar C=C), 1342 (C-N), 1157 (C=S).	3.7, S, 6 H. (OCH_3), 6.5-7.3, m, 6 H. (Ar-H), 9.9, S, 1 H. (HC=N),13.8, S, 1 H. (SH).	331.1 $[M+H]^+$
5e	1207 (C-O-C), 1647 (C=N), 3648 (N-H), 2932 (CH_3C-H), 1540 (Ar C=C), 1375 (C-N), 1167 (C=S).	2.5, S, 6 H. (CH_3), 3.1, S, 2 H. (NH_2) 3.8, bis S, 6 H. (OCH_3), 6.5-9.7, m, 5 H. (Ar-H), 9.5, S, 1 H. (HC=N), 13.8, S, 1H. (SH).	385.4 [M+2]
5f	1209 (C-O-C), 1647 (C=N), 3647 (N-H), 2939 (CH_3C-H), 1541 (Ar C=C), 1367 (C-N), 1165 (C=S), 1165-1209 (C-OH), 3613 (O-H).	2.8, S, 1 H. (OH) 3.7, bis S, 6 H. (OCH_3), 6.5-7.7, m, 7 H. (Ar-H), 9.8, S, 1 H. (HC=N), 13.7, S, 1 H. (SH)	357.1 $[M+H]^+$

Table 9: Antimicrobial activity of compounds 5a-5f by Cup and plate method (Zone of inhibition)

Compounds				5a	5b	5c	5d	5e	5f	STD
Zone of inhibition in mm	Gram positive	*E.coli*	100 µg/ml	16	15	29	10	25*	23	27
			150 µg/ml	19	17	33	16	27*	30	30
	Gram negative	*S.aureus*	100 µg/ml	11*	6	5	6	8	10	10
			150 µg/ml	14*	9	4	8	9	11	15

All the results were analyzed by one way ANOVA (n=3) using prism software and found to be significant (p==0.05)*

Table 10: Antimicrobial activity of compounds 5a-5fby serial dilution technique (Minimum Inhibitory Concentration)

Compounds				5a	5b	5 c	5d	5 e	5 f	STD
Minimum inhibitory concentration (MIC) in μM	Gram positive	*E.coli*	100 μg/ml	35	49	78	88	24*	28	26
			150 μg/ml	45	51	79	110	39*	38	40
	Gram negative	*S.aureus*	100 μg/ml	40*	39	33	48	50	59	44
			150 μg/ml	66*	90	130	68	110	70	66

All the results were analyzed by one way ANOVA (n=3) using prism software and found to be significant (p==0.05)*

All molecules showed 0.55 bioavailability Score and not violating any filter employed indicating that this molecule can be a drug could be synthesized and promoted to a further stage of a drug development pipeline.

Compound 5f showed significant antibacterial activity against gram positive bacteria's while compound 5a and 5d showed significant antibacterial activity against gram negative bacteria's.

4. CONCLUSION

We have predicted ADMET properties by using Swiss ADMET prediction tool before going for actual synthesis and biological activity. After analysis of predicted data series of 3, 5-dimethoxyphenyl bearing Schiff base triazole derivatives were synthesized. Structures of synthesized derivatives were characterized and confirmed by spectral analysis. All the synthesized compounds were screened for antibacterial activity and showed good antibacterial activity against all strains comparable to the standard. Hence, it is concluded that, there is ample scope for further study.

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