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Design and Synthesis of Biologically active Thiazolidinones nucleus containing 1, 3, 4-thiadiazole derivatives and evaluation of their Antimicrobial activity

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Abstract: In this work conventional as well as microwave techniques were used for the synthesis of 2-phenyl-3-(5 p-tolyl 1,3,4-thiadiazol-2-yl) thiazolidin-4-one and entire number of derivatives were synthesized from precursor Schiff's bases. Microwave-assisted organic synthesis (MAOS) is the study of chemical reactions under the effect of microwave radiation. Microwaves radiation have high energy electric fields and will generally heat any substance containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid. In recent year the synthesis of Schiff bases under influence of microwave irradiation was found much easier and faster than conventional heating. The synthesis in Microwave irradiation in solvent free or lower solvent conditions are good method for reduce the pollution, lowering the cost and increase the product together with simplicity in processing and handling. The synthesized compounds were screened for antibacterial activity compared against Gram-positive bacteria and Gram- negative bacteria was also studied using the minimum inhibition concentration method. The synthesized derivatives were showed better results for antibacterial evaluation against gram-positive (*Staphylococcus aureus, Bacillus subtilis*), gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and were found to be good antibacterial agent and for Antifungal activity against fungal strains (Candida albicans, A. niger) also showed better results. The advantages of this method include good to excellent yields, operational simplicity, shorter reaction time and easy work up procedures.

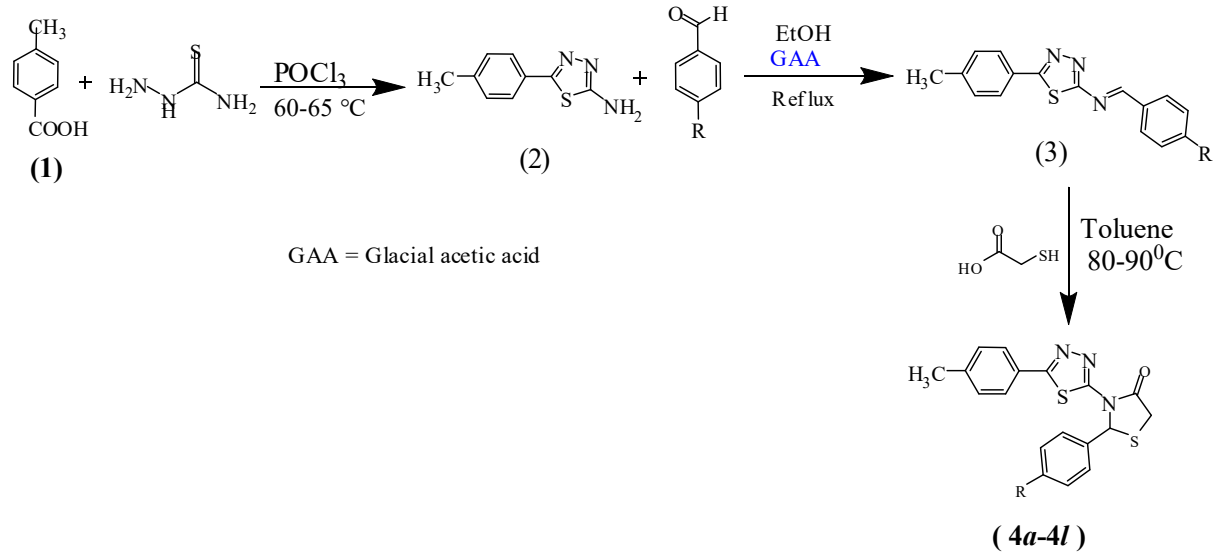
Keywords: Antibacterial, Schiff base, Gram-positive bacteria, Gram- negative bacteria, 1,3,4-thiadiazol, Antifungal, ADME prediction, Microwave.

Introduction: Hetero aromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Heterocyclic compound containing nitrogen atoms in the core structure shows a number of pharmacologically and biologically active compounds [1]. The 1,3,4-thiadiazole ring

is one of the most important and well-known heterocyclic nuclei, which has been wide range of scope in pharmaceutical industry because of their interesting biological activities such as antibacterial and antifungal and specially used in the preparation of antibacterial therapy of microbes and also many thiadiazole drugs have been developed and successfully used from many years for the treatment of bacterial and fungal diseases[2]. 1,3,4-thiadiazol, and thiazolidin these moiety is present into synthesis of a new class of heterocyclic molecules and attempt to develop possible biological active molecules[3]. Thiadiazole show a broad range of biological activities and are found in many potential biological active molecules such as antimicrobial [4-11] Antibacterial [12] and anticonvulsant drugs [13-14] anticancer [15] anti-inflammatory activity [16] anti-tubercular [17] and antifungal activities [18]. Due to the resistance of pathogenic bacteria towards available Antibacterial drugs is rapidly becoming a main worldwide problem, the design and synthesis of new class of chemical moieties to handle with resistant bacteria has become one of the significant areas of antibacterial research today. In pharmaceutical and medical healthcare field new drugs are discovered by molecular modification of the main compound of established activity. So an attempt was made to synthesize, new substituted 1,3,4-thiadiazoles compounds as antimicrobial with the help of Schiff base. Many natural occurring biologically active compounds possesses heterocyclic moiety including organic resources also which is essential to the life of modern society and is dependent on synthetic heterocyclic compounds for new discovery of drugs. The structures of these compounds were confirmed by means of MS, ^{1}H NMR.

Materials and method

The entire chemicals and solvents were used in the present investigation were purchased from commercial suppliers and used without further purification. The reactions and purity of the products were monitored by thin layer chromatography (TLC) using silica gel coated aluminum sheets. Melting points were determined on open capillary tubes and were uncorrected. Mass spectra were recorded on Shimadzu mass-spectrometer. NMR spectra were recorded on a Bruker advance II 400 NMR Spectrometer.



Scheme

Results and Discussion:

Desired products (4) were synthesized using an identical effective conventional and microwave synthetic route outlined in Scheme. Compound (4) was synthesized by reacting with 4-methyl benzoic acid and thiosemicarbazide in presence of phosphorus oxychloride at 60-65°C for one hour. The reaction mass was cooled and diluted with water and again refluxed for 3 h. The reaction was monitored by thin layer chromatography and filtered after completion of reaction. The filtrate was basified with potassium hydroxide and the precipitate was filtered off and then recrystallized from ethanol to give the desired compound (2) and then compound (2) was reacted with substituted aromatic aldehyde to form Schiff's base (3) and further compound (3) was reacted with thioglycolic acid and toluene as a solvent to form substituted compound (4) as a product in good yield.

Conventional vs. microwave irradiation method:

Schiff bases were synthesized by condensation of Substituted aromatic aldehyde with different substituted aromatic amines (2) (1:1 mole ratio) in ethanol (10 ml) at 80°C. On the other hands in microwave irradiation method, reactant mixtures were subjected to microwave power at 300 W from 30 sec to 2 min and temperature was maintained at 80°C. The progress of the reaction at different time interval was monitored by TLC (Table 2). On completion of reaction, the yellow coloured amorphous product (3) was separated, filtered, dried and recrystallized from methanol. In microwave assisted reaction as reaction occurred within very short time (30sec - 2 min), no reaction parameters were varied. Compounds (1-12) in table no (1) were synthesized maintaining a particular reaction condition.

General procedure for the synthesis of the derivative 2-phenyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one: (2)

In a clean four Neck RBF, take a solution of 4-methyl benzoic acid (0.05 mol) was refluxed with thiosemicarbazide (0.05 mol) in the presence of phosphorus oxychloride (15 ml) for 1 h. The reaction mixture was cooled and diluted with water and again refluxed for 4 h. The reaction was monitored by thin layer chromatography and filtered after completion. The filtrate was basified with potassium hydroxide and the precipitate was filtered off and then recrystallized from ethanol to give the desired compound 2. mp:204-206°C ^{1}H-NMR d (ppm) δ: 2.35 (3H, s, CH_3); 7.29-7.67 (4H, m, Ar-H); 7.22 (2H, s, -NH_2) MS: m/z 192 (M + 1).

(4-methylbenzylidene)-5-p-tolyl-1,3,4-thiadiazol-2-amine: (3)

A mixture of (2) (0.01 mol) and aromatic aldehyde (0.01 mol) were dissolved in 30ml of ethanol containing few drops of glacial acetic acid. The reaction was refluxed for 5h. Cooled and then poured into crushed ice and the resultant solid was recrystallized from ethanol.

2-Phenyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-one: (4)

To the Schiff's base (3) add thioglycolic acid in equimolar ratio and refluxed the above reaction mass using toluene as a solvent for 10-12 hrs. cool the reaction mass and then mix the reaction mass with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystallized from ethanol and melting point 201-205°C.

1) 2-p-tolyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-one:

$C_{19}H_{17}N_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz,) δ(ppm): 2.35-2.37 (6H, m, -CH_3), 7.30-7.68 (4H, m, Ar-H), 7.10-7.16 (4H, m, Ar-H), 3.85-3.95 (2H, s, -CH_2), 6.45 (1H, s, -CH), M/Z: m/z 368 [M+1].

2) 2-Phenyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{15}N_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz,) δ(ppm): 2.34 (3H, s, -CH_3), 7.28-7.67 (4H, m, Ar-H), 7.25-7.37 (5H, m, Ar-H), 3.84-3.96 (2H, s, -CH_2), 6.43 (1H, s, -CH), M/Z: m/z 354 [M+1].

3) 2-(4-hydroxyphenyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{15}N_3O_2S_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.35 (3H, s, -CH_3), 7.29-7.67 (4H, m, Ar-H), 6.63-7.78 (4H, m, Ar-H), 3.85-3.96 (2H, s, -CH_2), 6.44 (1H, s, -CH), 9.42 (1H, s, Ar-OH), M/Z: m/z 370 [M+1].

4) 2-(3-hydroxyphenyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{15}N_3O_2S_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.33 (3H, s, -CH_3), 7.30-7.69 (4H, m, Ar-H), 6.78-7.15 (4H, m, Ar-H), 3.83-3.94 (2H, s, -CH_2), 6.45 (1H, s, -CH), 9.43 (1H, s, Ar-OH), M/Z: m/z 370 [M+1].

5) 2-m-tolyl-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{19}H_{17}N_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.34 (1H, s, -CH_3), 2.36 (1H, s, -CH_3), 7.28-7.68 (4H, m, Ar-H), 7.03-7.43 (4H, m, Ar-H), 3.85-3.95 (2H, s, -CH_2), 6.44 (1H, s, -CH), M/Z: m/z 368 [M+1].

6) 2-(4-methoxyphenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{19}H_{17}N_3O_2S_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.32 (1H, s, -CH_3), 3.83 (1H, s, -CH_3), 7.25-7.69 (4H, m, Ar-H), 6.87-7.84 (4H, m, Ar-H), 3.83-3.95 (2H, s, -CH_2), 6.42 (1H, s, -CH), M/Z: m/z 384 [M+1].

7) 2-(3-methoxyphenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{19}H_{17}N_3O_2S_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.32 (1H, s, -CH_3), 3.83 (1H, s, -CH_3), 7.25-7.69 (4H, m, Ar-H), 6.87-7.84 (4H, m, Ar-H), 3.83-3.95 (2H, s, -CH_2), 6.42 (1H, s, -CH), M/Z: m/z 384 [M+1].

8) 2-(4-ethoxyphenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{20}H_{19}N_3O_2S_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.35 (1H, s, -CH_3), 1.32-4.10 (5H, m, -OC_2H_5), 7.25-7.69 (4H, m, Ar-H), 6.87-7.84 (4H, m, Ar-H), 3.83-3.95 (2H, s, -CH_2), 6.45 (1H, s, -CH), M/Z: m/z 398 [M+1].

9) 2-(4-bromophenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{14}BrN_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.33 (1H, s, -CH_3), 7.27-7.67 (4H, m, Ar-H), 7.12-7.85 (4H, m, Ar-H), 3.84-3.97 (2H, s, -CH_2), 6.43 (1H, s, -CH), M/Z: m/z 432 [M+1].

10) 2-(3-bromophenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{14}BrN_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.34 (1H, s, -CH_3), 7.28-7.66 (4H, m, Ar-H), 7.12-7.85 (4H, m, Ar-H), 3.84-3.95 (2H, s, -CH_2), 6.44 (1H, s, -CH), M/Z: m/z 432 [M+1].

11) 2-(4-chlorophenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{14}ClN_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.36 (1H, s, -CH_3), 7.26-7.67 (4H, m, Ar-H), 7.17-7.37 (4H, m, Ar-H), 3.85-3.96 (2H, s, -CH_2), 6.45 (1H, s, -CH), M/Z: m/z 432 [M+1].

12) 2-(3-chlorophenyl)-3-(5-p-tolyl-1,3,4-thiadiazol-2-yl)thiazolidin-4-one:

$C_{18}H_{14}ClN_3OS_2$ mp: 209-211^{0}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ(ppm): 2.34 (1H, s, -CH_3), 7.27-7.68 (4H, m, Ar-H), 7.15-7.38 (4H, m, Ar-H), 3.84-3.95 (2H, s, -CH_2), 6.44 (1H, s, -CH), M/Z: m/z 432 [M+1].

Table: 1

Sr. No	-R-	Product	Yield (%)
1	4-CH_3	$C_{19}H_{17}N_3OS_2$	78
2	H	$C_{18}H_{15}N_3OS_2$	75
3	4-OH	$C_{18}H_{15}N_3O_2S_2$	72
4	3-OH	$C_{18}H_{15}N_3O_2S_2$	70
5	3-CH_3	$C_{19}H_{17}N_3OS_2$	72
6	4-OCH_3	$C_{19}H_{17}N_3O_2S_2$	74
7	3-OCH_3	$C_{19}H_{16}ClN_3O_2S$	70
8	4-OC_2H_5	$C_{20}H_{19}N_3O_2S_2$	75
9	4-Br	$C_{18}H_{14}BrN_3OS_2$	68
10	3- Br	$C_{18}H_{14}BrN_3OS_2$	65
11	4-Cl	$C_{18}H_{14}ClN_3OS_2$	78
12	3- Cl	$C_{18}H_{14}ClN_3OS_2$	71

Antibacterial Activity:

In vitro antibacterial activity was determined by standardized disk diffusion methods. The newly synthesized compounds (1-12) were tested for their antimicrobial activity. In this work Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa bacterial strains were used. The test bacteria were subcultured using nutrient agar medium. Freshly prepared sterilized nutrient agar media were poured 20 ml into each petri plate and allowed to solidify with the respective strains of bacteria was transferred aseptically. The plates were kept undisturbed for at least 20 min in refrigerator to allow diffusion of the solution properly in the nutrient agar medium. The plates were incubated at 37 ± 1^{0}C for 24 h. Then a well 0.5cm was made in the medium by using sterile cork borer, 50µl of every compounds were transferred into separate wells. Then these plates were incubated at 37°C for 24 hours. After incubation period the results were observed and measured the diameter of inhibitor zone around the each well. The zones of growth inhibition around the well were measure after 24 hours at 37^{0}C. Streptomycin was used as standard drug for antibacterial activity.

Antifungal Activity:

In vitro antifungal activity was determined by agar well diffusion method. The newly synthesized compounds (1-12) were screened for their antifungal activity. In this work and Candida albicans and A.niger fungal strains were used. The test fungi were subcultured using potato dextrose agar medium. Freshly prepared sterilized potato dextrose agar media were poured 20 ml into each petri plate and allowed to solidify. The test fungal cultures were evenly spread over using sterile cotton swab. Then a well 0.5cm was made in the medium by using sterile cork borer, 50µl of each compound were transferred into separate wells. Then these plates

Table 2: Synthesized Antibacterial Derivatives:

Sr. No	C Compound	Product	S. aureus ZOI (mm)	B. subtilis ZOI (mm)	E. coli ZOI (mm)	P. aeruginosa ZOI (mm)
1	H	$C_{16}H_{13}N_3OS$	13	12	11	15
2	p-CH_3	$C_{17}H_{15}N_3OS$	10	13	11	08
3	p-OH	$C_{17}H_{15}N_3O_2S$	13	09	10	12
4	m-OH	$C_{17}H_{15}N_3OS$	16	13	17	13
5	m-CH_3	$C_{17}H_{15}N_3O_2S$	18	15	19	14
6	p-OCH_3	$C_{18}H_{17}N_3OS$	13	08	11	10
7	p-OC_2H_5	$C_{18}H_{17}N_3O_2S$	11	12	12	10
8	m-OCH_3	$C_{17}H_{14}ClN_3OS$	12	13	10	12
9	p-Br	$C_{16}H_{12}ClN_3OS$	11	12	14	12
10	p-Cl	$C_{16}H_{12}BrN_3OS$	12	14	12	11
11	m- Br	$C_{17}H_{14}ClN_3OS$	13	16	14	15
12	m- Cl	$C_{17}H_{14}BrN_3OS$	15	14	17	14
13	--- -	Steptomycin(Std)	19	20	22	18

were incubated at 27°C for 48-96 hours. After incubation period the results were observed and measured the diameter of inhibitor zone around the each well. The zones of growth inhibition around the well were measure after 48 to 96 hours at 28°C. Nystatin was used as standard drug for antifungal activity.

Table 3: Synthesized Antifungal Derivatives:

Sr. No	Compound	Product	C. albicans ZOI (mm)	*A. niger* ZOI (mm)
1	H	$C_{16}H_{13}N_3OS$	8	10
2	p-CH_3	$C_{17}H_{15}N_3OS$	16	11
3	p-OH	$C_{17}H_{15}N_3O_2S$	19	14
4	m-OH	$C_{17}H_{15}N_3OS$	22	19
5	m-CH_3	$C_{17}H_{15}N_3O_2S$	18	15
6	p-OCH_3	$C_{18}H_{17}N_3OS$	13	16
7	p-OC_2H_5	$C_{18}H_{17}N_3O_2S$	15	15
8	m-OCH_3	$C_{17}H_{14}ClN_3OS$	16	20
9	p-Br	$C_{16}H_{12}ClN_3OS$	10	15
10	p-Cl	$C_{16}H_{12}BrN_3OS$	13	17
11	m- Br	$C_{17}H_{14}ClN_3OS$	12	10
12	m- Cl	$C_{17}H_{14}BrN_3OS$	13	12
13	- -	Nystatin (Std)	23	26

Computational study

In silico ADME prediction

A computational study of all the synthesized (**4a-4l)** was performed for prediction of ADME properties and the value obtained is presented in **Table 4**. It is observed that, the compounds exhibited a good % ABS (% absorption) ranging from 86.11 to 93.11 %. Furthermore, only compounds **4l, 4j, 4k** and **4l,** violated Lipinski's rule of five (miLog $P \leq 5$). A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 .The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. using Molinspiration online property calculation toolkit. Absorption (% ABS) was calculated by: % ABS = 109-(0.345×TPSA) Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Conclusion:

In conclusion, we have designed and synthesized biologically active Thiazolidinone nucleus containing 1,3,4-thiadiazole derivatives by suitable methods. The satisfactory results obtained by the synthesized compounds, and the attracting significance of thiadiazole can be better explored in future as an effective candidate for antitubercular activity. It is also note that the toxicity studies have been carried out for these compounds and least toxicity is being found in all these compounds. The most compounds show high valuable character for further evaluation.

Furthermore, analysis of the ADME parameters for synthesized compounds showed good drug like properties and can be developed as oral drug candidate.

Table 4 : Pharmacokinetic parameters important for good oral bioavailability

Cpd	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
4a	93.11	46.04	3	298.50	353.47	4.40	4	0	0	-0.33
4b	93.09	46.09	3	315.06	367.5	4.85	4	0	0	-0.47
4c	86.11	66.32	3	306.50	369.47	3.92	5	1	0	-0.03
4d	86.11	66.32	3	306.01	369.47	3.90	5	1	0	0.29
4e	93.09	46.09	3	315.05	367.5	4.83	4	0	0	-0.23
4f	89.91	55.33	4	324.05	383.5	4.46	5	0	0	-0.47
4g	89.91	55.33	4	324.05	383.5	4.43	5	0	0	-0.15
4h	89.91	55.33	5	340.85	397.5	4.83	5	0	0	-0.29
4i	93.09	46.09	3	316.38	432.37	5.21	4	0	1	-0.43
4j	93.09	46.09	3	316.39	432.37	5.19	4	0	1	-0.31
4k	93.09	46.09	3	312.04	387.92	5.08	4	0	1	0.02
4l	93.09	46.09	3	312.04	387.92	5.05	4	0	1	0.02

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