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SYNTHESIS CHARACTERIZATION & ANTIMICROBIAL ACTIVITY OF SOME NOVEL OXADIAZOLE DERIVATIES

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ABSTRATED

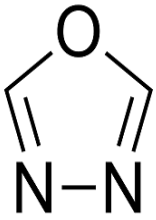
In present study oxadiazole derivatives were synthesized and microbialActivity and anti inflammatory activity of different derivatives were checked with various microbial stain and rates. Various intermediates was synthesized and characterized in between time to time by chromatography and special methods. Substituted salicylic acid and diethyl malonate were starting material and finally formed 3-(-4-acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazole-2-yl)-2h-chromene-2one, while in the intermediate steps ethanol react with s Schiff base with reflex to get ethyl2-oxa-2H-Chromene-3-corboxylate, than othe intermediate fond during synthesis in 2-oxo-N-[(1E)-1-phenylethylidene]-2H-chromene- 3-carbohydrazide 2 – hydroxy-N. The structure of the entire compound was established on the basis of element, chromatography and spectral analysis. The synthesized compound was for their antimicrobial activity and anti inflammatory activity show. The compound most active be against Staphylococcus aureus, Bacillus subtillis and Carrageenan induced rat hind paw edema.

KEYWARDS: Oxadiazole Antimicrobial, Anti-inflammatory, Salicylic acid,

INTRODUCTION

Oxadiazoles are cyclic compounds that containing one oxygen and two nitrogen atoms in a five membered ring structure.[1] Literature survey reveals that 1, 3, 4-oxadiazoles have attracted an interest in medicinal chemistry as ester and amide bioisosteres for a number of biological targets. As aconsequence of these characteristics the 1,3,4-oxadiazole derivatives have been found to biological activities such as antimicrobial[2,3] anti- AIDS,[4]

antitubercular,[5,6,7] anti malarial, analgesic,[8] anti-inflammatory,[9] anticonvulsant,[10,11] hypoglycemic and other biological properties such as genotoxic studies and lipid peroxidation inhibition. The sequence of these atoms may be different as following. Researchers have already reported that gram positive bacteria are much more susceptible to antimicrobial agents as compared to gram negative bacteria.[12] Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photosensitizers (Chem Abst, 1983) and liquid crystals Common synthetic approa Common synthetic approaches to oxadiazolesches to oxadiazoles. Typically, the reaction is promoted by heat and anhydrous reagents including thionyl chloride, phosphorous oxychloride, phosphorous pentoxide, triphenylphosphine, Lawesson's reagent, nd triflic anhydride.[13] Oxadiazoles are thermally stable compounds and their calculated resonance energy is equal to 167.4 kJ/mol. The thermal stability of oxadiazoles is increased with the substitution at the second position.[1,2,3]



Dioxadiazole

Experiment

Step I: Synthesis of ethyl-2-oxo-2H-chromene-3-carboxylate

In a round bottom flask 3.1 ml (0.0258 mol) of salicyaldehyde and 4.4ml (0.0275 mol) ofDiethyl malonate were dissolved in about 10 ml of ethanol and 0.25 ml of piperidine anda drop of glacial acetic acid was added. The reaction mixture was refluxed for 3.25 min and then cooled at room temperature toform the crystals. The cooled reaction mixture was kept in the refrigerator overnight. The product was filtered and washed with cold ethanol and dried to get white shinycrystals. IR (KBr, cm-1): 2929 (Ar CH Str),1714 (C=O, lactone),1616 (C=O, ester),1247 (C-O, coumarin),756 (Ar CH Bend).1H NMR (δ ppm): 1.42 (3H, t, CH3),4.44 (2H, q, CH2),7.27-7.69 (4H, m, Ar-H),8.53 (1H, s, Ar-H).

Step II: Synthesis of 2-oxo-2H-chromene-3-carbohydrazide

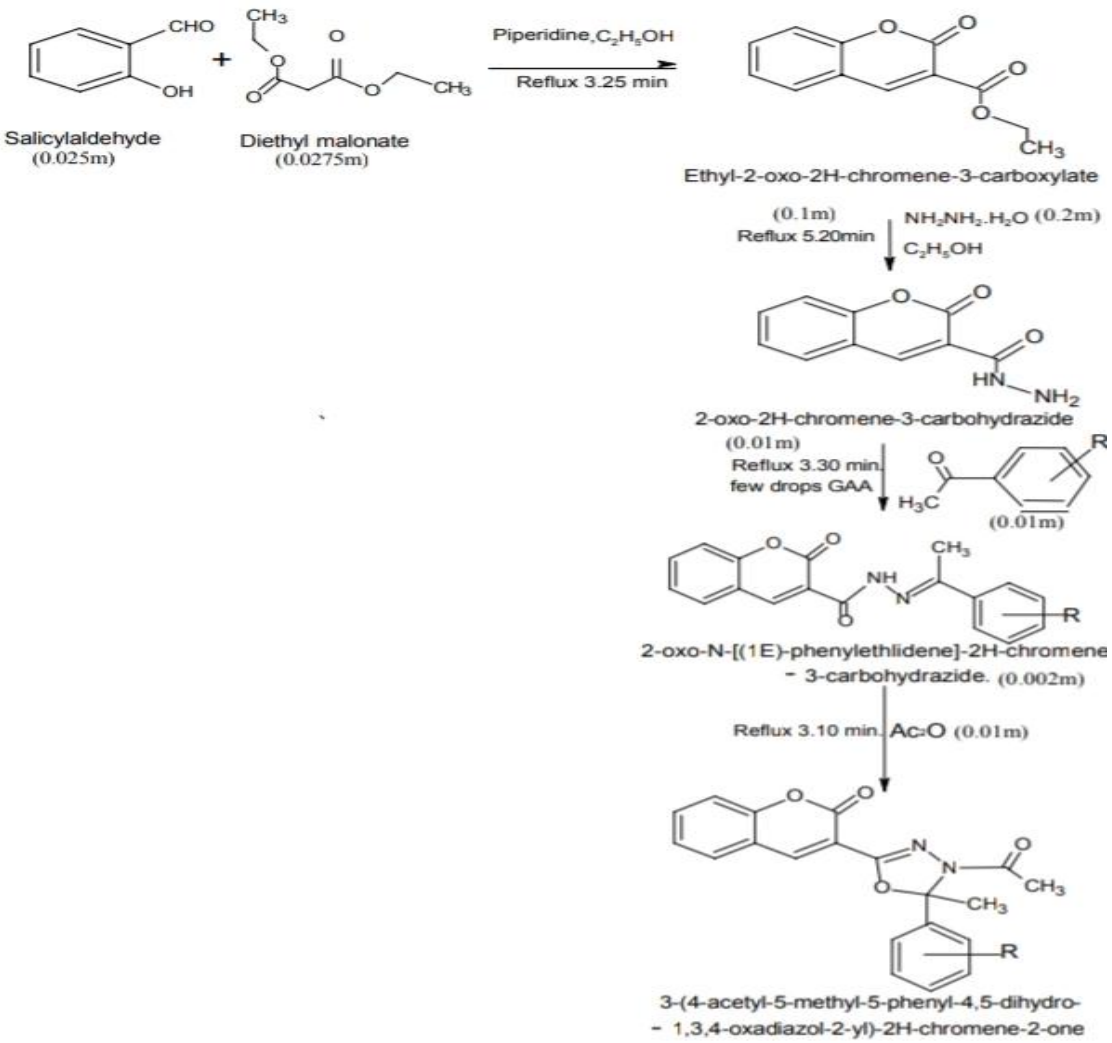
A mixture of 0.1 mol of ester and 0.2 mol of hydrazine hydrate were refluxed in 50ml of95% ethanol for 5.20 min. The resultant mixture was concentrated, cooled and poured on to crushed ice. The solid mass was separated out through filtered, dried and purified by

Recrystalizationfrom ethanol. IR (KBr, cm-1): 3382 (NH2), 2929(Ar CH), 1617 (C=O, lactone), 1572 (C=O, ketone), 1196 (C-O, coumarin), 754 (Ar CH**).**

Step III: Synthesis of 2-oxo-N-[(1E)-1-phenylethylidene]-2H-chromene- 3-carbohydrazide

In a round bottom flask equimolar mixture of 2-oxo-2H-chromene-3- carbohydrazide andsubstituted aromatic ketone were dissolved in ethanol and was subjected for refluxationon a water bath for 3.30 min in the presence of few drops of acetic acid. The reaction mixture was later poured into ice-cold water and the solid formed wasfiltered out and dried. The dried solid was then recrystallized from ethanol. IR (KBr, cm-1): 2916 (Ar CH Str.), 1691 (C=O, lactone), 1618 (C=O, ketone), 1525 (C=N), 1346 (C-NO2), 1197 (C-O, coumarin) 763 (Ar CH Bend.).

Scheme

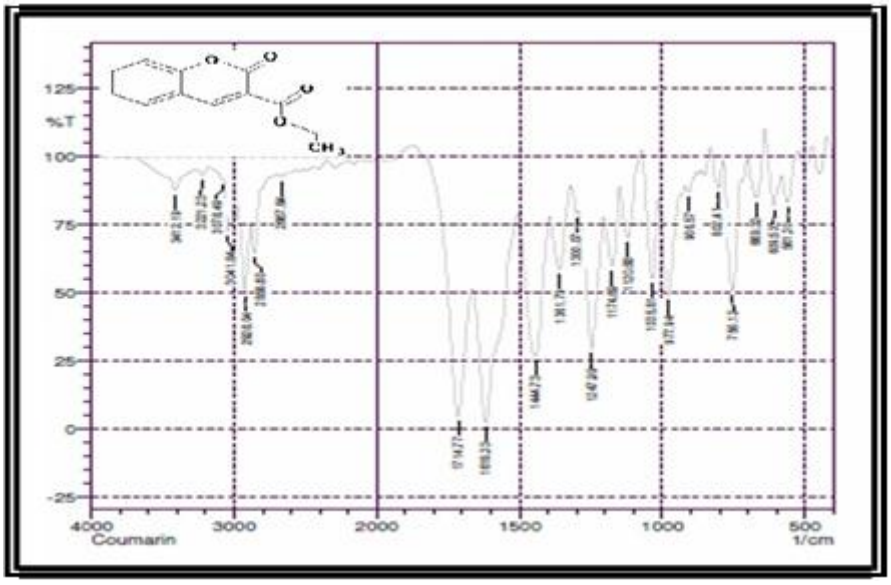


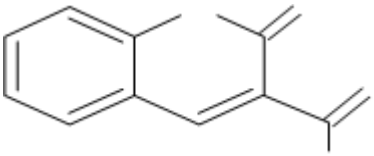
Step IV: Synthesis of 3-(4-acetyl-5-methyl-5-phenyl-4, 5-dihydro- 1,3,4-oxadiazol-2-yl)-2H-chromen-2-one

(0.002 mol) of 2-oxo-N-[(1E)-1-phenylethylidene]-2H-chromene-3-carbohydrazide in excessive acetic anhydride (10 mL) was subjected for refluxation for3.10 min. The excessive acetic anhydride was distilled off at reduced pressure and the residue waspoured into crushed ice. The solid product obtained was filtered and recrystallized from ethanol to give 3-(4-acetyl-5-methyl-5-phenyl-4, 5-dihydro-1,3,4-oxadiazol-2-yl)-2H- chromen-2-one. IR (KBr, cm-1): 3012 (Ar CH Str.), 1768 (C=O, lactone), 1616 (C=O, ketone), 1531 (C=N), 1369(C-NO2), 1280 (C-O-C) [oxadiazole nucleus],1199 (C-O, coumarin),763 (Ar CH Str.).1H NMR (δ ppm): 2.38 (3H, s, 2CH3), 7. 15 (4H, m, Ar-H), 7. 44 (1H, s, Ar-H), 7. 9 (2H, d, Ar-H), 8.11 (2H, d, Ar-H

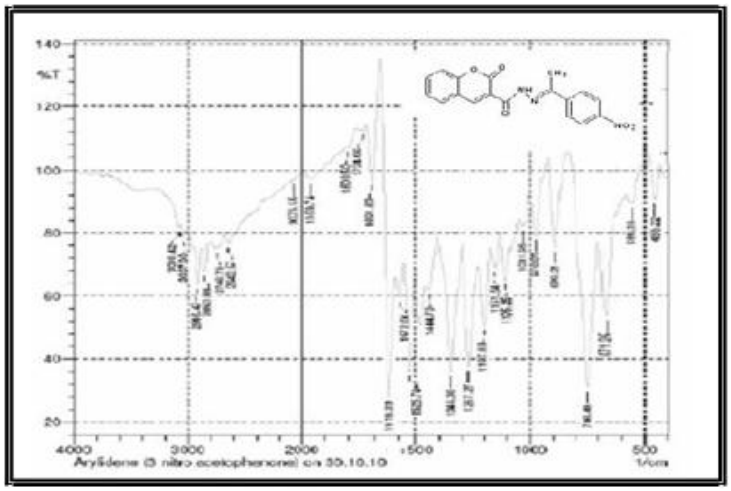
Table 1: List of compounds synthesized.

Compound code	R
R	H
1R	2,4 –dichloro
2R	2,4 –dihydroxy
3R	3- hydroxyl
4R	3-nitro
5R	2,4- dimethoxy
6R	4-nitro
7R	4-hydroxy
8R	2-hydroxy
9R	10 R 4-chloro





1] Ethyl-2-oxo-2H-chromene-3-carboxylate.



(4-acetyl-5-methyl-5-phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl)-2H-chromene-2-o

Pharmacological study

Antimicrobial study[15]

In our current study, the antimicrobial activity was carried out by Filter Disk.

Method

The responses of microorganisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drugs used in the

Microorganisms used

Four microorganisms selected for these study: Escherichia coli (Gram –ve), Pseudomonas aeruginosa (Gram –ve), Staphylococcus aureus (Gram +ve), Bacillus subtilis (Gram +ve).

The bacterial stock cultures were obtained from Microbiology department, Choithram hospital Indore.

Nutrient agar media: Beef extract 10.0 g, Agar 20.0 g, Peptone 10.0 g, Nacl 5.0 g, Distilled water 1000 ml present work was Amoxycillin trihydrate.

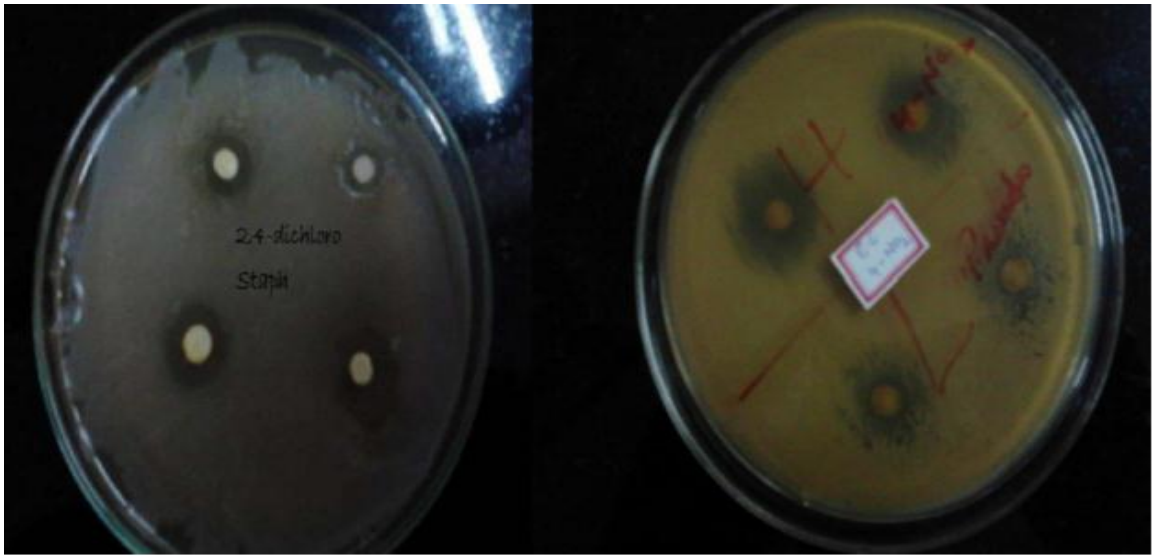


Figure No. 1: Zone of inhibition of standard compounds.

Table no. 2: Antibacterial activity of the synthesized compounds by.

S. N.	Compound Code	Zone of inhibition			
		1*	2*	3*	4*
1	Compound 1R	12	10		12
2	Compound 2R	11	10		11
3	Compound 3R	12	10	12	11
4	Compound 4R				
5	Compound 5R		14		16
6	Compound 6R				
7	Compound 7R	12			14
8	Compound 8R				
9	Compound 9R				
10	Compound 10R	11	15		12
STD	Amoxycillin trihydrate	23	22	23	24

1. **** S. aureus,***
2. **** B. subtilis,***
3. **** E.coli,***
4. ****P.aeruginosa***

Filter Disc method.

Anti-Inflammatory activity [16]

The anti-inflammatory activity of the newly synthesized acetylated Oxadiazole derivatives was carried out using Carrageenan induced rat hind paw edema

Method: Inhibition of carrageenan induced inflammation in rat paw.

- Animals used: Albino Wistar rats

- Number of animals used: n=6
- Dose of compound: 100 mg/kg
- Dose of standard drug: 50 mg/kg (Diclofenac)
- Route of administration: Oral (1% Sodium CMC Suspension)

Inflammation is a tissue-reaction to infection, irritation or foreign substance. Itis a part of host defence mechanism. The inflammatory reaction is readily produced in rats in the form of paw edemawith the help of irritants. Substances such as Carrageenan, Formalin, Bradykinin, Histamine, Mustard, when injected to the dorsum of the foot of rats, they produce acutepaw edema within a few min. of injection. Carrageenan is a sulphated polysaccharide obtained from sea weed (Rodophyceae), and by causing the release of histamine, 5-HT, Bradykinin andprostaglandin, it produces inflammation and edema. Experimental design and procedure[17,18] Rats were assigned into 12 groups of 6 animals each. They were marked with picric acid for individual animal identification. The animals were deprived of food overnight (allowed free access to water ad libitium) and the synthetic compounds were administered 1 hr prior to Carrageenan injection. Dose volume not exceeding 1ml/100mg orally was administered.

Group I: The solvent control received normal saline.

Group II: Positive control received Diclofenac Sodium (50mg/kg)

Group III: Received Acetylated Oxadiazole Derivative-1R at a dose of 100mg/kg suspended in 1%w/v CMC**.**

Group IV: Received Acetylated Oxadiazole Derivative-2R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group V: Received Acetylated Oxadiazole Derivative-3R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group VI: Received Acetylated Oxadiazole Derivative-4Rat a dose of 100mg/kg suspended in 1%w/v CMC.

Group VII: Received Acetylated Oxadiazole Derivative-5R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group VIII: Received Acetylated Oxadiazole Derivative-6R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group IX: Received Acetylated Oxadiazole Derivative-7R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group X: Received Acetylated Oxadiazole Derivative-8R at a dose of 100mg/kg

suspended in 1%w/v CMC.

Group XI: Received Acetylated Oxadiazole Derivative-9R at a dose of 100mg/kg suspended in 1%w/v CMC.

Group XII: Received Acetylated Oxadiazole Derivative-10R at a dose of 100mg/kg suspendedin 1%w/v CMC.

After 1 hour of test compound administration, 0.1 ml of 0.1%w/v of carrageenan innormal saline was injected into the sub plantar region of the left hind paw of the rat. Immediately after the Carrageenan injection, the volume of its displacement wasmeasured using Plethysmometer.

The readings were recorded at 0, 60, 120 & 180 mins. The % inhibition of edema was calculated at the end of 180 mins by using the formula

% inhibition = 100 x (1-Vt /Vc)

Vt/Vc = edema volume in the rat treated with test drug and control respectively.

Table no. 3: Effect of 1, 3, 4-oxadiazole derivatives on carrageenan induced hind paw edema in rats.

Compound	Volume Increased paw			%decreasedecreasein pawvolume.
	After 60 min	After120min.	After180min..	
Control	0.355±0.004	0.44±0.012	0.471±0.014	60.10
Diclofenac Sod.	0.093±0.003***	0.16±0.010***	0.188±0.009***	52.20
1	0.136±0.012***	0.193±0.009***	0.225±0.008***	50.10
2	0.153±0.019***	0.205±0.019	0.235±0.016***	34.18
3	0.153±0.019***	0.28±0.006***	0.31±0.005***	31.21
4	0.278±0.0172**	0.326±0.01**	0.324±0.018**	27.60
5	0.156±0.005***	0.296±0.059**	0.341±0.048*	53.29
6	0.28±0.014**	0.19±0.032***	0.22±0.03***	34.60
7	0.325±0.009ns	0.273±0.050**	0.308±0.03***	32.48
8	0.29±0.016*	0.295±0.004ns	0.318±0.04**	21.44
9	0.131±0.013***	0.333±0.01*	0.37±0.009ns	53.71

Where,* represents mild significant at P<0.05, ** represents moderate significant at P<0.01,

*** represents highly significant at P<0.001 & ns = non significant at P>0.05 Vs control.

Values are expressed as Mean ± SEM, [number of animal (n) = 6

RESULTS AND DISCUSSION

Oxadiazole derivatives are a class of heterocyclic compounds. Oxadiazole nucleus as suchi mpacted numerous drug discovery programs including- antispasmodics, nematocidal, fungicidal & microbicides, analgesics, anti-inflammatory, antibacterials, immunosuppressants, antiplatelets & antithrombics. These interesting pharmacological properties exhibited by Oxadiazole derivatives haveprompted us to synthesize some novel Oxadiazole derivatives as possible anti-inflammatory, anticonvulsant, antimicrobial, anti-tubercular and antioxidants. The reactions were monitored by TLC. The physical constants like melting point weredetermined for all the intermediates and final products. The compounds were furthercharacterized by IR and 1H NMR. All the compounds were evaluated for their antibacterial. The antimicrobial activity wascarried out by Filter Disc method and during screening, observed that compounds with acetophenone, 2, 4 di-chloro, 2,4 di-hydroxy, 4-nitro and 4-chloro substituted acetophenonederivatives showed moderate antibacterial activity against both gram positive and gramnegative organisms selected for the study. All the synthesized compounds were screened for their anti-inflammatory activityby Carrageenan induced rat hind paw edema method using Diclofenac sodium asstandard. As per the results obtained from animal studies as shown in the Table no 5, it can beconcluded that among the 10 synthesized compounds acetophenone, 2,4 di-chloro, 2,4 di-methoxy, 2,4 di-hydroxy, 4-nitro & 4-chloro substituted acetophenone derivatives were foundto show significant anti-inflammatory activity at the end of 180 min with $P<0.001$comparable with the standard Diclofenac sodium. 3-hydroxy & 4-hydroxy substitutedacetophenone derivatives exhibited moderate anti-inflammatory activity at the end of 180 minwith $P<0.01$ while 3-nitro substituted. Acetophenone derivative exhibited less potency with $P<0.05$ and 2-hydroxy substitutedacetophenone derivative did not show any anti- inflammatory activity with $P>0.05$.

SUMMARY & CONCLUSION

The main focus of this research work was to synthesize, characterize and evaluate forantibacterial, activities of the newly synthesized oxadiazole derivatives. A series of compounds i.e. [1R-10R] have been synthesized using appropriate procedures, as per the scheme given in the methodology. The % yield of the synthesized compounds was found to be in the range of 50% - 85%. Structures of the synthesized compounds were characterized and confirmed with the helpof analytical datas such as IR, 1H NMR. The antimicrobial activity was carried out by Filter disc method and the antioxidant activity by DPPH method. Among the ten synthesized compounds, acetophenone, 2, 4-dichloro, 2, 4-dihydroxy,nitro, 4-

nitro & 4-chloro substituted acetophenone derivatives showed moderateantimicrobial activity at the concentration of 400µg/ml using Amoxycillin trihydrateas standard, the remaining compounds were inactive. A single method used to perform the anti-inflammatory activity were Carrageenaninduced rat hind paw edema method respectively**.**

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