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Triazoles as antimicrobial: A review

Jyoti Sinha and Mamta Kadawla

Abstract

The chemistry of heterocyclic compounds has continued to be an active prospect in the field of organic chemistry. Triazole derivatives have been occupying a unique position in heterocyclic chemistry because of their biological activities. The small and the simple triazole nucleus which is present in compounds is involved in research work aiming at evaluating the new products possessing anti-microbial activity.

Keywords: Triazoles Derivatives, Anti-microbial

1. Introduction

1,2,4-Triazoles and their derivatives are important group of heterocyclic compounds characterized by a five-membered ring of two carbons and three nitrogen atoms. The biological activity of 1,2,4-triazoles and their derivatives have been demonstrated by various studies (Aggarwal). 1,2,4-triazole nucleus possess a wide range of pharmacological activities such as analgesic (Cansiz), antibacterial (Jantová), anti-inflammatory (Rezaeia) and antioxidant (Soud) properties. As a result of significant research on 1,2,4-triazoles, several formulations containing 1,2,4-triazole ring are now available in the pharmaceuticals market like triazolam and fluconazole (Doern). Interest in the field of microbial chemotherapy is increasing due to several reasons, for instance, emergence and reemergence of new pathogens and the challenging problem of emerging resistances (Engering). Therefore, there is a continuing need for new antimicrobial agents with more selectivity and lower side effect. Apparently, 1,2,4-triazoles are currently attracting more interest in the field of microbial chemotherapy due to their broad spectrum of biological activities.

2. Antibacterial and Antifungal Activity

Ilhan *et al.*, in 1996^[19] synthesized pyrrolidino-s-triazole-5-one derivatives synthesized and evaluated for antimicrobial activity. The study reveals that the synthesized compounds possess good antifungal activity.

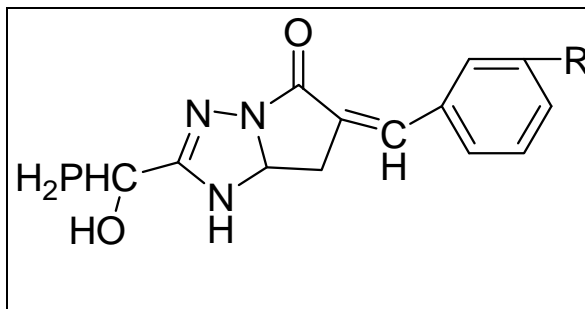


Fig 1

Synthesized few triazole derivatives were designed by molecular modeling. The synthesized compounds on screening for antibacterial activity exhibit moderate activity against *C. albicans* when compared with voriconazole.

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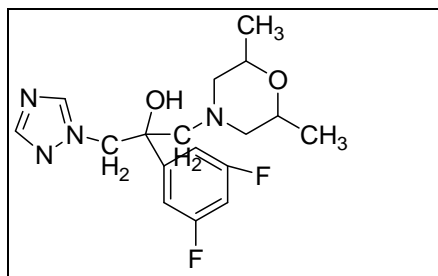


Fig 2

Nuray *et al.*, in 2001 ^[24] established a synthesis of new N-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides and tested for antimicrobial activity. Compound in fig 3 showed antibacterial activity against some bacteria.

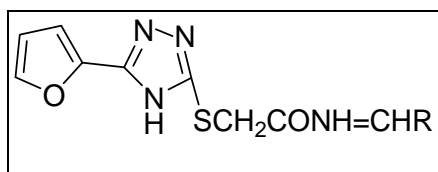


Fig 3

Hirpara *et al.*, in 2003 ^[17] carried out microwave assisted synthesis and biological activity of some triazolo thiazazole derivatives. The *in vitro* antibacterial screening of the synthesized compounds shows that these compounds possess significant activity against *B. megaterium* and *S. aureus*.

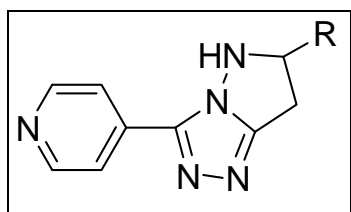


Fig 4

Synthesized few substituted triazoles and evaluated for antibacterial activity. The study reveals that some of the derivatives possess good activity against *E. coli*.

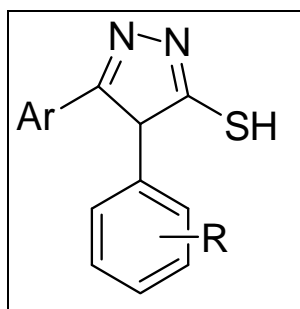


Fig 5

Klimesova *et al.*, in 2004 ^[22] synthesized a series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and *S*-substituted-1,2,4-triazoles and evaluated for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *M. avium*, and two strains of *M. kansasii*. Among all, two compounds (2a and 2b) showed moderate potency of MIC 32 μ M/L and 62.5 μ M/L respectively, against *M. tuberculosis* H37Rv on day 14.

And also compound 2b exhibited moderate potency against other strains. While, in a almost similar series 2-(4-substituted-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-ylthio)-1-phenylethanone, all the compounds 3 exhibited less than 90% inhibition at a concentration of 6.25 μ g/mL.

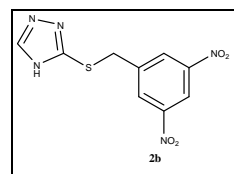
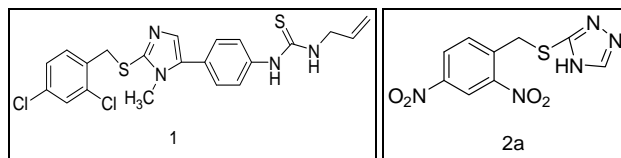


Fig 6

Synthesized some 3-(*p*-substituted-anilinoethyl)-4-(*p*-substituted phenyl)-5-thioxo-1,2,4-triazole derivatives and evaluated for antifungal activity against *C. albicans* and *A. niger*. Their study showed that the monochloro and monobromo substituted derivatives exhibit good antifungal activity.

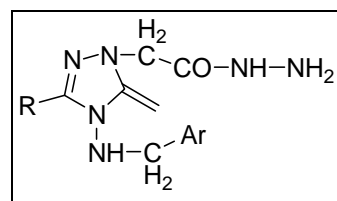


Fig 7

Alagarsamy *et al.*, in 2006 ^[3] synthesized some novel 1,4-disubstituted-1,2,4-triazolo [4,3-*a*]-quinazolin-5(4*H*)-ones and screened for anti HIV and antimicrobial activity. Their study indicates that the synthesized compounds do not exhibit significant anti-HIV activity while the synthesized derivatives possess good activity against *M. tuberculosis*, *C. albicans* and *A. niger*.

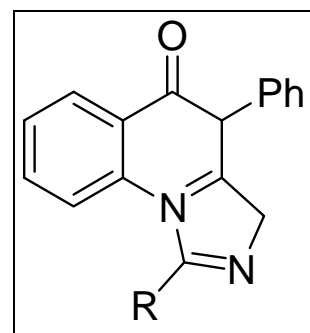


Fig 8

Reported a synthesis of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-(N-cyclopropyl-N-substituted-amino)-2-propanol derivatives and screened for their antifungal activity. Some of the title compounds had higher antifungal activity and broader antifungal spectrum than fluconazole.

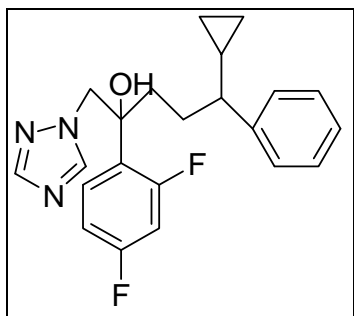
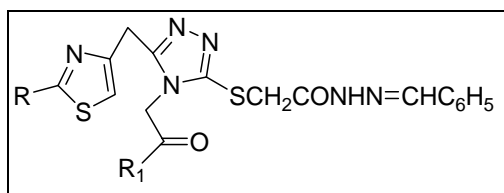
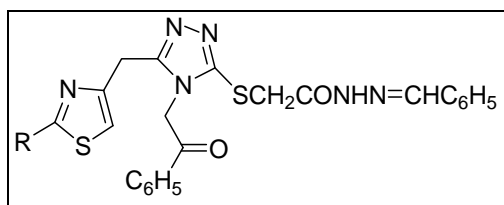


Fig 9

Shiradkar *et al.*, in 2007 [31] synthesized a number of eighty-five 3, 4, 5-substituted-1,2,4-triazole derivatives were synthesized and evaluated for their antitubercular activity against *M. tuberculosis* H37Rv. Among all, two compounds 1a and 1b have shown the best potency of MIC 0.39 μ M and 0.79 μ M respectively. In continuation, the same group optimized the above series and found two more compounds 2a, 2b having same activity profile of MIC 0.39 μ M and 0.79 μ M respectively against *M. tuberculosis* H37Rv.



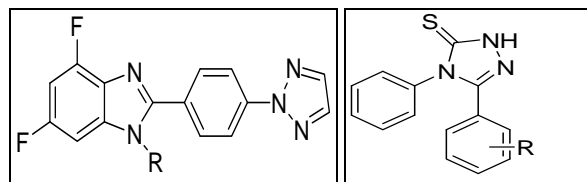
1a R - NHCOC₆H₅, R₁ - 3-NO₂-C₆H₄
 1b R - NHCOC₂H₅, R₁ - 3-NO₂-C₆H₄



2a R - NHCOC₆H₅
 2b R - NHCOC₂H₅

Fig 10

Jadhav *et al.*, in 2009 [20] synthesized a series of novel 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1H-benzo[d]imidazole derivatives were synthesized and evaluated for their antitubercular efficacy against *M. tuberculosis* H37Rv. Among all, two derivatives 1a and 1b have shown preeminent potency of MIC 0.36 μ g/mL and 0.58 μ g/mL respectively. While a number of three, 3,4-substituted-1H-1,2,4-triazole-5(4H)-thiones were synthesized by Kini *et al.* and all 2a, 2b and 2c have shown a surprising 100% inhibition at 1 μ g/mL.



1a R - CH₂(3-FC₆H₅)
 1b R - CH₂(3-ClC₆H₅)
 2c R - p-phenoxy
 2a R - o-phenoxy
 2b R - m-phenoxy

Fig 11

Rezaei *et al.*, in 2009 [29] synthesized substituted 1,2,4-triazole and 1,2,3-benzotriazole and evaluated for their antifungal activity. Some of the compounds showed good antifungal activity.

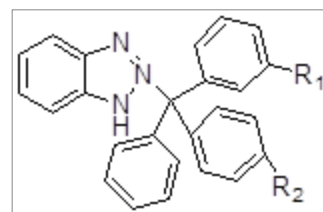


Fig 12

Stefania *et al.*, in 2009 [14, 33] reported synthesis of 2-[4-(4-X-phenylsulfonyl) phenyl]-6-(4-Y-phenyl)[1,3]thiazolo[3,2-b][1,2,4]triazoles and screened for their antibacterial activity.

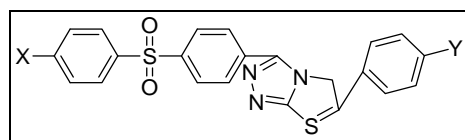


Fig 13

Gabriela *et al.*, in 2009 [14] synthesized 4-(Substituted-arylidene)amino-5-[4-(4-phenylsulfonyl) phenyl]-2-(morpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione evaluated for their antibacterial activity.

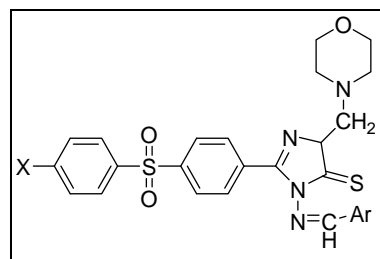


Fig 14

Palekar *et al.*, in 2009 [25] reported synthesis of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo[3,4-b]-1,3,4-thiadiazoles and 4-bis(substituted phenyl)-4-thiazolidinone derivatives and screened for their antibacterial activity. Several of these compounds showed potential antibacterial activity.

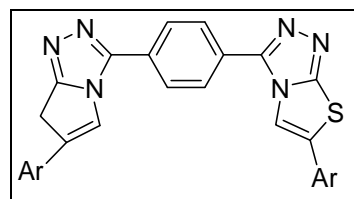


Fig 15

Gabriela *et al.*, in 2010 [13] reported synthesis of 3-[4-(4-X-phenylsulfonyl)phenyl]-6-(substituted phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and evaluated for their antibacterial activity. Some of compounds possessed good activity.

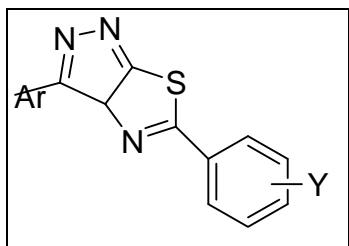


Fig 16

Demonstrated a synthesis of novel series of 3,6-disubstituted 1,2,4-triazolo [3,4- b]-1,3,4-thiadiazoles and evaluated for their antibacterial activity. Some of the compounds showed excellent antibacterial activity.

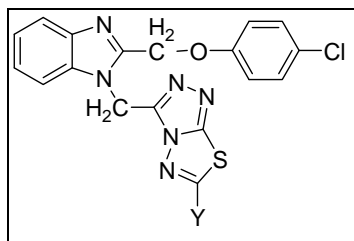


Fig 17

Bayrak *et al.*, in 2010 [8] synthesized novel 4-(2-Phenyl- 1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-yl)-5-(4-chlorobenzyl)-2- {[5-(arylamino)-1,3,4- thiadiazol-2-yl]methyl}-2,4-dihydro-3H-1,2,4-triazole-3-one and evaluated for their antimicrobial activity.

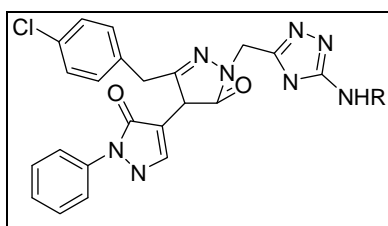


Fig 18

Guzeldemirci *et al.*, in 2010 [16] prepared a series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4- bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones and 2-alkyl/arylamino- 5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-thiadiazoles and screened for their antibacterial and antifungal activity.

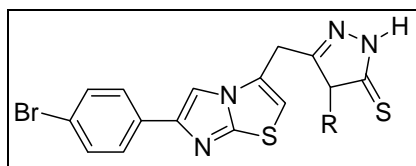


Fig 19

Kumar *et al.*, in 2010 [23] synthesized some new 4-(substituted benzylideneamino)-5-(4-isopropyl thiazol-2-yl)-2-substituted-2H-1,2,4-triazole-3(4H)-thione and 3-(4-isopropylthiazol-2-yl)-5-thioxo-1H-(1,2,4-triazol-4(5H)-yl) substituted benzamides and evaluated for their antitubercular activity. Some of the exhibited good antitubercular activity when compared with first line drug such as isoniazid.

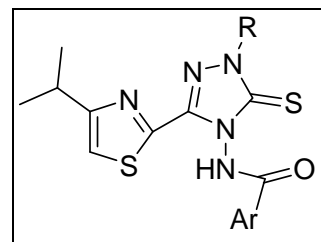


Fig 20

Patel *et al.*, in 2010 [26] synthesized series of 3-(3- pyridyl)-5-(4-methylphenyl)-4-(N-substituted-1,3-benzothiazol-2-amino)-4H-1,2,4-triazole and screened for their antimicrobial and antitubercular activity. Compound 22 showed better antitubercular activity compared to rifampicin.

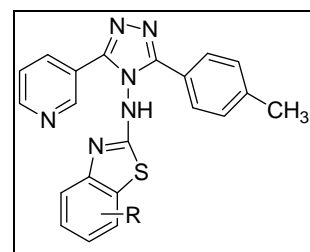


Fig 21

Kumar *et al.*, in 2010 [23] synthesized some new 4-(substituted benzylideneamino)-5-(4-isopropyl thiazol-2-yl)-2-substituted-2H-1,2,4-triazole- 3(4H)-thione and 3-(4-isopropylthiazol-2-yl)-5- thioxo-1H-(1,2,4-triazol-4(5H)-yl) substituted benzamides and evaluated for their antitubercular activity. Some of the exhibited good antitubercular activity when compared with first line drug such as isoniazid.

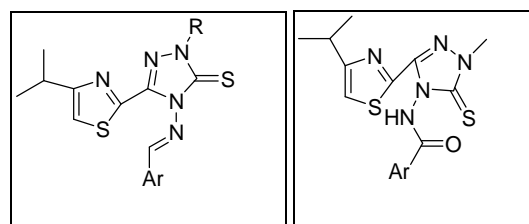


Fig 22

Concluded that incorporation of triazole nucleus, a biologically important and accepted pharmacophore, into benzimidazole ring system makes it versatile heterocyclepossesing wide spectrum of antifungal activity against candida albicans and aspergillus niger.

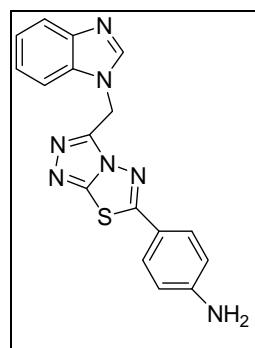


Fig 23

Pattan *et al.*, in 2012 ^[27] reported the synthesis of 5-mercapto 1,2,4-triazole derivatives and evaluated for their antitubercular and anti-inflammatory activities.

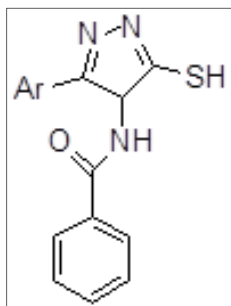


Fig 24

Pardeshi *et al.*, in 2011 ^[6] synthesized a series of 1-substituted 4-(4-(thiophen-3-yl)thiazol-2-yl)-1H-1,2,4-triazol-5(4H)-one derivatives and evaluated for antibacterial and antifungal activity. Some of the compounds showed potent activity.

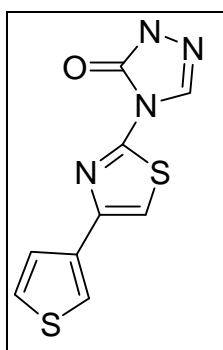


Fig 25

Aggarwal *et al.*, in 2011 ^[1-2] had reported a synthesis of nalidixic acid based Schiff bases of 4-amino-3-mercapto-1,2,4-triazole derivatives and screened for their antimicrobial activity.

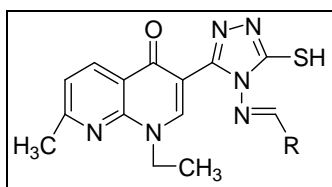


Fig 26

Gupta *et al.*, 2011 ^[15] reported synthesis of 1-substituted-8-aryl-3-alkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines. The title compounds were screened for their antifungal activity.

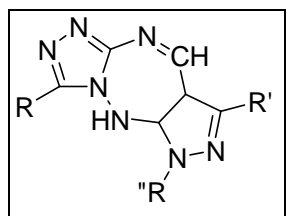


Fig 27

Plech *et al.*, in 2011 ^[28] demonstrated synthesis of 5-(3-chlorophenyl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones and evaluated for their antibacterial activity. Some of the compounds showed good activity.

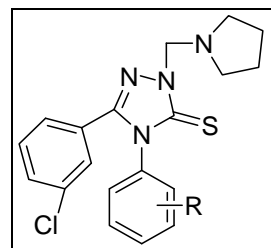


Fig 28

Badr *et al.*, in 2011 ^[6] synthesized new series off used 1,2,4-triazoles such as, 6-(aryl)-3-(5-nitrofuran-2-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, 6-(alkyl/arylamino)-3-(5-nitrofuran-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and 6-(4-substituted phenyl)-3-(5-nitrofuran-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines and evaluated for their antibacterial activity.

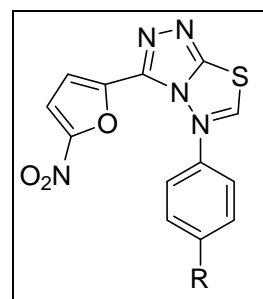


Fig 29

Chai *et al.*, in 2011 ^[10] synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-yl activity. Some of the compounds showed excellent antifungal activity.

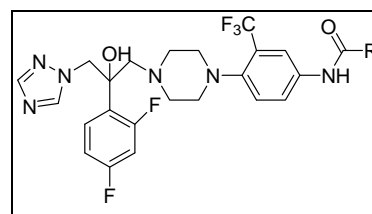


Fig 30

Zou *et al.*, in 2012 ^[36] prepared a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols. The *in vitro* antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi. Compound in fig 31 showed the best antifungal activity.

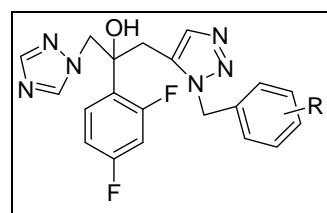


Fig 31

Zoumpoulakis *et al.*, in 2012 [37] prepared a variety of 5-[2-(N-dimethylsulfonyl)-4,5-dimethoxy-benzyl]-4-alkyl-1,2,4-triazole-3-thiones/3-ones and screened for their antifungal activity.

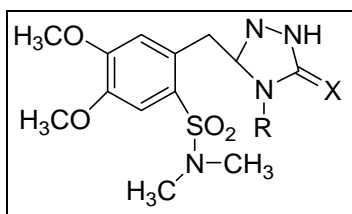


Fig 32

Zhang *et al.*, in 2012 [35] synthesized novel 1H-benzimidazol-1-yl acetates and 1H-benzimidazol-1-yl propionates containing 1H-1,2,4-triazole moiety and evaluated for their antifungal activity.

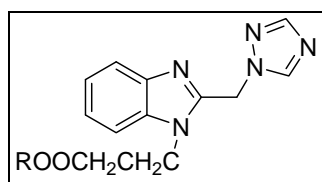


Fig 33

Barbuceanu *et al.*, in 2012 [7] synthesized some new 5-(4-(4-X-phenylsulfonyl)phenyl)-4-(R)-2H-1,2,4-triazol-3(4H)-thione and 5-(4-(4-Xphenylsulfonyl) phenyl)-N-(R)-1,3,4-thiadiazol-2- amines and screened for their antimicrobial activity.

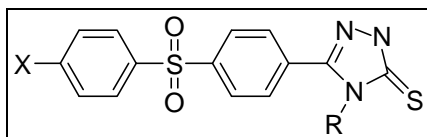


Fig 34

3. Conclusion

A large number of 1,2,4-triazole-containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, central nervous system stimulants, antianxiety and antimicrobial agents. To overcome the rapid development of drug resistance, new agents should preferably have chemical characteristics that clearly differ from those of existing agents.

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