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Pyridine scaffold: its diverse biological actions

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Abstract

Pyridine derivatives have a huge demand because they have shown tremendous pharmaceutical and agricultural uses. Also they have shown large and emergent biological activity such as in Poisoning, Antimicrobial, Antidiabetic , Anticancer, Anticonvulsant, Antihelmintic. Looking forward to this many researchers got interested and synthesized derivatives of it. By keeping it in consideration we have summarized the activity of Pyridine scaffold acting against poisoning in this reveiw.

Keyword- Pyridine, Pharmaceutical, Agricultural, Poisoning, Anticonvulsant, Antidiabetic, Antimicrobial, Anticancer, Antihelmintic, pyridine scaffold, Pyrrolo[3,4-c]pyridine Derivatives, Antiulcer activity

INTRODUCTION

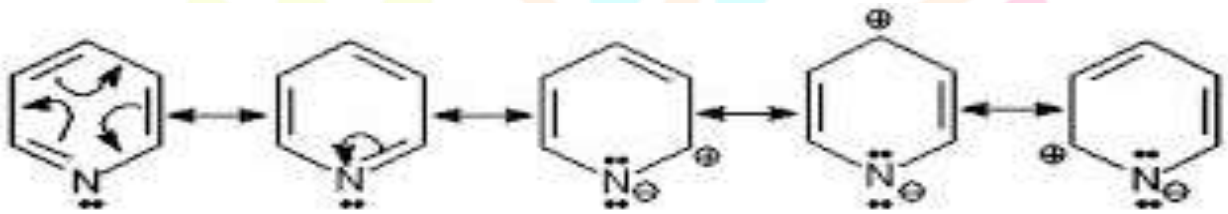
Pyridine is a heterocyclic compound which is a colourless to yellow liquid with a chemical formula C5H5N.It is also known as Azine or Pyridine. The structure is like benzene, with onemethine group replaced by a nitrogen atom.It has a conjugated system of six pi-electron like benzene that are delocalized over the heterocyclic ring[1].It has a sour, putrid, and fish-like odour. It can be synthesized from ammonia, formaldehyde, and acetaldehyde or it can be made from crude coal tar.

It is weakly basic and is miscible with water. It is highly flammable and when inhaled or ingested it becomes toxic. Some symptoms, when exposed to pyridine, are nausea, asthmatic breathing, vomiting, headache, laryngitis, and coughing[2]. It is widely used in the precursor to agrochemicals and pharmaceuticals. Also, it is used as an important reagent and organic solvent,used as solvent in Knoevenagel condensations. It is widely used as polar and aprotic solvent. It is miscible with broad range of solvents like hexane and water

Structural Characteristics

Aromatic compound which have five carbon atoms and one nitrogen atom. However, the nitrogen's lone pair of electrons is a sp2 orbital orthogonal to the orbitals of the ring. Hence it is not involved in maintaining[3] aromaticity,but it is available to react with protons thus pyridine is basic.

•Resonating structures of Pyridine are shown as follow:



Due to the greater electronegativity of nitrogen relative to carbons it tends to withdraw the electron density from carbon atoms at positions 2,4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge while the carbons at positions 3 and 5 remains neutral. Nitrogen containing six membered aromatic pyridine and its derivatives abundantly exist in nature and they play a vital role in the field of heterocyclic chemistry.

Properties

Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating that are unpleasant. It is the hydrogen derivative of this ring, it is benzene in which one CH- or methine group is replaced by a nitrogen atom. The structure of it, is completely analogous to that of benzene, being related by the replacement of CH with N[4].

C5H5N	Pyridine
Molecular Weight/ Molar mass	79.1 g/mol
Boiling point	115.5°C
Melting point	-41.6 °C
Density	982 kg/m³
Vapour pressure	18mmHg
Acidity (pka)	5.25
Dipole moment	2.2 D

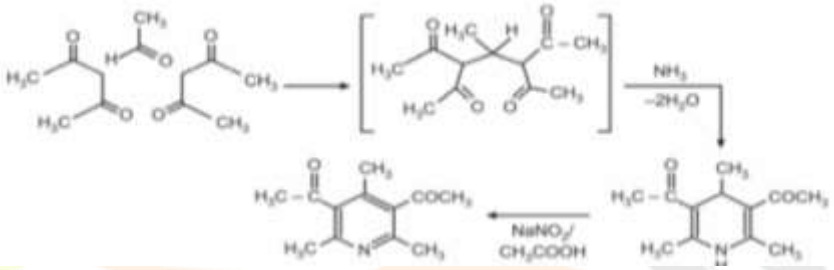
•Physical Properties -

1.Pyridine is a colourless refractive liquid.
2.It has characteristic unpleasant odour
3. Soluble in water and most organic solvent.
4. Pyridine is conventionally detected by the gas chromatography and mass spectrometer[3].

•Chemical properties -

1.When the pyridine reacts with alkyl halide then the formation of quaternary pyridinium salt and hydrochloric acid takes place[4].

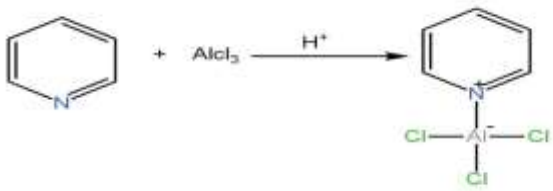
2.Metallic ions like aluminum, boron, beryllium, etc. combine with basic pyridine to produce complexes[4]



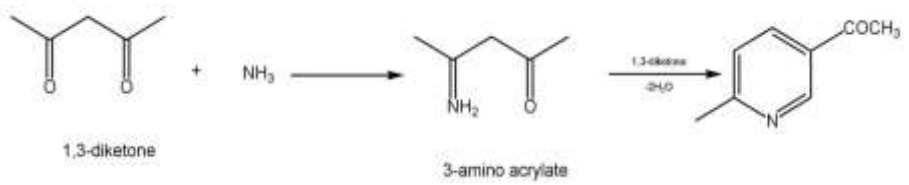
Synthesis

1. Acetaldehyde and formaldehyde are combined with ammonia to make pyridine.

2.Hantzsch synthesis - A tricarbonyl compound, an aldehyde,and ammonia are combined in efficient reaction.



3. A 1,3-dicarbonyl compound can be converted into unsymmetrically substituted pyridine through a reaction between a 1,3-dicarbonyl compound and 3- amino acrylate[4].



1,3-diketone

3-amino acrylate

Biological activity

A] Antidote activity

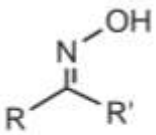
1] Antidote's for Irreversible Acetylcholinesterase Inhibitor

•Organophosphate -

These are absorbed from all sites including intact skin and lungs. They are hydrolysed as well as oxidised in the body and little is excreted unchanged[5].

•Formation of oximes-

Reaction of hydroxylamine with aldehydes or ketones affords oximes, which possess the desired nucleophilic oxygen atom. A pyridine ring was considered an attractive carrier for the oxime function, because such groups are common in a number of biochemical systems (e.g., NAD+ and NADP+), indicating a possible low order of toxicity[5]. Furthermore, three readily available positional isomers of pyridine aldehyde can be easily converted to oximes. Finally, the nitrogen atom of the pyridine ring can be converted to a quaternary ammonium salt by treatment with methyl iodide[6]. This cationic charge would be expected to increase affinity of the compound for the anionic-binding site of the phosphorylated AChE.

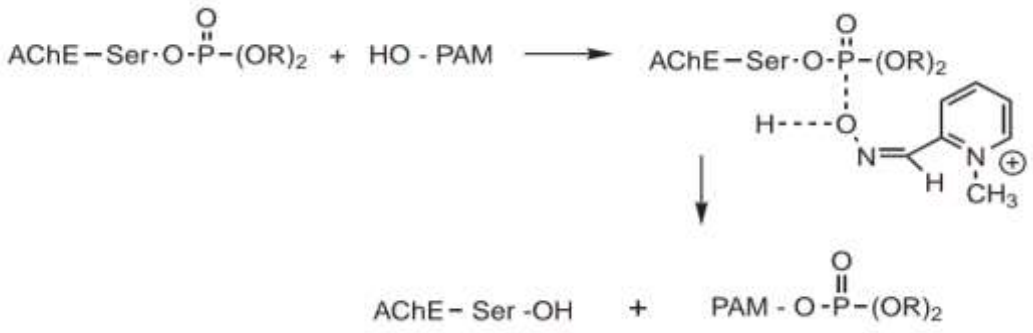


Oxime

•Cholinesterase reactivators-

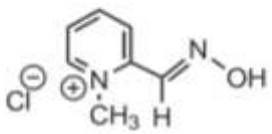
Oximes are used to restore neuromuscular transmission only in case of organophosphate anti-ChE poisoning. The phosphorylated ChE reacts very slowly or not at all with water. However, if more reactive OH groups in the form of oximes (generic formula R–CH = N–OH) are provided, reactivation occurs more than a million times faster[5]. Pralidoxime (2-PAM) has a positively charged quaternary nitrogen: attaches to the anionic site of the enzyme which remains unoccupied in the presence of organophosphate inhibitors. Its oxime end reacts with the phosphorus atom attached to the esteratic site: the oxime-phosphonate so formed diffuses away leaving the
reactivated ChE.

•Action of Drug containing pyridine ring as an antidote – Pralidome:



In 1955, Wilson and Ginsburg in the US and Childs et al. in England researched and published independently on the efficacy of the compound 2-PAM iodide (molecular weight 264.1Da) as a reactivator of phosphorylated cholinesterases[7].

The three isomeric pyridine aldoximemethiodides were synthesized and biologically evaluated. Of these, the most effective is the isomer derived from 2-pyridinylal-dehyde.The initial step involves binding of the quaternary ammonium nitrogen of 2-PAM to the anionic-binding site of phos-phorylatedAChE. This places thenucleophilic oxygen of 2-PAM in close proximity to the electrophilic phosphorus atom[5]. Nucleophilic attack of the oxime oxygen results in breaking of the ester bond between the serine oxygen atom and the phosphorus atom.The final products of the reaction are the regenerated active form of AChE and phosphorylated 2-PAM.

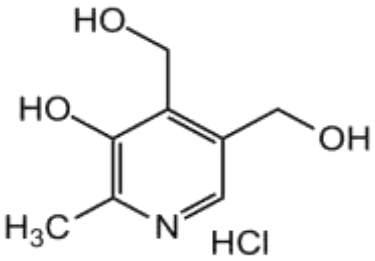


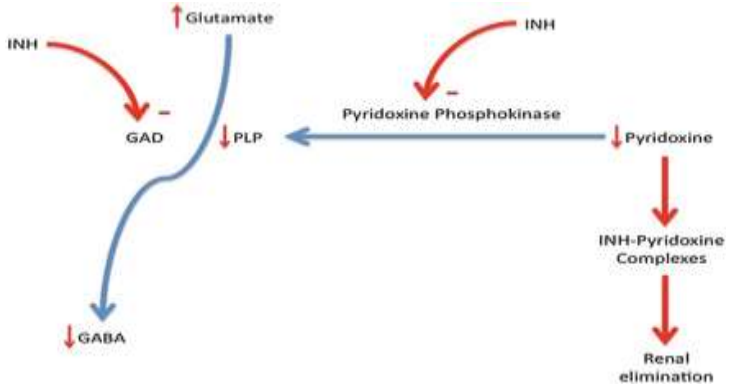
Pralidoxime chloride (2-PAM)

Pralidoxime is administered subcutaneously, intra-muscularly, or intravenously, and it must be given within a short period of time after enzyme phosphorylation, generally a few hours after exposure. Little reactivation is likely if given 36 hours after expo-sure. If the phosphorylated AChE has aged, 2-PAM will not regenerate the enzyme[7].

2] Antidote for Isoniazid

Isoniazid was introduced as a treatment for tuberculosis in the 1950s.It was soon found to cause peripheral neuropathy, which was established in 1954 as being due to a deficiency in pyridoxine (vitamin B6).Its metabolism is subject to polymorphic acetylation, with fast and slow acetylators having half-lives between 1 and 4 h,respectively[1].





•Toxicity-

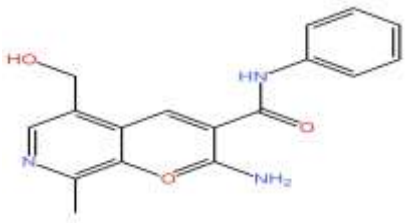
The toxic mechanism of action of isoniazid is through pyridoxine metabolism via a number of mechanisms. In chronic therapy it produces a pyridoxine deficiency by increasing the renal excretion of pyridoxine. In addition it inhibits pyridoxine kinase, the enzyme responsible for the production of pyridoxal phosphate, which is the active form of pyridoxine[5]. Pyridoxal phosphate is a co-factor in the synthesis of gamma aminobutyric acid (GABA) from glutamate by L-glutamic acid decarboxylase. Depletion of GABA, a major inhibitory neurotransmitter of the central nervous system, resulting from an isoniazid-induced pyridoxine deficiency is a major factor in the pathogenesis of isoniazid-induced seizures**.**

•Action of Pyridoxine-

To prevent and treat (10–100 mg/day) isoniazid, hydralazine and cycloserine induced neurological disturbances[8]. Acute isoniazid poisoning has been successfully treated with massive doses (in grams) of parenteral pyridoxine. Pyridoxine is routinely given along with anti-MDR-TB regimens.

B. Antibacterial Activity

Ivachtchenko et al. synthesized 2-imino-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c] pyridine-3-(N-aryl) carboxamides (1) that exhibited potency and selectivity (12.5–25 lg mL−1) toward fungal and bacterial straining and was also highly active in comparison with marketed drugs.[9]



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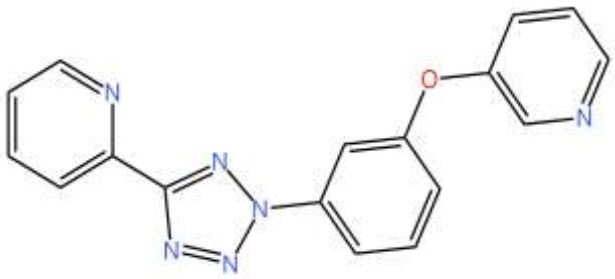
C. Anti-Convulsant Activity:

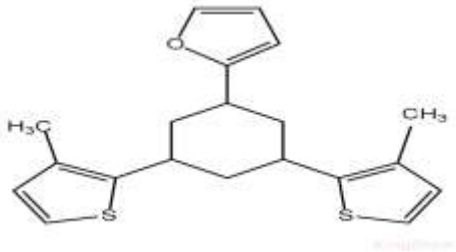
Huang et al 6 carried out structure-activity relationship studies on 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile that led to the discovery of 2-{2-[3-(pyridin-3- yloxy)phenyl]-2H-tetrazol-5-yl}pyridine, a highly potent and selective mGlu5 receptor antagonist with good brain penetration and in vivo receptor occupancy in rat and cross-species oral bioavailability[10]

2



D. Anticancer Activity:

Basnet et al synthesized a series of 2,6-dithienyl-4-furyl pyridine derivatives(3) and evaluated for the topoisomerase I and II inhibitory activity as well as cytotoxicity against several human cancer cell lines. Compound showed strong topoisomerase-I inhibitory activity[11]



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E. Antiviral activity

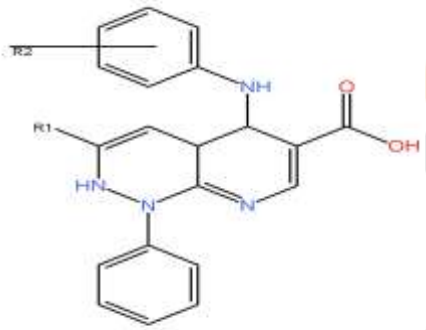
Bernardino et al. synthesized a series of 4-(phenylamino)thieno[2,3-b]pyridine derivatives (4) and evaluated their inhibitory property against Herpes simplex virus type 1 (HSV-1). To enhance the efficiency, similar type of derivatives with a new series of 4-(phenylamino)-1H-pyridazino [3,4-b]pyridine derivatives (5) were prepared and these analogues exhibited better anti-HIV activity, as compared to those in the earlier series[12]

Hartwich et al. synthesized phosphonylated triazolo[4,5b]pyridine(1-deaza-8-azapurine) (6a), imidazo[4,5-b]pyridine (1-deazapurine) (6b) and imidazo[4,5-b]pyridin-2(3H)-one(1-deazapurin-8-one) (6c) were evaluated for antimicrobial properties. Compound (6c) exhibited minimal activity (EC50 = 61.70 µM) when exposed to the varicella-zoster virus Oka strain in HEL cells16 while the other two compounds exhibited marginal activity[13]

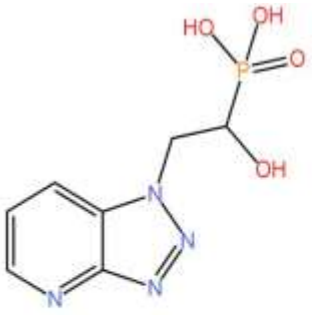
4

R=H, CH_2, OCH_3

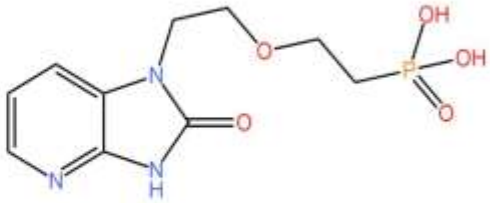
5



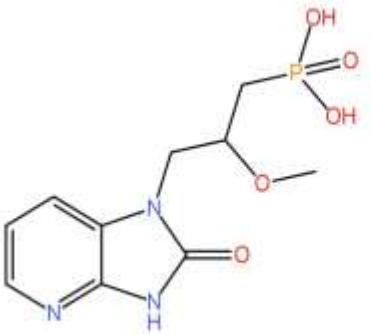
R_1=C_6H_5, CH_3
R_2=H,P-OCH_3



6a



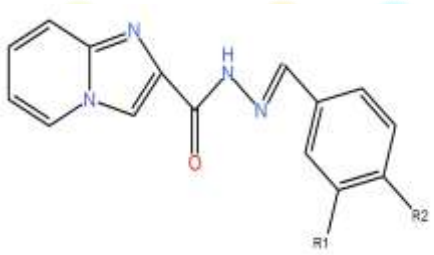
6b



6c

F. Antifungal activity

Ozdemir et al. reported a group of eight novel pyridine derivatives showing antifungal activity when exposed to a panel of ten human pathogenic Candida species . Among them, compound (7) exhibited strong inhibition (MIC 0.016 mg mL−1) against the screened Candida species.[11] The synthesis and antifungal activities of a few 3-aryl-5-(pyridin-3-yl)-4,5-dihydropyrazole-1-carbothioamide (8) were reported by Shekarchia et al[14]



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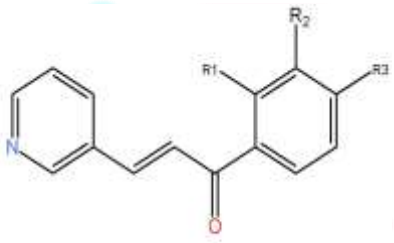

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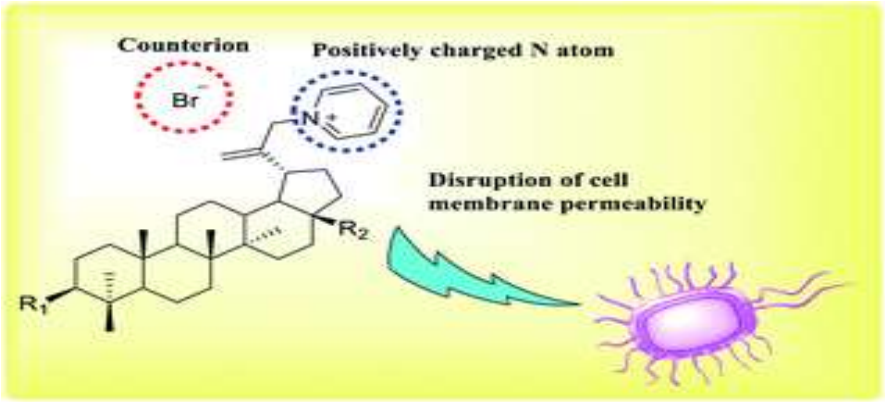
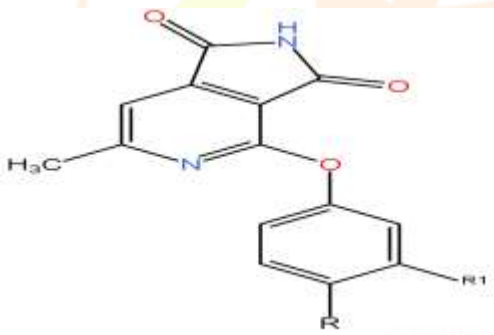


G. Pyrrolo[3,4-c]pyridine Derivatives

1] Antidiabetic Activity:

Knutsen et al. described 4-substituted 6-methyl-pyrrolo[3,4-c]pyridine-1,3(2H)-dione derivatives 6 that effectively reduce blood glucose levels without affecting the concentration of circulating insulin. The present compounds reduce blood glucose levels by stimulating glucose uptake into muscle and fat cells.The ability of pyrrolo[3,4-c]pyridine-1,3(2H)-dione derivatives 9 to stimulate the incorporation of glucose into lipids was tested. The maximum increase in insulin sensitivity achiev in the dose range of 0.3–100 µM of the tested compounds, normal to the full insulin dose-response(100%)was determined[15]



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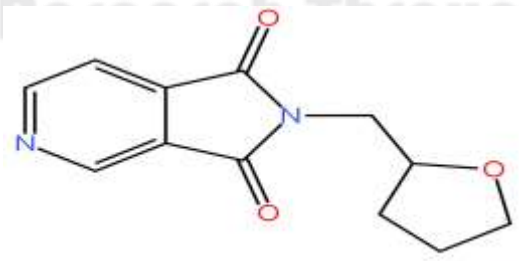
2] Anti-Inflammatory Activity:

Sondhi et al. synthesized 2-((tetrahydrofuran-2-yl)methyl)-2H-pyrrolo[3,4-c]pyridine-1,3-dione(9) and evaluated it for anti-inflammatory activity. Compound (10)showed 26% activity at a dose of 50 mg/kg per os.[16]



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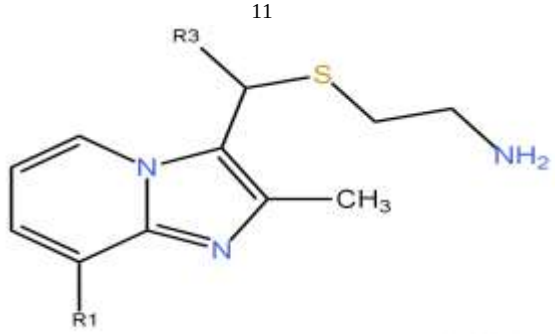
H. Antiulcer activity

Jhon E. Starrett Jr et al Synthesized midazo[1,2-a]pyridines compound (11) and screened for antiulcer agentsThe imidazo[1,2-a]pyridines were tested for cytoprotective activity in the EtOH and HC1 models in thats[17]

11



Uses[3]

1.It is used in the chemical industries as a very important raw material
2.It is used as an antiseptic in dental care products
3.It is used as a solvent which is suitable for dehalogenation
4.It is used in pharmaceuticals
5.It is used for antifreeze mixtures as a denaturant
6.It is used as a sulfonating agent
7.It is used as a reducing agent
8.It is used in dyes and paints
9.It is used as a disinfectant
10.It is used in coordination chemistry as a ligand

Conclusion:

From the article we can conclude that Pyridine has made tremendous account's not only in pharmaceutical and agricultural but also in chemistry. And has widely used it's scaffold fo
different poisoning which is beneficial for our routine.

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