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Recent Advances in the Synthesis of 2*H*-1,4-pyridoxazin-3-(4*H*)-one Derivatives and its Pharmaceutical Significance

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ABSTRACT

The wide occurrence of benzo fused and heterocyclic fused [1,4] oxazines in bioactive natural product and pharmaceuticals have made them important synthetic targets. 2H-1,4-pyridoxazin-3-(4H)-one has been studied intensively as important heterocyclic systems for building natural and designed synthetic compounds. They are utilized as suitable skeletons for the design of biologically active compounds, ranging from anti-inflammatory, analgesics, bacteriostatic, fungistatic and MAO inhibitors etc. Various researchers with help of organic and analytical chemistry developed 2*H*-1,4-pyridoxazin-3-(4*H*)-one using different synthetic route.

Keywords: anti-inflammatory, bacteriostatic, MAO inhibitors

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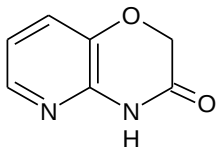
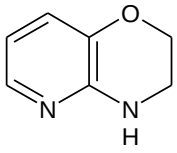
INTRODUCTION

The 2H-1,4-pyridoxazin-3-(4H)-ones (I) and 3,4-dihydro-2H-1,4 pyridoxazine(II) scaffolds have been studied intensively as important heterocyclic systems for building natural and designed synthetic compounds.[1]



(I)

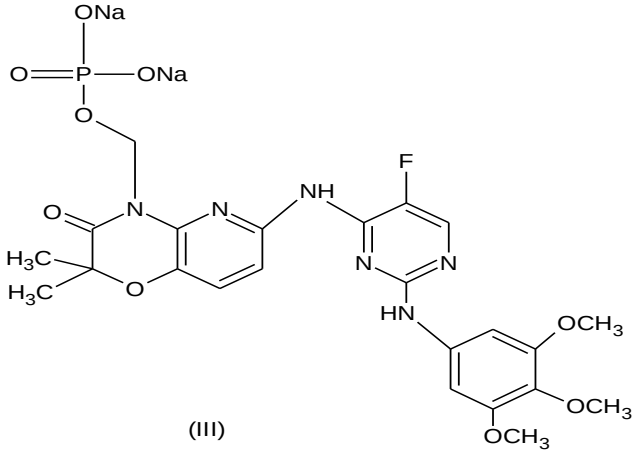


(II)

The benzo fused and heterocyclic fused [1,4] oxazines have been reported to possess in bioactive natural product and pharmaceuticals with different pharmacological activity which made them important synthetic targets.

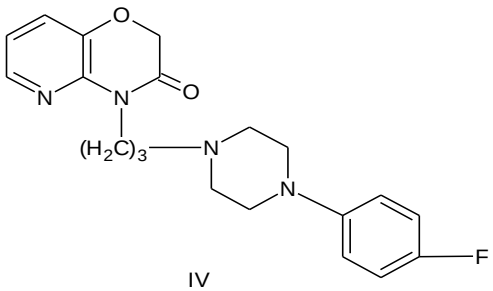
They are utilized as suitable skeletons for the design of biologically active compounds, ranging from anti-inflammatory,analgesics,bactriostatic, fungistatic and MAO inhibitors etc.[2]

Fostamatinib(III) disodium FDA approved drug for treatment of rheumatoid arthritis, immune thrombocytopenia and β cell lymphoma has basic structure containing pyridoxazinone.[3]



(III)

In the search for a new analgesic agents that are devoid of side effects of conventional opioid such as respiratory depression, tolerance constipation, dependence and NSAIDs such as gastric irritation lead to synthesis of novel Compound (IV) which showed potent analgesic activity against phenyl quinone induced writhing test against Aspirin as standard drug[4-6]



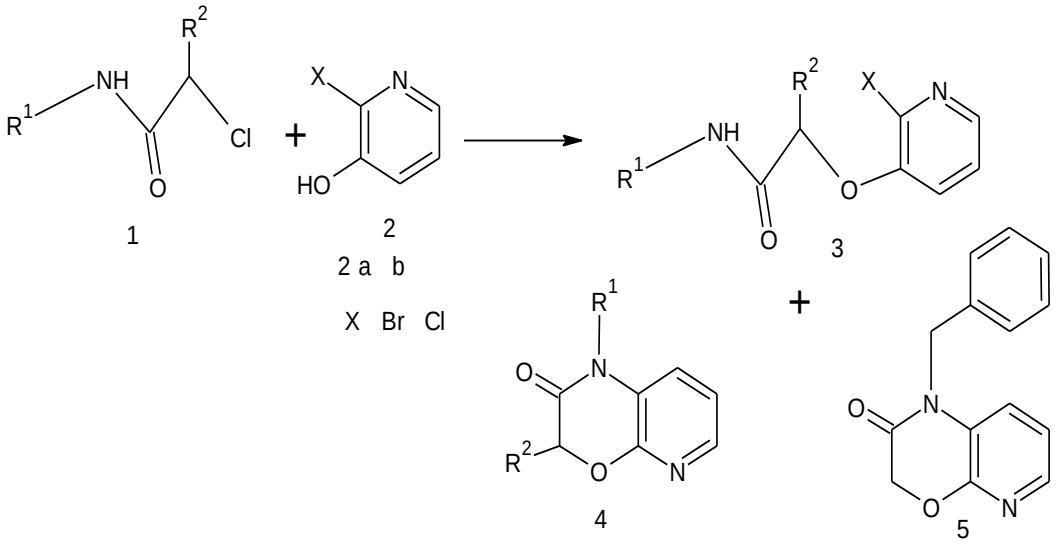
IV

In this review article, we will discuss the novel synthetic approach in designing 2H-1,4-pyridoxazin-3-(4H)-ones heterocyclic nucleus through various scheme.

Scheme-1

Pyrido(2,3-b)[1,4] oxazin-2-ones are conveniently prepared in excellent yield by a one pot annulations of N-substituted -2-chloroacetamides(1) with 2-halo-3-hydroxy-pyridines(2) with use of cesium carbonate in refluxing acetonitrile. The key transformation features a Smiles rearrangement of the initial O-alkylation product and subsequent cyclizationn to get substituted chloro acetamide derivatives (3) as major product and 1,3 substituted 2H-1,4-pyridoxazin-3-(4H)-ones as minor products. It can be explained by the reaction of 2-bromo-3-hydroxy pyridine (2a) with N-benzyl-2-chloroacetamide(1) in the presence of potassium carbonate yield N-benzyl-2-(2-bromopyridin-3-yloxy)acetamide (3a) as major product and bicyclic adduct 4a as only a minor product Scheme 1.[7]

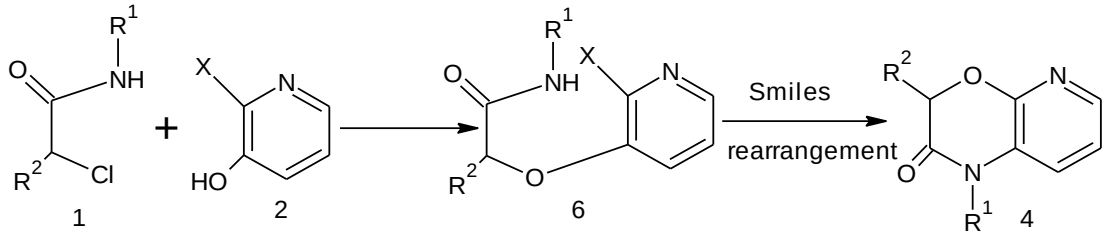
SCHEME-1



Scheme-2

The annulations can be well explained by a three step process in scheme-2. Alkylation of 1 by 2 generates adduct 6, which undergo rapid ring closure to yield 4.[7] The common alkali carbonate such as Lithium carbonate , sodium carbonate and potassium carbonate generate trace of 4a after prolonged refluxing However cesium and rubidium carbonate yield excellent amount of 4 just within 3 hr of refluxing in acetonitrile.The reaction in N,N. dimethyl formamide , an aprotic solvent also yield 4 . However, protic solvent, ethanol and nonpolar solvent toluene and dichloromethane were ineffective[8]

SCHEME-2

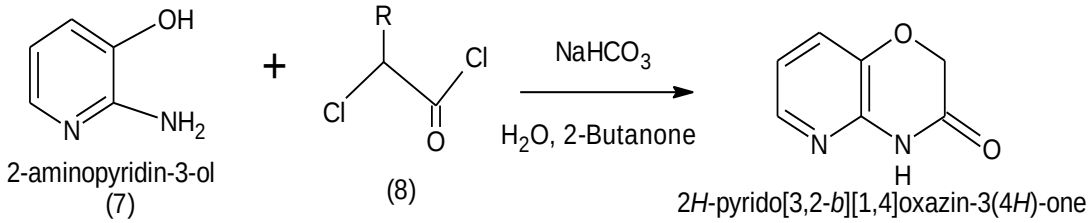


Scheme -3

New series of N.-substituted pyrido[3,2-b] oxazin-3(4H) –ones has been synthesized, pharmacologically evaluated of analgesic activity were carried out by using acetyl salicylic acid as standard drug using tail flick and hot plate method in rat . The compound with the maximal combination of safety and analgesics efficacy was 4—{3-[4-(4-fluorophenyl-1-piperazinyl)propyl]}-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one(IV) with ED_{50} value of 12.5 mg/kg po (mouse: phenylquinone writhing test) and 27.8 mg po(acetic acid writhing test)[9]

The starting material 2H-1,4-pyridoxazin-3-(4H)-ones (9) and 2-Phenyl- 2H-1,4-pyridoxazin-3-(4H)-one (10) can be prepared by Rufenacht et. al involving condensation of 2-amino-3-hydroxy pyridine(7) with appropriate quantity of substituted chloroacetylchloride (8)in presence of sodium bicarbonate.[10] The cyclisation reaction requiresbasic condition so bicarbonate neutralize liberated Hydrochloric acid in reaction and as the reaction is exothermic ,temperature is maintained between 0-5^{0}C.

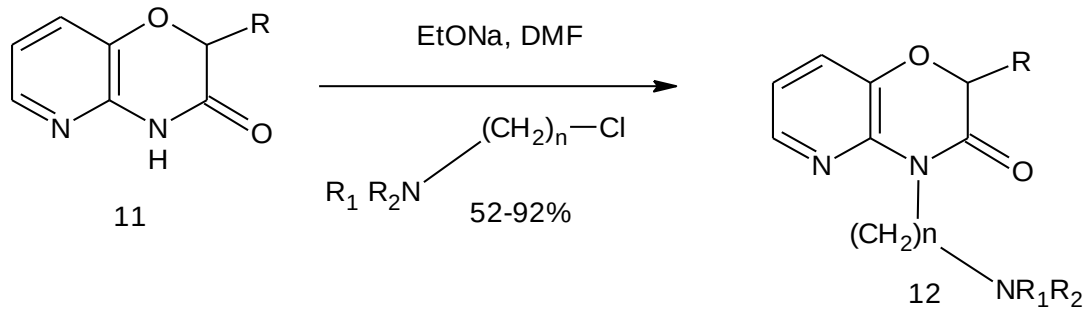
SCHEME-3



Scheme-4

The free nitrogen of the 2H-1,4-pyridoxazin-3-(4H)-ones was alkylated in anhydrous N,N-dimethyl formamide in the presence of sodium ethoxide with (2-chloroethyl)-or (3-chloropropyl) amines. [11]The nitrogen is not readily reactive hence we have to use either sodium ethoxide or dry sodium in super dry alcohol, replace Hydrogen from 1st position of 2H-1,4-pyridoxazin-3-(4H)-ones and can be easily attacked by (2-chloroethyl)-or (3-chloropropyl) amines . The compumd thus generated is refluxed for 3 hrs. The DMF is evaporated by rotatory evaporator. Purification compound 12 can be carried out by column chromatography.

SCHEME 4

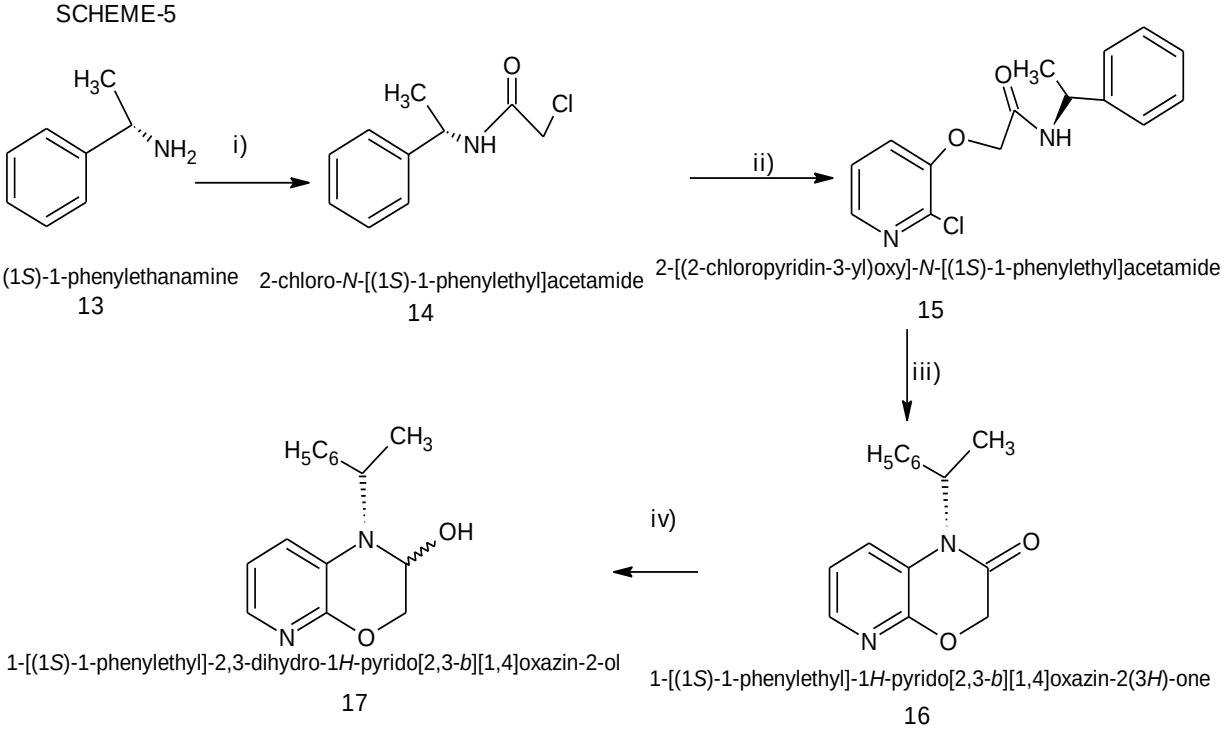


Scheme-5

The synthesis of 1 -Phenyl-(1-Phenylethyl)-1H-pyrido[2,3-b][1,4]oxazin(19) by using 2-chloro-3-hydroxy pyridine with (S)-2-(2-chloro-N-(1-phenylethyl) acetamide(13)in the presence of potassium carbonate furnishes (S)-2-(2-chloripyridin-3-yloxy)-N-(1-phenylethyl)acetamide(15) as a major product in 96% yield and cyclization by using cesium carbonate afford (S)-1-(1-phenylethyl)1H pyrido[2,3-b][1,4]oxazin-2(3H)-one(16). Through series of steps finally result 1-Phenyl-(1-Phenylethyl)-1H-pyrido[2,3-b][1,4]oxazine (19).[12]

In this reaction of 2-chloro-3-hydroxy pyridine with (S)-2-chloro-N-_(1-phenylethyl) acetamide (14) in the presence of potassium carbonate furnished compound15. Compound 14 was prepared by known procedures using chloroacetyl chloride with (S)-α-methyl benzylamine 13 in presence of potassium carbonate to get 95% yield .The use of cesium carbonate produced 16 .and reduction of 4 with sodium borohydride in THF produced compound 17.[13]

SCHEME-5



(1*S*)-1-phenylethanamine
13

2-chloro-*N*-[(1*S*)-1-phenylethyl]acetamide
14

2-[(2-chloropyridin-3-yl)oxy]-*N*-[(1*S*)-1-phenylethyl]acetamide
15

1-[(1*S*)-1-phenylethyl]-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-one
16

1-[(1*S*)-1-phenylethyl]-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-ol
17

Reagents and Conditions:

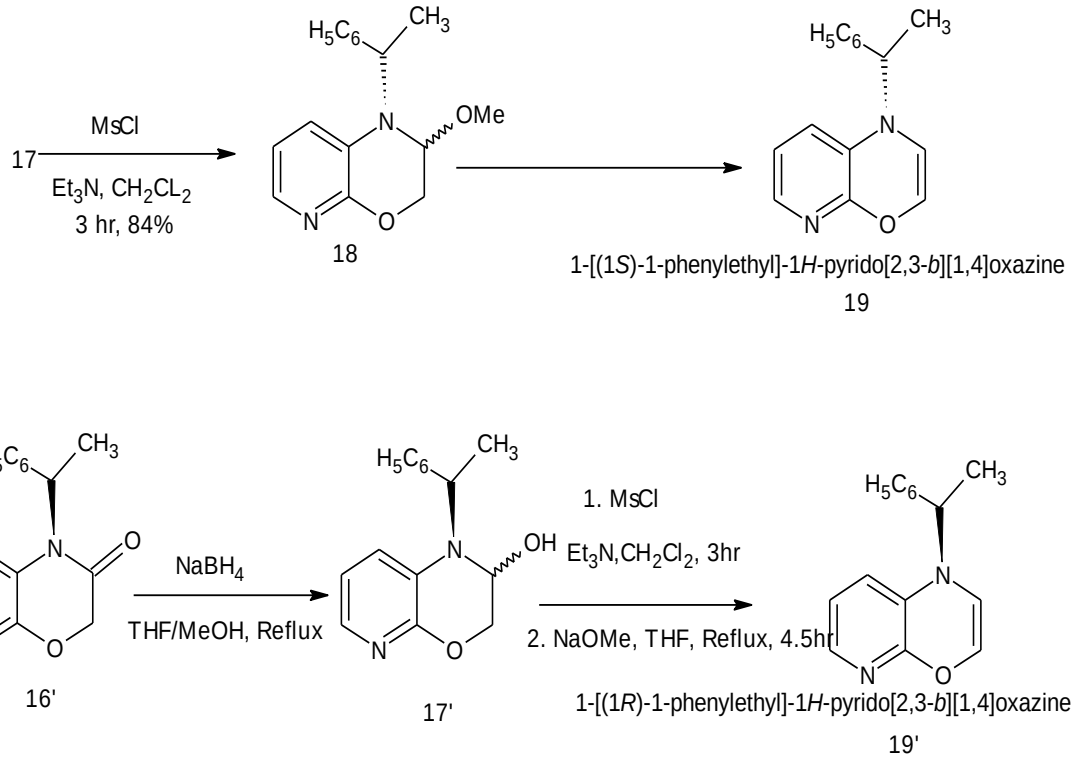
i) 2-Chloroacetyl Chloride, K_2CO_3, CH_2Cl_2,reflux, 95% ii) 2-Chloro-3-hydroxypyridine, K_2CO_3, CH_3CN,Reflux,96%
iii) Cs_2CO_3, CH_3CN,reflux, 96% iv) $NaBH_4$, THF/MeOH, reflux, 88%

Scheme-6

Compound 17 was first treated with methane sulfonyl chloride in dichloromethane in presence of triethylamine to produce methanesulfonic ester 18. The removal of mesyl ester by treatment with sodium methoxide in tetrahydrofuran under refluxing condition gives 19.

By use of same synthetic route 19' was synthesized. [14,15]

SCHEME-6



Scheme-7

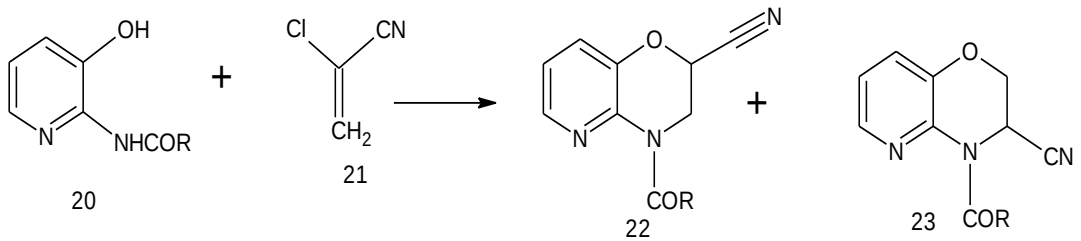
Te compounds having different substituent on the heterocyclic framework were prepared by several methods from 2-acetamido-3-hydroxy pyridine(20). The condensation of 2-protected – amino-3-hydroxy pyridine with 2-chloroacrylnitrile(21) or ethyl 2,3-dibromopropionate(27) provided in several cases two isomeric pyridoxazines. Whereas the reaction of 2-aetamido-3-hydroxypyridine with methyl 2,3-dibromopropionate or with α – halocarbonyl compounds gave exclusively the 2-substitutd pyrido-oxazine in a one-step operation.

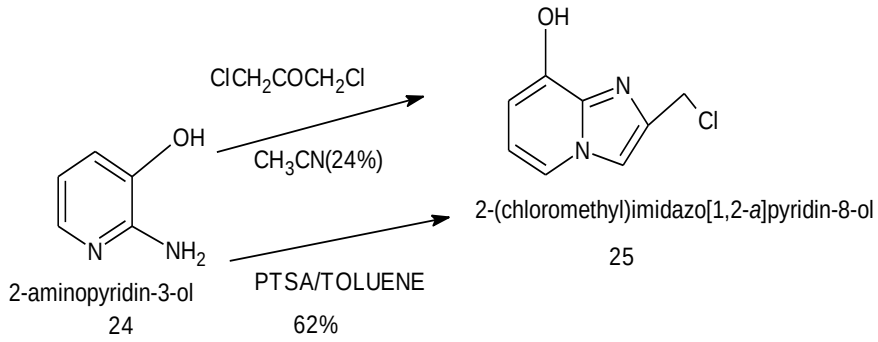
3,4-Dihydro-2H-1,4-benzoxazine derivatives (I) have attracted considerable interest due to their presence of biologically active compounds. Bioisosteric replacement of the benzene by pyridine leads to pyridoxazinone (II)

The protection of the amino group at C-2 by conversion to acetylamino, ethoxycarbomylamino or t-butyl carbonyl amino facilitates the condensation with alkylating reagents. The 2-acetamido-3-hydroxypyridine(20) was the best starting compound for the preparation of 2-substituted pyrido-oxazinones, where as the carbamate derivatives(26) leads to a mixture of 1:1 of 2-.3-substituted compounds (21, 22).

In the presence of K_2CO_3 and Cs_2CO_3 behave similarly where as DBU and triethylamine afforded the same product in lower yields. 22 & 28.

SCHEME-7

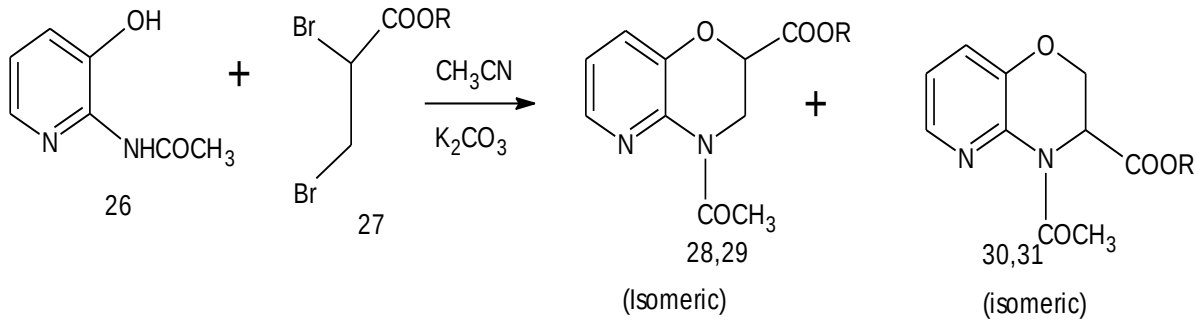




Scheme-8

Mixture of 27 &29 by condensation of acetamido 3 with ethyl 2,3-dibromoi-propionate to give α-olefinic ester .By region selective approach 28-30 were produced.

SCHEME 8



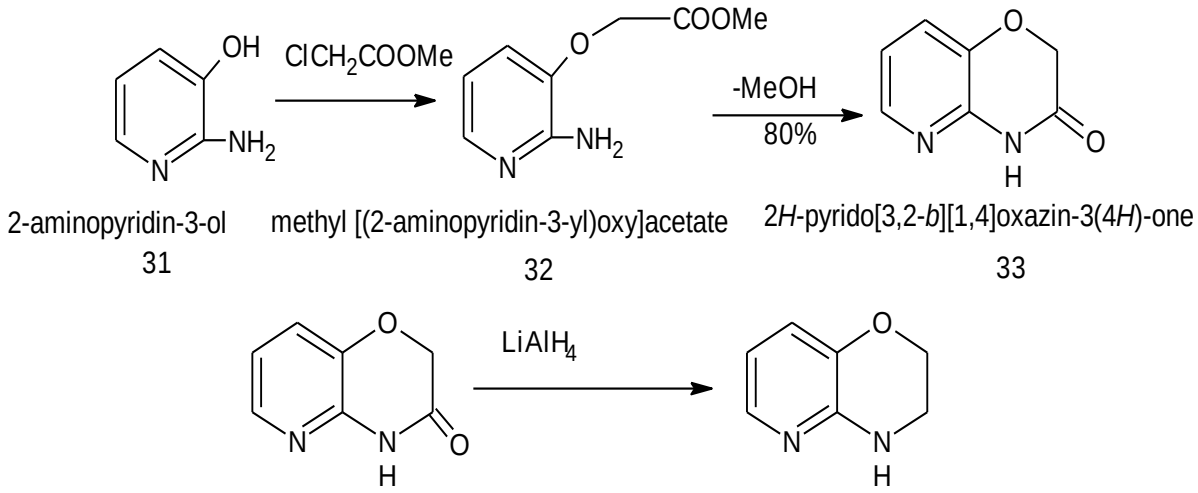
Scheme-9

Seven different 2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-ones(33) have been prepared from 2-amino-3-pyridinol(31). Reduction of these with lithium aluminium hydride gave corresponding dihydropyridoxazinones(34).[16]

It has been found that the suspension of sodium salt of 2-amino-3-pyridinol in dimethyl sulfoxide(DMSO) reacts with chloroacetic acid methyl ester to give 2H-pyrido[3,2-b]-1,4-

oxazin-3(4H) one. Reaction is initiated by an O-alkylation of the pyridinol and proceeds through the intermediate 3-alkoxy pyridine(II).[17]

SCHEME-9



2-aminopyridin-3-ol
31

methyl [(2-aminopyridin-3-yl)oxy]acetate
32

2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one
33

2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one
33

3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine
34

Six substituted halogenoacetic acid esters were found to react in the same way. Each of the Pyridoxazin-3(4H)-ones were reduced by lithium aluminium hydride to produce dihydro derivatives (34) in good yield.[18]

CONCLUSION:

This review covers the achievements in the synthesis of 2H-1,4-pyridoxazin-3-(4H)-ones in last few years. Various acetamide derivatives and substituted pyridine derivatives were used to get the novel compounds in good yield. Techniques like microwave irradiation proved to be helpful. These derivatives are easily accessible and functionalized heterocycles whose application in the synthesis of biologically active compounds will give rise with the increasing demand for peptide mimetics. Fostamatinib disodium FDA approved drug for treatment of rheumatoid arthritis, immune thrombocytopenia and β cell lymphoma has been already reported . More novel pharmacologically active nuclei can be synthesized by using developed reaction schemes.

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