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Recent Advances in the Chemistry and Pharmacology of 2-Pyridone Scaffolds

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Abstract

Heterocycles play an important role in bioactive libraries and the pharmaceutical industry. They play an important role in our biological system, so researchers are still designing and discovering novel pharmacologically active molecules that may help to solve recent health issues. Nitrogen-heterocycles are a common nucleus in many bioactive natural products and FDA-approved drugs, and they provide an important framework in drug discovery and agrochemical industries. Among all the common Nitrogen-heterocycles, 2-pyridone, a six-membered nitrogen ring, has piqued the interest of researchers due to its potent biological actions such as antibacterial, antitumor, antiinflammatory, antiproliferative, anti-hepatitis B virus, SARS-CoV-2 main protease inhibitor, and analgesic properties. According to a recent review, 2-pyridone structural motifs are important in the synthesis of alkaloids, which are an important class of natural organic compounds.

Keywords: 2-Pyridones synthesis • Biological activity • Antibiotics • Antitumor agents

Introduction

This review discusses recent advances in synthetic approaches for generating 2-pyridone libraries from cyclic and acyclic starting materials, such as metal-catalyzed annulation or ring rearrangement reactions using nanocatalysts and environmentally friendly methods such as microwave irradiation. The chemical reactivity of 2-pyridones has been discussed as 2-pyridone molecules undergo critical chemical transformations such as 1,6-carboannulation, coupling, cycloaddition, and CH functionalization. Selective N- versus O-functionalization of 2-pyridone systems is a difficult and important synthetic target for synthetic and medicinal chemists; thus, we demonstrated NH- and CO-functionalization of 2-pyridones in the construction of marketed drugs such as Perampanel and Pirfenidone, as well as bioactive compound production such as P2Y1 receptor antagonist and glucokinase activators for diabetes therapy, as shown in the graphical abstract.

Literature Review

The microwave strategy reduced reaction time and produced a high yield. Furthermore, aromatic aldehydes with electron-donating groups produced a higher yield than electron-drawing substituents. As a green strategy, microwave-assisted synthesis was used to create novel substituted 2-pyridone derivatives that resulted from the condensation of unsaturated ketone with cyanoacetamide under microwave irradiation. Furthermore, the coupling of arene diazonium chlorides with substituted 2-pyridone derivatives yields the corresponding azo-2-pyridone derivatives 81. Furthermore, a mixture of cyanocetamide and 2-arylhydrazono-1,3-disubstituted-propane-1,3-dione 80 in the presence of potassium hydroxide was microwave irradiated for 2-3 minutes to produce corresponding azo-2-pyridone derivatives. In an excellent yield (96%), a new one-pot microwave protocol was used to obtain the same target compounds 81 using base catalyst without solvent.

The one-pot reaction of ß-keto amide (N-Phenyl-3-oxo-3 phenylpropanamide) and phenyl propargylaldehyde or cheaper corresponding propargylic alcohol (3-phenylprop-2-yn-1-ol) was catalysed by a phosphazene-supported organocatalyst (P-BEMP) and transition metal oxide to produce N-aryl-substituted 2-pyridone 89 in excellent yield. 3-cyano-2-pyridone 90 was synthesised in a one-pot ethyl cyanoacetate, acetophenone, aromatic aldehydes, and ammonium acetate reaction with L-proline as an organo-catalyst while refluxing in ethanol. This protocol demonstrated how to make this type of useful heterocyclic compound in a simple operation using readily available starting materials. The annulation of N-methoxyamide and nitroalkene 92 in the presence of Cu(OAc)2 and hexafluoro-2-propanol (HFIP) as a solvent resulted in the formation of N-substituted 2-pyridone after 20 hours at 80°C.

Discussion

A nitrene insertion strategy to prepare multiple ring fused 2-pyridone poly-heterocycles 128, 129, and 130 from 6-azido-2-pyridones 127 for the synthesis of poly-substituted pyridine fused 2-pyridones capable of amyloid fibril binding. Singh et al. reported yet another synthetic route to tricyclic pyridine ring fused 2-pyridones via Lewis acid and transition metal catalysed Povarov and A3 reactions, respectively. As a result, the Povarov reaction and A3 coupling of 2,3-dihydrothiazolo2-pyridones 24a-c will be discussed in greater depth in this review. Nitration and reduction of 2,3-dihydrothiazolo-2-pyridones 24a-c resulted in 6-amino-2-pyridones. With the synthesis of 2-pyridone fused aza-diene 133, the Povarov reaction of 6-amino-2-pyridones was introduced by reacting 6-amino-2-pyridone 132a with p-nitrobenzaldehyde in methanol.

The reaction of 1,6-diamino-3,5-dicyano-2-pyridones 51 with pentafluoropyridine 156 under refluxing in the presence of potassium carbonate in acetonitrile as a solvent for 48 h produced dipyrido triazines major product and 6-amino-2-oxo-1-(perfluoropyridin-4-yl)amin o)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitriles 158 as a minor product. Compound formed by attaching an amino group to a nitrogen atom in the pyridone ring and transferring it to the 4-position of a pyridine ring, followed by intramolecular ring closure at the 3-position of the pyridine ring by another amino group 5a. The higher nucleophilicity of the N-amino group justifies the regioselectivity of nucleophilic attack on pentafluoropyridine 158 over the amino group.

To support selective N-H functionalization of 2-pyridones, selective N-alkylation of 2-pyridones was performed under acidic conditions with

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rhodium catalysts. The chiral N-allyl 2-pyridones were synthesised via a rhodium-catalyzed regioselective reaction of 2-pyridones with terminal allenes. This method to access glucokinase activators synthesis via the treatment of 4-(methylsulfonyl)-2-pyridone 203 with allene 204 and [Rh (cod)Cl]2 besides (s)-DTBM-MeOBIPHEP ((s)-L4) in 1,2- \sdichloroethane at 80 C affording 205 followed by Pinnick oxidation and methylation to yield product 206 which reacted with of different aminoheterocycles to produce glucokinase activators 207 for diabetes therapy.Timmerman and Widenhoefer demonstrated an intriguing method for selective N-alkylation of 2-pyridones using methylenecyclopropanes (MCPs) via gold-catalyzed intermolecular anti-Markovnikov hydroamination.

Ampicillin and ciprofloxacin were used as standard drugs in this study to evaluate antibacterial activity, and amphotericin B was used to evaluate antifungal activity. The most potent antimicrobial activity. The structure-activity relationship study discovered that compounds with electron-withdrawing groups, such as F and Cl, demonstrated activities close to the standard. Electron-donating groups, such as the methyl group on the phenyl ring, on the other hand, did not show remarkable activity against all microbes. Furthermore, the unsubstituted phenyl ring demonstrated modest activity against A. fumigatus, S. pneumonia, and *E. coli*, as well as low activity against other microbes. Although well-known drugs containing the N-sulfonylamino group, such as sulfamethoxazole and sulfadimidine, are potent antimicrobial agents, synthesised 2-pyridone analogues containing the N-sulfonylamino group exhibited low activities against all screened microbes when compared to amphotericin B and ciprofloxacin [1-5].

Conclusion

This review highlighted the updates on the synthetic strategies and reactivity of 2-pyridone molecules, particularly green chemistry methodologies under optimum conditions, which open a new door for researchers to construct numerous heterocycles using eco-friendly and safe approaches. Furthermore, as we gain a better understanding of their mode of action, fast and efficient synthetic pathways will be required, as it is expected that in the future, The data presented in this review clearly show that 2-pyridone derivatives have a high synthetic potential. Considering 2-pyridone motifs as a bioactive core in various vital drugs, the authors demonstrated the therapeutic importance of 2-pyridone derivatives by discussing structure-activity relationship studies and binding with several biological targets. Based on this heterocyclic ring, many biologically active heterocyclic compounds have been synthesised. Some of the most powerful molecules in terms of biological activity. This implies that 2-pyridone can be used to create novel, highly effective pharmaceuticals with a broad range of bio responses.

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Conflict of Interest

There are no conflicts of interest by author.

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