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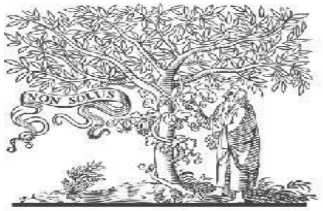

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INVESTICATING PROPERTIES AND ACTIVIES OF PYRIDO-DIPYRIMIDINES

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ABSTRACT
To facilitate access to a wide variety of pharmaceutically interesting and diversely functionalized compounds, a water-mediated and catalyst-free simple approach has been developed. 5-Alkyl-10-aryl or heteroaryl-2,8-dioxo or dithioxo-9,10-dihydropyrido[2,3-d:6,5-d']isoquinoline.analogs of 1,3,5,7-tetrahydrodipyrimidine-4,6-dione 5,5'-(1,4-phenylene)bis(10-alkyl/aryl-2,8-dioxo/dithio-9,10-dihydropyrido[2,3-d:6,5-d']quinoxaline) and 4 (4-1-4-42)The one-pot multicomponent reaction of barbituric/N,N-dimethyl barbituric/thiobarbituric acids (1), substituted amines (2), and aldehydes (3) at room temperature led to the development of dipyrimidine-4,6(1H,3H,5H,7H)-dione) 4′ (4′-1-4′-8). High atom-economy and low E-factor, good to excellent yields, reusability of reaction media, and a clean reaction profile are just some of the highlights of this protocol. Water is used as the reaction media, and the reaction takes place at room temperature under mild conditions.

Keywords: - Bioactive, Pharmaceutically, Antibacterial, Pyrimidine, Synthesis.

I. INTRODUCTION

Bioactive natural items, commercial medications, agrochemicals, dyes, and many other application-oriented materials all include heterocyclic moieties, especially polyfunctionalized heterocycles (PFHs). As a result, PFH synthesis studies have received more funding and attention. Antioxidant, anti-inflammatory, immunomodulatory, antibacterial, antiviral, and anticancer action are only some of the pharmacological characteristics attributed to pyrimidine and its derivatives among N-heterocycles.8-12 As a class of pharmaceutically promising pyrimidine derivatives, barbituric/2-thiobarbituric acids have the potential to be used in the production of a wide variety of barbiturate/thiobarbiturate drugs, including those with applications as hypnotics/sedatives/anticonvulsants/anesthetics/antioxidants/antifungals/CNS depressants.13-21 Synthesis of various derivatives with the necessary potential biological effects may therefore be possible by the combination of the barbituric/thiobarbituric acid moiety with other pharmacophoric groups. Given their broad range of potentially useful biological functions, pyrimidine-fused pyridines, and notably pyrido[2,3-d]pyrimidines, have been the subject of much research in recent years.22-29 Some derivatives of the pyrido[2,3-d:6,5- d']dipyrimidine scaffold have been the subject of intense study because of their potent antibacterial, antiviral, NAD-type redox catalytic,

anticorrosive, and anti--glucosidase and --amylase activities30,31,32,33,34,35,36 effects. It has also been suggested that such a framework may self-assemble into a supramolecular structure.37 A search of the published literature uncovered many routes to the synthesis of 10-unsubstituted 9,10-dihydropyrido[2,3-d:6,5-d'].Many procedures have been developed for the synthesis of dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones utilizing different catalysts32,38-44, including the use of organic solvents, heating/refluxing, microwave irradiation, and ultrasonic irradiation. However, syntheses of N10-substituted dihydropyrido[2,3-d:6,5-d']dipyrimidines were reported only by the research group of Khalafi-Nezhad from the three-component condensation reaction of barbituric acids, anilines, and aromatic aldehydes or sugars upon refluxing the reactants in ethanol either in the presence of tungstophosphoric acid (TPA)45 or p-toluenesulfonic acid46 or magnetic nanoparticle-supported tungstic acid (MNP-TA)47 as the catalyst. These older procedures have their advantages, but they also have drawbacks, such as lengthy reaction times, difficult reaction conditions, heating, refluxing, costly metal nano-catalyst/reagents, and high catalytic loading. Each of these techniques has a relatively restricted substrate range.

II. BIOLOGICAL RELEVANCY OF PYRIDO-DIPYRIMIDINES

Several biological and pharmacological actions are seen in pyrido[2,3-d:6,5-d']dipyrimidines.45,46,48-51 Kaya et al. tested a range of synthesized bisacridine-1,8-dione derivatives for antibacterial activity against a variety of gram-positive and gram-negative bacteria and yeast.48 Among the microorganisms tested, compounds I and II demonstrated antibacterial and antifungal action against Shigella sonnei, Bacillus cereus, Escherichia coli, and Pseudomonas aeruginosa, respectively.

All four compounds (I, II, III, and IV) produced demonstrated considerable efficacy in antifungal assays against Candida albicans and Saccharomyces cerevisiae. shows that produced pyrido[2,3-d:6,5-d']dipyrimidine compounds (V-IX) by H. Naeimi and colleagues are effective against gram-positive bacteria in vitro. Compound V, in particular, was the most effective of them. The inhibitory efficacy of glucosamine-based pyrimidine-fuse heterocycles (XI, XII, XIII, and XIV) as green corrosion inhibitors for mild steel in 1 M HCl was shown by M. A. Quraishi and colleagues50.

The inhibitory effect of many synthetic pyrimidine-fused derivatives against yeast and mouse -glucosidase was assessed by F. Panahi et al.45. The IC50 values of the prospective inhibitors were determined using Dixon plots, which revealed their pharmacological profile. Also employed as a positive control was the antidiabetic medication acarbose, which inhibits mammalian -glucosidase activity. Note that compound XV did not exhibit any inhibitory effect against yeast or mouse -glucosidases after synthesis. Both enzymes were inhibited by Compound XVI, with IC50 values of 148 1 and 159 3 M, respectively. The 4-(4-

aminobenzyl)benzenamine moiety in compound XVII showed the greatest inhibitory effect (IC50 = 9 1 M). In addition, compound XVIII showed some modest inhibitory action against yeast -glucosidases (IC50 = 376 1 M). Some poly-hydroxyl functionalized acridine molecules were tested for their ability to inhibit the activities of alpha-glucosidase and alpha-amylase by Z. Toobaei and colleagues in group 51. The chromeno[3',4':5,6]pyrido[2,3-d]pyrimidine moiety in compound XIX showed the greatest inhibitory efficacy against yeast and rat -Glucosidase enzymes of all the produced compounds. The thioxo-pyrido[2,3-d:6,5-d']dipyrimidine moiety of XX is also crucial to its ability to inhibit yeast - glucosidase. Vitamin B2 (riboflavin) is essential for development and well health. It facilitates the oxidation of oxygen and the breakdown of carbs, proteins, and lipids for energy. Riboflavin has a carbohydrate moiety and a varied polyfunctionalized heterocycle (PFH) ring. displays various examples of bioactive pyrido[2,3-d:6,5-d']dipyrimidines scaffolds.

- **Development of functionalized pyrido[2,3-d:6,5-d']dipyrimidines: A literature background**

A search of the scientific literature reveals many routes to the synthesis of N10-unsubstituted 9,10-dihydropyrido[2,3-d:6,5-d'].dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones using organic solvents, heating/refluxing, microwave/ultrasound irradiation, and a wide range of catalysts (e.g., DBU,38 SBA-15-SO3H,39 [H-NMP]+[HSO4],32 - Fe2O3@HAp-SO3H,40 nano-CuFe2O4,4143 nano-Fe3O4,44). However, syntheses of N10-substituted dihydropyrido[2,3-d:6,5-d']dipyrimidines were reported only by the research group of Khalafi-Nezhad from the three-component condensation reaction of barbituric acids, anilines, and aromatic aldehydes or sugars upon refluxing the reactants in ethanol either in the presence of tungstophosphoric acid (TPA)45 or p-toluenesulfonic acid46 or magnetic nanoparticle-supported tungstic acid (MNP-TA)47 as the catalyst.

- **Synthesis of functionalized pyrido[2,3-d:6,5-d']dipyrimidines using tungstophosphoric acid (TPA) as the catalyst under reflux conditions**

In 2013, Khalafi-Nezhad and his group45 reported a chemical synthesis of N10-substituted dihydropyrido[2,3-d:6,5-d']dipyrimidines (only seven compounds) via one-pot three- component condensation reaction of barbituric acids, amines, and aldehydes by refluxing (80ºC) the reactants in ethanol in the presence of tungstophosphoric acid (TPA) as highly expensive catalyst for 12 h (Scheme 2). By simply washing the crude product with ethanol-water, they were able to produce pure product with high to exceptional yields from this process. The enzymatic mechanism of inhibition of -Gls by the produced pyrimidine fused compounds was described. The impact of these scaffolds on porcine pancreatic -amylase (- Amy) was further investigated to improve the selective inhibition outcome. These synthetic chemicals may be used as a starting point for

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creating new -Gls inhibitors, which may more effectively inhibit -Gls and, perhaps more crucially, may have less adverse effects than the standard -Gls inhibitors like acarbose.

III. SCOPE OF THE DEVELOPED PROTOCOL

We then carried out two separate reactions, one using barbituric acid, 4-methylaniline, and 4-nitrobenzaldehyde, and the other including barbituric acid, 4-methylaniline, and 3-nitrobenzaldehyde, at the optimal circumstances; each reaction afforded the corresponding compounds, viz. A 5-(4-nitrophenyl)-10-(p-tolyl)(9,10)-Dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H, 5H,7H)(4-2)-tetraone and (5-(3-itrophenyl)-tetraone-10-(p-tolyl)Within 11-12 hours, we obtained 91% and 88% yields, respectively, of 2,4,6,8(1H,3H,5H,7H)-tetraone (4-3) Barbituric acid was reacted with a variety of aromatic amines (containing substituents like bromo, trifluoromethyl, methoxyl, and trifluoromethoxyl at varying positions) and aromatic aldehydes (containing functionalities like bromo, chloro, cyano, trifluoromethyl, mono-, di-, and tri-methoxyls and nitro) under the same reaction conditions to test the generality and efficiency of thedipyrimidine-2,4,6,8(1H,3H,5H,7H)yields of 57-93% for -tetraones (4-4 4-15) in 10-16 hours at room temperature. Ten-(4-(trifluoromethyl)phenyl) is formed.-5-(3,4,5-trimethoxyphenyl)-9,10-dihydropyrido[2,3-d:6,5-d']The 1,3,5,7-tetrahydro-2,4,6-dipyrimidine-tetraone (4-14). The 4-CF3 substituent provides an electron-withdrawing effect on the amine, and the 3,4,5-trimethoxyl moiety also imposes some steric limitation on the reactivity of the aldehyde, which may account for the modest yield of 57% at 16h.Aliphatic amines, such as n-propyl amine (2-16) and n-hexylamine (2-17), gave off their intended products, barbituric acid and 2-/3-nitrobenzaldehydes, respectively, when subjected to the identical reaction conditions. 5-(2-nitrophenyl)-10-propyl-9,10-dihydropyrido[2,3-d:6,5-d'] and 10-hexyl-5-(3-nitrophenyl)dipyrimidine (4-16) and dipyrimidine-,4,6,8(1H,3H,5H,7H)-tetraone (4-16).-- 2,4,6-dihydro-9,10-pyrido[2,3-d:6,5-d']dipyrimidine-7(1H,3H,5H,7H)-tetraone (4-17) with modest yields of 63.6% at 12h. The idea of amino acids as a distinct class of aliphatic/aromatic amines sparked our curiosity, and we were overjoyed to successfully synthesize 3-(4-hydroxyphenyl).-2-(5-(4-nitrophenyl)The reaction of tyrosine (2-18) with the combination of barbituric acid and 4-nitrobenzaldehyde in water at ambient conditions yielded 2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-d:6,5-d']dipyrimidin-10(5H)-)propanoic acid in 70% yield at 16h. Terephthalaldehyde (4-formylbenzaldehyde) was again reacted with barbituric acid and substituted amines on two separate occasions, however this time the conditions were

The equivalent products 4-19 (82%) and 4-20 (77%) with the 4-formyl group intact in their molecular structures were separated after 12 and 14 hours, respectively, under the same reaction conditions. There is significant chemistry interest in this unique

family of compounds that has a free formyl moiety.

Motivated by these findings, we substituted N,N- dimethyl barbituric acid for unsubstituted barbituric acid and proceeded to perform a series of seven separate reactions by combining 2 equiv. of this substituted barbituric acid with 1 equiv. of various amines (4-(methylthio)aniline, alanine, tyrosine, glucosamine, 4-trifluoromethylaniline) and al As predicted, we obtained 62-80% yields within 14-18 hours from all seven processes, resulting in a novel series of substituted 9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8-tetraones.

IV. CONCLUSION

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