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A REVIEW ON PYRONES, PYRONE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

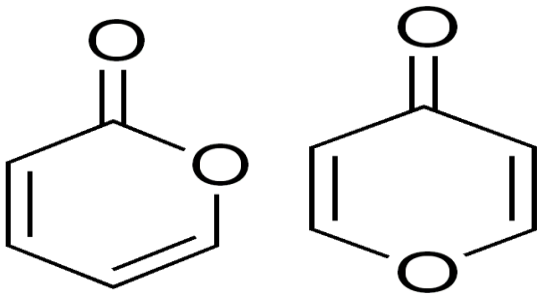
Pyrones or pyranones an unsaturated six membered ring heterocyclic compound. It contains oxygen atom and ketonic functional group. There are two isomers, denoted as 2-pyrone and 4- pyrone. The structure have offered a high value of diversity that is proven useful for the development of new medicinal drugs and improved potency, less toxicity and good pharmacological activity. Now a days pyrone and its derivatives are used for the treatment of an Anticancer, Antibiotics, Insecticidal, Anticoagulants, Herbicidal and HIVprptease etc. The aim of this review is to provide the recent efforts of scinentists in pharmacological screening of pyrones, importants and synthesis of pyrone derivatives,pharmacological action of pyrones and their biological activity.

KEYWORDS: Pyrones, Anticancer, Antibiotics, Insecticidal, Anticoagulants, Herbicidal and HIVprotease.

INTRODUCTION

Heterocyclic chemistry deals with heterocyclic compounds wich are widely distributed in nature and are essential to life.The majority of known molecules are heterocyclic and heterocycles dominate the fields of biochemistry, medicinal chemistry, dyestuffs and photographic. The pyrones are a class of heterocyclic compounds. There are two isomers such as 2-pyrones and 4- pyrones. The 2-pyrone is other wise called as α-pyrone, this structure found in coumarin ring system.[1] It is used an organic synthesis of more chemical structures.It is isolated from plants animals, marine organisms, bacteria,fungi and insects etc.

The 4- pyrone is other wise called as γ-pyrone. It is found in natural compounds such as chromone, maltol, kojic acid. The Quercetin, Apigenin is substituted with 4- pyrone. Both pyrones contains five sp^2 hybridized carbons. The furo coumarins and furo flavones are synthesized by starting with suitably substituted α-pyrone or γ-pyrone derivatives and then building up pyron ring on hydroxyl benzofurans. The pyrones have been identified as interesting compounds that are collaborate with various biological activities.[2]



2-Pyrone (or α-pyrone) 4-Pyrone (or γ-pyrone)

Biological activities of pyrone derivatives

1. Antimicrobial activity[3]

Naziabegum.P *etal* has been reported the synthesis and antimicrobial evaluation of some Chalcone derivatives of 3-cinnamoyl-4-hydroxy-6-methyl-2-**pyrones**. In an effort to develop antimicrobial agents, a series of Chalcone derivatives of 3- cinnamoyl-4-hydroxy-6- methyl-2-pyrones were synthesized by base catalyzed condensation of 3-acetyl-4-hydroxy-6-methyl-2-keto-2H-pyran (DHA) with different aromatic aldehydes. The synthesized compounds were characterized by means of their IR, and 1HNMR spectra's. The synthesized compounds were tested for their antibacterial and antifungal activities.

2. Anti cancer activity[5]

Liou S.S *et al* has been reported the gamma-pyrone compounds as potential anti-cancer drugs. The **gamma-pyrones**, artomunoxanthotrione epoxide, cyclocommunin, cyclomulberrin, and cyclocommunin exhibited potent inhibition of human PLC/PRF/5 and KB cells in-vitro. Dihydroisocycloartomunin showed significant and potent inhibition of human PLC/PRF/5 and KB cells in-vitro, respectively. Cyclomorusin, dihydrocycloartomunin and artomunoxanthone showed significant inhibition of KB cells in-vitro. Based on the above finding and the reported antileukaemic activity of xanthone psorospermin, a series of natural gamma-pyrones was prepared and the inhibition of human PLC/PRF/5 and KB cells in-vitro was measured. Structure-activity analysis indicated the

epoxide group substituted at 3-hydroxyl and 2, 6-; 3, 6-; and 3, 5-dihydroxyl xanthone enhanced the anti-tumour activity. The epoxide group substituted at the 6-hydroxyl group of 1, 6-dihydroxyxanthone did not show anti-tumour activity.

3. Spasmolytic activity[6]

Vicente C.D *et al* has been reported hyptenolide, a new α-pyrone with spasmolytic activity from *Hyptis macrostachys*. A new **α-pyrone** was isolated from aerial parts of *Hyptis macrostachys* Benth. Its structure was determined as 6*R*-[(5′*S*, 6′*S*-diacetoxy)-1′*Z*, 3′*E*-heptenyl]-5, 6-dihydro-2*H*-pyran-2-one, named hyptenolide based on a combination of 1D and 2D NMR techniques and CD data. Hyptenolide inhibited the contractions induced by CCh ($IC_{50} = 1.7 \pm 0.3 \times 10^{-4}$ M) or histamine ($IC_{50} = 0.9 \pm 0.05 \times 10^{-4}$ M) in guinea pig ileum, demonstrating for the first time a pharmacological activity for the pyrone.

4. Anti – Obesity activity[7]

Tomoyuki *et al* has been reported Anti-obesity activities of the yoshinone and the related marine **γ-pyrone** compounds. Marine cyano bacteria are known as important creators of novel natural products. From this valuable source, various bioactive compounds have been found and characterized in terms of their pharmacological and toxicological activities. In the recent work, we have reported the new marine γ-pyrones yoshinone A, B1 and B2 from *Leptolyngbya* sp., and determined their planar structures using NMR spectral analysis. Yoshinone A, as the major compound among them, showed inhibitory activity against the adipogenic differentiation of 3T3-L1 cells with an half maximal inhibitory concentration (IC_{50}) value of 420 nM without cytotoxicity (IC_{50}>50 μM). On the other hand, the yoshinone B1 and B2 showed only limited activity against 3T3-L1 cells, with higher concentrations compared with yoshinone A. Further studies of the structure–activity relationship lead us to conclude that the position of a pyrone ring and an olefin in the side chain will be important for the inhibition of adipogenic differentiation. These γ-pyrones have olefins in their side chain at positions 7 and 6 in the cases of yoshinones A and B1/B2, respectively. To express the effects on adipocyte, the olefin should not be conjugated with γ-pyrone moiety, such as yoshinone A. In the previous studies, kalkipyrone isolated from cyanobacteria, aureothin, and actinopyrones A and B isolated from streptomyces fell into the same 7-en γ-pyrones. Then, we confirmed that kalkipyrone and aureothin showed this activity, with IC_{50} values of 67.5 and 54.2 nM, respectively. On the basis of these data, we are focusing on the 7-en γ-pyrone (unconjugated type)

compounds. These pyrones are expected to be candidates for novel lead compounds for the treatment of obesity and related diseases. Studies on useful tools that regulate adipocytes will contribute to the prevention and treatment of these diseases. At the present stage of our research, we have evaluated the anti-obesity activities of the 7-en γ-pyrones using *in vitro* and *in vivo* experiments. In this study, we report on the interesting properties of these pyrones.

5. Tyrosinase inhibitory activity[8]

Dahai. Z *et al* has been reported A New α-pyrone derivative, 6-[(E)-Hept-1-enyl]-α-pyrone, with tyrosinase inhibitory activity from a Marine Isolate of the Fungus Botrytis. Microorganisms such as bacteria, fungi, and blue-green algae have proven to be a rich source of new biologically active secondary metabolites.1 Marine microorganisms, particularly marine fungi, have recently drawn much attention as an important source of biologically active secondary metabolites.2 Among marine fungi, those living in association with marine algae are promising sources of novel natural products due to their unique ecological niche. The association between algae and fungi appears to be highly developed since nearly one-third of all higher marine fungi described are namely algicolous or algae-associated organisms.3 Recently, marine-derived fungi have yielded unique biologically active metabolites, such as myrothenones,4 gliotoxin derivatives,5 and asperflavin ribofuranoside,6 suggesting that these organisms would be valuable producers of potential therapeutic agents. As part of our search for bioactive substances from marine microorganism, 6 the fungus was studied because the broth extract showed potent tyrosinase inhibitory activity.7 In order to identify the active compounds, the broth was further separated into single ones. Careful bioassay-guided fractionations resulted in isolation of a new α-pyrone derivative, 6- [(E)-hept-1-enyl]-**α-pyrone** (1), and two known compounds, 6-[(E)-pent-1-enyl]-α-pyrone (2) 8 and 4-hydroxyphenethyl alcohol (3) 9 from the marine isolate of fungus Botrytis sp.

6. Anti fungal activity[9,10]

Tarun Kumar C. *et al* has been reported Antifungal activity of 4-methyl-6-alkyl-2H-pyran-2-ones. A number of 4-methyl-6-alkyl-α-pyrones were synthesized and characterized on the basis of ^{1}H NMR and mass spectroscopy. These compounds were tested in vitro against pathogenic fungi, namely, *Sclerotium rolfsii* Saccardo, *Rhizoctonia bataticola* (Taub.) Butler, *Pythiumaphanidermatum* (Edson)Fitz. *Macrophominaphaseolina* (Tassi), *Pythium debaryanum* (Hesse), and *Rhizoctonia Solana* Nees. Lower homologues were less effective,

whereas compounds such as 4-methyl-6-butyl-α-pyrone, 4-methyl-6-pentyl-**α-pyrone**, 4-methyl-6-hexyl-α-pyrone, and 4-methyl-6-heptyl-α-pyrone were found effective against all of the test fungi. They inhibited mycelial growth by approximately 50% (ED_{50}) at 15−50 μg/mL. 4-Methyl-6-hexyl-α-pyrone, which was found most effective, was tested against *S. rolfsii* in a greenhouse at 1, 5, and 10% concentrations. The 10% aqueous emulsion of 4-methyl-6-hexyl-α-pyrone suppressed disease development in tomato by 90−93% as compared with the untreated infested soil in the green house after 35 days of treatment.

7. Anti inflammatory activity[11]

Ya Nan.S *et al* has been reported the Isolation and identification of chromone and **pyrone** constituents from *Aloe* and their anti-inflammatory activities**.** *Aloe* has long been used in food products, beverages and cosmetics, and as a traditional medicine to treat various diseases in many countries. In the present study, a new chromone, aloe resin E, and a new pyrone, aloenin C, together with thirteen known compounds were isolated from aqueous dissolved *Aloe* exudates and their structures were identified by spectroscopic analysis. Nuclear factor kappa B (NF-κB) inhibitory activity of the isolated compounds was evaluated using an NF-κB luciferase assay in HepG2 cells.Amongthem,7-hydroxy-5-(hydroxymethyl)-2-methylchromone,5-((*S*)-2′-oxo4′hydroxypentyl)2hydroxymethylchromone, and aloenin aglycone showed significant inhibitory effects against TNFα-induced NF-κB transcriptional activity in a dose-dependent manner with IC_{50} values ranging from 14.92 to 18.70 μM. Furthermore, the transcriptional inhibition of compounds was confirmed by a decrease in the expression of inducible nitric oxide synthase (iNOS) and intercellular adhesion molecule-1 (ICAM-1) genes in HepG2 cells.

8. Anticonvulsant and Antioxidant activity[12]

Shalini. K *et al* has been reported Anticonvulsant and Antioxidant actions of some dibenzo-a-pyrone derivatives in pentylene –induced kindling model in mice. The present study was carried out to investigate the effect of Dibenzo-**α-pyrone** derivatives on the course of pentylenetetrazole (PTZ)-induced chemical kindling and oxidative stress markers in PTZ-kindled mice. Kindling was induced by repeated injections of a sub convulsive dose of PTZ (25mg/Kg, i.p.) on alternate days for 5 weeks or until stage 5 of the seizure score was evoked on three consecutive administrations. Butyl amine, Diethyl amine and Pyrrolidine Derivatives of Dibenzo-α-pyrone were administered daily in three doses (10, 20 and 40mg/kg) per orally (p.o.) along with alternate day PTZ. Following PTZ kindling, oxidative stress parameters, i.e.

levels of malondialdehyde (MDA) and reduced glutathione (GSH), were assessed in isolated homogenized whole brain tissue. PTZ treatment progressively increased the seizure score in control mice. Biochemical analysis revealed a significant increase in MDA levels and decreased GSH levels in the brain homogenate of PTZ-kindled mice. Daily treatment with Butyl amine, Diethyl amine and Pyrrolidine Derivatives of Dibenzo-α -pyrone in doses of 20 and 40mg/kg significantly decreased the PTZ-induced seizure score. However, a low dose (10mg/kg) failed to improve the seizure score. Pretreatment of derivatives in all doses showed an ameliorating effect on biochemical alteration induced by PTZ treatment. The present study indicates the potential anticonvulsant activity of Dibenzo-α-pyrone derivatives against PTZ-induced kindling in mice.

9. Anti-Lymph edema activity[13]

John R. et al reported the Treatment of lymph edema of the arms and legs with 5, 6-benzo-[alpha]-pyrone. Benzo pyrones can reduce the volume of high-protein edema fluid by stimulating proteolysis. These compounds provide a method for removing excess protein and its consequent edema and reduce its clinical sequelae, such as chronic inflammation and secondary infections. We conducted a randomized, double-blind, placebo-controlled, crossover trial of 5, 6-benzo-[alpha]-**pyrone** in 31 patients with post mastectomy lymph edema of the arm and 21 patients with lymph edema of the leg of various causes.

10. Immunomodulatory effect[14]

Kwoknam. L *et al* has been reported Immunomodulatory Effects of Esculetin (6, 7-Dihydroxycoumarin) on Murine Lymphocytes and Peritoneal Macrophages. Coumarins belong to a diverse group of naturally occurring non-nutrient phytochemicals known as **benzo-αpyrones**. In this study, esculetin, a 6, 7-dihydroxy derivative of coumarin with pleiotropic biological activities, was found to have no significant cytotoxic effect on normal murine macrophages, but it could increase the in vivo migration of the thioglycollate-elicited macrophages in a dose-dependent manner. Moreover, esculetin significantly increased the endocytic activity, and augmented the nitric oxide production and iNOS gene expression in LPS-treated macrophages. In addition, in vivo administration of esculetin into mice was shown to increase the mitogenesis of splenic lymphocytes towards Con A and LPS stimulations, and induced the LAK activity of splenic lymphocytes. Collectively, our results indicate that esculetin could exert Immunomodulatory effects on murine macrophages and

lymphocytes, both in vitro and in vivo, and this might be one of the possible mechanisms by which coumarins can exert their chemo preventive and anti-tumor activities in vivo.

11. HIV protease inhibitors activity[15]

Thaisrivongs S. *et al* has been reported the Structure-based design of HIV protease inhibitors: 5, 6-dihydro-4-hydroxy-2-pyrones as effective, nonpeptidic inhibitors. From a broad screening program, the 4-hydroxycoumarin phenprocoumon (I) was previously identified as a lead template with HIV protease inhibitor activity. The crystal structure of phenprocoumon/HIV protease complex initiated a structure-based design effort that initially identified the 4-hydroxy-2-**pyrone** U-96988 (II) as a first-generation clinical candidate for the potential treatment of HIV infection. Based upon the crystal structure of the 4-hydroxy-2-pyrone III/HIV protease complex, a series of analogues incorporating a 5, 6-dihydro-4-hydroxy-2-pyrone template were studied. It was recognized that in addition to having the required pharmacophore (the 4-hydroxy group with hydrogen-bonding interaction with the two catalytic aspartic acid residues and the lactone moiety replacing the ubiquitous water molecule in the active site), these 5,6-dihydro-4-hydroxy-2-pyrones incorporated side chains at the C-6 position that appropriately extended into the S1' and S2' subsites of the enzyme active site. The crystal structures of a number of representative 5, 6-dihydro-4-hydroxy-2-pyrones complexed with the HIV protease were also determined to provide better understanding of the interaction between the enzyme and these inhibitors to aid the structure-based drug design effort. The crystal structures of the ligands in the enzyme active site did not always agree with the conformations expected from experience with previous pyrone inhibitors. This is likely due to the increased flexibility of the dihydropyrone ring. From this study, compound XIX exhibited reasonably high enzyme inhibitory activity (Ki = 15 nM) and showed antiviral activity (IC50 = 5 microM) in the cell-culture assay. This result provided a research direction which led to the discovery of active 5, 6-dihydro-4-hydroxy-2-pyrones as potential agents for the treatment of HIV infection.

12. Anticoagulant activity[16]

Arora.R.B *et al* has been reported the Relationship between structure and anticoagulant activity of coumarin derivatives. Thirty-five coumarin derivatives have been examined for their anticoagulant activity in rabbits by determining the prothrombin time by a modification of Quick's onestage method, in order to find out the structural features eliciting the activity. The compounds include methoxylated dicoumarols, substituted 4-hydroxycoumarins,

coumarins devoid of a 4-hydroxyl group, such as 3- and 4-phenylcoumarins and 4-methylcoumarins, and some complex coumarin derivatives having additional rings. The results show the complexity of the problem and the involvement of various factors. Among these the importance of molecular geometry is emphasized by the high activity of calophyllolide (31)* and a new synthetic compound, 4-methyl-2,5- dioxo-3-phenyl-2H,5H-pyrano[3,2-cl][]-**benzopyran** (30). The importance for the anticoagulant activity of a substituent in position 8 of the coumarin moiety, and the role of ability to ionize with regard to the vitamin-K-like property of some hydroxylated phenylcoumarins, are also indicated.

CONCLUSION

In the study of pyrone and pyrone derivative compounds gives different biological activity. The pyrone derivatives used in the treatment of an Anticancer, Antibiotics, Insecticidal, Anticoagulants, Herbicidal and HIVprotease etc.The study of pyrone molecule find most effective treatment of multi diseases. This review is expected to be a comprehensive, authoritative and critical review of the pyrone template to the chemistry country.

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