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SYNTHESIS AND BIOLOGICAL STUDIES OF 2-AMINO-4-PHENYLTHIAZOLE

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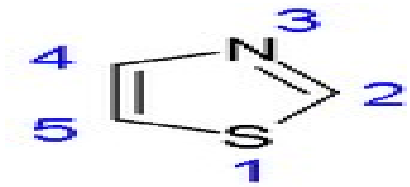
ABSTRACT

Synthesis of 2-Amino, 4-phenythiazole was carried out using Acetophenone, thiourea and Iodine as a catalyst by both Conventional and Microwave method. The synthesized compound was characterised by Spectroscopic studies like IR, NMR& MASS. The compound was tested for its anti-bacterial, anti fungal, anti-oxidant biological activity which showed excellent activity.

KEYWORDS: Acetophenone, thiourea, 2-amino-4-phenylthiazole,Microwave irradiation, Anti- bacterial, Anti-fungal, Anti-oxidant.

INTRODUCTION

Heterocyclic compounds form a major class of organic compounds. Thiazoles are aromatic five- membered heterocyclic compounds which is mostly studied because of its immense biological activities. Thiazole contains both sulfur and nitrogen at 1 and 3rd position. It was first described by Hantzsch and Weber in 1887.[1]

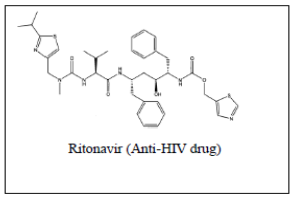


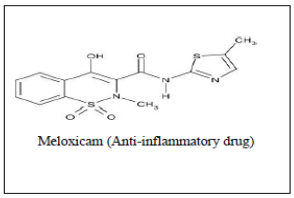
THIAZOLE STRUCTURE

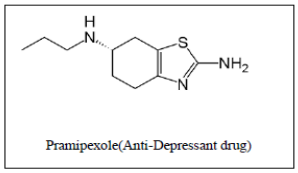
The thiazole ring present in vitamin B_1 and its coenzyme play a vital role as electron sink for the decarboxylation of α-keto acids.[2] As Thiazoles are important, their derivatives also shows a wide range of biological activities such as bactericidal.[3] fungicidal.[4] anti-inflammatory.[5] anaesthetic.[6] ardiotonic.[7] and sedative.[8] Benzothiozoles form an important class of derivatives which are of commercial importance . A derivative of benzothiazole is the light-emitting component of luciferin, found in fireflies.[9] Thiazole ring system also occurs in the bacitracin and penicillin antibiotics and in many synthetic drugs which includes antimicrobial agents Sulfathiazole and Acinitrazole.[10] anti-ulcer agent Nizatidine[11], anti-inflammatory drug Meloxicam.[12] and Fanetizole.[13], Anti-HIV drug-Ritonavir.[14] Anti-neoplastic agent Bleomycin and Tizofurin,[15] Anti-depressant Pramipexole.[16] and Anti-asthmatic drug Cinalukast.[17] Thiazoles comprising N=C-S moiety shows good antipsychotic.[18] and antibacterial activity.[19]The characteristic pharmacological features such as (a)Easy metabolism of compounds, (b) Built in biocidal unit,(c) Realtive stability and ease of starting materials,(d) Enhanced lipid solubility with hydrophilicity.[20] are found in this compound

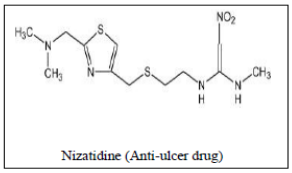
Thiazole compounds obtained from marine and microbial forms also shows antitumor and antiviral activities. It is also known to be a ligand of estrogen receptors.[21] and also as antagonists for adenosine receptors.[22]Thiazoles also contributes to the flavor of brewed coffee.[23] The 2,4-disubstituted thiazoles as latent pharmacophores, acts as a potential PGE2 antagonist for diacylhydrazine of SC-51089 have been reported.[24] For the treatment of breast cancer and osteoporosis 2,4 disubstituted thiazole class of Src Homology 2(SH2) as inhibitors have also been reported.[25]

The following are some of the drugs which possess thiazole moiety in their structure:


Ritonavir (Anti-HIV drug)

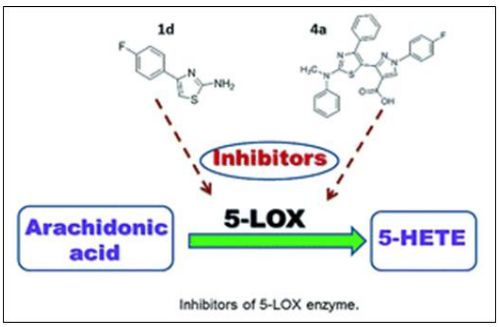

Meloxicam (Anti-inflammatory drug)


Pramipexole(Anti-Depressant drug)


Nizatidine (Anti-ulcer drug)

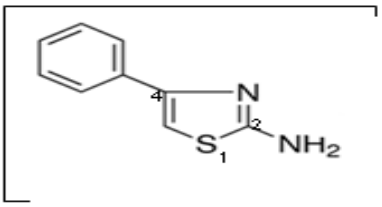
Human 5-lipoxygenase (5-LOX) is an important enzyme in the biosynthesis of leukotrienes and a target for

asthma and allergy treatment. *p*-fluoro substituted 2-amino-4-aryl thiazole(1d), with an IC_{50} of ~10 μM and a lead compound (4a), a thiazolopyrazole acid derivative (IC_{50} ~ 40 μM) are potential inhibitors of 5-LOX. Zileuton is the only drug currently marketed that targets this enzyme (IC_{50} ~ 1 μM). If the lead molecule is further improved, it could match the activity of the commercial drug.[26]



Since, many researchers are focussing on Thiazole compounds as it is having many applications and its structure is present in many pharmaceutical agents, it makes an important note to invest time into it to synthesis its derivatives.

Hantzsch's method for synthesis of Thiazole:
The one-pot condensation of α haloketones, and thiourea or thioamides in refluxing alcohol was reported by Hantzsch in 1887 with reaction time (24-25 h),and use of many solvents with harsh reaction conditions gave low yields.[27]In the present study, we report a comparison of the synthesis of 2-amino,4-arylthiazole by Conventional and Microwave method and a few of its Biological activities.



2-amino, 4-arylthiazole

EXPERIMENTAL METHOD

Synthesis of 2-amino-4-arylthiazole: By Conventional method:
A mixture of 7.6gms (0.1mole) of thiourea, 12ml (0.1mole) of acetophenone and 3.17gms (0.025moles) of Iodine was added to the reaction mixture.10 ml of ethanol was added and was refluxed for 15 hours in a hot water bath. The completion of reaction was monitored by TLC. Then the product was washed with ether and water. The final product was separated.

Yield: 70% M**elting point**: 148°C.The standard melting point reported was 147°C.[28]

By Microwave method
A mixture of 7.6gms (0.1mole) of thiourea, 12ml (0.1mole) of acetophenone and 3.17gms (0.025moles) of Iodine was added. The reaction mixture was irradiated in Microwave for 5-10 min (100-150 W) without any solvent. The completion of reaction was monitored by TLC. Then the product was washed with ether and water. The final product was separated.

Yield: 90% M**elting point**: 147°c
The synthesis of 2-amino-4-arythiazole, by both Conventional and Microwave method displays the difference of yield obtained and time required for the formation of product. Microwave Assisted Organic Synthesis (MAOS) process has shown high impact in enhancing the rates of reaction with less time and high yield. Therefore, for the synthesis of Thiazole derivatives, green method is more preferable when compared to conventional method.

	ONVENTIONAL METHOD	MICROWAVE METHOD
Time required	10-12hrs	10-12 min
Yield obtained	70%	90 %
	Less efficient	Rapid and efficient

BIOLOGICAL ACTIVITIES

Anti-microbial activity: The synthesised compound was screened for Gram positive bacteria Staphylococcus and E.coli using nutrient agar medium. Compound effect was resistant for E.coli and Sensitive for Staphylococcus species with (1.7cm) of zone of inhibition.
.

Fig; 1 Staphylococcus species with 2-amino,4-arylthiazole

Thus, the synthesized compound showed good anti-bacterial activity.

Anti-Fungal activity: The synthesised compound was tested for fungicidal activity against Fusarium species and Aspergillus niger. Compound effect was resistant for Aspergillus niger and Sensitive for fusarium species with (4.0cm) of zone of inhibition. Thus the compound displays good anti-fungal activity.

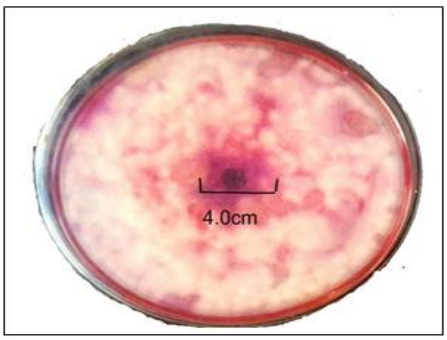


Fig2; Fusarium species with 2-amino,4-arylthiazole

Anti-Oxidant activity

Antioxidant compounds play an important role in food as health protecting factor. The main role of an antioxidant is its ability to trap free radicals. Scientific evidence shows that antioxidants reduce the risk for heart diseases and cancer. Primary sources of naturally occurring antioxidants are whole grains, fruits and vegetables. Methods measuring the radical scavenging activity of antioxidants against free radicals like the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, the superoxide anion radical ($O2^{-}$), the hydroxyl radical ($OH^{\bullet}$), or the peroxyl radical ($ROO^{\bullet}$).[29]

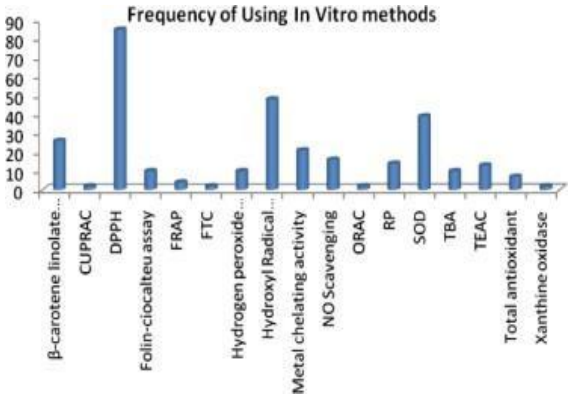


Fig3; Frequency of commonly used methods for anti-oxidant in vitro methods.

The synthesised compound was tested for Anti-Oxidant by DPPH method. The absorbance is measured at 517nm. The percentage of the DPPH radical scavenging is calculated using the equation below,

% inhibition of DPPH radical= [(Abr-Aar)] / Abr *100.

Where Abr is absorbance before the reaction & Aar is absorbance after the reaction takes place. The % of inhibition of the compound observed is 90.3%. Thus, the synthesised compound displays good anti-oxidant activity.

SPECTRAL DATA

IR (cm^{-1}):3434cm^{-1}, 3114cm^{-1}, 1597-1521cm^{-1}, 1482-1440cm^{-1}, 1337cm^{-1}, 1207-1031cm^{-1}, 909cm^{-1}, 771cm, 709cm^{-1} **1H-NMR:** δ =4.0 (2H, NH_2), δ= 6.7(s, 1H), δ= 7.25-7.31 (m, Ar- H),δ=7.36-7.40 (m, Ar-H) δ=7.76(dd, Ar-H) (J=8.5 Hz).

Mass: m/z =177 (M+1)=100%.

RESULTS & DISCUSSION

Based on the numerous biological activities possessed by thiazole moiety, 2-amino-4- phenylthiazole was synthesised by both Conventional and Microwave methods. The resulted yield and the reaction time proved that the solventfree microwave method is proved to be a better green method of synthesis when compared to conventional method. The progress of the reaction was monitored by TLC. The resulted compound was analysed by IR, NMR & MASS spectral data. The compound was tested for biological activities such as, Anti-microbial, Anti- fungal, Anti-oxidant & it showed good results.

CONCLUSION

We have reported a convenient, rapid and efficient protocol for the Synthesis and Biological activities of 2-amino-4-phenylthiazole.The application of microwave method over the conventional method was more propitious. Synthesized compound showed higher to moderate biological activities i.e.; for Anti-bacterial, Anti-fungal & Anti-oxidant. Therefore, it is concluded that there exists ample scope for further study in this class of compounds and their biological activities.

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