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A Novel Synthetic route to Bis –Isoxazoles.

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ABSTRACT

Heterocyclic Bis- β diketones have been synthesized from ester(o-aroyloxy/heteroaroyloxyacetophenones) by a base catalysed baker venkatramann transformation with NaoH in DMSO. A novel class of 4,6-bis(5-aryl/heteroaryisoxazol-3-yl) benzene-1,3-diols have been synthesized . Bis- β diketones obtained undergoes cyclisation to acheieve 4,6-bis(5- aryl/heteroaryisoxazol-3-yl) benzene-1,3-diols with impressive yields . Reaction mechanism for their formation have been elucidated .

Keywords: Baker venkatramann , Bis- β diketones ,bis-isoxazoles.

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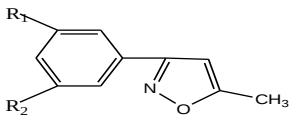
INTRODUCTION

Isoxazoles are aromatic compounds which forms an important class of five –membered heterocycles associated with bioilogical activities[1-4]. Some of pharmaologically important isoxazoles include the antibiotics oxacillin[5], cloxaciline[6], dicloxacillin and floxacillin[7] are markedly resistant to cleavage by penicillinase and are potent inhibitors of the growth of most penicillinase producing staphylococci.



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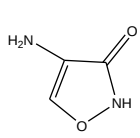
Some hydroxamic derivatives 3-(5)-phenoxymethyl isoxazoles exhibit α - and β –adrenolytix activity 3-halogen -5-phenyl-5-halogenisoxazoles **2** are reported as potent anthelminitics.[8]

The metabolite **3** showed ativity in lowering plasma FFA (free fatty acids) and blood sugar and is solely responsible for hypoglycemic activity[9]. 3,5-Dimethylisoxazole **4** lowered FFA but not blood sugar in rats.



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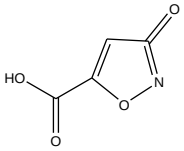

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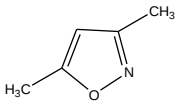

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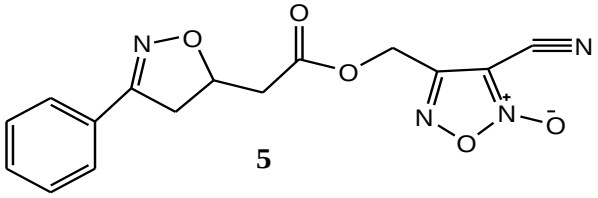
Biologically important isoxazoles derivatives proved to be antituberclosis, antibiotic, cycloserine or 4-aminoisoxazid. Some hydroxamic aid of the isoxazole series also displays a marked anti-tuberculosis activity[1] . Among other isxazole derivatives possessing activity one should especially mention the sulphonamides of the series and 4-hydroxyiminoxazole -5-ones[10]. Isoxazole derivatives involve substances with analgesics and local anesthetic activity. The novel isoxazole derivative, GIT-27NO **5**, generated by modifying the parental anti-inflammatory compound VGX-1027, is generated by direct linking of NO to the original compound[11-14] Determined by cell specificity, NO released from the compound, in association with reactive oxygen species, selectively affected MAP kinases pathways and promoted different type of programmed cell death.



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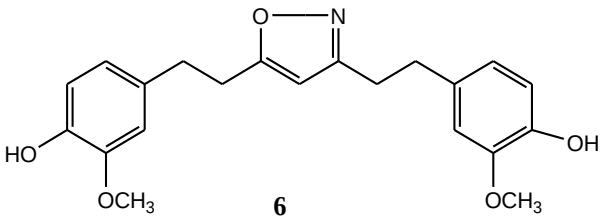
The effects of curcumin and of its novel, more potent, isoxazole analogue **6** in MCF7 breast cancer cell line and in its MCF-7R variant endowed with different mechanisms receptor (ER) α and overexpression of P-gp and different IAPs] of drug resistance.[15-17]



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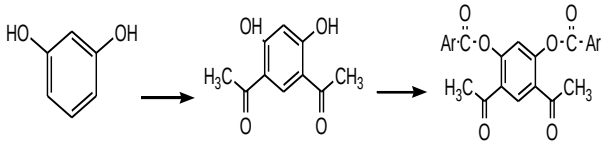
Scheme

1. 3-Diaroyloxy/heteroaroyloxy-4,6-diacetophenones



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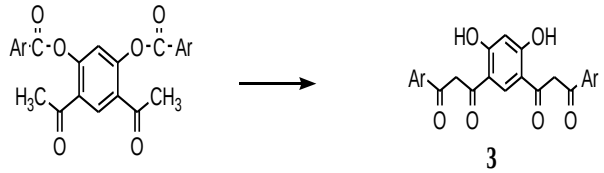
2. 3',3 –(4,6-dihydroxy-1,3-phenyl) bis (1-aryl/heteroaryl propane-1,3diones)



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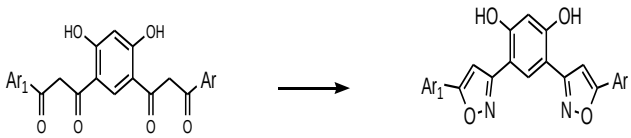
Ar = Ar_1 (a) C_6H_5
(b) 4-$CH_3C_6H_4$
(c) 4-$OCH_3C_6H_4$

3. 4,6-bis(5- aryl/heteroaryisoxazol-3-yl) benzene-1,3-diols



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Ar =Ar_1 (a) C_6H_5
(b) 4-$CH_3C_6H_4$
(c) 4-$OCH_3C_6H_4$

Present work

In the present wok, hydroxylamine hydrochloride (Bakervenkatraman method) have been employed for the cyclisation of β-diketones 3,3'-(4,6-dihydroxy-1,3-phenyl) bis (1-aryl/heteroaryl propane-1,3 diones) to the corresponding isoxazoles. Hydroxylamine hydrochloride is the chemical used .

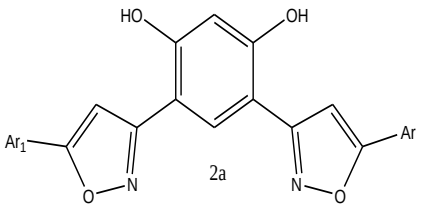
METHODOLOGY

3,3'-(4,6-dihydroxy-1,3- phenyl) bis (1-phenyl propane-1,3dione). 1,3-Dibenzoyloxy-4,6-diacetophenones (0.005moles) was dissolved in 4ml of DMSO. To that solution powdered NaOH (2g) was added with vigorous stirring for about five minutes. The stirring was continued for about 5 min further. The reaction mixture was then cooled and poured on

cold water. The pale yellow solid product obtained was washed with water dried and crystallized from alcohol.The yield 67% and m.p 121°c In the same way, the other diones have been prepared.

4,6-bis(5-(4-phenyl)isoxazol-3-yl)benzene-1,3-diol.
The mixture of 3'3-(4,6-dihydroxy-1,3phenyl)bis(1phenylpropane1,3dione)(2.36g,0.1mole),hydroxylaminehydrochloride(1g,0.004 mole), KOH(1g) and ethanol (30 ml) was refluxed for five hours . It was cooled to room temperature and was poured onto ice cold water and acidified with dil.HCl. A solid slowly separated out it was crystallized from ethanol. The yield is 75% and m.p 165°C.

Characterization data of 4,6-bis(5-aryl/heteroaryl) isoxazol-3-yl) benzene-1,3-diols **2a**



Compound	Colour of $Fecl_3$	Ar = Ar_1	M.F	Yield %	M.P* (0°c)	found (Cald) C	H	N
2a	Red	C_6H_5	$C_{24}H_{18}O_4N_2$	75.37	165	72.34 (72.36)	4.50 (4.52)	7.59 (7.62)
2b	Brown	4-OCH_3C6H_5	$C_{26}H_{22}O_6N_2$	65.5	175	68.10 (68.12)	4.6 (4.8)	6.08 (6.11)
2c	Brown	4-CLC6H_4	$C_{24}H_{16}Cl_2O_4N_2$	64.28	180	62.0 (62.2)	3.40 (3.42)	5.90 (5.99)

CONCLUSION

Using a modified Baker–Venkataraman reaction wehave synthesised a novel class of 4,6-bis(5-(4-phenyl)isoxazol-3-yl)benzene-1,3-diol. The reaction mechanism for their formation and the properties of bis isoxazoles have been elucidated. The present review represents a broad description for the methods used in the synthesis of isoxazoles and the rigid bicyclic isoxazoles fragment has been classified as a privileged structure in drug discovery, due to its use in a wide variety of pharmacologically active compounds such as anti-tumor, anti-inflammatory, and antibacterial activitiy , antiviral, and antifungal properties. antituberclosis, antibiotic.

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Conflicts of interest: The authors stated that no conflicts of interest.

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