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Synthesis and applications of Aryl-oxazole natural compound Hinduchelins A-D and derivatives: A hitherto advances review

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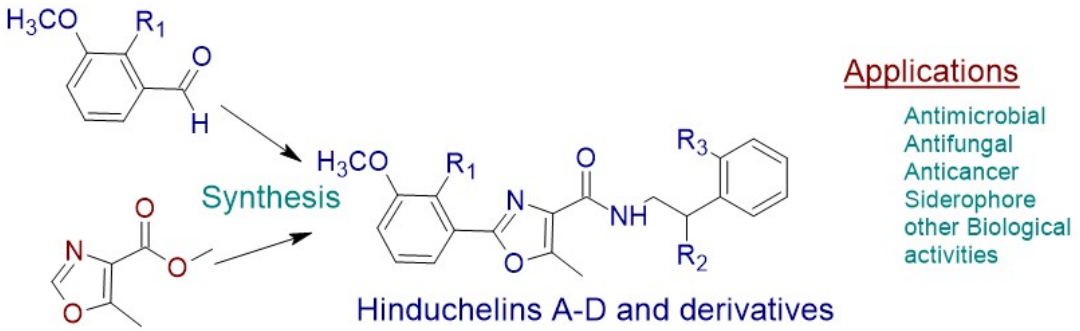
Review

ABSTRACT



The natural catechol siderophores Hinduchelins A-D, isolated from *Streptoalloteichus hindustanus*, are known for important role in Iron acquisition by the bacteria. These small molecules containing catechol moiety chelate the iron and makes the ferric ions available to microbial cells in different environmental conditions. The synthesis of Hinduchelins A-D and its derivates achieved hitherto via different synthetic pathways have been summarized here. With prospect of applicability of these molecules for antibacterial, antifungal, anticancer and other bioactivities, the evaluation outcomes from studies have been discussed along with proposition of future applications.

Keywords: Hinduchelins, Natural Product, Stereoselective synthesis, oxazole, biomedical applications, heterocyclic molecules

INTRODUCTION

The chemical compounds obtained from natural resources have a long history of exploration of a variety of molecules from different sources including plants and plant parts,[1] algae,[2] bacteria, fungi,[3] microbes and other organisms. The chemical exploration of natural resources has led to discovery of variety of molecules namely carbohydrates, peptides, terpenes, tannins, steroids, catechol, and many more[4] which find application in diverse fields like as drugs,[5] anti-microbials,[6] anti-oxidants,[7] antidiabetics,[8,9] perfumes, fragrances, etc.

Catechols[10] are natural compounds having aryl moieties with vicinal hydroxy groups (o-dihyroxyaryl) which have their versatile participation in biochemical processes with their unique properties, namely, moderate the equilibria of redox potentials and pH buffering, cross-linking participation in oxidation mechanisms,[11] excellent chelating properties[12] (though not exclusive, however, well recognized chelation of Fe^{3+}), and interaction of catechol moiety with different surfaces via different bonding patterns.[13,14]

Catechols involved in the biochemical process of Fe^{3+} chelation are referred as Siderophores.[15,16] The siderophores constitute a category of small, iron-chelating molecules involved in biochemical processes of small organisms, mainly, bacteria.[17] The conversion of iron into insoluble ferric hydroxides through oxidation at physiological pH leads to its unavailability for utilization by organisms. Many microorganisms adopt the release and use of siderophores for the chelation of ferric hydroxides (Fe^{3+}) to make it available to microbial cell.[17]

Recently, Abe et.al.[18] have isolated the aryl-oxazole alkaloids from the *Streptoalloteichus hindustanus*, a bacteria from the family *Pseudonocardiaceae*. These compounds named as Hinduchelins A-D (Figure 1) are oxazole with attached catechols moiety; have structural similarity with Amamistatin (isolated from the actinomycete) compounds known for their antiproliferative properties. The *Streptoalloteichus hindustanus* is also a well-known source of the Tallysomycin, a glycopeptide antibiotic, which has been extensively explored for its anti-tumour properties as an antitumour antibiotic.

The Hinduchelins A-D are known to participate in making available the insoluble ferric ion to the microbial cells through chelation of ferric ion.

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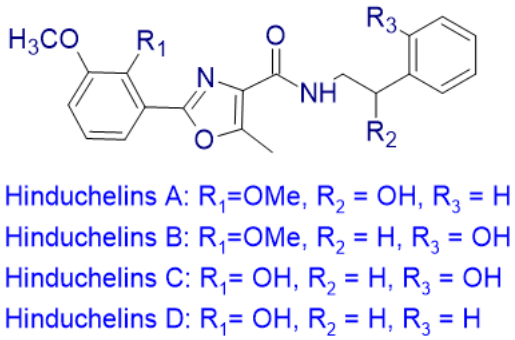


Figure 1. Structure of Hinduchelins A-D isolated from *Streptoalloteichus hindustanus* bacteria.

Owing to their significance in chelation of iron towards biological availability of Iron for the bacterial / microbial cells, the synthesis and further bioactivities have been reported by the researchers. Various substituted derivatives of Hinduchelins have been synthesized towards evaluation of significant biological activities. This review discussion includes the different synthetic methods reported so far for the synthesis of Hinduchelins and analogues along with results analysis obtained from the biological activities data reported.

SYNTHESIS

The Hinduchelins can be synthesized via different routes. The retrosynthetic method reported by S. Ke et.al.[19] have oxazole containing carboxylic acids as the key components (Figure 2). In retro construction, the first removal of amide bond leaves the fragment of carboxylic acid substituted oxazole which further can be constructed from substituted benzyl aldehydes i.e. o-vaniline and o-vertaldehydes. The beauty of this retrosynthesis is easy availability of starting materials and feasible reactions.[19]

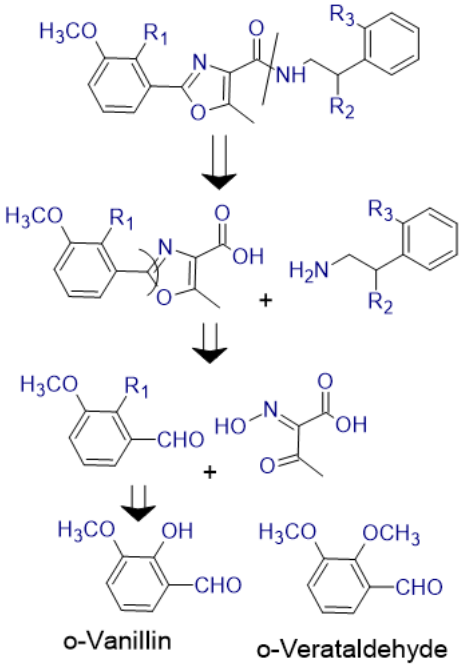


Figure 2. Retrosynthetic proposition by S. Ke et.al.[19]

In laboratory scale synthesis, S. Ke et.al. achieved the synthesis of Hinduchelin derivatives starting from the ethyl acetoacetate (**1**) as represented in figure 3. The hydroxylamine derivative (**2**) obtained by the reaction of ethyl acetoacetate with $NaNO_2$ was further reacted with Vanilline or Verataldehydes[20] to obtain the main intermediate oxazole (**5a, 5b and 6a, 6b**) compounds.

These intermediates **5a, 5b, 6a, 6b** on further reaction with hydroxy amine compounds (**7, 9** and **10**) led to formation of respective Hinduchelins A, Hinduchelins B, Hinduchelins C and Hinduchelins D (Figure 3).

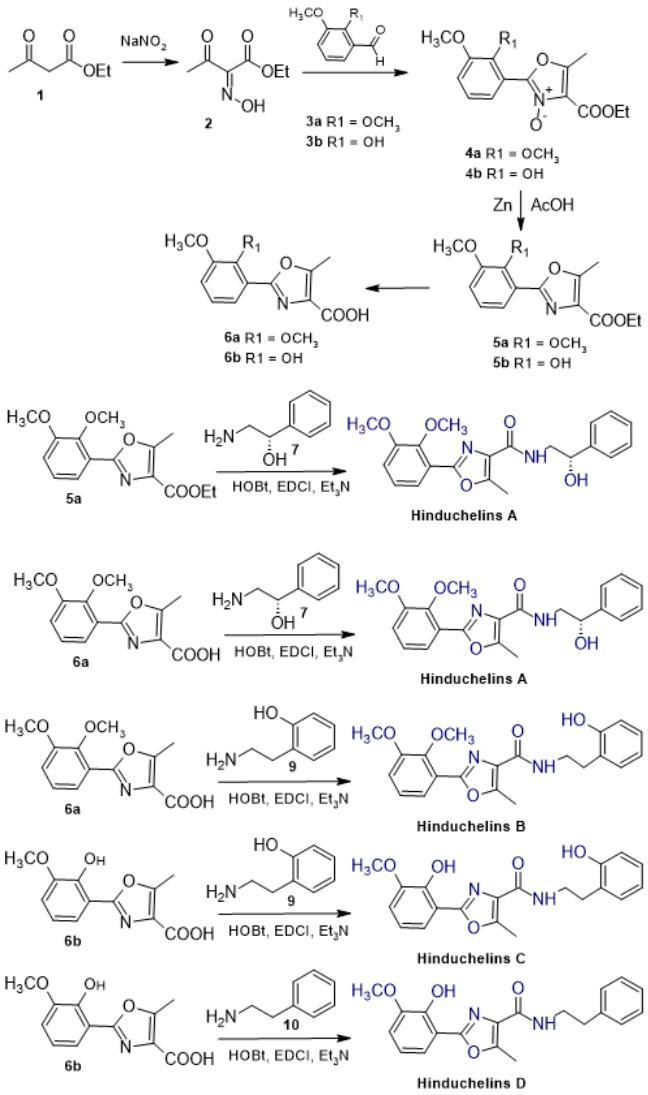


Figure 3. Synthesis of Hinduchelins A-D by S. Ke et.al. Scheme adapted from Ref [S.Ke. et.al., 2019].

C.W. Lindsley have reported the synthesis of Hinduchelins via a different rout starting from the methyl 5-methyloxazole-4-carboxylate (**11**) (figure 4).[21]

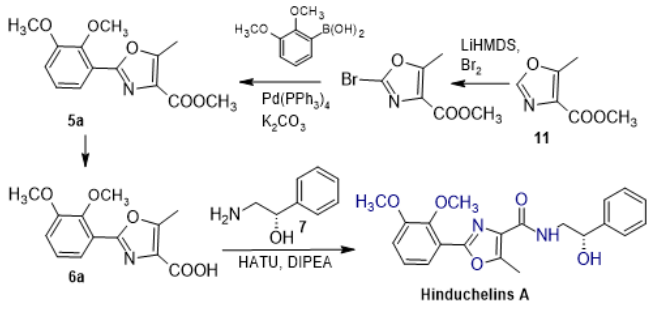
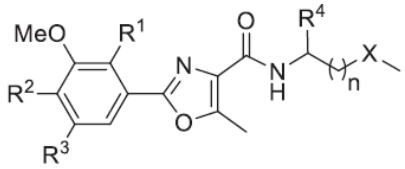


Figure 4. Synthesis of Hinduchelins as reported by Lindsley group

Analogue Synthesis

The Hinduchelins are known to act as siderophores and thus have role in the sustaining the life of microbial organism. Considering their significance in biological activities, S. Ke. et.al.[22] have synthesized different sulfur containing analogues (Figure 5) with perspective for application in biological activities.[22]



Substituents

R^1	R^2	R^3	R^4	n	X
OMe	H	H	H	1	SO2
OMe	H	H	H	1	S
OMe	H	H	COOMe	2	S
H	OMe	H	H	1	SO2
H	OMe	H	H	1	S
H	OMe	H	COOMe	2	S
H	OMe	OMe	H	1	SO2
H	OMe	OMe	H	1	S
H	OMe	OMe	COOMe	2	S
OH	H	H	H	1	SO2
OH	H	H	H	1	S
OH	H	H	COOMe	2	S
H	OH	H	H	1	SO2
H	OH	H	H	1	S
H	OH	H	COOMe	2	S

Figure 5. Various Sulfur containing analogues of Hinduchelins reported by S. Ke et.al.

Biological Activities

Hinduchelins and analogues have been evaluated for anti-bacterial, anti-fungal activities,[22] however, the inhibitory results obtained are not so promising. Similarly, the results obtained from the anti-cancer in vitro assays have given the similar inference. These results are indicative of the prospects of use these compounds in other suitable application based of structure activity relation evaluations.

Future Prospects

The Hinduchelins are recently discovered molecules and though, have initiated the involvement of researchers in the synthesis of these compounds and their analogues using different synthetic methodologies and synthesis routes, however, due to their limited biological activities obtained for the synthesized analogues, a more diversity of analogues will have to be designed. The future efforts need to be oriented in developing the more diverse derivative of Hinduchelins, including the hybrid synthesis using pharmacophores and evaluate for different biological activities.

Conclusion

Hinduchelins A-D are the recent oxazole catechol siderophores molecules responsible for chelation of insoluble ferric ions and making iron available to the microbial organisms. Owing to their structure, these molecules have enticed chemistry researcher to achieve the total synthesis of these molecules and further evaluate these molecules and their analogue derivatives for possible biological activities. Complete synthesis has already been achieved by researchers via different synthetic routes starting from different chemical entities. The biological activities of these analogues have not been promising, indicating more thorough evaluation with addition of diversity in substituents.

Acknowledgments

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