CHAPTER 1

1.1 GENERAL INTRODUCTION:

The use of α-hydroxy carboxylic acid is well cited in the literature as a building block for several natural products, their derivatives and analogues, reported to exhibit various pharmacological activities like hypoglycemic (1,2), hypolipidemic (3), antihypertensive (4), cardiovascular diseases, especially arteriosclerosis (4), renal diseases and prevention of microalbuminuria. The present work is related to the development of a novel Chiron approach for the synthesis of α-hydroxy carboxylic acids starting from α-amino acids.

Fig-1.

![Structure of α-hydroxy carboxylic acid](image)

(I)

Table-1.1 some of the compounds having α-hydroxycarboxylic Acid moiety

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Name</th>
<th>Structure</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-3-[2-(2-oxazolylmethyl) benzo [b] furan-5-yl]-2-hydroxy propanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>Hypoglycemic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Description</td>
<td>Activity</td>
<td></td>
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<tr>
<td>---</td>
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<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>2</td>
<td>(S)-3-[4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl]-2-hydroxypropanoic acid</td>
<td><img src="image1.png" alt="Molecule Image" /></td>
<td>Hypcholesterolemic</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>(S)-3-[4-[2-benzoazolyl]-N-methylamino]ethoxy]phenyl]-2-hydroxypropanoic acid</td>
<td><img src="image2.png" alt="Molecule Image" /></td>
<td>Hyperlipidemic</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>(s)-3-[4-[2-(2-oxazolyl)ethoxy]phenyl]-2-hydroxypropanoic acid</td>
<td><img src="image3.png" alt="Molecule Image" /></td>
<td>Hypcholesterolemic &amp; Hypoglycemic</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>(S)-3-[4-[2-pyridyl]-N-methylamino]ethoxy]phenyl]-2-hydroxypropanoic acid</td>
<td><img src="image4.png" alt="Molecule Image" /></td>
<td>Hyperlipidemic &amp; Hyperglycemic</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>(S)-3-[2-(4-benzyloxy benzyl)benzo [b] furan-5-yl]-2-hydroxypropanoic acid</td>
<td><img src="image5.png" alt="Molecule Image" /></td>
<td>Antiobesity</td>
<td>2</td>
</tr>
</tbody>
</table>
1.2 HYDROXY ACIDS:

**General methods for the synthesis of α-hydroxy carboxylic acids** (5)

a) Through the hydrolysis of aldehyde or ketone cyanohydrins.

Aldehydes and ketones add on hydrogen cyanide to form cyanohydrins followed by reaction with dilute sulphuric acid to give α-hydroxy carboxylic acids

\[
\text{C}=\text{O} + \text{HCN} \xrightarrow{\text{H}^+} \text{C} \quad \text{OH} \quad \text{CN} \quad \text{COOH}
\]

b) Through the hydrolysis of α-bromo acids.

\[
\text{RCHCOOH} + \text{H}_2\text{O} \xrightarrow{\text{NaOH}, \text{H}^+} \text{RCHCOOH} \quad \text{OH}
\]

c) By the controlled oxidation of 1,2-glycols with dilute nitric acid.

\[
\text{CH}_2\text{OH} \quad \text{CH}_2\text{OH} \quad \text{[O]} \quad \text{CHO} \quad \text{CHO} \quad \text{[O]} \quad \text{COOH} \quad \text{CH}_2\text{OH} \quad \text{CH}_2\text{OH}
\]

d) By the nitrosation followed by hydrolysis of α-amino acids.

\[
\text{RCHCOOH} + \text{HNO}_2 \xrightarrow{\text{H}^+} \text{RCHCOOH} \quad \text{OH}
\]

e) By the catalytic reduction of 2-keto-esters.
In recent years there has been an increasing interest in the chemistry of quinazolinones because of their pharmacological properties e.g., anti-microbial, hypotensive, anti-depressant, anti-inflammatory, and anti-allergic properties. Some of these compounds also have interesting biological properties such as anti-malarial activity and diuretic properties.

**GENERAL METHODS FOR SYNTHESIS OF QUINAZOLINONES**

*Connolly et al.*, [6] have prepared 2-methyl-4(3H)-quinazolinone (IV) from anthranilic acid (II) and imidate (III) in boiling methanol. (Scheme 1.1)

*Kametani et al.*, [7] have developed an efficient synthesis of glycosminine (VI) from anthranilic acid (II) via a sulfonamide anhydride (V). (Scheme 1.2)
Besson et al., [8] have reported the synthesis of 3H-quinazolin-4-one (VII) using microwave irradiation with improved yields and reduced reaction time. (Scheme 1.3)

Kametani et al., [9a] synthesized deoxyvasicinone (VIII) from the reaction of the sulfonamide anhydride (V) with o-methylpyrrolidine (Scheme 1.4) affording deoxyvasicinone (VIII) in 65% overall yield.
In a different approach by Eguchi [9b], azide (IX) and pyrrolidone (X) were treated with triphenylphosphine followed by cyclization at a higher temperature to give deoxyvasicinone (VIII). (Scheme 1.5)

Mhaske et al., [10] developed a new route to deoxyvasicinone (VIII) with 85% overall yield in 5 steps from anthranilamide (XII). (Scheme 1.6)

Kamal et al., [11] developed the synthesis of deoxyvasicinone (VIII), with FeCl₃–NaI as a reagent. (Scheme 1.7)
Ganesan et al., [12] have reported 3-Oxo-1H-pyrrolo [3,4-b]quinoline (XXIII) starting from o-nitrobenzaldehyde (XVIII) via quinoline in five steps. (Scheme 1.8)

Hermecz et al., [13] developed an efficient synthesis of rutaecarpine (XXVIII) via the natural product mackinazolinone (XXIV) in three steps with good yield. (Scheme 1.9)
Snider and Busuyek have [14] developed an efficient total synthesis of circumdatin F (XXXI) in 69% yield from the dione XXIX. (Scheme 1.10)

1.4 CHEMISTRY OF QUINOLINES:

Functionalized quinolines have found applications as pharmaceuticals, agrochemicals and useful synthetic blocks in the preparation of several alkaloids.
GENERAL METHODS FOR SYNTHESIS OF QUINOLINES:

Vladimir et al., (15) prepared quinoline derivatives from anilines XXXII in the presence of BiCl₃. Aromatization of the tetrahydroquinoline ring through elimination of 2-oxopyrrolidinone followed by dehydrogenation under appropriate conditions gives the required 2-(amino phenyl) quinoline derivatives XXXVI (Scheme 1.11)

Jiang et al., (16) have reported the synthesis of isoquinolone from 3-bromobenzaldehyde (XXXVII) and 2,2-dimethoxyethylamine (XXXVIII) through two separable isomers XXXIX and XL, followed by Combe’s quinoline synthesis and deprotection to furnish quinoline (XLII) (Scheme 1.12)
Woodrow et al., (17) synthesized quinoline-3-carboxylate (XLVII) from 4-iodo aniline (XLIII) with diethyl ethoxymethylene malonate followed by cyclization at 250°C in diphenylether to give the ester. The ester on hydrolysis and dichlorination with thionyl chloride followed by quenching with ammonium hydroxide gave the amide (XLV). Reaction of the amide (XLV) in acetonitrile with m-anisidine provided the desired compound (XLVI), which on further reaction with arylthiol in the presence of palladium catalyst afforded the sulfide XLVII (Scheme 1.13)
Vu et al., (18) produced a new class of 6H-chromeno [4,3-\textit{b}] quinoline-3,9-diol (\textbf{LIII}) derivatives from \textit{m}-methoxyphenol (\textbf{XLVIII}) in three steps via Friedel-Crafts acylation and Freidlander synthesis \textbf{(Scheme 1.14)}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.14.png}
\end{center}

\textit{Fan et al.}, (19) has developed a method with samarium iodide-mediated one-pot preparation of 2,4-diarylquinolines (\textbf{LV}) from 3-aryl-2,1-benzisoxazoles (\textbf{LIV}) \textbf{(Scheme 1.15)}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.15.png}
\end{center}
1.5 CHEMISTRY OF ISOQUINOLINONES:

Isoquinolinones are important compounds from both the synthesis and application points of view. Their structures are incorporated in several alkaloids [20] and are also of interest in medicinal chemistry. [21]

Due to their biological and pharmacological importance, several methods have been reported for the synthesis of isoquinolinones. [20]

GENERAL METHODS FOR SYNTHESIS OF ISOQUINOLINONES:

T-H Tsai et al., (22) produced isoquinolinone (LVIII) skeleton through 1,4-addition of an allylmagnesium bromide to LVI followed by alkylation and ring-closing metathesis (Scheme 1.16)

Li et al., (23) have annulated ethyl 3,4-dihydroisoquinoline-1-carboxylate (LIX) with ortho bromomethyl benzoate (LX) to afford an isoquinolinone adduct (LXI). (Scheme 1.17)
Coelho et al., (24) have synthesized 3,4-substituted isoquinolin-1(2H)-ones (LXIX), using Baylis-Hillman adducts as starting material with good yields (Scheme 1.18)

\[ \text{R1} \text{CHO} \xrightarrow{a} \text{R1} \text{R2} \text{R3} \xrightarrow{b,c} \text{R1} \text{R2} \text{R3} \xrightarrow{d} \text{R1} \text{R2} \text{R3} \xrightarrow{e} \text{R1} \text{R2} \text{R3} \xrightarrow{f} \text{R1} \text{R2} \text{R3} \xrightarrow{g} \text{R1} \text{R2} \text{R3} \xrightarrow{h} \text{R1} \text{R2} \text{R3} \]

\[ \text{LXII} \quad \text{LXIII} \quad \text{LXIV} \quad \text{LXV} \]

\[ \text{LXVI} \quad \text{LXVII} \quad \text{LXVIII} \quad \text{LXIX} \]

**Reagents:** a) methyl acrylate, ultrasound, rt, 24-72 h; b) TIPSOTf, Et3N, CH2Cl2, rt, 2 h; c)DIBAL-H, CH2Cl2, -78°C, 2 h; d) TBDPSCl, DMF, imidazole, rt, 14 h; e) 9-BBN, THF, 0°C to rt, 16 h, NaOH, H2O2, 0°C, 1.5 h; f)TPAP, NMO, CH2Cl2, 1 h, ethyl chloroformate, acetone, Et3N, 0°C, 45 min, NaN3, rt, 12 h; g) t-BuLi, THF, -78°C, 30 min; h) TBAF, THF, rt, 2 h.

Badia et al., (25) have prepared trans and cis phenanthridinones (LXXVI/LXXVII) in excellent yields through 3-phenyl-2-(p-toluene-sulfonyl)-1,2-dihydro-4(3H) isoquinolinone (LXXII) as the key intermediate (Scheme 1.19)
1.6. INDAZOLES AS NATURAL PRODUCTS

Indazoles are rare in nature [26], and to date only three natural products possessing the indazole ring have been isolated, Nigellicine (LXXVIII), Nigeglanine (LXXIX) and Nigellidine (LXXX). Their full synthesis was described in Scheme 1.20-1.22
GENERAL METHODS FOR SYNTHESIS OF INDAZOLES

Kelly et al., [27] have accomplished the total synthesis of LXXVIII in seven steps through the transformation of isatin indazole (LXXXI) (Scheme 1.20)

Sakamoto [28] reported another total synthesis of Nigellicine (LXXVIII) as shown in Scheme 1.21. Alkylation on indazole derivative gave a mixture of 1 and 2-substituted indazoles XC & XCI which on ring closure followed by saponification & demethylation yielded Nigellicine LXXVIII
........ Scheme 1.21

Demethoxycarbonylation of XC with aqueous acetone followed by reaction with BBr₃ gave Nigeglanine hydrobromide LXXIX (Scheme 1.22)

........Scheme 1.22

Lee’s et al., [29] have prepared Indazole ureas as described in Scheme 1.23. Nitrotoludines (XCIV) were treated with sodium nitrite and acetic acid in water to provide the 4-nitroindazole (XCV). Reduction of nitro functionality using palladium on carbon under hydrogen atmosphere gave the corresponding amino indazoles (XCVII), which on further reaction with suitable amine in presence of phosgene followed by Boc deprotection furnished indazole urea (XCIX)
Muller’s et al., [30] reported synthesis of 3,4-disubstituted indazoles (CIV) according to the procedure outlined in Scheme 1.24

Dai et al., [31] have reported the synthesis of C4-substituted amino indazoles (CIX) as shown in Scheme 1.25. 3-Amino-4-iodoindazole (CVI) was easily prepared by reaction of 2-fluoro-6-iodobenzonitrile (CV) with
hydrazine monohydrate which on further reaction with urea boronate **CVIIIa-s** produced the corresponding amines.

**PRESENT WORK:**

Synthesis of enantiomerically pure α-hydroxycarboxylic acids are of general interest and finds wide application in asymmetric organic synthesis. It provides a direct route to the preparation of a large variety of heterocyclic systems, as well as natural and pharmacologically interesting products (8). In this regard, preparation of α-hydroxycarboxylic acids is particularly important.

In the present work, it is considered worthwhile to take advantage of the facile conversion of α-amino acids to the corresponding α-hydroxycarboxylic acids with overall retention of configuration. The methodology could be demonstrated with six representative amino acids. Each selected amino acid was treated with sodium nitrite and sulphuric acid in acetone to give the desired α-hydroxycarboxylic acid.
Chirally pure α-hydroxycarboxylic acids & substituted quinazolinones were linked with piperazine moiety in the presence of potassium carbonate and catalytic amount of potassium iodide to give adducts in good yields.

Practical and efficient synthesis of (2S)-2-{[(2S, 4R)-1-[(2S)-2-hydroxy-3-phenylpropanoyl]-4-[[7-methoxy-2-(1H-1-pyrazolyl)-4-quinolyl]oxy]tetrahydro-1H-2-pyrrolyl]carbonyl} amino]-3-phenylpropanoic acid and its enantiomerically pure tripeptide quinoline analogues using standard coupling procedures in presence of commercially available and inexpensive coupling agent O-(7-azabenzotriazol-1-yl)-N,N,N',N’-tetramethyluronium hexafluorophosphate (HATU) and triethylamine as base in dichloromethane at room temperature.

Substituted isoquinolinones were condensed with different α-methoxycarboxylic acids, prepared from α-hydroxycarboxylic acids, with CIP (2-Chloro-1,3-dimethylimidazolidonium hexafluorophosphate) mediated coupling, was an efficient coupling agent to synthesis of various isoquinolinyl amide derivatives in good yields.

Selective protection technique was established on N1 & N2 isomers of indazoles and the structures were established via molecular crystal X-ray. Several benzoxazepin indazole derivatives were prepared from N1 isomer of indazole via Suzuki coupling.
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