FINAL REPORT

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On

Synthesis of medically interesting unsymmetrical vicinal diamines, their chiral transformation and investigation of their biological properties

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Submitted By

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SUMMARY OF THE WORK DONE

Title: ***Synthesis of medically interesting unsymmetrical vicinal diamines, their chiral transformation and investigation of their biological properties***

❖ Brief Introduction and Scope of the Project

Vicinal diamines are attractive motifs for more than decades, for their efficiency in facing the challenges in organic syntheses, especially in asymmetric synthesis. In addition, several reports constantly establishing diamines with unsymmetrical substitutions are unparalleled significant motifs in synthetic field as well as in medicinal filed, as they display broad spectrum of biological importance.

Chiral vicinal diamines (CVDs) are significant and well known for their catalytic efficiency, synthetic versatility and biological utility. Starting from the discovery of the anti-tumor effects of *cis*- platin, the significance of diamine based analogues keep on adding importance to CVDs in bio-field.

In spite of vast utility of CVDs, the problem in developing such CVDs is finding the facile and economical route of synthesis. Hence, the interest is focused on such methodology of preparing cost effective CVDs through chiral transformation strategy and exploring their structure through computational & docking studies to add one more feather on the research on CVDs.

Significance of the study: The methodology adopted in this project is **advantageous** to meet the challenges of developing wide range of chiral unsymmetrical vicinal diamines involving **general, facile, efficient and economical route of preparation** since it involves aldehydes and ketones as starting materials.

Scope: The present work has been designed in order to facilitate wide range of preparation of chiral vicinal diamines with unsymmetrical substitutions at the vicinal

carbon atoms as a greater variation in diamine structure which can be used as better catalysts to facilitate stereochemical synthesis and can also be utilized in discovering new drugs.

In addition to that, Design and developing a procedure for the transformation of simple molecules into a bioactive molecule with different functionalities is all time worthwhile contribution in organic synthesis. Schiff bases are privileged entrants both in synthetic and medicinal fields. Though Schiff bases are known for several decades, chemists are still interested in design and synthesis of new Schiff bases, as these are capable of coordinating with various metals, which find applications in fields of synthesis, medicine and material study.

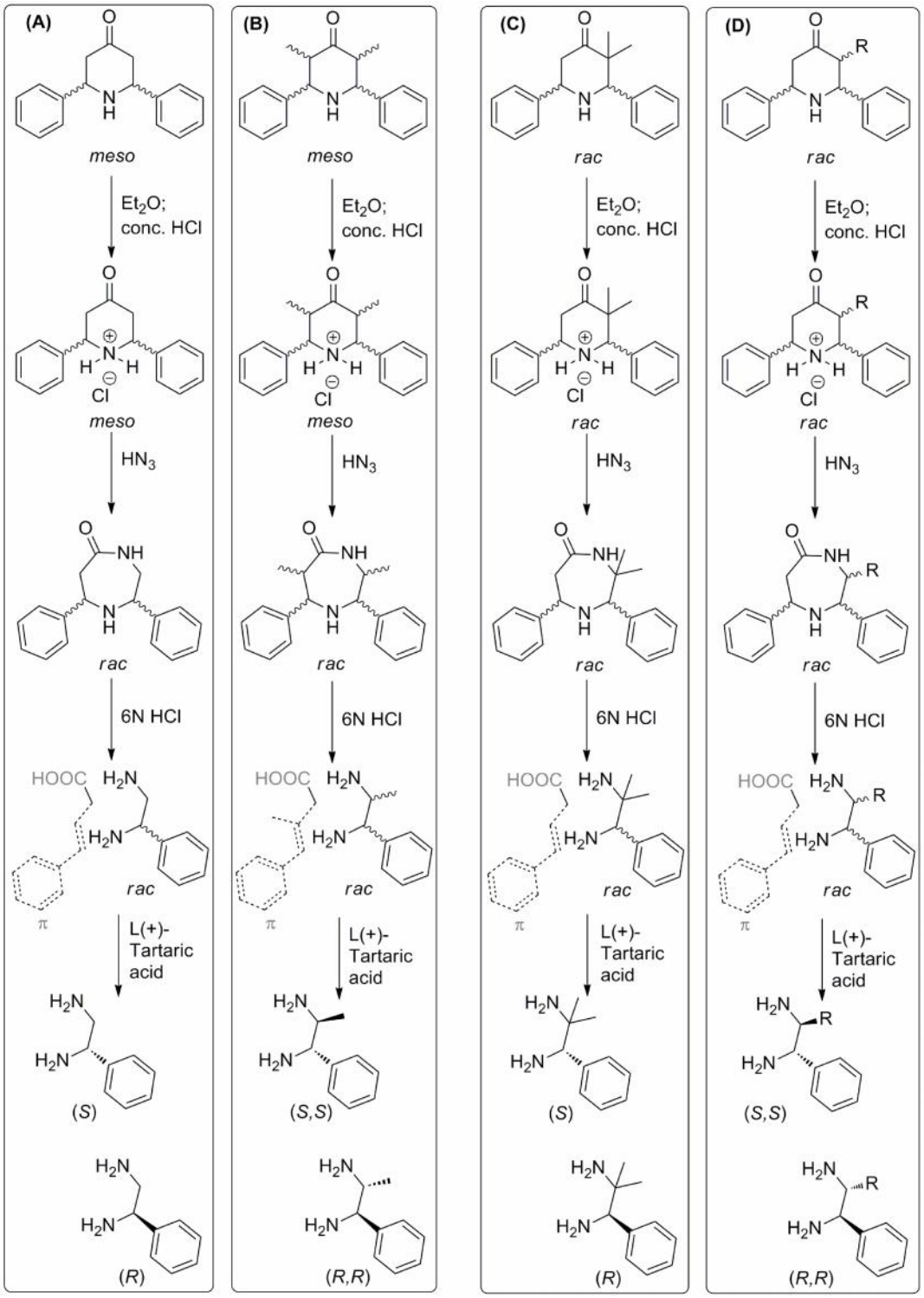
Owing to the importance of Schiff bases and vicinal diamines, it has been planned to incorporate vicinal diamine as backbone for structurally significant Schiff bases. This paved the way for the synthesis of derivatives of VCDs and exploring structure & applications of a few new Schiff bases. Hence, the present effort adds one more feather on the crown to the world of salen ligands as well.

❖ Results & Discussion

- Synthesis of Target molecules

Unsymmetrical-1,2-ethylenediamines (**1-10**) with both steric and non-steric substitutions at C_1 and C_2 of ethylenediamine have been achieved involving inexpensive aldehydes and ketones as starting materials *via*., condensation of respective aldehydes and ketones in presence of ammonium acetate to synthesize piperidones followed by Schmidt reaction and hydrolysis. Their chiral transformation has been effected through diastereomeric separation by commercially available optical pure tartaric acids. The two diastereomers separated have been

then reconverted to corresponding enantiomers using hydrochloric acid to produce respective enantiomers (**11**-**30**) (**Scheme 1**)



Scheme 1

[Synthesis and chiral resolution of: mono-substituted *rac*-diamines**(A)**, tri-substituted *rac*-diamines**(C)**, and di-substituted *rac*-diamines**(B)** & **(D)**]

The synthesized of mono-chiral and *homo*-dichiral vicinal diamines are:

1-Phenylethane-1,2-diammonium dichloride (**1**)

1-Phenylpropane-1,2-diammonium dichloride (**2**)

2-Methyl-1-phenylpropane-1,2-diammonium dichloride (**3**)

1- Phenylbutane-1,2-diammonium dichloride (**4**)

1-(4-Chlorophenyl)propane-1,2-diammonium dichloride (**5**)

1-(3-Chlorophenyl)propane-1,2-diammonium dichloride (**6**)

1-(2-Chlorophenyl)propane-1,2-diammonium dichloride (**7**)

1-(4-Nitrophenyl)propane-1,2-diammonium dichloride (**8**)

1-(4-Methylphenyl)propane-1,2-diammonium dichloride (**9**)

1-(4-Isopropylphenyl)propane-1,2-diammonium dichloride (**10**)

- Synthesis of Derivatives

The derivatives of synthesized target molecules have been achieved by the condensation of corresponding aldehydes with respective diamines in presence of ethanol and the synthesized Schiff Bases (**31**-**49**) are:

2,2'-((1E,1'E)-((1-phenylpropane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol (**31**)

2,2'-((1E,1'E)-((1-(p-tolyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol (**32**)

2,2'-((1E,1'E)-((1-phenylbutane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**33**)

2,2'-((1E,1'E)-((1-(2-chlorophenyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**34**)

2,2'-((1E,1'E)-((1-(3-chlorophenyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**35**)

2,2'-((1E,1'E)-((1-(4-chlorophenyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**36**)

2,2'-((1E,1'E)-((1-(p-tolyl)butane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**37**)

2,2'-((1E,1'E)-((1-(p-tolyl)hexane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**38**)

2,2'-((1E,1'E)-((1-phenylhexane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**39**)

2,2'-((1E,1'E)-((3-methyl-1-phenylbutane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))diphenol(**40**)

N^1E,N^2E)-N^1,N^2-bis((1H-indol-3-yl)methylene)-1-phenylpropane-1,2-diamine(**41**)

(N^1E,N^2E)-N^1,N^2-bis((1H-indol-3-yl)methylene)-1-(o-tolyl)propane-1,2-diamine(**42**)

(N^1E,N^2E)-N^1,N^2-bis((1H-indol-3-yl)methylene)-1-(2-chlorophenyl)propane-1,2-diamine(4**3**)

(N^1E,N^2E)-N^1,N^2-bis((1H-indol-3-yl)methylene)-1-(3-chlorophenyl)propane-1,2-diamine(**44**)

(N^1E,N^2E)-N^1,N^2-bis((1H-indol-3-yl)methylene)-1-phenylbutane-1,2-diamine(**45**)

1,1'-((1E,1'E)-((1-phenylpropane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(naphthalen-2-ol) (**46**)

1,1'-((1E,1'E)-((1-(o-tolyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(naphthalen-2-ol) (**47**)

1,1'-((1E,1'E)-((1-(2-chlorophenyl)propane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(naphthalen-2-ol) (**48**)

1,1'-((1E,1'E)-((1-(p-tolyl)butane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(naphthalen-2-ol) (**49**)

- The synthesized compounds have been characterized by IR, NMR (^1H & ^{13}C, and NOESY (for required compounds)) spectral studies and mass spectra have been recorded for some representative compounds to confirm the formation of compounds.
- Stereochemistry: The conformation and configuration of the synthesized diamines have been traced through ^1H NMR coupling constant values and Gaussian computational (structure optimization, and property exploration) results. The optical purity has also been assessed in spite of difficulties in yield and solubility for certain compounds.
- Single crystal XRD study: Single crystal for **seven** compounds (**1**, **9, 31**, **32**, **35**, **36** & **37)** have been achieved by slow evaporation technique and subjected for XRD study. Crystal data have been deposited in CCDC.

Compounds	Deposit Number (CCDC)
1	1008701
9	1008702
31	1448833
32	1448832
35	1412945
36	1412946
37	1553846

- Computational study: Selected compounds have been computationally analyzed for detecting their global minimum energy conformer. The global minimum energy conformers have been optimized using DFT (B3LYP) /6-31G(d,p) basis set. The optimized geometry has been used for computations. The molecular properties and the molecular reactivity have been studied. Though these attempts of molecular modeling studies are preliminary assay on these VCDs, they furnish the basic support for Structure

– Affinity relationship studies in future and supports any researcher working in this field of VCDs.

- Biological assay of synthesized compounds:

✓ Molecular docking studies: The docking studies of the enantiomeric diamine candidates have been carried out with human carcinoma and sarcoma protein receptors and some fungal protein receptors using Argus Lab 4.0.1 software and online docking server. With Argus Lab 4.0.1, the docking computations have been carried out using "*rigid*" and "*flexible*" docking modes and using molecular docking server, the docking computations have been carried out with "*blind*", "*activated*" and "*focused*" docking modes. The candidates with best docking pose energy have been identified. These findings are in good agreement with several earlier experimental (cytotoxic) reports on their analogues, (*i.e*) the homochiral diamines are found to be effective compared with heterochiral candidates. Furthermore, overall performance order of tested trial homochiral enantiomeric diamines have been observed as the R,R-isomers >>>S,S-isomers towards the tested receptors.

✓ Cytotoxic Study: The cytotoxicity of selected compounds has been tested against KB cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide -MMT assay. The cell viability at different concentrations and their cytotoxic potentials have been identified.

❖ **Conclusion:**

- **The objective of the project, synthesis and characterization of thirty target molecules and in addition, nineteen derivatives has been successfully achieved.**
- **Investigation of the stereochemical importance influencing molecular and biological properties has been explored through computational and experimental studies.**