DESIGN SYNTHESIS AND EVALUATION OF ANTI MICROBIAL ACTIVITY ON A NEW SERIES OF 1,2,3,4- TETRA HYDRO CARBAZOLES

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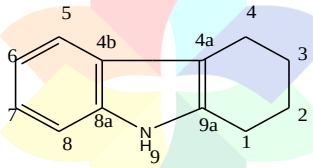
Abstract: The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new co2mpounds to deal with this resistance has become one of the most important areas of research today. Carbazole is a versatile moiety that exhibits a wide variety of biological activities. Review of literature says it is known that 1,2,3,4 – tetra hydro Carbazole are screened for enormous biological and pharmacological activities's , still need for developing new derivatives at sslead compounds level. Although there is availability of new technologies such as high – throughput screening, combinational technology, microwave assisted synthesis and computer aided drug design, for multitude of new safety requirements that have arisen has also brought unanticipated hurdles for the task of translating in vitro to in vivo studies. In the view of that synthesis of 1,2,3,4 – tetra hydro carbazole derivatives to explore as potential Anti –microbial active compounds still draw continuous interest in molecular manipulations of active moieties with ensure to obtain drugs of high potency with low toxicity.

IndexTerms - 1,2,3,4-tetra hydro carbazoles, Anti –microbial active compounds,

I. INTRODUCTION

i. 1,2,3,4 TETRAHYDRO CARBAZOLE

The tetrahydrocarbazole ring system has been the structural subunit of many naturally occurring alkaloids , biologically active molecules and medicinal important synthetic analogues.It is a heterocyclic organic compound .It has a tricyclic structure , .



Tetrahydrocarbazoles condensed with indole, futan, pyrimuidine, pyrazoline and thiophine, moieties have been known to processes wide spectrum biological activities. Carbazile it self and 1,2,3,4 – tetrahydrocarbazole, .1,2,3,4 – Tetrahydrocarbazole [THCz] derivatives are well known for their pharmacological activities several search for newer physiologically active compounds. They are used in the synthesis of (antibacterial and antifungal, cytotoxic against cancer cells lines, Screend for antinociceptive activity, antiobestic, antidiabetic (type IIdiabeties), antipsychotic activity, and anti emetic medicine

II. RESEARCH METHODOLOGY

Synthesis of 1,2,3,4 tetrahydrocarbazole: In a 500ml three necked flask fitted with a dropping funnel, a sealed stirrer unit reflux condenser, place a mixture of 49 g (0.5 moles) of cyclohexanone and 180 g of glacial acetic acid. Heat under reflux with stirring and add 54 g(49ml,0.5 mol) of redistilled phenyl hydrazine during one hour , continue the stirring for a further hour pour the reaction mixture into a 1 lit beaker and stir vigorously while it solidified .cool to 5^0C and filter at the pump through a Buchner funnel. Cool the filtrate in ice and filter through the same Buchner funnel. Wash the solid on the filter with 50ml of water , suck almost dry and then wash with 50 ml of 75% ethanol . Spread the crude solid upon the absorbent cotton paper and dry in the over night. Recrystalise the slightly damp solid from 350ml of ethanol, add a little decolorizing carbon and filter through a hot water funnel. The yield of 1,2,3,4 tetrahydrocarbazole, m.p 116-117^{0}C , is 65g (76%). A further 5g of product may be obtained by concentrating the mother – liquor to one quarter of the original volume.

Scheme-I

Step -1: Synthesis of N –(1,2,3,4 – tetrahydrocarbazole- 9-yl) acetyl chloride

In a 250 ml round bottomed flask , taken the above mixture (3.2 gm) , chloro acetic acid (10gm) add drop wise in presence of glacial acetic acid , reflux on water bath for about 1 : ½ hr , pour it into cold water , filtered ,dried.

Step- ll: synthesis of N – (1,2,3,4 – tetrahydro - 9-yl) acetyl (substituted) carbazole

The above compound taken in a 250ml beaker , dissolved in ethanol (20ml), added 3 gm K_2CO_3 , kept in ice bath (5^0C) then added guanidine HCl (10gm) for a 1 a compound , in portions with stirring , reaction mixture kept a side for ½ hr.then evaporate and undergo for drying.

Note: the same procedure for other derivatives by using aminoguanidine dehydrogenate for 1b and 1c , urea for 1d samples.

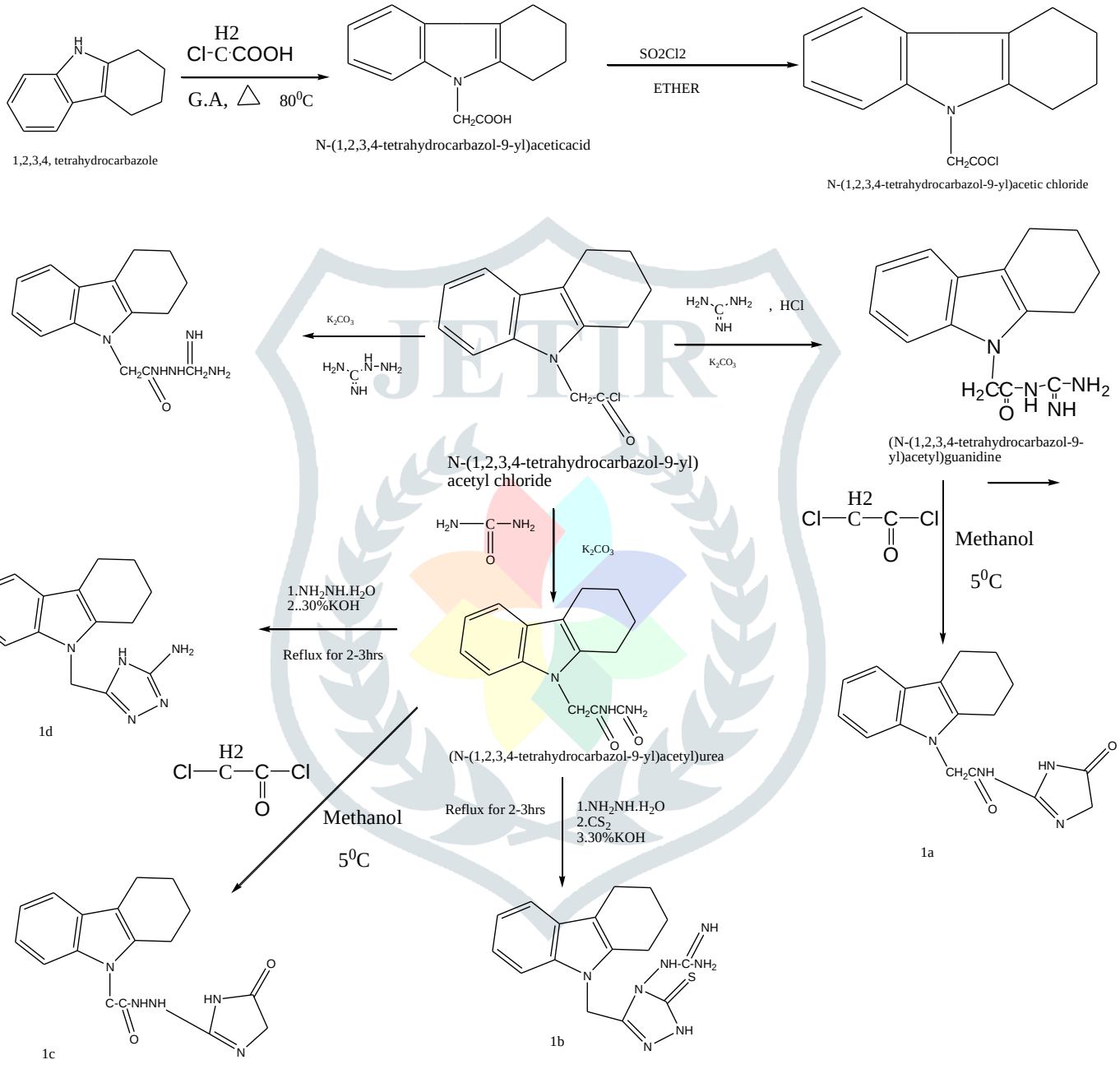
Step- lll: synthesis of N –(substituted -9 yl) 1,2 ,3,4 , tetrahydrocarbazole.

The above compound taken in a250ml beaker, dissolved in ethanol (20ml) ,added 3gm K_2CO_3 , kept in ice bath (5^0C) , added chloro acetyl chloride drop wise with vigorous stirring for 1a compound, reaction mixture kept aside for ½ hr. Excess solvent is evaporated,then filtered ,dried.

Note: the same procedure for 1c compound.For 1b, 1c compounds the above compound taken in a 250ml round bottomed flask , added hydrazine hydrate (20ml) , carbon disulphide (20ml) ,30% KOH (30ml). reflux on water bath for about 2-3 hrs , pour it cold water , filtered ,dried.

TCZ-1: 1,2,3,4 tetrahydro 9(H) carbazole:

SCHEME –I (CTZ 1a-1d)



Scheme-II

Step-I : 9- (benzyl)1,2,3,4 ,tetrahydrocarbazole. In a 250ml round bottomed flask , taken the above mixture (0.01 mol) , dissolve in ethanol (20ml) , benzyl chloride (0.01 mol), reflux on water bath for 2-3 hrs, pour it into cold water ,filtered dried.

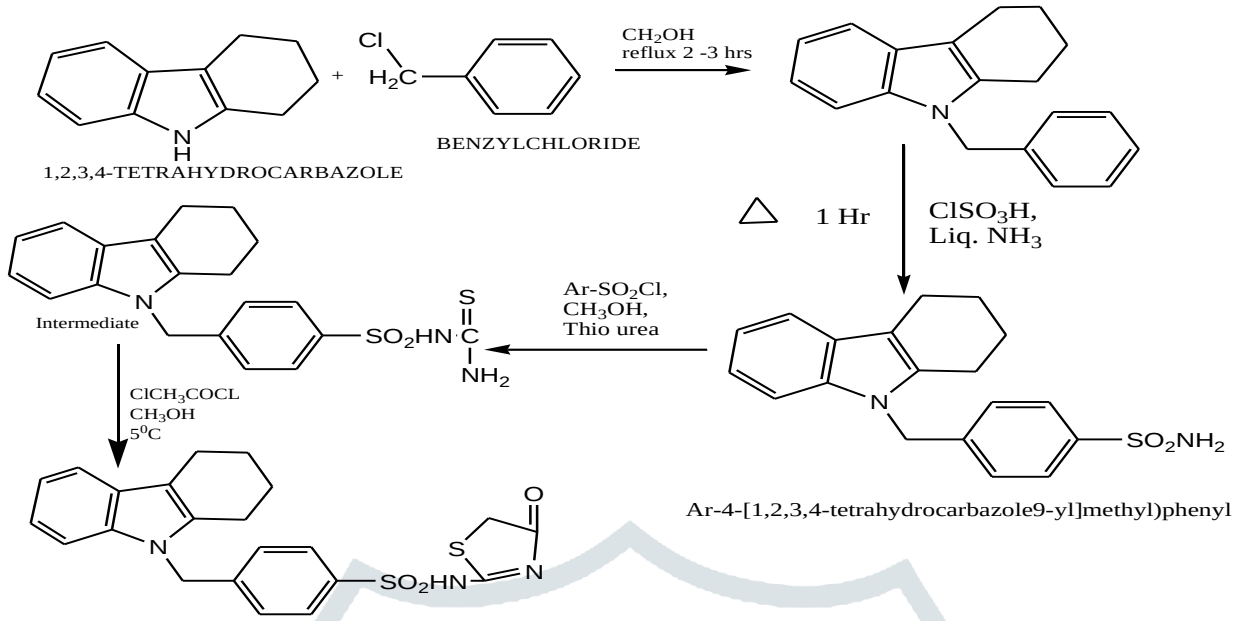
Step-ll: 1,2,3,4, tetrahydro-9- (benzyl substituted) carbazole.

The above compound taken in a 250ml round bottomed flask ,added chloro sulphonic acid (0.01 mol), concentrated ammonia (0.01 mol), reflux on water bath for about 2-3 hrs, pour it into cold water , filtered , dried.

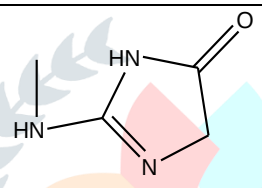
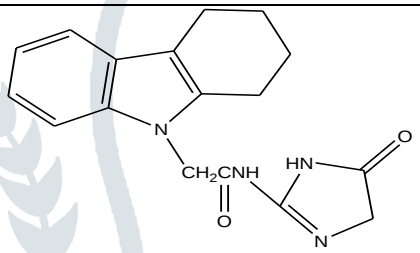
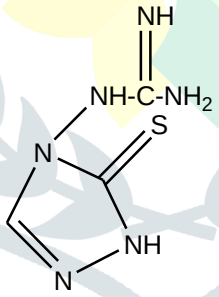
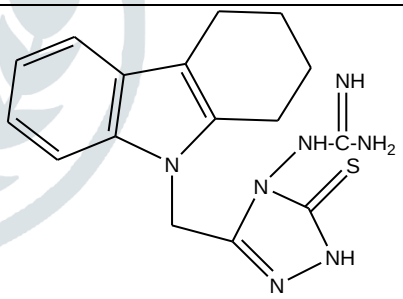
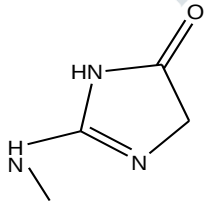
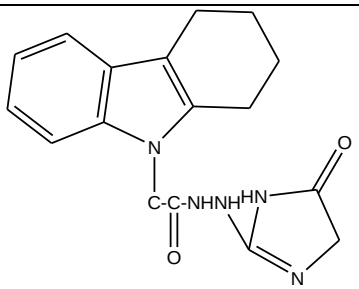
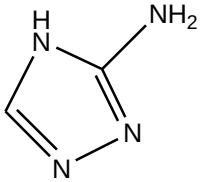
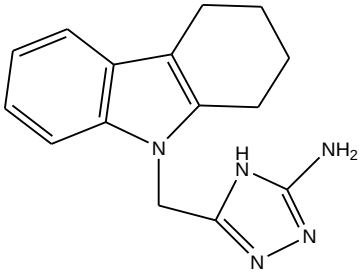
Step-lll: 9- [4(N-(4-oxo) thiazolidine -2-yl sulfamoyl] benzyl 1,2,3,4 – tetrahydrocarbazole.

The above compound taken in a 250 ml beaker, dissolved in ethanol (20ml) , added 3gm K_2CO_3 , kept in ice bath (5^0C) then added thio urea (0.001 mol) , chloro acetyl chloride (0.01 mol) in portions with stirring , reaction mixture kept aside for ½hr . Excess solvent is evaporated in water bath , then after reaction mixture dissolved in ice cold water , filtered, dried.

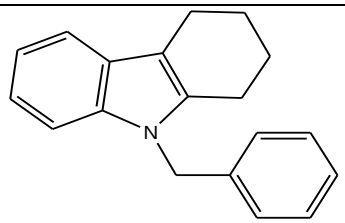
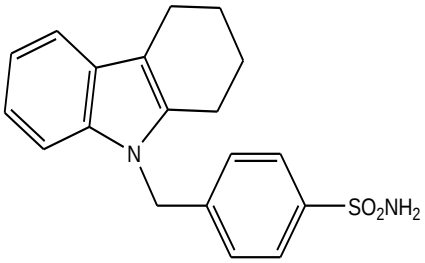
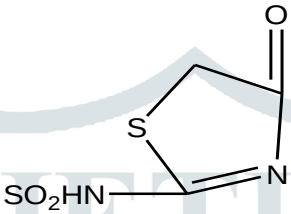
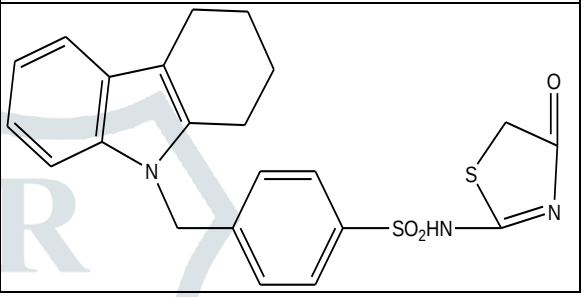
SCHEME -2 (TCZ-2 -2b)



List of first series compounds

S.NO	CODE	R	STRUCTURE
1	TCZ-1a		
2	TCZ -1b		
3	TCZ -1c		
4	TCZ -1d		

List of second series compound

S.NO	CODE	R	STRUCTURE
1	TCZ-2	----------	
2	TCZ-2a	$-SO_2NH_2$	
3	TCZ-2b		

III. BIOLOGICAL EVALUATION

Anti bacterial activity:

Method: Cup plate method was used to carry out this study.

Principle: The cup plate method depends on diffusion of antibiotic from a cup through a solidified agar layer in a petridish or petriplate to an extent such that growth added microorganism is prevented entirely in zone around cup or cylinder containing a solution of antibiotic.

Antifungal activity:

Method: Agar Diffusion Method was used to carry out the study.

Principle: The cup plate method depends on diffusion of antibiotic from a cup through a solidified agar layer in a Petri plate to an extant such that growth of added microorganism is prevented entirely in a zone around cup or cylinder containing a solution of antibiotic.

IV. RESULTS AND DISCUSSION

Physical Characterizsation data of synthesized compounds:

Compound Code	Molecular Formula	Molecular weight(g/mol)	Melting Point(^{0}C)	% Yield	R_f Value
TCZ-1	$C_{12}H_{13}N$	171.25	113-117	47.15	0.84
TCZ-1a	$C_{17}H_{18}N_4O_2$	312.16	107-112	52	0.86
TCZ-1b	$C_{16}H_{19}N_7S$	341.43	103-105	48	0.91
TCZ-1c	$C_{17}H_{19}N_5O_2$	325.57	108-110	36.54	0.85
TCZ-1d	$C_{15}H_{17}N_5$	267.33	105-109	42	0.80
TCZ-2	$C_{19}H_{21}N$	263.17	143-148	32.25	0.96
synthesized TCZ-2a	$C_{19}H_{20}N_2O_2S$	342.12	152-157	36	0.82
TCZ-2b	$C_{22}H_{24}N_4O_3S_2$	456.58	213-217	48	0.89

Antibacterial activity of Synthesized compounds:

S.No	Compound code	Gm +Ve				Gm-Ve	
		S. aures		B. subtilis		E. Coli	
		250 µg/ml	500 µg/ml	250 µg/ml	500 µg/ml	250 µg/ml	500 µg/ml
1	TCZ-1	8	6	6	9	10	12
2	TCZ-1a	11	15	11	10	9	13
3	TCZ-1b	12	17	14	18	17	19
4	TCZ-1c	8	8	8	8	8	8
5	TCZ-1d	9	13	7	10	-	11
6	TCZ-2	5	9	11	12	-	-
s7	TCZ-2a	13	15	17	18	18	19
8	TCZ-2b	14	17	17	18	11	12
Control	DMSO	-		-		-	
Standard	Streptomycin (400µg/ml)	18		20		20	

TCZ-1b and TCZ-2a are effective against both Gram +ve and Gram-ve, TCZ-1 ,TCZ-1a and TCZ-2b is found have moderate activity., TCZ-1d showed activity against pencillium notatum.

V. CONCLUSION

All the synthesized derivatives of 1,2, tetrahydrocarbazole evaluated with physical , analytical characterization and Biological methods .
All the compounds were subjected to Anti microbial activity i.e ., Antibacterial and Antifungal activities. TCZ-1b and TCZ-2a are effective against both Gram +ve and Gram-ve, TCZ-1a and TCZ-2b is found have moderate activity both Gram+ve and Gram-ve and TCZ-1a showed activity against E.coli . Other compound every having insignificant activity when compared to standard streptomycin .
Tcz-1b and TCZ -2a are effective against both organisms , TCZ-1 ,TCZ-1a and TCZ-2b is found have moderate activity and TCZ-1d showed activity against pencillium notatum .Other compound every having insignificant activity when compared to standard Micanazole nitate.

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