Heterocyclic Letters
Vol. 5 | No.4|579-594| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF 1,5-BENZOXAZEPINE DERIVATIVES CONTAINING CARBAZOLE RING

V. Prabhakar[*1], K.Sudhakar Babu[1], L.K.Ravindranath[1], M.SwarnaKumari 1, J. Latha[2]

[*1] *Department of Chemistry, Sri Krishnadevaraya University, Anantapuramu,(A P) INDIA.*
[2]*Department of Bio-technology, Sri Krishnadevaraya University College of Engineering & Technology, S.K.University, Anantapuramu – 515003 (A.P) India*
Corres. Author E-mail:- virupakshi.prabhakar@gmail.com
Mobile NO: 8297140295

ABSTRACT:
A new series of N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-chloro/ Bromo /Nitro phenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl/fluoro)aniline (9a-f) were synthesized and evaluated for their anti-inflammatory activity. All these compounds were screened in vivo, for their anti-inflammatory activity. Compound 9a was found to be most potent compound of this series and was compared with the reference drug diclofenac. The structures of these compounds have been established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

KEYWORDS: Benzoxazepine, Chalcones, Carbazole ring, Synthesis, Mannich Reaction Anti-inflammatory activity, Heterocycles, Diclofenac drug.

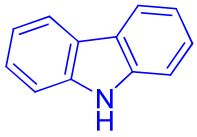
INTRODUCTION

Several organic compounds containing a fused seven membered heterocyclic ring, i.e., benzoxazepines make up a broad class that attracted attention in the past few years owing to its wide range of biological activities, **Benzoxazepine** derivatives have documented consistent advances in the design of novel anticonvulsant agents, benzoxazepine derivatives have been found to posses potent wide spectrum biological activities like anticonvulsant [**1–4**], antidepressant [**5**], CNS depressant [**6**], antipsychotic [**7,8**] and neuroleptic [**9**].

Carbazole is one of organic heterocyclic compounds containing a di benzo pyrrole, also known as 9-azo fluorine. Carbazole was synthesized by Borsche-Drechsel Cyclization [**10**] . Carbazoles are a large and an interesting group of organic compounds which one can find pharmaceutical activity[**11**] , dyestuffs, plastics [**12-14**] , and known to possess mutagenic and toxic activities and also to be are calcitrant molecule[**15**] . Carbazole derivatives showed anticancer [**16**] , antifungal[**17**] , anti malarial [**18**] , anti tumor (leuckemia, renal, colon), anti inflammatory, antiallergic antiviral, and anti hypertensive properties [**19-21**] .Due to their extensive biological activity carbazole derivatives and their chemistry have been studies at length. Keeping the above facts, we aimed to synthesize new

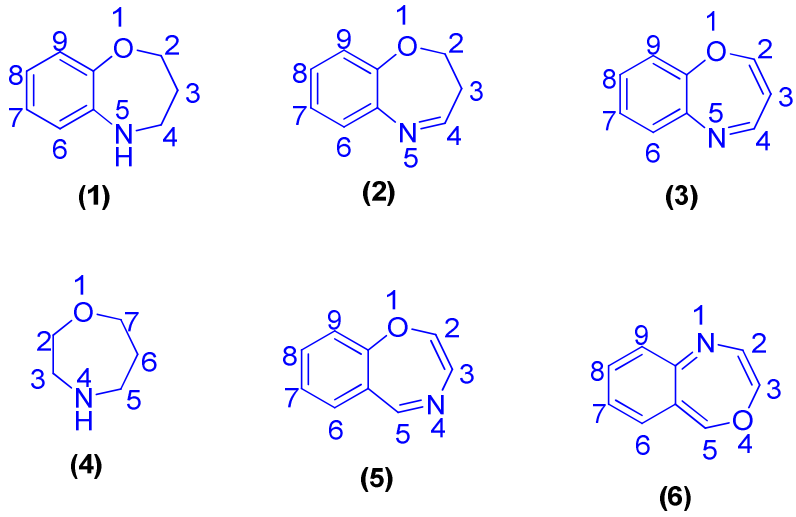
carbazole derivatives to thus obtain new hetero cyclic system which is expected to possess characteristic of biological activites.structure of carbazole as shown below.

Structure of Carbazole



The 1,5-benzoxazepines (1, 2,3) are Important nitrogen- and Oxygen-containing seven membered heterocyclic compounds in drug research since they possess diverse bioactivities. 1,5-Benzoxazepines are the most well-known representatives of benzologs of 1,4-oxazepine (4) and one of the three possible benzo condensed derivatives, viz. 1,4-(5), 4,1-(6) and 1,5- benzoxazepines .

General structures of 1, 5-benzoxazepine



(1) **(2)** **(3)**

(4) **(5)** **(6)**

In view of biological activities of benzo oxazepine derivatives, we report here in the synthesis of their new derivatives namely N-((2-(9-methyl-9H-carbazol-3-yl)-4-(4-chloro/Bromo/Nitro phenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl/Fluoro)aniline (9a–9f) along with their anti-inflammatory profile.

The literature study reveals that both carbazole and benzo oxa azepines are a significant pharmacophore and exhibits outstanding biological activities. Encourage by these observation, we synthesized a new series of benzoxazepines derivatives by incorporating the carbazole ring with the hope of obtaining better anti-inflammatory activity agent. All the synthesized compounds have been screened for their anti-inflammatory activities.

The synthetic routes of compounds are outlined in **scheme 1**. Chalcones were synthesized by the reaction of 4-substituted acetophenone derivatives and N-Methyl Carbazole in the presence of NaOH i.e. compounds (5 a-c). Compounds (5a–5c) on cyclization with 2- amino phenol in the presence of glacial acetic acid yielded compounds (7a–7c) respectively. Compounds 7a-7c further undergoes Mannich reaction with different substituted anilines to afford compounds 9a-9f

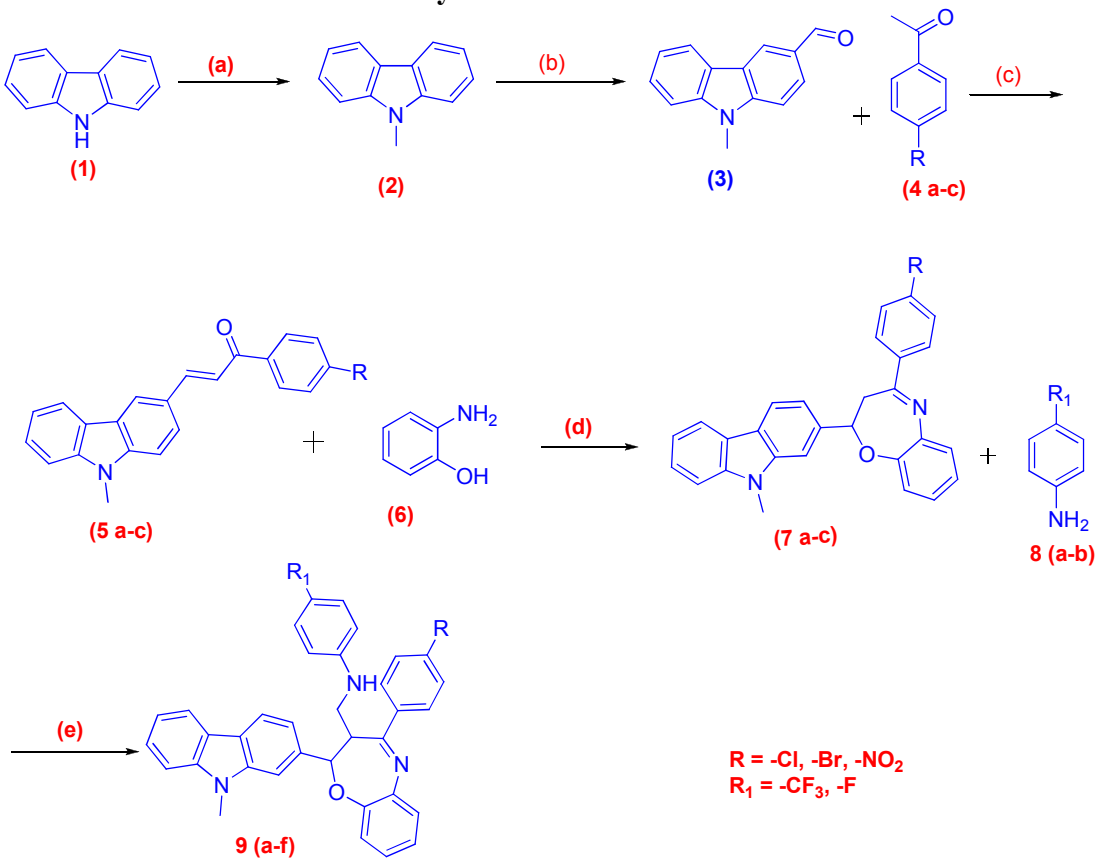
Materials and Methods:

Laboratory chemicals were provided by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene:ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light. The IR spectra were received by PerkineElmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H NMR &^{13} C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in $CDCl_3$. Elemental analysis of the new synthesized compounds were obtained by Carlo Erba 1108 analyzer. The synthesis of the compounds as per the following **Scheme I** given below.

The synthetic route was depicted in scheme **I**

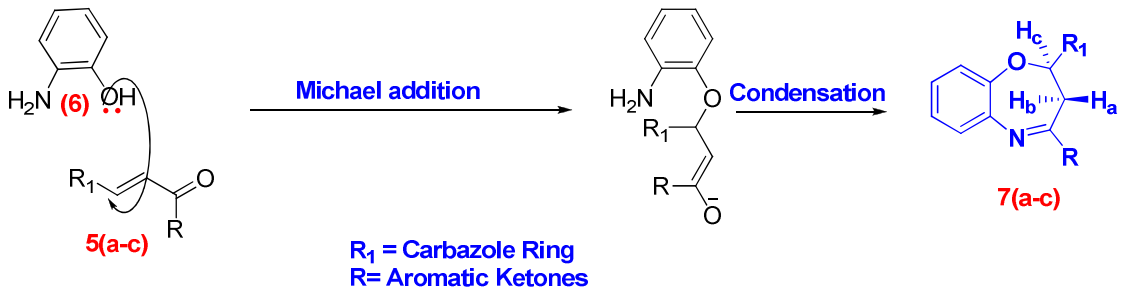
The title compounds 9(a-f) were synthesised in five sequential steps using different reagents and reaction conditions, the 9(a-f) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

Synthetic Scheme I



Reagents and Reaction conditions: ***(a)*** *Methyl Iodide (Me-I), tetra butyl ammomium bromide, potassium hydroxide in acetone, Reflux,1 hr* ***(b)*** *DMF,$POCl_3$, 80^{0}C* ***(c)*** NaOH, Ethanol, RT, 24–36 h. ***(d)*** *Methanol, glaceial Acetic acid, Reflux* ***(e)*** *formaldehyde,Methanol, Reflux*

Compound	9a	9b	9c	9d	9e	9f
R	-Cl	-Cl	-Br	-Br	$-NO_2$	$-NO_2$
R_1	$-CF_3$	-F	$-CF_3$	-F	$-CF_3$	-F



Designed series of molecules 7 (a-c) were characterized by spectral and elemental analysis before being evaluated for their anti- inflammatory activity. The structural assignments were made by NMR analysis by considering compound (7a) as the representative compound. In its ^{1}H NMR spectra, **Ha, Hb** and **Hc** protons of the benzoxazepine ring appeared as a doublet of doublet. The doublet of **Ha** appeared at δ 1.822 ppm; doublet of **Hb** appeared at δ 2.112 ppm; and that of **Hc** appeared at δ 3.665 ppm. Doublets of **Ha** and **Hb** are due to diastereotopic nature of methylene protons. Among **Ha**, **Hb** and **Hc** protons, **Hc** is the most deshielded due to its close proximity to benzene ring. **Hc** couples not only with **Ha** but also with **Hb** and appears as doublet of doublet instead of a triplet i.e., the methylene protons of benzoxazepine ring (**Ha and Hb**) exhibited a typical **ABX** spin system with **Hc** as a doublet of doublets as shown in diagram-7(a-c). Further it showed signals due to substituent and aromatic protons at the expected region. All compounds displayed the signals in the similar pattern.

EXPERIMENTAL SECTION:

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-d or DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

General procedure for the preparation of 9-methyl-9H-carbazole (2) [22]:

Carbazole (**10 m.mol**), tetra butyl ammonium bromide (**1 m.mol**) and potassium hydroxide (**40 m.mol**) dissolved in acetone (**20 ml**) were added to a 100 ml three-necked flask, the mixture solution was stirred for 40 minutes. Methyl Iodide (**12 m.mol**) was added drop wise to the solution with constant stirring. The mixture was refluxed for 1 h. The reaction mixture was then poured into ice water (**100 ml**) with vigorous stirring to obtain a great deal of deposit. The mixture was extracted with DCM, washed with water and the Purified by column chromatography to give N-Methyll carbazole (2)

Yield :68%.

^{1}H-NMR (400 M.HZ, DMSO-d_6): δ 7.3-8.4(8H,m,Ar-H), 3.9(3H,S, N-C**H**$_3$)
IR(KBr,cm-^{1}): 3110 cm^{-1} (Ar C-H stret), 1550 cm^{-1} (C=C Stret), 2900 cm^{-1} (SP^3 C-H Stretch),1240 cm^{-1} (C-N Stretch) Wave numbers respectively.

General procedure for the preparation of 9-Methyl-9H-carbazole-3-carbaldehyde (3) [23] :
9-Methyl carbazole (2) (**10 m.mol**) was dissolved in dry DMF (**20 m**l) under anhydrous condition. It was cooled to 0^0 C, $POCl_3$ (**1.87 ml**) was added drop wise for 30 min and stirring continued for 4 h at 80^0 C. After completion of reaction (TLC), the reaction mass was poured over crushed ice (50 g), basified with NaOH, extracted with chloroform and dried over anhydrous Na_2SO_4. Organic layer was concentrated and purified through silica gel column using chloroform as eluting solvent to yield product 3.
Yield: 55%; off white solid; **mp:** 76–78^0 C;
^{1}H-NMR (400 M.HZ, $CDCl_3$-d_1): δ 7.3-8.4(7H, m, Ar-H), 3.9(3H,S, N-C**H**$_3$), 9.9 (1H,S, **H**-C=O)
IR(KBr,cm-^{1}): 3110 cm^{-1} (Ar C-H stret), 1550 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1725 cm^{-1} (C=O Stretch) Wave numbers respectively.
General procedure for the preparation of (E)-3-(9-methyl-9H-carbazol-2-yl)-1-(4-chloro/Bromo/Nitro phenyl)prop-2-en-1-one 5(a-c) [24] :
A mixture of acetophenone derivatives 4(a-c) (**0. 1m. mol**), carbazole aldehyde (3) (**0.1 m.mol**) in ethanol (4 ml) and aqueous sodium hydroxide (**70%, 10 ml**) was stirred and kept at room temperature for 12 h. The mixtures were poured on crushed ice and acidified with dil 2N.HCl. The precipitate obtained after acidification were filtered and washed thoroughly with distilled water till it is free from acid and dried. The dry residue was re crystallized from a suitable solvent. The physical and spectral data of the compounds are the following.

Table 1 Yields & Melting Points of Corresponding Compounds (5 a-c) :

S.NO	Yield (%)	Melting Point (^{0}C)
5a	80	122-124
5b	78	153-154
5c	75	186-187

Table: 2 IR(KBr,cm-^{1}) data of Compounds **5 (a-c):**

Compound	ν_{max}, cm^{-1}
5a	3110 cm^{-1} (Ar C-H stret), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
5b	3110 cm^{-1} (Ar C-H stret), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 568 cm^{-1} (C-Br Stretch) Wave numbers respectively.
5c	3110 cm^{-1} (Ar C-H stret), 1610 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in –NO_2 Group) Wave numbers respectively.

Table: 3 ^{1}H –NMR data of Synthesised compounds 5(a-c):

Compound	**^{1}H-NMR ($CDCl_3$-d_1) (δ ppm)**
5a	δ 3.9(3H,S, N-C**H**$_3$), 7.4-8.4(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.6(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 7.9(2H,d,J=8HZ, meta to chloro group), 7.7(2H,d,J=8HZ,ortho to Chloro group)
5b	δ 3.9(3H,S, N-C**H**$_3$), 7.4-8.3(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group),), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 7.9(2H,d,J=8HZ, meta to Bromo group), 7.8(2H,d,J=8HZ,ortho to Bromo group)
5c	δ 3.9(3H,S, N-C**H**$_3$), 7.4-8.4(7H,m,Ar-H), 8(1H,d,J=14HZ,Beta alkene Proton from carbonyl group), 7.5(1H, d, J=14Hz,alpha alkene proton from carbonyl group), 8.1(2H,d,J=8HZ, meta to nitro group), 8.5(2H,d,J=8HZ, ortho to nitro group).

General procedure for the preparation of 2-(9-methyl-9H-carbazol-2-yl)-4-(4-chloro/Bromo/Nitro phenyl)-2,3-dihydrobenzo[b][1,4]oxazepine (7a-c) [25]:
The methanolic solution (5 mL) of p-substituted chalconyl benzenes (5a-5c) (**0.1 m.mol**) was added 2-amino phenol (6) (**0.1 m.mol**) with few drops of glacial acetic acid and refluxed for 3–5 h. After refluxing solvents were distilled off under reduced pressure and the solid thus obtained were re crystallized from suitable solvent. The physical and spectral data of the compounds are the following.

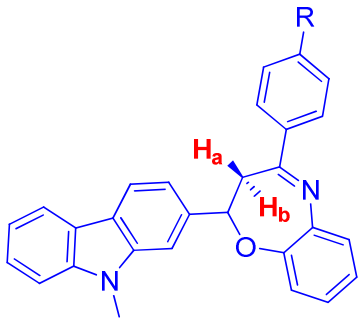
Table 4 Yields & Melting Points of Corresponding Compounds (7 a-c) :

S.NO	**Yield (%)**	**Melting Point (^{0}C)**
7a	65	173-174
7b	72	125-126
7c	70	144-146

Table: 5 IR(KBr,cm-^{1}) data of Compounds **7(a-c):**

Compound	**ν_{max}, cm^{-1}**
7a	3110 cm^{-1} (Ar C-H stret), 1043 cm^{-1} (C-O-C Stretch), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 768 cm^{-1} (C-Cl Stretch), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
7b	3110 cm^{-1} (Ar C-H stret), 1073 cm^{-1} (C-O-C Stretch), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 568 cm^{-1} (C-Br Stretch) Wave numbers respectively.
7c	3110 cm^{-1} (Ar C-H stret), 1143 cm^{-1} (C-O-C Stretch), 1610 cm^{-1} (C=C Stret), 2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in –NO_2 Group) Wave numbers respectively.

Table: 6 ^{1}H –NMR data of Synthesised compounds 7(a-c):



(7 a-c)

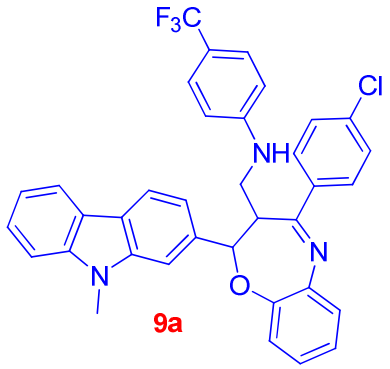
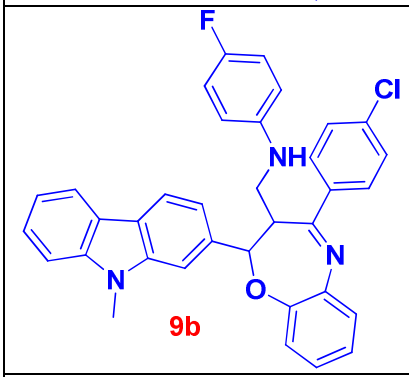
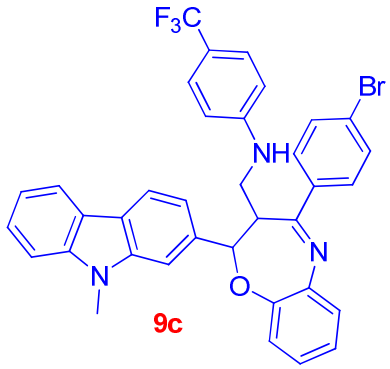
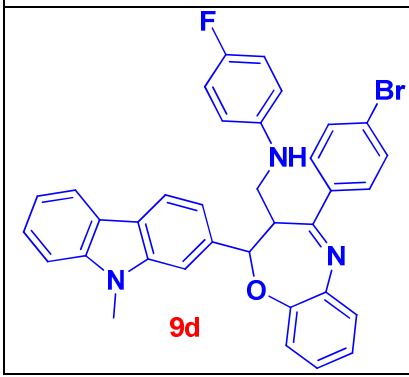
Where **H_a, H_b** Diastereotopic Protons.

Compound	^{1}H-NMR ($CDCl_3$-d_1) (δ ppm)
7a	δ 3.9(3H,S, N-C**H**$_3$), 7-7.4(11H,m,Ar-H), 2.2(1H,dd,J=14HZ, 7HZ O-CH-CH$_a$), 1.9(1H,dd, J=14HZ, 7HZ O-CH-CH$_b$), 7.9(2H,d,J=8HZ, meta to -Cl atom), 7.5(2H,d,J=8HZ, ortho to -Cl atom).
7b	δ 3.9(3H,S, N-C**H**$_3$), 7-7.4(11H,m,Ar-H), 2.2(1H,dd,J=14HZ, 7HZ O-CH-CH$_a$), 1.9(1H,dd, J=14HZ, 7HZ O-CH-CH$_b$), 7.8(2H,d,J=8HZ, meta to –Br atom), 7.6(2H,d,J=8HZ, ortho to –Br atom).
7c	δ 3.9(3H,S, N-C**H**$_3$), 7-7.4(11H,m,Ar-H), 2.2(1H,dd,J=14HZ, 7HZ O-CH-C**H**$_a$), 1.9(1H,dd,J=14HZ,7HZ,O-CH-C**H**$_b$), 8.1(2H,d,J=8HZ, meta to nitro group), 8.5(2H,d,J=8HZ, ortho to nitro group).

General procedure for the preparation of N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline (9a), N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-fluoroaniline (9b), N-((4-(4-bromophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline (9c), N-((4-(4-bromophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-fluoroaniline (9d), N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline (9e), N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-fluoroaniline (9f) [26] :

The mixture of Compound 7(a-c) (**0. 1 m.mol**), substituted aniline 8(a-b) (**0.1 m.mol**) and formaldehyde (**0.2 m.mol**) in methanol (3 ml) were refluxed for 4–6 h. The resultant reaction mixtures were concentrated, cooled and poured on to ice. The separated semi solid were kept overnight in petroleum ether(40–60^0 C). The solid thus formed were re crystallized from appropriate solvent. The physical and spectral data of the compounds are the following.

Table 7 Structures of final Compounds & Its corresponding Names :

Chemical Structure	Chemical Name
	N-((4-(4-chlorophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline
	N-((4-(4-chlorophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-fluoroaniline
	N-((4-(4-bromophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline
	N-((4-(4-bromophenyl)-2-(9-methyl-9H-carbazol-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-fluoro aniline

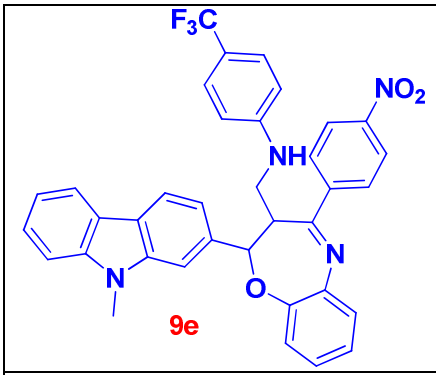
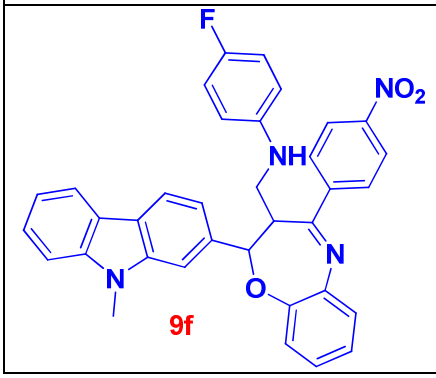
	N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)-4-(trifluoromethyl)aniline
	4-fluoro-N-((2-(9-methyl-9H-carbazol-2-yl)-4-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-3-yl)methyl)aniline

Table 8: Characterisation data of Novel Benzo oxazepine derivatives 9 (a-f):

Comp	M.P. /^{0}C	Molecular Weight (m/z)	YIELD(%)	Molecular Formula	Found % (Calculated %)		
					C	H	N
9a	140-142^{0}C	611[**M+Na**]	70	$C_{36}H_{27}ClF_3N_3O$	70.85 (70.88)	4.5 (4.5)	6.82 (6.89)
9b	163-165^{0}C	561[**M+H**]	75	$C_{35}H_{27}ClFN_3O$	75 (75.06)	4.83 (4.86)	7.5 (7.5)
9c	180-182^{0}C	655[**M+H**]	76	$C_{36}H_{27}BrF_3N_3O$	66 (66.06)	4.18 (4.2)	6.53 (6.5)
9d	147-148^{0}C	605[**M+H**]	74	$C_{35}H_{27}BrFN_3O$	69.51 (69.54)	4.50 (4.52)	6.92 (6.95)
9e	130-132^{0}C	621**[M+H]**	72	$C_{36}H_{27}F_3N_4O_3$	69.67 (69.68)	4.4 (4.39)	9.02 (9.03)
9f	139-140^{0}C	571[**M+H**]	77	$C_{35}H_{27}FN_4O_3$	73.62 (73.67)	4.72 (4.77)	9.8 (9.82)

Table: 9 IR(KBr,cm-^{1}) data of Compounds **9(a-f):**

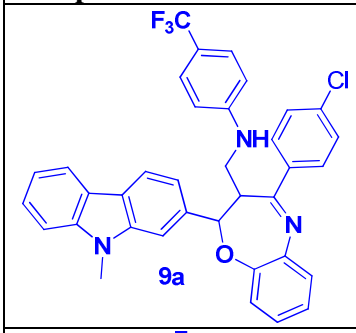
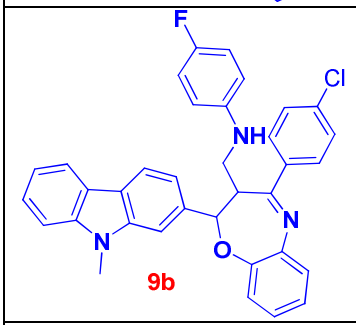
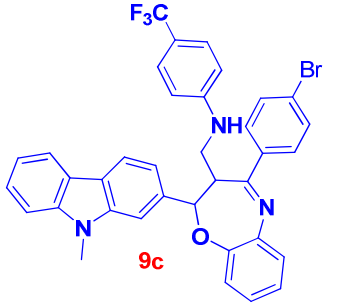
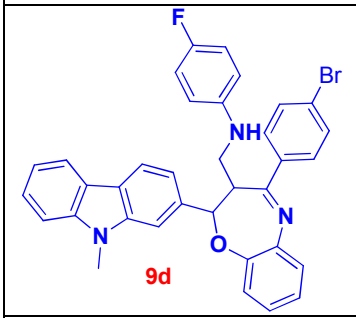
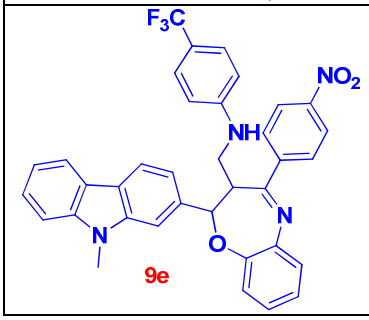
Compound	ν_{max}, cm^{-1}
9a	3110 cm^{-1} (Ar C-H stret), 1300 cm^{-1} (C-F Stretch), 1043 cm^{-1} (C-O-C Stretch), 2940 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 768 cm^{-1} (C-Cl Stretch), 3340cm^{-1} (N-H Stretch), 770 cm^{-1} (C-Cl Stretch) Wave numbers respectively.
9b	3100 cm^{-1} (Ar C-H stret), 1340 cm^{-1} (C-F Stretch), 1053 cm^{-1} (C-O-C Stretch), 2900 cm^{-1} (SP^3 C-H Stretching), 1550 cm^{-1} (C=C Stret), 778 cm^{-1} (C-Cl Stretch), 3350cm^{-1} (N-H Stretch), 780 cm^{-1} (C-Cl Stretch) Wave numbers respectively.

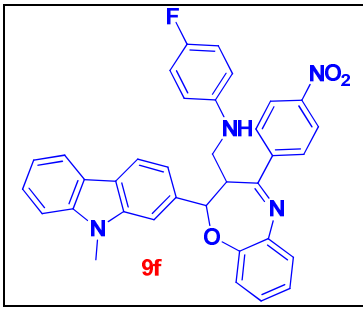
9c	3110 cm^{-1} (Ar C-H stret), 1050cm^{-1} (C-O-C Stretch), 2920 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 1340 cm^{-1} (C-F Stretch), 3350cm^{-1} (N-H Stretch), 568 cm^{-1} (C-Br Stretch) Wave numbers respectively.
9d	3100 cm^{-1} (Ar C-H stret), 1040cm^{-1} (C-O-C Stretch), 2900 cm^{-1} (SP^3 C-H Stretching), 1580 cm^{-1} (C=C Stret), 1360 cm^{-1} (C-F Stretch), 3370cm^{-1} (N-H Stretch), 570 cm^{-1} (C-Br Stretch) Wave numbers respectively.
9e	3110 cm^{-1} (Ar C-H stret), 3350cm^{-1} (N-H Stretch), 1073 cm^{-1} (C-O-C Stretch), 1610 cm^{-1} (C=C Stret), 1360 cm^{-1} (C-F Stretch),2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in $–NO_2$ Group) Wave numbers respectively.
9f	3100 cm^{-1} (Ar C-H stret), 3370cm^{-1} (N-H Stretch), 1053 cm^{-1} (C-O-C Stretch), 1600 cm^{-1} (C=C Stret), 1350 cm^{-1} (C-F Stretch),2900 (SP^3 C-H Stretch), 1525 & 1350 cm^{-1} (two bands,N-O Stretch in $–NO_2$ Group) Wave numbers respectively.

Table: 10 ^{1}H –NMR data of Novel Synthesised compounds 9(a-f):

Compound	**^{1}H-NMR (DMSO-d_6) (δ ppm)**
9a	δ 3.9(3H,S, N-C**H**$_3$), 6.7-8.2(11H,m,Ar-H), 5(1H, d,J=7HZ, O-C**H**), 2.6(1H,m), 3.2(1H,dd,J=14,7 HZ, –NH-C**H**$_a$), 2.9(1H,dd, ,-NH-C**H**$_b$), 7.9(2H,d,J=8HZ, meta to -Cl atom), 7.5(2H,d,J=8HZ, ortho to -Cl atom), 6.5(2H,d,J=7.3HZ,Meta to $–CF_3$), 7.4(2H,d,J=7.3HZ, Ortho to $–CF_3$), 4(1H,Bs, -NH)
9b	δ 3.8(3H,S, N-C**H**$_3$), 6.7-8.2(15H,m,Ar-H), 3.2(1H,dd,J=14, 7 HZ, 7HZ –NH-C**H**$_a$), 2.9(1H,dd,-NH-C**H**$_b$), 5(1H,d,-O-C**H**), 2.6(1H,m), 8(2H,d,J=8HZ, meta to -Cl atom), 7.5(2H,d,J=8HZ, ortho to -Cl atom) 4(1H,Bs, -NH).
9c	δ 3.8(3H,S, N-C**H**$_3$), 6.7-8.2(11H,m,Ar-H), 5(1H, d,J=7HZ, O-C**H**), 2.6(1H,m), 3.2(1H,dd,J=14, 7HZ, –NH-C**H**$_a$), 2.9(1H,dd, ,-NH-C**H**$_b$), 7.4(2H,d,J=8HZ, ortho to $–CF_3$), 6.5(2H,d,J=8HZ, Meta to $–CF_3$), 7.6(2H,d,J=7.3HZ,ortho to –Br), 7.8(2H,d,J=7.3HZ, meta to –Br), 4(1H,Bs, -NH)
9d	δ 3.9(3H,S, N-C**H**$_3$), 6.7-8.1(15H,m,Ar-H), 3.2(1H,dd,J=14HZ, 7HZ –NH-C**H**$_a$), 2.9(1H,dd,-NH-C**H**$_b$), 5(1H,d,-O-C**H**), 2.6(1H,m), 7.6(2H,d,J=8HZ, Ortho to -Br atom), 7.7(2H,d,J=8HZ, meta to -Br atom) 4(1H,Bs, -NH).
9e	δ 3.9(3H,S, N-C**H**$_3$), 6.7-8.2(11H,m,Ar-H), 5(1H, d,J=7HZ, O-C**H**), 2.6(1H,m), 3.2(1H,d,J=7HZ, –NH-C**H**$_a$), 2.9(1H,dd, ,-NH-C**H**$_b$), 7.9(2H,d,J=8HZ, meta to $–NO_2$ gp), 8.4(2H,d,J=8HZ, ortho to $–NO_2$ gp), 6.5(2H,d,J=7.3HZ,Meta to $–CF_3$), 7.4(2H,d,J=7.3HZ, Ortho to $–CF_3$), 4(1H,Bs, -NH)
9f	δ 3.8(3H,S, N-C**H**$_3$), 6.7-8.2(11H,m,Ar-H), 5(1H, d,J=7HZ, O-C**H**), 2.6(1H,m), 3.2(1H,d,J=7HZ, –NH-C**H**$_a$), 2.9(1H,dd, ,-NH-C**H**$_b$), 7.9(2H,d,J=8HZ, meta to $–NO_2$ gp), 8.4(2H,d,J=8HZ, ortho to $–NO_2$ gp), 6.5(2H,d,J=7.3HZ,Meta to $–CF_3$), 7.4(2H,d,J=7.3HZ, Ortho to $–CF_3$), 4(1H,Bs, -NH)

Table: 11 ^{13}**C –NMR** data of of Novel Synthesised compounds 8(a-g):

Structure of the compound	^{13}**CNMR (100 M.HZ, DMSO-d$_6$, δ ppm)**
 9a	110-165 (27 Aromati carbons), 77(O-**C**H), 30-40(3 Aliphatic Carbons),124 (-**C**F$_3$ carbon) respectively
 9b	110-165 (27 Aromati carbons), 77(O-**C**H), 30-40(3 Aliphatic Carbons) respectively
 9c	110-165 (27 Aromati carbons), 77(O-**C**H), 30-40(3 Aliphatic Carbons),124 (-**C**F$_3$ carbon) respectively
 9d	110-165 (27 Aromati carbons), 77(O-**C**H), 30-40(3 Aliphatic Carbons) respectively.
 9e	110-160 (27 Aromati carbons), 76(O-**C**H), 30-40(3 Aliphatic Carbons),125 (-**C**F$_3$ carbon) respectively.

 9f	110-160 (27 Aromati carbons), 75(O-CH), 30-40(3 Aliphatic Carbons) respectively.

BIOLOGICAL EVALUATION

In vivo anti-inflammatory activity :

All the newly synthesized benzoxazepines (9 a–f) were screened for their in vivo anti-inflammatory activity by paw edema method. Wister rats were used in the study were fed in house diet and water adlibitum and maintained at 10-12h dark light cycle, 25^0 C. Animals were administered Diclofenac 10 mg/kg, or test compound 10 mg/kg p.o., (n=3) two hours prior to injection of 0.1% formaldehyde in the paw. The anti-inflammatory was then calculated 120 minutes after induction and presented in Table –12 as the mean paw dimension in addition to the percentage inhibition. Paw dimension was measured by digital vernier calliper (Mitutoya, Japan.) The order of activity was **9a>9b>9e>9f>9c>9d**

Table–12: **Anti-inflammatory activity of Novel Benzoxazepine derivatives 9 a–f:**

Compound	**Animal**	**Paw volume (mm)**		**% Inhibition**
		Un induced	**Induced**	
9a	1	6.3	8.0	11
	2	6.4	8.6	
	3	6.1	7.9	
9b	1	6.4	8.2	7.50
	2	6.2	8.1	
	3	6.1	8.5	
9c	1	6.2	7.7	2.52
	2	6.2	8.3	
	3	6.1	8.1	
9d	1	6.2	7.7	1.4
	2	6.2	8.3	
	3	6.1	8.1	
9e	1	6.3	8.2	6.54
	2	6.2	8.0	
	3	6.2	7.6	
9f	1	6.1	8.2	4.75
	2	6.4	8.1	
	3	6.2	8.3	
Untreated	1	6.2	8.1	0.00
	2	6.1	8.3	
	3	6.3	8.2	
Diclofenac	1	6.3	7.2	14.35
	2	6.2	7.1	
	3	6.0	6.7	

Out of the six compounds tested, three compounds (**9a, 9b and 9e**) showed significant anti-inflammatory activity. Among these compounds, the compound 9a (**R_1= -CF_3**) was found to be highly active with 11 % inhibition activity, while **9b** and **9e** with **–-F** and **–CF_3** groups were also found have a respective inhibition rate of 7.50 % and 6.54 %. However, the compounds **9c** and **9d** with bromo groups were found to be less active with 2.52 and 1.4 % inhibition respectively. The 9a with -CF_3 group displayed considerable potent anti-inflammatory activity (11 % inhibition) comparable with diclofenac (14.35 % inhibition). However, none was found to be superior to the reference drug.

The present investigation reports the synthesis of 1, 5 benzoxazepine derivatives and the evaluation of their anti-inflammatory activity (**Figure 1**).

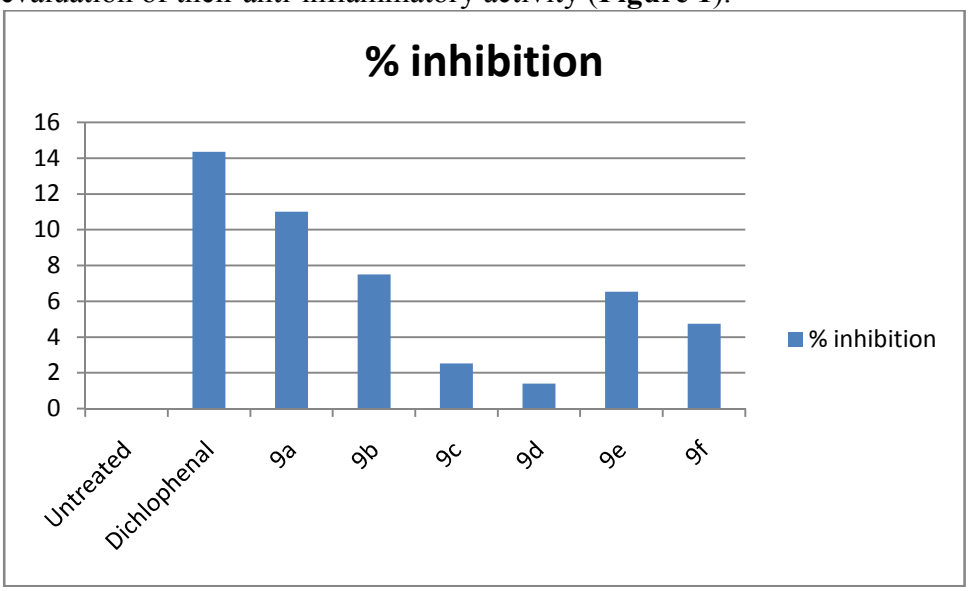


Table 13 Information about X-Axis & Y-Axis Values:

Compound(X-Axis)	**% inhibition (Y-Axis)**
Untreated	0
Dichlophenal	14.35
9a	11
9b	7.50
9c	2.52
9d	1.4
9e	6.54
9f	4.75

Results and discussions:

Chemistry

The target compounds were synthesized as shown in **Scheme 1**. Carbazole (1) on methylation with methyl iodide gave 9-methyl carbazole (2), which on Vilsmeier–Haack formylation gave 3-formyl-9-methylcarbazole (3). Chalcones were synthesized by the reaction of 4-substituted acetophenone derivatives and 3-formyl-9-methylcarbazole (3) in the presence of NaOH i.e. compounds (5 a-c). Compounds (5a–5c) on cyclization with 2- amino phenol in the presence

of glacial acetic acid yielded compounds (7a–7c) respectively. Compounds 7a-7c further undergoes Mannich reaction with different substituted anilines to afford compounds 9a-9f
All the synthesized compounds (9a-9f) were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.

Characterization:

The IR spectrum of the title Compounds 9(a-f) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2935 cm^{-1} is due to the stretching vibration corresponding to the SP^3 C-H (methyl gp).The strong Intensity absorption at 1350 & 1530 cm^{-1} is due to the stretching vibration of -N-O Stretching in Nitro group, 1360 cm^{-1} is due to The stretching vibration of C-F bond. 760 cm^{-1} is due to The stretching vibration of C-Cl bond. 560 cm^{-1} is due to the stretching vibration of C-Br bond. The weak Intensity absorption at 1620 cm^{-1} corresponds to a C=N Stretching vibration.1150cm^{-1} corresponding to C-O-C Stretching.

It has been observed from chemical structure of compound 9(a-f) that different pair of protons. The protons of methyl group which is attached to benzene ring appeared as a singlet at δ =2.3 ppm, The protons of methyl group appeared as a Singlet at δ =3.8 ppm, . The protons attached to benzene ring appeared between δ =7.2-8.4 ppm respectively.
The chemical shifts of the final compound carbon vary from δ = 165 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, The carbon chemical shift of the methyl group at δ= 23 ppm. The carbon chemical shift of the tri fluoro methyl carbon group at δ= 124 ppm.

Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of 1,5 Benzo di azepine derivatives. Formation of products was confirmed by recording their elemental analysis, ^{1}H NMR, ^{13}C,FT-IR,mass spectra. The elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values with in ±0.4% .

Anti inflammatory screening:

The results of anti inflammatory studies of newly synthesized compounds reveal that the compounds possess significant anti inflammatory activities. The results of these studies are given in **Table 12**. From anti inflammatory screening results, it has been observed that compounds 9a possess good activity.

CONCLUSION

We have synthesized a series of new 1, 5-benzoxazepines 9(a-f) containing bioactive heteryl pharmacophores such as Carbazole ring using convenient method.
In conclusion, the present investigation reports the synthesis of 1, 5 benzoxazepine derivatives and the evaluation of their anti-inflammatory activity (**Figure 1**).
The submission pattern of the 1, 5 benzoxazepine was rationalized to be correlated to the aryl heterocyclic template. Among all tested compounds, CF_3-substituted benzoxazepine derivative 9a showed the highest anti inflammatory activity (11 % inhibition) that was comparable to dichlophenal (14.35 % inhibition), while compounds 9b and 9e displayed good anti-inflammatory activity (7.50% and 6.54% inhibition), respectively. However, none of the newly synthesized compounds were found to be superior to the reference drug.

ACKNOWLEDGEMENTS:

- The authors are Thankful to Department of Chemistry, Sri Krishna Devaraya University, Anantapuramu.
- I am very thankful to S.K. University authorities for providing such an environment for doing better research very much.

➢

➢ It's my pleasure to express my thanks to Department of Chemistry for giving an opportunity to do research.

➢ I express my sincere thanks to my Research Supervisor **Dr. K. Sudhakar Babu.**

REFERENCES

[**1**]. K. Nagarajan, J. David, G.A. Bhat, *Indian J. Chem. 24B* (**1985**) *840–844*

[**2**]. K.M. Youssef, M.M. Said, Egypt. *J. Pharm. Sci. 37* (**1996**) *45–55*.

[**3**]. J.A. Diaz, E. Montero, S. Vega, V. Darias, M.L. Tello, S.S. Abdallah, *Arch. Pharm. 327* (**1994**) *157–161*.

[**4**]. G.D. Sarro, A. Chimirri, A.D. Sarro, R. Gitto, S. Grasso, M. Zappala, *Eur. J. Med. Chem. 30* (**1995**) *925–929*.

[**5**]. J.A. Diaz, S. Vega, M.A. Exposito, C.C.S. Mateo, V. Darias, *Arch. Pharm. 329* (**1996**) *352–360*.

[**6**]. K.J. Kevin, C.E. Richard, *J. Heterocycl. Chem. 30* (**1993**) *177–188*.

[**7**]. J.F.F. Liegeois, F.A. Rogister, J. Bruhwyler, J. Damas, T.P. Nguyen, M.O. Inarejos, E.M.G. Chleide, M.G.A. Mercier, J.E. Delarge, *J. Med. Chem. 37* (**1994**) *519–525*.

[**8**]. K. Bajaj, V.K. Srivastava, S. Lata, R. Chandra, A. Kumar, *Indian J. Chem. 42B* (**2003**) *1723–1728*. [**9**] K. Bajaj, V.K. Srivastava, A. Kumar, *Indian J. Chem. 42B* (**2003**) *1149–1155*

[**10**] F. G. Mann and C.S. Bernard, "*Practical Organic C hemistry",3th Ed.John wiley and Sons, London,* (**1952**).

[**11**] E. M. Arputharaj and J.R.P. Karnam, "Synthesis and characterization of carbazole derivatives and their antimicrobial studies", *Acta pharm., 56*, (**2006**), *79-86*.

[**12**]. C. Joanna, I. Krzysztof., S. Jadwiga, and C. Antoni, "Development in synthesis and electrochemical properties of thienyl derivatives of carbazole", *Tetrahedron, 62,* (**2006**), 758-764.

[**13**] S. Lengvinaite, J.V. Glrigalevicius, V. Jankauskas and S. Grigalevicius, "Carbazole-based aromatic amines having oxetan groups as materials for hole transporting layers", *Synthesis Matals, 157,* (**2007**), *529-533*.

[**14**] M. Inkyu, C. Chil-Sung and K. Nakjoong, "Synthesis and characterization of noval photo conducting carbazole derivatives in main-chain polymers for photorefractive application", *Polymer, 48,* (**2007**), *3461- 3467*.

[**15**] N. Hideaki, and O. Toshio, "Molecular Bases of Aerobic Bacterial Degradation of Dioxins: Involvement of Angular Dioxygenation", *Biosci. Biotechnol Biochem., 66(10), 2001-2016*.

[**16**] M. Laronze, M. Boisbrum, S. Leonce, B. Bfeiffer, P. Renard, O. Lozach, L. Meijer, A. Lansiaux, C. Bailly, J. Sapi and J. Laronze, "Synthesis and anticancer activity of new pyrrolocarbazole and pyrrolo- -carbolines", *Bioorganic & Medicinal chemistry, 13*, (**2002**), *2263- 2283*.

[**17**] A.D. Isravel and J.R.P. Karnam, "Synthesis and characterization of N,N -biscarbazolyl azine and N,N -carbazolyl hydrazine derivatives and their antimicrobial studies", *Acta Pharm., 54*, (**2004**), *133-142.*

[**18**] L.S. Tricia, Y. Xiaomei, P.G. Sobha, C. Grissell and C.G.S. Bjorn, "PalladiumCatalyzed synthesis of tetrahydro carbazolones as advanced intermediates to carbazole alkaloids", *Tetrahedron, 62*, (**2006**), *10835-10842*.

[**19**] Xiongwei, C., and Victor, S., "Combined Directed Ortho and Remote MetalationCross-coupling strategies. General Method for Benzo[a] carbazoles and the synthesis of an Unnamed Indolo [2,3-a] carbazole Alkaloid, *Organic Letters, 6(14*), (**2004**), *2294-2295*.

[**20**] R. Sylvain, M. Jean-Yves, D. Nathalie, L. Amelie, B. Christian, L. Olivier and M. Laurent, "Synthesis and Biological Evalution of Novel phenyl carbazole as potential Anticancer Agents", *Journal of Medicinal Chemistry, 49(2),* (**2006**), *789- 799*.

[**21**] L. Chun-Yann, T. Lo-Ti, H. Li-Jiau, W. Jih-pyang and K. Sheng-chu, "Synthesis of 3,9-Disubstituted carbazole Derivatives as Inhibitors of Microglial Cell Activation", *The Chinese pharmacyeutical Journal, 55,* (**2003**), *453-462.*

[**22**]. Wu, Limin; Wu, Panliang; Guo, Dongcai; Fu, Wenqiang; Li, Dong; Luo, Tao; *Croatica Chemica Acta; vol. 88; nb. 1*; (**2015**); *p. 1 - 6*

[**23**]. Babasaheb P. Bandgar, Laxman K. Adsul , Hemant V. Chavan, Sadanand N. Shringare , Balaji L. Korbad , Shivkumar S. Jalde , Shrikant V. Lonikar , Shivraj H. Nile , Amol L. Shirfule *Bioorganic & Medicinal Chemistry 20* (**2012**) *5649–5657*

[24]. Thanh-Dao Trana,, Haeil Parkb, Hyun Pyo Kimb, Gerhard F. Eckerc, Khac-Minh Thaia *Bioorg. Med. Chem. Lett. 19* (**2009**) *1650–1653*

[**25**]. Ganesh R. Mhaske, ShivdasS. Bajod, DamodharM. Ambhore and Sharad N. Shelke, *International Journal of Innovative Research in Science, Engineering and Technology ,Vol. 3, Issue 6, June* **2014**

[**26**]. Neha Garg , Trilok Chandra, Archana, Amit B Jain, Ashok Kumar *European Journal of Medicinal Chemistry 45* (**2010**) *1529–1535*

Received on August 22, 2015.