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# SYNTHESIS CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF 4-(9H-CARBAZOL-6-YL)-3-CHLORO-1-PHENYLAZETIDIN-2-ONE

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**ABSTRACT**
Schiff bases synthesis of carbazole derivatives bearing-4-oxazetiding ring were synthesised by the condensation of (Z)-N-((9H-carbazol-6-yl)methylene)benzenamine with 9H-carbazole-3-carbaldehyde this reaction was subjected in schiffs bases reaction .The structurer of these newly synthesis compounds were characterised by $H^1$ NMR,$C^{13}$NMR ,Mass ,IR, and elemental analysis.

**KEYWORDS;-** Azetidinones, Schiff bases, β- Lactam,

## INDRODUCTION

Heterocyclic compounds represents an important class of biological molecules.The hetero cyclic molecules which posses carbazole, azetidine moieties exhibit wide range of biological activities. Carbazole are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process. carbazole ring constitutes an important basic skelton and development of the drug.The classical carbazole drugs .

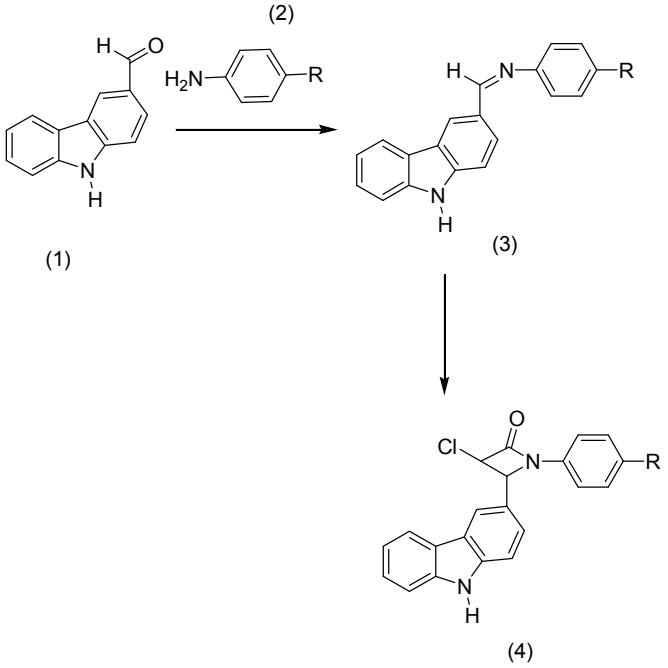
Carbazole derivatives found to posses high spectrum of biological activities which includes antibacterial [1,2]analgesic[1],antipyretic[2],antifungal[3],antiflamatory [4,8]anthelmintic [7],cardiovascular[ 8] ,anticonvalsant[9],and selective COX-2 inhibitary activities[13,16],anticonvalsant[9],and selective COX-2 inhibitary activities [13,16]

The chemistry of carbazole and its derivatives were found to play an important role in medicinal chemistry herbicidal [10], fungicidal [11], bactericidal [12], anti-inflammatory [13], antipyretic [14] antiviral [15], bloodpressure [16] lowering [10]and protease inhibitors [17 ]agents.

Azetidine skleton was found in β-lactam antibiotics, which were the most widely employed class of antibiotics. Azetidine derivatives were reported to show a variety of antimicrobial ,antitubercular, anticonvulsant, antitlammatory [17,18,22]and car diovascular activities. In view of above observations found in literature, we have reported an efficient synthesis for indole derivatives containing pyrazolone moiety besides β-lactamring .

## MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus .T.L.C. analysis were performed on precoated silicagel (E-Merck Kieselgel 60 $F_{254}$) plates and visualisation was done by exposing to iodine vapour. Solvent were purified by standard procedures before use. Column chromatography was conducted by using Silica gel with different solvent systems as elutes . IR Spectra were recorded KBr on perkin –elmer spectrum BX series FTIR spectrometer. $H^1$-NMR spectrum were recorded on varian zemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) $C^{13}$NMR spectra were recorded on a brucker 75MHz spectrometer . Mass spectra were scanned on a varian MATCH -7 and jeol JMSD-300 mass spectrometer at 70 ev.elemental analysis were carried out on carloerba 106 and perkin –analyser . All the chemicals used in the present investigation were perchased from Aldrich chemicals ;U.S.A. 5-Amino- 8-Hydroxy quinoline was prepared by a reported method [21].




| compound | 4a | 4b | 4c | 4d | 4e | 4f |
|---|---|---|---|---|---|---|
| R | H | $CH_3$ | $OCH_3$ | Br | $NO_2$ | $CF_3$ |

**Synthesis of (Z)-N-((9H-carbazol-6-yl)methylene)benzenamine (3)**

Equimolar quantity of aniline(3) and 9H-carbazole-3-carbaldehyde were dissolved in absolute alcohol, to this three drops of acetic acid is added then heated on a steam bath for 5-6hrs at $100^0$C. After standing for 24hrs at room temperature, the product was dried and recrystalised from warm absolute alcohol. The separated solid was identified as ethyl 2-(-3-(((-4-nitro phenyl)imino)me thyl)-1H-indol-1-yl)acetate. Yield 75%,m.p.:154-$156^0$C

**IR Spectra (√, $cm^{-1}$):**

IR (KBr) spectrum of 9H-carbazole-3-carbaldehyde 1(a)was recorded in the range 4000-667$cm^{-1}$ and IR absorption signals were found at 3032 (√ Ar-H), 2980 and 2960 (√ aliphatic $CH_2$ and $CH_3$), 1760 (√ CO of ester group), 1610(√ C=N group) and 1182(√ C-O-C of ester group).

**$^{1}$ H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ;**

$^{1}$H NMRSpectra (Z)-N-((9H-carbazol-6-yl)methylene)benzenamine was recorded in DMSO-d6 solvent. The NMR signal of (Z)-N-((9H-carbazol-6-yl)methylene)benzenamine was found at $\delta_{PPm,}$ 1.29(t,3H, J=13.2Hz, $CH_3$ of ethyl group), 4.13 (q, 2H, J=13.2Hz, $CH_2$ of ethyl group), 4.78(s, 2H, N-$CH_2$ group) and 6.92 , 7.58 (m, 10H, $C_8H_5N$ indole nucleus and $C_6H_5$ phenyl nucleus) and 8.44(s, 1H, N=CH group).

The compound (A) was converted into azetidine-2-one on treatement with chloro acetyl chloride. The formation compound was conformed by IR,NMR data.

NMR spectra ;1.29(t,3H,$CH_3$ of $C_2H_5$), 4.78(s,2H N-$CH_2$-C =O), 4.13(q,2H,-O-$CH_2$ Of $OC_2H_5$), 6.92-7.58(m,10H,Ar-H,8.44(N=CH).

IR spedtra ; The compound (A) shows signals at, 1610(C=N), 1760 (ester –C=O), 3032(Ar-H),1182(-C-O-C).

$^{1}$HNMR spectra ;1.29(t,3H,$CH_3$ of $C_2H_5$), 4.78(s,2H N-$CH_2$-C =O), 4.13(q,2H,-O-$CH_2$ Of $OC_2H_5$), 6.92-7.58(m,10H,Ar-H,8.44(N=CH ).Table: 2.2 1H NMR spectra of ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate (A)

**Synthesis of 4-(9H-carbazol-6-yl)-3-chloro-1-phenylazetidin-2-one 4(a)**

Equimolar quantities of (Z)-N-((9H-carbazol-6-yl)methylene)benzenamine was converted into azetidine - 2-one on treatment with chloro acetyl chloride Yield 75%,m.p.:155-150$^0$C. This general procedure was extended to substituted cabazoles to synthesis azetidin -2-one derivative 5(a-f) the structure of 1 (a-f ) were established by IR and H$^1$ NMR data

**$^{1}$ H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:-**

4-(9H-carbazol-6-yl)-3-chloro-1-phenylazetidin-2-one 4(a)

show signals 1.30 (t,3H,$CH_3$ of $C_2H_5$), 4.75 (s,2H N-$CH_2$-C =O), 4.15 (q,2H,-O-$CH_2$ Of $OC_2H_5$), 5.16(d,1H,-CH of azetidine attached to phenyl ring), 5.44(d,1H,-CH of azetidine attached to -Cl), 6.94-7.59 (m,10H,Ar-H). IR(KBr) spedtra ; The compound 1(a) shows signals at, 1578(C=N),1177(-C-O-C-),1765(-C=O),826(CCl) are due to strectching vibrations of –C=O , C=N,C-O-C , CCl respectively . *Anal.*Cacld. for (382);C,67.02;H,5.05;N,7.44 found(%);C:65.88,H:5.00,N:7.32

## PHARMACOLOGICAL STUDIES:

All the newly synthesized compounds **1(a-f),2(a-f),4(a-f)** were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities by using student's t test. These compounds were screened for their anti-inflammatory and analgesic activities at a dose of 50 mg/kg p.o.exhibited substantive anti-inflammatory activity of varying degree from 9.3-30.1% and analgesic activity evolution varying degree 6.4-33.0% are given in(Table -1).

The characteristic feature of this series is the substituents by the substituted phenyl at presence of moiety at second position of indole nucleus. It was obsereved that compound **4(e)**showed maximum anti-inflammatory 30.1% inhibition of oedema and analgesic 33.0% activities. This compound showed better anti-inflammatory activity and equipotent analgesic activity than standard drug phenyl butazone at the dose of 25, 50 and 100 mg/kg p.o.

## CONCLUSION:

**1.** Further more the substitution with phenyl group having a chloro group at p-position showed better activities than other group.

**2.** The azetidinones showed better anti-inflammatory and analgesic activities.

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## .PHARMACOLOGICAL EVOLUTION:

The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70 to 95 days weighing 120 to175 g. Acute toxicity was tested

in albino mice (15-25g). Food (chaw pallet) and water was given to the animals ad libitum. The compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

**Anti-inflammatory activity**

This study was done by following the procedure of Winter et al[22]. The rats were divided into three groups(control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1hr before the carrageenan injection. The paw volume of each rat was measured before 1 hr and after 3 hr of carrageenan treatment with the help of a Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below.

Percentage of inhibition of oedema = (1-Vt/Vc) ×100

Where Vt and Vc are the volume of oedema in drug,treated and control group, respectively.

**Analgesic activity**

Acetic acid writhing test was performed on mice by following the method of Davis at el [23]. Test compounds were given to the animals at the dose of 50mg/kg, 30 min later the animals were injected interperitoneally with 0.25 mL /mouse of 0.5% acetic acid.The mean number of writhes for each experimental groups and percentage decrease compared with the control group was calculated after 60 min.

**Ulcerogenic activity**

Ulcerogenic liabilities of newly synthesized compounds were checked by the method of Verma atel[24].. Albino rats were fasted for 24 hr prior to drug administration. All animals were sacrificed 8hr after drug treatment and then their stomachs and small intestines were microscopically examined to assess the incidence of hyperaemia, shedding of epithelium, petechial and frank haemorrhages and erosion ordiscrete ulceration with or without perforation. The presence of any one of these criteria was considered tobe an evidence of ulcerogenic activity.

**Acute toxicity**

Acute Lethal dose (ALD50) of all the compounds were investigated by the method of Smith,Q.E. [25]..

## RESULTS AND DISCUSSION

All the newly synthesized compounds **1(a-f),2(a-f),4(a-f)** were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities. These compounds were screened for their anti-inflammatory and analgesic activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 9.3-30.1% and analgesic activity of varying degree 6.4-33.0% are given in **Table 1**.The characteristic feature of this series is substituted phenyl moiety at second position of indole nucleus. It was obsereved that compound **4(e)** showed maximum anti-inflammatory 30.1% inhibition of oedema and inhibition of 33.0% of writhes. This compound showed better anti-inflammatory and analgesic activities than standard drug phenyl butazone at the three gradeddoses of 25, 50 and 100 mg/kg p.o. but showed lesser activity than reference drug indomethacin. Further more the substitution with chloro group at 2nd positionof phenyl ring showed better activities than othergroups. ALD50 of all compounds is > 1000 mg/kg p.o.

**Table- I: Anti inflammatory, analgesic, ulcorogenic and toxicity data of compounds 1(a-f),2(a-f),4(a-f)**

| **Comp. No.** | **Dose (mg/kg p.o.)** | **Anti inflammatory activity % oedema inhibition relative to control.** | **Analgesic activity % decrease of writhes in 60 min after treatment relative to control** | **UD50** | **ALD50** |
|---|---|---|---|---|---|
| 1(a) | 50 | 9.3 | 6.4 | - | >1000 |
| 1(b) | 50 | 9.8 | 6.8 | - | >1000 |
| 1(c) | 50 | 10.2 | 7.2 | - | >1000 |
| 1(d) | 50 | 10.5 | 7.5 | - | >1000 |
| 1(e) | 50 | 11.4 | 8.7 | - | >1000 |
| 1(f) | 50 | 11.6 | 9.8 | - | >1000 |
| 2(a) | 50 | 10.9 | 8.9 | - | >1000 |
| 2(b) | 50 | 11.2 | 9.5 | - | >1000 |
| 2(c) | 50 | 11.5 | 9.8 | - | >1000 |
| 2(d) | 50 | 12.0 | 10.2 | - | >1000 |
| 2(e) | 50 | 12.5 | 10.4 | - | >1000 |
| 2(f) | 50 | 13.6 | 10.8 | - | >1000 |
| 4(a) | 50 | 21.5 | 22.5 | - | >1000 |
| 4(b) | 50 | 24.5 | 24.8 | - | >1000 |
| 4(c) | 50 | 24.1 | 24.1 | - | >1000 |
| 4(d) | 50 | 25.8 | 27.2 | - | >1000 |
| 4(e) | 50 | 30.1 | 33.0 | - | >1000 |
| 4(f) | 50 | 29.5 | 28.3 | - | >1000 |
| Phenylbutazone | 25<br>50<br>100 | 17.6**<br>36.3***<br>65.6*** | 18.4*<br>34.1***<br>68.8 *** | 65.46 | |
| Indomethacin | 5<br>7.5<br>10 | 52.2<br>63.1<br>93.2 | | | |

*P < 0.05, **P < 0.01, ***P < 0.001.

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