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Studies on Anti-Inflammatory Behaviour of Chalconyl, Isoxazolinyl and Pyrazolinyl 1,2,3,4-Tetrahydrocarbazoles

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Abstract: The compounds Isoxazolinyl and Pyrazolinyl-1, 2, 3, 4-tetrahydrocarbazoles were individually prepared by usingChalconyl-1, 2, 3, 4-tetrahydrocarbazoleswithcondensationof hydroxylamine hydrate and hydrazine hydrate respectively. All titled compounds were evaluated against anti-inflammatory activities by using carrageenan induced edema model in rats.

Keywords: Anti-Inflammatory, Chalconyl, Isoxazolinyl and Pyrazolinyl 1,2,3,4-Tetrahydro carbazoles.

Introduction

The initial discovery of carbazole in the anthracene fraction of coal [1] tar followed by the first isolation of the antimicrobial murrayanine from the plant *Murraya koenigiispreng*, [2] started the enormous development of carbazole chemistry. Since, then there has been a strong interest in this area by chemists and biologists associated with many carbazole alkaloids. Several reports have been appeared on the syntheses of carbazole derivatives in connection with the search for newer physiologically active compounds. A large number of carbazole alkaloids have been isolated from *Rutaceae* family [3] are accomplished diversified pharmacological activities. The carbazole based compounds hyellazoles [4] and carbazomycins have been isolated from two completely non-related biological systems [5], a blue green alga of *Hyellacaespitosa* and an actinomycete *Streptoverticillium ehimense* respectively are found to be useful antibacterial, antifungal and antibiotic agents [6].

The fused heterocycles with the carbazole skeletons are also accomplished for their biological activities. The sclerotic of *Aspergillus tubingensis* contains two carbazoles with completely different structures namely; tubingensin A and tubingensin B have also been reported antiviral and cytotoxic [7] activities respectively. The anti-inflammatory activity of Caprofen found to inhibit the neutrophile macrophage function. The Nincazole[8] have been reported that the novel neuroleptic and antipyretic agents. Etodolaca class of drugs called non-steroidal anti-inflammatory drugs (NSAID). Etodolac blocks the enzyme that makes prostaglandins (cyloxygenase), resulting in lower concentration of prostaglandins. As consequences of the activity of the drug inflammation pain and fever are reduced. Other members of this class include ibuprofen, naproxen, indomethain and nubumetone are used for the management of mild to moderate pain, fever and inflammation [9].

Pyrazoline moieties occupy a special place in the field of nitrogen heterocycles, many of which possess wide-spread pharmacological properties such as antibacterial [10], antitumor and analgesic activities [11]. They are also well known for their pronounced anti-inflammatory activity [12]. Natural products containing pyrazole and pyrazoline rings are rare. It seems that the evolution of organisms has produced few enzymes which cause the formation of an N-N bond. However, many synthetically produced pyrazoles are biologically active [13]. Some of them used as Pharmaceuticals [14]e.g. the analgesic, anti-inflammatory and anti-pyretic. Ondansetron is a compound of 1,2,3,4-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)-methyl]-4H- carbazol-4-one.

It is the active ingredient of FDA approved antiemetic drugs that are indicated for treatment of nausea and vomiting associated with some cancer chemotherapy and radiotherapy and for the prevention of postoperative nausea and/or vomiting [15].

The aforesaid illustrations are inferred that the carbazole skeleton with extended heterocyclic ring system or governed by terpene appendage or simple substitutions at 1or 2 or 3or 4 portions are found to be an excellent pharmacological activity. It is decided to incorporate the pyrazoline and isoxazoline moieties in to 1,2,3,4-tetrahydrocarbazoles and to evaluate their anti-inflammatory activities.

Experiments

A)Synthesis of chalonoyl, pyrazolinyl and isoxazolinyl 1,2,3,4- tetrahydro-carbazoles

Synthesis of chalconyl-1,2,3,4- Tetrahydrocarbazols1(a-e)

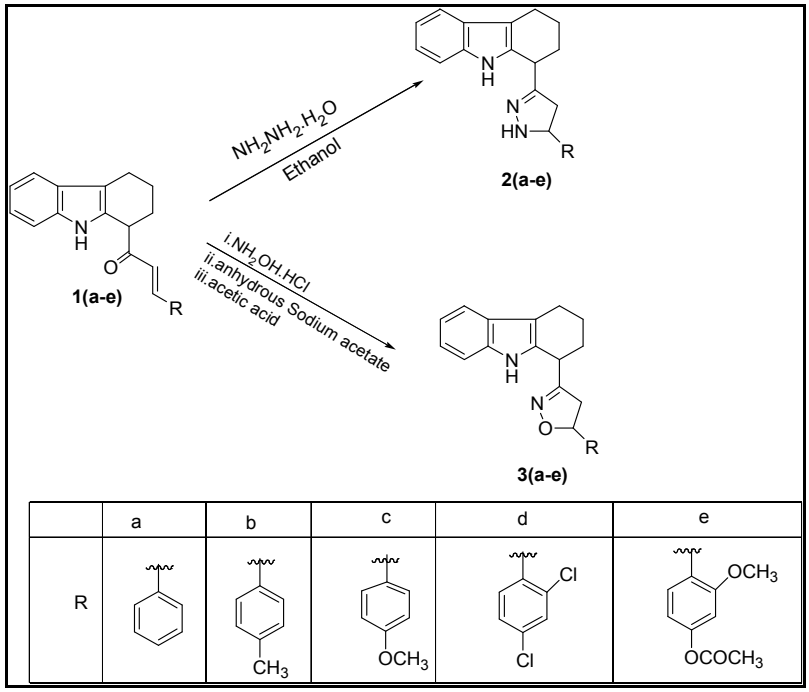
The compounds 1, 2, 3, 4-tetrahydrocarbazolyl-1-chalcones**1(a-e)** were derived by aldol condensation of 1-acetyl-1, 2, 3, 4-tetrahydrocarbazole with appropriate aldehydes using base as catalyst [16].

General procedure for the syntheses of pyrazolinyl-1,2,3,4-tetrahydrocarbazoles 2(a-e)

A mixture of appropriate 1,2,3,4-tetrahydrocarbazolyl chalcone**1(a-e)** (0.1mole) (Table 4.8) and hydrazine hydrate (0.5ml, 0.1mole) in ethanol (50ml) was refluxed. After a period of 2 hours, the solvent was removed under reduced pressure and the residue was washed with water and extracted with chloroform and the organic layer were dried over the anhydrous sodium sulphate. Then, the product was recrystallizated from petroleum ether–ethyl acetate yielded the desired compounds **2(a-e).** The characterization of the compounds **2(a-e)** were evaluated by Mass, IR, HNMR spectroscopy studies[17].

General procedure for the Syntheses of isoxazolinyl-1,2,3,4-tetrahydrocarbazoles 3(a-e)

A mixture of appropriate 1,2,3,4-tetrahydrocarbazolyl-chalcone **1(a-e)** (0.1mole) (Table 4.7) in ethanol (50ml) and anhydrous sodium acetate (0.8g, 0.01mole) dissolved in minimum amount of acetic acid was added to a solution of hydroxylamine hydrochloride (0.7 g, 0.1mole). The reaction mixture was refluxed on a water bath for 8 hours, concentrated and neutralized with sodium hydroxide. The product was isolated and recrystallized from ethanol to give compounds **3a-e.**The characterization of the compounds**3(a-e)** are evaluated by Mass, IR, HNMR spectroscopy studies [18].



Scheme.1: Synthesis of Chalconyl, Isoxazolinyl and Pyrazolinyl 1, 2, 3, 4-tetrahydrocarbazoles

B) **Anti-Inflammatory Activities**

The anti-inflammatory activities of the carbazole derivatives were studied by using carrageenan method. Among the many methods used for screening of anti-inflammatory drugs, one of the most commonly used techniques is based on the ability of such molecules to inhibit the edema produced in the hind paw of the rats after the injection of a phlogistic agent. The paw volume was measured by the method of Winter et al [19] using a mercury displacement plethysmograph.

Male Wistar rats with a body weight between 150-200 g were used. Colony inbred Wistar rats were randomly distributed to different groups with 6 animals in each group. The animals were housed in polypropylene cages with paddy husk bedding and kept in a well ventilated room. The study protocol received the approval of Institutional Animal Ethical Committee (IAEC) of CPCSEA.

Edema was induced by injecting 0.1 ml of a 1% solution of carragengeen in saline into the plantar aponeurosis of the left hind paw of the rats. The paw was marked with ink at the level of lateral malleolus and immersed in mercury up to that mark in a plethysmogrph. The carbazole derivatives and the control vehicle (DMF) were administered 60 minute prior to the injection of carrageenan. The volume of the injected paws was measured at 30, 60, 90, 120, 180 and 240 minutes after induction of inflammation using plethysmogrph (Bhatt et al 1977) and the percentage of anti-inflammatory activity was calculated.

Results and Discussion

Thecompounds chalconyl 1(a-e), isoxazolinyl 2(a-e) and pyrazolinyl 3(a-e)-1,2,3,4-tetrahydro cabazoles were screened for their anti-inflammatory activity in carrageenan induced edema model in rats . The anti-inflammatory activities of the compounds chalonyl-1, 2, 3, 4-tetrahydrocarbazoles 1(a-e) over 24 minutes are presented in table-I

Table I. Anti-inflammatory activities of compounds of chalconyl-1,2,3,4-tetrahydro carbazoles

Compound	60 minutes	90 minutes	120 minutes	180 minutes	240 minutes
Indomethacin	1.7±0.04	2.1±0.05	2.45±0.07	2.82±0.03	3.15±0.06
1a	1.62±0.02	1.80±0.05	1.78±0.02	1.74±0.02	1.77±0.01
1b	1.08±0.06	1.23±0.08	1.12±0.02	0.82±0.07	0.78±0.02
1c	1.53±0.02	1.75±0.09	1.90±0.06	1.88±0.03	1.57±0.08
1d	1.21±0.02	1.34±0.06	1.40±0.05	1.36±0.06	1.01±0.04
1e	1.60±0.05	1.75±0.01	1.80±0.05	1.90±0.02	1.96±0.03

Among the five compounds chalconyl-1,2,3,4-tetrahydrocarbazoles**1a-e,** the compound **1b,1c** and **1d** exhibited around 50% anti-inflammatory activity in carageenan induced hind paw edema in rats tested at the dose of 250mg/Kg/P.O. Whereas, the compound **11a** and **11e** showed their activity 42 and 38% respectively Shown in fig.1.

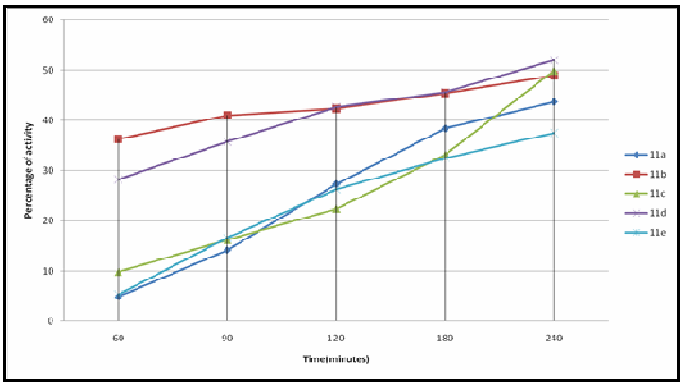


Fig.1.Anti-inflamatory activities of Chalconyl-1,2,3,4-terahydrocarbazoles

In the compounds of isoxazolinyl-1,2,3,4-tetrahydrocarbazoles**2a-e,** the compound **2a** and **2d** showed maximum inhibition of edema volume was observed 62 and 60 % respectively and it is presented in table-II.

Table II .Anti-inflammatory activities of compounds isoxazolinyl- 1,2,3,4-tertahydro carbazoles-

Compound	60 minutes	90 minutes	120 minutes	180 minutes	240 minutes
Indomethacin	1.7±0.04	2.1±0.05	2.45±0.07	2.82±0.03	3.15±0.06
2a	1.10±0.02	1.25±0.06	1.17±0.03	0.88±0.04	0.84±0.02
2b	1.54±0.05	1.69±0.06	1.83±0.03	1.90±0.08	1.78±0.02
2c	1.50±0.04	1.67±0.01	1.64±0.02	1.62±0.01	1.63±0.01
2d	1.45±0.08	1.42±0.06	1.22±0.03	1.00±0.04	0.93±0.1
2e	1.55±0.01	1.67±0.06	1.75±0.05	1.78±0.07	1.88±0.05

The anti-inflammatory activities of the other compounds 2b, 2c and 2e exhibited around 45, 40 and 48% respectively in carageenan induced hind paw edema in rats tested as described in the previous oral doses.

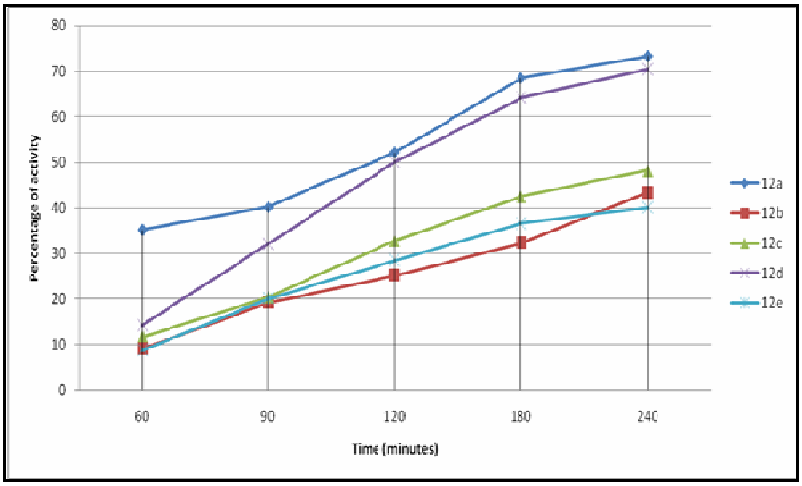


Fig.2.Anti-inflamatory activities of Isoxazolinyl-1,2,3,4-terahydrocarbazoles

Among the five compounds of 1,2,3,4-tetrahydrocarbazolyl-pyrazolines **3a-e,** the compounds**3a** and **3d** showed the excellent inhibition of edema volume 64 and 72 % respectively and the results were presented in table-III.

Table III.Anti-inflammatory activities of compounds pyrazolinyl-1,2,3,4- tetrahydrocarbazoles

Compound	60 minutes	90 minutes	120 minutes	180 minutes	240 minutes
Indomethacin	1.7± 0.04	2.1±0.05	2.45±0.07	2.82±0.03	3.15±0.06
13a	1.43±0.01	1.54±0.05	1.67±0.02	1.45±0.04	1.17±0.01
13b	1.50±0.02	1.67±0.01	1.76±0.04	1.80±0.02	1.72±0.06
13c	1.48±0.06	1.61±0.05	1.61±0.07	1.54±0.02	1.56±0.07
13d	1.42±0.03	1.40±0.05	1.19±0.08	0.09±0.03	0.86±0.07
13e	1.53±0.06	1.64±0.04	1.70±0.03	1.74±0.01	1.80±0.05

Whereas, the compounds **3c, 3d&3e** showedmoderate anti-inflammatory activities say50, 44 and 42 % respectively and shown in fig 3.

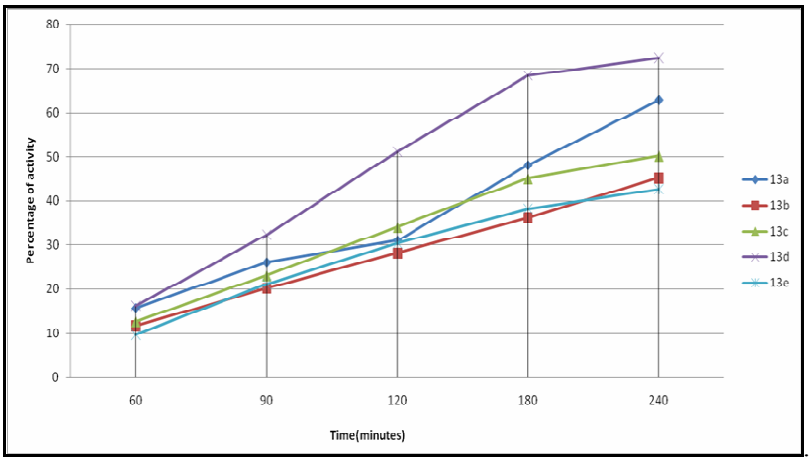


Fig.3.Anti-inflamatory activities of Pyrazolinyl-1, 2, 3, 4-terahydrocarbazoles

Out of the three different derivatives of **1a-e**, **2a-e** and**3a-e**,thepyrazolinyl-1,2,3,4-tetrahydrocarbazolyl **2a** and**3d** are shown excellent anti-inflammatory activity 73 and 72 % respectively. The compounds **1a**, **2b**, **2e** and **3e** showed minimum anti-inflammatory activities.

Conclusions

The Isoxazolinyl, Pyrazolinyl and Chalconyl-1, 2, 3, 4-tetrahydrocarbazoles were screened against anti-inflammatory activities. All most all the compounds fairly response in the anti-inflammatory activates.

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