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Design Synthesis Method Development and Validation of N-Substituted Tetrahydrocarbazoles for Analgesic and Anti-inflammatory Activity

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Abstract

Thrust in the preparation of new heterocyclic molecules is increasing due to their proven significant biological activities. The paramount importance of heterocycles such as indoles and their derivatives in natural product chemistry and pharmacology constantly drives the search for the new procedures for their construction and also for the preparation of variety of their derivatives to exploit their useful biological activities. A tetrahydrocarbazole had been synthesized by reacting cyclohexanones with substituted hydrazine hydrochlorides in the presence of glacial acetic acid to produce N-(1,2,3,4-tetrahydrocarbazole) which later used to synthesize compounds with different heterocyclic new rings containing, sulfur and nitrogen in structures i.e., substituted-N-(1,2,3,4-tetrahydrocarbazole) which were characterized by IR, ^{1}H and ^{13}C NMR spectral studies and these structures were investigated for analgesic and anti inflammatory activity.
Keywords: Cyclisation, phenyl hydrazine, cyclohexanone, Tetrahydrocarbazole.

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1. Introduction

The tetrahydrocarbazole ring system has been the structural subunit of many naturally occurring alkaloids, biologically active molecules and medicinal important synthetic analogues. tetrahydrocarbazoles condensed with indole, furan, pyrimidine, pyrazoline, and thiophene, moieties have been known to processes wide spectrum biological activities. There has been many methods of synthesis .In general the carbazoles synthesis is carried out by multistep Fisher reaction which requires the usage of organic solvents with very meager product yields. Hence a simple and efficient method for the synthesis of these pharmaceutically important class of compounds is highly desirable precluding the usage of organic solvents. Initially Substituted phenyl Hydrazine€s were used to optimize the reaction conditions such as different acids, solvents, and reaction temperature. Among, several Acids were tested, finally we found that glacial acetic acid given excellent yields. In presence of CH_3COOH, $ZnCl_2$ and HCl lesser amount of the desired product was obtained. The effect of solvents was also investigated and the highest yield was observed in glacial acetic acid, When the reaction was conducted at lower temperatures lower yields were obtained. Ideal temperature for the reaction was found to be 90°C. In the presence of electron releasing groups present in the Para position of phenyl Hydrazine€s observed more yield comparatively presence of electron

withdrawing groups. To the best of our knowledge this is a first report for the efficient and economic synthesis of carbazoles using readily available laboratory reagents with short reaction times.

2. Materials and methods

Melting points were taken in open capillaries and are uncorrected. FTIR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer as KBr disc. The 1H-NMR and 13C-NMR spectra were recorded on a make Bruker model ultrashield 300MHz NMR at the university of Jordan DMSO-d6 was used as solvent and TMS as internal reference. U.V. spectra were recorded on Shimadzu UV-Vis recorder.

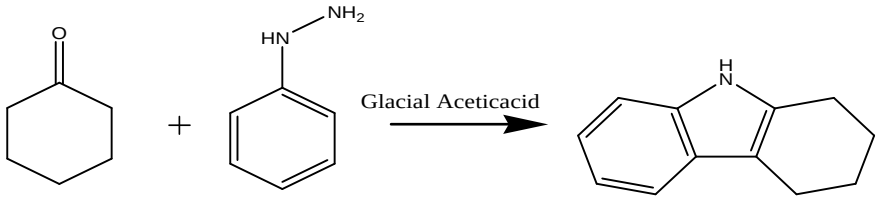
Chemicals:

Cyclohexanone, glacial acetic acid, phenyl hydrazine.

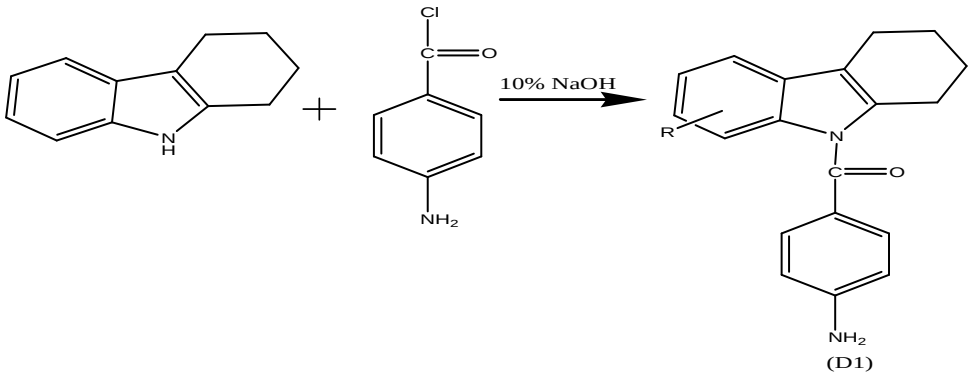
Methodology:

Synthetic scheme:

Step 1: **Preparation of tetrahydrocarbazole:**



Step 2: Synthesis of N (4 €Amino Benzoyl) 1,2,3,4-Tetrhydroacabazole



(D1)

Step I:

Synthesis of 1,2,3,4 tetrahydrocarbazole:

(The Fischer•s indolisation reaction)

The Fischer indolisation reaction occurs when the phenyl hydrazones of a suitable aldehyde or ketone undergoes Cyclisation with loss of ammonia, under the influence of various reagents, such as zinc chloride, ethanolic hydrogen chloride or acetic acid.

Experimental Procedure:

Dissolve calculated quantity of cyclohexanone (9.8 gm,0.1mol) in (34.65 gm,0.6 mol) of glacial acetic acid, add calculated . (10.8 gm,0.1mol) of phenyl hydrazine and boiled the solution under reflux for 10 minutes. Cooled the solution, where the tetrahydrocarbazoles was crystallized out, filtered at the pump, drained well and recrystallise from aqueous ethanol. The recrystallized was performed rapidly, since tetrahydrocarbazoles under goes atmospheric oxidation in hot solution. which has melting point of 146^0c. The purity of the compound was confirmed by melting point, TLC and IR Spectroscopy.

Step II:

1,2,3,4-Tetrahydrocarbazole (1 gm,5.78 m.mol) was added to 10% NaOH solution in a well cooled conical flask and then add 2ml of acid chloride, with constant shaking and cooled in water Shaken vigorously for 10 minutes until the odour of the benzoyl chloride was disappeared filtered off the solid N-substituted derivative, washed with a little cold water and recrystallise it from ethanol.

Characterization

The synthesized compounds were purified by recrystallisation. and conformation by M.P&TLC will be subjected to elemental analysis, spectral characterization, U.V-visible, IR-spectroscopy and NMR spectroscopy if necessary will be recorded and conformation of synthesized compound will be established.

Evaluation of analgesic activity

The analgesic activity of the synthesized compounds was evaluated by tail flick method. Wistar rats (n=6) were grouped by random sampling technique for the study. Diclofenac sodium at the dose of 10 mg/kg (p.o.) ** was administered as standard drug for comparison. The test compounds were administered by the oral routes at the dose level of 200 mg/kg b.w. The rats were hold in position by a proper restrainer with the tail extending out and the tail (up to 6 cm) was taken and dipped in a beaker. In that beaker water should be maintained at 56 ± 4^0C. The time in sec taken by the rats to withdraw their tail completely out of water was taken these are the reaction time. The observation was carried out at 0, 90, 120,180 min after the administration of our synthesized compounds. A cut off point of 15 sec was observed to avoid the tail damage. The percentage analgesic activity was easily calculated by the below mentioned formula.

PAA = [(B-A)/B] X 100%

B - Reaction time in sec after treatment

A -Reaction time in sec before treatment

PAA - Percentage analgesic activity.

Table I: Analgesic activity of the synthesized compounds at (100 mg/kg b.w.)

Compounds	Dose (mg/kg)	0 min	90 min		120 min		180 min	
		MEAN +SEM	MEAN +SEM	%	MEAN +SEM	%	MEAN +SEM	%
D1	100	2.66±0.21	5.83±0.70***	50.94	7.26±0.63***	60.60	7.00±0.44***	59.14
Diclofenac sodium	10	2.66±0.21	7.50±0.42***	64.53	10.33±0.98***	74.24	9.50±0.42***	72.00

*Significant differences with respect to control was evaluated by (ANOVA), Dunnet€st test ***P<0.001, ns (non significant), % (analgesic activity)*

Evaluation of Anti-inflammatory activity

Evaluation of anti-inflammatory activity was carried out by Carrageenan induced hind paw edema in rats .The animals were randomly divided into groups of 6 animals and were fasted for 24 hours before the experiment. The control group received only 0.5% carboxy methyl cellulose solution. Diclofenac sodium (13.5 mg/kg) was administered intra peritoneally as standard drug for comparison. The synthesized compounds were administered at two dose levels (100 and 200 mg/kg). Carrageenan solution 0.1 ml (1% in sterile 0.9% NaCl solution) were injected subcutaneously into the sub planter region of the right hind paw of each rat,1 hour before administration of the standard and test drugs. The right hind paw volumes were measured before and after 120, 180 and 240 min after administration with the aid of plethysmometer. The percentage of edema inhibition was calculated from the mean effect in the control and treated animals according the following equation.

Percent edema inhibition = **(VC-Vt / Vc) x 100**

Vt = Mean increase in the paw volume in rats tested with test compound.

$\mathbf{V_C}$ **=** Mean increase in the paw volume in control group of rats.

Table II: Anti-Inflammatory Activity of Synthesized Compounds (100mg/kg b.w.)

Compounds	Dose (mg/kg)	120 min		180 min		240 min	
		MEAN +SEM	%	MEAN +SEM	%	MEAN +SEM	%
D1	100	0.520 ± 0.011***	21.92	0.311 ± 0.017***	54.12	0.413 ± 0.016***	39.08
Diclofenac Sodium	13.5	0.325 ± 0.024***	51.12	0.220 ± 0.013***	67.55	0.260 ± 0.015***	61.65

*Significant differences with respect to control was evaluated by (ANOVA), Dunnet€st test ,***P<0.001, ns (non significant), % (percentage reduction of edema)*

3. Results and Discussion

Preliminary studies have been performed in the proposed project and few compounds are synthesized. They have been purified and characterized by spectral method and the synthesized compounds have significant analgesic anti-inflammatory activity new structure shall be proposed, synthesized, characterized and subjected to pharmacological studies conclusion will be drawn, accordingly.

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