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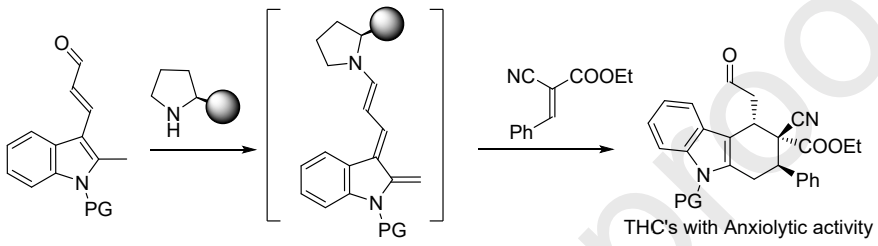

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Enantioselective synthesis of tetrahydrocarbazoles via trienamine catalysis and their anxiolytic-like activity.

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ABSTRACT

The first study about the anxiolytic activity of two chiral tetrahydrocarbazoles is presented. This new chiral compounds were prepared through an organocatalytic strategy via trienamine activation. The *in situ ortho*-quinodimethane species, formed by the condensation of the *N*-protected 2-methylindole acrylaldehyde with a sterically hindred diarylsilylprolinol ether derivative as catalyst, easily participate in a Diels–Alder reaction with the ethyl cyanophenyl acrylate as dienophile, in good yields and excellent stereoselectivity. These compounds showed activity against anxiety and mood disorders that can possibly contribute in the discovery of new drugs. In addition, the use of *N*-protected 2-methylindole acrylaldehyde will set a new base for the synthesis of medically and pharmacologically important tetrahydrocarbazoles via trienamine catalysis.

Chiral tetrahydrocarbazoles (THC's) are the most widely recognized class of natural indole alkaloids.[1] In the interest of its biological and pharmaceutical development which is consistently encouraging the discovery of new efficient synthetic pathways to establish novel chiral THC framework.[2] It has been observed over the century that the discovery of novel chiral THC's always appears with new extraordinary bioactivities as well as bunch of naturally occurring THC alkaloids are found in ancient medicines.[3] For instance, *Dasycarpidone* **I** and *Uleine* **II** exhibited antiplasmodial activity in vitro against *P. falciparum* and *T. cruzi*.[3a-b] Also, a novel synthetic drug with a THC core, the (*R*)-*Ramatroban* **III**, used in the treatment of allergic rhinitis, asthma and coronary artery disease.[3c-d] In the same way, *Fischambiguine B* **IV** showed inhibitory activity against *M. tuberculosis*.[3e] Nevertheless, some great examples of structurally simple synthetic drugs can explain a potential use of THC core, for example, the 1-ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid **V** was found to be a novel anti-inflammatory agent as well as 6-Chloro-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid **VI** was discovered as clinically active in the treatment of acute gout (Figure 1).[3f]

From the past 20 years, it has been observed that depression, anxiety and mood disorder are the cause of morbidity in the developed nations. Hence, the circumstance call for research for the discovery of new drugs or medicines that possess anxiolytic activity with no toxicity and withdrawal effect.[4] In this era, a number of drugs has been reported with this type of activity, whereas chiral THC alkaloids are pharmacologically important compounds that make worthy to synthesize it and perform biological tests to disclose new activities of these structures.

Consequently, over the past decades, chemists are focusing more towards new methodologies to synthesize known or novel chiral THC frameworks. At the same time, the newly developed trienamine catalysis strategy has attracted considerable attention for the synthesis of chiral privileged structures.[5] In fact, during its conceptualization, a new methodology was developed to synthesize chiral THC´s by using 2-methylindole acrylaldehyde **1** as a masked 2,4-dienal.[6] In this strategy, the condensation of a chiral secondary amine with the acrylaldehyde **1** lead to the formation of a *ortho*-quinodimethane intermediate ***I***, which is an active trienamine species with the ability to react with a variety

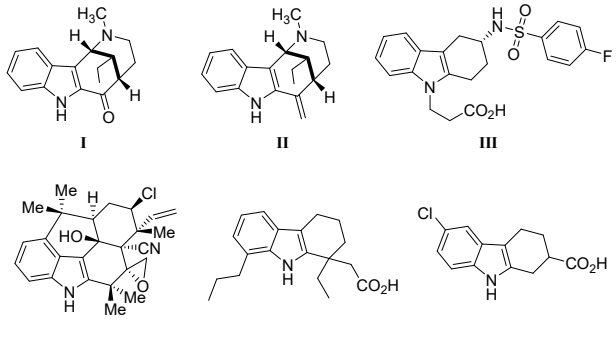
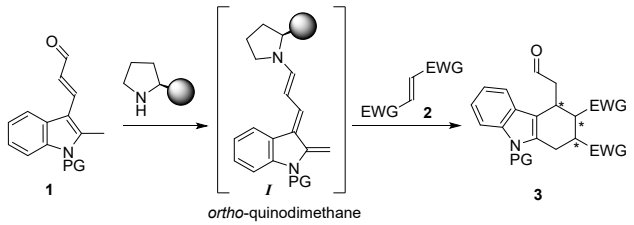


Figure 1. Some examples of THC's that possess potent biological activities

of d ned, (Scheme 1). Recently, many asymmetric transformations have been reported using this strategy along with the modification of previous methodologies but none of the chiral THC was studied before.[7]

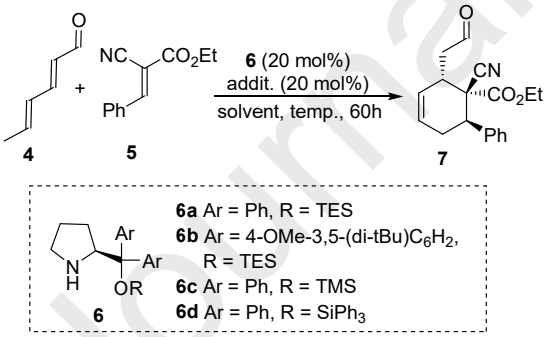
The purpose of this study is to synthesize novel THC's, which can be biologically and pharmacologically important and can be considered as a member of alkaloids. Herein, we report the asymmetric synthesis of two novel THC's efficiently via Diels–Alder cycloaddition reaction. In addition, the resulting THC's turn up with outstanding biological activities, that contribute to the medicinal field.



Scheme 1. The concept of THC synthesis via trienamine catalysis

We started this work by analysing the first report of trienamine strategy by Jørgensen.[8] In this study, the 2,4-dienal **4** condense with chiral amine **6a-b** to form the corresponding trienamine intermediate, which through a Diels–Alder cycloaddition with ethyl cyanophenyl acrylate **5** lead to the expected cyclohexene **7** (Table 1, entries 1 and 2). We initiate our work by improving the previous conditions. Initially, we check the reaction with different solvents, with or without additives and by varying the temperature (r.t. to 70 ºC). By using toluene as solvent and without additive, the reaction response was satisfied at 70 ºC. In the trial of use Jørgensen-Hayashi catalyst **6c**, the stereoselectivity was improved (entry 3). However, to our glad the best results (98% ee and 96:4 dr) were obtained in presence of more sterically hindered catalyst **6d** (entry 4). Thus, we improved the stereoselectivity of the reaction far better than the

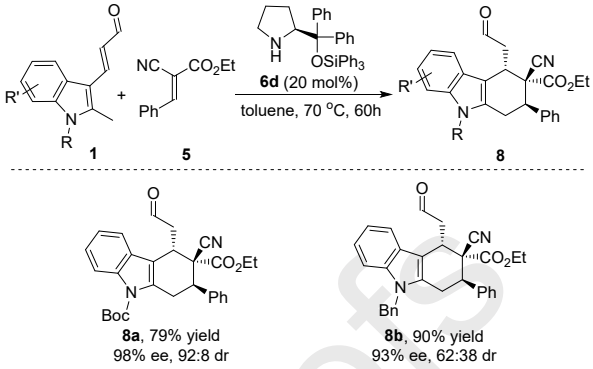
Table 1. Optimization table



Entry	Cat.	T (ºC)	Solvent	Addit	Yield (%)[d]	dr	ee (%)
1[a]	**6a**	50	$CHCl_3$	*o*FBA	81	86:14	89
2[a]	**6b**	50	$CHCl_3$	*o*FBA	87	80:20	86
3[b]	**6c**	70	toluene	-	75	82:18[c]	93[d]
4[b]	**6d**	70	toluene	-	73	96:4[c]	98[d]

[a]Conditions of previous report, [b]reactions were carried out in the scale of 0.1 mmol of dienophile, 0.2 mmol of aldehyde, and 0.02 mmol of catalyst for 60 h. [c]all values were calculated by ^{1}H NMR analysis, [d]detrminated after isolation of the product, by HPLC on a chiral stationary phase.

subsequently same conditions were tried with *N*-protected 2-methyl indole acrylaldehyde **1** along with individual optimization for compound **1** were performed consequently, earlier condition was found to be the best as well (Scheme 2).



Scheme 2. Synthesis novel THC's via trienamine catalysis.

Under the optimized conditions, we synthesized two different THC's **8a** and **8b** with different *N*-protecting groups, Boc and benzyl respectively. On the basis of this result as well as by considering the THC motif, we started performing different biological activity tests on **8a** and **8b**.

The findings showed that these THC molecules, orally administered 1h before the experiment, reduced the anxiety-like behaviour in a dose-dependent fashion in Balb/c mice in the cylinder exploratory test (Fig. 2 A and B), which is commonly used for the screening of drugs with anxiogenic or anxiolytic actions in rodents. The maximal effect shown by these compounds were: 72% (25 mg/kg, **8a)** and 83.4% (25 mg/kg, **8b**). These effects were almost comparable to those found with 1.5 mg/kg CNZ. (Fig. 2 A and B). The values for the effective dose 50 were: 3.3 mg/kg (**8a**) and 7.7 mg/kg (**8b**). Molecules **8a** and **8b** slightly reduced the time on the rotarod in a dose-dependent impairment. However, this effect was not significant compared to the vehicle group (Fig. 2C). Only molecule **8b** (100 mg/kg) significantly ($p<0.05$) reduced the time on rotarod at 60 min-post-treatment. However, this was a partial effect since mice recover their motor coordination 60 min later (Fig. 2D).

Although the anxiolytic-like actions of these two molecules were not comparable to those found with CNZ, these two molecules did not significantly affect motor coordination in mice at doses lower than 25 mg/kg (Fig.2). Pre-treatment with 0.7 bicuculline (an antagonist of GABAA receptor) partially abolished the anxiolytic-like effects of molecules **8a** and **8b**, whereas pre-treatment with ketanserin (a blocker of 5-hydroxytryptamine 2 receptor) or yohimbine (an α2-adrenoceptor blocker) did not change the anxiolytic-like effects of molecules **8a** and **8b** (Fig. 3). These findings suggest the partial participation of the GABAergic system in the anxiolytic-like actions of molecules **8a** and **8b**. However, other studies will confirm this hypothesis.

Our results showed that these THC molecules possess anxiolytic-like activity and can be used as lead compounds in the drug discovery area. In further studies, the anxiolytic-like activity of molecules **8a** and **8b** will be corroborated in other models of anxiety-induced in rodents. Also, the trienamine methodology for the synthesis of THC will set a new base for the organic chemists to contribute to the medicinal field as it is necessary to uncover this kind of chiral THC compounds and their biological activities.

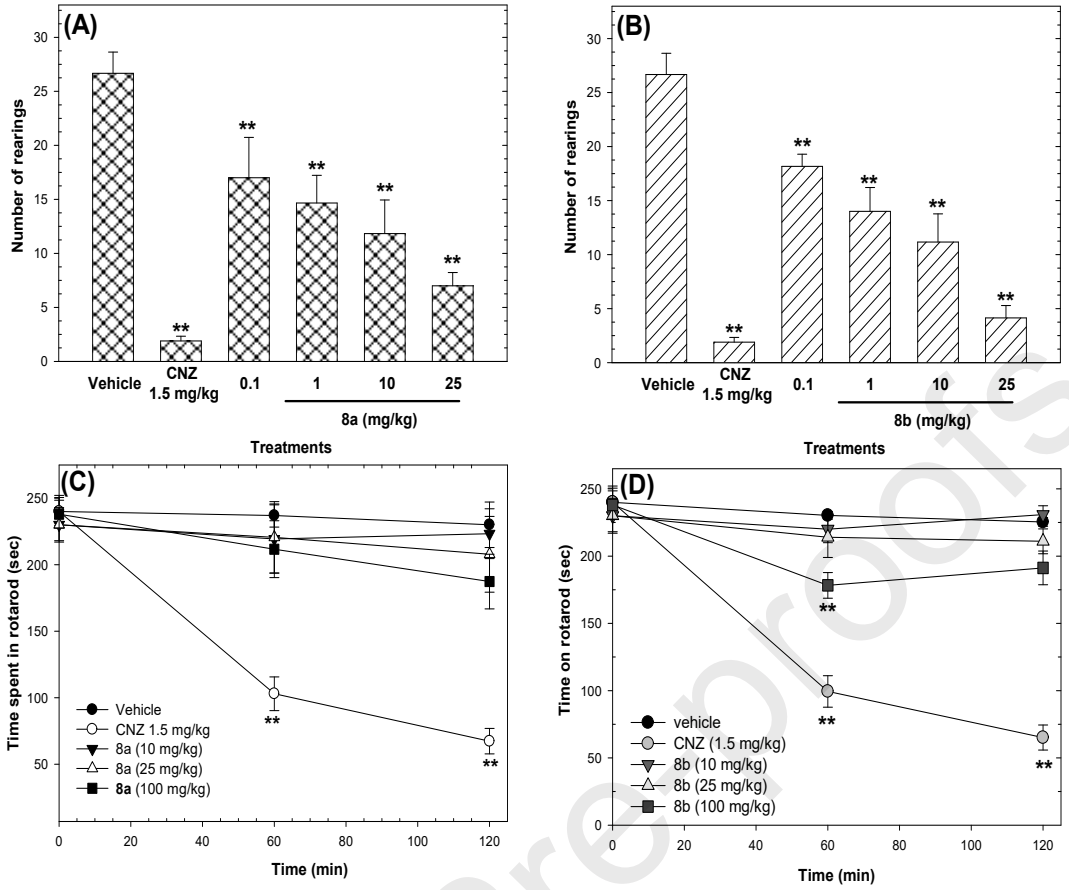


Figure 2. Anxiolytic-like and locomotor effects of molecules **8a** and **8b**. The anxiolytic effects of **8a** and **8b** (0.1–25 mg/kg p.o.) were evaluated using the cylinder exploratory test, recording the number of readings (A and B). The effects of **8a** and **8b** (10-100 mg/kg) on locomotion in mice were evaluated with the rotarod test (C and D). Additional groups were administered with 1.5 mg/kg clonazepam (CNZ) as the positive control or the vehicle (saline solution). Data are demonstrative of two parallel experiments (n = 8). Results represent the mean ± standard error media (SEM). ** represents $p \leq 0.05$ in comparison to the vehicle group, using ANOVA and Dunnett´s *post hoc* test.

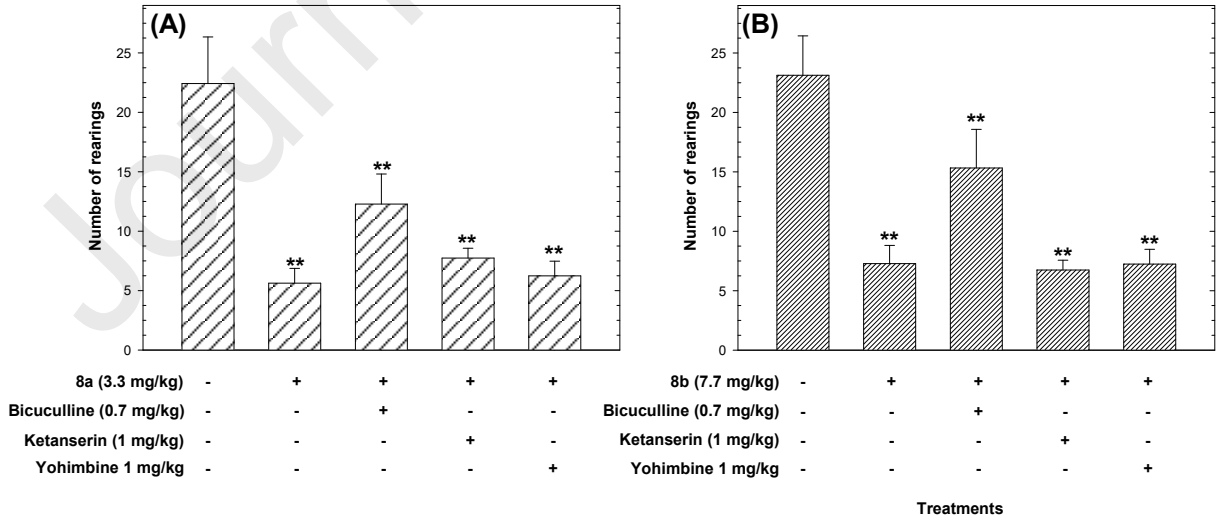


Figure 3. Possible mechanism of action of the Anxiolytic-like effects of molecules **8a** (A) and **8b** (B) in the cylinder exploratory test during 5-min exposure. Bars represent mean values (± SEM) for the experimental group. ** P<0.05, compared to the vehicle group.

Ack

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