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Synthesis and Characterization of Novel Bioactive Molecules from Citral-S Potent Anticancer Drug

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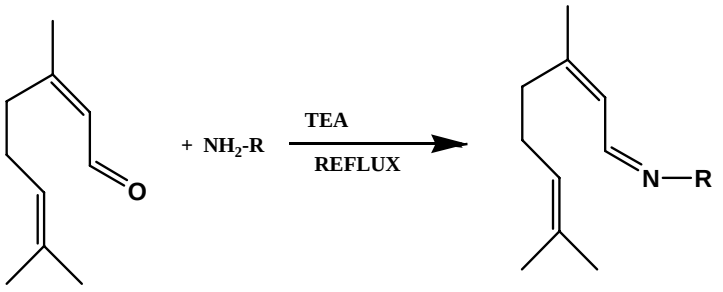
Abstract

Citral, a bioactive compound in Palmrose oil, had proved to possess good activity against microbial organisms. Citral has been shown to-cause apoptosis in cancer cells, in other words, it causes cancer cells to self-destruct. Introduction of active pharmacophores on these kind of small molecules is just a one step forward in the history of medicinal field. Though they are known to have antibacterial effect, their usage is not much taken up in current drug research. Chemical reactions performed on the existing functional group of the lead structure could enhance the utility of this compound. Hence the aldehyde moiety on citral was modified using various amines, both chiral and non chiral to produce the Schiff's base, a potential pharmacophore. The synthetic procedure and NMR data are presented.



Keywords: citral, Schiff base, anticancer drug, pharmacophore.

Introduction

Studies of a new kind of chemotherapeutic Schiff bases are now attracting the attention of biochemists.4, 5. Natural Products were the basis of the first pharmaceutical Practice and they continue to play an important role in modern

chemotherapy. They are the most successful source of drug leads. The global scenario is now changing towards the use of these non-toxic plant products having traditional medicinal use emphasizing the development of modern drugs from natural sources for the control of various diseases. Although herbal medicines in form of crude extracts have been used from time immemorial, modern drugs can be developed after extensive investigation of its bioactivity, mode of action, pharmacotherapecutics, and toxicity and after proper standardization and clinical trials. Citral seem to be a very good synthon for the development of active molecules. Citral, or 3, 7-dimethyl-2, 6-octadienal or lemonal, is either of, or a mixture of, a pair of terpenoids with the molecular formula $C_{10}H_{16}O$. The two compounds are double bond isomers. The *E*-isomer is known as geranial or citral A. The *Z*-isomer is known as neral or citral B.v. Citral was earlier known as an aliphatic aldehyde that is used in perfumery industry. But it is seldom used as a good therapeutic molecule. The U.S.Food and drug administration, vitapurity corporation, 20 may 08, has proved that 1000mg of Lemon Grass contains enough Citral to prompt cancer cells to commit suicide. Hence Lemon grass containing citral may be consumed as a preventative measure against certain cancerous cells. According to Israeli scientists, cancer prevention can be added to the list of attributes associated with Citral.

In the present study, an attempt has been made for the synthesis of novel anticancer compounds from citral.

Materials and Methods

Fresh Citral was purchased, and purified by distillation. The purity was confirmed by GC(Shimadzu GC-7A chromatograph fitted with a flame ionization Detector). Amino acid esters and solvents were purchased from Sigma-Aldrich, Buchhs, Germany and were used as supplied. Thin-layer chromatography (TLC) was performed on 0.25 mm pre coated silica gel 60 F254 aluminum sheets and column chromatography on silica gel 60 (0.063-0.2 mm) as well as silica gel 60 (<0.063 mm), products of Merck & Co. (Darmstadt, Germany). The C^{13} & H^{1}NMR spectra were recorded, with a Bruker (500 MHz) spectrometer, with TMS as internal standard.$CDCl_3$ was used as the solvent. Mass spectrometry was performed in JEOL GC mate in IITM.

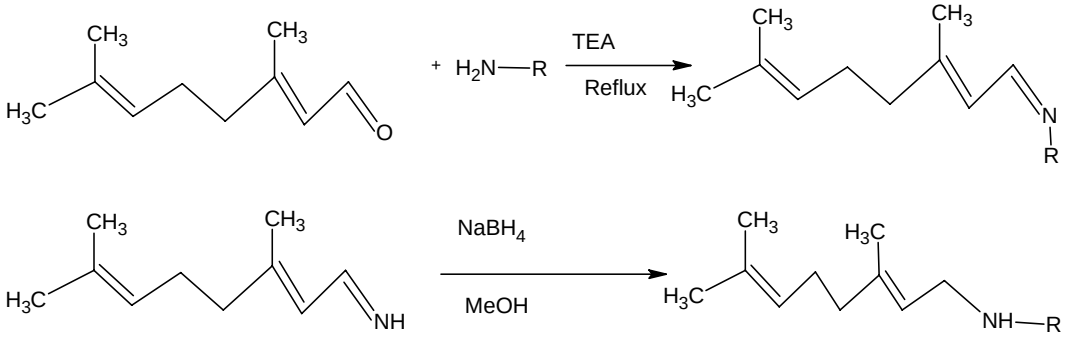
Experimental

Synthesis of azomethine from citral

In a typical procedure, weighed quantities of citral and amines taken in the ratio 1:1 was refluxed in methanol medium with stoichiometric amount of triethyl amine (TEA). The reaction was monitored by TLC ((60/120 mesh, Sigma Aldrich, Germany,). After 6-8 h methanol was distilled off in a rotary evaporator and the residue was subjected to column chromatography. Pure Schiff's base compound was eluted in 8:2 methanol: chloroform mobile phase. The purity and yield of the synthesized Schiff's bases are given in table 1 and Fig 1.

Azomethine was also synthesized using different hydroxyl amines, following the above procedure.

Scheme



R = **CH_3**, **$C_6H_5CH_2$**, **$CH_2CH(CH_3)_2$**, **$CH(CH_3)$ CH_2CH_3**, **CH_2SH**, **$CH_2CH_2SCH_3$**, $CH(CH_3)_2$

Synthesis of amines from azomethine

In a typical procedure, weighed quantities of synthesized Azomethine and sodium borohydride in the ratio of 1:1 was allowed to react under stirring in methanol medium, at room temperature. The reaction was monitored by TLC (60/120 mesh, (Sigma Aldrich, Germany). After 2-3 h, the reaction was quenched with dil.HCl. Methanol was distilled off in a rotary evaporator and the residue was subjected to column chromatography. Pure compound was eluted in 6:4 methanol:chloroform mobile phase. The purity and yield of the synthesized amines are also tabulated.

Fig.1 Structure of azomethine

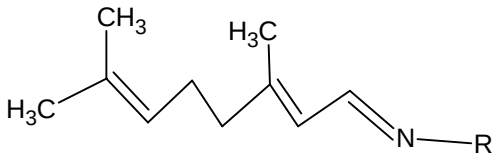
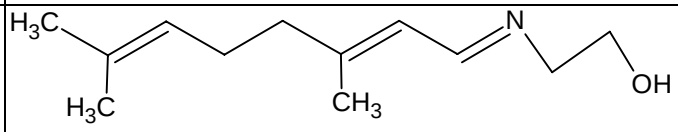
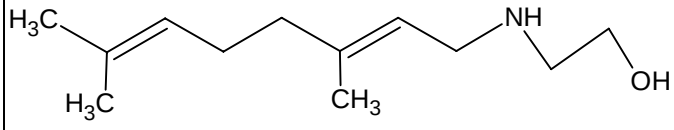
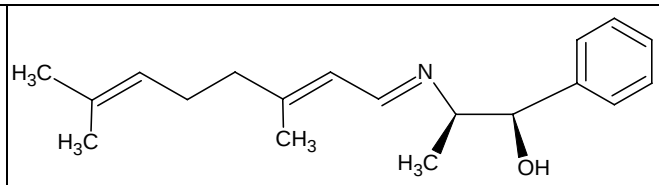
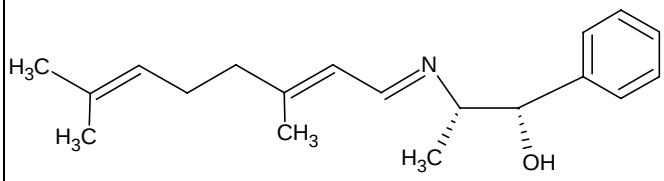
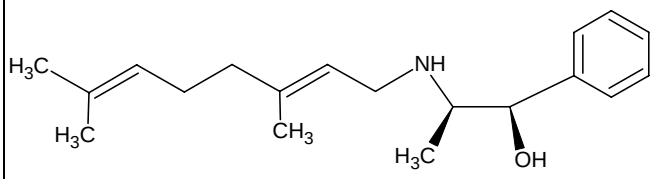
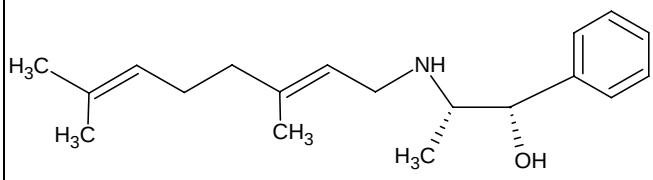
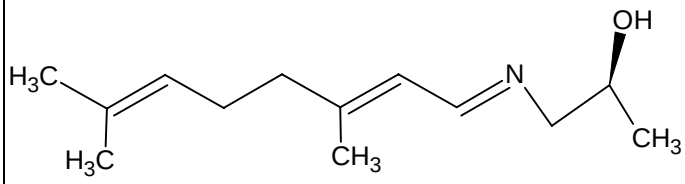
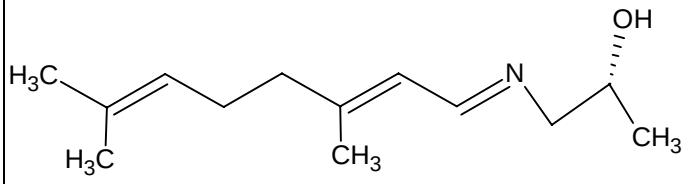
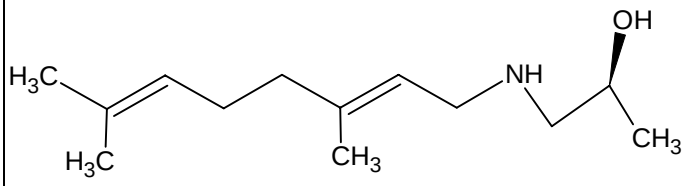
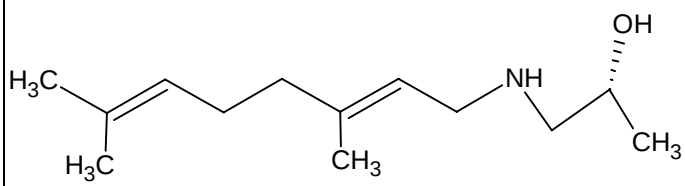


Table 1: Azomethine yield obtained from reaction of citral with different amines.

Compound no	Synthesised Compounds	Azomethine Yield (%)	ee
1a		86	-
2a		89	-

3a		89	77
4a		75	69
5a		67	75
6a		69	79
7a		71	66
8a		66	72
9a		73	67
10a		65	73

Results and Discussion

The Schiff's base obtained by refluxing citral and various amine hydrochloride in the ratio 1:1 was done in methanol medium with stoichiometric amount of triethyl amine (TEA). Various Schiff's base derivatives have been made using different amines. The imine esters further reduced to corresponding amine ester and characterised.The synthesized products include chiral products, and obtained the enantiomeric excess by calculating the specific rotation. All the chiral compounds exhibited more than 50% enantiomeric excess. The important feature observed is that the Schiff bases possess slightly increased activity than the parent citral molecule. This may be due to the fact that citral is already known to have anticancer effect, when coupled with essential amino acids definitely proves to exist as a synthon of pharmaceutical use. This enhanced activity shows promise for application in various antimicrobial treatment.

Supporting data

Compound 1a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 3.59, 2.41, 2.05-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):165.7, 132.6, 129.9, 60.8, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 195.3

Compound 2a: H^1NMR (500MHz, $CDCl_3$) δ (ppm):, 3.19, 2.44, 2.05-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):159.7, 151.2, 132.6, 126.9, 59.8, 61.2, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 196.5

Compound 3a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 3.32, 2.54, 2.15-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm): 152.3, 132.6, 126.9, 60.2, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.4. MS (EI) M+ = 281.1

Compound 4a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 3.32, 2.54, 2.15-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm): 152.3, 132.6, 126.9, 60.2, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.4. MS (EI) M+ = 281.1

Compound 5a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 3.73, 2.54, 2.15-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm): 152.3, 132.6, 126.9, 60.2, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.4. MS (EI) M+ = 282.6

Compound 6a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 3.75, 2.54, 2.15-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm): 152.3, 132.6, 126.9, 60.2, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.4. MS (EI) M+ = 282.8

Compound 7a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.17, 3.63, 2.34, 2.05-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):165.7, 151.3, 132.6, 129.9, 60.8, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 303.1

Compound 8a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.39, 3.19, 2.32, 2.05-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):165.7, 151.3, 132.6, 129.9, 60.8, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 268.9

Compound 9a: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.37, 3.59, 2.44, 2.05-2.04, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):165.7, 151.3, 132.6, 129.9, 60.8, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 265.4

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