



## CONSTITUTION AND SYNTHETIC STUDY OF A FLAVANONE LANNEA ACIDA PIGMENT A

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### **Abstract:**

Constitution of a new flavanone lannea acida pigment A has been confirmed by its synthesis as 7,2' – dimethoxy - 4', 5'-methylenedioxyflavanone ( 1 ). It was further proved by PMR, CMR, UV and other reactions. It utilised 2' – hydroxy -4', 2 –dimethoxy-4,5 – methylenedioxychalcone ( 2 ) as an essential intermediate. Moreover, a new and convenient synthesis of 3,4 –Methylenedioxyphenol (Sesamol) ( 4 ) and its derivatives was carried out which was utilized to synthesise this chalcone( 2 ) which when refluxed with alcoholic sulphuric acid gave this Flavanone ( 1 )

### **Keywords:**

Lannea Acida, Pigment A, 7,2' –dimethoxy - 4',5' –methylenedioxyflavanone ( 1 ), Sesamol

### **Introduction**

A new pigment Lannea acida A was isolated from the leaves of the plant *Lannea acida*<sup>(1)</sup>. This compound on the basis of its spectral data was proposed its constitution as 7,2' –dimethoxy - 4',5' –methylenedioxyflavanone ( 1 ). This is a flavanone compound. The basic unit is 2,3 –dihydro Benzo -  $\gamma$  -pyrone. This is a class of oxy-heterocyclic compound. This communication reports the synthesis of 7,2' –dimethoxy - 4',5' methylenedioxyflavanone ( 1 ). It also reports a convenient and new synthesis of 3,4 –Methylenedioxyphenol (Sesamol) ( 4 ) and its derivatives as important intermediate needed to synthesise the Flavanone ( 1 ).

During the course of the present work the synthesis of 3,4 –Methylenedioxyphenol (Sesamol) ( 4 ) was accomplished using 3,4 –Methylenedioxybenzaldehyde ( piperonal ) ( 3 ) . It was subjected to Baeyer Villiger oxidation using performic acid<sup>(II)</sup> to get 3,4 –

Methylenedioxyphenol (Sesamol) (4). To a well stirred solution of piperonal (3) in dry chloroform at 0°, a solution of performic acid was added dropwise by stirring continuously for 3 hrs. It was then treated with sodium bisulphite. After removing unreacted performic acid, the residue was made alkaline by 10% potassium hydroxide and refluxed for 1 hr<sup>(III)</sup>. On acidification gave 3,4-Methylenedioxyphenol (Sesamol) (4) which was further subjected to dry methylation with DMS – acetone<sup>(IV)</sup> as semi solid product 3,4 – Methylenedioxyanisole (5). This when treated with N : N – DMF and phosphorus oxychloride gave 3,4 Methylenedioxy -6-methoxybenzaldehyde (6) as important product<sup>(V)</sup> needed for the present work.

Resacetophenone was synthesized<sup>(VI)</sup> by Hoesch condensation of Resorcinol. The dry and selective methylation of Resacetophenone gave<sup>(VII)</sup> 2-hydroxy-4-methoxyacetophenone (7) which on condensation with 3,4-Methylenedioxy -6-methoxybenzaldehyde (6) in the presence of methanolic potassium hydroxide<sup>(VIII)</sup> gave 2'-hydroxy -4,2'-dimethoxychalcone (2). This chalcone (2) on refluxing<sup>(IX)</sup> with inorganic acid yields 7,2' – dimethoxy - 4',5' –methylenedioxyflavanone (1). This synthesised Flavanone (I) is characterized by following studies :

PMR spectrum<sup>(XV),(XVI)</sup> of this flavanone (I) shows that C-2 proton was coupled with two C-3 protons (in ring C) to get a quartet at  $\delta$  5.32 with coupling constant  $J = 11$  Hz and 5 Hz.

Further, the signal at  $\delta$  2.85 was a double quartet multiplet and found to represent the the two C-3 protons of ring C. This Flavanone has C-7 oxygenated (-OCH<sub>3</sub>) function in ring A. The C-5 proton was highly deshielded by C-4 carbonyl function and it had a signal as doublet at  $\delta$  7.80– 7.90 ( $J = 9$ Hz) indicating that it is ortho coupled with the aromatic protons at C-6 position of the molecule. C-6 proton was ortho coupled with C-5 and meta coupled with C-8 proton to get a multiplet at  $\delta$  6.30 - 6.50 ( $J = 2.5$  Hz).

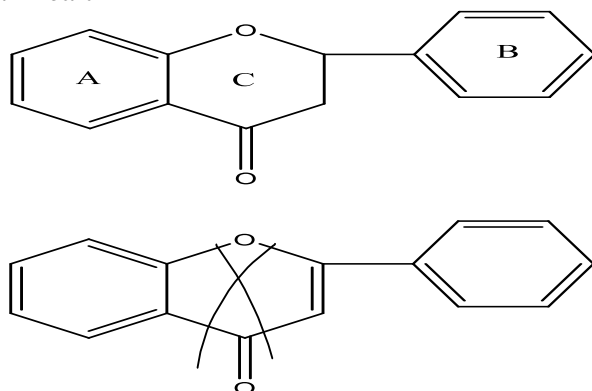
CMR - Carbon 13 magnetic resonance spectroscopic studies - Carbon 13 has a natural abundance of 1.1% exhibited small<sup>(XX),(XXI)</sup> but very significant paramagnetic properties in a magnetic field. CMR of this flavanone (1) was found to have chemical shift values from C-2 to C-10 and C-1' to C-6' carbon atoms. The observed values were found to be comparable to the calculated values.

In UV spectral studies, the oxy heterocyclic ring C of flavonoids had two Chromophores : Ring A as benzoyl chromophore and ring B as cinnamoyl chromophore<sup>(XVII),(XVIII),(XIX)</sup>. The benzoyl chromophore had absorption maxima in the low intensity range 240-285 nm (Band -II) whereas the cinnamoyl chromophore had absorption Maxima in the high intensity band range 300-400 nm (Band -II). However in case of flavanones, the double bond between C-2 and C-3 position was absent thereby the absorption maxima peak for the band (I) did not have any characteristic absorption maxima peak. Therefore the diagnostic reagent could not be employed to locate hydroxyl function in ring B. But they are very useful in locating oxygen function in the ring A of the flavanone (1). Due to oxygen function (-OCH<sub>3</sub>) at C-7 position in ring A of this Flavanone (I) a bathochromic shift of 15 nm with MeOH +NaOAc was observed. However, the precursor of this flavanone i.e the chalcone (2) shows both the band -I and -II UV absorption peaks. In Chalcone (2), a bathochromic shift of 15 nm was observed in Band -II (in MeOH +NaOAc shift Reagent) due to C-4' Oxygenated function & 25 nm in Band -I (in MeOH + NaOAc +H<sub>3</sub>BO<sub>3</sub>) due to 4', 5' oxygenated pattern (ortho dihydroxy type of oxygen function).

The Flavanone (1) on alkaline degradation gave 3,4 -Methylenedioxy -6-methoxybenzaldehyde (6) and its benzoic acid.

Methylenedioxy function is proved as the compound liberates formaldehyde when treated with Sulphuric acid. Secondly a highly deshielded proton shift value for methylenedioxy function is observed.

Flavanones have the basic 2,3 dihydro flavone in the flavonoids C<sub>6</sub> - C<sub>3</sub> -C<sub>6</sub> structure and lack the double bond between C<sub>2</sub> and C<sub>3</sub>, this makes them chiral at C<sub>2</sub> position. The chirality implies the B ring is twisted relative to the A -C rings and is not planar like the conjugated flavones. Such a difference in molecular orientation is highly relevant because it may impact on how the flavonoids interact with biological receptors and thus their bioactive properties. They are intermediates in the flavonoid biosynthesis pathway. They are quite beneficial to the human health



Benzoyl (C<sub>7</sub> System )  
Band II (240-285 nm )

Cinnamoyl (C<sub>9</sub> System )  
Band I (300-400 nm )

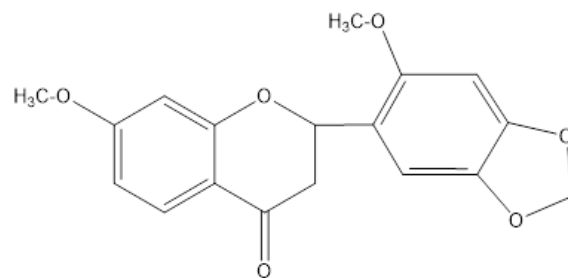
difference in molecular orientation is highly relevant because it may impact on how the flavonoids interact with biological receptors and thus their bioactive properties . They are intermediates in the flavonoid biosynthesis pathway . They are quite beneficial to the human health . For example

naringenin in grapefruit flavanone like Eriodictyl and naringenin are present in mature cereal grains example Sorghum

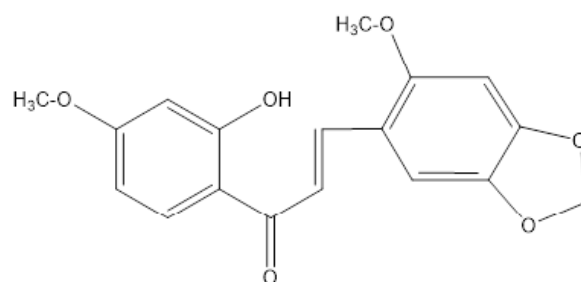
Flavanones are found to possess their excellent inhibitory action over the cyclo oxygenase 2 and act as a potential anti-inflammatory agent <sup>(X)</sup>.

Licoflavanone ,Pinocembrin and Glabranin <sup>(XI)</sup> obtained from Glycyrrhiza glabra L ( Licoric ) leaf extract has the best antioxidant and anti inflammatory activity. The flavanone naringenin present in citrus fruits is found to have anti zika virus and antitumoral activity <sup>(XIII)</sup> . Citrus Flavanones <sup>(XII)</sup> like Hesperidin and Naringin besides having antioxidative and anti-inflammatory effect play an important role in gastro intestinal health. They exert beneficial effect on intestinal barrier function and gastro intestinal inflammation.

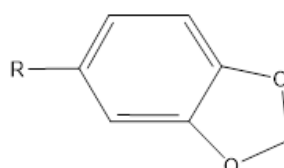
Lannea acida is a widely used herbal medicine <sup>(XIV)</sup> in West Africa. It belongs to the cashew or Anacardiaceae family. Moreover, the tree species is used as source of dye , food , medicine in West Africa.



(1)



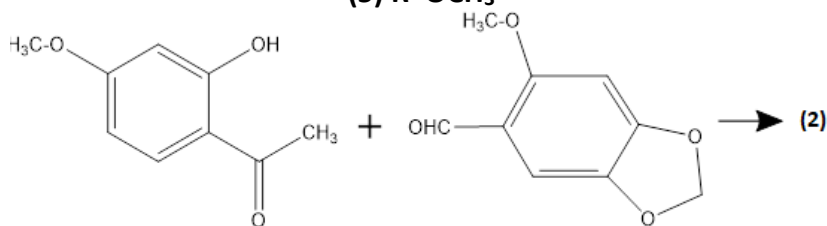
(2)



(3) R=CHO

(4) R=OH

(5) R=OCH<sub>3</sub>



(7)

(6)

(2)

In view of the above very important vital health properties of Flavanones and the Medicinal properties of the plant Lannea Acida, it is essential to synthesise 7,2'- dimethoxy-4',5'- methylene dioxyflavanone (1) also called Lannea acida pigment A

In order to synthesise (1), 3,4 methylenedioxy phenol (Sesamol)(4) was synthesized by a new and convenient method. Secondly 3,4 - methylenedioxy -6-methoxybenzaldehyde was synthesized by new and convenient method over the previous ones. This method involves the introduction of formyl group after methylation of hydroxyl group in 3,4- methylenedioxy phenol(4). This method does not involve any chelated hydroxy group to be with

methylated whereas the Suginome method<sup>(XXII)</sup> involves the introduction of formyl group before with methylation of hydroxyl group.

## Experimental

### Synthesis of 7,2' –dimethoxy - 4',5' –methylenedioxyflavanone ( 1 ) :

#### Performic acid:

Hydrogen peroxide ( 15 ml , 30% ) was added dropwise to formic acid ( 75ml , 98 - 100% ) with continuous shaking and the resulting mixture was warmed at 60 ° for 2-3 minutes . It was kept at room temperature for 2 hours with occasional shaking. The reaction mixture was cooled to 0° by keeping it in an ice bath and then stored in a refrigerator .

#### 3,4 –Methylenedioxyphenol ( 4 ) :

To a well stirred solution of 3,4 –Methylenedioxybenzaldehyde ( piperonal ) ( 3 ) 10 grams in dry chloroform ( 100ml ) cooled at 0 ° , a solution of performic acid ( 50ml ) was added dropwise till piperonal ( 3 ) was completely oxidized (check by TLC ). The reaction mixture was stirred for 3 hours keeping temperature at 0 ° It was then treated with sodium bisulfite ( 2.5 g ). Unreacted performic acid and chloroform were removed by distillation under reduced pressure and the resulting residue was made alkaline by adding alcoholic KOH ( 10% , 100 ml ).

It was then refluxed for 1 hour The residue left after alcohol removal was acidified with hydrochloric acid. 3,4 –Methylenedioxyphenol ( 4 ) that separated out was extracted with ether . It was dried over sodium sulfate and filtered. After removal , the residue containing ( 4 ) crystallized from petroleum - ether , 2 gm, m. p. 63 ° . It gave olive green colouration with alcoholic ferric chloride solution .

PMR Spectrum :  $\delta$  , CDCl<sub>3</sub> , TMS as an internal standard : 5.80 ( 2 H , s , -OCH<sub>2</sub>O - ) , 6.20 ( 1H , bs , 1 X – OH ) , and 6.60 -7.10 ( 3H , m , C-2-H , C-5-H and C-6-H )

#### 3,4 –Methylenedioxyanisole ( 5 )

3,4 –Methylenedioxyphenol ( 4 ) 2 g in dry acetone ( 100 ml ) was refluxed with dimethyl sulfate ( 1.5 mole 2.1 ml ) and ignited potassium carbonate 30 gms ) for 4 hours .Inorganic salts were filtered and washed with dry acetone. Acetone was distilled off and ice cold water was added to the residue . The required compound was extracted with chloroform . The chloroform extract was first dried over anhydrous calcium chloride and then filtered. The solvent was distilled off give a light brown semi solid ( 1.5 gm ). It did not give only green colouration with alcoholic ferric chloride .The semi solid containing 3,4 –Methylenedioxyanisole ( 5 ) was used as such for the next reaction .

PMR Spectrum :  $\delta$  , CDCl<sub>3</sub> , TMS as an internal standard : 3.85 ( 3H , s , C-1-OCH<sub>3</sub> ) 5.90 ( 2H , s , -OCH<sub>2</sub>O - ) and 6.60 -7.10 ( 3H , m , C-2-H , C-5-H and C-6-H )

#### 3,4 -Methylenedioxy -6-methoxybenzaldehyde ( 6):

To a solution of 3,4 –Methylenedioxyanisole ( 5 ) 2 g in N:N dimethyl formamide ( 40 ml ) cooled in an ice bath , Phosphorus oxychloride ( 20 ml ) was added carefully . The resulting solution was heated in an oil bath at 90 -100 ° for 6 hours . It was then cooled and treated with the saturated solution of sodium acetate ( 20 gm ) in water and heated under reflux for half an hour .It was cooled and the aldehyde ( 6 ) thus obtained was extracted with ether. The ether extract was washed with cold water and dried over anhydrous sodium sulfate and then filtered . The ether was distilled off from the filtrate. The residue was purified using petroleum ether , gave yellowish low melting crystals when further recrystallized from hot water to yield 3,4 Methylenedioxy -6-methoxybenzaldehyde ( 6 ) 2.1 gm as colourless crystals , m.p. 110 ° . It gave bright Orange colouration with 2 , 4 dinitrophenylhydrazine . It formed p- nitro phenylhydrazone m,p, 249 ° and also a semicarbazone m.p.220 ° .

PMR Spectrum :  $\delta$ , CDCl<sub>3</sub>, TMS as an internal standard : 3.98, (3H, s, 1 X -OCH<sub>3</sub>), 5.92 (2H, s, 1 X -OCH<sub>2</sub>O-), 7.12 (1H, s, C-5-H), 7.86 (1H, s, C-2-H) and 10.40 (1H, s, -CHO)

**2'-hydroxy-4',2-dimethoxy-4,5-methylenedioxychalcone( 2 ):**

A solution of 2-Hydroxy-4-methoxyacetophenone (7) (0.5 g) and 3,4-Methylenedioxy-6-methoxybenzaldehyde (6) (two moles) (1.1 g) was treated with aqueous potassium hydroxide (3 gm in 10 ml) and then stirred well for two hrs. It was kept at room temperature for 72 hrs. The reaction mixture was diluted with water and the excess of 3,4-Methylenedioxy-6-methoxybenzaldehyde (6) was removed by extraction with ether. The alkaline solution when acidified with hydrochloric acid in cold, gave the chalcone (2) which was filtered, washed first with sodium bicarbonate (10%), next with dilute hydrochloric acid and finally with water and then dried. 2'-hydroxy-4',2-dimethoxy-4,5-methylenedioxychalcone (2) thus obtained crystallized from chloroform-petroleum ether as light brown needles (1.5 gm) m.p. 180°. It gave a brown colouration with alcoholic ferric chloride solution.

UV Spectrum ( $\lambda$  max):

MeOH : 265, 369, 374 nm  
MeOH + NaOAc : 280, 369, 374 nm  
MeOH + NaOAc + H<sub>3</sub>BO<sub>3</sub> : 264, 373, 389 nm

PMR Spectrum :  $\delta$ , CDCl<sub>3</sub>, TMS as an internal standard :

3.81-3.98 (6H, m, 2X -OCH<sub>3</sub>), 6.00 (2H, s, 1 X -OCH<sub>2</sub>O-), 6.28-6.40 (2H, m, C-3'-H & C-5'-H), 6.70-7.10 (m, 3H, C- $\alpha$ -H, C- $\beta$ -H), 7.25-7.82 (1H, d, J=9Hz, C-6H) and 13.92 (1H, s, -OH)

CMR Spectrum : (ppm, CDCl<sub>3</sub>, TMS as an internal standard):

114.2 (C-1), 150.4 (C-2), 99.8 (C-3), 145.4 (C-4), 136.2 (C-5), 115.0 (C-6), 125.8 (C- $\alpha$ ), 138.6 (C- $\beta$ ), 191.1 (C=O), 116.9 (C-1'), 164.0 (C-2'), 101.8 (C-3'), 166.2 (C-4'), 107.6 (C-5'), 131.5 (C-6')

**7,2'-dimethoxy-4',5'-methylenedioxyflavanone ( 1 ):**

A solution of 2'-hydroxy-4',2-dimethoxy-4,5-methylenedioxychalcone (2) 2 g in alcoholic sulphuric acid (30 ml, 5%) was refluxed for 40 hours. After the removal of alcohol, the reaction product was obtained as colourless product. The reaction product was purified by column chromatography using neutral alumina as the adsorbent, and petrol-petrol-benzene and benzene alone as the eluting solvents. The purified compound thus obtained crystallized from alcohol to give racemic 7,2'-dimethoxy-4',5'-methylenedioxyflavanone (1) as colourless needles, (1.5 g) m.p. 180-87°. Flavanone (1) on alkaline degradation gave 3,4-Methylenedioxy-6-methoxybenzaldehyde (6) m.p. 110° and 3,4-Methylenedioxy-6-methoxybenzoic acid, m.p. 148°.

UV Spectrum ( $\lambda$  max):

MeOH : 265, 285, 295 nm  
MeOH + NaOAc : 280, 286, 295 nm

PMR Spectrum :  $\delta$ , CDCl<sub>3</sub>, TMS as an internal standard :

2.85 (2H, double quartet, C-3-H), 3.82-4.00 (6H, m, 2X -OCH<sub>3</sub>), 5.32 (1H, q, C-2-H, J=11Hz & 5Hz), 5.98 (2H, s, -OCH<sub>2</sub>O-), 6.30-6.50 (2H, m, C-6-H & C-8-H, J=2.5Hz), 6.82 (1H, s, C-3'-H), 7.22 (1H, s, C-6'-H) and 7.80-7.90 (1H, d, J=9Hz, C-5-H)

CMR Spectrum : (ppm, CDCl<sub>3</sub>, TMS as an internal standard):

75.2 (C-2), 43.1 (C-3), 191.9 (C-4), 127.8 (C-5), 109.1 (C-6), 166.7 (C-7), 101.0 (C-8), 163.1 (C-9), 115.6 (C-10), 113.9 (C-1'), 153.2 (C-2'), 96.7 (C-3'), 148.3 (C-4'), 139.9 (C-5') and 111.7 (C-6')

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### **References:**

- I. M.Ilyas and S.Sultana , Indian Journal of Chemistry , 1986 , 25 B , 416 .
- II. M. Sharma and L. D. Stiver , Tetrahedron , 1979 , 25 ,3887 .
- III. L . Syper , K .Kloc.and J. Mlochowski ,Tetrahedron ,1980 ,36 123 .
- IV. G. C . Sharma , Chemistry of Polyphenolic Compounds of some Medicinal Plants , Ph.D Thesis University of Delhi -110007 , 1977 , p 91 .
- V. Von .Fr . Schaff and A . Labouchere , Helv. Chun . Acta , 1924 ,7 , 357
- VI. S .R. Cooper , Organic Synthesis, 1941 , 21 , 103
- VII. R. Adams , J. Am Chem . Soc ., 1919 , 41 ,260
- VIII. M. Brockmann and K. Maier , Ann . 1938 , 535
- IX. Rocha D.H.A , Vaz P.A.A. , Diana C.G.A. , Pinto and Silva A.M.S, Synthesis Chalcones and their Isomerization into Flavanones and Azaflavanones , Methods and Protocols , 2019 , 2 , 70 .
- X. Kiruthiga N. , Alagumuthu M . , Selvinthanuja C. , Srinivasan K. , Sivakumar T. , Antiinflammatory & Anti Allergy Agents in Medicinal Chemistry , vol . 20 , 2021
- XI. Frattaruolo L , Carullo G , Brindisi M , Mazzotta S , Bellissimo L , Rago V , Curcio R , Dolce V , Aiello F and Cappello A.R. , Antioxidants 2019 , 8 (6) , 186 , Antioxidant and anti Inflammatory Activities of Flavanones from Glycyrrhiza Glabra L. (licorice Leaf ) ,Phytocomplexes :Identification of Licoflavanone as a modulator of NF-KB / MAPK Pathway .
- XII. . Stevens Y , Rymenant E.V. , Grootaert C , Camp J . V ., Possemiers S, Masclee A . and Daisy J .
- XIII. Nutrients 2019 , 11 ( 7 ) , The Intestinal Fate Of Citrus Flavanones and their Effects on Gastrointestinal Health .
- XIV. Oliveira Mendes L.A.D , Ponciano C . S , Cataneo A . H . D . , Wowk P . F . , Bordignon J . , Silva H. , Almeida M .V.D . , Ávila E .P , Chémico Biological Interaction , vol 331 , 2020 , 109218 , The anti –Zika virus and anti –tumoral activity of the citrus flavanone lipophilic narimengin based compounds
- XV. Maroyi A. , Asian Journal of Pharmaceutical and Clinical Research , vol 11 , Issue 11, 2018 , 69-74, Lannea Acida : A review of its Medicinal uses and Phytochemistry And Pharmacological Properties .
- XVI. K.R. Markham and T . J . Mabry ‘ The Flavanoids ‘ Chapman and Hall ,London , (Eds. J.B Harborne , T. J . Mabry and H. Mabry ) , 1975 , p 62-68 .
- XVII. T . J Mabry , K .R . Markham and M. B . Thomas , ‘The Systematic Identification of Flavonoids ‘ Springer Verlag (New York ) , 1970 , p 253 ,267
- XVIII. T . J Mabry , K .R . Markham and M. B . Thomas , ‘The Systematic Identification of Flavonoids ‘ Springer Verlag (New York ) , 1970 , p 41 ,165 .
- XIX. K.R. Markham and T . J . Mabry ‘ The Flavanoids ‘ Chapman and Hall ,London , (Eds. J.B Harborne , T. J . Mabry and H. Mabry ) , 1975 , pg 45 ,50 .
- XX. L . Jurd , The Chemistry of Flavanoid Comppunds , Pergamon Press , London (Ed .T .A . Geismann ) 1962 , p 107.
- XXI. P . K . Aggarwal , ‘ Carbon -13 NMR of Flavanoids ‘ , Elsevier Science Publishing Company , New York , (Ed. P. K . Aggrawal ) , 1989 , p 507 , 513 .
- XXII. .P .K . Aggarwal , Chemical Investigation of Medicinal Plants , Ph.D. Thesis ,University of Lucknow ,Lucknow 1980 , p 3

XXIII. H . Suginome , Bulletin of the Chemical Society of Japan , 1966 , 39 , 1525 .

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