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SYNTHESIS AND CHARACTERIZATION OF NEW PYRAZOLINE RING CONTAINED PODOPHYLLOTOXIN ANALOGUES.

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Abstract:

Structural and mechanistic aspects of podophyllotoxin have provided the basis for the synthetic endeavours that followed. The most important aryltetralin lignans are found in large quantity in plants of the genus podophyllum. Plants of podophyllum are the main sources of aryl tetralin type lignans. In Berberidaceae plants such as podophyllum emodiwall, podophyllum peltatumlinnaeus, podophyllum pleianthum the cytotoxin lignan lactone and /or antitumour activity producing compound podophyllotoxin is present. The Podophyllum hexandrum rhizomes are known to contain several lignans. Because of Podophyllotoxin definitive biological activity in blocking mitosis and its use as the starting compound of the semi-synthetic chemotherapeutic drugs etoposide, teniposide, and etopophos is used. These antineoplastic pharmaceuticals block DNA toposisomerase II and have been used for the treatment of small and large cell lung, refractory testicular, stomach, pancreatic cancers, and myeloid leukaemia's .

Key words: *Synthesis of 1H-3, 5-diaryl-2-pyrazolines and its derivatives.*

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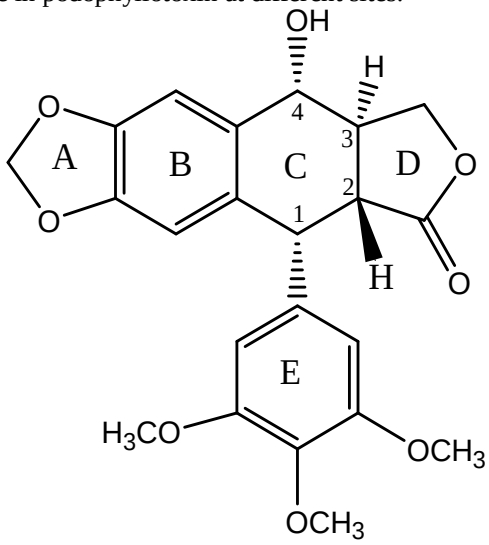
INTRODUCTION:

Podophyllotoxin shows anticancer activity and also it is having more side effects, hence modification has done in podophyllotoxin at different sites.



1. Structure of podophyllotoxin

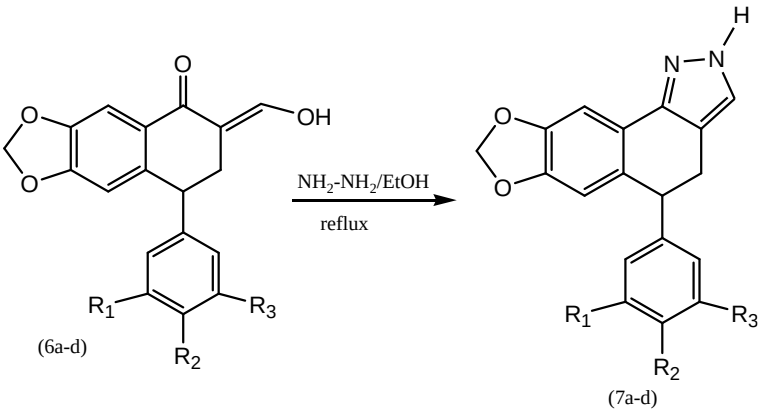
Modification of **A** ring gives compounds having significant activity but less than that of etoposide, whereas modification of the **B** ring resulted in the loss of activity. E ring is essential for its anticancer activity and D ring in lactone form is preferred for better activity. So only modification site of podophyllotoxin is ring C preferred. Modifications at the C-4 position in ring C are mostly acceptable and bulky groups at this position enhance anticancer activity and topoisomerase activities . Pyrazoline, is a five-membered nitrogen heterocyclic scaffold, exhibits many biological activities and is widely used in the design of anticancer agents. pyrazoline scaffolds, encompassing the antibacterial, anti-inflammatory, analgesic, cytotoxic, and anti-tumor activities. Most favourably, in the presence of a unique chemical structure, pyrazolines have made it easier to produce a very new substitutions with the low toxicity as compared to their natural analogue.

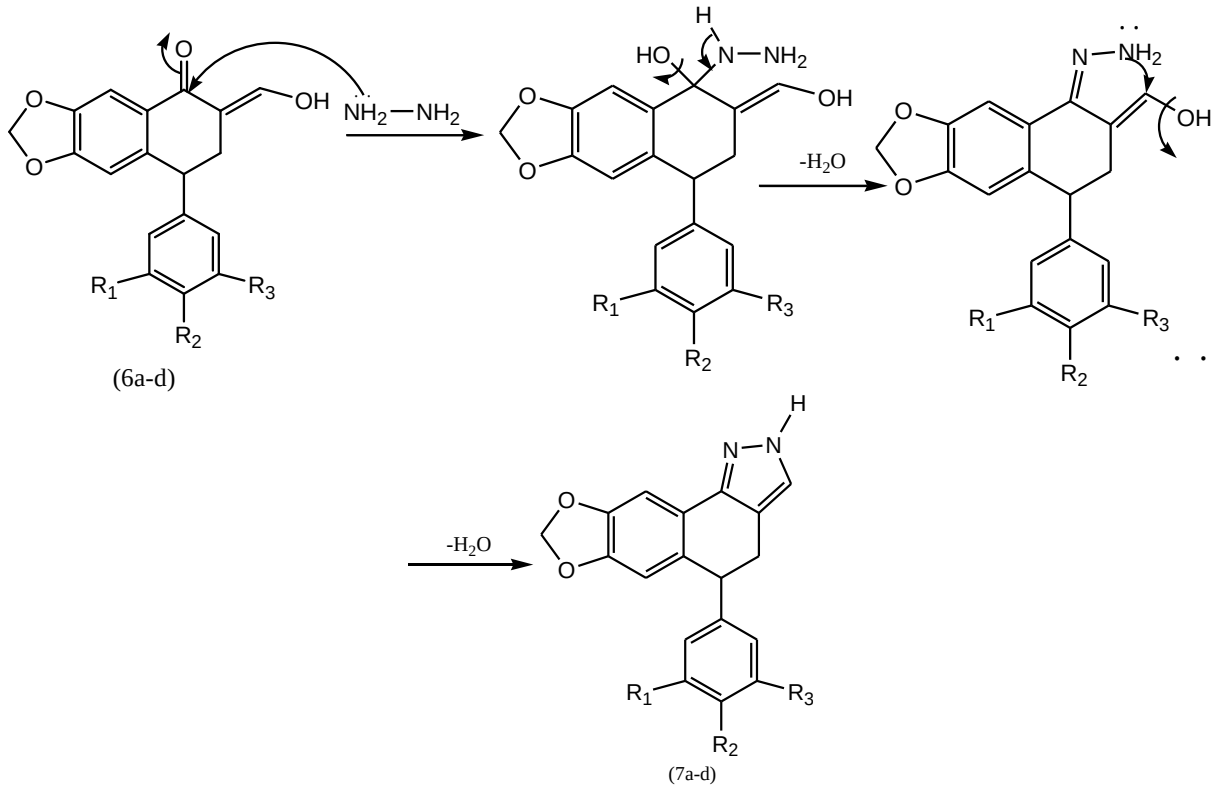
EXPERIMENTAL:

Materials and Methods:

All the required reagents and chemicals were purchased from Sigma aldrich and Merck company. They were used without further purification. Melting points were taken in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) is performed with E. Merck precoated silica gel plates (60F-254) with iodine as a developing agent to check the product purity. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using tetramethyl silane (TMS) as an internal reference on Bruker spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Hitachi RMU-61spectrophotometer. The products formed were purified by the repeated recrystallization and by column chromatography using silica gel [60-120] mesh as an adsorbent

Structural Synthesis:





Here, a= R_1=H, R_2=H, R_3=H.
b= R_2=OCH_3, R_1=H, R_3=H..
c=R_1=OCH_3, R_2=OCH_3, R_3=H.
d=R_1=OCH_3, R_2=OCH_3, R_3=OCH_3.

General procedure for synthesis of 1H-3, 5-diaryl-2-pyrazolines (7a-d):

Hydroxymethine tetralone (6a-d) (3g) is added to the hydrazine hydrate (1 ml) in the presence of 15ml of absolute ethanol in a 100ml round bottomed flask. The reaction mixture was refluxed for three hours at 25° C. The solid product 1H-3, 5-diaryl-2-pyrazolines (7a-d) was formed and stored, recrystallised, analysed through spectral data.

The hydroxyl methylene tetralone with Hydrzene hydrate and with ethanol on refluxing gives the following reaction. Hydrazene is deprotonated. Hydrazene undergoes nucleophillic attack at the α carbon of the α, β-unsaturated carbonyl carbon of the tetralone compound. Proton shift takes place from Nitrogen atom of Hydrazene Hydrate to a highly electronegative oxygen atom of tetralone gives enol which further on rearrangement ketonises to give an intremediate ketoamine will formed. To attain the stability the product, the ketoamine undergoes again intramolecular proton transfer takes place to give an intermediate. i.e., Double bond on hydroxyl group which is nucleophillic in nature accepts the proton from primary nitrogen atom of the ketoamine of its carbonyl carbon with the liberation of water final (7a-d) is formed and it is confirmed by the spectal data. The product produced is nitrogen containing new analogs of podophyllotoxin.

5-phenyl-4, 5 - dihydro - 2H - 7 , 9 - dioxa - 1 , 2 - diaza - dicyclopenta [α, g] naphthalene:

Molecular formula: $C_{18}H_{14}N_2O_2$. Molecular weight: 290.32. Colour: Dark brown solid. Melting point: 147-149°C. IR(KBr) (υ/cm-^{1}): 1660.33(C=N), 2921.13(C-H), 1606.91(ArC=C).^{1}H NMR (DMSO, 400 MHz) δ: 5.960 (s, 2H, -O-CH_2-O), 3.854 (d, 2H,-CH_2), 3.870 (t,1H,CH), 6.808-7.691 (m ,7H, Ar-H), 7.340(=CH, 1H, d). ^{13}C NMR (DMSO, 100MHz) δ: 148.255, 146.255, 144.377, 143.701, 134.486, 132.986, 129.331, 129.012, 128.701, 127.954, 126.422, 122.011, 114.954, 113.599, 112.701, 101.850, 46.453, 33.204.

MS (ESI,m/z): 291.30(M+1). Elemental analysis: Calculated (in %): C=74.47, H=4.86, N=9.65. Found (in %): C=74.45, H=4.89, N=9.64.

5-(4-methoxy-phenyl) -4, 5-dihydro-2H-7,9-dioxa-1,2-diaza-dicyclopenta [α, g] naphthalene:
Molecular formula: $C_{19}H_{16}N_2O_3$. Molecular weight:320.12. Colour: Dark brown solid. Melting point: 152-154ºC. IR(KBr) (υ/cm-^{1}): 1661.62(C=N), 2919.76(C-H), 1605.14(ArC=C). ^{1}H NMR (DMSO, 400MHz) δ: 5.960(s, 2H, -O-CH_2-O), 3.871(d, 2H, -CH_2) , 3.893 (t ,1H, CH), 6.828-7.560 (m ,6H, Ar-H), 7.340 (=CH), 13.581 (N-H).

^{13}C NMR (DMSO, 100MHz) δ: 159.701, 150.055, 148.255, 145.377, 135.956, 134.886, 133.986, 129.431, 129.012, 128.701, 115.954, 114.499, 114.211, 113.912, 113.701, 91.150, 56.011, 40.453, 33.904. MS (ESI,m/z): 321.10 (M+1). Elemental analysis: Calculated (in %): C=71.41, H=5.03, N=8.74. Found (in %): C=71.40, H=5.06, N=8.73.

5-(3,4-dimethoxy-phenyl)-4,5-dihydro-2H-7,9-dioxa-1,2-diaza-dicyclopenta [α, g] naphthalene:
Molecular formula: $C_{20}H_{18}N_2O_4$. Molecular weight: 350.37. Colour: Dark brown solid. Melting point: 165-167ºC. IR(KBr) (υ/cm-^{1}): 1671.75(C=N), 2926.67(C-H), 1604.7 (ArC=C), 3010 (Ar).^{1}H NMR (DMSO, 400MHz) δ: 5.983(s, 2H, -O-CH_2-O), 3.870(t, 1H, -CH), 3.854(d, 2H , CH_2) , 6.828-6.915 (m, 5H,Ar), 7.136 (s ,1H, =CH), 13.680(d, 1H, N-H).

^{13}C NMR (DMSO, 100MHz) δ: 150.055, 148.258, 148.177, 145.331, 145.015, 136.866, 134.886, 134.086, 129.011, 121.701, 115.954, 115.459, 114.215, 113.915, 113.701, 91.253, 56.311, 56.005, 40.333, 33.304.MS (ESI,m/z): 351.35 (M+1). Elemental analysis: Calculated (in %): C=68.56, H=5.18, N=8. Found (in %): C=68.55, H=5.20, N=7.79.

5-(3,4,5-trimethoxy-phenyl)-4,5 – dihydro-2H-7,9-dioxa-1,2-diaza-dicyclopenta [α,g] naphthalene:
Molecular formula: $C_{21}H_{22}N_2O_5$. Molecular weight: 382.41 Colour: Dark brown solid .Melting point: 171-173ºC. IR(KBr) (υ/cm-^{1}): 1663.25 (C=N), 2923.25(C-H), 1610.5(ArC=C), 3019.25 (Ar). ^{1}H NMR (DMSO, 400MHz) δ: 5.960(s, 2H, -O-CH_2-O), 3.899(t, 1H, -CH), 3.854(d, 2H , CH_2) , 7.254-7.340 (m ,4H, Ar-H), 7.293 (d, 1H, =CH), 13.210(d, 1H, N-H) . ^{13}C NMR (DMSO, 100MHz) δ: 151.847, 149.347, 149.011, 147.055, 144.177, 137.987, 135.087, 134.086, 130.444, 129.601, 115.811, 114.599, 114.005, 107.422, 107.083, 91.550, 56.731, 56.412, 56.001, 40.200, 33.304. MS (ESI,m/z):383.39(M+1).
Elemental analysis: Calculated (in %): C=67.41, H=5.66. Found (in %): C=67.40, H=5.68.

CONCLUSIONS:

In this summary, a convenient synthesis of podophyllotoxin analogues containing pyrazoline ring have been developed. This method gave good yields of Podophllotoxin analogues. We have used environmental friendly chemicals and conditions. They are very useful for the synthesis of analogues of podophyllotoxin.

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