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MODELING AND ANALYSIS OF NMR, UV-VIS AND MS SPECTRA FOR THE CHARACTERIZATION OF THE COMPOUND NARCISSIN

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ABSTRACT
The biogeographical situation of Algeria, which stretches between the Mediterranean and Africa south of the Sahara Desert, gives it a very rich and diverse flora. There are more than 3000 species. It belongs to several plant families. A small exploration of the potential of this plant from this point in chemistry and pharmacology. This field is an important axis of scientific research, particularly in the field of biologically active natural materials. The separation of certain compounds from the butanol extract resulted in the isolation of several types of products, the most common of which are flavonoids that are the subject of phytochemical and pharmacological studies. This work allowed several spectroscopic analyses to be carried out to determine and suggest the structure of the resulting pure materials. So, the main objective of this project is to analyses the different spectral arrays to prove and predict the structure and modeling of the molecule and define their QSAR descriptors.

KEYWORDS – Separation; Spectroscopic analyses; Predict the structure; Narcissin; QSAR descriptors**.**

I. INTRODUCTION

Saharian plants are known by their resistance to several stress factors. Under extreme climatic conditions, these plants could constitute a reservoir of new natural, safe and effective biomolecules[i].
Traganum nudatum, (Chenopodiaceae family) is an herbaceous wild plant native to Algeria and is used in medicinal plants widely used in Algerian traditional medicine. *T. nudatum* known locally as '*Damran*'[ii-v].

Phytochemical investigation of different extracts prepared from the aerial part of *T. nudatum.* The chemical structure was separated from n-butanol extract. Using spectroscopic methods, including 1D and 2D (NMR), UV-Vis and MS spectra, to identification the structure and find QSAR descriptors for each compound.

In drug design field and medicinal chemistry, QSAR (Quantitative structure-activity relationship) descriptors are considered as the main properties for any drug discovery, because it attempt to predict the relationship between physicochemical properties or biological activities of molecular from its chemical structural features, which enhance the realization of biological phenomena and fundamental processes [vi].

II. MATERIALS AND METHOD

II.1. Preparation of Extract and Isolation

The aerial parts of *T. nudatum* were collected from Touggourt (gamaa region) in April 2013. The plants were identified by Pr. Abdelmadjid Chehma from Ouargla University and voucher specimens, were deposited at the Chemistry Department, University of Ouargla. The plant materials were dried under shade and then ground and stored in closed container away from light and moisture.

The extracts were prepared by soaking 500 g of the plant powder in a solution of EtOH/H_2O (70/30) for 24 H. The procedure was repeated three times and the filtrates were combined before being evaporated under reduced pressure. The resulting extracts were diluted with distilled water and left for a whole night. The filtrates were then subjected extraction by various solvents with increasing polarity (petroleum ether, dichloromethane, ethyl acetate, and butanol). The resulting organic phases every time they dry leach and then evaporate under pressure and melt the deposit into methanol [vii-ix].

The butanolic extract was subjected to a series of chromatographic separation on the stationary phase silica gel using different polar mobile phases and from one of the separated compounds; the compound TR5I that appeared as a precipitate on a yellow powder in one of the obtained fractions [viii, x, xi].

II.2. Physicochemical methods

II.2.1 Mass spectrometry

It is a very sensitive valuable analytical method which depends on determining the chemical structure of the compound by defining the molecular treasure, or collecting structural information, starting from the nature of the fragments. The result, the main advantage of it is that it needs a very small amount of the sample, the principle of this technique is the displacement of the sample, and there is a determination of the molecular spectra. Applying this method to

The flavinoids allow the following information to be elaborated :

- Determining the molecular spectrum or the aggregated formula.
- The nature of the substitutions and the locations of their connection to the French structure

Also called mass spectroscopy, analytic technique by which chemical substances are identified by the sorting of gaseous ions in electric and magnetic fields according to their mass-to- charge ratios.

Method : ESI positive (+) and negative (-) / Operator: FTMS User / Instrument :
apex –IV [viii, xii, xiii]

II.2.2 Magnetic resonance spectrometry

It is one of the most important analytical methods available to you in various fields. Physical based on magnetic and mechanical properties, such as quantitative flaking of atom. To study molecules in terms of structure and stereotyped formation, which are applied in chemistry to determine Formulas of compounds with various problems, as this technique is used in

qualitative analysis each purified compound was analyzed in NMR in order to establish its structure [vii, xiii-xv]. For this, we used :

The NMR (^{1}H and ^{13}C) spectra were carried out at the University of Jordan, Department of Science and chemistry instrument model :

Bruker 500 MHz-Avance III, Solvent DMSO. Solvent DMSO NMR equipped with a cryoprobe. The data are processed and exploited by Top Spin 2.1 or 3. 2 software.

The samples are prepared in analytical tubes of 5 mm diameter in Deuterated solvents DMSO-d6 depending on the solubility of the analyzed compound

II.2.3. UV absorbance detection

The positions, types and number of substituent in the conjugated systems could be speculated via means of UV spectrum. Most of the flavonoids in methanol possess two main absorption bands. Band I is at 300–400 nm, which is caused by electron transition of cinnamoyl group. Band II is at 240–280 nm, which is caused by electron transition of benzoyl group [vii, xvi].

II. 2.4 Quantitative structure-activity relationships (QSAR)

Used when there is little or no receptor information, but there are measured activities of (many) compounds. It is correlate chemical/biological activities with structural features or atomic, group or molecular (physico-chemical) properties. The Quantitative Structure-Activity Relationships (QSAR) study has two steps :

a. Drawing of molecule : For drawing of structure of molecule the Chem-Draw software version 18 [xvii].

b. Geometry Optimization: All molecular structure optimization calculations were performed using HyperChem 8.08 software Professional Edition [xviii-xx].

The calculations of biological properties were accomplished using semi-empirical PM3 method with a gradient norm of 0.01Kcal/mol and Fletcher-Reeves as an algorithm.

III. RESULTS

Identified by analysis using spectroscopic techniques, Ultra-Violet (UV), Nuclear Magnetic Resonance 1D (^{1}H-NMR,^{13}C-NMR), 2D (COSY, HMQC, HMBC) and Mass and define their QSAR descriptors.

III.1. Analyse of Ms Spectra

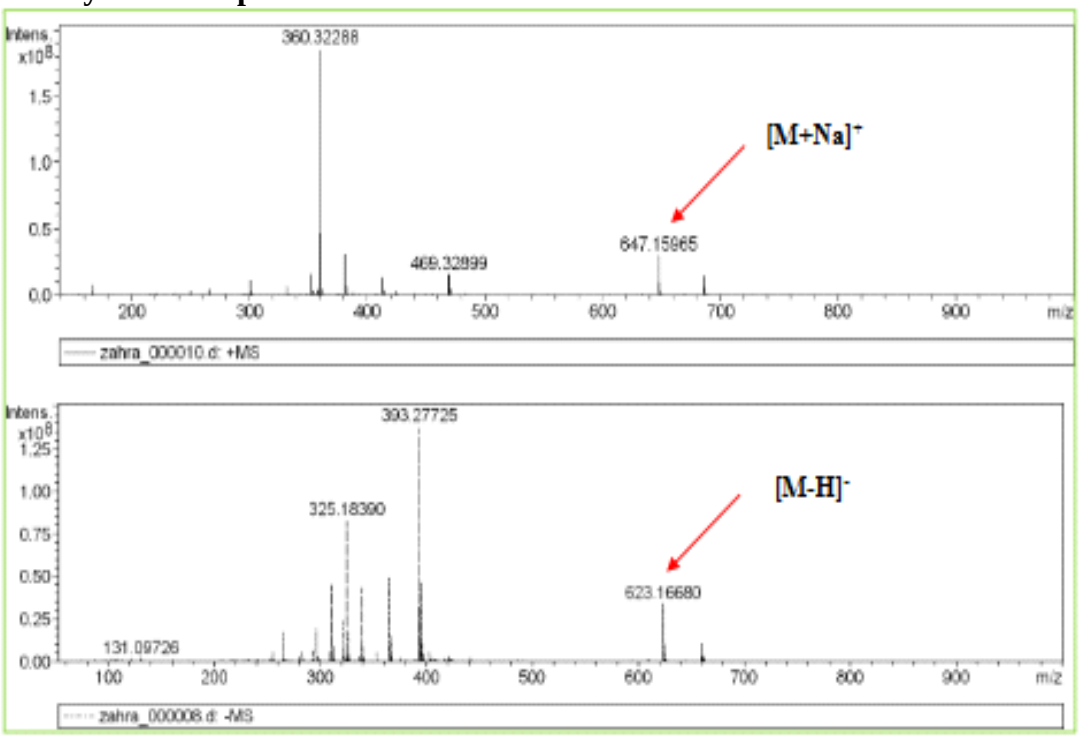

Fig. 1 : Mass spectroscopy ESI-MS (+) and (-) of Compound TR5I

III.2. Analyse of NMR (^{1}H and ^{13}C) spectra

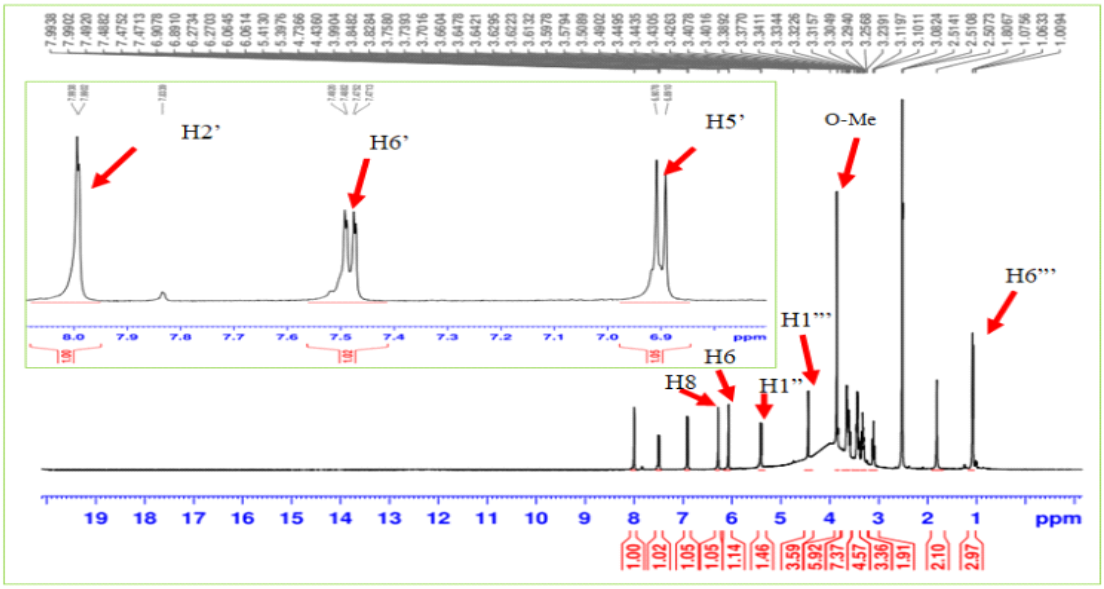

Fig. 2 : ^{1}H NMR Spectrum of Compound TR5I in (DMSO-d6 500 MHz).

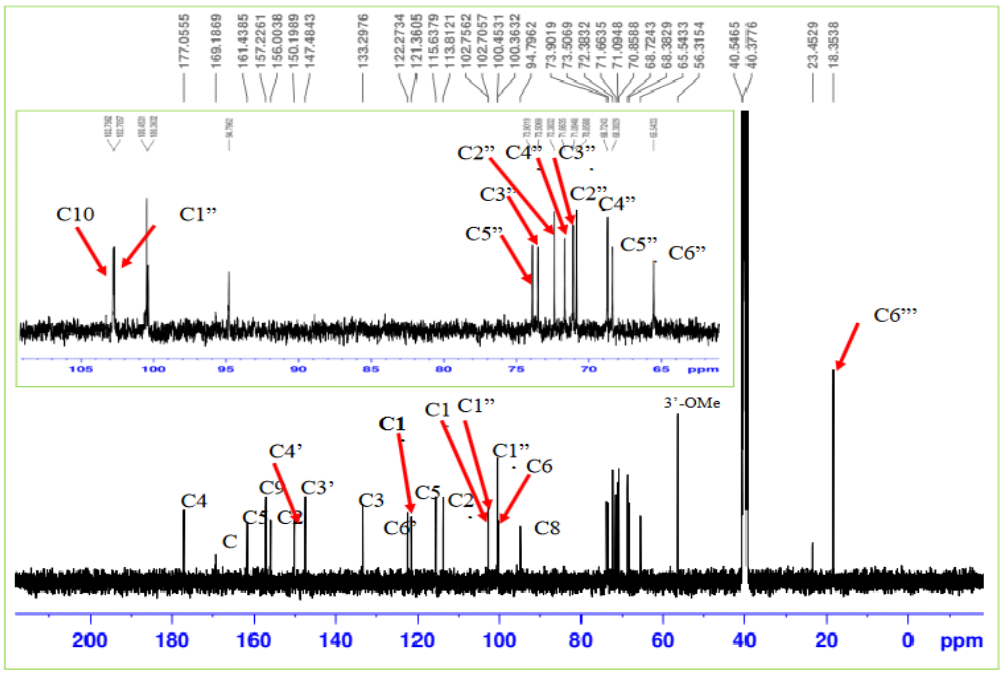

Fig. 3 : **^{13}C NMR Spectrum of Compound TR5I in NMR (DMSO-d6).**

III.3. ANALYSE of NMR. DEPT 135° and 90° spectra

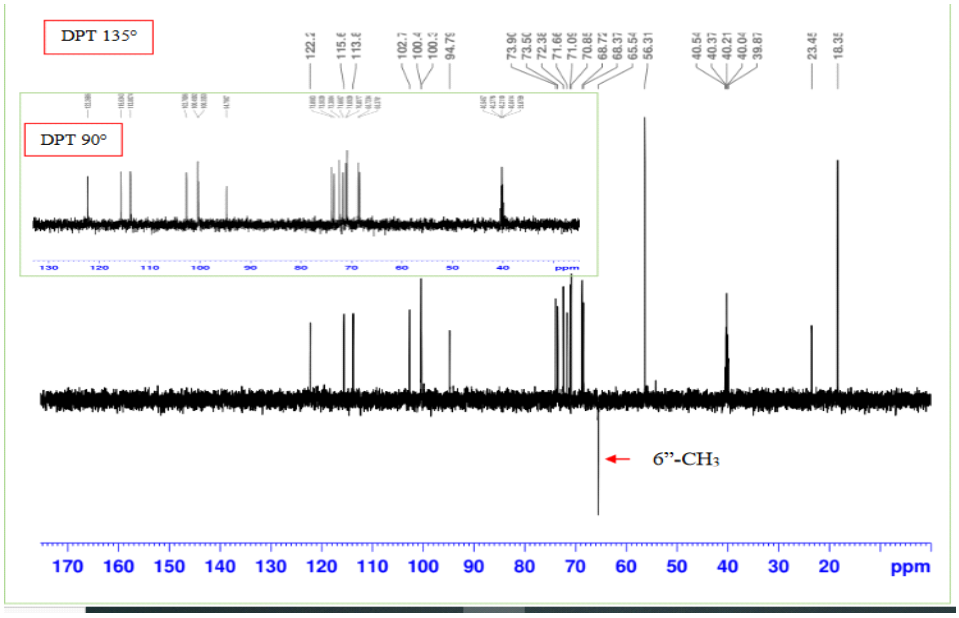

Fig. 4 : DEPT 135° and 90° of Compound TR5I.

III.4. ANALYSE of UV

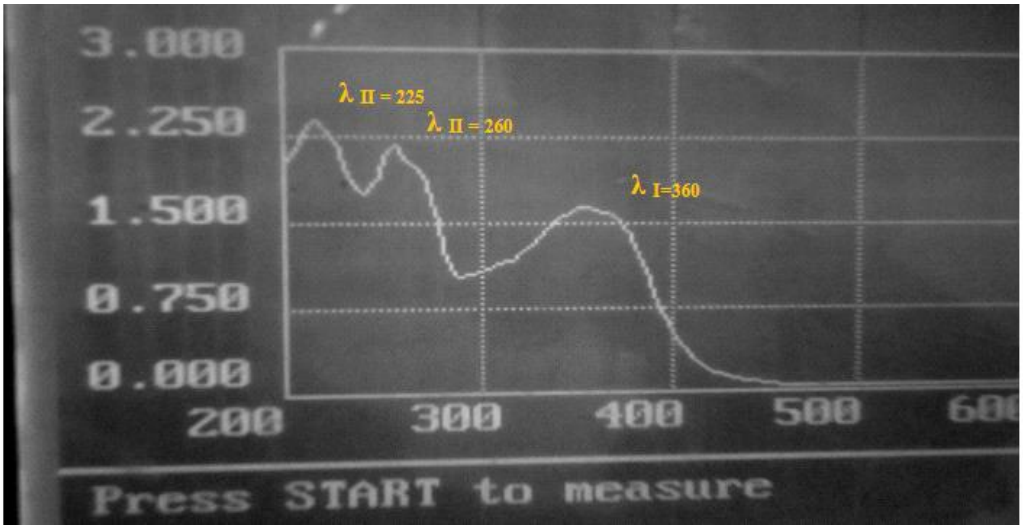

Fig. 5 : UV spectra of the compound TR5I.

III.4. ANALYSE of NMR (2D)

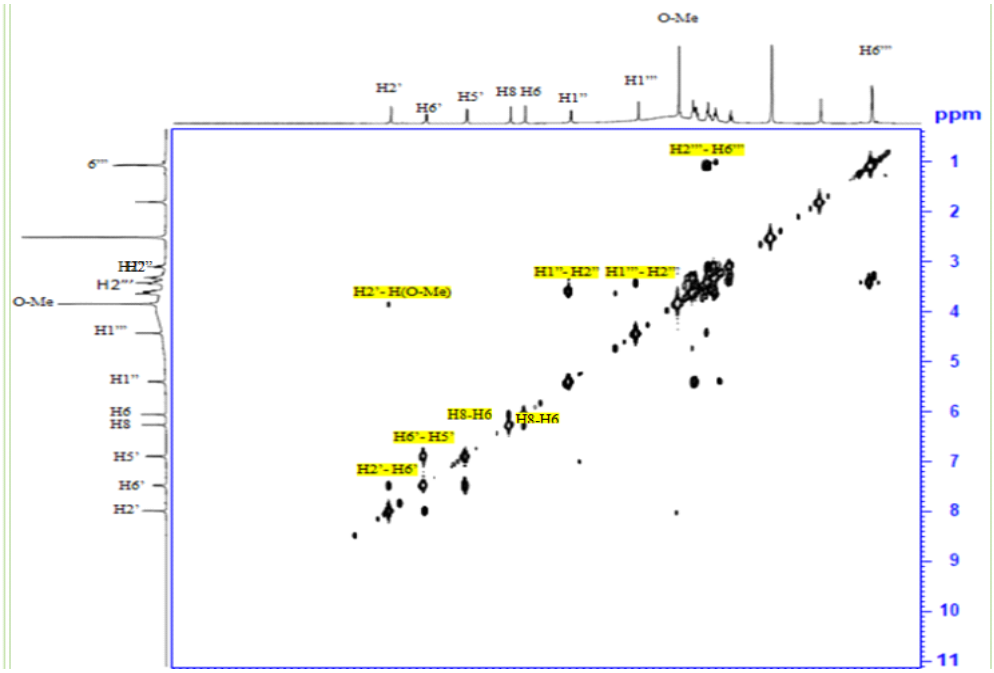

Fig. 6 : COSY of Compound TR5I.

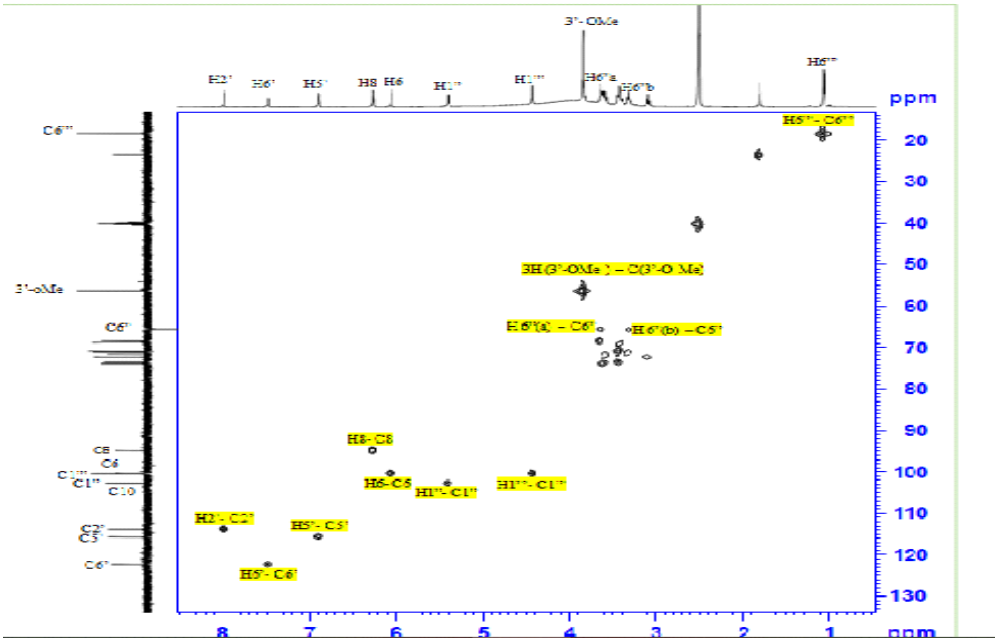

Fig. 7 : HMQC of Compound TR5I.

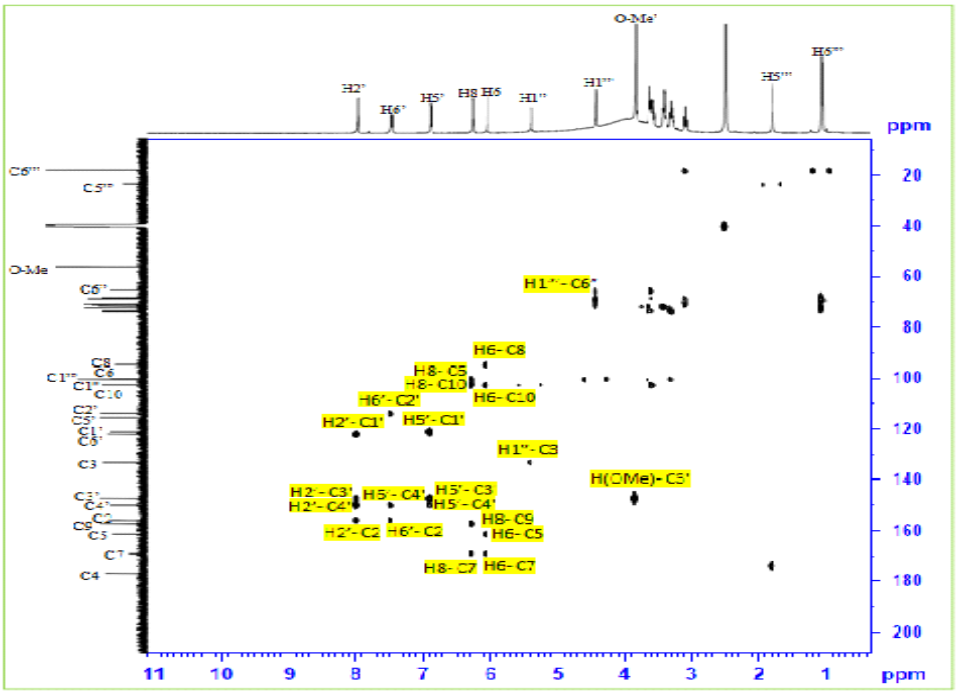

Fig. 8 : HMBC of Compound TR5I.

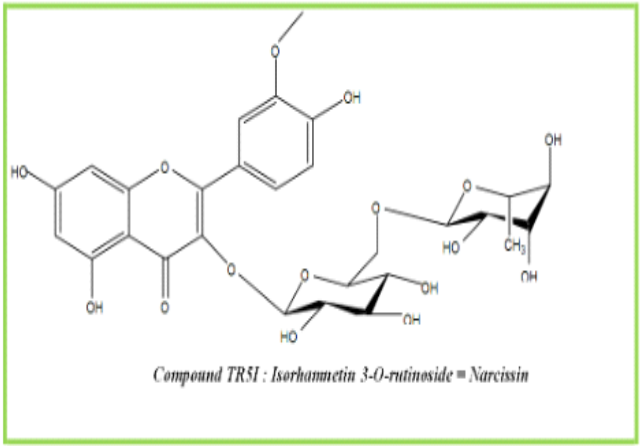

Fig. 9 : Structure of compound TR5I; isorhamnetin 3-O-rutinoside = narcissin

Structure of compounds from Cham Draw 2D and 3D :

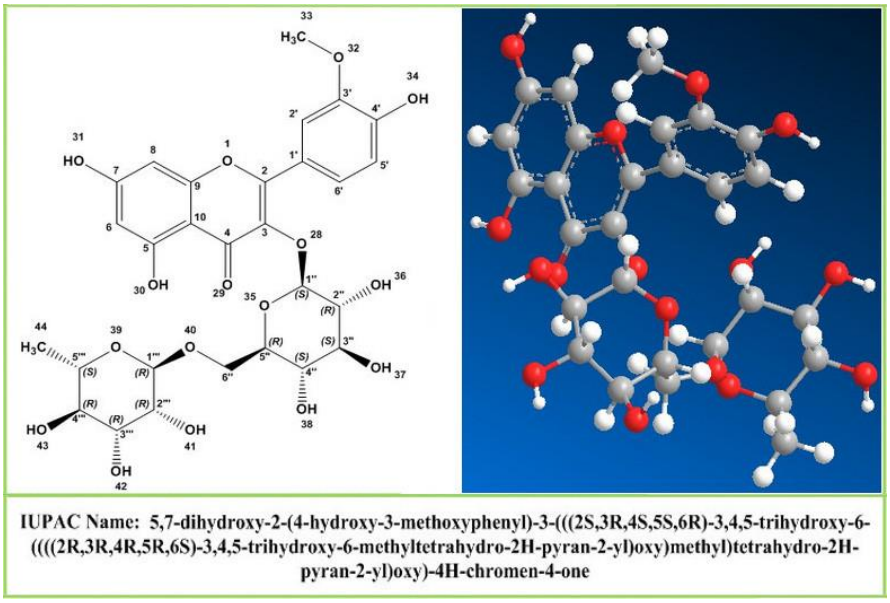

Fig. 10 : 2D and 3D structure and IUPAC name of compound TR5I.

III.6. Properties QSAR of Compound TR5I:

Table 1 : Physicochemical properties of isorhamnetin 3-O-rutinoside compound

Highest Occupied Molecular Orbital (HOMO) eV	-0.54763
Lowest Unoccupied Molecular Orbital (LUMO) eV	-8.85673
Energy gap (ΔE) eV	8.30910
Heat of formation(kcal/mol)	-585.6552
Dipole Moment (Debyes)	1.781

Table 2: Net charge (left) and bond length (right) of TR51 atoms

Atom	**Charge**	**Atom**	**Charge**
O1	-0.096	O34	-0.205
C2	0.109	C1''	0.185

Bond	**PM3**	**Exp** [6]
C5'-C6'	1.391	1.398
C4'-C5'	1.397	1.394

C3	-0.109	C2''	0.025
C4	0.395	C3''	0.019
C5	0.235	C4''	0.010
C6	-0.303	C5''	0.023
C7	0.203	C6''	0.037
C8	-0.297	O35	-0.245
C9	0.187	O36	-0.308
C10	-0.291	O37	-0.313
O28	-0.202	O38	-0.307
O29	-0.314	C1'''	0.200
O30	-0.187	C2'''	0.033
O31	-0.221	C3'''	0.041
C1'	-0.074	C4'''	0.007
C2'	-0.124	C5'''	0.043
C3'	0.048	O39	-0.260
C4'	0.088	O40	-0.286
C5'	-0.177	O41	-0.306
C6'	-0.057	O42	-0.326
O32	-0.165	O43	-0.326
C33	0.046	C44	-0.122

C3'-C4'	1.419	1.393
C2'-C3'	1.394	1.391
C1'-C6'	1.393	1.403
C1'-C2'	1.400	1.403
C9-O1	1.375	1.372
C8-C9	1.400	1.396
C7-C8	1.399	1.386
C6-C7	1.400	1.402
C5-C6	1.401	1.384
C10-C9	1.405	1.397
C10-C5	1.416	1.402
C4-O29	1.218	1.225
C4-C10	1.478	1.482
C3-C4	1.492	1.456
C2-C1'	1.475	1.475
C2-O1	1.378	1.363
C2-C3	1.358	1.475

Table 3 : QSAR properties of isorhamnetin 3-O-rutinoside compound

Property	**Value**
Hydration energy (Kcal/mol)	-44.72
Log P	-5.88
Polarizability (Å³)	56.88
Refractivity (Å³)	151.24
Molar Mass (amu)	624.55
Surface Area [Grid] (Å²)	820.51
Surface Area [Approx] (Å²)	680.41
Volume (Å³)	1497.21
hydrogen bond acceptor (HBA)	16
hydrogen bond donor (HBD)	9
number of rotatable bond (NRB)	7

Note : HBA, HBD and NRB calculated by Chem3D 19.0

VI. DISCUSSION

Mass spectroscopy :
The ESI MS spectrum of compound TR5I showed a $[M+Na]^+$ at m/z : 624+Na=647.(calcd 647. 55). And we confirmed with [M -H] – m/z : 624-H = 623 had the formula

NMR ^{1}H :
The compound was obtained as a yellow powder. From the 1H NMR spectrum (Fig.2) signals in the weak domain characteristic of aromatic protons can be distinguished. More precisely of as flavonoid :

***** Anomeric protons at 4.52 ppm (d. J = 1.3 Hz) and 5.4 ppm (d. J= 7.7 Hz) with coupling constants characteristic of the anomeric H configuration α and β respectively: Peaks at 6.90 ppm (d. J= 8.3 Hz .H-5') 7.48 (dd. J= 1.9 and 8.45 Hz. H-6') and 7.99 (d. J= 1.8 Hz. H-2') are attributable to three protons characteristic of a 3,4-disubstituted B ring.
***** Two broad singletons meta coupling related H-6 and H-8 appeared at 6.27 ppm (d. J = 1.55 Hz.H-8) and 6.02 ppm (d .J =1.55 Hz. H-6) indicating the bisubstitution of ring A.
* The absence of a single peak in the weak region attributable to H-3 of ring C.
* A three proton integration singlet at 3.84 ppm, characteristic of a methoxyl group (3H, s, 3′-OCH_3).
* A three-proton integrating singlet at 1.06 ppm (d. J = 6.15 Hz.3H-6''') characteristic of a methyl group specific to rhamnose.

NMR ^{13}C :
In addition, the 13C NMR spectrum (Fig.3) showed 28 signals of the following carbons. As follows : - Peaks δ 102.70 ppm (C-1") and δ 72.38 (C-2 "), 73.50 (C-3"), 68.72 (C-4 "), 73.90(C-5") and 65.54 (C-6 ") correspond to glucose.
- Peaks δ 100.45 ppm (C-1'"), δ 70.85 (C-2 '"), 71.09 (C- 3 '"), 71.66 (C-4'"), 68.38(C-5 '") and 18.35 (C-6'") correspond to rhamnose.
- The low-field shift of the signal δ 65.54 ppm assignable to C-6" relative to glucose, indicates that the C-6" carbon is the glycosylation site.
- A methoxyl group at 56.31 ppm
Ultraviolet-visible Absorption : The spectral series of the compound (Fig. 5) was carried out by UV-visible spectrophotometry using characteristic reagents. Shows :
***** Appearance of band I in methanol at λI = 360 nm leads us to a 3-substituted flavone or flavonol and as the 1H NMR spectrum excluded a flavone structure, therefore the structure can only be a3 substituted flavonol.
***** By adding a few drops of NaOH, we notice a bathochromic shift of the I band without the decrease of the optical density ΔλI (NaOH / MeOH) = 60 nm, indicating an OH group in the 4' position. As well as the stability of the spectrum after five minutes indicates the absence of a 3,4 dihydroxy system.
***** Thus, the appearance of a new peak at 320 nm, indicating that position 7 has a free hydroxyl group. To define the position of the two substituents : methoxyl and sugar, an acid hydrolysis (HCl, 6N) was performed. hydrolysis (HCl, N) was performed. The UV spectrum of the aglycone recorded in methanol (Fig.5) showed two bands: λII = 260 and λI = 360 nm, which proves that the aglycone is a flavonol, where C-3 has become containing a hydroxyl group, which shows that the released sugar was located at the C-3 position and the methoxyl at the C-3'.

COSY :
According to the COSY spectrum (Fig.6) the following correlation spots can be distinguished : H- 2’ and H- 3’- OMe, H-6' and H-5' H-8 and H-6, H-1’' and H-2’', -H-1’" and H-2”’ -H-2”" and H-6”".

HMQC :
According to the HMQC experiment (Fig.7), each carbon is assigned its corresponding proton is assigned to each carbon :
Between C- 6’ (δ 122.27 ppm) and H-6’ (δ 7.48 ppm)
• C- 5’ (δ 115.63 ppm) and H-5’ (δ 6.89 ppm)
• C- 2’ (δ 113.81 ppm) and H-2’ (δ 7.99 ppm)

• C- 1” (δ 102.70 ppm) and H-1” (δ 5.4 ppm)
• C- 6 (δ 100.36 ppm) and H-6 (δ 6.06 ppm)
• C- 1''' (δ 100.45 ppm) and H-1''' (δ 3.82 ppm)
• C- 8 (δ 94.79 ppm) and H-8 (δ 6.27 ppm)
• C- 6” (δ 65.54 ppm) and H-6”(a) (δ 3.6 ppm)
• C- 6” (δ 65.54 ppm) and H-6”(b) (δ 3.3 ppm)
• C-(3’-OMe) (δ 56.31 ppm) and H-(3’-OMe) (δ 3.84 ppm)
• C- 6”’ (δ 18.35 ppm) and H-6”’ (δ 1.06 ppm)

HMBC :
The HMBC experiment (Fig.8) shows the following correlations:
• C-2 (δ 156 ppm) shows 2 spots of correlations with H- 2' (δ 7.99 ppm), H-6’ (δ 7.48 ppm)
• C-3 (δ 133.29 ppm) shows 1 spot of correlation with H-1” (δ 5.4 ppm)
• C-5 (δ 161.43 ppm) shows 1 spot of correlation with H-6 (δ 6.06 ppm)
• C-6 (δ 100.36 ppm) shows 1 spot of correlation with H-8 (δ 6.27 ppm)
• C-7 (δ 169.18 ppm) shows 2 spots of correlation with H-6 (δ 6.06 ppm)
H-8 (δ 6.27 ppm)
• C-8 (δ 94.79 ppm) shows 1 spot of correlation with H-6 (δ 6.06 ppm)
• C-9 (δ 157.22 ppm) shows 1 spot of correlation with H-8 (δ 6.27 ppm)
• C-10 (δ 102.75 ppm) shows 2 spots of correlation with H-6 (δ 6.06 ppm), H-8 (δ 6.27 ppm)
• C-1’ (δ 121.36 ppm) shows 2 spots of correlation with H-5’ (δ 6.89 ppm), H-2’ (δ 7.99 ppm) between C-2’ (113.81ppm) and H-6’ (7.48 ppm)
• C-3’ (δ 147.48 ppm) shows 2 spots of correlation with H-2’ (δ 7.99 ppm), H-5’ (δ 6.89 ppm)
• C-4’ (δ 150.19 ppm) shows 3 spots of correlation with H-2’ (δ 7.99 ppm), H-5’ (δ 6.89 ppm) H-6’ (δ 1.013 ppm)
• C-5’ (δ 115.63 ppm) shows spot of correlation with H-6’ (δ 7.48 ppm)
• C-6’ (δ 122. 27 ppm) shows 2 spots of correlation with H-2’ (δ 7.99 ppm), H-5’ (δ 6.89 ppm)
• between C- "6 (65.54) and H- '"1 (4.43)
On the basis of these data, the compound is assigned as isorhamnetin 3-O-rutinoside or isorhamnetin 3-O-α –L- rhamnopyranosyl - (1 6)-β- D- glucopyranoside also called Narcissin. The chemical structure of TR5I is shown in (Fig.9). was elucidated using spectroscopic data such as MS, UV-VIS, NMR 1D (^{1}H, ^{13}C) and NMR 2D (COSY, HMQC, HMBC) are in agreement with the literature [ixx-xxiii].
The separation of this compound is reported for the first time from the species *T. nudatum*

Structure activity relationships:
Through modeling, we were able to calculate some physic-chemical properties and identify the QSAR descriptors, shown in the table.1, 2 and 3.
According to table 1, compound TR51 has significant gap of energy (ΔE = 8.3091 eV), which calculated by E_{LUMO} - E_{HOMO}. In fact, low gap of energy makes the molecule less stable which allows electrons to flow easily and became more reactive. As an electronic descriptor, dipole moment (1.781) represents the electronic information of molecular, and reveals the separation of average charge in a compound [xiv], relatively, can reflect molecular polarity.
From table 2 (left), the lowest electron densities are located at C3 that shows the maximum positive charge (0.395). This carbon, relatively, could be attacked by nucleophile. While, O3 is relative to the preferential electrophilic attack for having a minimum negative charge (-0.326), because of the highest electron densities are located on it, the atoms with low charge have strong ability to electron-donating, and more capable to form hydrogen bonds with other molecules. For the general structure of TR51 compound (flavone), the bond length values

calculated by the PM3 method are not in good agreement with experimental values, particularly when considering substitutions (OH, CH3, and rutinoside) effects. However, the C2-C1' bond length (1.475 Å) matches the experimental value. On the other hand, bond lengths C9-O1, C6-C7, C2'-C3', C4'-C5', and C1'-C2' are too close to each other, as shown in table.

QSAR properties of isorhamnetin 3-O-rutinoside compound (**Fig. 9**) were studied are: Hydratation energy, the Octanol/Water partition coefficient (LogP), refractivity, molecular weight (MW), Molecular volume (MV), Molecular surface (MS), polarizability, hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), number of rotatable bond (NRB). The results are listed in Table 3.

The octanol/water partition coefficient (LogP) is used to predict the oral drug solubility which should be under 5. The solubility in water increases if LogP decreases, so is the absorption, and that could be noted for TR51 LogP value (-5.88). A negative value for LogP reveals that the TR51 compound is too hydrophilic. Whereas, compounds with0< LogP<3 value considered as better drug for oral bioavailability [vi]. But, molecular weight, H-bond donors (demonstrated as the sum of NHs and OHs, and H-bond acceptors (expressed as the sum of Os and Ns) are 624.55 DA, 9 and 16, whereas they should be less than 500 DA, 5 and 10, respectively, and that is according to Lipinski rules [xxv], for a good absorption and permeability of drugs. So is Veber et al [xxvi, xxvii] identified two other descriptors, they are: Number of Rotatable bonds (NRB) are under 10 that is validated for TR51 (NRB = 7), and Polar surface area (PSA) is under 140 $Å^2$.

V. CONCLUSION

In this study, We known the flavonoid (Isorhamnetin 3-Orutinoside) were identified by analysis using spectroscopic techniques, Ultra-Violet (UV), Nuclear Magnetic Resonance 1D (^{1}H-NMR,^{13}C-NMR), 2D (COSY, HMQC, HMBC) and Mass and define their QSAR descriptors. This compound isolated from the (n-butanol) extract, of the aerial parts of plant *T. nudatum*.

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REFERENCES

i. Bouaziz M, Dhouib A, Loukil S, Boukhris M, Sayadi S. Polyphenols content, antioxidant and antimicrobial activities of extracts of some wild plants collected from the south of Tunisia. Afric. *J.Biotechn*. 2009 ; 8:(24):7017-7027. http://www.academicjournals.org/AJB

ii. Chehma. A. M., 2006.- Catalogue des Plantes Spontanées du Sahara Septentrional Algérien. Dar Elhouda Ain M'lila, Algérie, 140p. https://camed.cirad.fr/content/download/4374/32172/version/2/file/Chehma+2006+Catalogue+des+plantes+spontan%C3%A9es+du+Sahara+septentrional+alg%C3%A9rien_compressed.pdf

iii. Ould Elhadj M. D., Hadj-Mahammed M., Zabeirou H., 2003.- Place des Plantes Spontanées dans la Médicine Traditionnelle de la Région d'Ouargla (Sahara Septentrional Est). Courrier du Savoir, 3: 47-51. http://archives.univ-biskra.dz/bitstream/123456789/395/1/6-Ould%20H%20didi.pdf

iv. Allaoui Messaouda, Cheriti Abdelkrim, Chebouat Elyacout, Dadamoussa Belkhir and Gherraf Nouredine, comparative study of the antioxidant activity and phenols and

flavonoids contents of the ethyl acetate extracts from two saharan chenopodacea: Haloxylon scoparium AND Traganum nudatum, *Algerian journal of arid environment*, Juin 2016, vol. 6(1), 71-79. https://journals.univ-ouargla.dz/index.php/AJAE/navigationMenu/view/Home

v. M Allaoui, A Cheriti , S Al-Gharabli , N Gherraf , E Chebouat , B Dadamoussa , and A Al-Lahham, A Comparative Study of the Antibacterial Activity of Two Chenopodiaceae: Haloxylon scoparium (Pomel) and Traganum nudatum Del., *Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS)*, 2014: 5(5), 85-89. https://www.researchgate.net/profile/Allaoui-Messaouda/publication/331558414_A_Comparative_Study_of_the_Antibacterial_Activity_of_Two_Chenopodiaceae_Haloxylon_scoparium_Pomel_and_Traganum_nudatum_Del/links/5c80047f458515831f8b07c4/A-Comparative-Study-of-the-Antibacterial-Activity-of-Two-Chenopodiaceae-Haloxylon-scoparium-Pomel-and-Traganum-nudatum-Del.pdf

vi. Smida, K., et al., Theoretical studies of structure/activity relationships applied to flavone derivate for drug discovery. Res J Pharm Biol Chem Sci, 2015. 6: p. 874-885. https://www.researchgate.net/publication/282222469_Theoretical_studies_of_structureactivity_relationships_applied_to_flavone_derivates_for_drug_discovery
Ø. M. Andersen, K. R. Markham. Flavonoids: Chemistry, Biochemistry and Applications, Press Taylor & Francis Group, 2005, 1197. https://doi.org/10.1201/9781420039443

vii. E. Grotewold. The Science of Flavonoids, Springer Science Business Media Inc., 2006, 273. https://www.researchgate.net/profile/Loic-Lepiniec/publication/226053992_The_Regulation_of_Flavonoid_Biosynthesis/links/0912f50f71222c1d87000000/The-Regulation-of-Flavonoid-Biosynthesis.pdf

viii. Li-jing Lin, Xiao-bing Huang and Zhen-cheng Lv, Isolation and identification of flavonoids components from Pteris vittata L., *Springer Plus* (2016) 5:1649, 1-3. https://springerplus.springeropen.com/articles/10.1186/s40064-016-3308-9

ix. D. S Nahari, S Prasetyawan, M A G Beltran and A Aulanni'am, Separation of Flavonoids in The Extract Polyalthia longifolia (Sonn.) Thw. Leaves from Indonesia and the Philippines, *Journal of Physics : Conference Series 1374*, (2019) 012001, 1-7. doi:10.1088/1742-6596/1374/1/012001

x. Gabriel Kahiking, Rymond J. Rumampuk, Emma J. Pongoh, Isolation and Identification of Flavonoid Derivative Compounds from n-Butanol Fraction of Red Pakoba (Syzygium sp.), *Fullerene Journ. Of Chem*, Vol.5 No.2: 53-57, 2020, 53-57. doi 10.37033/fjc.v5i2.152

xi. F. Cuyckens, M. Claeys. J. Mass Spectrom., 2004, 39, 1-15. DOI: 10.1002/jms.585

xii. J. Barbry, K. R. Makham, M. B. Thoma. The Systematic identification of flavonoids, Springer-Verlag : New york, 2012, 60, 9-14. https://books.google.dz/books?id=9JH_CAAAQBAJ&source=gbs_navlinks_s
https://books.google.dz/books?hl=en&lr=&id=9JH_CAAAQBAJ&oi=fnd&pg=PA3&dq=J.+Barbry,+K.+R.+Makham,+M.+B.+Thoma.+The+Systematic+identification+of+flavonoids,+Springer-Verlag+:+New+york,+2012,+60,+9-14.&ots=yDHB7hIKDQ&sig=pRVZ3X_KSPaY4W_FiOdIRjCsbHA&redir_esc=y#v=onepage&q&f=false

xiii. C. Tringali. Bioactive Compounds from Natural Sources, Taylor & Francis: London, 2001, 693. DOI : https://doi.org/10.1201/9781482289268

xiv. T. N. Mitchell, B. Costisella. NMR: From Spectra to Structures, 2 nd Edition, Springer: Berlin, 2004, 207. DOI : https://doi.org/10.1007/s00216-004-2810-z

xv. J. Marbone, T. J. Mabry, M. Mabry. The Flavonoids, Chepman and Hall: London, 1975, 46-61. https://nla.gov.au/nla.cat-vn356407

xvi. Evans, D.A., History of the Harvard ChemDraw project. Angewandte Chemie International Edition, 2014. 53(42): p. 11140-11145.

xvii. S. Chtita, Modélisation de molécules organiques hétérocycliques biologiquement actives par des méthodes QSAR/QSPR. Recherche de nouveaux médicaments, 2017. https://www.archives-ouvertes.fr/tel-01568788/document

xviii. Guillaume F, Développement de modèles QSPR pour la prédiction des propriétés d'explosibilité des composés nitroaromatiques, 2010. https://pastel.archives-ouvertes.fr/pastel-00006157/document

xix. Howard, A.; McIver, J.; Collins, J. HyperChem Computational Chemistry. Hypercube Inc. Waterloo. 1994.

xx. Boubaker, J., et al., Ethyl acetate extract and its major constituent, isorhamnetin 3-O-rutinoside, from Nitraria retusa leaves, promote apoptosis of human myelogenous erythroleukaemia cells. Cell Proliferation, 2011. 44(5) : p. 453-461. https://doi.org/10.1111/j.1365-2184.2011.00772.x

xxi. Sriseadka, T., S. Wongpornchai, and M. Rayanakorn, Quantification of flavonoids in black rice by liquid chromatography-negative electrospray ionization tandem mass spectrometry. *Journal of agricultural and food chemistry*, 2012. 60(47) : p. 11723-11732. DOI: 10.1021/jf303204s

xxii. Abdullabekova, V.N., N.A. Yunuskhodjaeva, and M.A. Khodjaeva, Implementation Chemical Research of the Woolly Erva Plants Growing in the Republic of Uzbekistan. *Annals of the Romanian Society for Cell Biology*, 2021: p. 682-694. https://www.annalsofrscb.ro/index.php/journal/article/view/2500

xxiii. Li, X., et al., Quantitative structure–activity relationship for prediction of the toxicity of phenols on Photobacterium phosphoreum. Bulletin of environmental contamination and toxicology, 2012. 89(1): p. 27-31. DOI 10.1007/s00128-012-0662-3

xxiv. Christopher A, Lipinski, Franco Lombardo, Beryl Dominy, Paul J F, Advanced Drug Delivery Reviews, 2012; 64:4–17.

xxv. Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD, J Med Chem. 2002;2615–2623.

xxvi. Eun Ha Lee, Hyoung Ja Kim, Yun Seon Song, Changbae Jin, Kyung-Tae Lee, Jungsook Cho, andYong Sup Lee, Constituents of the Stems and Fruits of Opuntia ficus-indica var. Saboten, *Arch Pharm Res* 2003, Vol 26(12) 1018-1023. https://koreascience.kr/article/JAKO200311922937821.pdf

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