Journal

J. Biol. Chem. Environ. Sci., 2009, Vol. 4(4): 877-890
www.acepsag.org

NOVEL β–CARBOLINE ALKALOID FROM *PEGANUM HARMALA* AS ANTIBACTERIAL AGANT

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ABSTRACT

A novel β–carboline alkaloid isolated from the aerial parts of Peganum harmala L. (Gen: Phyeophylaceae) have been characterized as l-thioformyl-8-β-D-glucopyranoside-bis-2,3-dihydro-isopyridinopyrrol. It is one of β–carboline alkaloids derivatives. The chemical structure was elucidated on the basis of elementary analysis and spectroscopic studies (UV, IR, ^{1}H-NMR & MS). The isolated compound showed significant antibacterial activity against Streptococcus pyogenus.

Key words: Peganum harmala, β–carboline, alkaloids, antibacterial.

INTRODUCTION

Harmal (Peganum harmala), or Syrian Rue, is a plant of the family Zygophyllaceae. It is grows in semi-arid conditions, native from the eastern Mediterranean region east to India. It is also known as Syrian Rue, an inaccurate name, since it is not in the rue (Ruta, Rutaceae) family. It is the plant from which harmine was first isolated, as well as a source of alkaloids, i.e., harmaline and tetrahydroharmine. Total β-Carboline content runs almost 4% by weight in the seeds of harmal (Hilal and Young ken, 1983; El-Bahri and Chemli, 1991 & Mills and Bone, 2000). Locally**,** the seeds of the plant are well known for fragrance and for insect killing properties when burnt. It is used as devil repellent and against evil eyes.

The alkaloids in harmal, has a wide spectrum of pharmacological actions in various scales. The different parts of harmal are used in traditional systems of medicine for the treatment of a variety of human

ailments as antispasmotic and antipyretic actions (Chopra et al., 1956). Also, it has been detected some effects as anticancerous (Bellakhdar, 1997), central nervous system effects (Bruinvels and Sourkes, 1968), hallucinogenesis (O'Hern and Mollivar, 1993), central monoamine oxidase inhibition (Nelson et al., 1979), binding to various receptors including 5-HT and benzodiazepine (McCormick and Tunnicliff, 1998), platelet aggregation inhibitory (Saeed et al.,1993), immunomodulatory effects (Li, 1996). Alkaloids of harmal include systemic arterial blood pressure reduction (Shi et al., 2000 and 2001). It is considered a rich sources of natural medicinal substances (El-Bahri and Chemli, 1991). These substances are found in a major amounts in the harmal seeds and a minor amounts in the aerial parts of plant. The β-carboline alkaloids (harmine, harmal, harmaline and harmalol) were reported by Wü et al. (1999) and Ma et al. (2000).

It is also consider as important resources of natural biological compounds useful in human medicine, Antimicrobial and plant protection (Towers, et al., 1989 and Kang, et al., 1992)). Also for phenolic compounds (Sharaf, et al., 1997 and Lambert, et al., 2005). Triterpenoids (Melek, et al., 1995 and Xü, et al., 1998) and steroidal glucosides compounds (Wang, et al., 1997).

The aerial parts of harmal have been give little attention. The objective of this study tend to isolate novel natural active compound from the leaves P. harmal L. and evaluate the compound against some pathogenic bacteria. The chemical structure elucidation of the active compound was also studied.

MATERIALS AND METHODS

Plant materials:

The green plants were collected from Matrouh governorate, Egypt. Fresh leaves were washed, air dried, ground to flour and kept in a closed container at 4°C until used.

Bacterial strains:

Three bacterial strains were used in this study (Bacillus subtilus, Shegilla sonnei and Streptococcus pyogenus) to evaluate the antibacterial activity.

Extraction and fractionation:

The fine powder of the plant material (100g) was extracted (Soxhelt) with n-hexane, followed by CCl_4 then MeOH, to obtained

three crude extracts. The three crude extracts were evaluated against the tested bacteria as will describe later. The MeOH extract showed the highest antibacterial activity.

Methanolic extract was fractionated into 5 fractions as described by Al Kofahi et al, (1996). Bioassaying test was performed scan the most fraction against the tested bacteria. Chromatographic separation using TLC was carried out for the fraction using an optimal solvent system (CCl_4:MeOH:H_2O, 9:1:1) according to the method of Stahl (1972). Four compounds were separated by the TLC. Each compound was bioassayed. Purification and determination was carried out for the highest active fraction.

Bioassay:

Different concentrations (50, 100, 150 and 200 μg/ml) from the crude extracts were prepared. The inhibitions width zone method, described by Jain and Kar (1971), was used to evaluate the antibacterial activity. The artificial antibiotic, Cursafe, was used to compare the relative percent of antibacterial activity.

Chemical structure elucidation:

The chemical structure elucidation of the purified active compound was studied by both of the elementary analysis and spectroscopic analysis (UV, IR, MS and ^{1}H–NMR). It was performed in the central laboratory, faculty of science, Cairo university.

Statistical analysis:

Statistical analysis was carried out using Duncan's rang test as described by Steel and Torrie (1981) and Gomez and Gomez (1984).

RESULTS AND DISCUSSION

Harmal (Piganum harmala) is used as an analgesic and antiinflammatory agent. In Yemen it was used to treat depression, and it has been established in the laboratory that harmaline, an active ingredient in Peganum harmala, is a central nervous system stimulant and a "reversible inhibitor of MAO-A (RIMA)," a category of antidepressant. Smoke from the seeds kills algae, bacteria, intestinal parasites and molds. Peganum harmala has "antibacterial activity," including antibacterial activity against drug-resistant bacteria. The "root is applied to kill lice" and when burned, the seeds kill insects. It also inhibits the reproduction of the Tribolium castaneum beetle. It is

also used as an anthelmintic (to expel parasitic worms). Reportedly the ancient Greeks used powdered Peganum harmala seeds to get rid of tapeworms and to treat recurring fevers (possibly malaria). Peganum harmala is an abortifacient, and, in large quantities, it can reduce spermatogenesis and male fertility in rats (Prashanth and John, 1999; Al Sharma et al., 1981; Abaza and Asar, 2003; Monsef et al., 2004; Sanchiata et al., 2004; Splettoesser et al., 2005; El-Dwairi and Banihani, 2007 & Arshad et al., 2008).

The extraction of natural products from harmal leaves using several solvents showed that crude methanolic extract was the major amount (2.61 %) as dry weight bases and the most effective against the tested bacteria particularly S. pyogenus (16.0 ± 0 mm).

Fractionation of methanolic extract:

Methanolic extract was fractionated into five fractions (F1-F5) as described by Al Kofahi et al. (1996). The Bioassaying against the tested bacteria (Table 1) showed that the first fraction (F1) was the most active one. Chromatographic separation (TLC) of the later fraction (F1) showed the presence of four compounds (C_1, C_2, C_3 and C_4), as indicated in Table (2).

The four compounds were bio-assayed to scanning for the most active one. The data showed that the major and most active one was the third compound (C_3) that has Rf value (0.55) against all tested bacteria, particularly S. pyogenus (18 ± 2 mm). Therefore, this compound was eluted and purified.

Different doses from the purified active compound (C_3) were used 50, 100, 150 and 200 µg/ml and bioassayed against the three tested bacteria, individually with comparing to cursafe (artificial antibiotic) in dose (200 µg/ml). Relative percentages of the inhibitory effect (Table 3) showed that the third and last dose (150 and 200 Mg) were the most active and its relative percentages 72.8 and 73.8 % against S. pyogenus, respectively (Table 3).

It is interest to indicate that some natural compounds extracted from harmal leaves has potent antibacterial activity and this inhibition increased with the increasing of doses (Nychas, 1995).

Table (1): Inhibitory effect of methanolic fractions against the tested bacteria.

Fractions	Tested bacteria					
	B. subtilus		*S. sonnei*		*S. pyogenus*	
	IW	ID	IW	ID	IW	ID
Control	0	(-)	0	(-)	0	(-)
F1	12±2	(++)	09±2	(+)	18±2	(+++)
F2	0	(-)	0	(-)	0	(-)
F3	0	(-)	0	(-)	0	(-)
F4	07±1	(+)	08±1	(+)	11±1	(++)
F5	0	(-)	0	(-)	07±0	(+)

Table (2): Inhibitory effect of the purified compounds separated from (F_1) against the tested microorganisms.

Fractions	Tested bacteria					
	B. subtilus		*S. sonnei*		*S. pyogenus*	
	IW	ID	IW	ID	IW	ID
Control	0	(-)	0	(-)	0	(-)
C1	0	(-)	0	(-)	7±1	(+)
C2	8±1	(+)	7±1	(+)	11±2	(++)
C3	13±2	(++)	10±1	(++)	20±1	(+++)
C4	0	(-)	0	(-)	0	(-)

All measurement were done in triplicates.
IW = Inhibition width zone (mm) ID = Inhibition degree
(+)= less than 10mm, (++)= from 10 to 15mm, (+++)= more than 15mm

Table (3): Means of relative percentages of antibacterial activity at different doses for purified active compound (C_3) compared to Cursafe as standard against the tested Bacteria.

Doses (µg/ml)	*B. subtilus*		*S .sonnei*		*S. pyogenus*	
	Mean/ mm	R.%	Mean/ mm	R.%	Mean/mm.	R.%
Control	-----	-----	-----	----	-----	-----
50	12.66 I	42.72	10.00 J	34.48	20.00 DE	58.25
100	15.33 H	51.69	12.00 I J	41.38	22.00 D	64.07
150	18.33 EFG	61.80	16.00 J H	55.17	25.00 C	72.81
200	19.00 EF	64.06	16.66 FGH	57.45	25.33 C	73.79
Cursafe	29.66 B	100	29.00 B	100	34.33 A	100

Cursafe = artificial antibiotic. R.% = Relative % compared with cursafe inhibition.
L.S.D 5% for conc. within columns. (A) = 1.3, within raws (B) = 1.041, (AB) = 2.32

Chemical structure elucidation:

Elementary analysis:

The elemental analysis on the purified active compound showed that it contained: C, H, N, S, O in percentages of 49.70%; 5.18%; 10.95%; 8.11% and 26.06%, respectively. The relative numbers of C, H, N, O, S atoms in the molecule are 16.7, 20.7, 3.12, 6.5 and 1 respectively. Thus the empirical formula is ($C_{16.7}H_{20.7}N_{3.12}O_{6.5}S$). As indicated by the mass spectroscopic measurements the molecular weight of the active compound is (411.3) indicated that the possible proposed molecular formula is $C_{17}H_{21}N_3O_7S$ must be the correct one. The active compound contain a number of nine unsaturated centers (4.5 π bond) with colorless fine needle crystals , m.p. 94 -95 ^{0}C $[\alpha]_d^t$ = - 39.3 (MeOH) and R_f value = 0.55 in the solvent system : $CHCl_3$/MeOH/H_2O (9/1/1).

The results showed that C, H, N, O, S atoms are 16.7, 20.7, 3.12, 6.5 and 1.0, respectively. Thus the empirical formula is C_{17} H_{21} N_3 O_7 S for the active compound. The active compound contain a number of 9 unsaturated centers (4.5 π bond) with colorless fine needle crystals, mp 95ºC and (α) d ^{t} = - 39.3 CC, 0082, $CHCl_3$-MeOH (1:1), Rf = 0.46 in solvent system (benzene:ethylacetate, 1:7) and MW = 411.

Spectroscopic analysis:

UV spectrum:

The UV data showed the presence of four absorption maximum bands at 232 nm, characteristic to dihydropyridinopyrrol ring A/B or D/B chromophors; at 262 nm. characteristic to C–S bond; 267 nm. represented the pyrrol ring (B) and at 275 nm. related to C=O bond (Scott, 1964).

IR spectrum:

The IR spectrum show absorption bands at 3416 ; 3024 and 1610 cm^{-1} corresponding to the amino group (NH) as a secondary amine. Another bands at 3507cm^{-1} (O-H); 2585cm^{-1} (C-S-C) and 1685.6cm^{-1} (six-membered cyclic γ-lactone). Absorption bands at 2680cm^{-1} and 1757.5cm^{-1} corresponding to (H and C=O) for aldehyde group. The absorption band at 896.9cm^{-1} indicated to the presence of β-glycosides linkage.

^{1}H–NMR spectrum:

The ^{1}H-NMR spectrum showed 21 proton in ratio (4:3:2:1:2:1:1:1:4:1:1) in eleven chemical shift groups (Fig 1). It

shows three protons doublet of doublet (dd) at δ 4.67ppm for three secondary amino groups (N_2, N_7 and N_9). It also showed four protons as multiplet at δ 3.84ppm attributed to two methylene groups(-CH_2-) as a doublet signal indicated the presence of two nitrogen functions on vicinal C-1/C-3 and C-6/C-8. The downfield shift triplets resonating at δ 5.38ppm, assignments to the C-4 and C-5 methene protons (-C-H) vicinal to C-3 and C-6 respectively (Atta-Ur-Rahman,1986). The other signals, which summarized in Table (4) indicated the presence of 7-azo-2,3,6,7-tetrahydro-β-carboline nucleus moiety.

Table (4): ^{1}H-NMR chemical shift for relevant protons of the active compound.

Signal	No. of protons	δ-values (chemical shift,ppm)
I	4H	3.84ppm (m,$C_3$and C_6)
II	3H	4.67ppm (dd,N-H at N_2,N_7 and N_9
III	2H	5.38ppm (t,C-$_4$ and C-$_5$)
IV	1H	8.95ppm (s, H-C(O)-S-)
V	2H	4.30ppm ($d_{1,C\text{-}6}$)
VI	1H	5.49ppm (dd,C-3)
VII	1H	5.51ppm (dd,C-4)
VIII	1H	5.59ppm (m,C-5)
IX	4H	5.83ppm (m, for all of (-OH)groups)
X	1H	6.01ppm (d,C-2)
XI	1H	7.50ppm (d,C-1)

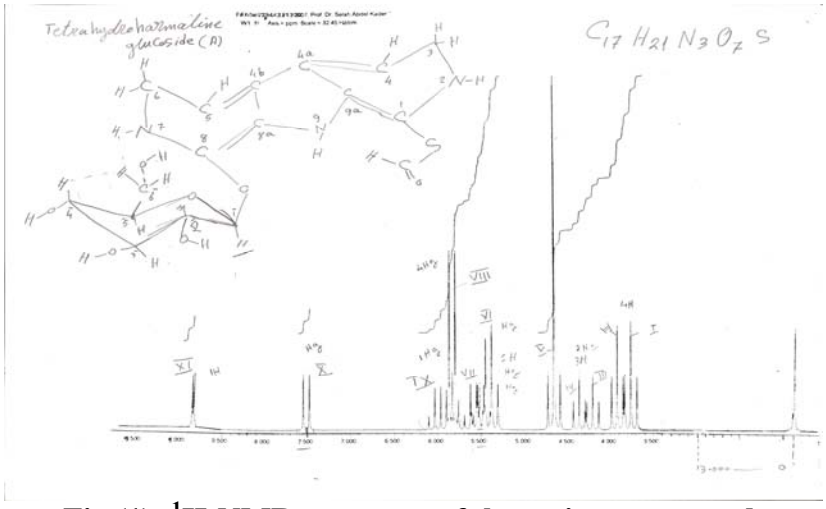


Fig (1): ^{1}H-NMR spectrum of the active compound.

Mass spectrum:

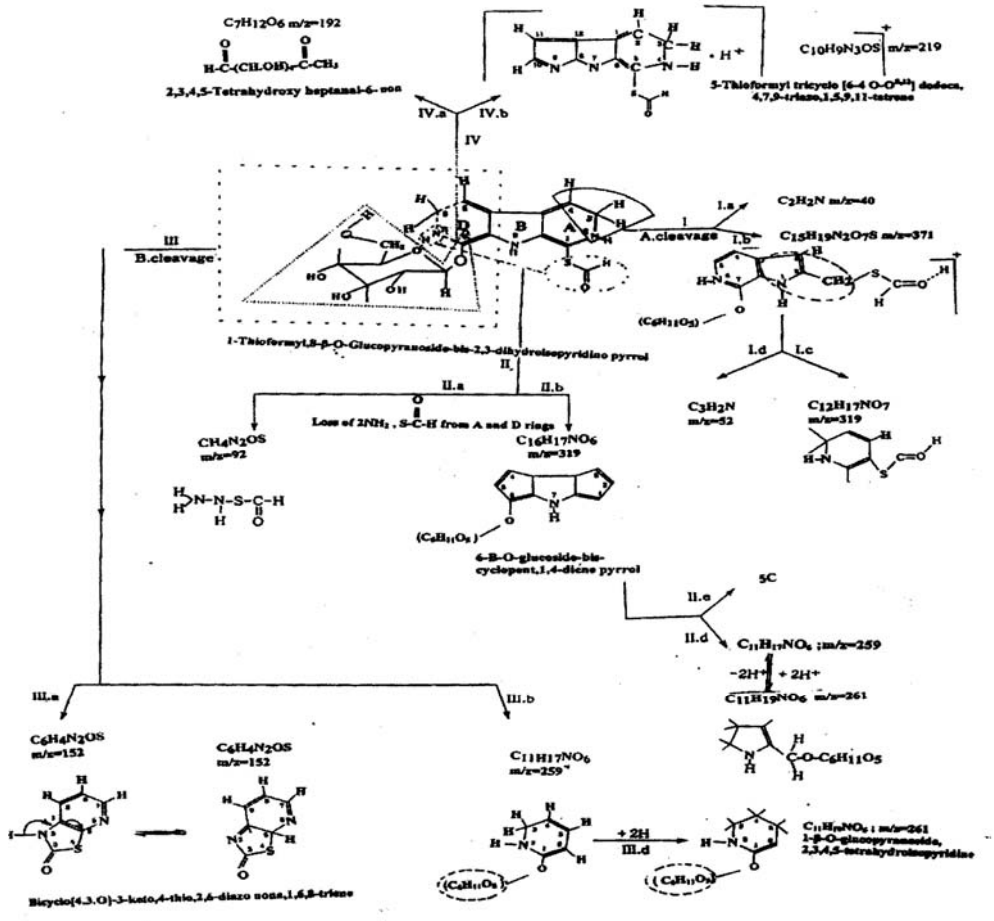
The mass spectrum showed a molecular peak (M^+) at m/z 412.47 (m/z 411.3) as determined by high resolution electron impact mass spectrum (HREI-MS). Corresponding to the molecular formula $C_{17}H_{21}N_3O_7S$. there are 9 degrees of unsaturated sites (with 4.5 π bonds). Eight unsaturated sites used for the tricyclic alkaloid skeleton (A/B ring or D/B ring in β-carboline), and one for aldehydic carbonyl group at C_1 (ring A as -S-C).

The presence of one O and one S and three N functions in rings A, B and D of the β-carboline-7-azo was indicated by the fragments at m/z 317 ($C_{15}H_{19}N_2O_7S$), 319 (C_3H_2N), 261 ($C_{11}H_{19}NO_6$) and at m/z 192 ($C_7H_{12}O_6$) as shown in scheme (1) and (2) indicated of β-carboline-7-azo (Mckenna and Towers, 1981). Also, these results indicated the presence of hexose moity was attach to D-ring at position (6) in isopyridine ring or at 8 position (8).

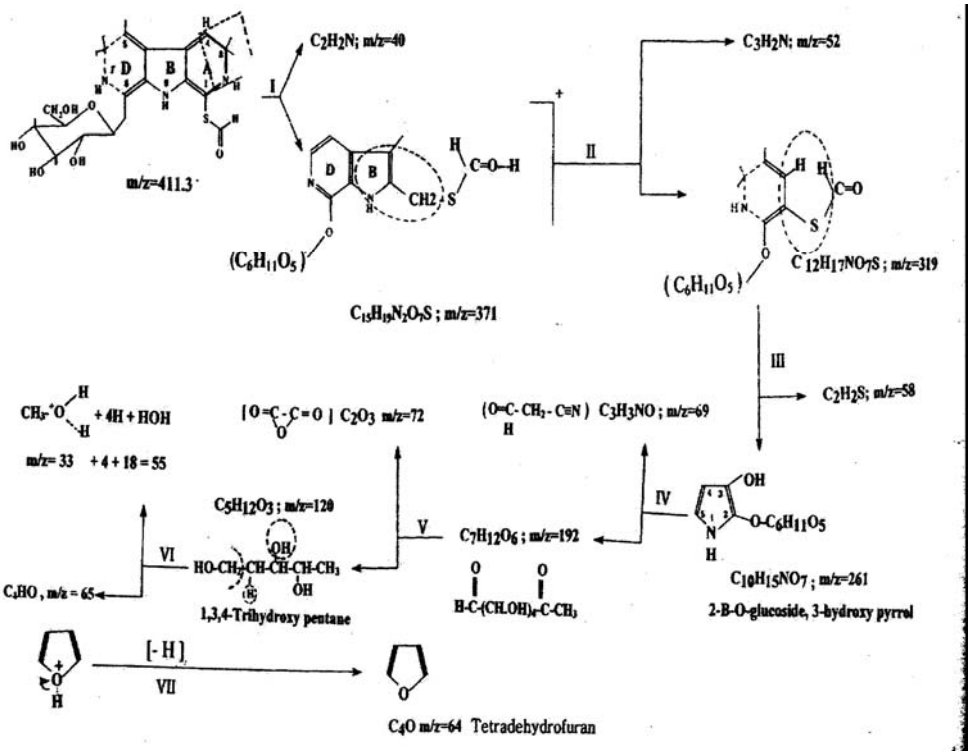
The fragment at m/z = 371, ($C_{15}H_{19}N_2O_7S$) resulted from cleavage between $N\text{-}_2$ and C_4 (in ring A) indicating the presence of one nitrogen function in ring A. The fragments at m/z 319 and m/z 52 (C_3H_2N) arose by the cleavage of the fragment at m/z 371. The peak at m/z 261, ($C_{11}H_{19}NO_6$) arise by the cleavage of ring B, was indicative of the presence of one oxygen , one sulfer and two nitrogen functions in rings A and B of the molecule (VandeVelde and lavie, 1983). The fragment at m/z 261 may arise also by the loose of a five carbon atoms from the fragment at m/z 319.

The fragment ion at m/z 192, ($C_7H_{12}O_6$) resulting by the cleavage of ring D, indicating the presence of six oxygenatoms, while the chemical composition of the remaining ion at m/z219 ($C_{10}H_9N_3OS$). Indicated the presence of one oxygen, one sulfur and three nitrogen functions in rings A, B and D (Mckenna and towers, 1981 and Aqeel et al., 1992). These results indicated the presence of hexose moiety attached to D-ring at position (6) in isopyridin ring or/and at position 8 in the active molecule by ether linkage. The presence of hexose moiety at $C\text{-}_8$ in the molecule (D-ring) was ensured by the analysis of the mass fragment at m/z 69 ($C_3H_3NO_2$) resulting by the loss of a $C_7H_{12}O_6$ (m/z192) fragment from the fragment at m/z 261. The fragment ion at m/z120 ($C_5H_{12}O_3$) resulting by the loss of a C_2O_3 (m/z=72) fragment from the fragment at m/z192.

The base ion at m/z 65 again resulted by the further loss of the chemical compositions of the remaining ion at m/z 55 (CH_3-O,HOH and 4H) from the fragment at m/z120. The presence of two 2,3-dihydroisopyridine rings linkages between C_2 / C_3 and C_4 /C_5 at the pyrrol ring was adduced by the fragments at m/z 371, 319, 261, 219 and at m/z 152. The later fragments indicted also the presence of only three nitrogen functions in the rings A,B and D (bis-2,3-dihydro isopyridino pyrrol or β-carboline-7-azo) and the presence of pyrrol ring (Siddiqui et al., 1987 and Berrougui et al., 2006). The overall mass fragmentation pattern of this compound was represented in schemes (1 and 2).



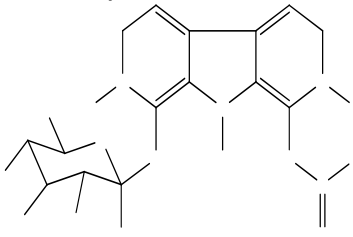
Scheme (1)



Scheme (2)

The previous spectroscopic studies led to the assignment of the active compound structure. 1-Thioformyl-8-β-O-D-glucopyranoside-bis-2,3-dihydroisopyridinopyrrol or 1-Thioformyl-8-β-O–D-glucopyranoside–β–carboline-7-azo.

It could be concluded from all of the previous spectroscopic data studies, A novel β–carboline alkaloid isolated from the aerial parts of Peganum harmala L. (Gen: Phyeophylaceae) have been characterized as l-thioformyl-8-β-D-glucopyranoside-bis-2,3-dihydro-isopyridinopyrrol. It is one of β–carboline alkaloids derivatives



1-Thioformyl-8-β-O-D-glucopyranoside-bis-2,3-dihydroisopyridinopyrrol

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مركب جديد من مشتقات البيتا-كاربولين الكالويد من نبات ال *PEGANUM HARMALA* كمضاد بكتيري

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قسم الكيمياء الزراعية – كلية الزراعة – جامعة المنيا

تم فصل مركب قلويدى جديد من مشتقات البيتا-كاربولين من نبات الحرمل (Peganum harmala L. (Gen: Phyeophylaceae). والمركب هو β-D-8-yl-thioformyl-glucopyranoside-bis-2,3-dihydro-isopyridinopyrrol .

وتم التعرف عليه بعد دراسة تركيبه الكيميائي بواسطة طرق التحليل العنصرية وطرق التحليل المتقدمة (UV, IR, ^{1}H-NMR & MS) . ووجد للمركب نشاط حيوي كبير كمضاد للبكتريا، خاصة بكتريا Streptococcus pyogenus .