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SYNTHESIS OF SOME GLYCYRRHETIC ACID SULFONAMIDE DERIVATIVES WITH PROSPECTED ANTIMICROBIAL ACTIVITY

By

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تخليق بعض مستحضرات السلفا مع حمض الجلسريهيتك وكفاءة نشاطها المضاد للميكروبات

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حضرت بعض مستحضرات السلفا مع حمض الجليسريهيتك (١– ٨) وذلك بتفاعله مع بعض لأدوية السلفا ، حيث أكد التركيب الكيميائي بالتحليل الجزئي للهيدروجين ، والأشعة تحت الحمراء ، والرنين النووي المغناطيسي ، والكربون ١٣ كما درس طيف الكتلة وقد درست كفائتها كمضادات للميكروبات بالمقارنة مع ٣ – بيتا أسيتوكسي كلوريد حمض الجليسريهتيك (أ) ولأدوية السلفا الأم وكذلك المذيب المستخدم (بروبلين جليكول) .

وقد أظهرت مستحضرات السلفا المحضرة (١ –٨) كفاءة ضد الميكروبات الإيجابية الجرثم (الميكروب العنقودي المكور الذهبي – عصويات الجمرة الخبيثة – والكريني باكتيريا عثرة الأبقار) وكذلك بكتريا سالبة الجرثم (الكلبسيللا والبروتيس والميكروب القولوني) بدرجات متفاوتة .

كما وجد أن كلوريد حمض الجليسريهتيك له كفاءة قاتلة للميكروبات خاصة ميكروب المكور العنقودي الذهبي وعصويات الجمرة الخبيثة والميكروب القولوني .

ويمكن إيجاز القول بأن تخليق مركبات جديدة من جزئيات السلفا وحمض الجليسريهيتك مرتبطة لها فاعلية مضادة لبعض المبكروبات إيجابية وسالبة الجرم بدرجات متفاوتة ، كما أن كلوريد حمض الجليسريهيتك له قدرة على قتل بعض الميكروبات .

Key Words: Glycyrrhetic acid sulfonamide derivatives, Microbial activity

ABSTRACT

Some glycyrrhetic acid sulfonamide derivatives (I-VIII) were prepared. Apart from their chemical structures which were confirmed by elemental analysis, IR, ^{1}H and ^{13}C-NMR, their behaviour under electron impact was also investigated; their antimicrobial activity was studied in comparison with 3 β-acetoxy glycyrrhetic acid chloride (A), parent sulfa drugs (1-8) and the solvent used (propylene glycol). It was noticed that the prepared sulfonamide derivatives (I-VIII) gave activity against Gram positive bacteria (*Staphylococcus aureus; Bacillus antherasis* and *Crynibacteria bovis*) and Gram negative bacteria (*Kebsilla pneumonie; Proteus valgaris* and *E. coli*) in different manner. Also glycyrrhetic acid chloride showed bacteriostatic effect against *Bacillus antherasis, Staphylococcus aureus* and *E.coli*. It could be concluded that the synthesis of new derivatives from glycyrrhetic acid gave activity against Gram negative bacteria in different manner. Also the glycyrrhetic acid chloride (original material) may be useful as curative against *B. antherasis, E. coli* and *S. aureus*.

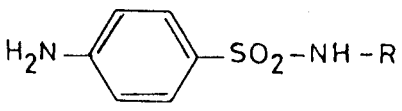
INTRODUCTION

The striking pharmacological properties of glycyrrhizin and its aglycone 18 b-glycyrrhetic acid as anti-inflammatory, antiulcer, viricidal and analgesic agents are well documented[1]. In last few years, the clinical application of glycyrrhetic acid derivatives and deglycyrrhizinated liquorice for promoting the healing of gastric ulcer have been reported[2].Another characteristic behaviour for liquorice root extract was its anti-microbial activity[3]. Segal *et al.*[4,5] reported that the ability of liquorice and glycyrrhizin to inhibit in vitro plaque formation by *Streptococcus mutans*. Many patents[4,5] for topical preparations contained glycyrrhizin dispersing agent showed also synergistic effect with antibiotics, fungicide and viricide activities. Also some other glycyrrhetic acid derivatives were found to possess anti ulcer and viricidal activities[6]. Thus the aim of the present investigation was to prepare some glycyrrhetic acid sulfonamide derivatives which may have anti microbial activity.

MATERIAL AND METHODS

I- Sulfa drugs Fig. 1

1- Sulfanilamide	2- Sulfacetamide sodium
3- Sulfaguanidine	4- Sulfathiazole
5- Sulfamethoxazole	6- Sulfadiazine
7- Sulfamerazine	8- Sulfadimidine



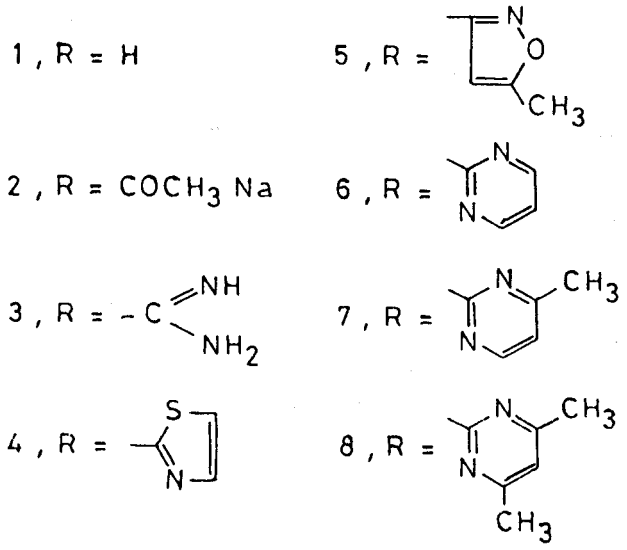
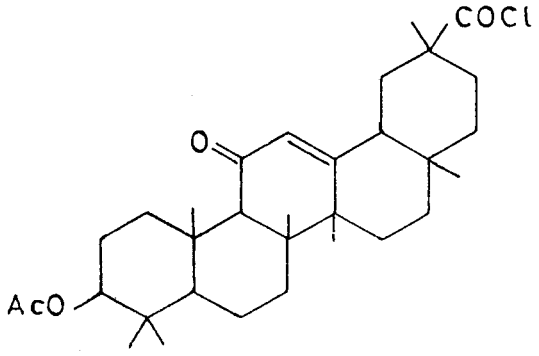


Fig. 1

II- Glycyrrhetic acid chloride (A)

Glycyrrhetic acid chloride (Fig. 2) was prepared according to Dean *et al.* [7].



3 β-Acetoxy-glycyrrhetic acid chloride

(A)

Fig. 2

III- Bacteria

Gram positive bacteria (*Staphylococcous aureus; Bacillius antherasis* and *Crynibacteria bovis*) and Gram negative bacteria (*Kebsilla pneumoni; Proteus valgaris*; and *E. coli*) were isolated and identified according to Cruickshank *et al.* [8].

Melting points are uncorrected. The IR spectra were recorded on Carl Zeiss Spectrophotometer IMR 16, MS on Varian MAT CH-5 at 70 eV and ^{1}H and ^{13}C-NMR on Bruker A. M-400 and 100.6 MHz respectively.

Synthesis of 3β-acetoxy-18β-glycyrrhetic acid sulfonamide derivatives (Fig. 3)

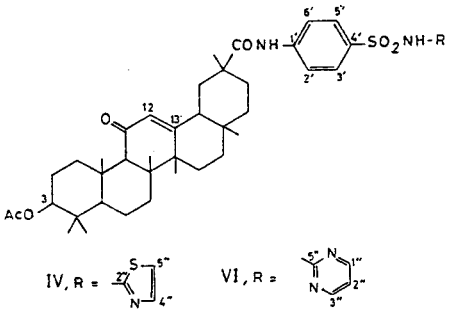


Fig. 3

Glycyrrhetic acid chloride (A) (one mole) was dissolved in benzene (15 ml) and added to a solution of sulfa drugs 1-8 (1.2 mole) in benzene (15 ml) containing pyridine (2 ml). The reaction mixture was refluxed and controlled by TLC. After cooling the reaction mixture was washed with 10% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent under vaccum gave solid material which was purified by PTLC and crystallised from $CHCl_3$-MeOH[9]

Determination of the possible antimicrobial activity of glycyrrhetic acid sulfonamide derivatives

The antimicrobial activity of each compound as well as the solvent was determined against *Staphilococcous aureus; Bacillius antherasis; Kebsilla pneumonie; Proteus valgaris; Crynilbacteria bovis* and *E. coli* using paper disk plate methods[10,11]. Whatman No. 1 filter paper disks (10 mm) were saturated with the tested materials, then placed on the agar plates surface which were previously inoculated with bacteria (enriched on nutrient broth for 24 hours) for one hour at 37° C. The plates were again reincubated at 37° C for further 24 hours. The disks which had been previously inocubated on the agar plate were observed to note the zone of growth inhibition adjacent to those disks containing the tested materials to which the bacterium is sensitive. The development of a zone of growth inhibition of any size around a disk indicated that the organism was susceptible to examined material. Resistant bacteria grow right up to the margin of the disk. The minimal inhibitory concentration of each tested compounds was determined by using a constant amount (60 μmg) of the components.

RESULTS AND DISCUSSION

The reaction between equimolar quantities of 3 β acetoxy-glycyrrhetic acid chloride (A) and the appropriate sulfa drugs (1-8) afforded the corresponding sulfonamide derivatives (I-VIII) as shown in Table 1. The IR spectra showed the presence of NH group at (3540-3440 cm^{-1}), ester group at (1735-1710 cm^{-1}), SO_2 at (1375-1325, 1162-1128) and the expected elemental analysis.

Table 1
The IR and elemental analysis of glycyrrhetic acid sulfonamide derivatives

Compound No.	m. p° C	Yield %	Molecular Formula (M^+, ion)	IR cm^{-1}				Analysis % Calculated-found		
				NH	Ester	C=O	SO_2	C	H	N
I	230-235	30	$C_{38}H_{54}O_6N_2S$	3340	1725	1656	1330	68.4	8.1	4.20
			(666)	3100		1640	1155	62.9	8.0	4.25
II	256-260	30	$C_{40}H_{56}O_7N_2S$	3420	1725	1660	1330	68.4	7.7	7.5
			(708)		1710	1640	1155	62.9	7.9	8.0
III	251-253	40	$C_{39}H_{56}O_6N_4S$	3440	1730	1690	1350	66.1	7.9	7.9
			(708)	3338		1655	1135	65.9	8.0	7.7
IV	280-282	65	$C_{41}H_{55}O_6N_3S_2$	3540	1720	1655	1360	65.7	7.3	5.6
			(749)	3340		1638	1140	70.3	7.7	5.1
V	188-190	45	$C_{42}H_{57}O_7N_3S$	3560	1735	1690	1325	67.5	7.6	6.4
			(747)	3380	1720	1660	1160	62.5	7.7	6.5
VI	282-2283	60	$C_{42}H_{56}O_6N_4S$	3540	1718	1680	1330	67.7	7.5	7.5
			(744)	3410		1648	1145	67.5	7.9	8.0
VII	320-322	60	$C_{43}H_{58}O_6N_4S$	3400	1725	1660	1330	68.1	7.6	7.4
			(758)				1162	67.9	7.9	7.1
VIII	305-308	65	$C_{44}H_{60}O_6N_4S$	3440	1722	1685	1375	68.4	7.7	7.2
			(772)	3160		1650	1128	68.9	8.4	7.3

The mass spectra of the prepared compounds showed the expected molecular ions [M^+], which are concordant with their molecular formulae although their existances were with very low intensity (Table 2 and Chart 1). Elimination of acetic acid from the molecular ions led to the formation of ion a which is predominent in compounds IV & VI but it was undetected in II & V. Ion a in compounds IV, VI-VIII may probably suffers from the loss of 43 mass units which are due to CO-NH-radical or CN_2H_3 residue in compound III with hydrogen ion transfer to give their corresponding ion *b*. Analogous ion at *m/z* 691 was detected in V after expulsion of -CO-NH-group and a methyl radical with hydrogen ion transfer from the parent ion (*m/z* 747). The eliminated methyl radical may be from the methoxazole ring (Chart 1).

Table 2
Fragmentation pattern of glycyrrhetic acid sulfonamide derivatives.

Com-pound No	M^+ %	*m/z* (relative intensity) *a*	*b*	*c*		*m/z* 527 *d*	*m/z* 512 *e*	*m/z* 649 *f*	*m/z* 466 g	*m/z* 406 *h*	*m/z* 257 *i*	*m/z* 216 *i*	*m/z* 175 *k*	*m/z* 149 *l*	Others
		M^+-AcOH	a-CONH	a-SO_2											
I	666 0.04	606 (0.06)	-	-		0.1	2.4	0.04	3.5	3.5	6.3	13.2	22.9	9.7	279(25.0), 167(43.0)
II	708	-	-	-		18.2	7.6	-	2.1	9.4	7.6	12.5	43.1	16.6	457(9.0), 388(12.0), 341(10.5), 277(20.0), 189(65.0), 135(60.0)
III	708 0.03	648 (0.23)	606 (12.4)	584 (0.7)		11.8	4.9	12.4	0.7	13.7	11.8	13.2	48.6	22.2	484(10.0), 452(10.0), 433(20.0), 418(17.0), 390(25.5), 378(10.0), 284(19.0), 189(57.0)

Table 2 Contd.

Compound No	M^+ %	*m/z* (relative intensity) *a* M^+-AcOH	*b* a-CONH	*c* a-SO_2	*m/z* 527 *d*	*m/z* 512 *e*	*m/z* 649 *f*	*m/z* 466 g	*m/z* 406 *h*	*m/z* 257 *i*	*m/z* 216 *i*	*m/z* 175 *k*	*m/z* 149 *l*	Others
IV	749 0.28	689 (48.8)	646 (41.9)	625 (2.3)	11.6	18.6	9.3	8.5	13.6	33.9	34.0	52.5	20.3	452(25.0), 391(12.0), 363(13.0), 303 (45.0), 189(25.0), 135(100.0)
V	747 0.70	-	-	-	22.9	9.0	0.7	9.0	20.1	9.0	20.1	56.3	23.6	587(19.9), 559(20.0), 388(15.0), 378(14.0), 309(23.0), 189(82.0)
VI	744.7	684 (63.2)	641 (58.1)	620 (93.0)	9.3	4.7	65.1	11.0	4.3	19.5	23.7	56.8	14.4	452(11.0), 437(10.0), 317(40.2), 303(90.0), 262(87.0)
VII	758 0.40	698 (2.4)	655 (1.0)	634 (4.4)	2.0	0.9	-	0.9	1.9	2.1	3.4	11.0	5.9	309(8.0), 189(19.0), 135(20.0)
VIII	772 0.04	712 (0.4)	669 (0.4)	648 (0.8)	-	5.9	0.8	14.7	13.5	24.4	47.5	55.9	19.3	452(9.0), 437(9.0), 303(31.0), 262(35.0), 135(90.0)

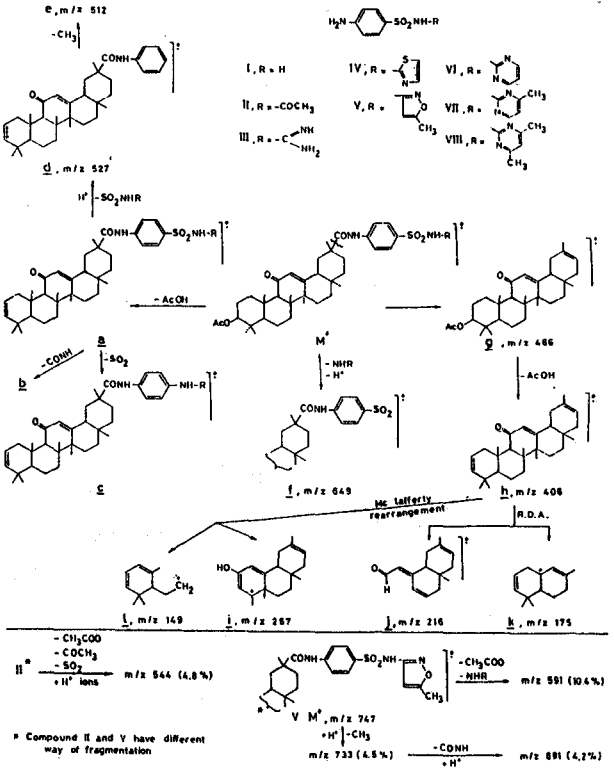


Chart 1

The loss of SO_2 from ion a in compounds III, IV, VI and VII was accompanied by skeletal rearrangement with the formation of C-N bond, to give ion c. This is common in arensulfonamide derivatives and not in alkyl sulfonamide congeners[12]. Consequently, compounds I and II do not show such type of prominent rearrangement. The unstability of compound II led to the spontaneous loss of SO_2, acetyl radical and acetate group with hydrogen ions transfer to afford an ion at *m/z* 544 (4.8%). Such ion is the unique ion which appears with high *m/z* value since there is no peak represents the molecular ion found in its spectrum (Chart 1).

The relative abundance of the prominant ions a, b, c is very high in diazine VI when compared with those found in merazine VII and dimidine VII and this reflects the stability of VI under electron impact. Such remarked differences could be used as a diagnostic tool for the differentiation between them.

The entire elimination of sulfonamide moiety linked to the aryl ring in ion species *a* found in all compounds, except compound VIII, affords ion *d* at *m/z* 527. The last ion suffers from the loss of methyl radical to give ion e at *m/z* 512.

With the exception of compound II and VII the cleavage of SO_2-NH-R linkage found in sulfonamide moiety, attached to the parent ion, led to the removal of -NH-R residue to form ion f at m/z 649. This ion is well represented in compound III, IV and VI. Analogous ion to f is found at *m/z* 591 in compound V which is

formed by the cleavage of the similar bond which led to the direct removal of both NH-R and acetyl radical.

The entire elimination of CO-NH-sulfonamide residue attached to C-20 from the molecular ion in all compounds affords ion g at *m/z* 466 which suffers from the removal of acetic acid to give ion *h* at *m/z* 406. Collapse of rings B and C by Mclafferty rearrangement and retro-Diels-Alder reaction[13] of the ion *h* led to the formation of the characteristic ions *i* and j at *m/z* 216 alongside with the remenants of rings A and B represented by ions k and l at m/z 175 and 149 respectively. The relative abundance of ions g-l are present with different ratio (Table 2).

The chemical structure of the prepared derivatives was confirmed by inspecting their ^{1}H-NMR and ^{13}C-NMR spectra. Apart from methyl signals which are found at the expected positions, the ^{1}H-protons and ^{13}C-NMR signals are existing without remarked up or down field shift (Tables 3,4 & Fig. 3). The existence of H-18 as singlet and signals due to C-12 and C-13 without any up field shift indicated that all the prepared sulfonamide compounds are derived from 18-β glycyrrhetic acid acetate[14,15].

Table 3

^{1}H-chemical shifts of compounds IV and VI(a)

Hydrogen	Compound IV	Compound VI
3	4.50q	4.50q
12	5.65s	5.65s
Acetate	2.03	2.03
NH	8.23,12.67	7.97,11.77
2'(b)	7.78	8.02
3'(b)	7.64	7.65
5'(b)	7.64	7.65
6'(b)	7.78	8.02
1"	-	8.60
2"	-	6.95
3"	-	8.60
4"	7.05d	-
5"	6.5d	-

(a): In ppm 400.12MHz, relative toTMS, solventCHCl$_3$

(b): The four protons in the benzene ring form AA'XX' system, two of them form a signal due to H-2'/6' and the signal for H-3'/5'

Table 4

^{13}C-Chemical shifts of compound IVandVI(c)

Carbon No.	CompoundIV	CompoundVI
3	80.53	80.52
11	200.28	200.18
12	128.30	128.41
13	169.68	169.36
CH_3COO	171.06	171.04
-CON	174.80	174.66
1'	135.68	133.98
2'	119.81	119.21
3'	127.76	129.73
4'	142.01	142.61
5'	127.76	129.73
6'	119.81	119.21
1"	-	156.64
2"	?	115.80
3"	-	156.64
4"	124.35	-
5"	108.13	158.55

(c): In ppm 100.2 MHz relative to internal TMS solvent $CHCl_3$

Regarding the effect of the solvent and the glycyrrhetic acid chloride (A), it was observed that the solvent has an inhibition zone on 6 bacteria ranging from 2 up to 6 mm. The original material gave an inhibitory effect which differs according to the type of bacteria. It is clear that the original material (A) has a powerful activity on Gram positive bacteria as *B. anthrasis* (27 mm) and on Gram negative bacteria as *E.coli* (21 mm) as well as a moderate action on *S. aureus* (15 mm) (Table 5). The sulfonamide derivatives I has a powerful and a moderate effect (22 and 10 mm) on the Gram negative bacteria (*P. valgaris* and *K. pneumonie*) respectively. Also it has a moderate effect (15 mm) on the Gram positive (*B. antherasis*) bacteria.

The sulfonamide derivatives II as well as its parent sulfa drug 2 have the same effect on all tested bacteria except II which has a powerful effect (20 mm) on *E. coli* and no effect on *K. pneumonie* (Table 5).

Also sulfa guanidine derivative III was effective on *S. aureus* (20 mm); *P. valgaris* (18 mm) and *E. coli* (10 mm) if it compared with 3. The effect of III was decreased or abolished on *B. antherasis* and *K. pneumonie.*

Sulfathiazole derivative IV has a powerful effect on *S. aureus*, *B. antherasis* and a moderate on *K. pneumonie*. However, its effect was decreased on *C. bovis* and *P. volgaris* than that 4.

The sulfa methoxazole derivative V and Merazine VII derivative, have no effect on tested bacteria in comparison with that of 5 and 7. The sulfadiazine derivative VI has a powerful activity on *B. antherasis* (20 mm) while the parent sulfa drug 6 has no effect. Meanwhile, the glycyrrhetic acid chloride (A) is highly effective (27 mm) than VI. This indicates that the derived compound from the reaction of sulfa drug (No. 6) with the acid chloride (A) decreases the activity of the parent terpenoid compound but promotes the activity of the sulfa drug against *B. antheraasis* (Table 5).

Table 5
Effect of the compounds (I-VIII) on the 6 bacteria

Tested compound	Gram positive bacteria			Gram negative bacteria		
	S.aureus	*B.anthrasis*	*C. bovis*	*K. Pneumoni*	*E.coli*	*P.valgaris*
Solvent(propylleneglycon)	4	6	2	2	3	4
Original compound (A)	15	27	5	3	21	6
Sulfanilamide (I)	30	6	10	5	5	8
Sulfanilamide+original (I)	30	15	4	10	7	22
Sulfacetamide sodium (2)	30	30	3	8	10	12
Sulfacetamide+original (II)	30	30	9	0	20	10
Sulfaguanidine (3)	10	30	10	7	3	8
Sulfaguanidine+original (III)	20	10	7	0	10	18
Sulfathiazole (4)	20	5	9	2	10	22
Sulfathiazole+Original (IV)	30	30	2	10	8	9
Sulfamethoxazol (5)	30	2	9	10	15	16
Sulfamethoxazole+original (V)	30	0	9	0	3	10
Sulfadiazine (6)	35	0	4	18	5	8
Sulfadiazine+original (VI)	17	20	8	2	7	10
Sulfamerazine (7)	30	0	8	6	12	10
Sulfamerazine+original (VII)	0	0	2	8	10	9
Sulfadimidine (8)	30	4	0	0	6	14
Sulfadimidine+original (VIII)	32	20	12	9	7	6

The sulfadimidine derivative VIII has a marked powerful effect on *B. antherasis, C. bovis* and *K. pneumonie,* but its effect on *P. volgaris* is weak than that of 8 (sulfadimidin) itself.

Table 5 illustrates that the parent triterpenoid compound (A) has a powerful broad spectrum activity against Gram positive represented in *B. antherasis* and Gram negative bacteria represented in *E. coli.* The prepared compounds III, IV and VIII have broad spectrum activity against Gram positive and Gram negative bacteria while compound I is only effective against Gram negative bacteria.

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