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### New Types of Mono and Bis Sulfonamides, Tosylamino Acids and Thiosulfonic Ester Derived from Xanthotoxin, Bergapten and Visnagin with Biological Interest

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## New Types of Mono and Bis Sulfonamides, Tosylamino Acids and Thiosulfonic Ester Derived from Xanthotoxin, Bergapten and Visnagin with Biological Interest

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*Xanthotoxin, bergapten, and visnagin sulfonyl chlorides have been reacted with diamines, hydrazine, amino acids, and imidazolidineiminothiones to produce the corresponding mono-, bis-sulfonamide, and tosylamino acid derivatives. Interaction of xanthotoxin-4-sulfonyl chloride with thiohydantoin furnished the respective thiosulfonic ester. The new products exhibited better antibacterial and antifungal activities.*

**Keywords** Bergapten; imidazolineiminothiones; tosylamino acids; thiohydantoin; visnagin; xanthotoxin

### INTRODUCTION

The furanocumarins (xanthotoxin, bergapten, ammajin, and psoralen), which were isolated from *Ammi majus* L.<sup>1,2</sup> are well known to be very helpful, not only for plants as antifungal and antibacterial factors,<sup>3</sup> but also for human disease treatment.<sup>4</sup> Elicitation of secondary metabolites in vitro cultures of *Ammi majus* L. have been studied.<sup>5</sup> This group of secondary metabolites has been successfully and effectively used because of its photoreactive properties in the treatment of leucoderma, vitiligo, and psoriasis diseases,<sup>6</sup> as well as in neurology-symptomatic treatment of demyelinating diseases, particularly in multiple sclerosis.<sup>7</sup> Xanthotoxin and bergapten could be also isolated and purified from *Cnidium monnieri* (L.) Cusson by high-speed counter-current chromatography.<sup>8</sup>

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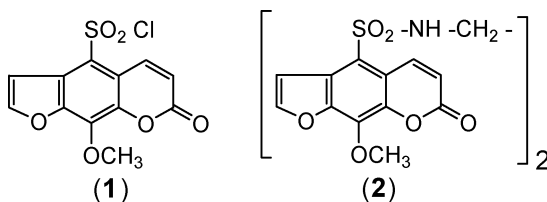
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Variation in xanthotoxin content in *Ammi majus* L. cultures during in vitro flowering and fruiting has been also studied.<sup>9</sup>

4-Methoxy-7-methyl-5  $\delta$  H-furo [3,2-g  $\delta$ ] benzopyran-5-one (Visnagin) isolated from *Ammi visnaga* L. has long been used as an analgesic and as strong coronary vasodilator for renal colic and renal stones. It has also selective antispasmodic effect upon the ureter, bronchial, muscles, and gall bladder, but its use appeared to be limited by undesirable side effects,<sup>10</sup> which attracted the authors to improve its activity. El-Sharief et al.<sup>11,12</sup> synthesized some xanthotoxin, bergapten, and ammajin derivatives with potential biological activities. They also,<sup>13-15</sup> prepared some visnagin derivatives containing biologically active units and some metal complexes of these ligands.<sup>16,17</sup>

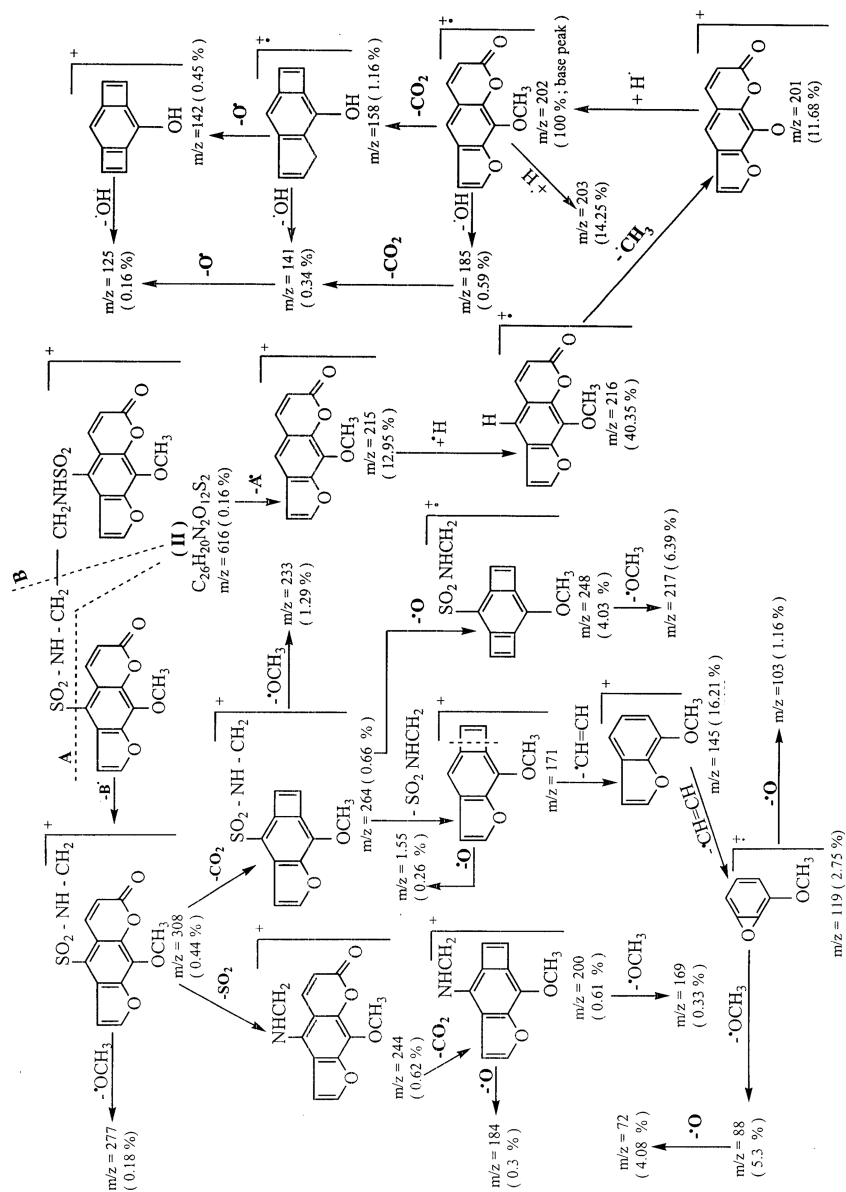
Since, a considerable number of bis heterocyclic compounds exhibited much better activities including (antibacterial, antifungal, tuberculostatic, and plant-growth regulative properties) than heterocyclic compounds,<sup>18,19</sup> the authors, in the present article, synthesized some heterocyclic compounds containing bis (xanthotoxin, bergapten, and visnagin) moieties linked together by a sulfonamide group, which have remarkable biological static activities.<sup>20</sup> Thus, xanthotoxin-4-sulfonyl chloride **1**<sup>21</sup> has been reacted with ethylenediamine (1:1 ratio) to produce bis-xanthotoxinsulfonamide derivative **2** which was characterized by elemental and spectral data (Scheme 1).

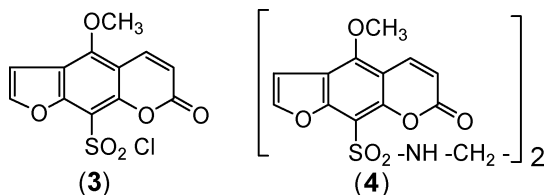


## SCHEME 1

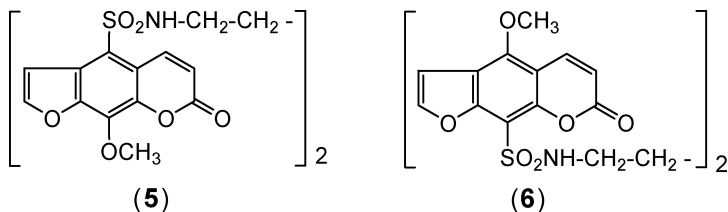
The <sup>1</sup>H nmr spectrum of **2** showed the expected signals assigned to 2 CH<sub>2</sub>, 2 OCH<sub>3</sub> and 8 Ar-H. The 2 NH appeared as broad signal and disappeared after the addition of D<sub>2</sub>O. Fragmentation pattern of **2** is illustrated in Figure 1. Similarly, bergapten-9-sulfonyl chloride **3**<sup>11</sup> has been reacted with ethylenediamine to yield the bis-heterocyclic product **4** (Scheme 2).

The IR and <sup>1</sup>H nmr spectra were consistent with structure **4**. Mass spectrum exhibited a fragment peak at m/z(308;0.5%,M./2); also, the fragments of bergapten and ethylenediamine were indicated. In a similar fashion, xanthotoxin, and bergapten sulfonyl chlorides **1** and **3** were reacted with 1,4-diaminobutane to give the bis heterocycles **5** and **6**, respectively (Scheme 3).

1559 **FIGURE 1**

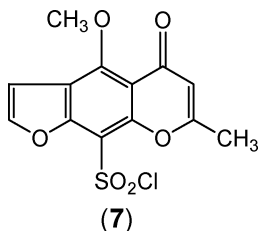


SCHEME 2



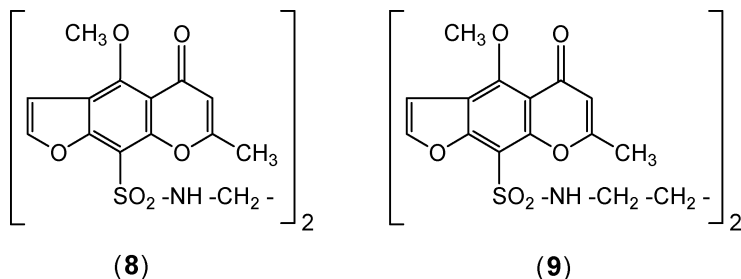
SCHEME 3

Structures **5** and **6** were elucidated by IR,  $^1\text{H}$  nmr, Mass spectra, and elemental analyses. The  $^1\text{H}$  nmr spectra of both exhibited two signals for the methylene and one for the methoxy protons, while the aromatic protons appeared as complex multiplets. In the down field region, a hump characteristic for 2 NH was observed and disappeared after addition of  $\text{D}_2\text{O}$ . The mass spectrum of **V** revealed fragments at  $m/z$  428 (M.-xanthotoxin), 202 (base peak, 9-hydroxypsoralin) and 84 diaminobutane. Visnagine-9-sulfonyl chloride **7** (Scheme 4)<sup>13,15</sup> was similarly reacted with ethylenediamine and 1,4-diamobutane to produce the bis-compounds **8** and **9**, respectively (Scheme 5).



SCHEME 4

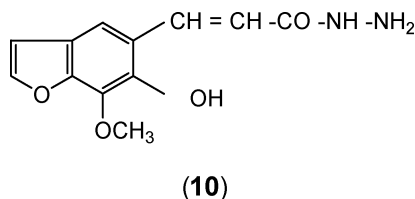
These structures of compounds **8** and **9** (Scheme 5) were confirmed by IR,  $^1\text{H}$  nmr, mass spectra, and elemental analyses. The IR spectra of **8** and **9** exhibited NH absorption at  $3170\text{ cm}^{-1}$ . The mass spectrum of **8** exhibited a fragment peak at  $m/z$  322, M/2, and 216 (base



SCHEME 5

peak, visnagin-CH<sub>3</sub>); also, the <sup>1</sup>H nmr showed the expected signals for aliphatic, aromatic, and variable hydrogens. The mass spectrum of 9 showed fragment peaks at m/z 336, M/2, and 216, 100% base peak (visnagin-CH<sub>3</sub>); <sup>1</sup>H nmr showed the respective signals for 4H(2 × CH<sub>2</sub>-C), 6H(2 × CH<sub>3</sub>-Ar), 4H(2 × CH<sub>2</sub>-N), 6H(2 × OCH<sub>3</sub>), 6H(Ar-H), and 2NH (disappeared after addition of D<sub>2</sub>O), respectively.

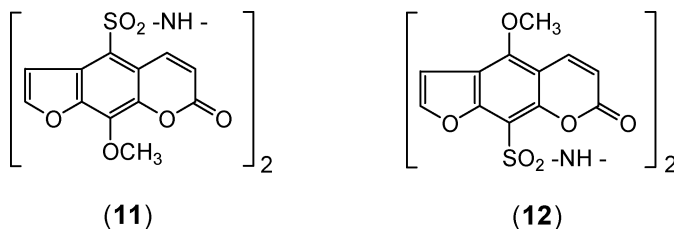
It was reported<sup>22</sup> that the interaction of hydrazine hydrate with xanthotoxin in boiling ethanol for longer reaction time (17 h) caused fission of the α-pyran ring and gave the hydrazide **10** (Scheme 6).



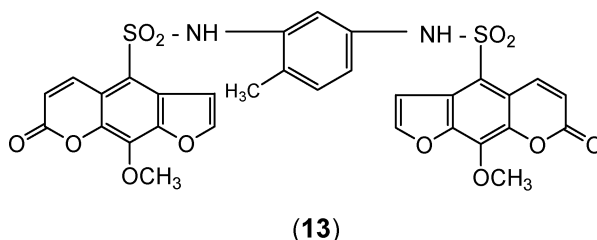
SCHEME 6

In the present investigation, xanthotoxin-4-sulfonyl chloride **1** has been reacted with hydrazine hydrate in boiling ether for one hr to give the bis-compound **11** and not open the α-pyranone ring.

Similarly, bergaptin-9-sulfonyl chloride **3** has been reacted with hydrazine hydrate under the same conditions to give **12**. The structures **11** and **12** were confirmed by elemental and spectral data (Scheme 7). The mass spectra of **11** and **12** resembles the mass spectrum of most of the synthesized bis-compounds, which exhibited half of the molecular weight, also most of them (xanthotoxin & bergaptin) showed the psoraline moiety as a base peak. Another type of bis-heterocyclic compounds could be achieved through the reaction of xanthotoxin-4-sulfonyl chloride **1** with 2,4-diaminotoluene (2:1) where the obtained product was consistent with structure **13** (Scheme 8).



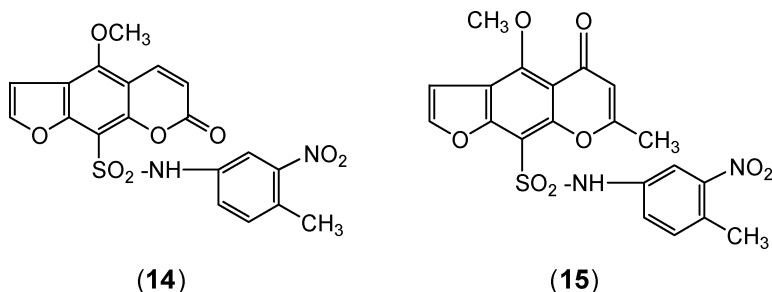
SCHEME 7



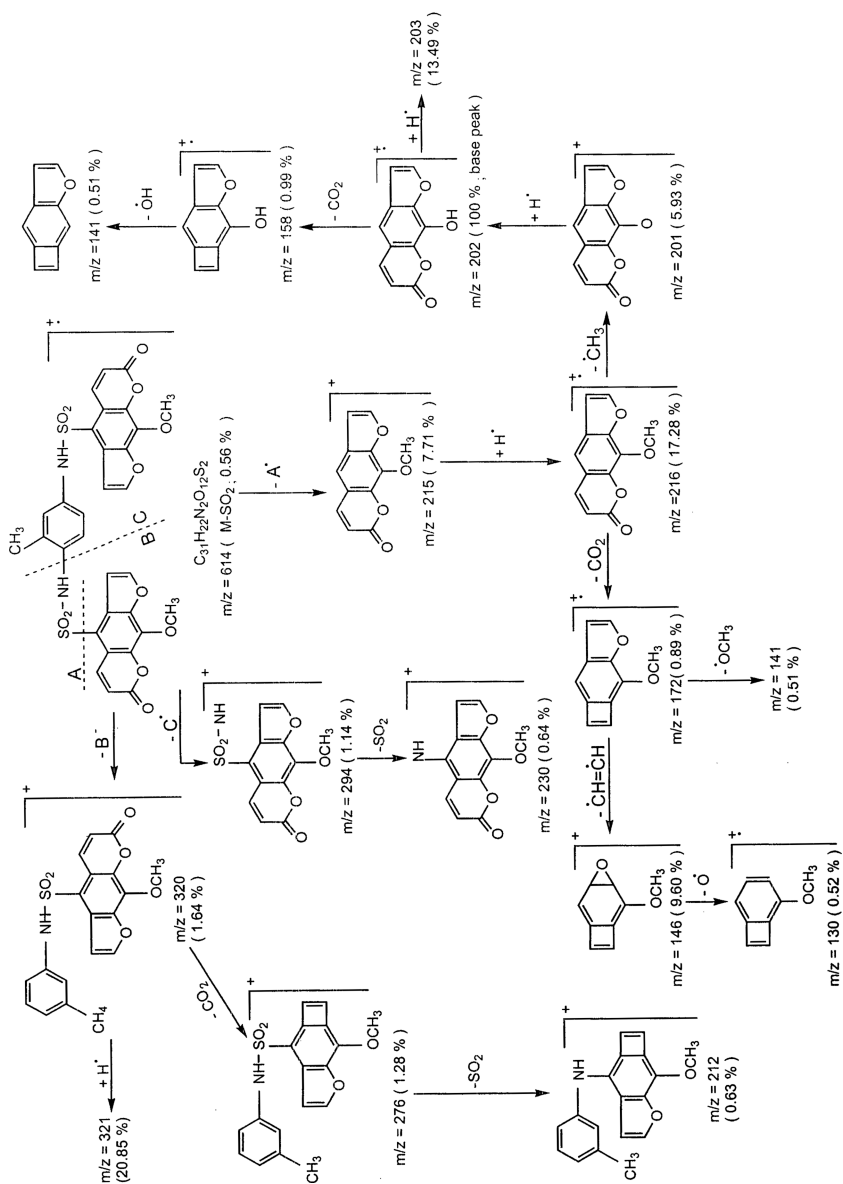
SCHEME 8

$^1\text{H}$  NMR of **13** showed in the up field region two singlets for the methyl and the two methoxy protons. The aromatic protons appeared as multiplets while the remaining hydrogens (2 NH) showed up as broad signal and disappeared after addition of  $\text{D}_2\text{O}$ . The fragmentation pattern of **13** is illustrated in Figure 2.

Attempted reaction of bergapten-9-sulphonyl chloride **3** or Visnagin-9-sulphonyl chloride **7** with 2,4-diaminotoluene hopping to obtain bis-heterocyclic compounds was unsuccessful, and instead, one amino group only reacted with the sulfonyl chloride while the other was oxidized by the atmospheric oxygen under the reaction conditions to the nitro group where bergapten and visnagin-9-sulphonamides **14**<sup>23</sup> and **15** were obtained, respectively (Scheme 9).

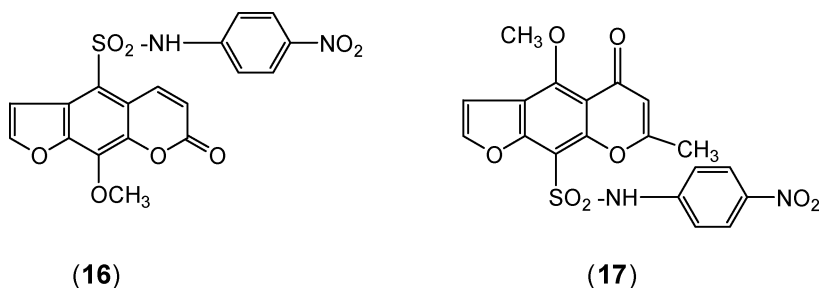


SCHEME 9

1563 **FIGURE 2**

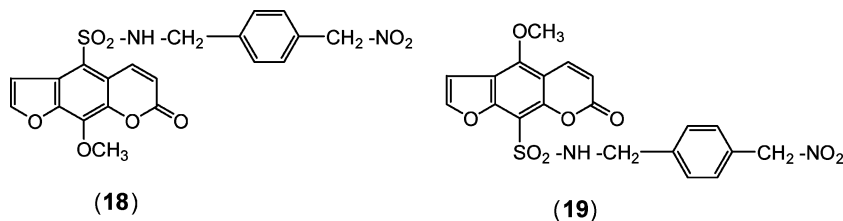


The structures **14** and **15** were established by IR,  $^1\text{H}$  nmr, mass spectra, and elemental analyses. Similarly, reacting p-phenylenediamine with xanthotoxin-4-sulfonyl chloride **1** or visnagin-9-sulfonyl chloride **7** to obtain bis-heterocyclic compounds was also unsuccessful, and instead, the corresponding p-nitrophenylaminosulfonyl derivatives **16** and **17** were obtained which were confirmed by elemental and spectral data (Scheme 10). Authentic samples of the nitro compounds **16** and **17** could be prepared through interaction of xanthotoxinsulfonyl chloride **1** and visnaginsulfonyl chloride **7** with p-nitroaniline in benzene as solvent and pyridine as catalyst (m.p. and m.m.p.).



**SCHEME 10**

Also, reaction of  $\alpha,\alpha$ -diamino-p-xylene with xanthotoxin-4-sulfonyl chloride **1** or with bergaptin-9-sulfonyl chloride **3** failed to give bis-heterocyclic products and instead one amino group reacted with the sulfonyl chloride and the other was oxidized to yield p-nitromethylphenyl derivatives **18** and **19**, respectively (Scheme 11). IR,  $^1\text{H}$  nmr, mass spectra and elemental analyses corroborated these structures.

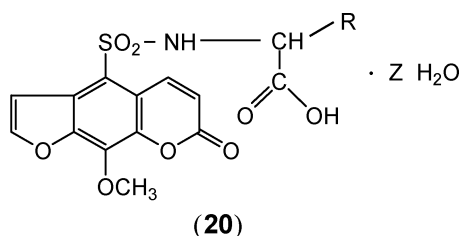


**SCHEME 11**

The mass spectrum of **18**, exhibited  $\text{M}^+$ ,  $\text{M}-1$ ,  $\text{M}-2$  and  $\text{M}-\text{CH}_3$ ; the  $^1\text{H}$  nmr of **18** and **19** showed three singlets for the aliphatic protons (two types of  $\text{CH}_2$  and one for the methoxyl protons). The eight aromatic protons appeared as multiplets and the NH as hump underneath the aromatic protons which disappeared after addition of  $\text{D}_2\text{O}$ .

In conclusion, (xanthotoxin, bergapten, and visnagin) sulfonyl chlorides **1**, **3**, and **7** have been reacted with aliphatic diamines (ethylenediamine and 1,4-diaminobutane), aromatic diamines (p-phenylenediamine and 2,4-diaminotoluene), as well as aralkyl diamines ( $\alpha,\alpha$ -diaminop-xylene) and hydrazine, hoping to obtain bis-heterocyclic compounds. It was found that aliphatic diamines and hydrazine gave bis products, while aromatic diamines and aralkyl diamines gave the mono sulphonamido products. Xanthotoxin-4-sulfonyl chloride and 2,4-diaminotoluene yielded a bis-product, which could be attributed to the fact that it is the most isolatable one. In the case of the diamines, which furnished mono sulfonamide, the other amino group was oxidized by the atmospheric oxygen under the reaction conditions to nitro group.<sup>24</sup>

The use of amino acids as starting materials for the design and synthesis of new potent biologically active compounds is the subject of interest<sup>25</sup> El-Sharief et al.<sup>26</sup> reported a facile synthesis for several heterocyclic compounds containing six, seven, and eight member rings fused to quinazoline moiety starting from amino acids. They also<sup>27</sup> synthesized a number of novel triazoles, triazolothiadiazoles, triazolothiadiazines, and triazolotriazines starting from amino acids. Thus, our interest in the chemistry of amino acids<sup>26,27</sup> and the chemistry of (xanthotoxin, bergapten, and visnagin)<sup>11-17</sup> led us to couple both in one moiety through a sulfonamide linkage hoping to obtain products with better activities. Thus, interaction of xanthotoxin-4-sulfonyl chloride **1** with L-alanine, DL-phenylalanine and L-tyrosine in presence of NaOH solution (10%) with subsequent acidification furnished the tosylamino acid derivatives **20** (Scheme 12).

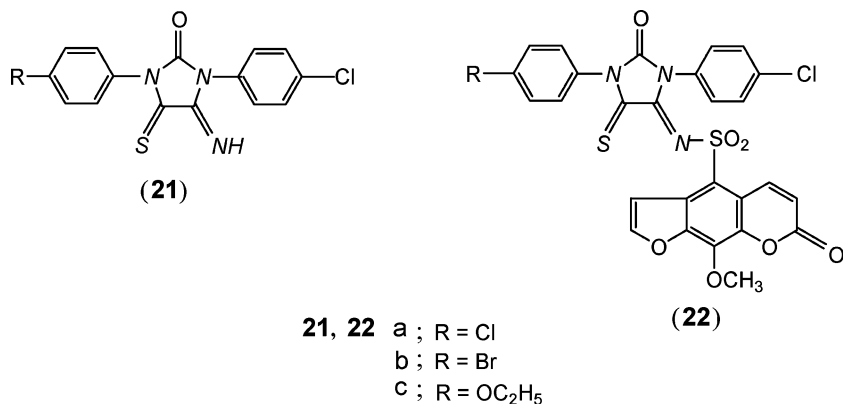


- 20 a** ; R = CH<sub>3</sub> ; Z = 0  
**b** ; R = CH<sub>2</sub> · C<sub>6</sub>H<sub>5</sub> ; Z = 0  
**c** ; R = CH<sub>2</sub> · C<sub>6</sub>H<sub>4</sub> · OH + p ; Z = 2

## SCHEME 12

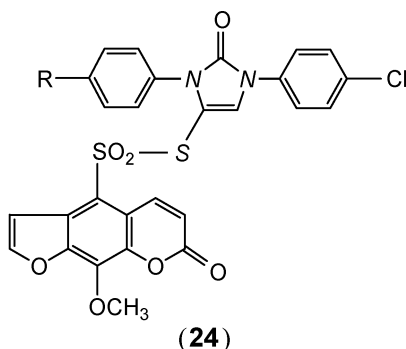
The MS of **20a** showed M<sup>+</sup> at m/z 367(8.71%), M+1 368 (1.46%) and base peak 215 (100%, xanthotoxin), also the mass spectra of **20b,c** were compatible with their structures. <sup>1</sup>H nmr spectrum of **20b**

exhibited in the aliphatic region (d, t, and s) corresponding to methylene, methyne and methoxy protons, respectively, while aromatic region exhibited (m and two broad s), which were characteristic for Ar-H and the reaining hydrogens (disappeared after addition of D<sub>2</sub>O). Imidazoles and their fused derivatives are key components of many bioactive compounds of both natural and synthetic origin.<sup>28</sup> Hydantoin derivatives are used in therapy as anticonvulsants and chemotherapeutics,<sup>29</sup> also biological and pharmacological activities were stated among derivatives of thiohydantoin.<sup>30–33</sup> Due to these activities and our interest in the chemistry of imidazoles,<sup>34–38</sup> and thiohydantoin,<sup>39–42</sup> we coupled xanthotoxin with imidazole and with thiohydantoin derivatives through a sulfonamide and thiosulfonic ester linkage, respectively, hoping to obtain new products with better biological and pharmacological activities. Thus, interaction of xanthotoxin-4-sulfonyl chloride **1** with imidazolidineiminothiones **21a–c**<sup>43</sup> proceeded easily through elimination of HCl to give **22a–c** respectively (Scheme 13). The IR spectrum of **22** revealed the absence of NH, also the <sup>1</sup>H nmr, mass spectrum and elemental analyses were compatible with structure **22**.



**SCHEME 13**

El-Sharief et al.<sup>42</sup> reacted thiohydantoin with chloroacetic acid and its derivatives through elimination of HCl to give the S-alkyl derivatives. In the present investigation thiohydantoin **23**<sup>43</sup> has been reacted successfully with xanthotoxin-4-sulfonyl chloride **1** to produce the thio-sulfonic acid ester derivative **24** which its structure was elucidated by elemental and spectral data (Scheme 14).



**23, 24** ; R = Br

## ANTIMICROBIAL ACTIVITY

## Antibacterial Activity

## ***Gram Negative Bacteria***

Compounds 1,4-bis (Xanthotoxin-4-sulfonamido) butane (**5**) and Xanthotoxin-4-sulfonamido derivative (**18**) possess a very high antibacterial activity towards (*E. coli*, NCTC-10416) they have the same effect as the standard chloramphenicol at all concentrations (1, 2.5, and

5 mg/ml). The bis compounds **6**, **8**, and **13**, the mono sulfonamido derivative, which contain nitrophenyl group **15**, **16**, **17** and **19**, and the tosyl amino acid derivative (**20c**) showed a high antibacterial activity against the same organisms (*E. coli*, NCTC-10416); the compounds exhibited the same effect as the standard chloramphenicol at MIC (1 g/ml). The bis xanthotoxin sulfonamides **2** and **5** exhibited a high antibacterial activity against the gram negative bacteria (*Salmonella typhi*, ATCC-13311). They exhibited the same effect as standard chloramphenicol at MIC (2.5 g/ml). Also, compound **14** exhibited moderate antibacterial activity against the same organism at all concentrations used (1, 2.5, and 5 g/ml). Compounds **4**, **6**, **8**, **11**, **12**, **18**, **19**, **20a**, and **20b**, also showed moderate activity against the same organism (*Salmonella typhi*, ATCC-13311) at MIC 1 and 2.5 mg/ml. The results of antibacterial activity against Gram negative bacteria are summarized in Table I.

### Gram Positive Bacteria

Most of the synthesized compounds exhibited various antibacterial activities towards the bacterial strains used (*Staphylococcus aureus*, NCTC-7447 and *Bacillus subtilis*, NCIB-3610). Thus, compounds **17** and **20c** possess the highest activity against (*Staphylococcus aureus*, NCTC-7447) at MIC (2.5 g/ml), also, compounds **9**, **15**, **17**, and **20c** showed the same activity against the same organism at MIC (5 g/ml). Compounds **2**, **4**, **8**, and **11** also exhibited the highest activity against (*Bacillus subtilis*, NCIB-3610) at MIC (2.5 and 5 mg/ml). All the synthesized compounds used, except No. **20c**, showed moderate activity against the same organism (*Bacillus subtilis*) at MIC (1 mg/ml). However, none of the tested compounds showed superior activity compared with the reference antibiotic. The results are represented in Table II.

### AntiFungal Activity

Most of the prepared compounds were tested for their antifungal activity using (*Aspergillus terreus*, Ferm-BAM-C21 and *Aspergillus flavus*, Ferm-BAM-C22). The results of the antifungal activity and (MIC) are summarized in Table III. Some of the synthesized compounds exhibited various antifungal activities towards the two test fungus used. Compound (**28**) showed the highest activity against (*Aspergillus flavus*, Ferm—BAM - C22) at MIC 5 mg/ml. Also, compounds **4**, **12**, **17**, **20a**, **c** exhibited moderate antifungal activities against both the two tested fungus used in all concentration (1, 2.5, and 5 mg/ml), while compound (**20b**) showed moderate activity against (*Aspergillus terreus*, Ferm-BAM-C21) at MIC (1 mg/ml).

**TABLE I Antimicrobial Activity Against (Gram Negative Bacteria)**

Sample no.	Test organisms/concentration (mg/ml)					
	<i>E. Coli</i>			<i>Salmonella typhi</i>		
	1	2.5	5	1	2.5	5
<b>2</b>	+	+	++	+	++	++
<b>4</b>	+	++	++	+	+	+
<b>5</b>	++	+++	+++	+	++	++
<b>6</b>	++	++	++	+	+	+
<b>8</b>	++	++	++	+	+	+
<b>9</b>	+	++	++	0	+	+
<b>11</b>	+	+	++	+	+	+
<b>12</b>	+	+	++	+	+	+
<b>13</b>	++	++	++	0	0	0
<b>14</b>	+	++	++	+	+	++
<b>15</b>	++	++	++	0	0	+
<b>16</b>	++	++	++	0	0	0
<b>17</b>	++	++	++	0	+	+
<b>18</b>	++	+++	+++	+	+	+
<b>19</b>	++	++	++	+	+	+
<b>20a</b>	+	++	++	+	+	+
<b>20b</b>	+	+	++	+	+	+
<b>20c</b>	++	++	++	0	0	+
<b>22d</b>	++	++	+++	+	+	++
<b>St.</b>	++	+++	+++	++	++	+++

The organisms were tested against the activity of different concentrations of the sample. St. = Reference standard; Chlorampfenicol was used as a standard antibacterial agent and Grisofluvine was used as standard antifungal agent. The test was done using the diffusion agar technique. Well diameter. 1 cm ... (100 ul of each conc. was tested). Inhibition values = 0.1–0.5 cm beyond control = +; inhibition values = 0.6–1.0 cm beyond control = ++; inhibition values = 1.1–1.5 cm beyond control = +++; 0 = not detected.

## CONCLUSION

The sulphonyl chloride derivatives (**1**, **3**, and **7**) of xanthotoxin, bergapten, and visnagin were reacted with various diamines. Most of these reactions produced the expected bis sulfonamides, while the others gave unexpected products due to the formation of mono sulfonamides with oxidation of the other amino group to nitro, which could be attributed to atmospheric oxygen oxidation under the reaction conditions. Xanthotoxinsulfonyl chloride (**1**) was also reacted with different amino acids, imidazole, and thiohydantoin derivatives. Many of the new products exhibited activity against (*E. Coli*) as the reference standard

**TABLE II Antimicrobial Activity Against (Gram *Positive* Bacteria)**

Sample no.	Test organisms/concentration (mg/ml)					
	<i>Staphylococcus aureus</i>			<i>Bacillus subtilis</i>		
	1	2.5	5	1	2.5	5
<b>2</b>	+	+	+	+	++	++
<b>4</b>	+	+	+	+	++	++
<b>5</b>	+	+	+	+	+	+
<b>6</b>	+	+	+	+	+	+
<b>8</b>	+	+	+	+	++	++
<b>9</b>	+	+	++	+	+	+
<b>11</b>	+	+	+	+	++	++
<b>12</b>	+	+	+	+	+	++
<b>13</b>	+	+	+	+	+	+
<b>14</b>	+	+	+	+	+	+
<b>15</b>	+	+	++	+	+	+
<b>16</b>	+	+	+	+	+	+
<b>17</b>	+	++	++	+	+	+
<b>18</b>	+	+	+	+	+	+
<b>19</b>	+	+	+	+	+	+
<b>20a</b>	0	0	+	+	+	+
<b>20b</b>	0	0	+	+	+	+
<b>20c</b>	+	++	++	0	+	+
<b>22c</b>	+	+	++	+	++	++
<b>St.</b>	+++	+++	+++	++	+++	+++

The organisms were tested against the activity of different concentrations of the sample. St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Grisoflavin was used as standard antifungal agent. The test was done using the diffusion agar technique. Well diameter: 1 cm ... (100 ul of each conc. was tested). Inhibition values = 0.1–0.5 cm beyond control = +; inhibition values = 0.6–1.0 cm beyond control = ++; inhibition values = 1.1–1.5 cm beyond control = +++; 0 = not detected.

chloramphenicol. Antiviral and antitumor activities of these products will be tested, and the results will be reported in due course.

## EXPERIMENTAL

All melting points are uncorrected and were determined on an electrothermal STUART melting point apparatus (SCIENTIFIC Co. Ltd., UK). IR spectra ( $\text{cm}^{-1}$ ) were determined with a Jacso FT/IR 5300 spectrophotometer using KBr technique.  $^1\text{H}$  NMR spectra were measured using a Jeol FX-100 spectrometer 60 MHz and a Varian Gemini 200 instrument 200 MHz (Cairo Univ.) and 250&300 MHz using TMS as an internal standard, DMSO- $d_6$  as solvent and chemical shift were expressed

**TABLE III Antifungal Activity**

Sample no.	Test organisms/concentration (mg/ml)					
	<i>Aspergillus terreus</i>			<i>Aspergillus flavus</i>		
	1	2.5	5	1	2.5	5
<b>2</b>	0	0	0	0	+	+
<b>4</b>	+	+	+	+	+	+
<b>5</b>	0	+	+	+	+	+
<b>6</b>	0	0	+	0	+	+
<b>8</b>	0	0	0	0	0	+
<b>9</b>	0	+	+	+	+	+
<b>11</b>	0	0	+	+	+	+
<b>12</b>	+	+	+	+	+	+
<b>13</b>	0	0	+	+	+	+
<b>14</b>	0	+	+	0	+	+
<b>15</b>	0	0	+	0	0	+
<b>16</b>	0	+	+	+	+	+
<b>17</b>	+	+	+	+	+	+
<b>18</b>	0	+	+	+	+	++
<b>19</b>	0	0	0	0	+	+
<b>20a</b>	+	+	+	+	+	+
<b>20b</b>	+	+	+	0	+	+
<b>20c</b>	+	+	+	+	+	+
<b>22c</b>	—	—	+	—	—	+
St.	++	+++	+++	+++	+++	+++

The organisms were tested against the activity of different concentrations of the sample. St. = Reference standard; Chlorampfenicol was used as a standard antibacterial agent and Grisofluvine was used as standard antifungal agent. The test was done using the diffusion agar technique. Well diameter: 1 cm ... (100  $\mu$ l of each conc. was tested). Inhibition values = 0.1–0.5 cm beyond control = +; inhibition values = 0.6–1.0 cm beyond control = ++; inhibition values = 1.1–1.5 cm beyond control = +++; 0 = not detected.

in  $\delta$  values. Mass spectra were obtained by use of a Shimadzu–GC MS–QP 1000EX instrument using the direct inlet system. Elemental analyses were determined using a Perkin–Elmer 240 (Microanalyses) instrument, at Cairo University. Antibacterial and antifungal activities of the synthesized products were carried out by Fermentation Biotechnology & Applied microbiology (FERM–BAM) Center, Al-Azhar University, Cairo, Egypt, and are shown in Tables I–III. Physical data of these compounds are shown in Table IV.

### Condensation of (1, 3, or 7) with Aliphatic Diamines

A mixture of (1, 3; 3.14 g or 7; 3.28 g; 10 m moles); ethylenediamine (0.6 g; 10 m moles) or 1,4-diaminobutane (0.88 g; 10 m moles) in dry ether



TABLE IV Physical Data of the Synthesized Compounds

Compd. no.	Yield (%)	M.P. [°C]	Cryst. solvent	Mol. formula (Mol. wt.)	Elemental analyses Calcd./found [%]				
					C	H	N	S	Cl
<b>2</b>	20	171–173	E/W (1:1)	C <sub>26</sub> H <sub>20</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (616)	50.65 50.40	3.25 3.30	4.55 4.60	10.39 10.50	—
<b>4</b>	23	183–185	E/W (1:1)	C <sub>26</sub> H <sub>20</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (616)	50.65 50.80	3.25 3.20	4.55 4.50	10.39 10.50	—
<b>5</b>	23	160–162	E/W (1:1)	C <sub>28</sub> H <sub>24</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (680)	49.41 49.50	3.53 3.60	4.12 4.10	9.41 9.30	—
<b>6</b>	25	191–192	E/W (1:1)	C <sub>28</sub> H <sub>24</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (680)	49.41 49.30	3.53 3.50	4.12 4.10	9.41 9.50	—
<b>8</b>	15	205–207	E	C <sub>28</sub> H <sub>24</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (644)	52.17 52.30	3.73 3.70	4.35 4.40	9.94 9.70	—
<b>9</b>	20	175–173	E	C <sub>30</sub> H <sub>28</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (672)	53.57 53.70	4.17 4.20	4.17 4.00	9.52 9.40	—
<b>11</b>	15	167–169	E/W (1:1)	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (588)	48.98 49.00	2.72 2.70	4.76 4.70	10.88 10.70	—
<b>12</b>	15	215–217	E/W (1:1)	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (588)	48.98 49.00	2.72 2.80	4.76 4.60	10.88 10.90	—
<b>13</b>	25	221–223	E	C <sub>31</sub> H <sub>22</sub> N <sub>2</sub> O <sub>12</sub> S <sub>2</sub> (678)	54.87 55.00	3.24 3.20	4.13 4.00	9.44 9.50	—
<b>15</b>	20	240–242	E	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>8</sub> S (444)	54.05 54.00	3.60 3.70	6.31 6.30	7.21 7.10	—
<b>16</b>	23	287–289	E	C <sub>18</sub> H <sub>12</sub> N <sub>2</sub> O <sub>8</sub> S (416)	51.92 52.10	2.89 2.90	6.73 6.60	7.69 7.60	—
<b>17</b>	20	277–279	E	C <sub>19</sub> H <sub>14</sub> N <sub>2</sub> O <sub>8</sub> S (430)	53.02 53.10	3.26 3.10	6.51 6.70	7.44 7.30	—
<b>18</b>	25	235–237	E	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>8</sub> S (444)	54.05 54.00	3.60 3.70	6.31 6.30	7.21 7.10	—
<b>19</b>	25	222–224	E	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>8</sub> S (444)	54.05 54.20	3.60 3.50	6.31 6.30	7.21 7.10	—
<b>20a</b>	20	>250	E	C <sub>15</sub> H <sub>13</sub> N O <sub>8</sub> S (367)	45.05 45.10	3.54 3.50	3.82 3.9	8.72 8.60	—
<b>20b</b>	25	>250	E	C <sub>21</sub> H <sub>17</sub> N O <sub>8</sub> S (443)	56.88 57.00	3.84 3.70	3.16 3.10	7.22 7.20	—
<b>20c</b>	23	>250	E	C <sub>21</sub> H <sub>21</sub> N O <sub>11</sub> S (495)	50.91 51.00	4.24 4.10	2.82 2.80	6.47 6.50	—
<b>22a</b>	30	<b>178–180</b>	E	C <sub>27</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub> S <sub>2</sub> Cl <sub>2</sub> (628)	51.59 51.70	2.39 2.40	6.69 6.60	10.19 10.00	11.30 11.40
<b>22b</b>	35	<b>220–222</b>	E	C <sub>27</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub> S <sub>2</sub> ClBr (672.5)	48.18 48.00	2.23 2.20	6.25 6.30	9.52 9.70	—
<b>22c</b>	30	<b>188–190</b>	E	C <sub>29</sub> H <sub>20</sub> N <sub>3</sub> O <sub>8</sub> S <sub>2</sub> Cl (637.5)	54.59 54.70	3.14 3.10	6.59 6.50	10.04 10.00	5.57 5.70
<b>24</b>	25	<b>188–190</b>	E	C <sub>27</sub> H <sub>16</sub> N <sub>2</sub> O <sub>7</sub> S <sub>2</sub> ClBr (659.5)	49.13 49.00	2.43 2.40	4.25 4.30	9.70 9.70	—

B = Benzene; C = chloroform; D= Dioxane; E = Ethanol; H = n-Hexane; W = water.

(30 ml) was heated under reflux on a water bath for 3 h. The reaction mixture was concentrated and the product was purified by dissolving in dil. NaOH and precipitated by dil. HCl then crystallized from the proper solvent to give bis (xanthotoxin, bergapten, or visnagin)sulfonamide derivatives (**2**, **5**), (**4**, **6**), and (**8**, **9**), respectively, (Table IV).

### 1,2-Bis (Xanthotoxin-4-sulfonamido)ethane (**2**)

IR; 3170(NH), 2950(CH-aliph.), 1735(CO), and 1350,1170 (SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 2.75(4H, s, 2  $\times$  CH<sub>2</sub>), 4.50(6H, s, 2  $\times$  OCH<sub>3</sub>), 6.33(2H, d, J = 9.7 Hz, 2  $\times$  C-3H), 7.35(2H, d, J = 2.1 Hz, 2  $\times$  C-5H), 7.85(2H, d, J = 2.1 Hz, 2  $\times$  C-6H), 8.15(2H, d, J = 9.7 Hz, 2  $\times$  C-2H) and 10.05–10.25 ppm (2H, broad s, 2  $\times$  NH, disappeared after addition of D<sub>2</sub>O). Mass spectrum of **2** (C<sub>26</sub>H<sub>20</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) showed M<sup>+</sup> at m/z 616(0.16%) and base peak (202, 9-hydroxypsoralen, 100%). Fragmentation pattern of **2** is illustrated in Figure 1.

### 1,2-Bis (Bergapten-9-sulfonamido)ethane (**4**)

IR spectrum; 3175(NH), 2960(CH-aliph.), 1740(CO), and 1350, 1165(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 2.90(4H, s, 2  $\times$  CH<sub>2</sub>), 4.37(6H, s, 2  $\times$  OCH<sub>3</sub>), 6.32(2H, d, J = 9.9 Hz, 2  $\times$  C-3H), 7.14(2H, d, J = 2.3 Hz, 2  $\times$  C-5H), 7.75 (2H, d, J = 2.3 Hz, 2  $\times$  C-6H), 8.18 (2H, d, J = 9.9 Hz, 2  $\times$  C-2H) and 9.85–9.95 ppm (2H, broad s, 2  $\times$  NH, disappeared after addition of D<sub>2</sub>O). Mass spectrum of **4** (C<sub>26</sub>H<sub>20</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) exhibited at m/z 308(0.5%; M/2), 309(0.36), 310(2.40), 311 (0.55), 216(68.23, bergapten), 217(9.89), the base peak at 202(4-hydroxypsoralen, 100), and 50(14.9, ethlenediamine).

### 1,4-Bis (Xanthotoxin-4-sulfonamido)butane (**5**)

IR; 3190(NH), 2970–2930(CH-aliph.), 1745(CO), and 1350,1160(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 1.70(4H, t, 2  $\times$  C-CH<sub>2</sub>-C), 2.82(4H, app q, 2  $\times$  CH<sub>2</sub>-N, after addition of D<sub>2</sub>O it is appeared as t), 4.50 (6H, s, 2  $\times$  OCH<sub>3</sub>), 6.50–8.10 (8H, m, Ar-H), and 9.90–10.10 ppm (2H, hump, 2  $\times$  NH, disappeared following the addition of D<sub>2</sub>O). Mass spectrum of **5** (C<sub>28</sub>H<sub>24</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) showed a peak at m/z 428(1.29%, M-xanthotoxin), with a base peak at m/z 202(9-hydroxypsoralen). Other significant peaks appeared at m/z 203 (12.87), 215(8.17), and 216(7.36).

### 1,4-Bis (Bergapten-9-sulphonamido)butane (**6**)

IR and <sup>1</sup>H NMR of **6** revealed approximately the same bands as those of **5**. Mass spectrum of **6** (C<sub>28</sub>H<sub>24</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) exhibited a peak at m/z 428(0.57%, M-bergapten), with a base peak at m/z 202

(9-hydroxypsoralen). Other significant peaks appeared at  $m/z$  203(13.05), 204(1.44), 215(1.80), 216(21.40), and 217(3.20).

### 1,2-Bis (Visnagin-9-sulphonamido)ethane (8)

IR; 3175(NH), 2930–2890(CH-aliph.), 1715(CO), and 1360,1170(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 2.45(6H, s, 2  $\times$  CH<sub>3</sub>-C), 2.75(4H, s, 2  $\times$  CH<sub>2</sub>-N), 4.25(6H, s, 2  $\times$  OCH<sub>3</sub>), 6.20(2H, S, 2  $\times$  CH= of  $\gamma$ -chromon), 7.85 (4H, q, two AB system, J<sub>AB</sub> = 2.6 Hz), and 8.75(2H, broad s, 2  $\times$  NH, disappeared after addition of D<sub>2</sub>O). Mass spectrum of 8(C<sub>28</sub>H<sub>24</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) revealed a peak at  $m/z$  322(0.1% M/2), with a base peak at  $m/z$  216(100%, visnagin-CH<sub>3</sub>). Other significant peaks appeared at  $m/z$  295(1.72) and 280(1.19).

### 1,4-Bis (Visnagin-9-sulfonamido)butane (9)

IR; 3170(NH), 2950–2830(CH-aliph.), 1710(CO) and 1365,1170(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 1.72(4H, t, 2  $\times$  C-CH<sub>2</sub>-C), 2.50(6H, s, 2  $\times$  CH<sub>3</sub>-C), 2.79 (4H, app q, 2  $\times$  CH<sub>2</sub>-N; after addition of D<sub>2</sub>O it is appeared as t), 4.30(6H, s, 2  $\times$  OCH<sub>3</sub>), 6.25(2H, s, 2  $\times$  -CH=), 7.90(4H, q, two AB system, J<sub>AB</sub> = 2.7 Hz), and 9.10–9.30 ppm (2H, hump, 2  $\times$  NH, disappeared following the addition of D<sub>2</sub>O). Mass spectrum of **9** (C<sub>30</sub>H<sub>28</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) showed peaks at  $m/z$  428(1.2%, M-vinagin-CH<sub>3</sub>), 336(0.11%, M/2), and 216(100%, base peak, visnagin-CH<sub>3</sub>).

### Codensation of (1 and 3) with Hydrazine Hydrate

A mixture of (**1** or **3**) (3.14 g; 10 m moles) and hydrazine hydrate (0.5 g; 10 m moles) in dry ether (30 ml) was heated under reflux for one h. The reaction mixture was concentrated and the obtained product crystallized to give bis(xanthotoxin and bergapten)sulfonamides (**11** and **12**), respectively (Table IV).

### Bis Xanthotoxin-4-sulphonamide (11)

IR; 3230(NH), 1740(CO) and 1370,1175(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 4.55(6H, s, 2  $\times$  OCH<sub>3</sub>), 6.70–8.30(8H, m, Ar-H), and 9.50–10.50 ppm (2H, broad s, 2  $\times$  NH, disappeared after addition of D<sub>2</sub>O). Mass spectrum of **11** (C<sub>24</sub>H<sub>16</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) exhibited a peak at  $m/z$  294(1.81%, m/2), base peak at 268(100%), and other significant peaks at 248(22.33), 225(34.33), 205(28.83), and 194 (15.54).

### Bis Bergapten-9-sulfonamide (12)

IR and <sup>1</sup>H NMR spectra of **12** revealed approximately the same data as those of **11**. Mass spectrum of **12** (C<sub>24</sub>H<sub>16</sub>N<sub>2</sub>O<sub>12</sub>S<sub>2</sub>) exhibited a peak

at  $m/z$  294 (5.14%, M/2), base peak at 202(100%, 9-hydroxypsoralen), and 216(82.88%, 9-methoxypsoralen).

### Reaction of (1, 3, and 7) with 2,4-diaminotoluene

A mixture of (1, 3; 3.14 g or 7; 3.28 g; 10 m moles); 2,4-diaminotoluene (1.22 g; 10 m moles) and pyridine (0.5 ml) in dry benzene (30 ml) was heated under reflux for 3 h. The reaction mixture was then concentrated cooled and 20 ml. of cold dil. HCl (1:1) was added. The product was dissolved in dil NaOH, filtered, precipitated by dil. HCl and crystallized to give bis xanthotoxinsulfonamide derivative (13), and (bergapten and visnagin)sulfonamide derivatives (14<sup>23</sup> and 15) (Table IV).

### Tolyl-2,4-bis(xanthotoxin-4-sulfonamide, Derivative (13)

IR; 3250(NH), 3070–3020(CH-arom.), 2950–2900(CH-aliph.), 1735(CO), and 1375, 1170  $\text{cm}^{-1}$ (SO<sub>2</sub>-N). <sup>1</sup>H NMR of 13;  $\delta$  = 2.30(3H, s, CH<sub>3</sub>-Ar), 4.50(6H, s, 2 × OCH<sub>3</sub>), 6.50–8.30(11H, m, Ar-H), and 9.50–10.10 ppm(2H, broad s, 2 × NH, disappeared after addition of D<sub>2</sub>O). Mass spectrum of 13 is shown in Figure 2, which exhibited M<sup>+</sup>, base peak, and the fragmentation pattern.

### Bergapten-9-sulfonamido-(1-yl-3-nitro-4-methylbenzene) (14)

IR; 3230(NH), 1735(CO), 1540,1335(NO<sub>2</sub>), and 1350,1160(SO<sub>2</sub>-N). <sup>1</sup>H NMR;  $\delta$  = 2.30(3H, s, CH<sub>3</sub>-Ar), 4.35(3H, s, OCH<sub>3</sub>), 6.35–8.15(7H, m, Ar-H), and 10.10 ppm(1H, hump, disappeared following the addition of D<sub>2</sub>O). Mass spectrum (C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>8</sub>S) showed the following peaks; at  $m/z$  414 (1.01%, M-O), 399(0.72%, M-OCH<sub>3</sub>), base peak at 202(100%, 9-hydroxypsoralen) and 216(9.69%, 9-methoxypsoralen), (m.p. and m.m.p. with authentic sample prepared according to Attia et al.<sup>23</sup>).

### Visnagin-9-sulfonamido-(1-yl-3-nitro-4-methylbenzene) (15)

<sup>1</sup>H NMR;  $\delta$  = 2.35(3H, s, CH<sub>3</sub>-Ar), 2.55(3H, s, CH<sub>3</sub>,  $\gamma$ -chromone), 4.35(3H, s, OCH<sub>3</sub>), 6.25(1H, s, CH,  $\gamma$ -chromone), 7.35–8.35(5H, m, Ar-H), and 9.85(1H, broad s, NH,disappeared after addition of D<sub>2</sub>O). Mass spectrum (C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>S) exhibited the following peaks at  $m/z$  443(0.07%, M-1), 442(0.18, M-2), 429(0.13, M-CH<sub>3</sub>), 428(M-O), 413(0.26, M-OCH<sub>3</sub>), 310(0.29, visnaginsulfonamide), 230(1.16, visnagin), and 215(base peak, 100, Visnagin-CH<sub>3</sub>).

**Interaction of Xanthotoxin-4-sulfonyl Chloride, Bergapten-9-sulfonyl Chloride or Visnagin-9-sulfonyl Chloride (1, 3, and 7) with p-Phenylenediamine and  $\alpha,\alpha$ -Diamino-p-xylene**

A mixture of (1, 3; 3.14 g or 7; 3.28 g; 10 m moles); and p-phenylenediamine (0.54 g; 5 m moles) or  $\alpha,\alpha$ -diamino-p-xylene (0.68 g; 5 m moles), and pyridine (0.5 ml) in dry benzene (30 ml) was heated under reflux for 3 h and treated as above to give the corresponding xanthotoxin, bergapten or visnagin sulfonamides (**16–19**), respectively, (Table IV).

**Xanthotoxin-4-sulfonamido-(1-yl-4-nitrobenzene) (16)**

$^1\text{H}$  NMR;  $\delta$  = 4.40(3H, s,  $\text{OCH}_3$ ), 6.50–8.30(8H, m, Ar–H), and 9.85 ppm (1H, hump, NH, disappeared after addition of  $\text{D}_2\text{O}$ ). Mass spectrum ( $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_8\text{S}$ ) exhibited the following peaks at  $m/z$  415(0.30%,  $\text{M}^+$ ), 418(0.18,  $\text{M}+2$ ), 419(0.27,  $\text{M}+3$ ), 415(0.24,  $\text{M}-1$ ), 414(0.70,  $\text{M}-2$ ), 400(3.87,  $\text{M}-\text{O}$ ), 386(13.63,  $\text{M}-\text{OCH}_3$ ), and 107(100, base peak, nitrosobenzene).

An authentic sample of **16** was prepared as follows: a mixture of xanthotoxin-4-sulfonyl chloride (1; 3.14 g, 10 m moles), p-nitroaniline (1.38 g, 10 m moles), and pyridine (0.5 ml) in dry benzene (30 ml) was heated under reflux for 5 h and treated as above to give (**16**; m.p. and m.m.p.)

**Visnagin-9-sulfonamido-(1-yl-4-nitrobenzene) (17)**

IR; 3220(NH), 3020(CH-arom.), 2950(CH-aliph.), 1720(CO), 1545,1345( $\text{NO}_2$ ) and 1335,1135( $\text{SO}_2\text{-N}$ ).  $^1\text{H}$  NMR;  $\delta$  = 2.45(3H, s,  $\text{CH}_3\text{-Ar}$ ), 4.45 (3H, s,  $\text{OCH}_3$ ), 6.15(1H, s, CH,  $\gamma$ -chromone), 7.35–8.35(6H, m, Ar–H), and 9.75 ppm(1H, hump, NH, disappeared after addition of  $\text{D}_2\text{O}$ ). Mass spectrum ( $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_8\text{S}$ ) exhibited at  $m/z$  430(0.84%,  $\text{M}^+$ ), 429(1.56,  $\text{M}-1$ ), 428(6.28,  $\text{M}-2$ ), 415(1.29,  $\text{M}-\text{CH}_3$ ), and 135(100, base peak).

An authentic sample of **17** was prepared as follows: a mixture of Visnagin-9-sulfonyl chloride (7, 3.28 g, 10 m moles), p-nitroaniline (1.38 g, 10 m moles), and pyridine (0.5 ml) in dry benzene (30 ml), was heated under reflux for 5 h and treated as above to give (**17**; m.p. and m.m.p.).

**Xanthotoxin-4-sulfonamidomethyl-(1-yl-4-nitrotoluene) (18)**

IR; 3170(NH), 3010(CH-arom.), 2950(CH-aliph.), 1740(CO), 1535, 1335 ( $\text{NO}_2$ ) and 1330,1135( $\text{SO}_2\text{-N}$ ).  $^1\text{H}$  NMR;  $\delta$  = 4.25(2H, s,  $\text{N-CH}_2\text{-Ar}$ ),

4.50(3H, s, OCH<sub>3</sub>), 4.65(2H, s, CH<sub>2</sub>-NO<sub>2</sub>), 6.50–8.10(8H, m, Ar-H), and 9.95 ppm (1H, hump, NH, disappeared following the addition of D<sub>2</sub>O). Mass spectrum; (C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>S) revealed the following peaks at m/z 444(0.2%, M<sup>+</sup>), 448(0.9, M+4), 443(0.3, M-1), 442(0.6, M-2) 428(1.2, M-O), 413(3.2, M-OCH<sub>3</sub>), and 202(100, base peak, 9-hydroxypsoralen).

### Bergapten-9-sulfonamidomethyl-(1-yl-4-nitrotoluene) (19)

IR and <sup>1</sup>H NMR of **19** exhibited approximately the same bands as those of **18**. Mass spectrum (C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>S) showed at m/z 444(0.2%, M<sup>+</sup>), 428(1.2, M-O), 429(1.1, M-CH<sub>3</sub>), 413 (3.2, M-OCH<sub>3</sub>), and 202 (100, base peak, xanthotoxin).

### General Procedure for Synthesis of Tosylamino Acids (20a–c)

The tosylamino acid derivatives (**20a–c**) were prepared similar to the reported methods,<sup>24,25</sup> whereby the amino acid (alanine, 0.89 g; phenylalanine, 1.65 g; or tyrosine, 1.81 g; 10 m moles) was dissolved in 1N sodium hydroxide (25 ml), and over a period of 15 min, a solution of xanthotoxin -4-sulfonyl chloride (**1**, 3.14 g, 10 m moles) in dry benzene (30 ml) was added in portions. The mixture was stirred at room temperature for 3 h. The excess of sulfonyl chloride was separated off, and the solution was treated with 2N HCl until acidic to Congo red (pH 5). Cooling and acidification caused precipitation of the product, which was filtered off, washed with water, air dried and crystallized to give (**20a–c**) (Table IV).

### Tosylalanine Derivative (20a)

IR; 3200–2750(-COOH overlapped with NH, arom., and aliph.CH), 1720,1650(2 CO), and 1350,1130(SO<sub>2</sub>-N). <sup>1</sup>H NMR; δ = 1.50(3H, d, CH<sub>3</sub>-C), 4.45(3H, s, OCH<sub>3</sub>), 4.65(1H, q, N-CH : CH<sub>3</sub>. COOH), 6.20(1H, d, J=9.8 Hz, C-3H), 7.30(1H, d, J = 2.3 Hz, C-5H), 7.75(1H, d, J = 2.3 Hz, C-6H), 8.05(1H, d, J = 9.8 Hz, C-2H), and 10.10, 11.35 ppm (2H, 2 broad s, NH & OH, disappeared after addition of D<sub>2</sub>O). Mass spectrum (C<sub>15</sub>H<sub>13</sub>NO<sub>8</sub>S) showed M<sup>+</sup> at m/z 367(8.71%,) with a base peak at m/z 215(100, xanthotoxin). Other significant peaks were observed at m/z 368(1.64, M+1), 369(0.8, M+2), 352 (59.51, M-CH<sub>3</sub>), and 295(2.34, xanthotoxin-4-sulfonamide).

### Tosylphenylalanine Derivative (20b)

IR measurements are approximately as those of (**20a**). <sup>1</sup>H NMR; δ = 2.85(2H, d, CH<sub>2</sub>), 4.40(3H, s, OCH<sub>3</sub>), 4.75(1H, t, N-CH-COOH), 6.20–8.00(9H, m, Ar-H), and 10.05, 11.30(2H, 2 broad s, NH and OH, disappeared after addition of D<sub>2</sub>O).

### Tosyl-L-Tyrosine Derivative (20c)

IR; 3450–3350(OH), 3250–2750(broad band due to overlap of  $\nu$  NH, COOH, arom., and aliph. CH), and 1720,1630(2 CO). Mass spectrum ( $C_{21}H_{21}NO_{11}S$ ) showed the following peaks at  $m/z$  495(4.90,  $M + 2 H_2O$ ), 462(5.9,  $M+3$ ), and 216(100, base peak, xanthotoxin).

### Synthesis of the Sulfonamide Derivatives (22a–c)

A mixture of the iminothione (**21a**, 1.75 g; **21b**, 1.97 g or **21c**, 1.80 g; 5 m mols), xanthotoxin-4-sulfonyl chloride (**1**, 1.57 g, 5 m moles) and pyridine (0.5 ml) in dry benzene (30 ml) was refluxed for 3 h. The reaction mixture was treated with cold dil. HCl and the obtained product was filtered off, washed with water, and then crystallized to give **22a–c** (Table IV).

### Sulfonamide Derivative (22a)

IR; 3030 (CH-arom.), 2950 (CH-aliph.), 1740,1680 (2 CO), 1485, 1170 (CS-N), and 1355,1170 ( $SO_2$ -N).  $^1H$  NMR;  $\delta$  = 4.45(3H, s,  $OCH_3$ ) and 6.70–8.10 (12H, m, Ar–H). Mass spectrum of **22a** ( $C_{27}H_{15}N_3O_7S_2Cl_2$ ) exhibited a peak at  $m/z$  602 (9.7%,  $M-C_2H_2$ ), 248(100, base peak), 350(8.2, imidazolineiminothione), and 215(10.5, 9-methoxypsoraline).

### Synthesis of (22b)

IR and  $^1H$  NMR spectra showed approximately the same bands as those of **22a**. Mass spectrum ( $C_{27}H_{15}N_3O_7S_2ClBr$ ) revealed a peak at  $m/z$  460(1.5%,  $M-p-Br.C_6H_4.NCS$ ), 462(42.1), 463(40.8), 216(38.8, xanthotoxin), 173(51.3,  $p-Br.C_6H_4.NH_2$ ), 136(3.9,  $p-Cl-.C_6H_4NC$ ), and 86(100, base peak).

### Synthesis of (22c)

IR; 3020(CH-arom.), 2950–2850(CH-alph.), 1730,1670(2 CO), 1490,1175(CS-N), and 1350,1160( $SO_2$ -N).  $^1H$  NMR,  $\delta$  = 1.1(3H, t,  $CH_3-C$ ), 4.45(3H, s,  $CH_3-O$ ), 5.1(2H, q,  $CH_2-O$ ), and 6.6–8.10 ppm (12H, m, Ar–H). Mass spectrum ( $C_{29}H_{20}N_3O_8S_2Cl$ ) showed a peak at  $m/z$  636(80.1%,  $M-1$ ), 359(100, base peak, the corresponding imidazolidineiminothione), 346(27.3, the respective thiohydantoin), 179(77.1,  $p$ -ethoxyisothiocyanate), and 153(27.3,  $p$ -chlorophenylisocyanate).

## Synthesis of the Thiosulfonicacid Ester (24)

A mixture of the thiohydantoin **23** (0.80 g, 2 m moles), xanthotoxin-4-sulfonyl chloride **1** (0.63 g, 2 m moles), and sodium ethoxide (2 m moles) in absolute ethanol (30 ml) was refluxed for 6 h. The reaction mixture was poured on to cold dil. HCl, and the obtained product was crystallized to give **24** (Table IV).  $^1\text{H}$  NMR spectrum exhibited the following signals at  $\delta = 4.51(3\text{H}, \text{s}, \text{CH}_3\text{-O})$ ,  $6.3(1\text{H}, \text{s}, =\text{CH-N})$ , and  $6.90\text{--}8.30$  ppm ( $12\text{H}, \text{m}, \text{Ar-H}$ ).

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