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Synthesis of Some new Sulfonamide Schiff's Bases and Study Their Gastroprotective Activity

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ABSTRACT

Substituted sulfonamides were reacted with thiophene carbaldehydes and piperenal to form Schiff's bases. The structures of synthesized compounds were confirmed by their IR, ^{1}H NMR spectroscopic data and mass spectra.Different necrotizing agents (80% ethanol, 0.2 M NaOH and 25% NaCl) were used to induced gastric lesions. The compounds were given orally 30 min before the administration of necrotizing agents. The percentages for compounds to ulcer protective were calculated. Compound 4 was more effective than other compounds and omeprazole itself.Compound 1 was approximate equal to omeprazole activity, and after that compounds 3 and 2 respectively were less active.

Keywords: Substituted sulfonamide, Schiff's bases, gastroprotective, anti-ulcer agent.

تحضير بعض قواعد شيف جديده ودراسه فعاليتها للوقايه من القرحه المعدية

فائزة عبد الكريم ناصر أسامة هادي رمضان أحمد مجيد جاسم

الخلاصة

تتفاعل مشتقات السلفانميد مع الثايوفين ٢-الديهيد والبايبرينايل لتكوين قواعد شيف .شخصت المركبات المحضرة بقياس أطياف الأشعه تحت الحمراء والرنين النووي للبروتون وطيف الكتله .أستعملت عدة عوامل مخدشه للمعدة وهي (الايثانول ٨٠% وهيدروكسيد الصوديوم ٠,٢ مولاري وكلوريد الصوديوم ٢٠%) لاستحداث قرحه المعده .واعطيت المركبات عن طريق الفم قبل نصف ساعه من تناول العامل

المخدش.حسبت النسبه المئويه للوقايه من القرحه وكانت النتائج كالتالي المركب ٤ اكثر فعاليه من المركبات الاخرى ومن دواء الامبرازول وفعاليه المركب ١ مقاربه الى فعاليه الامبرازول بينما أظهر المركبان ٢و٣ أقل فعاليه على التوالي.

INTRODUCTION

Schiff bases have been widely investigated and become one of the research hotspots for a long period of time owing to their strong coordination capability and diverse biological activities, such as antibacterial, antitumor activities, etc.[1-3]. Many Schiff bases are known to be medicinally important and used to design medicinal compounds [4-7]. Moreover, Schiff's bases derived from aromatic amines and aromatic aldehyde have a wide variety of applications in many fields as sulfonamide Schiff's bases have been reported to posses antimicrobial activity[8-15] , Schiff base compounds can be classified by their photochromic and thermochromic characteristics[16]. As is known to all, sulfanilamide derivatives have intensively antibacterial actives. However, to the best of our knowledge, Schiff base containing sulfanilamide moieties have been seldom reported[17]. Therefore, investigations of the synthesis and properties of these compounds seem to be a very interesting problem. In view of this study, we describe the synthesis, crystal structure, identification and study their qastropoteective activity of the compounds 1-4.

Peptic ulcer is a common disorder of the entire gastrointestinal tract, they occur mainly in the stomach and the proximal duodenum. The basic physiopathological of gastric ulcer results from an imbalance between some endogenous aggressive factor(s) [hydrochloric acid, pepsin, refluxed bile, leukotrienes, reactive oxygen species (ROS)] and cytoprotective factors, which include the function of the mucus-bicarbonate barrier, surface active phospholipids, prostaglandins (PG), mucosal blood flow, cell renewal and migration, nonenzymatic and enzymatic antioxidants and some growth factors and defensive (mucus secretion, gastric mucosal integrity) factors[18,19]. The objective of the present study was to investigate the antiulcer activity of sulphonyl compounds to cure ulcer as a gastroprotective agents.

Experimental :

MATERIALS AND METHODS

Melting points were determined on a capillary melting point apparatus type Thermo Scientific. Infrared spectra were recorded in Shimadzu FT-IR8400s spectrophotometer (KBr) and ^{1}H NMR spectra in $DMSO_4$-d6 on Brucker spectrospin-500 MHz, Faculty of science .The mass spectra were measured by using a Agilent technologies 597c University of Tarbiat Modares Tahran.

Synthesis of Schiff's bases

General method: Equimolar quantities (0.01 mole) of substituted sulfonamide with different aldehydes were dissolved in 15 ml of ethanol. Glacial acetic acid (2 drop) was added to reaction mixture and refluxed for 2-3 h. The content was cooled in ice. The crystalline product was collected by filtration, dried and recrystallized from hexane. Table 1show the physical properties of the prepared compounds.

Table 1: physical properties of compounds (1-4)

No	Name of compounds	Mp c◦	%
1	4-(benzo[d][1,3]dioxol-5-ylmethyleneamino) benzenesulonamide	200-201	80
2	4-(thiophen-2-ylmethyleneamino) benzenesulonamide	202-203	95
3	4-(4-aminophenylsulfonyl)-N-(thiophen-2-ylmehylene)aniline	213-214	80
4	4-(4-aminophenylsulfonyl)-N-(benzo[d][1,3]dioxol-5-ylmethylene)aniline	219-220	85

The Animals

Wistar albino mice of either sex, approximately of same age, weighing 20-25 g were obtained from Animal House, College of Education, University of Basrah. They were maintained under standard conditions of temperature, humidity and light (12 h dark, 12 h light) and having free access to food and water. Before testing, the animals were fasted for 36 h with access to water. The experiments and the procedure of sacrifice (using ether).

Gastric lesions induced by necrotizing agents (Cytoprotection):

The necrotizing agents were administered in doses of 0.1 ml per 20 g b.w. (80% ethanol, 0.2 M NaOH and 25% NaCl). The compounds were given orally 30 min before the administration of necrotizing agents in dose 100 mg/kg dissolved in olive oil and the control group received 0.1 ml olive oil only. The positive control group was received omeprazole at the dose of 30 mg/kg, as a standard drug. One hour after the administration of ethanol and alkalis the rats were sacrificed and examined for lesions in the stomach. The scoring of lesions in the stomach were observed as follows: the patchy lesions of stomach induced by ethanol were scored according to using the following scale: 0 = normal mucosa; 1 = hyperaemic mucosa or up to 3 small patches; 2 = from 4 to 10 small patches; 3 = more than 10 small or up to 3 medium-sized patches; 4 = from 4 to 6 medium-sized patches; 5 = more than 6 medium-sized or up to 3 large patches; 6 = from 4 to 6 large patches; 7 = from 7 to 10 large patches; 8 = more than 10 large patches or extensive necrotic zones. The percentages of protective were calculated as equation below [20,21].

$$\% \text{ Protective} = \frac{\text{Control mean ulcer index} - \text{test mean ulcer index}}{\text{Control mean ulcer index}} \times 100$$

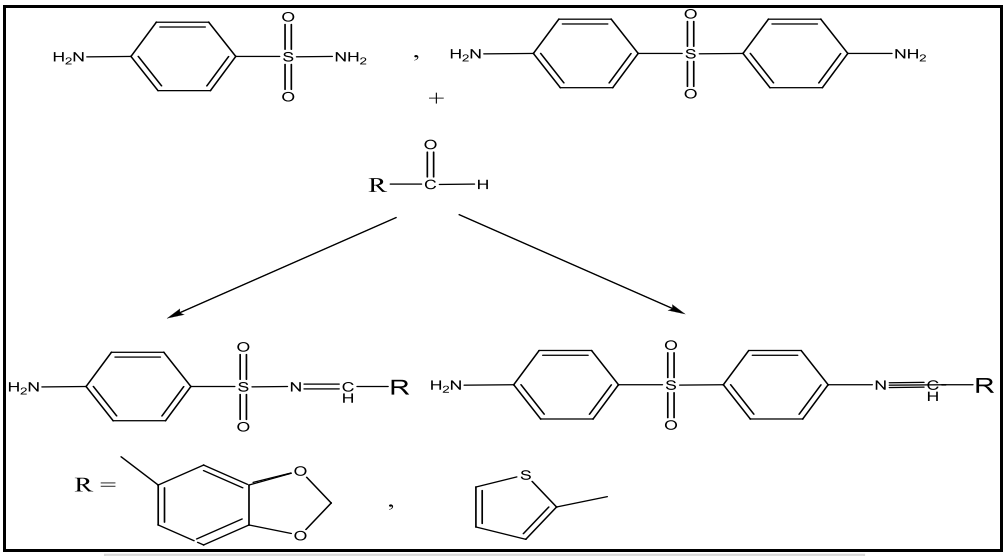
Statistical analysis

Data obtained from the animal experiments was expressed as mean ± SEM statistical tests including a one-way analysis of variance (ANOVA) significant difference test were used to analyze any differences between the groups that

were subjected to testing. A p-value of less than 0.01 was considered as being statistically significant.

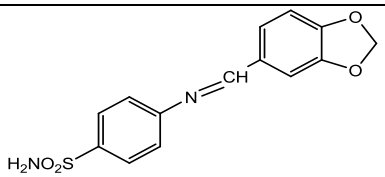
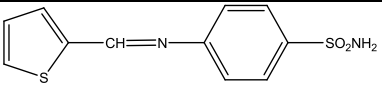
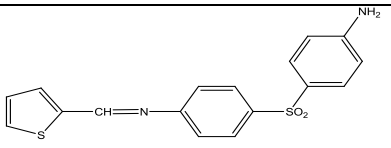
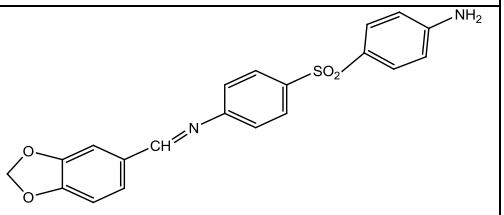
Results and Discussion

Sulfonamides Schiff bases are prepared by the acidic catalyzed reaction of thiophen and piperenal with substituted sulfonamides in ethanol as shown in scheme 1 and Table 2



Scheme 1: The rout of synthesis compounds 1-4

Table (2): Structure of proper compounds 1-4

Sym.	Name of compounds	Structure of compounds
1	4-(benzo[d][1,3]dioxol-5-ylmethyleneamino) benzenesulonamide	
2	4-(thiophen-2-ylmethyleneamino) benzenesulonamide	
3	4-(4-aminophenylsulfonyl)-N-(thiophen-2-ylmehylene)aniline	
4	4-(4-aminophenylsulfonyl)-N-(benzo[d][1,3]dioxol-5-ylmethylene)aniline	

IR spectra

The IR spectra of all compounds are recorded in the solid state using the KBr disk technique. Selected bands of diagnostic importance are collected in Table (3)

The formation of Schiff bases (1-4) were indicated by their IR spectra from the appearance of azomethine C=N stretching band at 1638-1652 cm^{-1} combined with the disappearance of IR band in region 1710-1730 cm^{-1} corresponding to C=O group of aldehydes[22,23].The azomethine hydrogen CH=N gives bands at 2915-2976 cm^{-1} .The absorption bands at 1332-1385 $cm^{-1}$for SO_2,(Asymmetrical str) and 1135-1152 $cm^{-1}$for SO_2,(symmetrical str) [24].

Table (3): Selected bands of diagnostic importance from the IR spectra of compounds (1-4).

Compounds	NH-sulph cm^{-1}	C-H Azom cm^{-1}	Ar-H cm^{-1}	C=C Ar cm^{-1}	O=S=O cm^{-1}	C=N Azom cm^{-1}
1	3448	2976	3120	1450	1346 Asy 1152 sym	1645
2	3380	2925	3105	1445	1332 Asy 1150 sym	1638
3	3377	2915	3188	1495	1385 Asy 1135 sym	1652
4	3365	2930	3155	1498	1338 Asy 1138 sym	1648

^{1}H-NMR spectra

The singals observed in the^{1}H-NMR spectra of the compounds (Figs 1,2,3,4) are collected in Table(4).The spectra exhibit amultiple at δ 6.53-8.72 ppm for the aromatic rings hydrogen [25].The azomethine hydrogen CH=N (1H) appear as singlet of at δ 8.44-8.77 ppm [26]. The spectra of compounds 1,2 show asingle with an integration intensity equivalent to two hydrogen at δ(6.09 and 6.10)ppm respectively corresponding to the (2H) of the CH2 group .While the other compounds have a single (2H) of the NH2 group at δ 6.11-7.30 ppm [27].

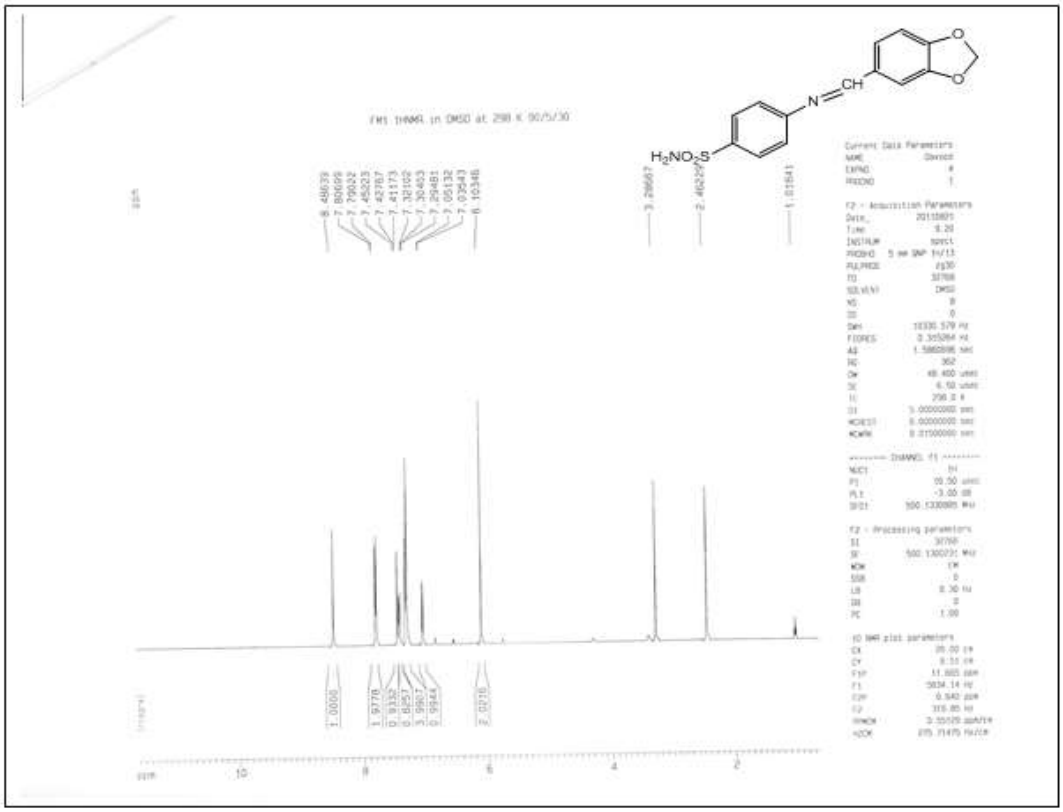


Figure 1: HNMR Spectrum of compound 1

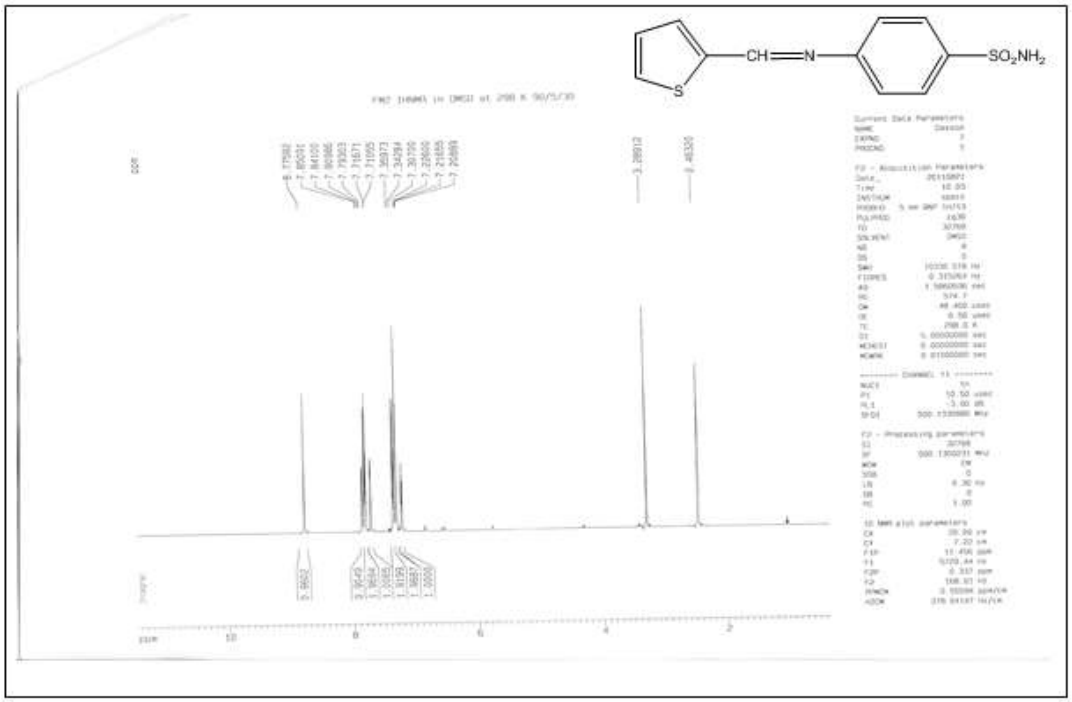


Figure 2: HNMR Spectrum of compound 2

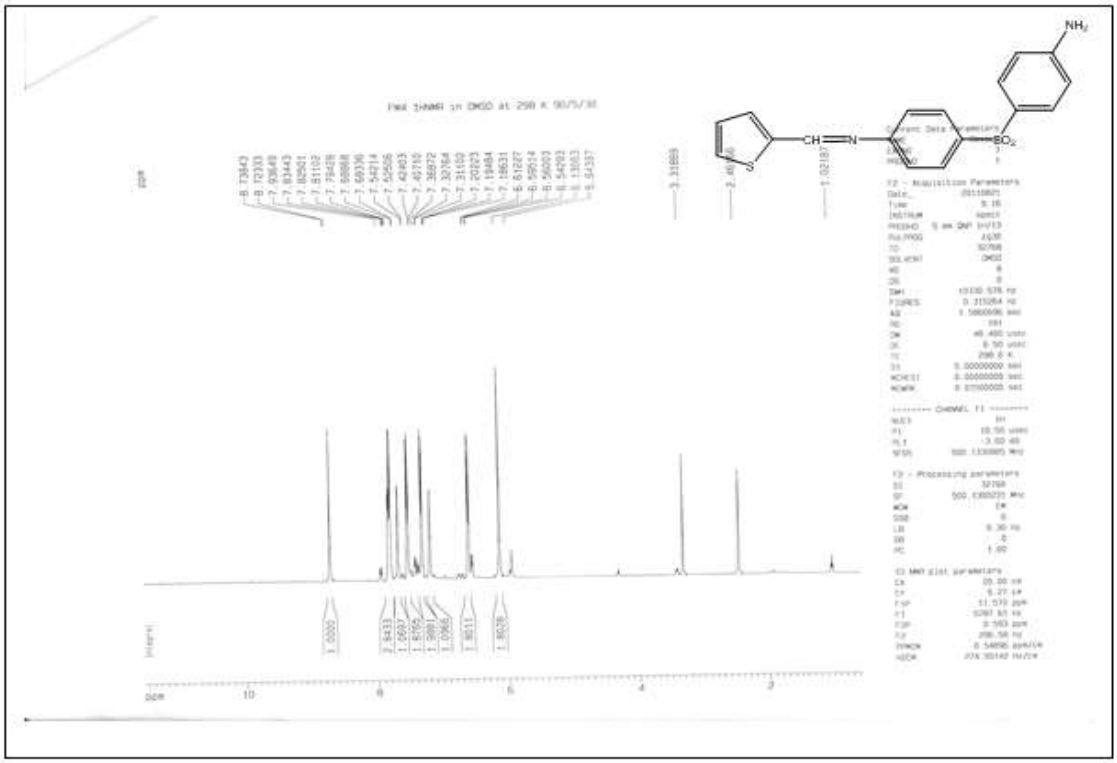


Figure 3: HNMR Spectrum of compound 3

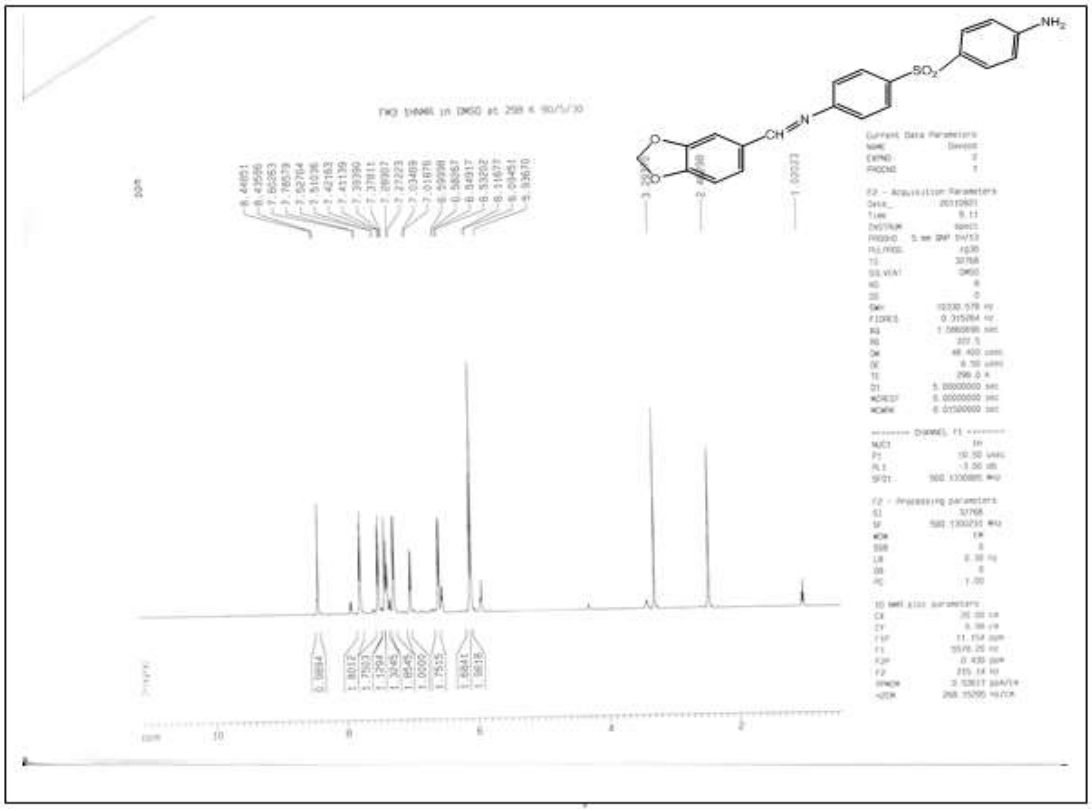


Figure 4: HNMR Spectrum of compound 4

Table (4): ^{1}H-NMR spectra of compounds (1-4).

Compounds	CH2	NH2	C-H Ar	N=CH
1	6.10	7.29	7.03-7.80	8.48
2	-	7.30	7.20-8.77	8.77
3	6.09	6.11	6.53-7.80	8.44
4	-	6.13	6.54-7.93	8.73

Mass spectra

The mass spectra of Schiff bases (1-4) were measured and the fragmentation routes for these compounds were suggested, as shown in schemes (1-4) .with the parent peaks at m/z 304,266,380,341 respectively. Table (5) shows the import ions that appear in the spectra of these compounds. The base peaks are appeared as shown in (Figs 5-8). The other peaks support the structure of these compounds.

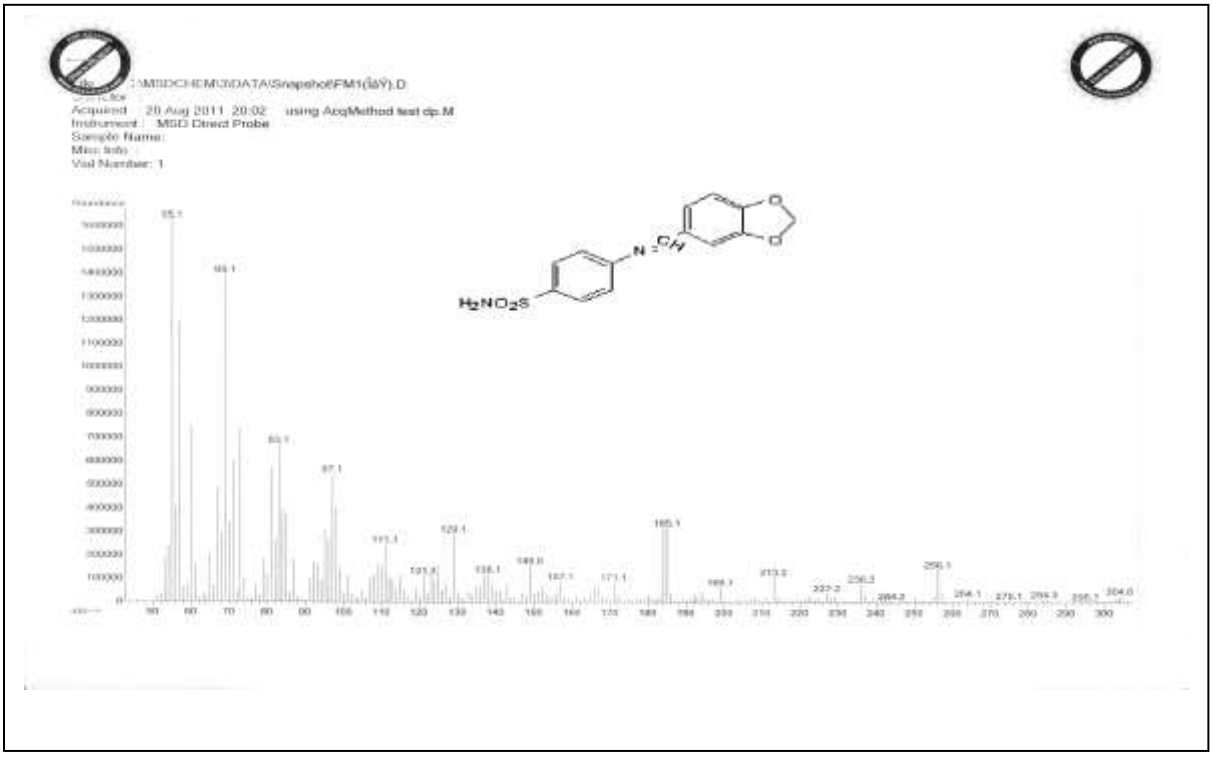
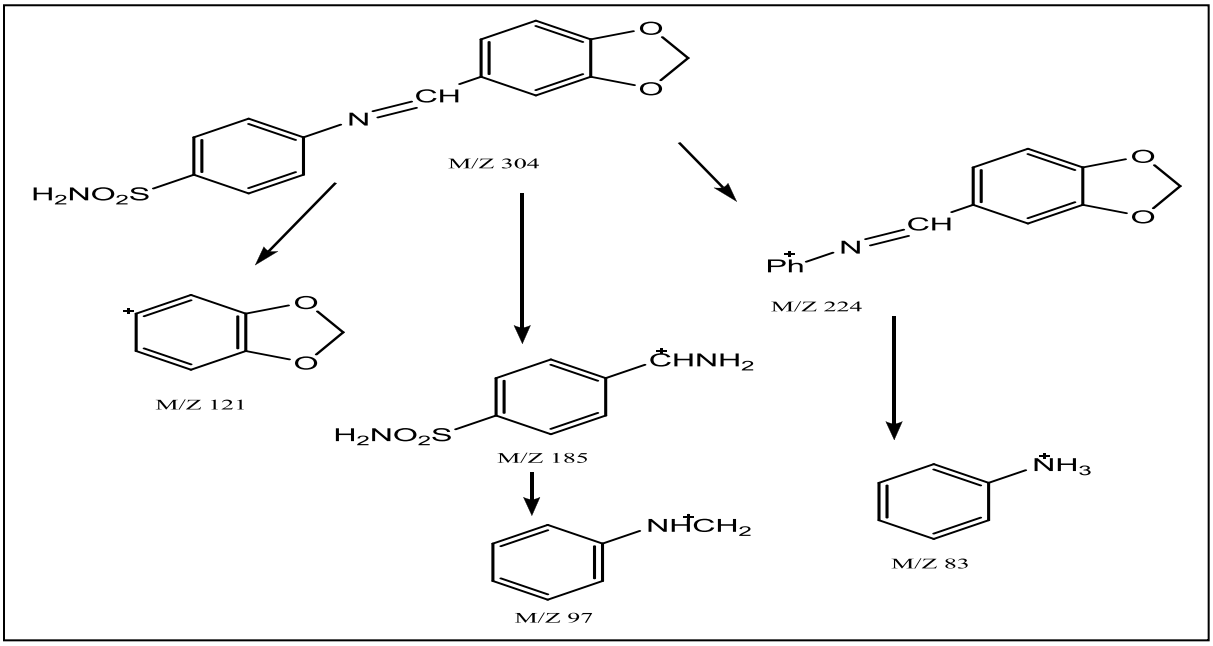


Figure 5: Mass Spectrum of compound 1



Scheme 2: Fragmentation routes of compound 1

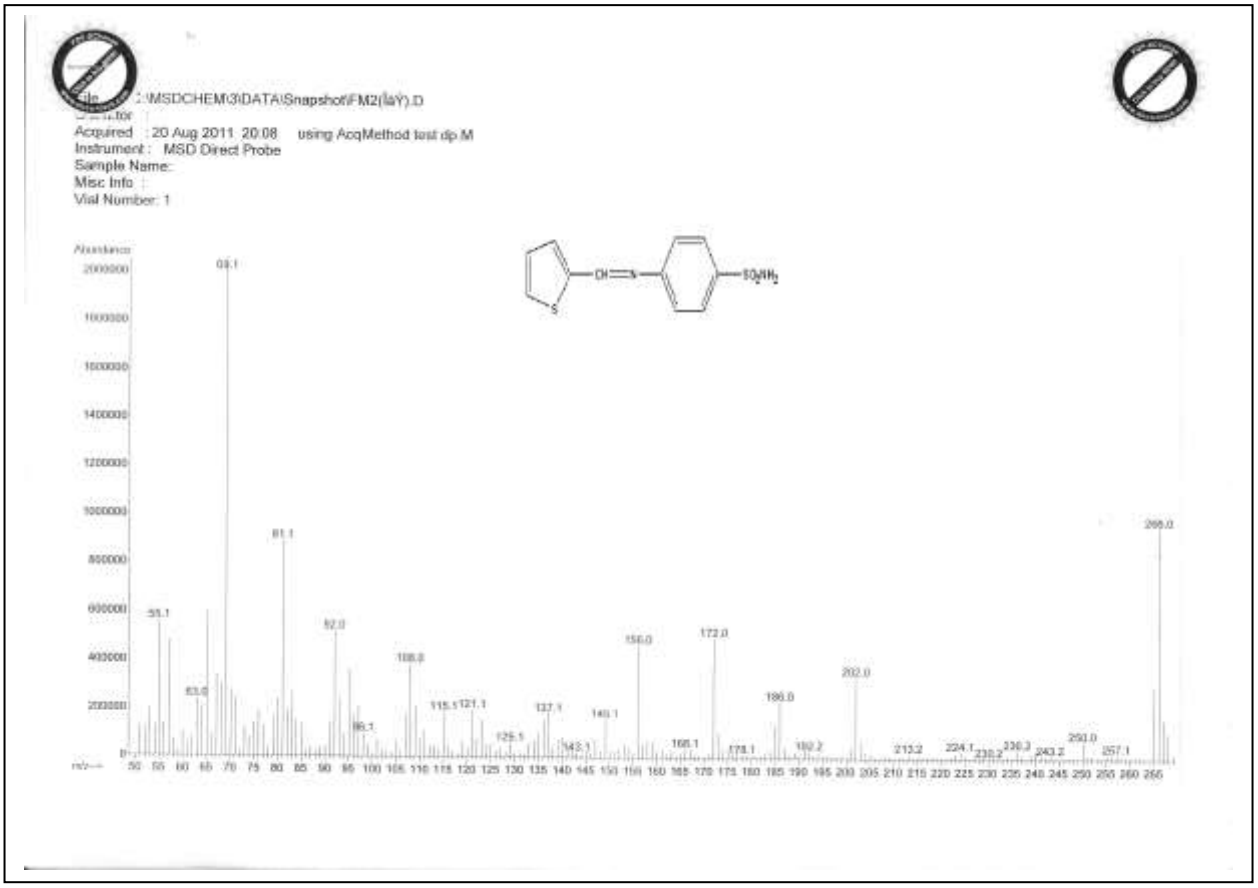
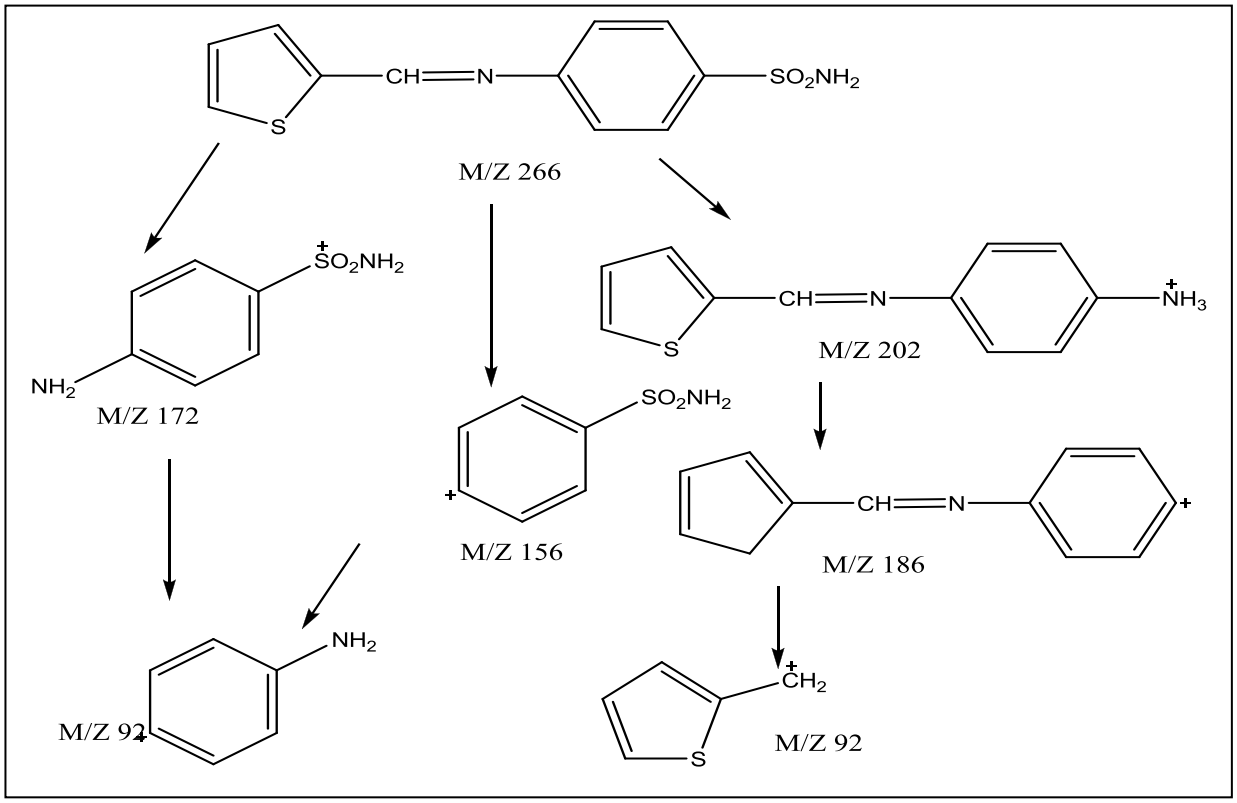


Figure 6: Mass Spectrum of compound 2



Scheme 3: Fragmentation routes of compound 2

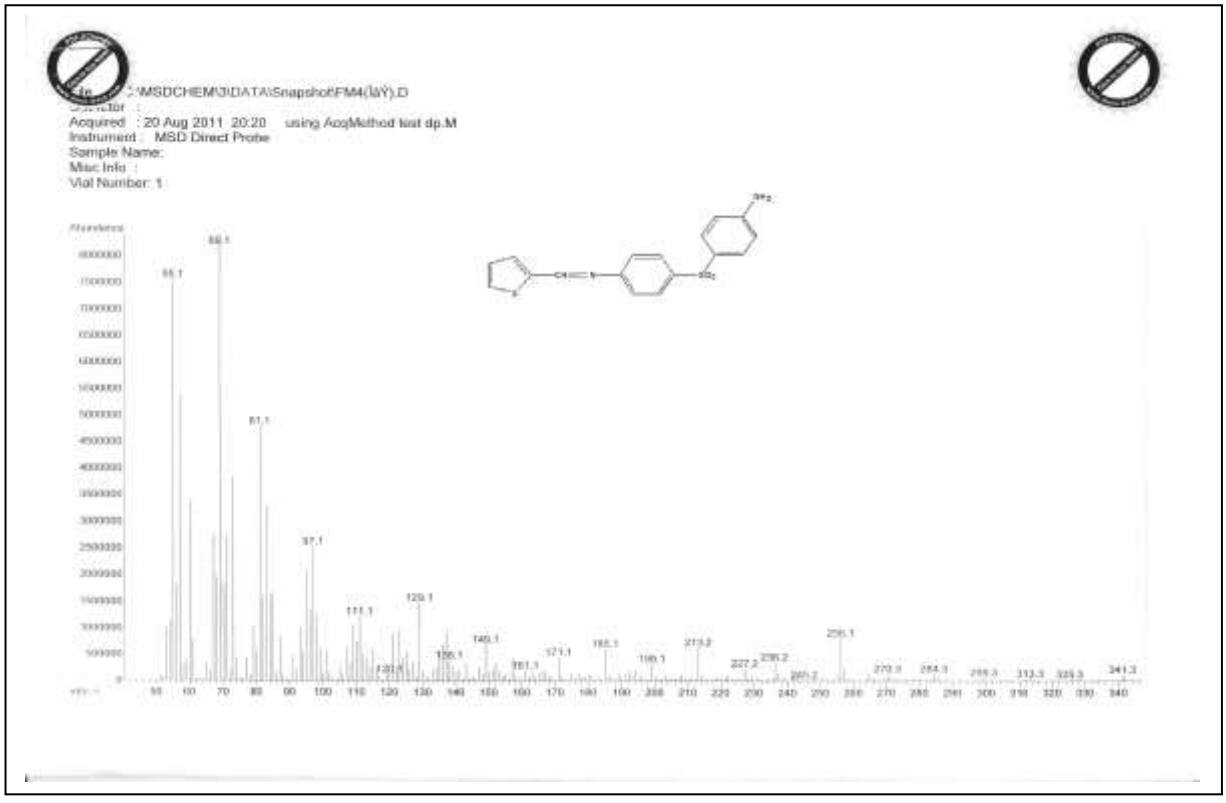
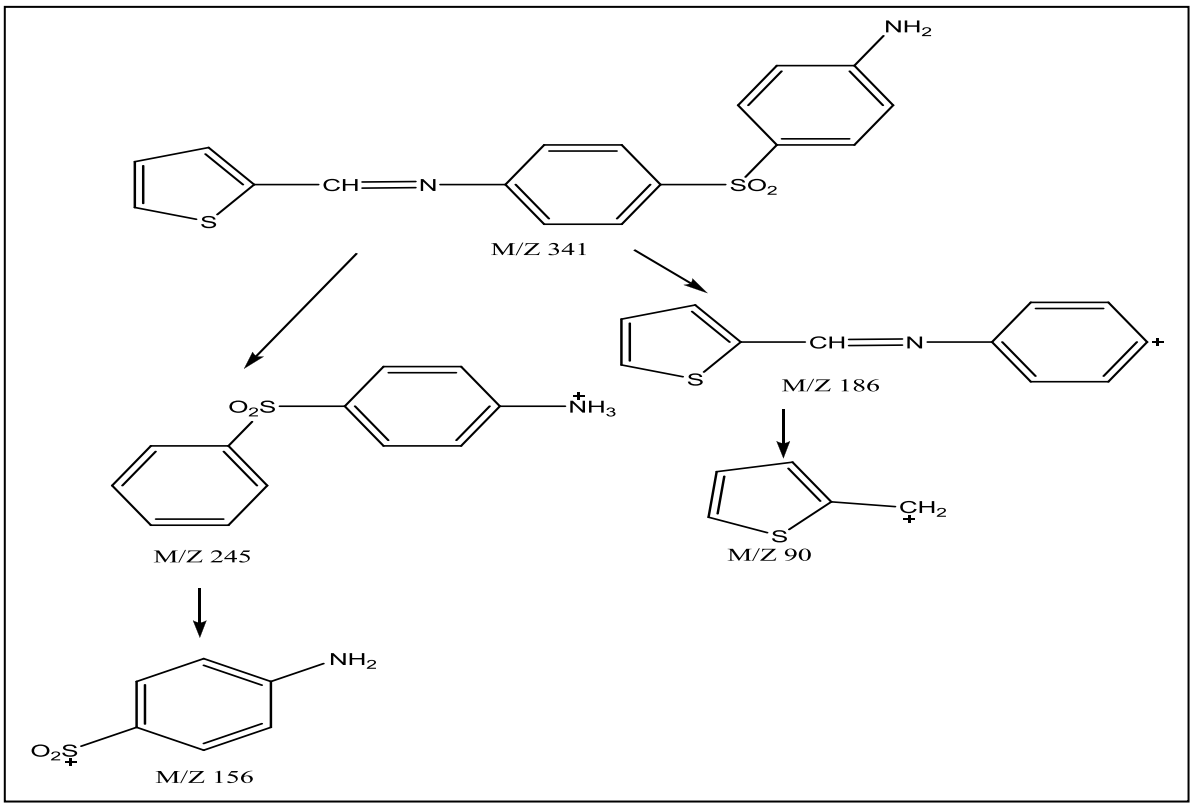


Figure 7: Mass Spectrum of compound 3



Scheme 4: Fragmentation routes of compound 3

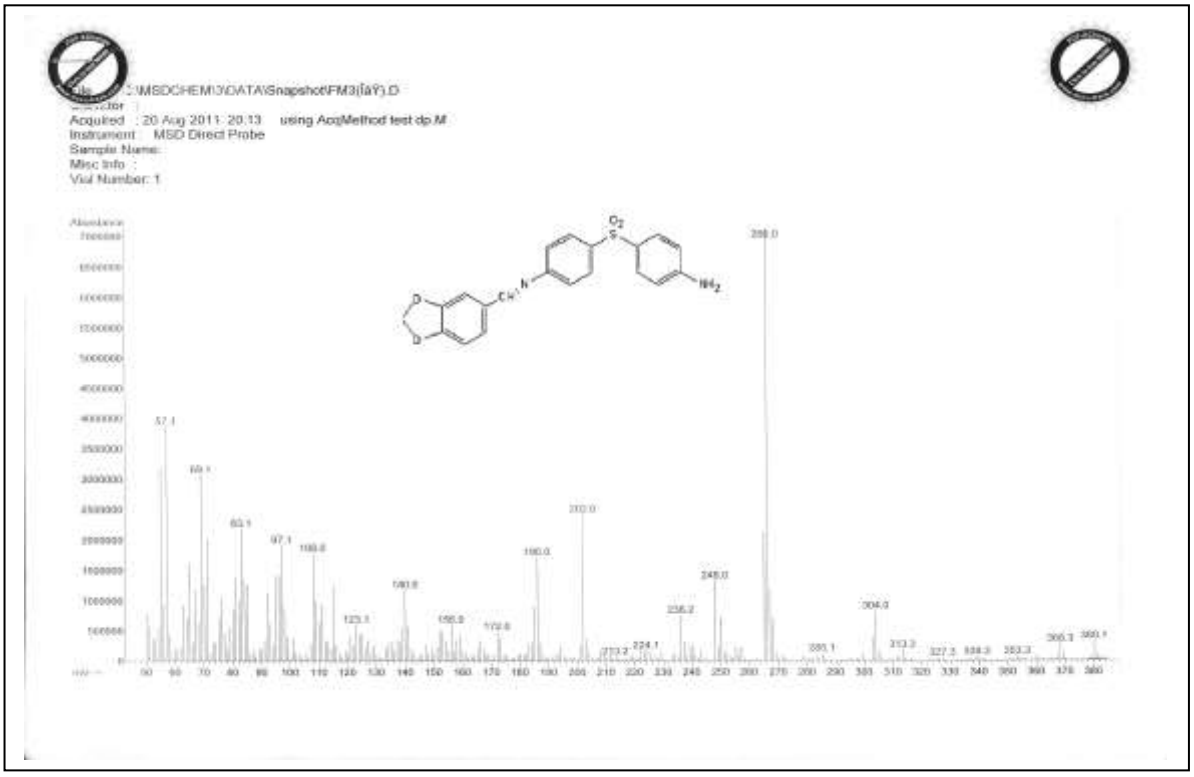
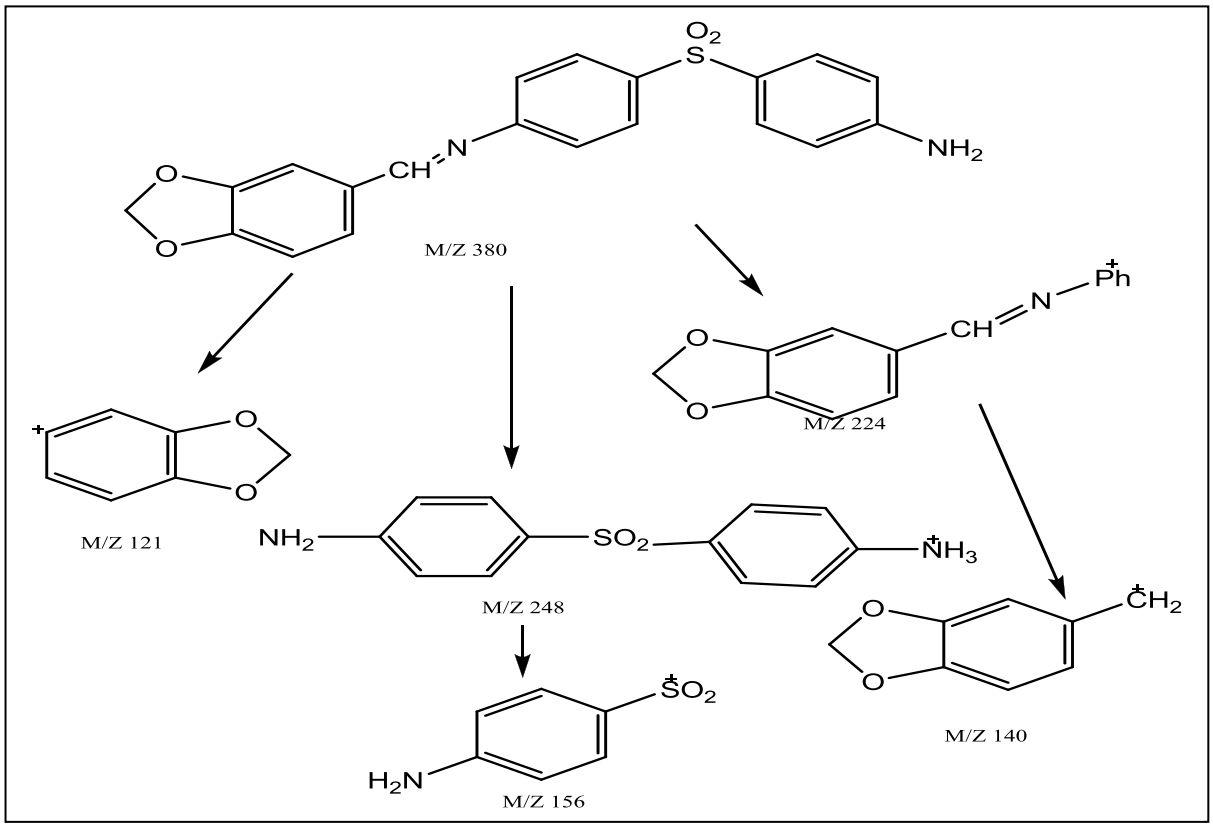


Figure 8: Mass Spectrum of compound 4



Scheme 5: Fragmentation routes of compound 4

Table (5): Fragmentation pattern of compounds.

Comp	Parent ion	M^+	$^+$PhCH2O2	PH2C2O2N$^+$	PhN$^+$	$^+$PhNCH2	$^+$PhSO2NH2	$^+$C5H4S
1	304	185	121	224	83	97	156	-
2	266	172	-	-	83	97	156	92
3	380	114	121	224	83	97	156	-
4	341	129	-	-	83	97	156	92

Results of Gastroprotective Activity

Table (6) shows the effects of the compounds on gastric lesions induced by different necrotizing agents. Compound 4 was more effective than the others and omeprazole itself. Compound 1 was approximate equal to omeprazole activity, and after that compounds 3 and 2 respectively were less active. The percentages for compounds to ulcer protective were shown in Table (7).

Table 6: Effects of the compounds on gastric lesions induced by necrotizing agents.

Treatment n=6	Ulcer Index (mean ± S. E.)		
	80% EtOH	0.2 M NaOH	25% NaCl
Control	7.71 ± 1.2	7.5 ± 0.98	7.78 ± 0.97
1	2.35 ± 0.59***	3.3 ± 0.84***	1.6 ± 0.65***
2	4.38 ± 0.64	4.19 ± 0.47	5.11 ± 0.91
3	3.45 ± 0.67*	2.82 ± 0.68*	3.74 ± 0.73*
4	1.13 ± 0.76***	0.62 ± 0.44***	0.91 ± 0.37***
Omeprazole	2.24 ± 0.85***	2.43 ± 0.72***	2.09 ±0.81***

*= p<0.01; ***= p<0.001, ANOVA t-test

Table 7: The percentages for compounds of ulcer protective

Treatment n=6	% Protective		
	80% EtOH	0.2 M NaOH	25% NaCl
1	69.5	56.0	79.4
2	43.1	44.1	34.3
3	55.2	62.4	51.9
4	85.3	91.7	88.3
Omeprazole	70.9	67.6	73.1

Discussion

Gastric ulcers result from an imbalance involving gastric protection and aggressive factors. Gastric protection depends on a number of factors such as the release of prostaglandin E2 (PGE2), bicarbonate secretion, gastric mucus production and the regulation of gastric mucosal blood flow. Factors leading to gastric offensives are the hyper secretion of HCl or pepsin. Ethanol is well known to induce gastric ulcers via multi-factorial mechanisms such as the impairment of gastric defensive factors like mucus dissolution or by increasing offensive factors such as acid secretion or gastrin release [28]. There are many products in the market for the treatment of gastric ulcer, including antacids, proton pump inhibitors, anticholinergics and histamine H_2-antagonists[29].The pepsin is one of three principal protein degrading, or proteolytic, enzymes in the digestive system, the other two being chymotrypsin and trypsin and HCl are important for formation of pylorus ligated ulcers. The gastric protective effect of the compounds is related to cytoprotective properties; it is possible that the inhibitory effect is due the solubility of compounds in olive oil, associated with anti-ulcerogenic activity. The ethanol administration show significant reduction in non-protein sulfhydryls (NP-SH) content of gastric mucosa [30]. This result suggested that compounds increase the mucosal sulfhydryl groups content to protected the stomach.

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