Synthesis of New Derivatives of N- Substituted Saccharin Via Glycine Derivatives.

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Abstract

The present work include the synthesis of *N* – α- saccharylbenzyl-N-phenylglycine and its derivatives were achieved which expected to have some biological activity. The first step was the treatment of primery aromatic amine with primery aromatic aldehyde in boling ethanol to give Schiff's bases , which is converted to N- α- chlorobenzyl-N-phenylglycine by its reaction with chloroacetic acid in dry benzene. The synthesized glycine derivatives were reacted with saccharine to give *N* – α- saccharylbenzyl-N-phenylglycine. The new prepared compounds were identified by physical properties and UV/Vis., IR and ^{1}HNMR spectrum.

الخلاصة

تم في هذه الدراسة تحضير مشتقات جديدة للسكرين يؤمل أن تكون فعالة بيولوجيا، الخطوة الأولى لتحضير هذه المشتقات تمت بتحضير قواعد شف بتفاعل الأمينات الاروماتية الأولية مع الالادهيدات الاروماتية الأولية يلي ذلك مفاعلة قواعد شف المحضرة مع كلوريد حامض ألخليك للحصول على مشتقات الكلايسين ثم مفاعلة السكرين مع مشتقات الكلايسين المحضرة . تم تشخيص المركبات المحضرة بقياس درجات الانصهار وأطياف الأشعة فوق البنفسجية وكذلك أطياف الأشعة تحت الحمراء وأطياف الرنين النووي المغناطيسي لذرة الهيدروجين.

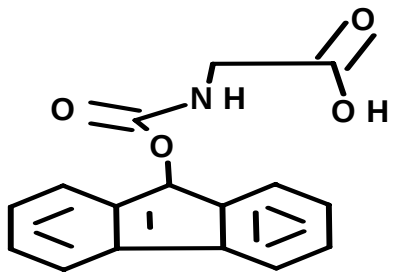
Introduction

Twenty amino acid comprise the building blocks of proteins, which are chemical species indispensable to perform a huge number of biological functions, as exemplified by the role of enzymes[1].

Glycine ($^+H_3NCH_3COO^-$) is the simplest one among the twenty natural amino acid, representing approximately one-third of the collagen composition. However, its loss of hydrogen atom make it available to act as hydrogen bond former[1]. The oxygen and nitrogen centers in the structure of amino acid enable them to act as potential sites for binding metal ion[2].

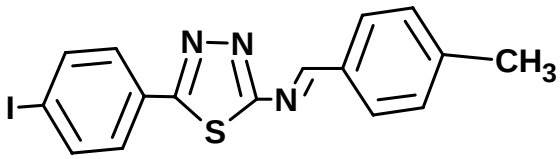
Glycine can be prepared by the interaction of chloroacetc acid and ammonia[3,4], and by the hydrolysis of methyleneaminoacetonitrile by successive treatments with barium hydroxide and sulfuric acid[5].

Many kinds of glycine derivatives were prepared, compound (1) which possessed biological activity[6].



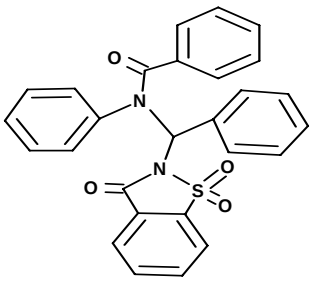
(1)

Many of Schiff bases have biologic activity, compound (2) for example, was used as anti bacterial[(7)] .

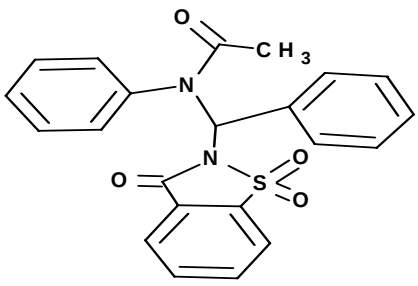


(2)

The compounds (3),(4) was prepared as saccharine derivatives which possessed biological activity [(8),(9)].



(3)



(4)

Experimental

Melting points were determined by Stuart melting point apparatus and uncorrected; IR spectra were recorded on a Shimadzu S.N A2 10\4000 188LP FT- IR- 84005 spectrophotometer in the 4000 – 200 cm^{-1} range using KBr discs, UV/Vis. spectra were recorded on TRSP – Spectrophotometer, triup International Corp in the 320 - 1000 nm range, 10^{-3} M solution of compounds in ethanol. The ^{1}HNMR spectra were recorded on a Bruker 400 MHz in Baath university collage of science in Syria, $CDCl_3$ was used as solvent and TMS as internal reference.

1- Synthesis of Schiff's Bases:

A mixture of 0.01mole (0.93 ml) of aromatic amine, 0.01 mole (1.1ml) of aromatic aldehyde , 10 ml ethanol and one drop of glacial acetic acid, was heated in a water bath at (70- 80º C) for 30 min. then left to cool in a bath of ice-water, whereby yellowish white crystals separated out . The crystals were filtered, washed with 2% HCl, then with water and recryastallized from ethanol[8,9]. Table (1) give m.p, λ_{max} and percent of yield . Table (2) give IR data.

2- Synthesis of N-α-chlorobenzyl-N-phenylglycine and its derivatives.

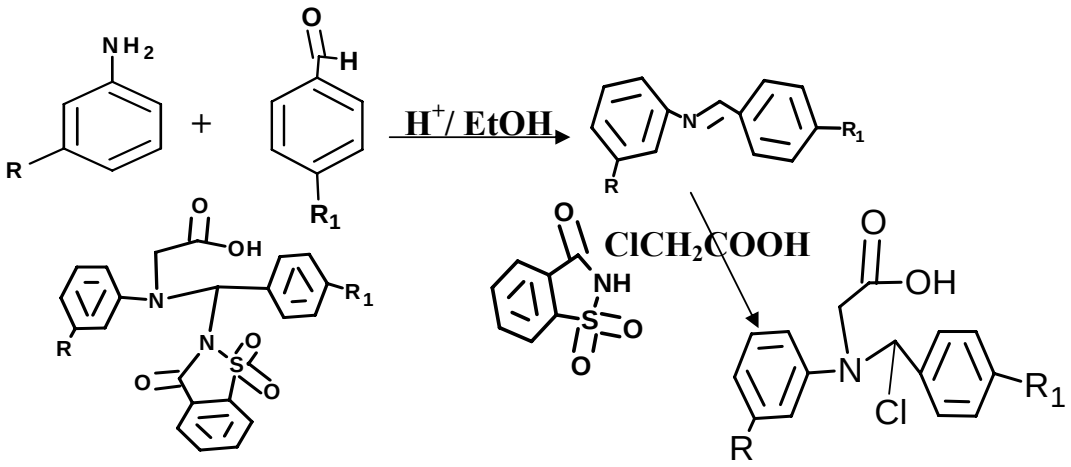
To 0.011 mole (1.9gm) of Schiff's bases in 10 ml of dry benzene was added 0.011 mole (1.03 ml) of chloroacetic acid and the reaction mixture was heated in water bath for 1 h. The solvent was evaporated and the remaining green crystals was separated and recrystallized from ethanol. Table (3) give the physical data and Table (4) give IR data.

3- Synthesis of N- α-Saccharylbenzyl -N-phenylglycine and its derivatives.

A mixture of 0.0036 mole (1gm) of N-α- chlorobenzyl-N-phenylglycine and 0.0036 mole (0.66gm) of Saccharine in 15 ml DMF was heated at 140 C^{o} for 4h . The crystals were recrystallized from ethanol. Table (5) give the physical data and Table (6) give FT- IR absorption bands.

Results and Discussion

Schem (1) summarizes all reactions in this work



The starting material Schiff's bases was prepared from the reaction between primary aromatic amine and aromatic aldehyde in presence of acetic acid glacial[10,11]. The IR absorption spectra of Schiff's bases showed the absence of two absorption band due to NH_2 stretching of aniline derivatives, and appearance of a C=N absorption bands near 1630 cm^{-1}, the major infra red absorption of Schiff's bases are given in Table (2) and Table (1) shows all physical data.

Table (1) :- Physical data of Schiff's bases, UV deduct in ethanol.

substituents	m.p C°	Yields %	λ_{Max} nm, (Absorbance)
R,R_1 =H	50	80.00	360,(1.74)
R= NO_2 R_1= $N(Me)_2$	102-103	93.50	355(1.60)
R= NO_2 R_1= H	53 - 54	90.60	350,(098)
R= H R_1= $N(Me)_2$	88 - 90	90.00	345,(0.89)

Table (2) : IR spectral data of Schiff's bases.

substituents	Characteristic absorption bands cm^{-1}		
	υ* C=N	**υ C=C Aromatic**	**Additional bands**
R,R_1 =H	1630	1585 – 1480	1190 υ C-N Bend
R= NO_2 R_1= $N(Me)_2$	1610	1590-1485	1410 δCH_3.
R= NO_2 R_1= H	1620	1590 – 1490	750δ C-H o.o.p** disubstituted benzene
R= H R_1= $N(Me)_2$	1630	1575 – 1505	1400 δCH_3.

υ* = vibration , o.o.p = Out of plain**

We found that Schiff's bases react with chlroacitic acid in dry benzene to give *N* – α- chlorolbenzyl-N-phenylglycine. The reaction is followed by disappearance of C=N absorption bands at 1630 cm^{-1}, appearance of O-H absorption bands at (3450) cm^{-1}, appearance of C=O absorption bands at (1670) $cm^{-1}$and appearance of C-Cl at (850) cm^{-1} in their IR spectra . The ^{1}HNMR of compound (2) showed :- δ(ppm) 0.9(S,6H,2CH_3),1.1(S, 2H, -CH_2), 4.2(S,1H,CH) ,7-8 (m,8 H, Aromatics), 9.9(S,1H, -OH). See Tables (3,4) and Figs (1,2).

Table (3) physical data for *N* – α- chlorolbenzyl-N-phenylglycine

Compounds No.	substituents	m.p C°	Yields %	λ_{Max} nm, (Absorbance)
1	R,R_1 =H	120-122	70	350(1.849),430(0.63)
2	R= NO_2 R_1= $N(Me)_2$	220-223	75	360(1.999),410(1.966)
3	R= H R_1= $N(Me)_2$	170-172	80	360(1.999), 420(1.952)
4	R= NO_2 R_1 =H	160-165	85	360(1.90) 415(0.44)

Table (4) FT-IR absorption bands for functional groups in KBr disc.

Comp .No.	substituents	Characteristic absorption bands cm^{-1}				
		υ * O-H	υ C=O	υ C=C Aromatic	υ C-H St*. Ar.	υ C-H St. Benzylic
1	R,R_1 =H	3400	1650	1600	3050	2600
2	R= NO_2, R_1=NMe_2	3450	1620	1600	3040	2650
3	R= H R_1= NMe_2	3450	1750	1600	3050	2650
4	R= NO_2 R_1 =H	3450-3350	1650	1600	3050	2600

υ * = Vibration, St*= Stretching.

N – α- chlorolbenzyl-N-phenylglycine have one chiral center, and are expected to be optically active. However, since they are prepared from a chiral starting compounds, they are actually racemic mixtures. No attempt to resolve these racemic mixtures was made. It was found that *N* – α-chlorolbenzyl-N-phenylglycine reacts with saccharin in DMF to give *N* – α-Saccharylbenzyl-N-phenylglycine .

The reaction is followed by disappearance of C-Cl absorption band at 850 cm^{-1} and appearance of SO_2 absorption band at 1330 to 1150 cm^{-1} in their FT-IR spectra. The ^{1}HNMR of compound (6) showed :- δ 0.9 (S, 6H, $2CH_3$) , 1.1(S, 2H, -CH_2),4.2(S,1H,CH),7-8.1(m,14H, Aromatics), 10.1(S,1H, -OH). The new synthesized compounds identified by their melting points, U.V/Vis. and FT-IR, ^{1}HNMR spectra see Table (5,6).Fig 3,4.

Table (5) physical data of *N* – α- Saccharylbenzyl-N-phenylglycine , ethanol used as a solvent in rome temperature.

Comp. No.	substituents	m.p C°	Yields %	λ_{Max} nm, (Absorbance)
5	R,R_1 =H	167-170	60	330(1.288),595(0.206)
6	R= NO_2 R_1= $N(Me)_2$	290	42.23	340(1898),570(0.097)
7	R= H R_1= $N(Me)_2$	213-215	46.12	335(1.999),560(0/078)

Table (6) FT-IR for *N* – α- Saccharylbenzyl-N-phenylglycine in KBr disc.

Comp. No.	substituents	Characteristic absorption bands cm^{-1}					
		υ *O-H	υ C=O I	υ C=O II	υ C=C Aromatic	υ SO_2 I	υ SO_2 II
5	R,R_1 =H	3440	1700	1690	1600	1320	1165
6	R= NO_2 R_1=NMe_2	3400	1740	1650	1600	1310	1160
7	R= H R_1= NMe_2	3430	1700	1680	1610	1330	1170

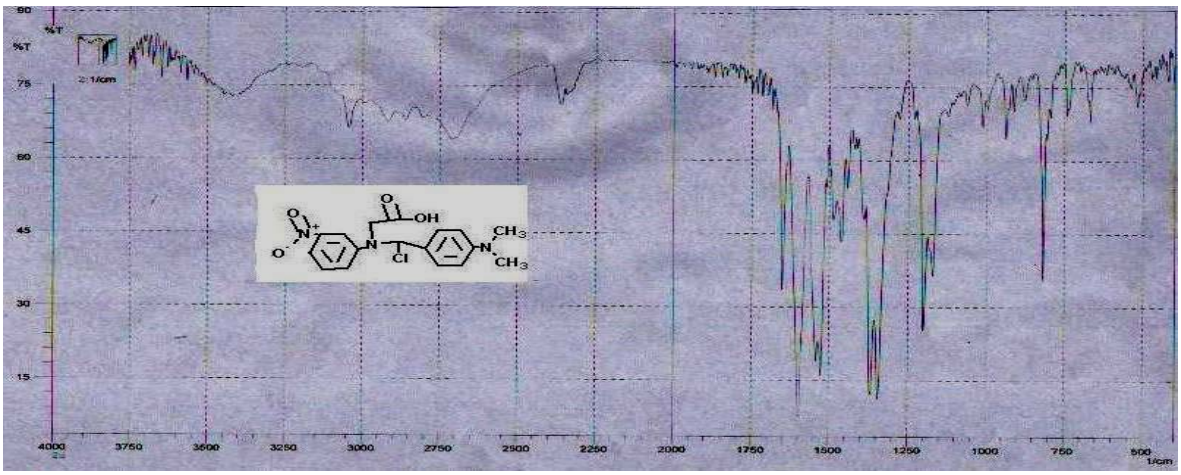


Fig (1) FT-IR spectra of compound (2) in KBr .

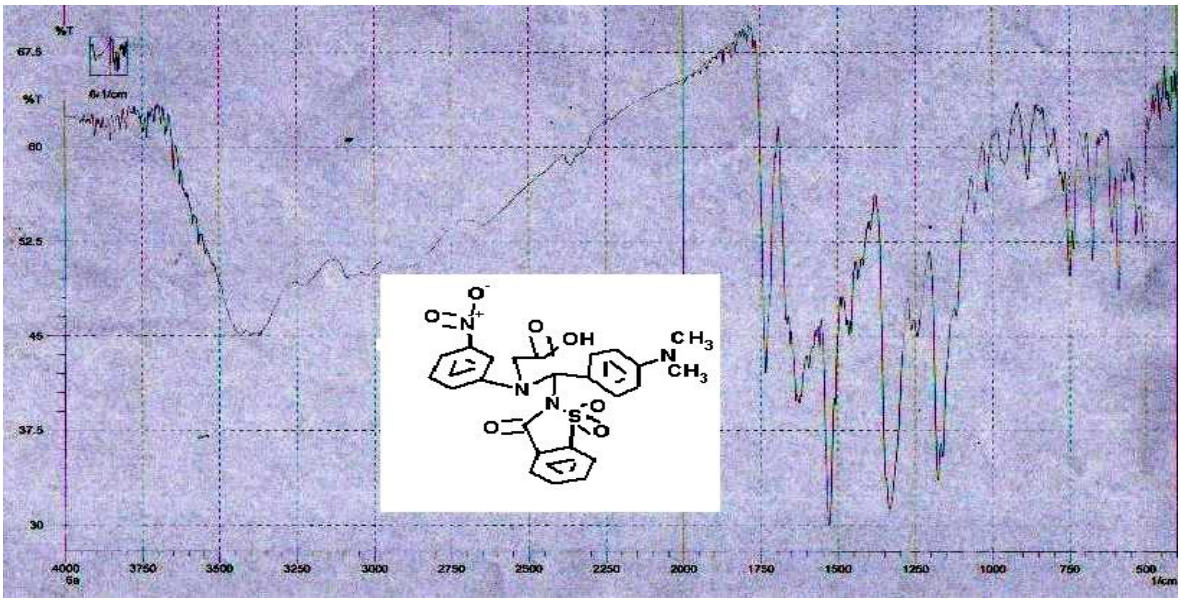


Fig (2) FT-IR spectra of compound (6) in KBr .

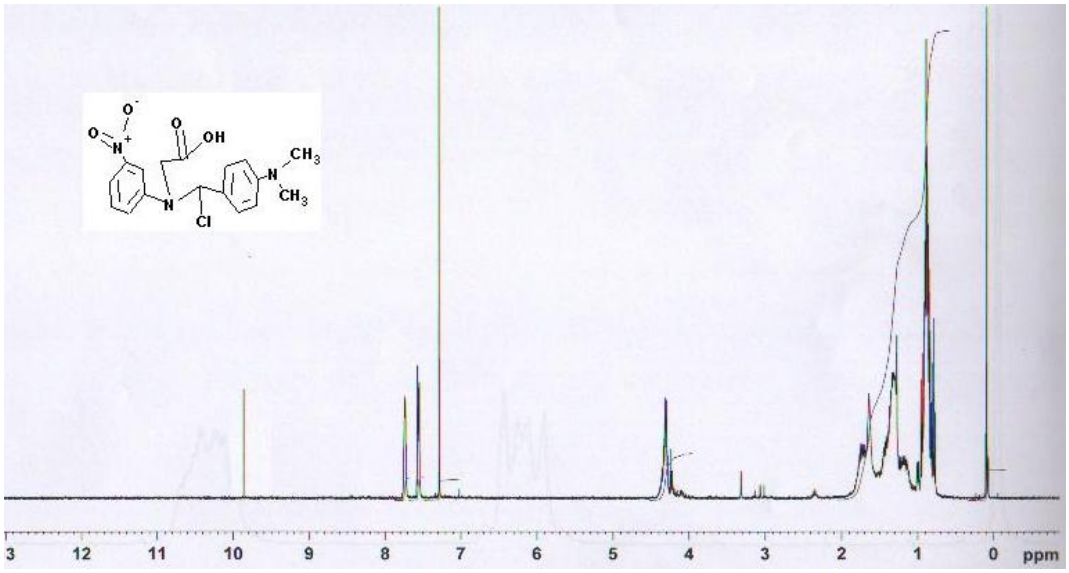


Fig (3) ^{1}HNMR spectra of compound (2) in $CDCl_3$.

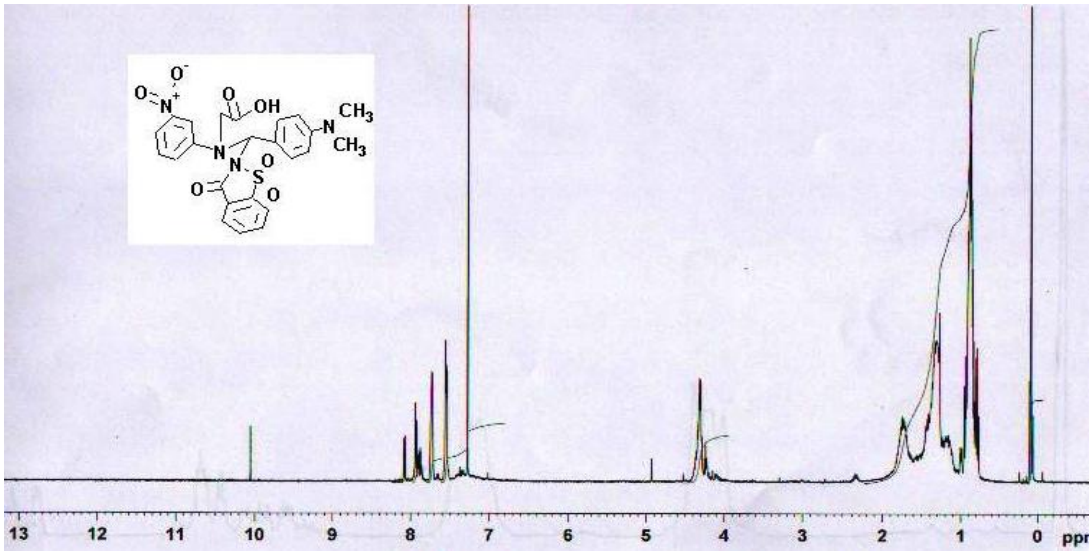


Fig (4) ^{1}HNMR spectra of compound (6)in $CDCl_3$.

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