Synthesis and Characterization of New Schiff Bases Linked to Sulfonamido Succinimide Moiety with biological Activity

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ABSTRACT
October Some new Schiff bases linked to sulfonamido succinimidi moiety have been synthesized via multistep synthesis. The first step involved reaction of succinic anhydride with aniline producing N-phenyl succinamic acid which was subsequently dehydrated to the corresponding N-phenyl succinimide via treatment with acetic anhydride and anhydrous sodium acetate. The synthesized imide was treated with chlorosulfonic acid in the third step producing 4-(N-succinimidyl)phenyl sulfonyl chloride which on amination with hydrazine hydrate in the fourth step afforded 4-(N-succinimdyl)phenyl sulfonyl hydrazine and this in turn when introduced in condensation reaction with various aromatic aldehydes and ketones afforded the target new Schiff bases. Structures of the prepared compounds were elucidated on the basis of FTIR, 1HNMR and 13CNMR spectral data which agreed with the proposed structures. The newly synthesized compounds are expected to have biological activity since they are built from biologically active components including succinimide, sulfonamide and Schiff base.

تحضير وتشخيص قواعد شيف جديدة مرتبطة بمكونة سلفون اميدو سكسن ايمايد ذات فعالية بايولوجية متوقعة

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الكلمات المفتاحية: حامض السكسن اميك، 4-(N-سكسن ايميديل) فنيل كلوريد السلفونيل، 4-(N-سكسن ايميديل) فنيل سلفونيك هيدرازين

الخلاصة
تم في هذا البحث تحضير عدد من قواعد شيف الجديدة المرتبطة بمكونة سلفون اميدو سكسن ايمايد وذلك من خلال انجاز التحضير المتعدد الخطوات، حيث تم في الخطوة الاولى اجراء تفاعل بين انهيدريد السكسنيك والانيلين للحصول على حامض N-فنيل سكسن اميك الذي سحب منه الماء في الخطوة الثانية بمعاملته مع انهيدريد الخليك وخلات الصوديوم اللامائية للحصول على N-فنيل سكسن ايمايد. اما في الخطوة الثالثة فقد تم معاملة N-فنيل سكسن ايمايد المحضر مع كلوروحامض السلفونيك للحصول على 4-(N-سكسن ايميديل) فنيل كلوريد السلفونيك والذي بدوره ادخل في تفاعل مع الهيدرازين في الخطوة الرابعة لانتاج 4-(Nسكسن ايميديل) فنيل سلفونيل هيدرازين والذي تم ادخاله في الخطوة الخامسة في تفاعل تكاثف مع الديهايدات وكيتونات مختلفة لانتاج قواعد شيف الجديدة. تم اثبات صحة تراكيب المركبات المحضرة من خلال الاعتماد على مطيافية الاشعة تحت الحمراء FTIR والرنين النووي المغناطيسي بنوعيه ^{1}HNMR و^{13}CNMR حيث كانت النتائج المستحصلة مطابقة للتراكيب المقترحة. من المتوقع ان تكون قواعد شيف الجديدة فعالة بولوجيا سيما وان جزيئاتها قد بنيت اساسا من مكونات فعالة بايولوجيا وهي السكسن ايمياد، سلفون امايد وقاعدة شيف.

1. INTRODUCTION

The compounds carrying azomethine functional group (-C=N-) which are known as Schiff bases gain importance in medicinal(1,2) and pharmaceutical field due to the most versatile organic synthetic intermediates and also showing a broad range of biological activities(3-5) such as antituberculosis, anticancer, analgesic, anti-inflammatory(6-8), anticonvulsant, antibacterial and antifungal activities(9).

On the other hand cyclic imides represent an important class of bioactive molecules that shows a wide range of pharmacological activities such as androgen receptor antagonistic(10),

anti-inflammatory(11), anxiolytic(12), antiviral, antibacterial, antitumor, antispasmodic, antinociceptive and antineoplastic properties(13-15).

Keeping in view the facts mentioned we decide to prepare new compounds having structural features of both cyclic imides and Schiff base which were predicated to have useful biological activities.

2. MATERIALS AND METHODS

Melting points were determined on Thomas Hoover apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared Spcetrophotometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300 MHz instrument in Al-Albate University in Jordan using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent.

2.1. Synthesis of N-Phenyl Succinamic Acid [1]

To a solution of (0.01 mol, 1 g) of succinic anhydride in (20 mL) of acetone, (0.01 mol) of aniline was added dropwise with stirring and cooling[16]. Stirring was continued for two hours at room temperature then the resulted precipitate was filtered, dried then purified by recrystallization from ethanol.

2.2. Synthesis of N-Phenyl Succinimide [2]

A mixture of (0.01 mol, 1.93 g) of compound [1] in (25 mL) of acetic anhydride and (0.002 mol, 0.16 g) of anhydrous sodium acetate was refluxed for two hours with stirring[17]. The resulted solution was cooled to room temperature before pouring into crushed ice then the obtained precipitate was filtered, dried and purified by recrystallization from acetone.

2.3. Synthesis of 4-(N-Succinimidyl)phenyl sulfonyl chloride [3]

Chlorosulfonic acid (4 mL) was added dropwise to (0.01 mol, 1.78 g) of compound [2] during two hours with stirring and keeping temperature at zero°C[17]. Stirring was continued for ten hours at room temperature then the resulted mixture was poured into crushed ice carefully with stirring. The obtained precipitate was filtered, washed thoroughly with cold water, dried and purified by recrystallization from acetone.

2.4. Synthesis of 4-(N-Succinimidyl)phenyl sulfonyl hydrazine [4]

To a solution of (0.01 mol, 2.76 g) of compound [3] in (15 mL) of absolute ethanol, (0.01 mol) of hydrazine hydrate was added dropwise with stirring and keeping temperature at zero°C. the resulted mixture was refluxed for six hours then cooled to room temperature before pouring on crushed ice with stirring[18]. The resulted precipitate was filtered, washed with cold water, dried and finally recrystallized from ethanol.

Physical properties of compounds [1-4] are listed in Table (1).

2.5- Synthesis of Schiff Bases [5-1

A mixture of 4-(N-succinimidyl)phenyl sulfonyl hydrazine (0.01 mol, 2.72 g), aromatic aldehyde or ketone (0.01 mol) and (2-3) drops of glacial acetic acid in absolute ethanol (20 mL) was refluxed for 6 hours[19].

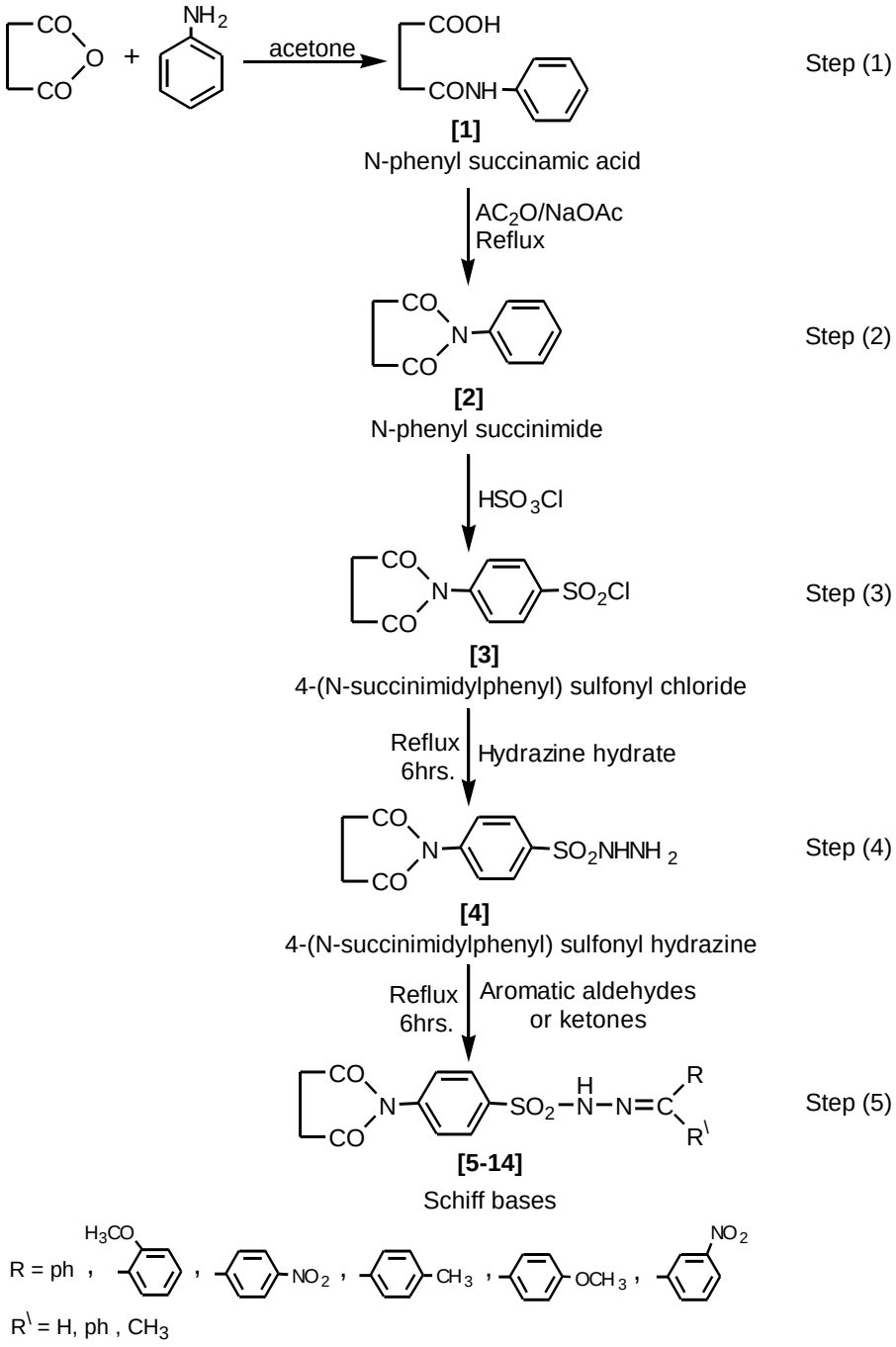
After cooling the obtained precipitate was filtered then washed with clod ethanol, dried and recrystallized from a suitable solvent.

Physical properties of compounds [5-14] are listed in Table (2).

3. RESULTS AND DISSCUSION

Since both succinimides and Schiff bases belong to a widely used group intermediates important for production of many types of pharmaceuticals and have wide spectrum of biological applications the target of the present work has been directed towards building of new molecules containing these two active moieties. Thus the newly synthesized compounds

containing both succinimide and Schiff base moieties linked together through phenyl sulfonamido component. Performing this target was made via multistep synthesis which described in Scheme (1).



Scheme (1)

The first step involved preparation of N-phenyl succinamic acid [1] via reaction of equimolar amounts of succinic anhydride and aniline. Dehydration of compound [1] using acetic anhydride and anhydrous sodium acetate in the second step afforded compound [2] N-phenyl succinimide. In the third step compound [2] was introduced in chlorosulfonation reaction via treatment with chlorosulfonic acid producing compound [3] which inturn was introduced in the fourth step in reaction with hydrazine hydrate producing succinimidyl phenyl sulfonyl hydrazine [4]. In the final step the prepared hydrazine [4] was introduced in condensation reaction with different aldehydes and ketones producing the desired new Schiff bases [5-15].

Physical properties of compounds [1-4] and [5-14] are listed in Tables (1) and (2) respectively.

Structures of the prepared compounds were confirmed by FTIR, ^{1}HNMR and ^{13}CNMR spectral data.

FTIR spectrum of compound [1] showed clear absorption bands at 3311 cm^{-1} and 3193 cm^{-1} due to ν(O-H) carboxyl and ν(N-H) amide.

Absorption bands due to ν(C=O) carboxyl and ν(C=O) amide appeared at 1697 cm^{-1} and 1664 cm^{-1} while absorption band due to ν(C=C) aromatic appeared at 1602 cm^{-1}. ^{1}HNMR spectrum of compound [1] showed signals at (δ=2.75) ppm belong to (CH_2CH_2) protons, signals at (δ=6.99-7.59) ppm belong to aromatic protons and signals at (δ=9.91 and 12.09) ppm belong to (NH) amide and (OH) carboxyl protons respectively[20]. ^{13}CNMR spectrum of compound [1] showed signals at (δ=28.79-28.8) ppm belong to (CH_2CH_2) carbons, signals at (δ=118.91-139.25) ppm belong to aromatic carbons and signals at (δ=170 and 173.72) ppm belong to (C=O) amide and (C=O) carboxyl carbons respectively.

FTIR spectrum of compound [2] showed disappearance of absorption bands due to ν(O-H) carboxyl and ν(N-H) amide indicating success of dehydration reaction which leads to imide formation. Besides the spectrum showed absorption bands at 1776 cm^{-1} and 1704 cm^{-1} which belong to asym. and sym. ν(C=O) imide and bands at 1593 cm^{-1} and 1392 cm^{-1} belong to ν(C=C) aromatic and ν(C-N) imide. ^{1}HNMR spectrum of compound [2] showed signal at (δ=2.78) ppm belong to (CH_2CH_2) protons and signals at (δ=7.25-7.61) ppm belong to aromatic protons. ^{13}CNMR spectrum of compound [2] showed signals at (δ=28.4-31.2) ppm belong to (CH_2CH_2) carbons, signals at (δ=118.93-139.29) ppm belong to aromatic carbons and signals at (δ=173.49-176.82) ppm belong to (C=O) imide carbons[20].

FTIR spectrum of compound [3] showed absorption bands at 1776 and 1706 due to asym. and sym. ν(C=O) imide and bands at 1589 cm^{-1} and 1394 cm^{-1} due to ν(C=C) aromatic and ν(C-N) imide respectively[20]. Besides the spectrum showed two new absorption bands at 1379 cm^{-1} and 1170 cm^{-1} which are attributed to asym. ν(SO_2) and sym. ν(SO_2) and this confirmed the success of compound [3] formation.

^{1}HNMR spectrum of compound [3] showed signal at (δ=2.78) ppm belong to (CH_2CH_2) protons and signals at (δ=7.05-7.96) ppm belong to aromatic protons. ^{13}CNMR spectrum of compound [3] showed signals at (δ=28.43-28.78) ppm belong to (CH_2CH_2) carbons, signals at (δ=117.89-147.9) ppm belong to aromatic carbons and signals at (δ=173.46-176.83) ppm belong to (C=O) imide carbons.

FTIR spectrum of compound [4] showed strong absorption bands at 3311 and 3292 cm^{-1} which belong to ν(-$NHNH_2$) group and this is an excellent proof for the success of hydrazine compound formation.

^{1}HNMR spectrum of compound [4] showed signals at (δ=2.02-2.14), (4.64-4.95) ppm and 8.77 ppm which belong to NH_2 and NH protons of hydrazine moiety while signals of (CH_2CH_2) protons and aromatic protons appeared at δ=2.36 and (6.21-7.05) ppm respectively. ^{13}CNMR spectrum of compound [4] showed signals at (δ=28.3-28.94) ppm

belong to (CH_2CH_2) carbons, signals at (δ=97.28-148.86) ppm belong to aromatic carbons and signals at (δ=170.21-170.93) ppm belong to (C=O) imide carbons.

FTIR spectrum of prepared Schiff bases [5-14] showed disappearance of absorption band at 3311 which belong to NH_2 group in hydrazine compound and appearance of new clear absorption band at (1598-1666) cm^{-1} due to ν(C=N) imine. These two points are excellent proofs for the success of Schiff base formation[20]. Besides FTIR spectra of Schiff bases [5-14] showed also clear absorption bands at (1650-1699) cm^{-1} due to ν(C=O) imide and bands at (1508-1602) cm^{-1} due to ν(C=C) aromatic. Other absorptions appeared at (1317-1361) cm^{-1}, (1135-1188) cm^{-1} and (1280-1396) cm^{-1} which belong to asym. ν(SO_2), sym. ν(SO_2) and ν(C-N) imide respectively.

All details of FTIR spectral data of compounds [1-4] and [4-18] are listed in Tables (3) and (4) respectively.

^{1}HNMR spectrum of Schiff base [5] showed signal at (δ=2.96) ppm belong to (CH_2CH_2) protons, signals at δ=(7.41-7.99) ppm belong to aromatic protons and signals at (δ=8.16 and 8.71) ppm belong to (NH) amide and (-CH=N-) imine protons respectively. ^{13}CNMR spectrum of compound [5] showed signals at (δ=28.5) ppm belong to (CH_2CH_2) carbons, signals at (δ=126.58-131.29) ppm belong to aromatic carbons and signals at (δ=133.78 and 161.29) ppm belong to (C=N) and (C=O) imide respectively.

^{1}HNMR spectrum of compound [6] showed signal at (δ=2.5 and 3.89) ppm belong to (CH_2CH_2) protons and (OCH_3) protons. Other signals appeared at (7.03-7.54) ppm, (7.99 and 8.93) ppm which belong to aromatic protons, (NH) amide proton and (-CH=N-) imine proton respectively.^{13}CNMR spectrum of compound [6] showed signals at (δ=28.7 and 55.82) ppm belong to (CH_2CH_2) carbons and (OCH_3) carbon. Signals belong to aromatic carbons appeared at (δ=112.05-132.96), while signals belong to (C=N) and (C=O) imide carbons appeared at (δ=156.42 and 158.75) ppm respectively.

^{1}HNMR spectrum of compound [8] showed signals at (δ=2.27) ppm belong to CH_3 protons, signals at (δ=2.67-3) ppm belong to (CH_2CH_2) protons, and signals at (δ=7.41-7.92) ppm belong to aromatic protons.

Table (1): Physical properties of compounds [1-4]

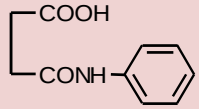
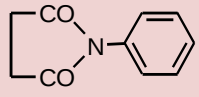
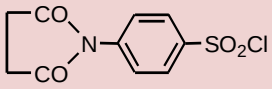
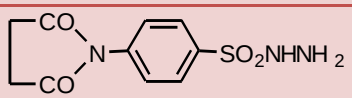
Comp. No.	Compound structure	Color	Melting points °C	Yield %	Recrystallization Solvent
1		White	140-142	86	**Ethanol**
2		Pale Yellow	150-153	80	**Acetone**
3		Gray	119-122	75	**Acetone**
4		**Brown**	**131-133**	**70**	**Ethanol**

Table (2): Physical properties of compounds [5-14]

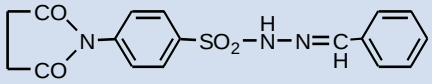
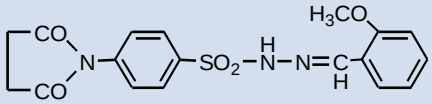
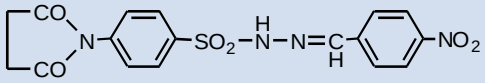
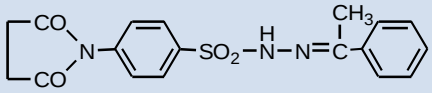
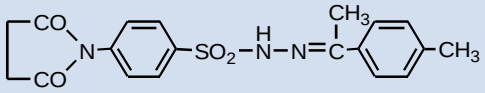
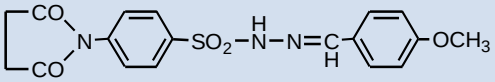
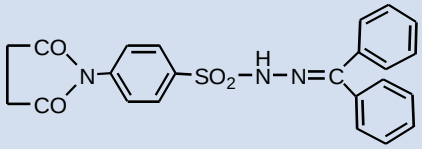
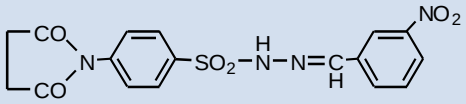
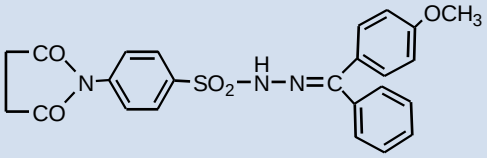
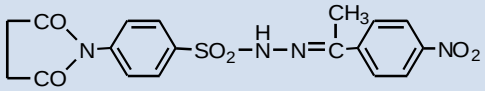
Comp. No.	Compound structure	Color	Melting points °C	Yield %	Recrystallization Solvent
5		White	161-164	70	**Acetone**
6		White	126-128	78	**Acetone**
7		Pale yellow	155-158	80	**Ethanol**
8		White	122-125	82	**Ethanol**
9		Yellow	130-132	75	**Acetone**
10		Brown	190-192	85	**Ethanol**
11		Off white	183-186	68	**Acetone**
12		Yellow	133-136	77	**Acetone**
13		Pale yellow	174-177	72	**Ethanol**
14		**Pale yellow**	**182-184**	**66**	**Ethanol**

Table (3): Spectral data (cm-1) of the compounds [1-4]

Comp. No.	**ν(O-H) carboxylic**	**ν(N-H) amide**	**ν(C-H) aromatic and aliphatic**	**ν(C=O) carboxylic**	**ν(C=O) amide**	ν(C=C) aromatic
1	3311	3193	3064 2933	1697	1664	**1602**

Comp. No.	**ν(C-H) aromatic**	**ν(C-H) aliphatic**	**ν(C=O) imide**	**ν(C=C) aromatic**	ν(C-N) imide	
2	3109	2937	asym. 1776 sym. 1704	1593	**1392**	
Comp. No.	**ν(C-H) aromatic and aliphatic**	**ν(C=O) imide**	**ν(C=C)**	**asym. ν(SO_2)**	**Sym. ν(SO_2)**	ν(C-N) imide
3	3103 2937	asym. 1776 sym. 1706	1589	1379	1170	**1394**
Comp. No.	**ν(NH_2) ν(NH)**	**ν(C-H) aromatic and aliphatic**	**ν(C=O) imide**	**ν(C=C) aromatic**	**asym. ν(SO_2)**	**Sym. ν(SO_2)**	ν(C-N) imide
4	**3311 3292**	**3041 2910**	**asym. 1677 sym. 1627**	**1550**	**1370**	**1150**	**1350**

Table (4): Spectral data (cm-1) of the compounds [5-14]

Comp. No.	FTIR spectral data cm^{-1}							
	ν(N-H)	**ν(C-H) aromatic and aliphatic**	**ν(C=O) imide**	**ν(C=N)**	**ν(C=C) aromatic**	**ν(SO_2) asym. ν(SO_2) sym.**	**ν(C-N) imide**	Others
5	3199	3031 2968	1664	1625	1596	1323 1172	1390	-
6	3371	3001 2943	1699	1618	1600	1323 1157	1292	ν(C-O-C) **asym. 1249 sym. 1157**
7	3203	3043 2925	1680	1652	1596	1346 1188	1330	ν(NO_2) **1519, 1458**
8	3178	3062 2921	1689	1618	1600	1361 1137	1396	-
9	3191	3064 2918	1691	1602	1562	1361 1135	1380	-
10	3220	3020 2927	1652	1620	1602	1323 1166	1301	ν(C-O-C) **asym. 1251 sym. 1108**
11	3272	3055 2920	1690	1618	1585	1334 1170	1360	-
12	3290 3205	3074 2923	1672	1666	1598	1352 1180	1392	ν(NO_2) **1533, 1444**
13	3205	3053 2933	1650	1598	1508	1317 1172	1280	ν(C-O-C) **1255**
14	**3259 3205**	**3074 2925**	**1676**	**1654**	**1596**	**1346 1168**	**1390**	ν(NO_2) **1519, 1444**

CONCLUSION

A series of new Schiff bases containing two biologically active components was synthesized successfully by application of multistep synthesis. The newly synthesized compounds were expected to possess high biological activity since they contain three known biologically active moieties.

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