Synthesis, Characterization and Antimicrobial Screening of New Schiff Bases Linked to Phthalimidyl Phenyl Sulfonate Moiety

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Abstract

A series of Schiff bases linked to phthalimidyl phenyl sulfonate moiety have been synthesized via multistep synthesis.

The first step involved reaction of phthalic anhydride with aniline producing N-phenyl phthalamic acid which was subsequently dehydrated to the corresponding N-phenyl phthalimide via treatment with acetic anhydride and anhydrous sodium acetate. The synthesized imide was treated with chlorosulfonic acid in the third step producing 4-(N-phthalimidyl) phenyl sulfonyl chloride which was introduced in reaction with 4-hydroxy acetophenone in the fourth step producing 4-[4\-(N-phthalimidyl) phenyl sulfonate] acetophenone and this in turn was introduced successfully in condensation reaction with various aromatic primary amines affording the desired new Schiff bases. The newly synthesized compounds were characterized through spectral data including FTIR, ^{1}HNMR and ^{13}CNMR. Antimicrobial activity of the prepared Schiff bases was evaluated against two types of bacteria and one type of fungi and the new Schiff bases were found to exhibit good antimicrobial activity against the tested organisms.

Key words: phthalimide, phthalimidyl phenyl sulfonyl chloride, phthalimidyl phenyl sulfonate

Introduction:

Schiff bases are important intermediates for the synthesis of some bioactive compounds such as β-lactams, and they form a significant class of compounds in medicinal and pharmaceutical chemistry with a variety of interesting biological actions including antibacterial, antifungal, antimouse hepatitis virus (MHV), and adenovirus type 5 (Ad 5), anticancer and herbicidal activities[1-5].

Similarly phthalimides which are bicyclic non-aromatic nitrogen heterocycles are important compounds with a variety of applications and a wide range of properties [6-8]. Generally they are used as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores, synthesis of pesticides and lately are being under intense biomedical research due to their important biological effects [9-12]. In light of the interesting variety of biological activities seen in compounds containing phthalimidies and azomethine linkages it was thought of interest to examine the effect of having these two functionalities present simultaneously in one structure.

Based on this notion we decide to synthesize several new Schiff bases linked to phthalimidyl sulfonate moiety and to test them against types of bacteria and fungi.

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Material and Methods:

Melting points were determined on Thomas Hoover apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR 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 a solvent.

1- Preparation of N-phenylphthalamic Acid (1)

To a solution of (0.01 mol, 1.48 g) phthalic anhydride in (25 mL) of acetone, (0.01 mol, 1 mL) of aniline was added dropwise with continuous stirring under cooling conditions [13], then was stirred for two hours at room temperature. The resulted precipitate was filtered, dried then purified by recrystallization from ethanol.

2- Preparation of N-phenyl phthalimide (2)

A mixture of (0.01 mol, 2.41 g) of N-phenyl phthalamic acid in (25 mL) of acetic anhydride and (5%) by weight of anhydrous sodium acetate was refluxed for two hours with stirring [14].

The resulted homogenous solution was cooled to room temperature then poured into crushed ice with stirring and the obtained precipitate was filtered, dried and recrystallized from acetone.

3- Preparation of 4-(N-phthalimidyl) phenyl sulfonyl chloride (3)

Chlorosulfonic acid (4 ml) was added dropwise to(0.01 mol, 2.23 g) of N-phenylphthalimide during two hours with stirring and keeping temperature at zero °C [14].

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, dried then recrystallized from acetone.

4- Preparation of 4-[4\-(N-phthalimidyl) phenyl sulfonate]acetophenone (4)

In a three necked flask equipped with a stirrer and a thermometer a mixture of (0.015 mol, 2.04g) of 4-hydroxy acetophenone and (3 mL) of pyridine was placed. The flask was surrounded by a bath sufficiently cold to lower the mixture temperature to 10°C then 4-(N-phthalimidyl)phenyl sulfonyl chloride (0.01 mol, 3.22g) was added in portions during twenty minutes with continuous stirring [15].

The resulted mixture was refluxed for two hours on a water bath then poured into cold water with stirring until the resulted oily layer solidified. The solid product was filtered, washed with water, dried then recrystallized from ethanol. Physical properties of compounds (1, 2, 3, 4) are listed in Table (1).

5- Preparation of 4-[4\-(N-phthalimidyl) phenyl sulfonate] methyl benzylidene (5-11)

In a suitable round bottomed flask (0.01 mol, 4.21 g) of compound (4) 4-[4\-(N-phthalimidyl) phenyl sulfonate] acetophenone was dissolved in (20 mL) of absolute ethanol then (0.01 mol) of primary aromatic amine was added followed by addition of (2-3) drops of glacial acetic acid with stirring [2]. The mixture was refluxed for four hours then cooled to room temperature and the obtained precipitate was filtered, dried and purified by recrystallization from a suitable solvent. Physical properties of

compounds (5-11) are listed in Table (2).

6- Biological study

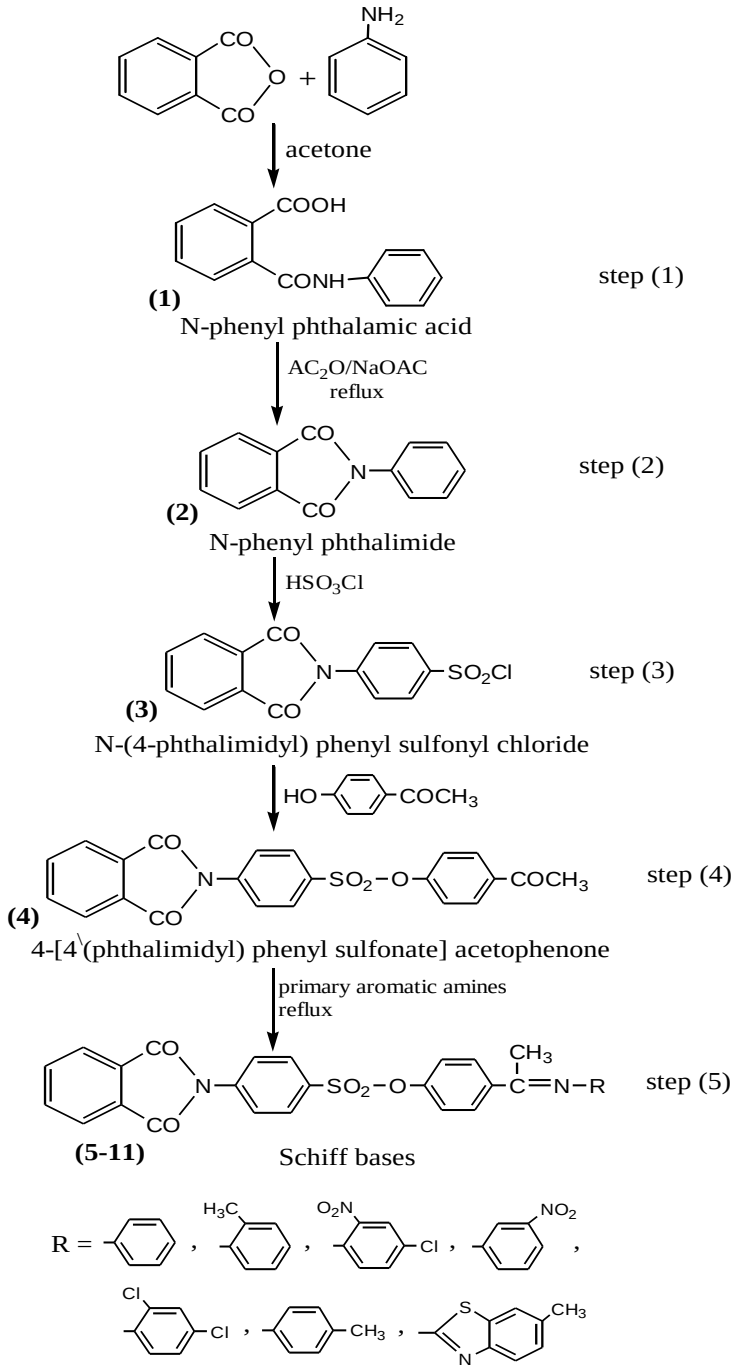
The cup plate method using nutrient agar medium was employed in studying the antimicrobial activity of the prepared Schiff bases [14]. DMF was used as sample solution and sample size for all compounds was fixed at (0.1 mL). Using a sterilized cork borer cups were scooped out of agar medium contained in a petridish which was previously inoculated with the microorganisms. The tested compound solution (0.1 mL) was added in the cups and the petridishes were subsequently incubated at 37°C for 48 hrs. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (5).

Results and Discussion

Since both phthalimides 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 phthalimide and Schiff base moieties linked together through phenyl sulfonate component. Performing this target was made via multistep synthesis which described in Scheme (1).

The first step involved preparation of N-phenyl phthaliamic acid via reaction of equimolar amounts of phthalic anhydride and aniline in acetone. Dehydration of compound (1) using acetic anhydride and anhydrous sodium acetate in the second step afforded compound (2) N-phenyl phthalimide.

In the third step the prepared imide (2) was introduced in chlorosulfonation reaction via treatment with chlorosulfonic acid producing compound (3) which in turn was introduced in the fourth step in esterification reaction with 4-hydroxy acetophenone producing compound (4). In the final step of this work the prepared new ketone (phthalimidyl phenyl sulfonate acetophenone) (4) was introduced in condensation reaction with different primary aromatic amines producing the desired target Schiff bases (5-11).



Scheme (1)

The strategy which we depend on in building the new Schiff bases involved introducing of sulfonyl chloride group in para position of phenyl ring attached to phthalimide moiety then this compound which represents acid chloride introduced in esterification reaction in which nucleophilic replacement of chloride with p-acetophenoxide moiety was performed and by this step the resulted new compound (4) contain carbonyl group which was ready for nucleophilic attack by amines during condensation reaction in the final step affording the desired Schiff bases. Structures of prepared compounds were confirmed by FTIR, ^{1}HNMR and ^{13}CNMR spectral data.

FTIR spectrum of compound (1) showed strong absorption bands at 3325 and 3136 cm^{-1} due to ν(O-H) carboxylic and ν(N-H) amide. Other absorptions appeared at 1720 cm^{-1},

1643 cm^{-1} and 1600 cm^{-1} due to ν(C=O) carboxylic, ν(C=O) amide and ν(C=C) aromatic respectively[17]. FTIR spectrum of compound (2) showed disappearance of ν(O-H) and ν(N-H) absorption bands proving success of dehydration reaction and appearance of two bands at 1735 cm^{-1} and 1708 cm^{-1} due to asym. and sym., bands of ν(C=O) imide. FTIR spectrum of compound (3) showed two clear bands at 1365 cm^{-1} and 1188 cm^{-1} due to ν(SO_2)asym. and ν(SO_2)sym. respectively indicating success of introducing sulfonyl chloride moiety in phenyl phthalimide molecule. FTIR spectrum of compound (4) showed absorption bands at 1739cm^{-1} and 1720 cm^{-1} due to asym. and sym. ν(C=O) imide. The appearance of new band at 1674 cm^{-1} belong to ν(C=O) ketone is a good proof for success of compound (4) formation [17].

Other bands appeared at 1593 cm^{-1} , 1361 cm^{-1} and 1176 cm^{-1} due to ν(C=C) aromatic, asym. and sym. ν(SO_2) respectively. Finally FTIR spectra of the new Schiff bases (5-11) showed disappearance of absorption band at 1674 cm^{-1} belong to ν(C=O) ketone and appearance of clear strong absorption band at (1681-1690) cm^{-1} due to ν(C=N) imine.

Other absorption bands in FTIR spectra of compounds (5-11) are shown at (1725-1743) cm^{-1}, (1710-1726) cm^{-1}, (1593-1595) cm^{-1}, (1361-1385) cm^{-1} and (1176-1199) cm^{-1} due to asym. ν(C=O) imide, sym. ν(C=O) imide, ν(C=C) aromatic, asym. and sym. ν(SO_2) respectively. All details of FTIR spectral data of compounds (1-4) and (5-11) are listed in Table (3) and (4).

^{1}H-NMR spectrum of compound (1) showed signals at δ= (7.04-7.89) ppm belong to aromatic protons and (N-H) proton and a clear signal at δ= 10.33 ppm due to (O-H) carboxylic proton [17], while ^{13}C-NMR spectrum of this compound showed signals at δ= (119.9-140), 167.8 and 167.92 ppm due to aromatic carbons, (C=O) amide and (C=O) carboxyl respectively.

^{1}H-NMR spectrum of compound (2) showed disappearance of (OH) carboxyl proton signal and appearance of two multiplet signals at δ= (7.44-7.56) and (7.89-7.97) ppm belong to protons of two aromatic rings. ^{13}C-NMR spectrum of compound (2) showed signals at δ= (123.8-135.1) ppm and at δ= 167.4 ppm belong to aromatic and (C=O) imide respectively. ^{1}H-NMR of compound (4) showed signals at δ= 2.56 and δ= (7.28-8.13) ppm due to (CH_3) group protons and aromatic ring protons, while ^{13}C-NMR spectrum of this compound showed signals at δ= 27.2, (122.6-153), 166.8 and 198 ppm belong to CH_3 group, aromatic ring carbons, (C=O) imide and (C=O) ketone respectively.

^{1}H-NMR spectrum of Schiff base (6) showed two signals at δ= 2.35 and 2.56 ppm due to two (CH_3) groups and signals at δ= (7.28-8.12) ppm due to aromatic protons. ^{13}C-NMR spectrum of the same compound (6) showed signals at δ= 27.21, (122.5-138.2), 152.6 and 166.8 ppm belong to CH_3 groups, aromatic rings cabons, (C=N) imine and (C=O) imide. Finally ^{1}H-NMR spectrum of Schiff base (9) showed signals at δ= 2.54, 2.56 ppm due to two (CH_3) groups, signals at δ= (7.1-8) ppm are due to aromatic protons while ^{13}C-NMR of the same compound (9) showed signals at δ= 27.2, (122-135), 153 and 168 ppm belong to CH_3 groups, aromatic ring carbons, (C=N) imine and (C=O) imide respectively.

Biological Activity

The synthesized imides in this work were expected to possess

biological activity since they have two active moieties in their molecules thus a prileminary evaluation of antibacterial activity of the new Schiff bases were tested against two types of bacteria *Staphylococcus aureus* (Gram positive) and *Escherichia Coli* (Gram negative).

Antifungal activity of the new Schiff bases against *Candida albicans* fungi were tested also and the results which are listed in Table (5) indicated that compound (11) showed very high activity against *S. aureus*, compounds (5, 6, 9) showed high activity while compounds (7, 8, 10) showed moderate activity against this bacteria. On the other hand compound (11) showed very high activity and compounds (5, 7, 8, 10) showed high activity against *E. Coli* while compounds (6, 9) showed moderate activity against this bacteria. Finally compound (11) showed high activity against *Candida albicans* fungi, compounds (5, 7, 10) showed moderate activity and compounds (6, 8, 9) showed slight activity against this fungi.

Conclusion:

The presence of the two active functionalities phthalimide and Schiff base in the new synthesized molecules exhibit them biological activity and this activity was affected by type of substituents present in the molecules, thus the presence of the known biologically active benzothiazole moiety in compound (11) increased the activity of this compound among the others.

Table (1): Physical properties of prepared compounds (1-4)

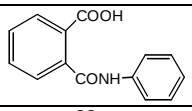
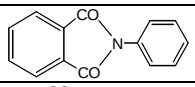
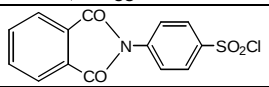
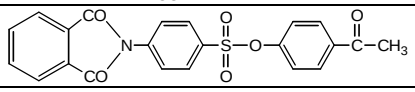
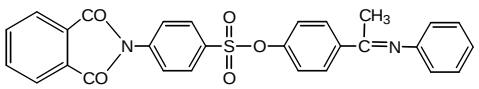
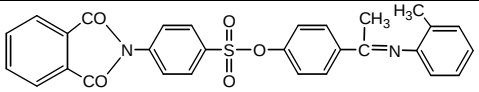
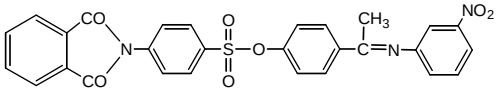
Comp. No.	Compound structure	color	Melting points °C	Yield %	Solvent of recrystallization
1		White	170-172	88	Ethanol
2		Off white	204-205	85	Acetone
3		Brown	200 dec.	72	Acetone
4		Pale brown	152-154	70	Ethanol

Table (2): Physical properties of prepared compounds (5-11)

Comp. No.	Compound structure	Color	Melting points °C	Yield %	Solvent of recrystallization
5		Pale brown	155-156	72	Ethanol
6		Off white	148-150	66	Ethanol
7		Pale yellow	159-160	88	Acetone

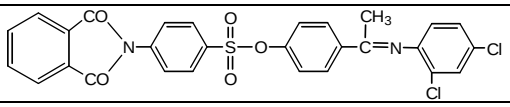
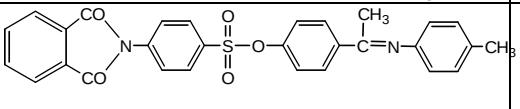
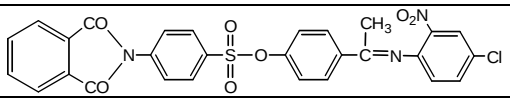
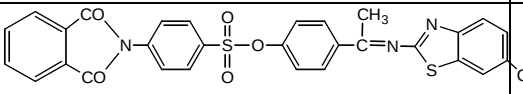
Comp. No.	Compound structure	Color	Melting points °C	Yield %	Solvent of recrystallization
8		Pale brown	172-173	90	Ethanol
9		Off white	163-164	63	Ethanol
10		Pale yellow	180-182	85	Acetone
11		Pale brown	167-168	77	Cyclohexane

Table (3): FTIR spectral data of compounds (1-4)

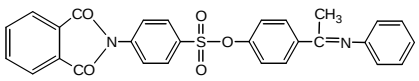
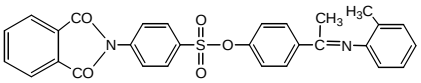
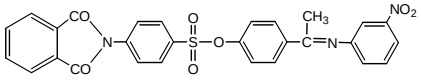
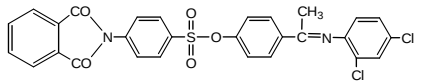
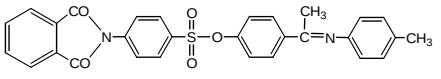
Comp. No.	FTIR spectral data cm^{-1}					
	ν(O-H) carboxylic	ν(N-H) amide	ν(C-H) aromatic	ν(C=O) carboxlyic	ν(C=O) amide	ν(C=C) aromatic
1	3325	3136	3062	1720	1643	1600

Comp. No.	ν(C-H) aromatic	ν(C=O) imide	ν(C=C) aromatic	ν(C-N) imide
2	3074	1735 1708	1593	1384

Comp. No.	ν(C-H) aromatic	ν(C=O) imide	ν(C=C) aromatic	$\nu(SO_2)$ asym.	$\nu(SO_2)$ sym.	ν(C-N) imide
3	3101	1743 1720	1585	1365	1188	1300

Comp. No.	ν(C=O) imide	ν(C=O) ketone	ν(C=C) aromatic	$\nu(SO_2)$ asym.	$\nu(SO_2)$ sym.
4	1739 1720	1674	1593	1361	1176

Table (4): FTIR spectral data of compounds (5-11)

Comp. No.	Compound structure	FTIR spectral data cm^{-1}							
		ν(C-H) aromatic	ν(C=O) imide	ν(C=N) imine	ν(C=C) aromatic	$\nu(SO_2)$ asym.	$\nu(SO_2)$ sym.	ν(C-N) imide	Others
5		3109	1739 1720	1685	1593	1373	1180	1300	-
6		3062	1740 1720	1685	1593	1373	1176	1296	-
7		3100	1743 1722	1683	1593	1385	1182	1300	$\nu(NO_2)$ 1496 1355
8		3100	1739 1726	1687	1593	1369	1182	1355	ν(C-Cl) 1078
9		3109	1743 1720	1685	1593	1373	1199	1300	-

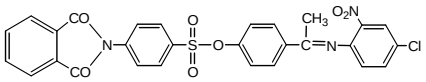
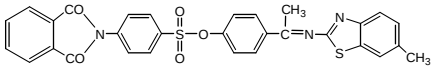
Comp. No.	Compound structure	FTIR spectral data cm^{-1}							
		ν(C-H) aromatic	ν(C=O) imide	ν(C=N) imine	ν(C=C) aromatic	ν(SO_2) asym.	ν(SO_2) sym.	ν(C-N) imide	Others
10		3080	1725 1710	1690	1593	1372	1185	1300	ν(NO_2) 1490 1350 ν(C-Cl) 1090
11		3109	1737 1720	1685	1593	1373	1199	1300	ν(C-S) 609

Table (5): Antimicrobial activity of compounds (5-11)

Comp. No.	Gram positive bacteria	Gram negative bacteria	Candida albicans fungi
	Staphylococcus aureus	*Escherichia Coli*	
5	+++	+++	++
6	+++	++	+
7	++	+++	++
8	++	+++	+
9	+++	++	+
10	++	+++	++
11	++++	++++	+++

Key to symbols: slightly active = (+) = inhibatiotion zone 6-9 mm
Moderately active = (++) = inhibition zone 9-12 mm
Highly active = (+++) inhibition zone 13-17 mm
Very high activity = (++++) inhibition zone > 17 mm

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تحضير وتشخيص ودراسة الفعالية المضادة للمايكروبات لقواعد شيف جديدة مرتبطة بمكونة فثال ايميديل فنيل سلفونات

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الخلاصة:

تم في هذا البحث تحضير عدد من قواعد شيف الجديدة المرتبطة بمكونة فثال ايميديل فنيل سلفونات بواسطة التحضير المتعدد الخطوات.

تضمنت الخطوة الاولى تفاعل انهيدريد الفثاليك مع الانيلين لتكوين N-فنيل حامض الفثال آميك والذي تم سحب الماء منه بمعاملته مع انهيدريد الخليك وخلات الصوديوم اللامائية لتحويله الى N-فنيل فثال ايمايد. في الخطوة الثالثة تم ادخال الفثال ايمايد المحضر في تفاعل مع كلورو حامض السلفونيك مما اسفر عن تكوين 4-(N-فثال ايميديل) فنيل كلوريد السلفونيل والذي بدوره ادخل في تفاعل مع 4-هيدروكسي اسيتوفينون في الخطوة اللاحقة لتكوين 4-[4/-(N-فثال ايميديل) فنيل سلفونات] اسيتوفينون وهذا بدوره عند ادخاله في تفاعل تكاثف مع امينات اروماتية اولية مختلفة تم الحصول على قواعد شيف الجديدة المطلوبة.

تم تشخيص المركبات المحضرة بمطيافية الاشعة تحت الحمراء والرنين النووي المغناطيسي ^{1}HNMR و ^{13}CNMR. كذلك تضمن البحث تقدير فعالية قواعد شيف المحضرة ضد نوعين من البكتريا ونوع من الفطريات وقد اوضحت النتائج بانها ذات فعالية جيدة ضد المايكروبات قيد الدراسة.