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Original Research Article

Design, Synthesis and Antimicrobial Activity Evaluation of New Bisimidyl Sulfonamido Ketone Comprising Drug component

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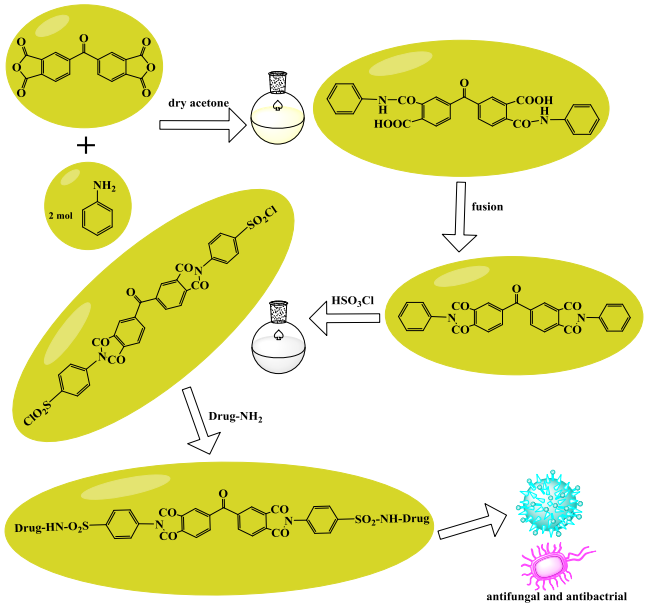
ABSTRACT

This work involved design and synthesis of four new compounds which their molecules contain three biologically active segments, including *β*-lactam containing drug, cyclic imide and sulfonamido group. Synthesis of the compounds was performed by several steps. In the first step, compound (1) bis[*N*-phenyl phthalamic acid] ketone was synthesized via reaction of aniline with benzophenone 3,3',4,4'-tetra carboxylic dianhydride. In the second step, compound (1) was dehydrated by fusion to give the corresponding bis phthalimide (2) which in turn was introduced in reaction with chloro sulfonic acid. The third step involved producing compound (3), the corresponding bis phthalimidyl benzene sulfonyl chloride. Compound (3) is the important key compound from which the target compounds (4-7) were prepared through its reaction with different *β*-lactam containing drugs. Antibacterial and antifungal activities of compounds (4-7) were screened and the results indicated that they have high biological activity.

GRAPHICAL ABSTRACT



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Introduction

Sulfonamides represent an important class of organic compounds present in many natural products and pharmaceuticals, which are employed as preventative and chemotherapentic agents against many diseases [1-3]. Sulfonamide derivatives have wide range of biological activity like antiviral, antimicrobial, anticancer and aromatase inhibitor [4-8] due to their potential bioactive scaffolds and ability in multiple interactions with different biological targets.

On the other hand, cyclic imides constitute an important type of compounds that have wide domain of various biological activities; besides they are valuable building blocks in synthesis of many pharmaceuticals and bioactive compounds [9-11]. Amoxicillin, cefotaxim [12], cifixime and cephalexen are pharmacologically active β-lactam antibiotics widely used in treatment of various infections [13,14]. In view of all the above mentioned facts and due to the growing resistance of bacteria against different antibiotics and the need for new more active drugs, we approached designing and synthesizing new compounds, whose molecules contain the three moieties sulfonamide, cyclic imide and drug component together since the combination of all these biologically active moieties in the same molecule may give the chance for producing new developed drugs more effective against broad range of different types of bacteria and fungi.

Material and methods

Chemicals used in this work were purchased from Fluka, BDH and Merk Companies. Melting points were determined on Gallen Kamp capillary melting point apparatus and were uncorrected. FTIR spectra were recorded on Shimadzu FT-IR 8400 Fourier Transform Infrared spectrophotometer while ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Nuclear magnetic resonance Bruker 400 MHz apparatus.

Synthesis of bis[N-Phenyl phthalamic acid] ketone (1)

Aniline (0.02 mol, 1.86 g) dissolved in (30 mL) dry acetone was added dropwise to the solution of (0.01 mol, 3.22 g) benzophenone 3,3',4,4'- tetra carboxylic dianhydride dissolved in dry acetone (30 mL) with Stirring [15]. The resulting mixture was stirred for 4 h at room temperature, then the formed precipitate was filtered, dried and purified by recrystallization from ethanol.

Synthesis of bis[N-phenyl phthalimide-4-yl]ketone (2)

Compound (2) was synthesized by heating 5gm of compound (1) in oil bath until complete fusion then heating was continued for 2h at ten degrees above melting point of compound (1) [9]. The resulted product was cooled to room temperature, then recrystallized from acetone.

Synthesis of bis[N-(4-benzene sulfonyl chloride) phthalimide -4'-yl] ketone (3)

Chloro sulfonic acid (4 mL) was added dropwise to (0.01 mol, 4.72 g) of compound (2) during 2h with stirring at Zero °C [16]. After completion of addition, stirring was continued for 10h at room temperature, then the mixture was poured carefully onto crushed ice with stirring and the formed precipitate was filtered, washed with cold water several times then with ether, dried and recrystallized from ethanol.

Synthesis of bis[N-(4-benzene sulfonamido drug)-4'-yl phthalimide] ketone (4-7)

Compound (3) (0.01 mol, 6.69 g) was added in portions to the solution of amino-containing compound (drug) (0.02 mol) dissolved in (30 mL) dry pyridine with stirring and keeping temperature below 40°C [16]. After completion of addition, the mixture was refluxed for 4h before pouring into excess ice water with forcible stirring. The formed precipitate was filtered, washed with cold water, then with ether, dried and recrystallized from a suitable solvent.

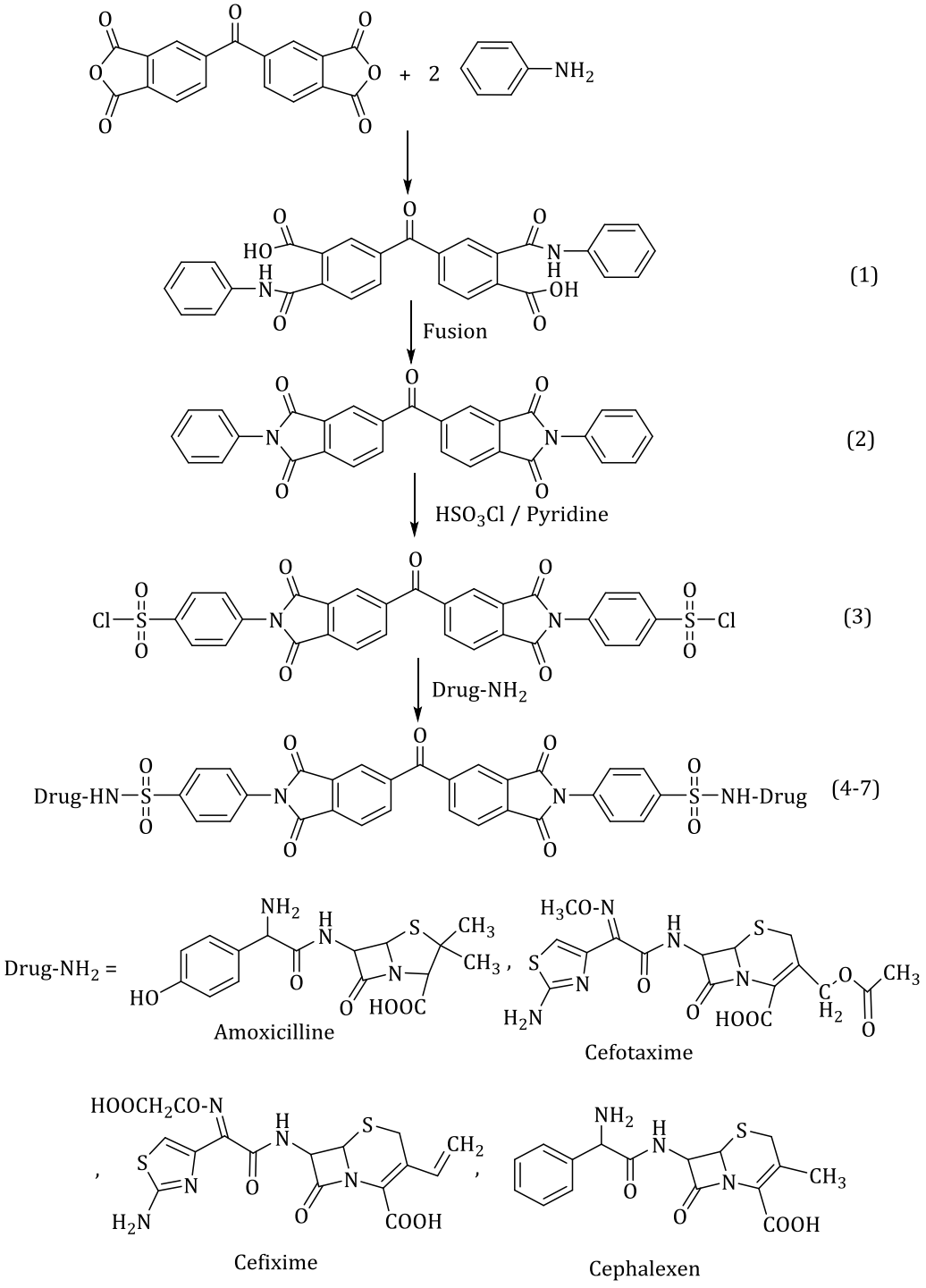
Antibacterial activity study

The antibacterial activity of producing bis-imides against a variety of microorganisms was studied using the cup plate technique. In addition to DMSO, nutrient agar medium was employed. Sample volume and sample solution for all of the examined compounds were renamed (0.1 mL). Scooping out of cups in an agar medium enclosed in a petri dish. Previously, the bacteria were

incubated. The examination was done in the cups, (0.1 mL) of compound solution was added, and the petri dishes were incubated for 48 hours at 37 ℃. Zones of influence for each compound's inhibition was measured in millimeters. Table (5) summarizes the findings.

Result and Dissection

This work aimed to design and synthesis of new biologically active compounds. The idea of the new design was based on combination of three known biologically active segments, namely β-lactam drug, cyclic imide, sulfonamide, in the same molecule with hopes that the presence of these three segments together may provide the opportunity for producing more effective drugs, which contribute to fighting various types of bacteria and fungi. In so doing, multistep synthesis was carried out as described in the Scheme 1.



Scheme 1: multistep synthesis of bisimidyl sulfonamido ketone compounds

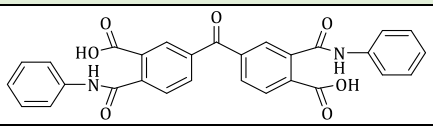
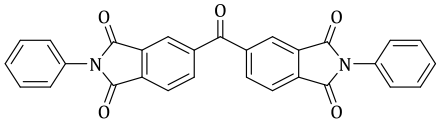
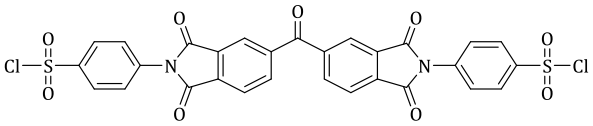
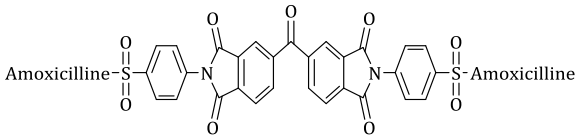
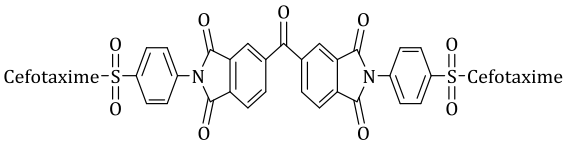
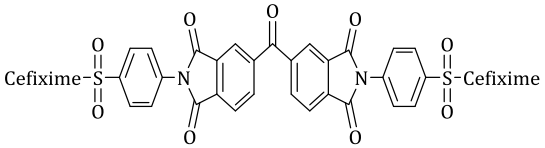
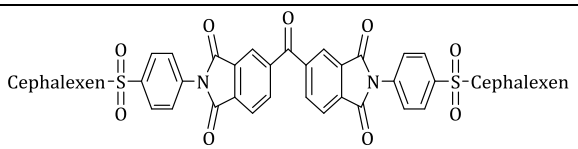
The first step involved preparation of compound (1) bis[*N*-phenyl phthalamic acid] ketone from reaction of one mole of benzophenone 3,3',4,4'-tetra carboxylic dianhydride with two moles of aniline in acetone solvent at room temperature. In the second step, compound (1) was introduced in dehydration reaction, thus by applying of fusion process, two water molecules were eliminated, followed by ring closure and bis imide formation compound (2).

In the third step, compound (2) bis[*N*-phenyl phthalimide-4'-yl] ketone was introduced in reaction with chloro sulfonic acid gaveing a compound (3) bis[*N*-(4-benzene Sulfonyl chloride)phthalimide-4'-yl] ketone in which the two phenyl rings were substituted with sulfonyl chloride at para position. In the fourth step, compound (3) was introduced in reaction with four β-lactam containing drugs gaveing compounds (4-7) Physical properties of compounds (1-7) are shown in Table 1. Chemical structures of compounds (1-7) were proved by FT-IR as shown in Table 2; ^{1}H-NMR and ^{13}C-NMR Spectroscopies are shown in Tables 3 and 4.

Biological Activity Study

This study also addressed the evaluation of antibacterial activity of the target compounds against some Gram-negative bacteria and Gram-positive using Muller Hinton agar as medium and incubation of samples was made at 37 °C for 24 h. Inhibition zones in (mm) which caused by the target compounds (4-7) against the tested bacteria are shown in Table 5. The results indicated that compounds (5-7) showed very high activity against *Staphylococcus aurus*, *Klebsiella pneumoniae* and *Bacillus subtilis* bacteria.

Table 1: Physical properties of compounds (1-7)

Comp. No.	Compound Structure	Colour	Melting Point °C	Yield %	Recrystal. solvent
1		Off whit	128-130	90	Ethanol
2		Brown	278-280	84	Acetone
3		Gray	310-312	80	Ethanol
4		Dark red	261-262	86	Acetone
5		Brownish green	230-232	83	Ethanol
6		Brown	198-200	80	Acetone
7		Black brown	240-242	79	Ethanol

Compounds (5,6) showed good activity against *Pseudomonas auroginosa* while compound (7) showed high activity against this bacterium. Compound (4) showed good activity against all the tested bacteria. On the other hand, antifungal activity of compounds (4-7) was also evaluated. The inhibition zones (mm) caused by these compounds against *Rhizosporium fungi* are listed in Table 5. Compounds (4,7) showed high activity while compounds. The compounds (5,6) showed moderate activity against the tested fungi. As a final conclusion, the results of both antibacterial and antifungal activities of the newly synthesized compounds (4-7) are very promising.

Table 2: FT-IR spectral data (cm^{-1}) of compounds (1-7)

Comp. No.	ν (O-H) ν (N-H)	ν (C-H) Aromatic	ν (C-H) Aliphatic	ν (C=O) Lactam and asym. ν (C=O) Imide	ν (C=O) Carboxyl and ν (C=O) Ester	ν (C=O) Ketone	ν (C=C) Aromatic	ν (C-N) Imide	asym. ν (SO_2)	sym. ν (SO_2)
1	3456 3359 3255	3058	-------	-------	1710	1658	1600	-------	-------	-------
2	-------	3060	-------	1780 1722	-------	1654	1596	1394	-------	-------
3	-------	3064	-------	1782 1730	-------	1670	1589	1390	1367	1172
4	3444 3382 3195	3070	2977 2885	1778	1718	1656	1602	1392	1375	1174
5	3444 3253 3105	3050	2991 2890	1772	1720	1656	1596	1394	1375	1193
6	3448 3380 3193	3072	2977 2887	1776	1681	1650	1600	1396	1371	1161
7	3429 3253 3109	3072	2940 2889	1775	1718 1665	1637	1600	1396	1371	1159

Table 3: ^{1}H-NMR spectral data (ppm) of compounds (1,2,4,5)

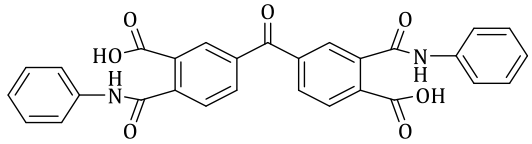
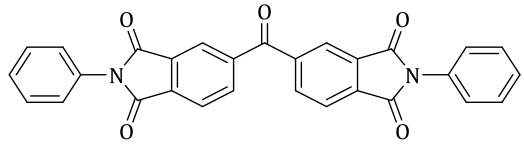
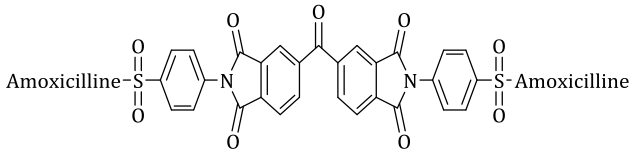
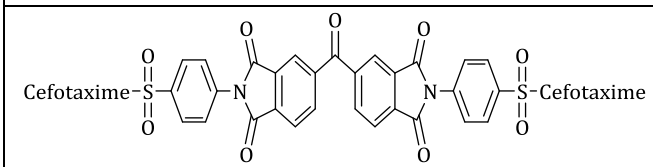
Structure	^{1}H-NMRSignals data, δ(ppm)
	δ=6.56-8.34 (N-H amide), δ=10.56-10.61 (COOH), δ=6.81-8.39 (-CH aromatic)
	δ=6.89-8.26 (-CH aromatic)
	δ=2.56-2.60 (), δ=2.74-2.90 (-CH in hetero ring), δ=3.19 (-CH benzylic), δ=4.25-4.8 (-CH in lactam ring), δ=7.03-8.30 (-CH aromatic), δ=8.65 (NHCO), δ=9.5 ($NHSO_2$), δ=10.6-10.9 (O-H)
	δ=2.58 (-CH_3), δ=2.89 (-CH_2S), δ=3.94 (-OCH_2), δ=4.2 (-OCH_3), δ=4.65,4.80 (-CH in lactam ring), δ=6.2 (-CH vinylic), δ=7.07-8.44 (-CH aromatic), δ=8.80 (NHCO), δ=11.6 ($NHSO_2$), δ=13.1 (-COOH)

Table 4: ^{13}C-NMR spectral data (ppm) of compounds (1,2,4,5)

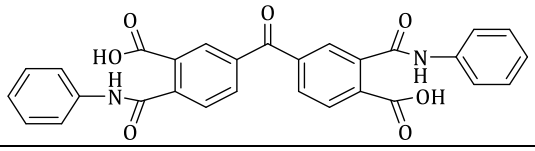
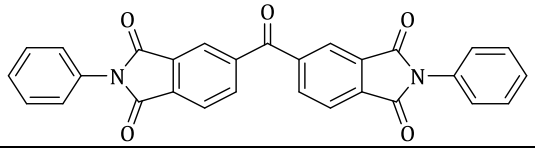
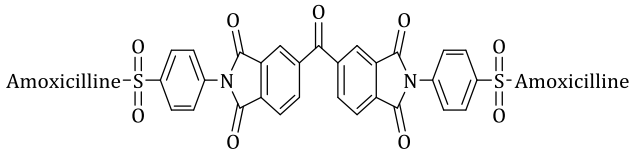
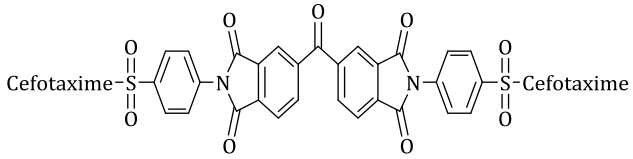
Structure	^{13}C-NMRSignals data, δ(ppm)
	δ=112.79-147.93 (-CH aromatic), δ=166.81-167.09 (C=O amide), δ=167.58-168.71 (C=O carboxyl), δ=194.00-194.20 (C=O ketone)
	δ=114.37-150.50 (-CH aromatic), δ=165.09-167.01 (C=O amide), δ=191.08 (C=O ketone)
	δ=11.38-14.37 ( ),δ=22.86 ( ),δ=28.84 (-C-COOH), δ=34.83 (-CH benzylic), δ=59.98 (-CH lactam ring), δ=124.41-148.10 (-CH aromatic), δ=166.65 (C=O amide), δ=167.93 (C=O lactam), δ=168.90 (C=O carboxyl), δ=174.64 (C=O imide), δ=191.40 (C=O ketone)
	δ=14.38 (-CH_3), δ=22.87 (-CH_2S), δ=34.87 (-C-COOH), δ=50.18 (-CH lactam ring), δ=57.32 (-CH_2O), δ=71.38 (-OCH_3), δ=124.41-136.33 (-CH aromatic & vinylic), δ=142.09 (C=N), δ=148.34 (C=O amide), δ=156.39 (C=O lactam & carboxyl), δ=166.67 (C=O imide), 193.85 (C=O ketone)

Table 5: Inhibition zone (mm) of Antibacterial and Antifungal Activities of compound (4-7)

Comp. No.		*pseudomonas auroginosa*	*Staphylococcus aurus*	*Klebsiella pneumoniae*	*Bacillus subtilis*	*Rhizosporium fungi*
4		++++	++++	++++	+++	++++
5		+++	++++	++++	++++	++
6		++++	++++	++++	++++	+++
7		++++	++++	++++	++++	++++
Control	Amoxicilline	+++	++	+++		+++
	Cefotaxime	+++	+++	+++	+++	+
	Cefixime	+++	+++	+++	+++	+
	Cephalexen	+++	+++	+++	+++	+
DMSO		-	-	-	-	-

Conclusion

In this research, the changes in various physical properties of the obtained compounds were investigated. The properties were studied by FTIR, ^{1}HNMR and ^{13}CNMR spectroscopy. The development was carried out on several drug molecules by introducing biscyclic imide and sulfonamide segments into the parent drug molecule. The introduction of these fractions increases the antibacterial and antifungal activity of the resulting molecules, so most of them exhibit very high antibacterial and antifungal activity. These promising results could lead to the discovery of new drugs that can fight various bacterial infections.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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