Synthesis, Characterization, and Antibacterial Evaluation of New N-Phenylnaphthalimides linked to Benzothiazole moiety

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Abstract

In this work several new naphthalimides linkd to substituted benzothiazole moiety were prepared. Preparation of the new naphthalimides was performed via multistep synthesis which include reacted of naphthalic anhydride with 4-aminobenzoic acid, then the product subsequently introduced in reaction with thionyl chloride producing 4-(N-naphthalimidyl) benzoyl chloride which in turn introduced in reaction with substituted benzothiazoles affording the target new naphthalimides. The prepared compound were screened for their antimicrobial activity against gram positive (*Staphylococcus aureous*, *Streptococcus pyogenes*), gram negative (*Escherichia coli* and *Pseudomonas aureginosa*) and yeast (*Candida albicans*). The results indicated that they exhibit good antimicrobial activity against the tested organism.

تحضير وتشخيص وتقدير الفعالية البايولوجية لـ N- فنيل نفثال ايمايدات جيدة مرتبطة بمكونة البنزوثايازول

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الخلاصة

تم في هذا البحث تحضير عدد من النفثال ايمايدات الجديدة المرتبطة بمكونة البنزوثايازول المعوضة. تم تحضير النفثال ايمايدات الجديدة بطريقة التحضير متعدد الخطوات، تم في الخطوة الأولى مفاعلة انهيدريد النفثالك مع 4- امينو حامض البنزويك ومن ثم تم مفاعلة الناتج مع كلوريد الثايونيل لتكوين 4- (N- نفثال ايميديل) كلوريد البنزويل والذي يدخل في تفاعل مع بنزوثايازولات معوضة لتكوين النفثال ايمايدات الجديدة. قيست الفعالية البايولوجية للنفثال ايمايدات الجديدة ضد بكتريا موجبة لصبغة غرام (ستافيلوكوكس اريوس وستريبتوكوكس بايوجينز) وبكتريا سالبة لصبغة غرام (اشريشيا كولاي وبسيدوموناس اوريجينوزا) والخميرة كانديدا البيكانس، حيث أثبتت النتائج امتلاكها فعالية بايولوجية ضد الأحياء المجهرية قيد الدراسة.

Introduction

Cyclic imides represent a very important compounds in drug discovery due to their wide spectrum of biological and pharmacologicl properties (1, 2, 3, 4). Naphthalimides first discovered by Brana and co-workers (5, 6), are DNA-targeted chemotherapeutic agents acting primarily by attacking DNA at some level (synthesis, replication, or processing) (7). Therefore plenty of naphthalimide based anticancer drugs have been synthesized (8, 9, 10), and promising results have been obtained (11). The benzothiazole scaffold is prevalent in a variety of pharmacologically active synthetic and natural compounds exhibiting antimicrobial (12, 13, 14, 15, 16, 17), anticancer (18, 19, 20), anthelmintic (21), and anti-diabetic activity (22). They are widely found in bioorganic and medicinal chemistry with application in drug discovery (23, 24). Taking into consideration the above described beneficial effects of cyclic imides and benzothiazole, we realized that it would be of interest to synthesize novel structural hybrids containing both heterocyclic ring systems.

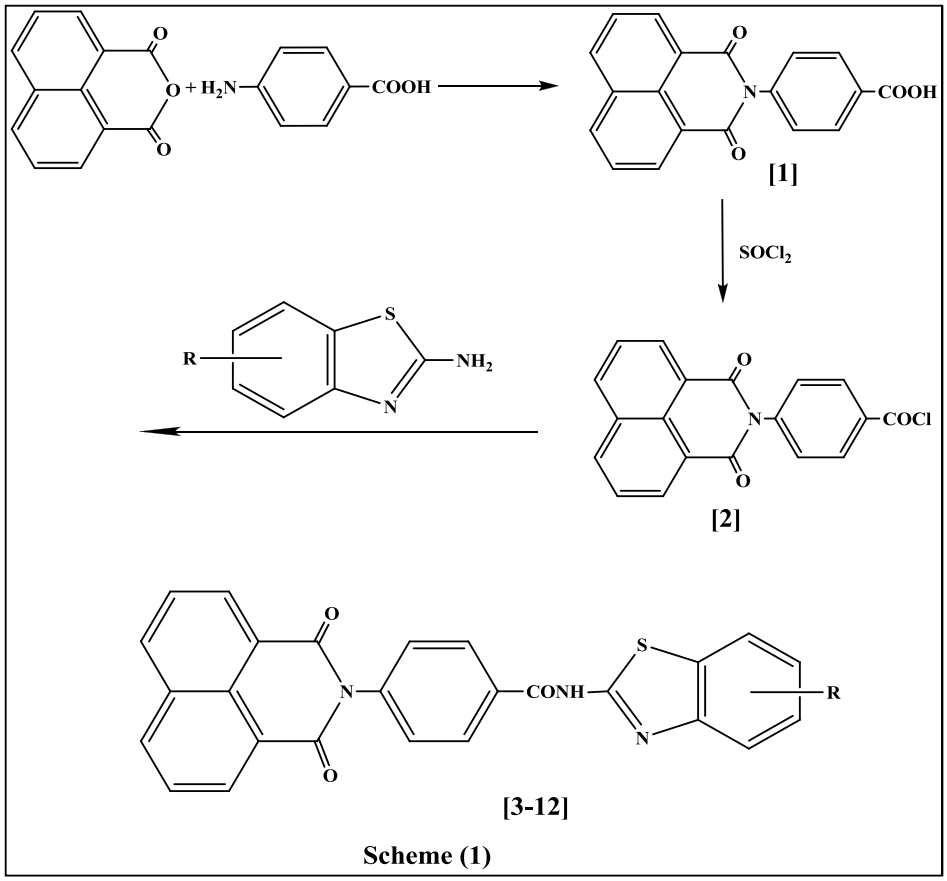
Materials and Methods

Chemicals used in this work are supplied from BDH and Fluka companies and are used without further purification. Melting points were determined on Gallenkamp capillary melting point apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer using KBr discs. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300MHz instrument using deuterated dimethyl sulfoxide (DMSO-d_{6}) as a solvent and trimethylsilane (TMS) as internal reference.

- **Synthesis of 4-(N-naphthalimidyl) benzoic acid [1]**: The titled compounds were prepared according to literature procedures (25). (0.01mol,1.98g) of naphthalic anhydride and (0.01mol, 1.37g) of 4-aminobenzoic acid were placed in a wide dry Pyrex tube which was immersed in an oil bath and provided with a thermometer. The oil bath was heated until fusion of the amic acid then temperature was maintained at ten degrees above the melting point of the used amic acid for (30-45) minutes. After cooling to room temperature the obtained solid was boiled with 10% sodium bicarbonate for 20 mints and purified by recrystallization from ethanol. Yield 85%, melting point > 300 ºC.
- **Synthesis of 4-(N-naphthalimidyl)benzoyl chloride [2]:** A mixture of 10g of 4-(N-naphthalimidyl) benzoic acid and (1.25g, 7.7mL) of thionyl chloride in 100mL round bottomed flask fitted with a double surface reflux condenser carrying a calcium chloride guard tube was heated on water bath with occasional shaking for 1 hour. The excess of thionyl chloride was distilled at 77ºC (26) .
- **Synthesis of 4-(N-naphthalimidyl)-N-(substitutedbenzothiazol-2-yl) benz- amide [3-12]:** To the solution of (0.01 mol) of 4-(N-naphthalimidyl)benzoyl chloride in 100mL. of ethanol was added (0.01mol) of substituted benzothiaol. The mixture was refluxed on a water bath for 6 hours. After cooling, the precipitate was collected, washed with distilled water, and recrystallized from suitable solvent(27). Physical properties of prepared compounds are listed in Table (1).
- **Biological Study:** The cup plate method (28) using nutrient agar medium was employed in studying the antimicrobial activity of the prepared imides against four types of bacteria including *Staphylococcus aureous*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aureginosa* respectively and yeast *Candida albicans* fungi. Dimethyl form amide (DMF) was used as sample solution which fixed at (0.1 mL) for all compounds using a sterilized cork borer cups were scooped out of agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the petri dishes 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 (3).

Results and Discussion

- **Chemistry:** Since both naphthalimides and benzothiazoles are biologically active components having wide spectrum of medicinal and pharmacological applications, the present work is directed toward synthesis of new compounds containing these two active moieties with expected biological activity. The target of present work is synthesis of new naphthalimides linked to benzothiazole moiety. Performing of this target involved many steps, the first one involved synthesis of 4-(N-naphthalimidyl) benzoic acid [1] via direct reaction between 1,8-naphthalic anhydride and 4-aminobenzoic acid under fusion condition. Compound [1] was introduced in reaction with thionyl chloride in the second step producing 4-(N-naphthalimidyl) benzoyl chloride [2]. Reaction of compound [2] with different substituted benzothiazole in the third step gave the corresponding 4-(N-naphthalimidyl)-N-(substitutedbenzothiazol-2-yl) benzamide [3-12]. The synthetic route of the new compounds is outlined in Scheme (1).



Scheme (1)

Structures of the prepared compounds were confirmed by FTIR, ^{1}HNMR and ^{13}CNMR spectra data. FTIR spectrum of compound [1] showed appearance of ν(C=O) of carboxylic acid at (11687) cm^{-1} and ν (C=O) imide at (1700) cm^{-1} absorption bans indicating success of imidation reaction. Besides the spectrum showed characteristic absorption bans at (3325-3461) cm^{-1} due to ν (OH) carboxylic acid and ν (NH) amide and at (1666) cm^{-1} due to ν(C=O) amide. FTIR spectra of imides [3-12] showed clear absorption bands at (3270-3365) cm^{-1}due to ν(NH) amide, bands at (1643-1682) cm^{-1} due to ν(C=O) amide and bands at (1680-1718) cm^{-1} due to ν(C=O) imide. Other bands appeared at (1588-1665) cm^{-1},(1542-1595) cm^{-1} and at (625-710)cm^{-1} due to ν(C=N) thiazol, ν(C=C) aromatic and ν(C-S) thiazol respectively. All details of FTIR spectral data of compounds [3-12] are listed in Table (2)(29). ^{1}HNMR spectrum of compound [1] showed clear signals at (δ = 7.7-8.5) ppm and at δ = 12.3 ppm belong to aromatic protons and (OH) proton while ^{13}CNMR spectrum of the same compound [1] showed signals at (δ = 124.2-136.3) ppm and 162.8ppm belong to aromatic carbons and (C=O) carbons respectively. ^{1}HNMR spectrum of compound [4] showed clear signals at δ = 2.32 ppm, (δ = 7.2-8.6) ppm and δ = 11.8 ppm due to CH_3 aromatic protons and (NH) proton, while ^{13}CNMR spectrum of the same compound [4] showed signals at δ = 22 ppm, (δ = 118.5-157) ppm, 162.8 ppm and 164.1ppm belong to CH_3, aromatic carbons,(C=N) and (C=O) carbons respectively. ^{1}HNMR spectrum of compound [7] showed signals at δ = 3.85 ppm, (δ = 7.31-8.72) ppm and δ = 10.9 ppm due to (OCH_3), aromatic protons and (NH) proton respectively, while ^{13}CNMR spectrum of the same compound [7] showed signals at δ = 55.8 ppm, (δ = 106.5-153.9) ppm, 157.8 ppm and 165.2 ppm belong to (OCH_3), aromatic carbons, (C=N) and (C=O) carbons respectively. ^{1}HNMR spectrum of compound [11] showed clear signals at δ = 2.2 ppm, (δ = 7.43-8.56) ppm and δ = 11.2 ppm belong to two methyl groups, aromatic protons and (NH) proton respectively, while ^{13}CNMR spectrum of the same compound [11] showed signals at δ = 15.4 and 18.3 ppm belong to two methyl groups and signals at (δ = 113.5-140.1) ppm, 141.28ppm and 163.82ppm belong to aromatic carbons, (C=N) and (C=O) carbons respectively.

- **Biological Study:** Antimicrobial activity of the synthesized imides were tested against four types of bacteria and *Candida albicans* yeast using cup plate method.

Most of the tested bacterial organisms showed sensitivity to synthesized imides compared to standard antibiotics. Inhibition zones caused by each compound was measured in (mm) and the results are listed in Table (3). The results indicated that compounds (8, 9) are highly active against all types of tested bacteria. Compound [10] also highly active against *S. aureus* and *S. pyogenes* and moderate active against *E. coli*. Compound (10) is highly active against *Candida albicans* yeast while compound (8) showed moderate activity against *Candida albicans* fungi. The rest of imides were found to be moderately active against the tested organisms.

Table (1) Physical properties for prepared imides [3-12]

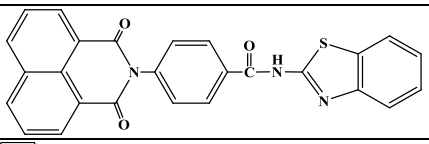
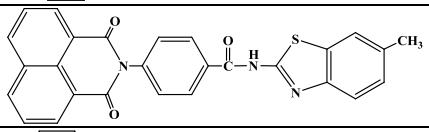
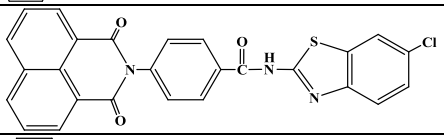
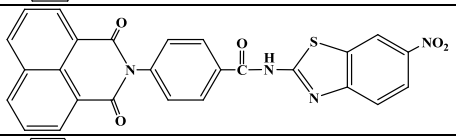
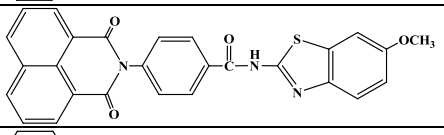
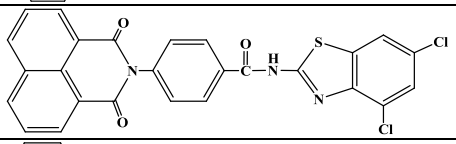
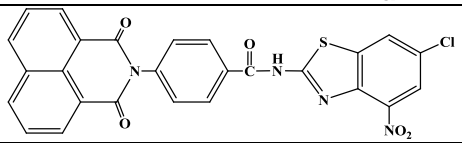
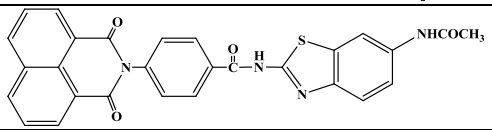
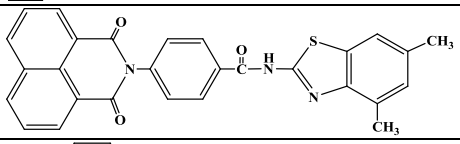
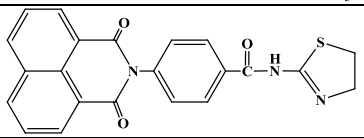
Comp. No.	Compound structure	Color	Melting point °C	Yield %	Solvent of Recr.
3		White	230-232	75	Ethanol
4		Light brown	255-257	83	Ethanol
5		Off white	295-297	70	Ethanol
6		Yellow	>300	65	Ethanol
7		Violet	>300	85	Ethanol
8		Gray	220-222	75	Ethanol
9		Deep yellow	>300	68	Ethanol
10		Greenish yellow	>300	78	Ethanol
11		Brown	>300		Ethanol
12		Brown	245-247	87	Ethanol

Table (2) FTIR spectral data of naphthalimides [3-12]

Comp. No.	FTIR spectral data cm^{-1}						
	ν(N-H) amide	**ν(C=O) amide**	**ν(C=O) imide**	**ν(C=N) thiazole**	**ν(C=C) aromatic**	**ν(C-S) thiazole**	**others**
3	3310	1678	1680	1610	1585	670	-
4	3382	1682	1715	1638	1560	675	-
5	3270	1675	1718	1600	1589	677	**ν(C-Cl)aromatic** 1095
6	3285	1666	1685	1625	1593	688	**ν(C-NO_2)** 1500, 1410
7	3360	1665	1718	1665	1542	710	**ν(C-O-C)** 1220,1175
8	3295	1650	1695	1635	1589	708	**ν(C-Cl)aromatic** 1068
9	3310	1670	1689	1615	1593	678	**ν(C-NO_2)** 1440, 1327 **ν(C-Cl)** 1055
10	3325	1678 1643	1698	1595	1581	668	-
11	3365	1678	1710	1645	1578	673	-
12	3305	1680	1705	1588	1595	625	-

Table (3) Inhibition zones for some of the prepared compounds measured in (mm)

Comp. No.	Gram-positive bacteria		Gram-negative		Yeast
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeuroginosa*	*Candida albicans*
3	12.5	10	9.5	8.6	8.8
5	13	11.2	10.8	11.5	9.5
6	10.2	8.5	9.5	8.5	7.2
8	14.6	12.5	14	12.4	12
9	14.8	12.5	15.2	13.4	8.5
10	16	11.5	10.5	8.2	15.7
ampicillin	17	12.5	12	14	-
DMSO	-	-	-	-	-

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