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Synthesis and pharmacological profile of some new 2-substituted-2, 3-dihydro-1*H*-perimidine

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Abstract

Background and objective: The development of new antimicrobial drugs is still demanded as there is increasing resistance of microorganisms to currently available antimicrobial drugs and searches for safer nonsteroidal anti-inflammatory agents with greater cyclooxygenase COX II selectivity is challenging. The new series of 2-substituted-2,3-dihydro-1*H*-perimidine (4a-j) that are close analogs to Naproxen 5, might inhibit COX II enzyme in a similar manner to naproxen 5. This study aimed to synthesize some new heterocyclic compounds for enhancing biological activity.

Methods: 1,8-Diaminonaphthalene 2 was condensed with a variety of aldehydes and ketones 3 to afford a new series of 2-substituted-2,3-dihydro-1*H*-perimidines4a-j using a suitable synthetic strategy. All the synthesized 2,3-dihydro-1*H*-perimidine compounds 4a-jwere screened for their *invitro* antimicrobial activities against two identifiable strains using the agar diffusion method. At the same time, the synthesized pyrimidine derivatives 4a-were evaluated for their COX inhibition activity. Supplementary to these, the constitutions of the newly synthesized 2,3-dihydro-1*H*-perimidines 4a-j had been confirmed on the basis of their IR, ^{1}H- and ^{13}C-NMR spectral data.

Results: The synthesized 2-substituted-2,3-dihydro-1*H*-perimidine compounds 4a-j exhibited promising antibacterial activity against *Escherichia coli* microorganism, while none of the synthesized derivatives 4a-jshowed likely result against *Staphylococcus aureus* strain. In addition, compound 4b had the most potent anti-inflammatory activity with an inhibition rate of 47% at 1000 nM.

Conclusion: The synthesized products4a-j possessed antibacterial activity (towards *Escherichia coli* microorganism; however, compounds 4c,4e, and 4j took the highest activity) and anti-inflammatory activity (compound 4b showed the highest inhibition rate).

Keywords: 1,8-diaminonaphthalene; Carbonyl compounds; Dipolar cyclisation; 2,3-dihyroperimidin; Antibacterial.

Introduction

One of the most interesting compounds in our daily life is heterocyclic compounds. Heterocyclic compounds containing one or more hetero atoms. Having a wide range of application such as used as pharmaceuticals, as agrochemicals and a s veterinary products.[1-3] In addition, they have applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff. Importantly, few antibiotics such as penicillin, cephalosporin have heterocyclic moiety.[4] Moreover, perimidine-2-thiol derivatives and their ligands ($C_{24}H_{14}N_4S_2O_2$) H2L1 and ($C_{26}H_{18}N_4S_2O_2$) H2L2 had been documented with transition metal ions, such as Copper (II), Silver (I), Cobalt (II) and Ruthenium (III) for their antimicrobial, analgesic and anti-inflammatory activities.[5] On the other hand, the development of novel antimicrobial drugs is still in demand as there is increasing resistance of microorganisms to the currently available antimicrobial drug.[6] Among the heterocyclic compounds, such as

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perimidine derivatives are of wide interest because they exhibit a diverse range of biological activities (Figure 1).[7] The derivatives of perimidine described as DNA–intercalating antitumor agents against the carcinogenic line.[8,9] 2,3-Dihydro-1 *H*-perimidine 1 is a saturated form of perimidine at 2 and 3 position which is a synthetic tricyclic compounds including two nitrogen atom.[10] Several preparative methods for the synthesis of perimidine derivatives have been documented.[11] Cyclisation reaction is one of the most important reactions of imines for the preparation of different heterocyclic compounds.[12] Interestingly, one of the major targets for curing bacterial infection is the cell wall of bacteria. The cell wall synthesis inhibited by ß-lactams, such as penicillins and cephalosporins, which inhibit peptidoglycan polymerization, and by vancomycin, which combines with cell wall substrates.[13] Polymyxins disrupt the plasma membrane, causing leakage.[14] Accordingly, the synthesis, the spectral data, and the biological studies of the new compounds 4a-j were achieved. The antibacterial activity of the new synthesized compounds was against gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*. This study aimed to synthesize some new heterocyclic compounds for enhancing biological activity.

Methods

This experimental study was designed to evaluate newly synthesized perimidine derivatives through the condensation of 1,8-diaminonaphthalene 2 with the corresponding aldehydes and ketones 3 to afford the 2-substituted-2,3-dihydro-1*H*-perimidines4a-j using a suitable synthetic strategy, as illustrated in Scheme 1. All the synthetic procedures were held at Hawler Medical University, College of Pharmacy, Pharmaceutical and Organic Chemistry Lab. between 8th of April 2015 to 1st of October 2016. Then after, the synthesized perimidine derivatives should fully characterized and tested for their antibacterial and anti-inflammatory activities.

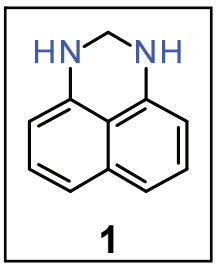
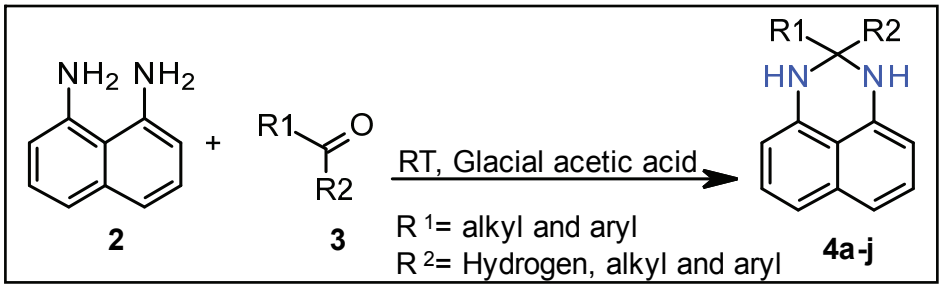


Figure 1: Structure of perimidine.



Scheme 1: Synthesis of 2-substituted-2,3-dihydro-1*H*-perimidine (4a-j)

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The melting points of the synthesized compounds were determined on a Gallen Kamp electrothermal apparatus by the open capillary method and are uncorrected. IR spectra were recorded on a Thermo-Mattson-300 Spectrophotometer and Bio-Rad Merlin, as KBr disc (Chemistry Department, College of Science, Salahaddin University/Erbil). ^{1}H- and ^{13}C-NMR spectrum were measured using a Bruker ultra shield 300 MHz with internal TMS (Central Lab., Jordan University of Science and Technology, Jordan); chemical shifts are given in ppm. Then after, the synthesized 2,3-dihydro-1*H*-perimidine compounds 4a-jwere screened for their *invitro* antimicrobial activities against two identifiable strains using agar diffusion method at Hawler Medical University, College of Pharmacy, Microbiological Lab. Additionally, the synthesized perimidine derivatives 4a-jwere evaluated for their COX inhibition activity at Central University of Lancashire, School of Pharmacy and Biomedical Sciences, UK.

Synthesis of 2-substituted-2,3-dihydro-1*H*-perimidine 4a-j

A mixture of 1,8-diaminonaphthalene 2 (1.582 g, 0.01 mole) and appropriate aldehyde and ketones 3(0.01 mole) in 10 mL of absolute ethanol and in the presence of a few drops of glacial acetic acid was stirred for about 40-48 hours at room temperature (the progress of the reaction was monitored by TLC).[15] After completion of the reaction, the reaction mixture was cooled down, and then the solid that separated out was filtered off, dried and re-crystallized from appropriate solvent.[16]

Biological study

General procedure for the COX inhibitor screening assay

The COX activity assay carried out here was Cayman's COX fluorescent inhibitor screening assay which uses a convenient fluorescence-based method for screening both bovine COX I and human recombinant COX II for isozyme-specific inhibitors.[17]

1- 100% initial activity wells: added 150 µl of assay buffer, 10 µl of heme, 10 µl of ADHP (10-acetyl-3,7-dihyroxyphenoxazepine), 10 µl of enzyme (either COX I or COX II), and 10 µl of DMSO.
2- Background wells: added 160 µl of assay buffer, 10 µl of heme, 10 µl of ADPH, and 10 µl of DMSO.
3- Inhibitor wells: added 150 µl of assay buffer, 10 µl of heme, 10 µl of ADPH, 10 µl of enzyme (either COX I or COX II), and 10 µl of inhibitors*.
4- The reactions were initiated by quickly adding 10 µl of arachidonic acid solution to all the wells being used.
5- The wells were incubated for two minutes at room temperature.
6- The plate was read using an excitation wavelength between 530-540 nm and an emission wavelength between 585-595 nm.
7- The average fluorescence of each sample was determined.
8- The fluorescence of the background wells was subtracted from the fluorescence of the 100% initial activity and the inhibitor wells.
9- The percent inhibition was determined for each sample by subtracting each inhibitor sample value from the 100% initial activity sample value, the result divide by the 100% initial activity value and then multiplied by 100 to give the percent inhibition.

*Inhibitor (compounds 4a-j) solutions were prepared in a concentration of 10, 100 and 1000 nm using DMSO as a solvent.[17]

Antibacterial Activity

The sensitivity of 2-substituted-2,3-dihydro-1*H*-perimidine (4a-j) was carried out against two kinds of bacteria, gram-positive *S. aureus* and gram-negative bacteria *E. coli* using disc agar diffusion method. The tests were performed using Muller Hinton agar. The medium was prepared using nutrient agar for the preservation of pure culture, then sterilized by autoclave, and poured in Petri dish to a depth of 4 mm. Activation of each type of bacteria gram-positive (*S. aureus*) and

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Gram-negative (*E. coli*) was done before culturing on the nutrient agar in a nutrient broth, which was used for dilution of bacterial and cultivation of culture isolates for 24 hours in 37°C, then inoculation of the plates. The discs of the synthesized compounds were prepared by mixing a compound with KBr powder (1:3). The mixture was pressed under pressure KBr which has been used as a blank disc. The dried surface of the Muller Hinton agar plate was streaked; tow dried discs were placed on the surface of the cultured media per petri dish. The plates were then incubated at 37℃ for 18 to 24 hours and then after the inhibition zone were manually measured in mm.

Statistical Analysis

All data are expressed as mean±SD of triplicate experiments.

Results

The structure of the obtained new 2,3-dihydro-1*H*-perimidines (4a-j) was elucidated by various spectroscopic techniques. The infrared as well as ^{1}H- and ^{13}C-NMR spectral data of some synthesized compounds are consistent with the expected structures. For example, the infrared spectrum of 2,2-dibenzyl-2,3-dihydro-1*H*-perimidine 4h which is shown Table 1, revealed the most important features of the dipolar cyclisation of 1,8-diaminonaphthalene2 with the carbonyl carbon atom of the carbonyl compounds 3by exhibiting a medium and a diagnostic sharp peak at3329 to 3396cm^{-1} due to NH stretching vibration and disappearance of four bands belong to two NH_2 stretching vibration in IR spectra at 3412, 3386, 3332, 3304 cm^{-1}of 1,8-diaminonaphthalene. The first evidence for the synthesis of the new compounds comes from the physical properties for example the melting point and color which compared with the starting materials. The reaction product were solid obtained with high yields as shown in Table 1

Table 1: Some physical constants and the diagnostic stretching band for NH moiety in IR absorption of perimidine compounds 4a-j

Entry	Carbonyl comp.	MP °C	Color	% Yield	NH Str.
4a	Cinnamaldehyde	172-174	Pink	85	3387
4b	2-chlorobenzaldehyde	200-202	Colorless	81	3396
4c	2-hydroxybenzaldehyde	159-161	Pink	84	3338
4d	3,4-dihydroxybenzaldehyde	186-188	Yellow	80	3329
4e	Furfural	166-168	Red	84	3368
4f	ethyl methyl ketone	157-159	Yellow	53	3381
4g	1,1-dimethoxy-3-butanone	178-180	Pink	85	3338
4h	Dibenzylketone	239-241	Brown	90	3373
4i	3,4-dimethoxyacetophenone	120-122	Orange	95	3368
4j	4-nitroacetophenone	160-162	Brown	92	3361

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The structure of 2-(substituted phenyl)-2,3 -dihydro-1*H*-Perimidine was indicated from the ^{1}H-NMR spectra Table 2 by observation of one proton at δ 5.2 ppm due to single C-H proton. In addition, the appearance of multiplet signals at δ 6.4 to 8 ppm for ten protons belongs to phenyl and naphthyl rings which supported the formation of the desired product. The formation of compounds (4g), (4i) and (4j) established from the^{1}H-NMR spectra through the appearance of signals at δ1.5, 1.78,1.8, 3.1, 3.9 ppm attributed to CH_3 and OCH_3 protons respectively. The singlet signal belongs to two N- H of perimidine moiety seen between 4.2 to 6.5 ppm, also the spectra of compounds 4g and 4h showed CH_2 group as a doublet at δ 2.05 and 2.99 ppm (Table 2). The structure of the products were established from ^{13}C-NMR spectra, such as observation ofa line due to C-HNcarbon at δ (63.5 to76) ppm for all the synthesized compounds, and lines attributed to aromatic regionfor phenyl and naphthyl ringsatδ (105- 154) ppm which were recorded as 10 lines in ^{13}C- NMR spectrum for compound (4j) and 12 linesfor compounds (4b and 4i). Spectra of compounds (4g) and (4i) were showed another evidence which was a line for OCH_3 carbon at δ 53,08 and 56.01 ppm, while the appearance of a lineatδ 43.23 and 44 ppm related to CH_2 carbon were supported the formation of compounds 4g and 4h, the methyl carbon was observed atδ 26.82,28.19.30.38 ppm (Table 3).

Table 2: Diagnostic peaks in^{1}H-NMR spectra for some synthesized2-substituted-2,3-dihydro-1*H*-perimidine(4a, 4b, 4g, 4h, 4i and 4j), where the solvent was $CDCl_3$.

Compound	N─H(s) ppm	C─H(m) (aromatic)ppm	OCH_3(s)	C-H(s) ppm	CH=CH-Ar	CH_2(d) ppm	CH_3(s) Ppm
4a	6.42	7.45-7 (11H)		6.5	Mixed within aromatic region		
4b	4.3	6.5─7.7(10H)		5.2			
4g	4.5	6.4-7.2(6H)	3.1	4.7		2.05	1.5
4h	4.2	6.4-7.5 (16H)				2.99	
4i	4.5	6.4-7.5 (6H)	3.9				1.78
4j	6.5	7-8(10H)					1.8

Table 3: Diagnostic peaks in^{13}C-NMR spectra for some synthesized 2-(substituted)-2, 3-dihydro-1*H*-perimidine(4a, 4b, 4g, 4h, 4i and 4j), where the solvent was $CDCl_3$.

Compounds	C(Ar)	C-H	C-NH	OCH_3	CH_2	C=C	CH_3
4a	108-140.35		76			Mixed within aromatic region	
4b	105-141		63.52				
4g	106-140	102.9	65.25	53.08	43.29		26.82
4h	106.4-139.73		68.1		44		
4i	106-148.97		68.04	56.01			28.19
4j	107-154		68.1				30.38

S= singlet, d= doublet, m= multiplet, Ar= aromatic.

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Microbial growth inhibition were indicated by measuring the diameter of the zone of inhibition (using disk agar diffusion method) and the results were represented in Table 4. All the synthesized used compounds were tested for their antibacterial activity against both bacteria *S. aureus* and *E. coli*. The synthesized compounds were more active against *E. coli* than the *S. aureus*. The most effective compounds of perimidine derivatives were 4a, 4c, 4e, and 4j,while other compounds (4b, 4d, 4f, 4g, 4h and 4i) were showed moderate activity against *E. coli.* The percentage of the sensitivity of the bacteria species under the study were investigated against *S. aureus* and *E. coli*, sensitivity of *S. aureus* against the synthesized compounds was 0% it means that 100% resisted where as the *E. coli* showed 100% sensitivity and 0% resistance against the new compounds as shown in Table 5.

Table 4: Antibacterial activity of the synthesized 2-(substituted)-2,3-dihydro-1*H*-perimidine (4a-j) against *S. aureus (*ATCC 25923) and *E. coli (*ATCC 35218).

Compounds	*S. aureus* ATCC 25923	*E. coli* ATCC 35218
4a	++	++++
4b	++	+++
4c	++	++++
4d	++	+++
4e	++	++++
4f	++	+++
4g	++	+++
4h	++	+++
4i	++	+++
4j	++	++++

Zone of inhibition after 24 hrs, zone size: 10-20mm= ++; 21-35mm= +++; 36-50mm= ++++

Table 5: The percentage of the active compounds against *S.aureus* and *E. coli* susceptibility.

Types of bacteria	Sensitive (%)	Resistance (%)
S. aureus	0	100
E. coli	100	0

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COX inhibition activity

The COX inhibitory activity assay was carried out by applying the *in vitro* Cayman's COX fluorescent inhibitor screening protocol in which the inhibitors were tested against both bovine COX I Table 6 and human recombinant COX II Table 7.[17]

Table 6: *In vitro* bovine COX I assay results.

Compounds	COX I % inhibition					
	F	10 nM	F	100 nM	F	1000 nM
Naproxen	23885±363	37	17451±378	54	4752±279	88
4a	24005±274	37	23119±251	39	22842±218	40
4b	29188±666	23	27533±445	27	26992±234	29
4c	27149±612	28	26600±184	30	23262±265	39
4d	33824±567	11	25696±408	33	23082±53	40
4e	31611±404	17	27504±499	28	24246±160	37
4f	28412±258	26	27192±112	29	24936±325	35
4g	29819±625	22	28600±407	25	25838±169	32
4h	33621±444	12	25692±213	33	22826±160	41
4i	33311±240	13	29052±234	24	25245±116	34
4j	32251±105	16	30296±501	21	26851±79	30

F= Mean±SD of the initial fluorescence activity. nM= Nano-molar concentrations of the synthesized perimidine derivatives 4a-j.

Table 7: *In vitro* human recombinant COX II assay results.

Compounds	COX II % inhibition					
	F	10 nM	F	100 nM	F	1000 nM
Naproxen	27310±246	31	26424±329	33	13530±528	66
4a	27047±437	32	26625±461	33	23780±408	40
4b	24931±459	37	22437±697	44	21063±680	47
4c	30500±441	23	26859±899	32	24297±61	39
4d	29506±597	22	25489±572	33	22863±528	40
4e	27556±386	27	27293±664	28	23987±266	37
4f	28099±21	26	26725±208	29	24729±292	35
4g	29482±335	22	24859±415	35	22252±253	42
4h	29515±584	22	25410±325	33	22325±218	41
4i	29167±444	23	25670±347	32	21229±81	44
4j	28158±63	26	26725±208	31	24557±287	35

F= Mean±SD of the initial fluorescence activity. nM= Nano-molar concentrations of the synthesized perimidine derivatives 4a-j.

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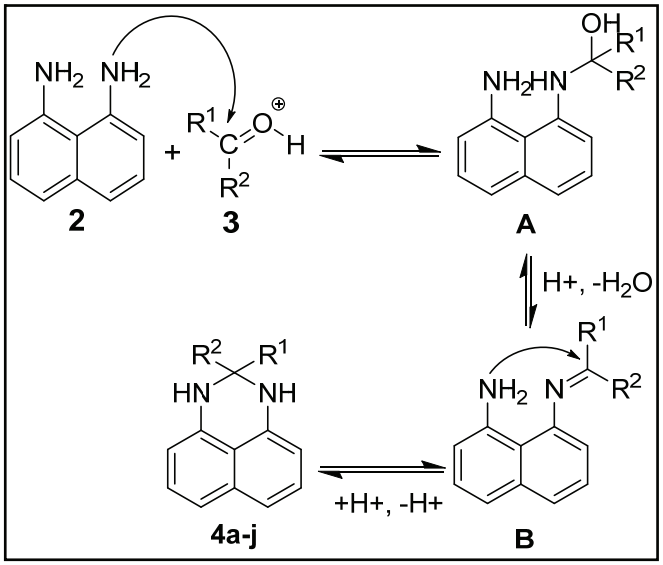
Discussion

The impartial of this study was to synthesize, characterize, and evaluate the antibacterial activity of some new 2-(substituted)-2, 3dihydro-1*H*-perimidines 4a-j. Preparation of 2,3-dihydro-1*H*-perimidine from the reaction of 1,8-diaminonaphthalene 2 with various carbonyl compounds 3 could be important if the desirable catalyst was inexpensive and readily available. The treatment of 1,8-diaminonaphthalene 2 with various aldehydes and ketones 3in the presence of glacial acetic acid as a catalyst produced a series of new 2-substituted-2,3-dihydro-1*H*-perimidine 4a-j in high yield, as shown in Scheme 1. Cinnamaldehyde and various aromatic aldehydes bearing electron-withdrawing and electron-donating groups reacted with 1,8-diaminonaphthalene2 to give 2-substituted-2,3-dihydro-1*H*-perimidines4a-d in very good yields. Similarly, heteroaromatic aldehyde such as furfural afforded the product 4e in 84% yield, as shown in Table 1. Since at room temperature-condition, the reactions were progressed smoothly and products were obtained in very good yields, and in high purity, the dipolar cyclization process of 1,8-diaminonaphthalene2 was extended for the preparation of five other new 2,3-dihydro-1*H*-perimidines 4f-j using various aliphatic and aromatic ketones3. In general, the reaction of aliphatic ketones requires a longer time than aromatic ketones because the conjugating factor of the phenyl ring in aromatic ketones played a key role in affecting the rate of reaction. Herein, it is believed that the 1*H*-perimidine ring formation in 2,3-dihydro-1*H*-perimidines4a-j may proceed via a mechanistic pathway, which is shown in Scheme 2. Addition of an amino group 2 to the protonated carbonyl group of aldehydes and ketones 3leads to the formation of (8-amino-naphthalen-1-ylamino)-phenyl-methanol (A) via standard nucleophilic addition. Although this is likely to be an equilibrium reaction, “hemiaminals” (A) are expected to undergo rapid dehydration in the presence of acid to a highly reactive N8-benzylidene-naphthalene-1,8-diamine (B). Then the carbon of the imine system in (B) underwent 1,6-dipolar cyclization with the remaining amino group to afford 2,3-dihydro-1*H*-perimidine (4a-j).



Scheme 2: Plausible mechanistic pathway for the formation of 2-substituted-2,3-dihydro-1*H*-perimidine (4a-j)

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The ^{1}H-NMR spectral data of compound (4h) for example had supported the infrared finding by displaying a broad singlet signal at 4.2 ppm due to the NH groups of the 1*H*-perimidine ring, in addition; the spectrum has also revealed another singlet signal at 2.9 ppm due to the methylene groups. Further verification for the formation of the 1*H*-perimidine ring was attained from ^{13}C-NMR spectrum, with the signals at 69 and 44 ppm due to the carbon atom that attached to the nitrogen atoms of the 1*H*-perimidine ring and the methylene groups respectively, and for our awareness the depicted signals in the aromatic region are in convenient with the number of carbon atoms of the naphthalene and phenyl rings, for example, compounds 4a, 4b, 4g, 4h, 4i and 4j showed 12,10,6,12,10 and 10 lines, respectively for different types of carbons in the aromatic region, as shown in Table 2 and 3.

Antimicrobial activities

Experiments were performed to evaluate the activities of the synthesized compounds against two species of bacteria *S. aureus and E. coli*. Anti-microbial study was assessed by measuring the minimum inhibitory zone (using disk agar diffusion method), and the results were represented in Table 4. The biological interest of perimidine derivatives were recorded in the literature. Therefore, the antibacterial study was done, and the activity was determined by the disc diffusion method at the concentration of 50 µg per disk. All the synthesized used compounds were tested for their antibacterial activity against both bacteria *S. aureus* and *E. coli*. The amoxicillin, azithromycin, ciprofloxacin, and gentamicin were chosen as a standard antibacterial agent. Gentamicin and ciprofloxacin have a wide effect on protein synthesis in bacteria. Ciprofloxacin medication is used to treat a variety of bacterial infections. The synthesized compounds were more active against *E. coli* than the *S. aureus*. The compound 4i was moderately active against both the gram-positive and the gram-negative tested bacteria, whereas the most effective compounds of perimidine derivatives were 4a,4c, 4e, and 4j, due to the presence of furan moiety (in case of compound 4e) and the presence of double bond and the aromatic ring (in case of compound 4a) which increase the lipophilicity of the tested synthesized compounds and give the highest inhibition effect. While compounds (4b,4d, 4f,4g,4h and 4i) were showed moderate activity against *E. coli*. All the synthesized compounds were found to exhibit more activity than the standard drug gentamicin that has a wide effect on the *E. coli* and they showed more activity than the amoxicillin, azithromycin that have a wide effect on gram positive bacteria. The results showed the effect of substituents on the activity of perimidine derivatives against both bacteria walls. Bacteria cell walls contain peptidoglycan, lipopolysaccharide, lipoprotein, phospholipid, and protein. The increased activity may be attributed to the enhancement of lipophilicity due to incorporation of aromatic benzene ring and substituent NO_2 and OCH_3 groups at meta and para positions with the presence of perimidine moiety or (OH); these compounds tend to be highly bound to protein, the more lipophilic compound, the greater binding. Table 5 investigates the percentage of the sensitivity of the bacteria species under the study, which was 0% for *S. aureus,* while the sensitivity of *E. coli* was 100%.

Anti-inflammatory activities

As can be seen from Tables 6 and 7, only compound 4b showed any appreciable activity (47% inhibition at 1000 nM) against COX II. This greater COX II selectivity is attributed to introducing larger substituents (COOH replaced bychloro-benzene) to fit into the active site volume of COX II.[18] Marnett *et al*. demonstrated similar results when they attempted to shift the enzyme selectivity of indomethacin from COX I to COX II while maintaining potency at the same level and reducing the unwanted side-effects at the same time.[19] In their

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studies, they converted the non-selective NSAIDs to esters and amides in order to obtain selective COX II inhibitors. The acidic center of NSAIDs is crucial for their activities as they interact with the cationic site of the receptor; therefore, the more acidic, the better the inhibition. Based on this, the reason behind the reduced activity of the prepared derivatives 4a-j against COX I (29-40% inhibition) might be attributed to the fact that the perimidines are not acidic where as NSAIDs with carboxylic acid (such as naproxen 5, Figure 2) functionalities are.[20-22] Naproxen 5 is a relatively simple molecule with a naphthyl scaffold, similar to compounds 4a-j. Moreover, it had been established by Zhang *et al*, when they did docking study for 19 triazole containing permidines, that the compounds could shrink the cavity space in the same manner as naproxen molecule could in the COX II binding pocket, thereby enhancing the interaction force.[23] Additionally, the perimidine ring can interact with the upper right hydrogen bond donor, in a manner equivalent to that of the carbonyl group of naproxen acting as hydrogen bond acceptor. Therefore compound 4b might had a stronger interaction with COX II. This resulted in a better inhibitory effect on COX II.[23] (Figure 3).

Conclusion

A simple, efficient, and environmentally friendly approach and easy work-up has been used for the preparation of perimidines 4a-j with a view to acquiring a good antibacterial activity. The antibacterial profile of all the synthesized compounds 4a-j, Table 4 revealed that the prepared 2-substituted-2,3-dihydro-1*H*-perimidine 4a-j possessed significant antibacterial activity towards Escherichia coli microorganism and the highest activity was observed for compounds (4c,4e, and 4j), and they were more active than the standard drugs against both gram negative and gram positive bacteria. The synthesized compounds 4a-jwere effective against Gram negative bacteria because their cell walls contain a thin peptidoglycan

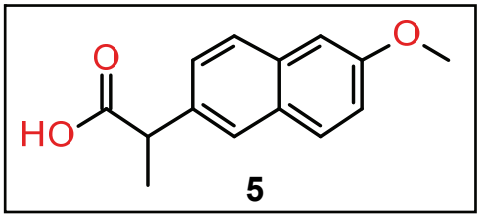

Figure 2: Naproxen structure.

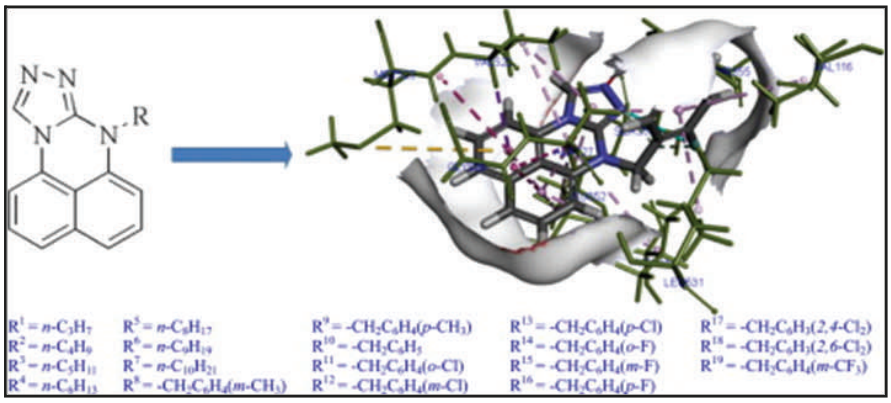

Figure 3: Triazole containing permidines tested by Zhang and his coworkers.[23]

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layer (without techoic acids) that is surrounded by a thick plasma membrane. On the other hand, the compounds were inactive against Gram positive bacteria because of their thick peptidoglycan cell wall. In addition, the synthesized perimidine derivatives 4a–jwere evaluated for their anti -inflammatory activities using the Cayman's assay. Compound 4b showed the most potent anti-inflammatory activity with an inhibition rate of 47% at 1000 nM, which can be attributed to incorporating larger substituents to enable a better fit into the active site volume of COX II. However, naproxen5 showed around 88% and 66% inhibitory activity against COX I and COX II, respectively, due to a reduced interaction with the receptor. Accordingly, the perimidine scaffold is a promising candidate for finding safer anti-inflammatory activity and greater COX II selectivity.

Competing interests

The authors declare no competing interests.

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