Synthesis and pharmacological profile of some new 2-substituted-2,3-dihydro-1H-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-1H-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-1H-perimidines 4a-j using a suitable synthetic strategy. All the synthesized 2,3-dihydro-1H-perimidine compounds 4a-j were screened for their in vitro 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-1H-perimidines 4a-j had been confirmed on the basis of their IR, 1H- and 13C-NMR spectral data.

Results: The synthesized 2-substituted-2,3-dihydro-1H-perimidine compounds 4a-j exhibited promising antibacterial activity against Escherichia coli microorganism, while none of the synthesized derivatives 4a-j showed 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 products 4a-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-dihydropirimidin; 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 as veterinary products. 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. Moreover, perimidine-2-thiol derivatives and their ligands (C_{21}H_{14}N_{4}S_{2}O_{2}) H2L1 and (C_{26}H_{18}N_{4}S_{2}O_{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. 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. Among the heterocyclic compounds, such as
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\(H\)-perimides 4a-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.

**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\(H\)-perimides 4a-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)
The melting points of the synthesized compounds were determined on a Gallenkamp 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). H- and 13C-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-1H-perimidine compounds 4a-j were 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-j were 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-1H-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). 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.

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

#### Antibacterial Activity

The sensitivity of 2-substituted-2,3-dihydro-1H-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...
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; two dried discs were placed on the surface of the cultured media per petri dish. The plates were then incubated at 37°C 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-1H-perimidines (4a-j) was elucidated by various spectroscopic techniques. The infrared as well as 1H- and 13C-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-1H-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 by exhibiting a medium and a diagnostic sharp peak at 3329 to 3396 cm\(^{-1}\) 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    |

71
The structure of 2-(substituted phenyl)-2,3-dihydro-1H-perimidine was indicated from the 1H-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 1H-NMR spectra through the appearance of signals at δ 1.5, 1.78, 1.8, 3.1, 3.9 ppm attributed to CH₃ and OCH₃ 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 CH₂ group as a doublet at δ 2.05 and 2.99 ppm (Table 2). The structure of the products were established from 13C-NMR spectra, such as observation of line due to C-HN carbon at δ (63.5 to 76) ppm for all the synthesized compounds, and lines attributed to aromatic region for phenyl and naphthyl rings at δ (105-154) ppm which were recorded as 10 lines in 13C-NMR spectrum for compound (4j) and 12 lines for compounds (4b and 4i). Spectra of compounds (4g) and (4i) were showed another evidence which was a line for OCH₃ carbon at δ 53.08 and 56.01 ppm, while the appearance of a line at δ 43.23 and 44 ppm related to CH₂ carbon were supported the formation of compounds 4g and 4h, the methyl carbon was observed at δ 26.82, 28.19, 30.38 ppm (Table 3).

Table 2: Diagnostic peaks in 1H-NMR spectra for some synthesized 2-substituted-2,3-dihydro-1H-perimidine (4a, 4b, 4g, 4h, 4i and 4j), where the solvent was CDCl₃.

| Compound | N─H(s) ppm | C─H(m) (aromatic) ppm | OCH₃(s) | C─H(s) ppm | CH=CH-Ar ppm | CH₂(d) ppm | CH₃(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 13C-NMR spectra for some synthesized 2-(substituted)-2,3-dihydro-1H-perimidine (4a, 4b, 4g, 4h, 4i and 4j), where the solvent was CDCl₃.

| Compounds | C(Ar) | C-H | C-NH | OCH₃ | CH₂ | C=C | CH₃ |
|-----------|-------|-----|------|------|-----|-----|-----|
| 4a        | 108-140.35 | 76 |      |      |     |     |     |
| 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.
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 while 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-1H-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              |
**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.\(^1\)

**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-1H-perimidines 4a-j. Preparation of 2,3-dihydro-1H-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 3 in the presence of glacial acetic acid as a catalyst produced a series of new 2-substituted-2,3-dihydro-1H-perimidines 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-diaminonaphthalene 2 to give 2-substituted-2,3-dihydro-1H-perimidines 4a-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-diaminonaphthalene 2 was extended for the preparation of five other new 2,3-dihydro-1H-perimidines 4f-j using various aliphatic and aromatic ketones 3. 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 1H-perimidine ring formation in 2,3-dihydro-1H-perimidines 4a-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 3 leads 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-1H-perimidine (4a-j).

\[
\begin{align*}
\text{NH}_2\text{NH}_2 & \quad + \quad \text{C}_6\text{H}_4\text{CO}^{\text{+}}\text{H} \quad \xrightarrow{R_1, R_2} \quad \text{NH}_2\text{NH} \\
\text{A} & \quad \xrightarrow{\text{H}^+, \text{H}_2\text{O}} \quad \text{B} \\
\text{4a-j} & \quad \xrightarrow{+\text{H}^+, -\text{H}^+} \quad \text{4a-j}
\end{align*}
\]

Scheme 2: Plausible mechanistic pathway for the formation of 2-substituted-2,3-dihydro-1H-perimidine (4a-j)
The $^1$H-NMR spectral data of compound (4h) for example 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, 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. 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. In their
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.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{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-1H-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.](image)

![Figure 3: Triazole containing permidines tested by Zhang and his coworkers.](image)
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–j were 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, naproxen 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.

References
1. Mistry K, Desai K. Synthesis of novel heterocyclic 4-thiazolidinone derivatives and their antibacterial activity. J Chem 2004; 1(4):189–93.
2. Manojkumar P, Ravi T, Subbuchettiar G. Synthesis of coumarin heterocyclic derivatives with antioxidant activity and in vitro cytotoxic activity against tumour cells. Acta Pharma 2009; 59(2):159–70.
3. Palekar VS, Damle AJ, Shukla SR. Synthesis and antibacterial activity of some novel bis-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and bis-4-thiazolidinone derivatives from terephthalic dihydrazide. Eur J Med Chem 2009; 44(12):5112–6.
4. Arora P, Arora V, Lamba H, Wadhwa D. Importance of heterocyclic chemistry: A review. Int J Pharm Sci Res 2012; 3(9):2947.
5. Bassyouni FA, Abu-Bakr SM, Hegab KH, El-Eraky W, Ahmed A, Rehim MEA. Synthesis of new transition metal complexes of 1H-perimidine derivatives having antimicrobial and anti-inflammatory activities. Res Chem Intermed 2012; 38(7):1527–50.
6. Malladi S, Isloor AM, Isloor S, Akhila DS, Fun H-K. Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases. Arab J of Chem 2013; 6(3):335–40.
7. Liu KC, Chen HH. Reaction of 2-hydrazinoperimidine with acetylacetone. J Heterocycl Chem 1984; 21(3):911–2.
8. Isikdag I, Incesu Z, Gülnaz D, Özşay Y. Cytotoxic Effects of Some Perimidine Derivatives on F2408 and 5Rp7 Cell Lines/Perimidin Türelerinin F2408 ve 5Rp7 Hücre Hatları Üzerine Sitotoksik Etkileri. FABAD J Pharm Sci 2008; 33(3):135.
9. Herbert JM, Woodgate PD, Denny WA. Potential antitumor agents. 53. Synthesis, DNA binding properties, and biological activity of perimides designed as minimal DNA-intercalating agents. J Med Chem 1987; 30(11):2081–6.
10. Pozharskii AF, Dal'Nikovskaya V. Perimides. Russ Chem Rev 1981; 50(9):816–35.
11. Davis R, Tamaoki N. Novel photochromic spirotetrahydrocyclic molecules via oxidation of 1, 8-diaminonaphthalene. Organic lett 2005; 7(8):1461–4.
12. Kahveci B, Karaali N. Synthesis of new perimidine derivatives from the reaction of 1, 8-diaminonapthalene with iminoester hydrochlorides. J Chem Res 2013; 37(6).
13. Nikolaidis I, Favini-Stabile S, Dessen A. Resistance to antibiotics targeted to the bacterial cell wall. Protein Sci 2014; 23(3):243–59.
14. Helander I, Nurmiaho-Lassila E-L, Ahvenainen R, Rhoades J, Roller S. Chitosan disrupts the barrier properties of the outer membrane of Gram-negative bacteria. Int J Food Microbiol 2001; 71(2-3):235–44.
15. Varsha G, Arun V, Robinson P, Sebastian M, Varghese D, Leeju P, et al. Two new fluorescent heterocyclic perimides: first syntheses, crystal structure, and spectral characterization. Tetrahedron Lett 2010; 51(16):2174–7.
16. Salih KM, Azeez HJ. Synthesis, characterization and biological activity of 2-aryl-2, 3-dihydro-1H-perimidine. Res Pharm Biotech 2014; 5(1):1–6.
17. Nile SH, Ko EY, Kim DH, Keum Y-S. Screening of ferulic acid related compounds as inhibitors of xanthine oxidase and cyclooxygenase-2 with anti-inflammatory activity. Rev Bras Farmacogn 2016; 26(1):50–5.
18. Dannhardt G, Kiefer W. Cyclooxygenase inhibitors–current status and future prospects. Eur J Med Chem 2001; 36(2):109–26.
19. Kalugutkar AS, Crews BC, Saleh S, Prudhomme D, Marnett LJ. Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors. Bioorg Med Chem 2005; 13(24):6810–22.
20. Flower RJ. The development of COX2 inhibitors. Nat Rev Drug Disc 2003; 2(3):179.
21. Hadjipavlou-Litina D. Quantitative structure-activity relationship (Q SAR) studies on non steroidal anti-inflammatory drugs (NSAIDs). Curr Med Chem 2000; 7(4):375–88.
22. Abdou WM, Ganoub NA, Sabry E. Synthesis and quantitative structure–activity relationship study of substituted imidazophosphor ester based tetrazolo [1, 5-b] pyridazines as antinococeptive/
anti-inflammatory agents. Beilstein J Org Chem 2013; 9:1730.
23. Zhang HJ, Wang XZ, Cao Q, Gong GH, Quan ZS. Design, synthesis, anti-inflammatory activity, and molecular docking studies of perimidine derivatives containing triazole. Bioorg Med Chem Lett 2017; 27(18):4409–14.