Chapter - III

Synthesis, Crystal Structure, SHG and Antimicrobial activity of Chiral Ibuprofen Amides
INTRODUCTION

The Second Harmonic Generation (SHG) is usually observed in non-centrosymmetric materials. Majority of the NLO materials synthesized are based on an electron donor-acceptor structure, bridged via \( \pi \)-conjugation. This gives rise to molecular dipole moment. Increasing the length of \( \pi \)-conjugation enhances molecular hyperpolarizability (\( \beta \)) and favours large second order nonlinear optical response. However, the electrostatic interactions induces the molecules to arrange and align themselves in centrosymmetric fashion in macroscopic level or in solid state (crystal symmetry). Only about 25% of all achiral molecules crystallize in acentric space group\(^1\) among which only few organic dipolar chromophoric molecules were arranged in acentric manner in solid state (macroscopic level). In a centrosymmetric system the overall dipole moment gets cancelled and the SHG activity of the individual molecules gets nullified. It is a critical issue in the development of new crystalline second-order NLO material, to form non-centrosymmetric environment. Approaches such as electrode or corona poling of polymer films,\(^2\) Langmuir-Blodgett film formation,\(^3\) controlling molecular self-assembly through H-bonding and steric hindrance, and introducing chiral centre in the molecule were used to achieve acentric nature in crystalline material.

Effect of molecular self-assembly or steric hindrance in SHG activity

Failure of simple additive models in explaining the SHG trend is analyzed using quantum chemical computations of the hyperpolarizability of molecular clusters which establishes the dominant influence of noncovalent intermolecular interactions. A simple additive approach to relate the molecular and bulk NLO responses fails, suggesting that intermolecular interactions play a significant role in determining the solid-state SHG.\(^4\)
Chapter-III Introduction

Even though it is known that intermolecular interactions can modify the bulk SHG, strong and direct influence of such effects in crystals has not been widely demonstrated. M. Jaya Prakash et al., synthesized and studied new family of N-(2-aminoethyl)-4-nitroaniline (AENA) salts with a homologous series of carboxylic acids and N-(2-aminoethyl)-4-nitroaniline (Figure 1). It is a well known achiral remote functionalized NLO chromophore. The authors explained, how the impact of SHG clearly manifested by supramolecular interactions of the solid-state. Crystallographic investigations reveal a systematic variation in the superstructure formation of the NLO-

Figure 1. Molecular structures of N-(2-aminoethyl)-4-nitroaniline salts (a) AENA-för, (b) AENA-ace, (c, d) AENA-pro, and (e) AENA-but; H atoms of only amino and ammonium groups are shown for clarity.
phore unit across the series, and the intensities of the SHG from microcrystalline samples are found to correlate with the assembly pattern.

Muthuraman et al.,\textsuperscript{5} assessed a new design strategy for the molecular complexation of new materials that show quadratic nonlinear optical behavior. Six molecular complexes formed between 4-hydroxy-4′-nitrophenyl/stilbene and 4-substituted pyridine-1-oxide were prepared. Five of them crystallized in noncentrosymmetric space groups hence exhibited second harmonic generation (SHG) activity (Figure 2).

\textbf{Figure 2.} Complexes formed between 4-hydroxy-4′-nitrophenyl/stilbene and 4-substituted pyridine-1-oxide

Supramolecular interactions were thoroughly examined. In complexes 1-4, the pyridine-1-oxide component is arranged in a herringbone motif, with an optimal orientation thus contributing favorably to the bulk NLO efficiency (Figure 3). In the crystal structure of complexes 1-5, the pyridine-1-oxide moiety occupies the interslab spaces and is bound to the slabs with strong O-H...O and O-H...N and weak C-H...O interactions.
hydrogen bonds. However, in the crystal structure of complex 5, the 4-nitropyridine-1-oxide occupies the space between the slabs in the form of antiparallel dimmers which generates centro-symmetric arrangement (Figure 6).

Crystal structure of compound 6 is different from others, the slab structure is much changed, without any interslab spacing, and the 4-nitropyridine-1-oxide is also involved in slab formation and complex arranged in herringbone motif.

**Figure 3.** Quasi-ideal herringbone orientation of 4-methylpyridine-1-oxide in complexes 1 and 2 and 4-cyanopyridine-1-oxide in complexes 3 and 4
Similarly, Nangia *et al.*, explored how the halogen...halogen interactions (X...X, X= F, Cl, Br and I), facilitate the arrangement of non-centrosymmetric space groups in 2-halo-3-hydroxypyridine, pyridine-N-oxides, and 2-halo-3-aminopyridine compounds (Figure 5).

X...X interaction of halo atoms such as Cl, Br, and I steer crystallization of these compounds in noncentrosymmetric space groups efficient for nonlinear optical materials. This above study illustrates the feasibility of exploiting supramolecular structural feature for enhancement of NLO response of molecular materials.
Chirality in NLO materials

Among the other methods used to prepare NLO active materials, introduction of chirality to the part of a molecule is most successful. In general, the enantiopure compounds does not crystallize in centrosymmetric manner and such molecules are necessarily noncentrosymmetric. Their second-order NLO response is therefore nonzero. In addition, when chiral molecules were used as guest of NLO molecules, it crystallizes without mirror planes or inversion centers. Herein we outline some of the NLO active chiral molecules found in the literature. Nesterov et al., synthesized three chiral (2S)-2-(methoxymethyl)pyrrolidine derivatives. In the course of study, the authors found that introduction of chiral fragments into the target NLO chromophores helps to bring acentricity to the resulting crystalline materials (Figure 6). Supramolecular architecture of the molecule was studied. The authors also made theoretical calculations to explain observed SHG activity of the molecules.

\[
\begin{align*}
\text{Figure 7. Chiral (2S)-2-(methoxymethyl)pyrrolidine derivatives}
\end{align*}
\]

Kelderman et al., synthesized a series of chiral pyrrolo[1,2-α] quinoline derivatives and studied the microscopic and macroscopic hyperpolarizability properties using EFISH and Kurtz-peri method respectively (Figure 7). The authors also prepared a simple D-pi-A system with similar substitution and compared it with each other. The chiral pyrrolo[1,2-α] quinoline derivatives showed good NLO activity.

\[
\begin{align*}
\text{Figure 7. Chiral pyrrolo[1,2-α]quinolone derivatives}
\end{align*}
\]
Mosurkal Ravi et al.\textsuperscript{9} synthesized a new chiral push-pull quinonoid compound, 7,7-bis(3(R)-hydroxypyrrolidino)-8,8-dicyanoquinodimethane (BHPDQ) and studied crystal structure and SHG property. This study reveals how the extensive intermolecular H-bonding in the molecules helps to promote the SHG efficiency (Figure 8).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Figure8.png}
\caption{Chiral push-pull quinonoid compound 7,7-,bis(3(R)-hydroxypyrrolidino)-8,8-dicyanoquinodimethane (BHPDQ) \textsuperscript{9}}
\end{figure}

G. Lacroix et al.\textsuperscript{10} synthesized a new chiral hemicarboxonium salt, (ephem)(BF\textsubscript{4}) by reaction of α-1-((methylamino)ethyl)benzyl alcohol and (-)-ephedrine on a carboxonium tetrafluoroborate salt (Figure 9). The authors explored SHG activity by growing large single crystal for application in optics.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Figure9.png}
\caption{Chiral hemicarboxonium salt and N-(4-nitrophenyl)-(L)-prolinol (NPP) \textsuperscript{9}}
\end{figure}

N-(4-Nitrophenyl)-(L)-prolinol (NPP) is a successful example of molecular engineering, in which chirality and hydrogen bonding are employed to achieve the optimum NLO value (Figure 9).\textsuperscript{11} Youping et al.\textsuperscript{12} grew single crystal of NPP and characterized it. Single crystal of 2-(N-prolinol)-5-nitropyridine (PNP) was also found to be NLO active.\textsuperscript{13}
Figure 10. (-)-2-α-(methylbenzylamino)-5-nitropyridine (MBANP)

Bailey et al.,\textsuperscript{14} prepared (-)-2-α-(methylbenzylamino)-5-nitropyridine (MBANP) single crystals and studied electro optic property (Figure 10).

**Chiral polymer based materials:**

Philip et al.,\textsuperscript{15} reported solvatochromic behaviour of a new series of chiral polyesters. These polymers with π-conjugated donor-acceptor segments were synthesized with a view to be suitable for SHG (Figure 11). The polyesters were prepared by the reaction of diacid chlorides with biphenolic azo chromophores with optically active dihydroxy compound (isosorbide) and in all respects these polyesters are suitable for NLO studies. The chiral building blocks induced a macroscopic chirality in the material even in the absence of poling. They exhibited high Tg values and good thermal stability. Therefore a moderately good SHG can be expected from these chiral polyesters.

![Chemical structure of MBANP](image)

**Figure 11. Chiral polymer based materials**
A series of chiral bis(trimethyltin)binaphthalene derivative containing diiodo-functionalized chromophore were prepared by Stille coupling reaction. The optical purity of the chiral binaphthalene monomer was varied, and its influence on the conformation of the polymers was investigated (Figure 12). The mobility of the chromophore in the polymers, prepared from optically impure monomers, is much higher than that in polymers obtained by polymerization of optically pure monomers. Hyper-Rayleigh scattering measurements demonstrated that this difference in mobility is due to different macromolecular structure.

![Figure 12. Binaphthalene based chiral polymers](image)

The authors demonstrated that polymerization of optically impure binaphthalene monomers leads to nonhelical polymers. DSC and SHG measurements indicated higher mobility of the chromophores in the random-coil-like polymers, compared to the helical polymers. \(^{16}\)

**Chiral Amino Acids as NLO materials**

Among organic crystals used for NLO applications the amino acid based materials offer rich choice. In general, all amino acids have a proton-donating carboxyl and proton accepting amino group and except glycine, all the other molecules contains...
chiral carbons in part of the structure. Hence, several new compounds incorporating the amino acid with different organic/inorganic acids were reported for suitable for NLO applications. Among this some of pure amino acids such as L-arginine, L-histidine, L-alanine, etc, are found to be good NLO materials.

The amino acid based organic NLO materials have unique properties comparable with other organic materials. Molecular chirality secures non-centro (acentric) symmetric crystallographic structure. Absence of strongly conjugated bonds leads to wide transparency ranges in the visible and UV spectral regions. Zwitter ionic nature of the molecule, favors crystal hardness.\(^1\)\(^7\) Hence, so many compounds including, amino acid salt with various acid and other metal salts has been reported so far. In addition to this, several doped materials also reported.

In 1983, Xu et al., reported the L-arginine phosphate monohydrate (LAP) as a potential NLO material and gave a new dimension for NLO materials.\(^\)\(^1\)\(^8\) Later several groups followed it and compounds such as L-arginine formate,\(^1\)\(^9\)\(^a\) L-arginine diphosphate,\(^1\)\(^9\)\(^b\) L-arginine halide family\(^1\)\(^9\)\(^c\) were reported.

A novel organic nonlinear optical crystal of L-pyrrolidone-2-carboxylic acid (L-PCA) has been grown and found to be phase matchable for SHG.\(^2\)\(^0\)\(^a\) Single crystals of L-lysine acetate, an organic NLO material have been grown by controlled evaporation of its aqueous solution. The optical behavior, including transmittance and SHG was investigated.\(^2\)\(^0\)\(^b\) L-prolinium picrate \((C_5H_{10}NO_2)^+.(C_6H_2N_3O_7)^-\) an organic NLO material possessing large SHG efficiency (74 times higher than that of the standard KDP) was grown by slow evaporation method.\(^2\)\(^0\)\(^c\) Similarly several more amino acid based NLO materials including metal salts are reported.

**Ibuprofen and its derivatives**

Ibuprofen, \((2R,S)-1[4-(2-methyl propyl) phenyl\) propionic acid, was the first member of propionic acid derivatives introduced in 1969. Ibuprofen was discovered by Dr. Stewart Adams and his colleagues in the United Kingdom in the 1950s, patented in 1961, and first made available in 1969. It is a popular drug used as analgesic (pain-relieving) and antipyretic (fever-reducing). Ibuprofen has anti-inflammatory properties, and it belongs to a class of therapeutic agents known as nonsteroidal anti-inflammatory
drugs (NSAIDs). It is used for the treatment of inflammatory and painful disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute gouty arthritis, postoperative pain, postpartum pain and soft tissue injuries, generally at doses up to 3200 mg per day.\(^{21}\) Like acetylsalicylic acid (aspirin), another NSAID, and acetaminophen, ibuprofen works by inhibiting the activity of a class of enzymes called cyclo-oxygenases (COX) which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation, fever and play protective role against the development of stomach ulcers.

Ibuprofen was shown to protect neurons from glutamate toxicity in vitro. Glutamate cytotoxicity has been implicated in Alzheimer’s disease, Parkinson’s disease and other neurodegenerative diseases, meaning that ibuprofen could be a promising protective agent against these ailments.\(^{22}\)

Of late, several theoretical studies were made on ibuprofen. In 2008, Vueba \textit{et al}.\(^{23a}\) studied the conformational stability of ibuprofen to get a better understanding of the structure–activity relationships underlying their biological activity. They used both experimental approach and density functional theory (DFT) method and showed a thorough conformational analysis of ibuprofen. The mid-, far-infrared and Raman vibrational spectra of ibuprofen was measured at room and low temperatures and analyzed by means of ab initio calculations.\(^{23b}\) Although the study of nonsteroidal anti-inflammatory drug (NSAID) ibuprofen is very popular, there are still many unsolved problems in the area of the theoretical study of it.\(^{23c}\)

**Applications of Chiral Ibuprofen amides**

Some of the amide derivatives 9 of ibuprofen 7 were reported as anti-inflammatory, analgesic and antiulcer agents (Scheme 1).\(^{24a}\)

![Scheme 1. Synthesis of Ibuprofenamide derivatives](image-url)
A series of heterocyclic amides 10 of ibuprofen with heteroaromatic amines was synthesized and assayed in vivo for their analgesic properties by means of writhing test in rats. When compared to parent ibuprofen some of the new amides exhibited a comparable or improved analgesic activity and a lower ulcerogenic effect (Scheme 2).24b

\[
\begin{align*}
\text{Scheme 2. Synthetic pathways to heterocyclic ibuprofen amides} \\
\text{It has been established that derivatives of arylpropionic acids as esters and amides may retain the activity of the parent acids and decrease their gastrointestinal toxicity.25 A set of ester and amide derivatives of some acidic NSAIDs, including ibuprofen (7), ketoprofen (11) and mefenamic acid (12) were synthesized (Figure 13) and evaluated for their in vivo analgesic and anti-inflammatory activity using the p-benzoquinone-induced writhing test and the carrageenan-induced paw edema model respectively.}
\end{align*}
\]

\[
\begin{align*}
\text{Figure 13. Structure of Ibuprofen 7, Ketoprofen 11, Mefenamic acid 12} \\
\text{Two methods are generally utilized for the synthesis of N- (pyridyl or pyrimidyl)-2-(4-isobuty-phenyl)propionamides 10 are outlined in Scheme 2 and both utilized commercially available ibuprofen 7 and heterocyclic amines as starting materials. Ibuprofen was treated with thionyl chloride to generate acid chloride, this after purification by distillation, was reacted with an appropriately substituted amine in the presence of potassium carbonate to yield the desired amides 10 (Method A).}
\end{align*}
\]
Since this synthetic procedure gave some troubles in purification step of the target amides, due to partial decomposition of starting amines, propionamides 10 were also synthesized starting directly from ibuprofen and the appropriate amine in the presence of 1,1-carbonyldiimidazole, CDI (Method B). This second synthetic pathway is milder, utilizes less toxic reagents and gives better yields respect to method A.

Several patents can be found on ibuprofen derivatives, and its salts with various amines.26 Three new Y(III), Zr(IV), and U(VI) complexes of ibuprofen were synthesized and characterized and their magnetic behavior was examined.27 The ibuprofen has two donating centers, oxygen atoms of carboxylate; when chelated with Y(III) there are six bonds formed, four with two ibuprofens and two water molecules (Figure 14).

The Zr(IV) complex is coordinated with one water molecule to complete the octahedral structure. The biological activity of these compounds was tested against different bacterial species, such as _E. coli_ K32, _S. aureus_ K1, _B. subtilis_ K22, _Br. otitidis_ K76, _P. aeruginosa_ SW1, and _K. oxytoca_ K42. The biological assay shows that all the complexes were more bio-active compared to free ibuprofen and metal salts.

Treatment of parent NSAIDs with the appropriate phenol or amine derivatives in the presence of N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDCI), as the carboxyl group activator, and dimethyaminopyridine (DMAP) afforded the desired amide products 14a-d, 15a-d, and 16a-d in 50%-70% yield (Scheme 3).28

![Figure 14. Coordination mode of Y(III), Zr(IV) and U(VI) with ibuprofen](image)

![Scheme 3. Reaction of parent NSAIDs with the appropriate phenol or amine derivatives](image)
Among the synthesized compounds, ester derivatives of ketoprofen showed especially potent analgesic and anti-inflammatory activity as compared to the parent drug. *In vitro* chemical stability studies revealed that ester and amide derivatives were chemically stable in simulated gastric (pH 1.2) and intestinal fluids (pH 6.8). In 80% human plasma, the ester derivatives were found to be relatively stable against plasma esterases over periods of 24 h, indicating that the observed activity was not due to the parent NSAIDs. Most of the compounds were found to be non-ulcerogenic under the tested conditions.

**Crystal structure**

Shankland *et al*., studied the crystal structure of racemic ibuprofen at 100 K. Authors found that (R)- or (S)- ibuprofen crystals belongs to the centro-symmetric space group P21/c (monoclinic system) and the unit cell parameters are: a=14.667Å, b=7.886 Å, c = 10.730 Å, β=99.3628, Z =4. The unit cell of racemic ibuprofen consists of (R) and (S) molecules paired with O-H…O hydrogen bonding via acid dimer off as hydrogen-bonded dimmers (Figure 15).

![Figure 15. The acid dimer motif of racemic ibuprofen molecule](image)

Later, A.B Brandl *et al*., crystallized the racemate ibuprofen and (+) ibuprofen to study the thermodynamic differences and crystal energy calculations. However, (+)-ibuprofen crystallized in P21 space group, two symmetrically independent molecule was present in the asymmetric unit with S- conformation.
The cyclic dimer was formed through hydrogen bonds of this carboxylic group (Figure 16). In contrast, the racemate ibuprofen dimer is formed by hydrogen bonds across a center of inversion (space group P21/c), with one molecule in the $R$ configuration and the other in the $S$-configuration.$^{30}$
PRESENT WORK

Ibuprofen is a popular drug which shows analgesic, antipyretic, anti-inflammatory activity. Ibuprofen amides and esters were studied as an alternative to ibuprofen which retains the activity of the parent acids and decrease gastrointestinal toxicity. Some of the metal complexes of ibuprofen were also prepared and found to show better anti-microbial activity. The crystal structure of ibuprofen and its inclusion complex with cyclodextrin as well as heptakis(2,3,5-trimethyl-bCD) is reported. Theoretical studies were made on ibuprofen to get better understanding on the structure–activity relationships underlying their biological activity.

Early study on organic NLO materials focused mainly on the development of molecular systems with large hyperpolarizabilities. Organic molecules with very high polarisability and dipole moment loose SHG activity either due to centrosymmetry in individual molecules or in centrosymmetric nature of the bulk crystals. Use of chiral molecules and macromolecular assemblies to achieve NLO activity is an important approach which gained attention only recently. Chiral crystals have the distinct advantage of necessarily lacking inversion symmetry and therefore always exhibiting symmetry-allowed SHG. However, symmetry alone does not necessarily provide a direct indication of the efficiency of SHG activity. Several enantiopure amino acids which lack conjugated double were found to act as good NLO materials we examined NLO properties of ibuprofen amide derivatives.

*p-Nitroaniline (p-NA) is the classical push–pull conjugated molecule and it has good hyperpolarisability, thus a potential candidate for SHG activity. However, the main drawback is p-NA itself has a centrosymmetric crystal lattice, hence several modification of its structure was carried out and SHG activity was examined. The simplest successful modifications is m-nitroaniline (m-NA) and 2-methyl-4-nitroaniline (MNA), both molecule have noncentrosymmetric crystal lattices and show powder SHG of 20 and 80 U respectively (1 U=SHG of urea). Similarly, the chiral derivative of 2,4-dinitrophenyl-(L )-alanine methyl ester (MAP) shows a moderate SHG of 10 U. The most successful derivatives is N-4-nitrophenyl-(S)-prolinol (NPP), which is designed to exploit intermolecular H-bonding interactions and
molecular chirality simultaneously and has a near optimal orientation of the dipoles in the crystal lattice leading to a high SHG capability of 150 U.\textsuperscript{37}

Ibuprofen is one of the cheap and readily available chiral compounds. Asymmetric synthesis of ibuprofen is well established and it is available worldwide. Considering the chiral nature, simple structure, ready availability in optically pure form ibuprofen was identified a useful building block for introducing chirality on dipolar organic molecules. Several 2-(4-isobutylphenyl)-N-(nitrophenylamino)propionamides as well as other propionamide derivatives 9a-h were prepared and its crystal structure and SHG property was examined.

The literature background shows that three methods were mainly used for the preparation of amide derivatives of ibuprofen.\textsuperscript{24} The first and basic method is the addition of acid chloride to amine in the presence of base, second method is anhydride formation using ethyl chloroformate and triethylamine in MDC at 0 °C under nitrogen atmosphere and the third approach is using coupling reagents such as CDI, EDC, DCC and etc., For the present study the synthesis of some ibuprofen amide derivatives was carried out using the first route.

2-(4-isobutylphenyl) propionic acid (ibuprofen, DL-7) was treated with thionyl chloride in the presence of DMF (catalyst) in chloroform at 60 °C for 3 h to afford 2-(4-isobutylphenyl) propionyl chloride 8. The acid chloride was added slowly to a mixture of 3-nitroaniline (17b) and triethylamine (TEA) at 0-5 °C over a period of 30 min. (Method A). The mixture was allowed to attain room temperature slowly and stirred for about 8 h. Initially, we optimized the reaction time and conditions using 3-nitroaniline (17b) and ibuprofen (7). When 1.5 equiv. of SOCl\textsubscript{2} was used for the preparation of acid chloride at 60 °C during 3 h and treatment with 3-nitroaniline (17b) the ibuprofenamide (DL-9b) was obtained in 60% yield after 8 h. However, the quantity of SOCl\textsubscript{2} was increased to 5 equiv. to study the optimization condition, when the 3 equiv. SOCl\textsubscript{2} was obtained in higher yield (85%). When more than 5 equiv. of SOCl\textsubscript{2} was the yield reduced and side products increased.

Similarly, 4-nitroaniline (17a) was treated with DL-ibuprofen acid chloride, and (D)-ibuprofen acid chloride prepared using 3 equiv. of SOCl\textsubscript{2}, to get ibuprofenamide
DL-9a (95%) and D-9b (93%) respectively. However, in case of 2-nitroaniline (17c) the reaction failed to take place at rt and when the temperature was increased up to 70 °C the product was obtained in low yield. Increasing the reaction duration only led to the formation of the desired product in very low yield (10%). Another reaction was tried using K₂CO₃ as base (method B). To a solution of 2-nitroaniline (17c) in acetone and water mixture 3 equiv. of K₂CO₃ was added at 0-5 °C and stirred for 2 h, then the acid chloride 8 was added slowly in to a mixture for a period of 30 mints. Then reaction mixture was allowed to raise rt and stirred for 24 h. After completion of the reaction, reaction mixture was poured into crushed ice and stirred well. The residue was filtered and dissolved in ethyl acetate, washed with dil. HCl, sodium bicarbonate solution and brine solution. The product DL-9 or D-9 was obtained in high yield (upto 95%) from the organic layer after concentration under vacuum.

**Table 1:** Synthesis of ibuprofenamide

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Amine</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>17a</td>
<td>8</td>
<td>95</td>
<td>DL-9a</td>
</tr>
<tr>
<td>2.</td>
<td>17a</td>
<td>8</td>
<td>93</td>
<td>D-9a</td>
</tr>
<tr>
<td>3.</td>
<td>17b</td>
<td>8</td>
<td>91</td>
<td>DL-9b</td>
</tr>
</tbody>
</table>
4-nitroaniline gave high yield of the product 9a under the method B, and the yield decreased when TEA was used as base. Thus, all the amide derivatives DL-9 or D-9 using method B in good yield (up to 95%). With 1-/2-aminoanthroquinone
(17d/17e) the reaction time was quite large (24 h, reflux) compared with the 2/3/4-nitroaniline (17a/17b/17c). When 2-/3-/4-aminopyrdine (17f/17g/17h) was used as amine, the quantity of K$_2$CO$_3$ was increased to 4 equiv. in order to get good yield. All the synthesized products were characterized by FT-IR, $^1$H NMR, $^{13}$C NMR study.

**Crystallography study**

Among all the synthesised compounds, 3-NO$_2$ aniline derivatives of ibuprofen DL-9b and D-9b were crystallized to give good quality single crystals by slow evaporation method using ethyl acetate and hexane (2:8 (v/v)) mixture as solvent. The XRD data was collected at rt (296 K) and the crystal structure was refined. Compound DL-9b crystallized in orthorhombic space group in which one molecule was present in the asymmetric unit (Figure 17).

![Image of compound DL-9b ORTEP diagram](image-url)

*Figure 17. Compound DL-9b ORTEP diagram drawn at the 50% probability level (at 296 K)*

However, atoms C11, C12 and C13 of aromatic ring and carbon atoms of isobutyl group were split in two positions. Attempts to identify the position of the disordered atom C11, C12 and C13 of compound 9b, using PART instructions and different Fourier map was not successful (Figure 18). It may be because the thermal vibration of the molecule is very high. In order to resolve the problem, the XRD data was collected at 173K (-100°C).
Compound DL-9b crystallized in orthorhombic with space group P2₁2₁2₁ and two independent molecules (molecule A & molecule B) could be found in the asymmetric unit. These two independent molecules have opposite configuration. Part of the ibuprofen moiety in the second molecule (B) (bottom left) is disordered over two positions, for which the occupancies is 0.4 and 0.6 (part1: part2 = 0.4:0.6). The Friedel pairs were merged as it was not possible to determine the absolute configuration.

**Figure 18.** The thermal ellipsoids diagram of DL-9b drawn at the 50% probability level (at 173 K)

**Figure 19.** The independent molecules A & B are linked by N-H…O hydrogen bonds (dotted lines).
Interaction between the amide carbonyl oxygen atom and amide N – H led to the formation of a intermolecular C=O…H–N bond with C(4) motif along the \(oa\) axis. This gives rise to a one dimensional hydrogen bond chain. The hydrogen bond chain was made up of molecule A and molecule B was arranged in alternatively (Figure 19).

![Figure 19](image)

**Figure 20.** ORTEP diagram of compound D-9b drawn at the 50% probability level (at 296 K).

Compound D-9b crystallized in orthorhombic crystal system with two crystallographically independent molecule in the asymmetric unit (Figure 20). The isobutyl unit of ibuprofen moiety is disordered. Only we established the crystal structure. Our attempts to identify the position of the disordered atoms, using PART instructions and different Fourier map was not successful. It may be resolved by the collecting of XRD – data at lower temperature.

**SHG study**

Based on the previous literature reports and on our expectations we examined SHG activity for all the ibuprofen amides DL-9a to DL-9h and D-9a D-9c by Kurty-Perry method. The 2-nitroaniline amides compounds DL-9c and D-9c were obtained as
a viscous liquid, hence its powder SHG could not be examined. In general, the enantio-
pure amide compounds shows higher SHG value compared with racemic compounds.
Thus higher SHG value was observed for optically pure compounds D-9a and D-9b,
compared to the racemic compound DL-9a and DL-9b (Table 2).

Table 2. SHG activity of ibuprofenamide derivatives.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ibuprofenamide</th>
<th>SHG</th>
<th>Space Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DL-9a</td>
<td>2.5</td>
<td>P2_12_1</td>
</tr>
<tr>
<td>2.</td>
<td>D-9a</td>
<td>6</td>
<td>P2_12_1</td>
</tr>
<tr>
<td>3.</td>
<td>DL-9b</td>
<td>2.1</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>4.</td>
<td>D-9b</td>
<td>4.6</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>5.</td>
<td>DL-9c</td>
<td>Not tested</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>6.</td>
<td>D-9c</td>
<td>Not tested</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>7.</td>
<td>DL-9d</td>
<td>0.5</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>8.</td>
<td>DL-9e</td>
<td>0.4</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>9.</td>
<td>DL-9f</td>
<td>Very less</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>10.</td>
<td>DL-9g</td>
<td>Very less</td>
<td>Single crystal not obtained</td>
</tr>
<tr>
<td>11.</td>
<td>DL-9h</td>
<td>Very less</td>
<td>Single crystal not obtained</td>
</tr>
</tbody>
</table>

Both optically pure compounds D-9b and racemic compound DL-9b crystallised
under non-centrosymmetric space group P2_12_1. In case of ibuprofen amides (DL)-9d
to (DL)-9h prepared from aminoanthroquinones (17d nad17e) and aminopyridines
(17f-h) the observed SHG value was very low. This indicates that the presence of an
effective push-pull substitution is important to achieve good SHG values. This situation
is different from SHG value observed with zwitter ionic amino acid salts. Thus the
introduction of chirality using ibuprofen skeleton on push-pull type molecule such as
nitroaniline and aminoanthroquinone did not yield fruitful result.

Antimicrobial Activity

The compounds DL-9f, DL-9g and DL-9h were screened for their antimicrobial
activity against C. albicans, C. tropicalis, M. smegmatis and B. Subtilis. Preliminary
screening reveal that compound DL-9h showed moderate activity compared to DL-9f
and DL-9g (Table 3).
### Table 3. Antimicrobial Activity of Ibuprofen Amides

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound</th>
<th>0.5 mg/disc – ZOI (mm)</th>
<th>C. albicans</th>
<th>C. tropicalis</th>
<th>M. smegmatis</th>
<th>B. Subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ibuprofen</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>DL-9f</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>DL-9g</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DL-9h</td>
<td>11</td>
<td>11</td>
<td>15</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Amphotericin B-50 µg</td>
<td>18.25±0.25</td>
<td>13±0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Streptomycin 25 µg</td>
<td>-</td>
<td>-</td>
<td>34±0.2</td>
<td>18±0.25</td>
<td></td>
</tr>
</tbody>
</table>

In conclusion a series of ibuprofen amide derivative of nitroaniline, aminoanthroquinone and aminopyridine were prepared in high yield. Both chiral and racemic ibuprofen amide derivative of 3-nitroaniline gave single crystals with non-centrosymmetric space group P2₁2₁2₁. Interaction between the amide carbonyl oxygen atom and amide N – H led to the formation of a intermolecular C=O…H–N bond with C(4) motif along the oa axis. This gives rise to a one dimensional hydrogen bond chain. Nitroanilne derivatives has higher SHG values compared to aminoanthroquinone and aminopyridine derivatives. The enantio-pure amide compound shows a higher SHG value compared to the racemic compounds.
EXPERIMENTAL SECTION

General procedure for the preparation of 2-(4-isobutylphenyl)propionyl chloride (8)

To a mixture of ibuprofen (7, 0.05 g, 2.4 mmol), freshly distilled thionyl chloride (5.95 mL, 4.8 mmol) few drops of DMF was added as catalyst in benzene or chloroform at 60 °C for 3 h. After completion of reaction excess of thionyl chloride was removed under reduced pressure to get 2-(4-isobutyl-phenyl)-propionyl chloride 8 as the residue.

General procedure for the synthesis of ibuprofenamide (DL-9 or D-9)

To a mixture of an amine 17 (1.0 equiv.) and K₂CO₃ (3.0 equiv.) in acetone: water (3:1 v/v) maintained at 0 °C to 5 °C and add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone over a period of 30 min. The reaction mixture was stirred for 8 h and monitored by TLC. After the completion of the reaction, the reaction mixture was concentrate and poured into crushed ice. The residue obtained was filtered, dissolved in chloroform (100 mL), washed with 5% hydrochloric acid (3 × 50 mL), 5% sodium bicarbonate (3 × 50 mL) and finally with brine solution (2 × 25 mL). The organic layer was separated, dried and crystallised from petroleum ether/ethyl acetate (6:4) to get the corresponding product DL-9 or D-9 up to 95 % yield.

Preparation of 2-(4-isobutylphenyl)-N-(4-nitrophenyl)propanamide (DL-9a)

The reaction was carried out as mentioned in the general procedure using 4-nitroaniline (17a, 335 mg, 2.42 mmol) and K₂CO₃ (1000mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min -1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (DL-9a, 750 mg, 95%). Compound crystallizes from petroleum ether:ethyl acetate (6:4/v/v). ¹H NMR (400 MHz, CDCl₃): δ = 0.79 (d, J = 6.8 Hz, 6H), 1.48 (d, J = 7.2 Hz, 3H), 1.72-1.79 (m, 1H), 2.37 (d, J = 7.2 Hz, 2H), 3.62 (q, J = 6.8 Hz, 1H), 7.06 (d, J = 8Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H ), 7.48 (dd, J =
7.2, 5.2 Hz, 2H), 8.04 (d, \(J = 7.2, 4.8\) Hz, 2H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 18.4, 22.4, 30.2, 45.0, 48.0, 118.9, 125.0, 127.2, 127.4, 129.4, 130.1, 137.2, 141.6, 143.4, 143.7, 173.0\) ppm.

**Preparation of 2-(4-isobutylphenyl)-N-(4-nitrophenyl)propanamide (D-9a)**

![D-9a](image)

The reaction was carried out as mentioned in the general procedure using 4-nitroaniline (17a, 335 mg, 2.42 mmol) and K\(_2\)CO\(_3\) (1000 mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (D-9a, 735 mg, 93%). Compound crystallizes from petroleum ether/ethyl acetate (6:4). The Spectral data is same as that provided for compound DL-9a.

**Preparation of 2-(4-isobutylphenyl)-N-(3-nitrophenyl)propanamide (DL-9b)**

![DL-9b](image)

The reaction was carried out as mentioned in the general procedure using 3-nitroaniline (17b, 335 mg, 2.42 mmol) and K\(_2\)CO\(_3\) (1000 mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (DL-9b, 720 mg, 91%). Compound crystallizes from petroleum ether/ethyl acetate (6:4 v/v). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.84\) (d, \(J = 6.8\) Hz, 6H), 1.53 (d, \(J = 7.2\) Hz, 3H), 1.74-1.84 (m, 1H), 2.41 (d, \(J = 7.2\) Hz, 2H), 3.66 (q, \(J = 7.2\) Hz, 1H), 7.10 (d, \(J = 8.0\) Hz, 2H), 7.19 (d, \(J = 8.4\) Hz, 2H), 7.35 (t, \(J = 8.4\) Hz, 1H), 7.78 (d, \(J = 8.0\) Hz, 1H), 7.83 (d, \(J = 8.0\) Hz, 1H), 8.19 (bs, 1H (N-H)) ppm. \(^{13}\)C NMR
(100 MHz, CDCl₃): δ = 18.4, 22.4, 30.2, 45.0, 48.0, 114.4, 118.8, 125.5, 127.4, 129.7, 130.1, 139.0, 141.5, 148.5, 173.0 ppm.

**Preparation of 2-(4-isobutylphenyl)-N-(3-nitrophenyl)propanamide (D-9b)**

![Structure D-9b]

The reaction was carried out as mentioned in the general procedure using 3-nitroaniline (17b, 335 mg, 2.42 mmol) and K₂CO₃ (1000 mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (D-9b, 705 mg, 89%). Compound crystallizes from petroleum ether/ethyl acetate (6:4). The Spectral data is same as that provided for compound DL-9b

**Preparation of 2-(4-isobutylphenyl)-N-(2-nitrophenyl)propanamide (DL-9c)**

![Structure DL-9c]

The reaction was carried out as mentioned in the general procedure using 2-nitroaniline (17c, 335 mg, 2.42 mmol) and K₂CO₃ (1000 mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 48 h. The product was obtained as light yellow colour paste (DL-9c, 355 mg, 45%). Compound crystallizes from petroleum ether/ethyl acetate (6:4). ¹H NMR (400 MHz, CDCl₃): δ = 0.90 (d, J = 6.8 Hz, 6H), 1.63 (d, J = 7.2 Hz, 3H), 1.83-1.90 (m, 1H), 2.47 (d, J = 7.2 Hz, 2H), 3.79 (q, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8Hz, 1H), 8.12 (t, J = 8Hz, 1H), 8.79 (d, J = 8Hz, 1H), 10.28(s, 1H) ppm. ¹³C
Preparation of 2-(4-isobutylphenyl)-N-(2-nitrophenyl)propanamide (D-9c)

The reaction was carried out as mentioned in the general procedure using 2-nitroaniline (17c, 335 mg, 2.42 mmol) and K₂CO₃ (1000 mg, 7.3 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min -1 h. Conditions: room temperature, 48 h. The product was obtained as light yellow colour paste (D-9c, 315 mg, 40%). Compound crystallizes from petroleum ether/ethyl acetate (6:4). The Spectral data is same as that provided for compound DL-9c.

Preparation of N-(9,10-Dioxo-9,10-dihydro-anthracen-1-yl)-2-(4-isobutyl-phenyl)-propionamide (DL-9d)

The reaction was carried out as mentioned in the general procedure using 1-aminoanthroquinone (17d, 223.23 mg, 1.0 mmol) and K₂CO₃ (414 mg, 3.0 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min -1 h. Conditions: room temperature, 24 h. The product was obtained as light yellow colour solid (DL-9d, 267 mg, 65%). Compound crystallizes from petroleum ether/ethyl acetate (6:4v/v). ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (d, J = 7.2 Hz, 6H), 1.28 (d, J = 7.2 Hz, 3H), 1.83-1.90 (m, 1H), 2.43 (d, J = 7.2 Hz, 2H), 3.50 (q, J = 7.2 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.62-7.72(m, 2H), 7.88 (t, J = 7.2, 2H), 8.29 (d, J = 8.0 Hz, 2H), 8.48(d, J = 8.0 Hz, 2H) ¹³C NMR (100 MHz,
CDCl$_3$): $\delta$ = 15.4, 22.8, 29.0, 42.5, 44.5, 117.9, 124.4, 125.0, 126.8, 132.1, 133.7, 133.6, 133.8, 141.9, 172.7, 182.1, 185.7 ppm.

Preparation of N-(9,10-Dioxo-9,10-dihydro-anthracen-2-yl)-2-(4-isobutyl-phenyl)-propionamide (DL-9e)

The reaction was carried out as mentioned in the general procedure using 2-aminoanthroquinone (17e, 223.23 mg, 1.0 mmol) and K$_2$CO$_3$ (414 mg, 3.0 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5ml) over a period of 30 min -1h. Conditions: room temperature, 24 h. The product was obtained as light yellow colour solid (DL-9e, 309 mg, 70%). Compound crystallizes from petroleum ether/ethyl acetate (6:4). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.91 (d, $J$ = 7.2 Hz, 6H), 1.28 (d, $J$ = 7.2 Hz, 3H), 1.82-1.92 (m, 1H), 2.43 (d, $J$ = 7.2 Hz, 2H), 3.50 (q, $J$ = 7.2 Hz, 1H), 7.06 (d, $J$ = 8.0 Hz, 2H), 7.26 (d, $J$ = 8.0 Hz, 2H), 7.86-7.88(m, 2H), 7.95 (t, $J$ = 6.8, 2H), 8.12(d, $J$ = 8.0 Hz, 2H) 8.29 (d, $J$ = 8.0 Hz, 2H), $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 15.4, 22.8, 29.0, 42.5, 44.5, 115.6, 128.6, 128.8, 132.1, 133.8, 140.1, 172 7, 182.1 ppm.

Preparation of 2-(4-Isobutyl-phenyl)-N-pyridin-2-yl-propionamide (DL-9f)

The reaction was carried out as mentioned in the general procedure using 2-aminopyridine (17f, 94.11 mg, 1.0 mmol) and K$_2$CO$_3$ (536 mg, 4.0 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (DL-9f, 212 mg, 75%). Compound crystallizes from petroleum ether/ethyl acetate (6:4v/v). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.92 (d, $J$ = 6.8 Hz, 6H), 1.59 (d, $J$ = 7.2 Hz, 3H), 1.82-1.92 (m, 1H), 2.48 (d, $J$ = 7.2 Hz, 2H), 3.76 (q, $J$ = 7.2
Hz, 1H), 7.15 (d, \( J = 8.0 \) Hz, 2H), 7.23 (dd, \( J = 8.4, 3.6 \) Hz, 1H), 7.26 (d, \( J = 8.0, 2H \)), 8.08 (br, 1H), 8.14 (d, \( J = 8.0, 1H \)), 8.25 (d, \( J = 4.8 \) Hz, 1H), 8.46 (d, \( J = 2.4 \) Hz, 1H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 18.6, 22.4, 30.2, 45.0, 47.5, 123.7, 127.3, 127.4, 129.8, 135.2, 137.8, 140.9, 141.2, 144.7, 173.5 \) ppm.

**Preparation of 2-(4-Isobutyl-phenyl)-N-pyridin-3-yl-propionamide (DL-9g)**

The reaction was carried out as mentioned in the general procedure using 3-aminopyridine (17g, 94.11 mg, 1.0 mmol) and K\(_2\)CO\(_3\) (536 mg, 4.0 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (DL-9g, 229 mg, 81%). Compound crystallizes from petroleum ether/ethyl acetate (6:4v/v). \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.91 \) (d, \( J = 6.8 \) Hz, 6H), 1.58 (d, \( J = 8.0 \) Hz, 3H), 1.82-1.92 (m, 1H), 2.47 (d, \( J = 7.2 \) Hz, 2H), 3.75 (q, \( J = 6.8 \) Hz, 1H), 7.12 (d, \( J = 8.0 \) Hz, 2H), 7.20 (dd, \( J = 8.4, 4.8 \) Hz, 1H), 7.25 (d, \( J = 7.6 \) Hz, 2H), 8.14 (d, \( J = 8.0 \), 1H), 8.25 (d, \( J = 2.8 \) Hz, 1H), 8.46 (d, \( J = 1.6 \) Hz, 1H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 18.6, 22.4, 30.2, 45.1, 47.5, 123.7, 127.3, 129.3, 129.8, 135.3, 137.9, 140.9, 141.1, 144.7, 173.5 \) ppm.

**Preparation of 2-(4-Isobutyl-phenyl)-N-pyridin-4-yl-propionamide (DL-9h)**

The reaction was carried out as mentioned in the general procedure using 4-aminopyridine (17h, 94.11 mg, 1.0 mmol) and K\(_2\)CO\(_3\) (536 mg, 4.0 mmol) in acetone:water (3:1 v/v) stirred and maintained at 0 °C to 5 °C and slowly add the 2-(4-isobutyl-phenyl)-propionyl chloride 8 (1.1 equiv.) in acetone (5 mL) over a period of 30 min - 1 h. Conditions: room temperature, 8 h. The product was obtained as light yellow colour solid (DL-9h, 189 mg, 67%). Compound crystallizes from petroleum ether/ethyl acetate (6:4v/v). \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.82 \) (d, \( J = 6.4 \) Hz, 6H),
1.49 (d, $J = 7.6$ Hz, 3H), 1.70-1.80 (m, 1H), 2.35 (d, $J = 7.2$ Hz, 2H), 4.19 (q, $J = 6.8$ Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 8.24 (dd, $J = 21.2$, 6.8 Hz, 1H), 9.54 (br, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 18.6$, 22.4, 30.1, 44.9, 46.9, 114.9, 127.3, 127.5, 129.3, 123.7, 127.3, 129.3, 129.5, 137.2, 138.1, 140.5, 140.9, 141.6, 153.4, 175.7 ppm.
REFERENCES


