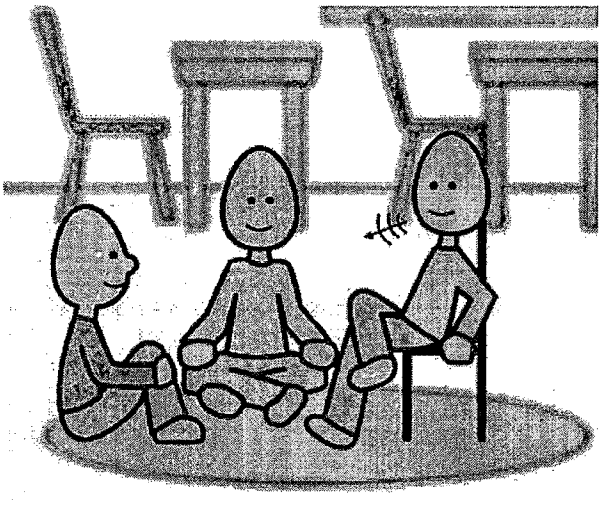
CHAPTER-3



Results and Discussion

3 RESULTS AND DISCUSSION

The work carried out towards achieving the proposed plan has been discussed under the following two main headings:

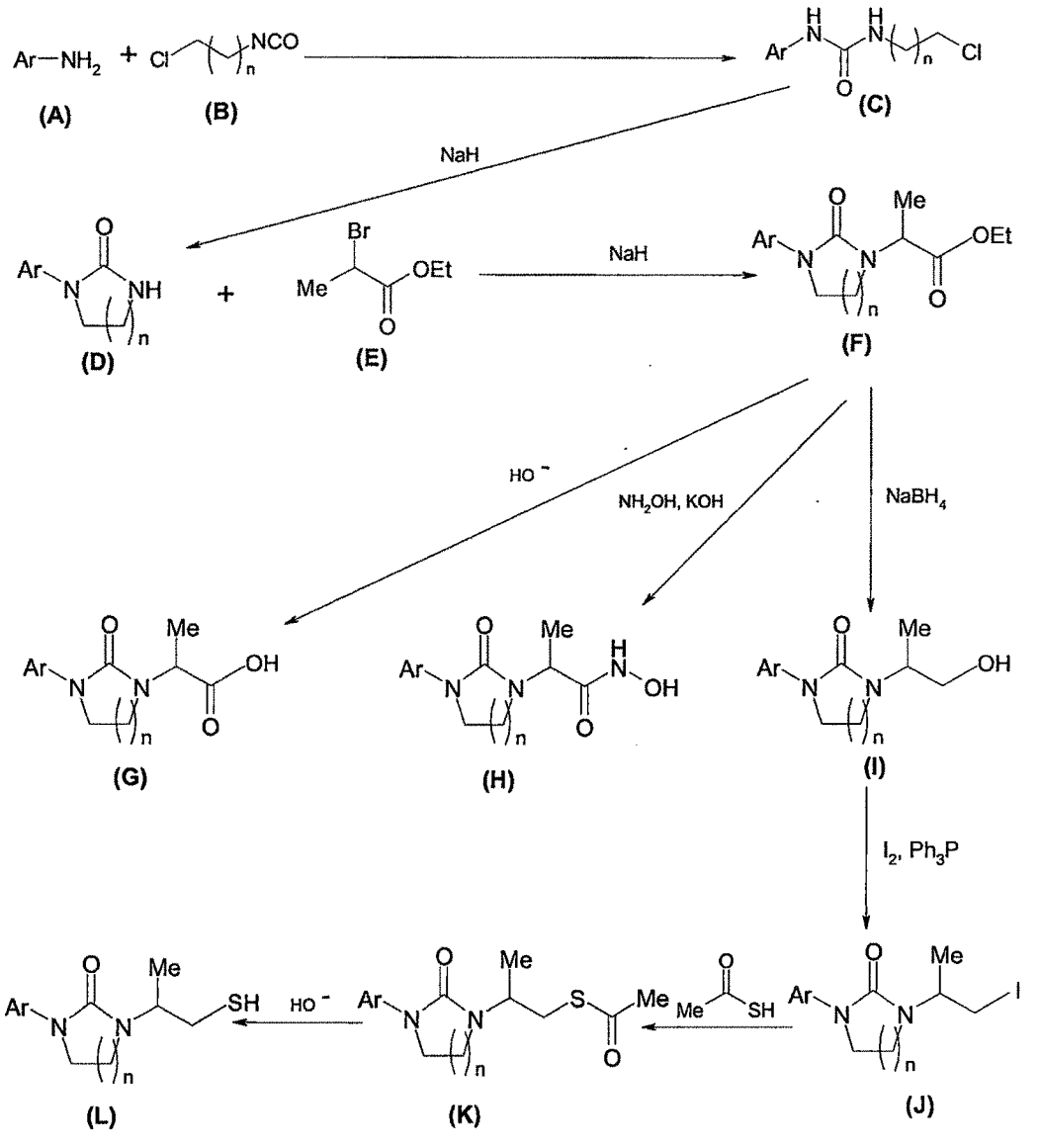
1. Chemical Studies and
2. Biological Studies

3.1 Chemical Studies

To synthesize the envisaged compounds, a scheme was planned as given in general Scheme-1, wherein arylamines (A) were reacted with chloroalkyl isocyanates (B) to obtain the expected urea derivatives (C). The urea derivatives were cyclized under strong basic conditions to obtain the desired five/six membered heterocycles (D). The required side chain was attached by reacting the cyclized products (D) with ethyl 2-bromopropionate (E) to obtain the esters (F). The esters were converted to the three types of zinc binding ligands using three different sequence of reactions. The esters (F) were saponified to the free acids (G) using lithium/sodium hydroxide while hydroxylamine hydrochloride treatment of the esters (F) under basic conditions offered the desired hydroxamates (H). In a separate sequence of reactions the esters (F) were first reduced to alcohols (I) by sodium borohydride treatment, which on further treatment with iodine, triphenyl phosphine and imidazole offered the iodo derivatives (J). The iodo derivatives (J) were treated with thiolacetic acid to obtain the desired thioesters (K), which on hydrolysis under basic conditions yielded the desired thiols (L).

In order to execute Scheme-1, various arylamines (A) and isocyanates (B) were required as the starting chemicals. Some of the amines were available commercially while others were synthesized in the laboratory. Considering the instability of isocyanates (B), these were prepared afresh whenever required. The work related to the synthesis of arylamines (A), isocyanates (B), intermediates (C-F and I-K) and the targeted products (G, H and L) has been described under the following major heads:

- Synthesis of arylamines,
- Synthesis of isocyanates,
- Synthesis of 2-imidazolidinone Derivatives and
- Synthesis of tetrahydropyrimidin-2(1*H*)-one Derivatives



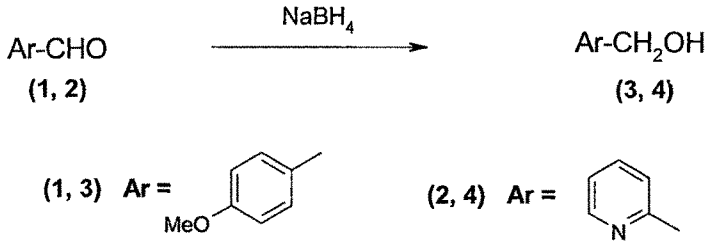
Scheme-1

3.1.1 Synthesis of Arylamines

The arylamines used for reacting isocyanates were ether/thioether-substituted arylamines. Their preparation involved the synthesis of different intermediates which are discussed under different headings.

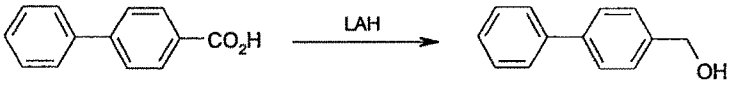
3.1.1.1 Synthesis of Alcohols

In Scheme-2, aromatic aldehydes (1, 2) were reduced to aromatic alcohols (3, 4) by using sodium borohydride. The desired products were obtained as oils in excellent yields (around 90 %).



Scheme-2

In Scheme-3, biphenyl-4-carboxylic acid (5) was converted to the corresponding alcohol (6) by lithium aluminium hydride (LAH). The yield of the reaction was around 80 %. As the melting point of the product (97-98 °C) matched with the literature value (Lit.[142] 99-101 °C), no spectral data were generated for the product (6).

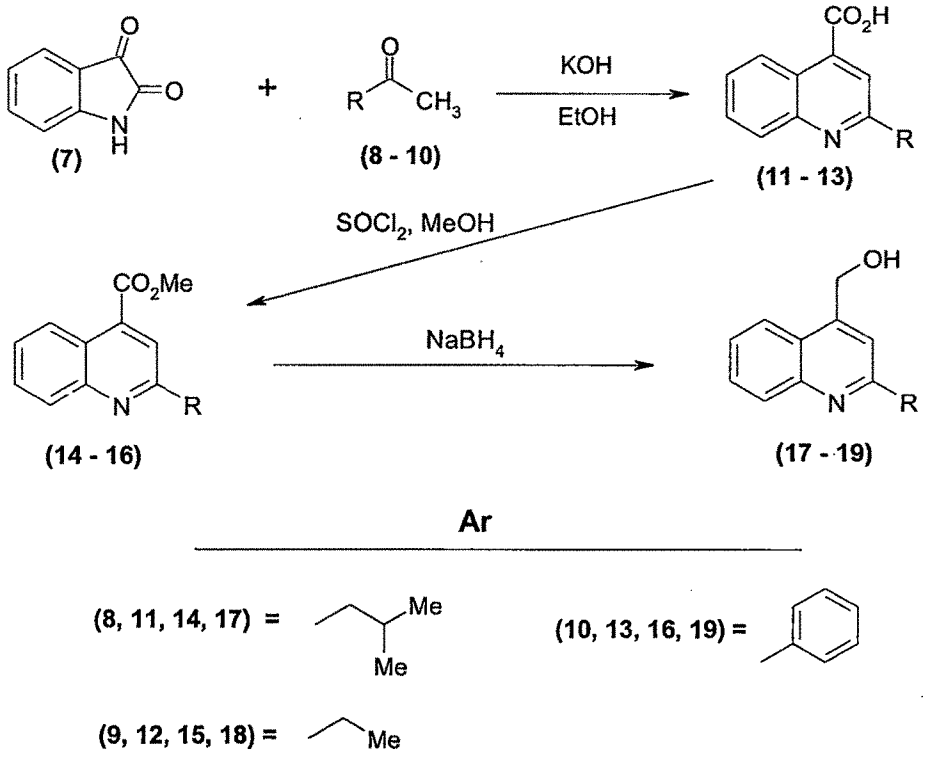


(5) **(6)**

Scheme-3

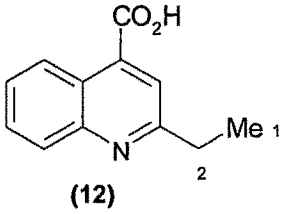
Scheme-4 was employed to synthesize 2-substituted quinolin-4-ylmethanols (17-19) from isatin (7) in a three step process. In the first step, isatin was reacted with a ketone in presence of a strong base like potassium hydroxide in ethanol to form 2-substituted quinoline-4-carboxylic acid. In the literature, this reaction was carried out by conventional heating[143] as well as by using microwave reactor[144]. It was observed during the course of this work that conventional heating of the reaction mixture was converting only half of the starting material into the product, even after refluxing the reaction mixture overnight (as observed by TLC). Hence, microwave reactor was used to carry out this reaction. When the reaction was carried out as per reported method[144], it led to formation of side products along with the desired product. Hence, the reported procedure was slightly modified. The reaction mixture was irradiated only for 5 minutes instead of 15 minutes as reported in the literature. It was observed that the reaction got completed in 5 minutes and the number of side products also got reduced. This modification increased the yields of quinoline-4-carboxylic acids to around 60 % instead of 40 % as reported. The crude products were obtained as precipitates after adjusting the pH of the aqueous medium to 4. The crude products thus obtained were crystallized from methanol. It was observed that when the reaction mixtures were irradiated in

microwave reactor for more than 5 minutes, repeated crystallizations were required to obtain the pure products. The compounds (11, 13) were identified on the basis of their melting points as reported in literature[144].



Scheme-4

In the IR spectrum of compound (12), the stretching vibrations of O-H group were observed at 3412 cm^{-1}. The C=O stretching was seen at 1660 cm^{-1}. In the PMR

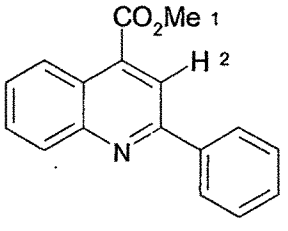


(12)

spectrum of compound (12), aromatic protons were observed at δ 7.93-7.95 (m, 1H), 7.76-7.78 (m, 1H), 7.64-7.68 (m, 1H), 7.51-7.55 (m, 2H). The aliphatic protons were observed at δ 3.01-3.04 (2-CH_2) as quartet (J = 7.7 Hz) and 1.37-1.40 as triplet (J = 7.6 Hz) for (1-CH_3).

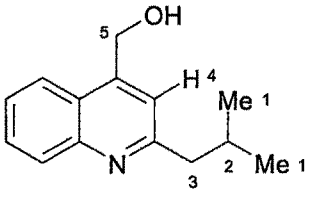
In the next step, the carboxylic acids (11-13) were converted into the methyl esters (14-16) by refluxing the methanolic solution of the acids in presence of thionyl chloride. It was observed that these esters were low melting and probably due to this reason, compound (15) was isolated as liquid.

In the IR spectrum of compound (14), the C=O stretching was observed at 1724 cm^{-1} and the C-O stretching was observed at 1246 cm^{-1}. PMR spectrum of compound (16) shows the presence of (1-C*H*$_3$) protons at δ 4.0 as singlet. The aromatic protons appeared at δ 8.73-8.75 (m, 1H), 8.4 (s, 1H; 2-C*H*) 8.18-8.23 (m, 3H), 7.74-7.78 (m, 1H), 7.59-7.64 (m, 1H), 7.50-7.56 (m, 2H) and 7.46-7.49 (m, 1H).



(16)

These esters (14-16) were then reduced to the corresponding alcohols (17-19) by treating them with sodium borohydride in methanol. Although sodium borohydride is not a suitable reagent for the conversion of esters to alcohols, it was used because of its ready availability. It was observed that at least 5 equivalents of sodium borohydride were necessary for completion of this reaction. PMR spectra of these alcohols (17-19) show



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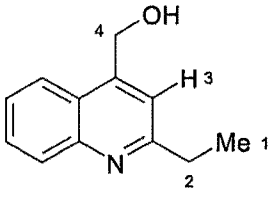

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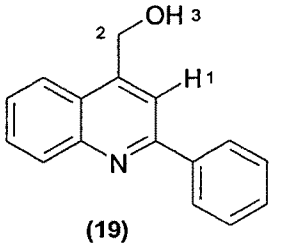


(19)

the presence of C*H*$_2$OH protons at about δ 5.2 as singlets. In the PMR spectrum of compound (17), the doublet at δ 2.8 was due to (3-C*H*$_2$) and the multiplet at δ 2.2 was due to (2-C*H*). Six protons of (1-C*H*$_3$) came at δ 0.95 as doublet and the singlet at 5.20 was due to (5-C*H*$_2$). The aromatic protons were observed at δ 8.06-8.09 (m, 1H), 7.89-7.91 (m, 1H), 7.64-7.66 (m, 1H), 7.47-7.51 (m, 1H) and 7.41 as singlet (4-C*H*). For compound (18), aliphatic protons came at δ 2.9-3.0 (q, 2H, J = 7.6 Hz; 2-C*H*$_2$), 1.3-1.4 (t, 3H, J = 7.6 Hz; 1-C*H*$_3$) and δ 5.21 a singlet for (4-C*H*$_2$). Aromatic protons appeared at 8.06-8.08 (m, 1H), 7.89-7.91 (m, 1H), 7.66-7.70 (m, 1H), 7.52-7.58 (m, 1H) and 7.46 (s, 1H; 3-C*H*). The PMR spectrum of compound (19) showed presence of aromatic protons at δ 8.17-8.21 (m, 3H), 8.10 (s, 1H; 1-C*H*), 7.95-7.97 (m, 1H), 7.69-7.74 (m, 1H),

7.50-7.56 (m, 3H) and 7.43-7.48 (m, 1H). The methylene protons (2-C*H*$_2$) were observed at δ 5.21 as singlet and the proton of the alcoholic group (3-O*H*) came as a broad singlet at δ 4.90.

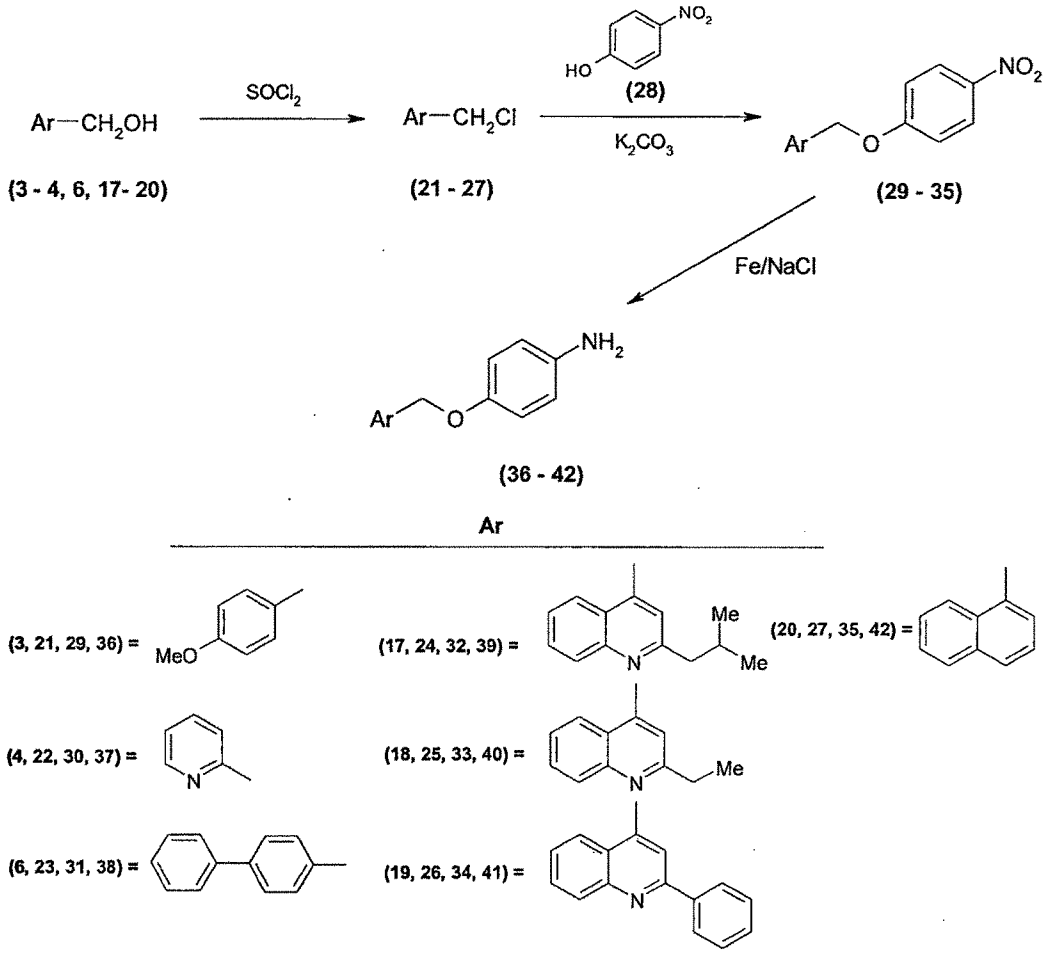
3.1.1.2 Synthesis of ether substituted phenylamines

For the synthesis of required ether intermediates, the alcohols [commercially available (**20**) or synthesized as per Schemes 2-4 (**3, 4, 6, 17-19**)] were converted into chloro derivatives (**21-27**) (Scheme-5) by thionyl chloride treatment in excellent yields (more than 85 %). The chloro derivatives were obtained as oils except for compounds (**23** and **26**) which were isolated as solids at RT. Conversion of the alcohols into the chloro derivatives was monitored by TLC and the products so obtained were used as such for next step without characterization.

The chloro compounds (**21-27**) were then reacted with 4-nitrophenol (**28**) in presence of anhydrous potassium carbonate to prepare the nitro derivatives (**29-35**). The most interesting point in this reaction was the role DMF played. The progress of the reaction depended mainly on the amount of DMF used to dissolve the starting chloro compounds. If the amount was more, the reaction would take longer time and if lesser quantity of DMF was used then the number of side products increased, leading to decreased yields. It was observed that the reaction takes about 4-5 hours if the quantity of DMF is double the weight of the chloro compound with formation of lesser number of side products. All the nitro compounds so synthesized were solid in nature at RT and were insoluble in methanol. Hence, they were purified by washing the crude products with chilled methanol. The yields varied widely for different aromatic systems, the highest being 99 % for compound (**35**) and the lowest 50 % for compound (**31**).

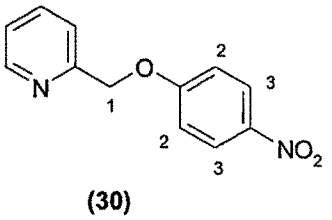
IR spectra of these compounds (**29-35**) showed two strong peaks at about 1450 cm^{-1} and 1330 cm^{-1} for asymmetric and symmetric stretching vibrations of the nitro group, respectively.

IR spectrum of compound (**29**) showed strong peaks at 1249, 1176 and 1028 cm^{-1} for C-O stretching of the ether groups. Two strong peaks at 1454 and 1336 cm^{-1} for stretchings of the nitro group were also observed.



Scheme-5

PMR spectrum of compound (30) showed the presence of aromatic protons at δ 8.62-8.63 (m, 1H), 8.19-8.23 (d, 2H; 3-C*H*), 7.72-7.77 (m, 1H), 7.47-7.49 (m, 1H),



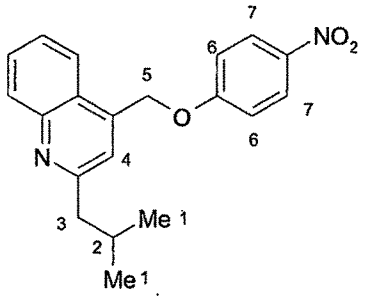
(30)

7.26-7.29 (m, 1H) and 7.04-7.08 (d, 2H; 2-C*H*). The methylene protons were observed at δ 5.30 as singlet (1-CH_2).

IR spectrum of compound (31), showed strong peaks at 1491 and 1338 cm^{-1} due to the asymmetric and symmetric vibrations of nitro group. The peaks at 1251 and 1170 cm^{-1} were observed due to C-O stretching.

PMR spectrum of compound (32) showed the presence of aromatic protons at δ 8.23-8.25 (d, 2H; 7-C*H*), 8.12-8.14 (m, 1H), 7.90-7.92 (m, 1H), 7.72-7.76 (m, 1H), 7.54-

7.58 (m, 1H), 7.38 (s, 1H; 4-C*H*) and 7.10-7.12 (d, 2H; 6-C*H*). The methyl protons (1-CH_3) were observed at δ 0.95-0.97 as doublet. The methylene protons (3-CH_2) and (5-CH_2) were seen at δ 2.84-2.86 as doublet and 5.62 as singlet, respectively. The (2-C*H*) proton appeared at δ 2.22- 2.28 as multiplet.



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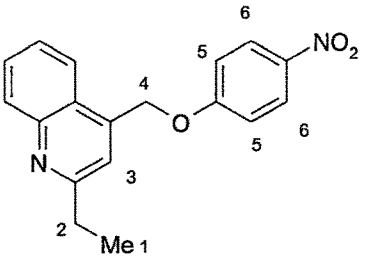
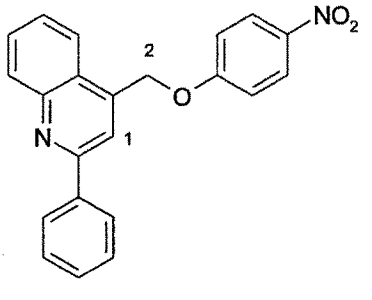


(33)

IR spectrum of compound (33) showed strong peaks at 1446 and 1338 cm^{-1} due to asymmetric and symmetric vibrations of nitro group, respectively. The C-O stretching vibrations appeared at 1267 and 1172 cm^{-1}. PMR spectrum of this compound showed peaks at δ 2.98-3.03 (q, 2H, J = 7.7 Hz) and 1.37-1.41 (t, 3H, J = 7.7 Hz) for (2-CH_2) and (1-CH_3), respectively. The other methylene protons (4-CH_2) were observed at δ 5.67 as singlet. The aromatic protons appeared at δ 8.23-8.25 (d, 2H; 6-C*H*), 7.98-8.07 (m, 2H), 7.70-7.75 (m, 1H), 7.55-7.59 (m, 1H), 7.50 (s, 1H; 3-C*H*) and 7.21-7.23 (d, 2H; 5-C*H*).

PMR spectrum of compound (34) showed aromatic protons at δ 8.25-8.28 (m, 3H), 8.14-8.16 (d, 2H), 8.00 (s, 1H; 1-C*H*), 7.95-7.97 (m, 1H), 7.77-7.81 (m, 1H), 7.59-7.61 (m, 1H), 7.48-7.56 (m, 3H) and 7.14-7.16 (d, 2H). The aliphatic methylene protons (2-CH_2) were observed at δ 5.69 as singlet.



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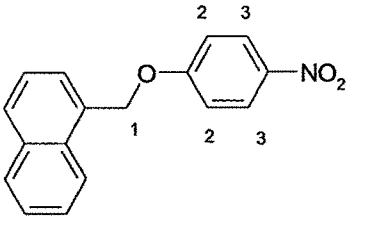


(35)

The aromatic protons of compound (35) appeared at δ 8.22-8.24 (d, 2H; 3-C*H*), 8.01-8.03 (m, 1H), 7.89-7.94 (m, 2H), 7.59-7.63 (m, 1H), 7.48-7.58 (m, 3H) and

7.15-7.18 (d, 2H; 2-C*H*). The aliphatic protons were obtained as singlet at δ 5.6 for (1-CH_2).

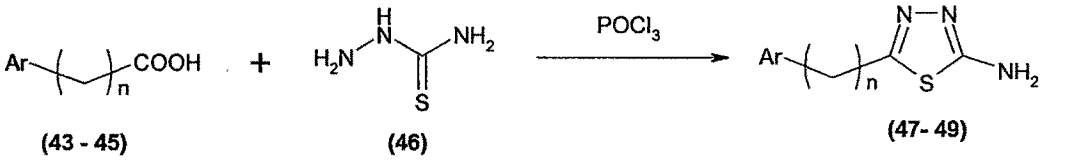
These nitro compounds (**29-35**) were then treated with iron and aqueous sodium chloride in methanol to synthesize the desired ether substituted amino compounds (**36-42**). This reaction took around 11-13 hours to complete for all the compounds. This was a longer time than expected, probably due to the poor solubility of the nitro compounds in methanol.

The aminoethers (**36-42**) showed two distinct peaks at 3400 and 3300 cm^{-1} for the primary amines while the C-O peaks appeared around 1240 and 1178 and 1030 cm^{-1} in their IR spectra.

3.1.1.3. Synthesis of Aminothiadiazoles

2-Aminothiadiazoles (**47-49**) were prepared (Scheme-6) by reacting the acids (**43-45**) with thiosemicarbazide (**46**) in presence of phosphorous oxychloride as per reported method[146,147]. The reported method was modified slightly to obtain higher yields. After quenching the reaction mixture with water, the suspended matter was removed by filtration before basifying the aqueous solution. This slight change in processing the reaction mixture not only improved the yield but also improved the purity of the product.

The prepared compounds showed the stretching vibrations of N-H group of primary aromatic amines as two peaks at around 3200 cm^{-1}. The peaks observed at 1610 cm^{-1} were due to the stretching vibrations of C=N.



(43 - 45) **(46)** **(47- 49)**

(43, 47) Ar = -C_6H_5, n = 1

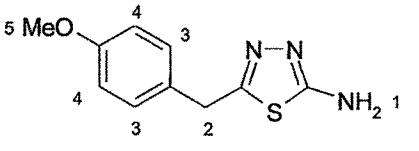
(44, 48) Ar = -C_6H_4OMe (p), n = 0

(45, 49) Ar = - C_6H_4OMe (p), n = 1

Scheme-6

IR spectrum of compound (47) showed N-H stretching vibrations as two strong peaks at 3101 and 3084 cm^{-1} and N-H deformation as a moderate peak at 1610 cm^{-1}. IR spectrum of compound (48) showed N-H stretching at 3406 and 3379 cm^{-1}. N-H deformation peak was observed at 1606 cm^{-1}. The C-O stretching of ethereal group was observed at 1246 and 1172 cm^{-1}.

IR spectrum of compound (49) showed the presence of primary amine by two strong peaks at 3254 and 3103 due to N-H stretching and a moderate peak at 1616 cm^{-1} due to N-H deformation. The C-O stretching peaks of the ether moiety were observed at 1261, 1178 and 1030 cm^{-1}. PMR spectrum of compound (49) showed

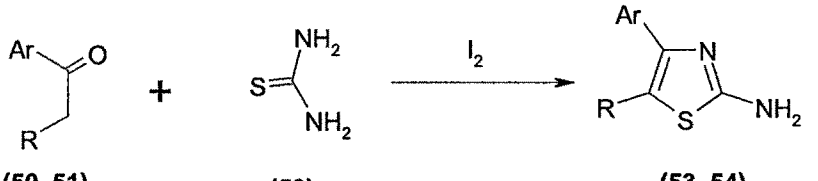


(49)

the presence of aromatic protons at δ 7.17-7.19 (d, 2H; 3-C*H*) and 6.83-6.85 (d, 2H; 4-C*H*). The methylene protons (2-CH_2) were observed at δ 4.12 as singlet. The protons attached to the nitrogen (1-NH_2) came at δ 6.01 as broad singlet. The methoxy protons (5-OCH_3) were observed at δ 3.79 as singlet, as expected.

3.1.1.4 Synthesis of Aminothiazoles

Scheme-7 was employed to prepare 2-aminothiazole derivatives (53, 54) by a known process[148]. In this scheme, acetophenone derivatives (50, 51) were heated to 100 °C with iodine and thiourea (52). It was noted that color impurities were generated during



(50, 51) **(52)** **(53, 54)**

(50, 53) Ar = -C_6H_5, R = -C_6H_5

(51, 54) Ar = -C_6H_4Me (p), R = -H

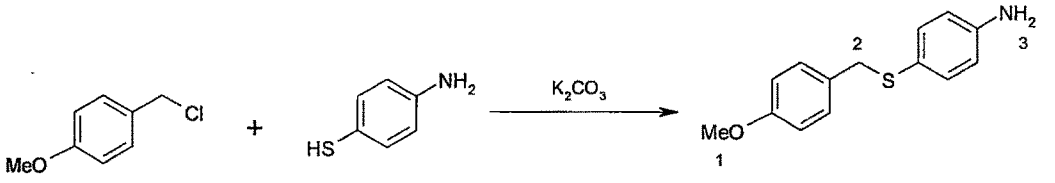
Scheme-7

the course of this reaction, which was washed properly by ether before the basification of the reaction mixture; otherwise the yields and the purity of the amines were not

satisfactory. The melting points of both the compounds matched with the literature values[148].

3.1.1.5 Synthesis of thioether substituted phenylamine

1-(4-Aminothiophenoxymethyl)-4-methoxybenzene (**56**) was synthesized from 4-methoxybenzyl chloride (**21**) and 4-aminothiophenol (**55**) in presence of potassium carbonate as base as per Scheme-8. The isolated compound was purified by column chromatography on neutral alumina. PMR spectrum of the compound showed the



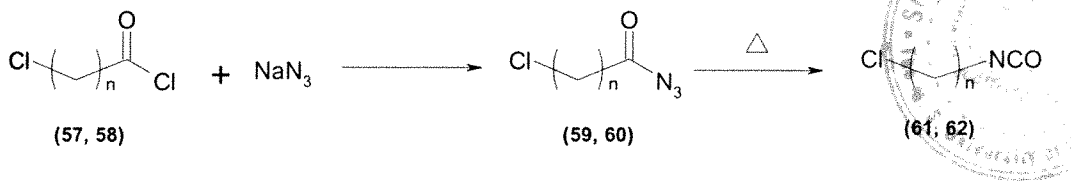
(21) (55) (56)

Scheme-8

presence of aromatic protons at δ 7.09-7.25 (m, 4H), 6.76-6.79 (m, 2H) and 6.51-6.57 (m, 2H). The (1-O*CH*$_3$) and (2-*CH*$_2$) protons were observed at δ 3.77 and δ 4.23 as singlets, respectively. The protons of the free amino group (3-N*H*$_2$) were observed at δ 3.68 as a broad peak.

3.1.2 Synthesis of Isocyanates

Isocyanates were prepared in a two step process[149] according to Scheme-9. The first step is the nucleophilic acyl substitution reaction, in which the acid chlorides (**57, 58**) are reacted with sodium azide at -5 °C to provide the acyl azides (**59, 60**). As acyl azides are unstable, no efforts were made to isolate them. The acyl azides, as soon as formed, were subjected to Curtius rearrangement. Acyl azides were heated to reflux in benzene wherein rearrangement took place. Nitrogen gas was evolved during the course of the reaction. As soon as the evolution of nitrogen gas stopped, the reaction was over. It has been observed that the reaction takes about 3 hours for completion. The isocyanates (**61, 62**) are unstable at RT, sensitive to light and moisture and lachrymatory in nature. Hence, no efforts were made to isolate or purify the isocyanates (**61, 62**). These isocyanates were prepared *in situ* and were not stored in refrigerator. It was observed that even if stored in a tightly closed amber colored vial at -5 °C, they were unsuitable for



(57, 58) (59, 60) (61, 62)

(57, 59, 61) n = 2

(58, 60, 62) n = 3

Scheme-9

synthetic purposes after a week. The benzene solutions of isocynates were used for further reactions in the next step. It was assumed that the yield of isocyanates were quantitative for the calculation purposes.

3.1.3 Synthesis of 2-Imidazolidinone Derivatives

Shia *et al* [150] and Chern *et al* [151] have reported the synthesis of *N*-(2-chloroethyl)-*N'*-pyridyl urea by reacting pyridylamines with 2-chloroethylisocyanate. They have reported the refluxing of the mixture of amine and isocyanate in toluene for 4-5 hours. This method was modified not only to improve the yield but also to decrease the reaction time. The aromatic amines [prepared in Schemes-5 to 8 (**36-42, 47-49, 53, 54, 56**) and available commercially (**63-68**)] were either dissolved or suspended in benzene and 2-chloroethyl isocyanate (**61**) was added drop-wise. It was observed that the reaction became vigorous and the temperature of the reaction mixture rose in most of the cases from 30 °C to around 60 °C. But, cooling of the reaction mixture before the addition of isocyanates was not required as the rise in temperature of the reaction mixture was not associated with formation of impurities. The reaction mixture was stirred at RT for about 30 minutes during which solid material got precipitated out in the reaction mixture. The solids were filtered out and washed with cold benzene to afford the linear urea derivatives (**69-87**) in sufficiently pure form.

The method was modified for 4-benzyloxyaniline hydrochloride (**67**). The compound was first treated with triethylamine to release the free amino group, followed by treatment with 2-chloroethyl isocyanate. In the work up, solvent was removed, dilute hydrochloric acid added to remove any unreacted amine and the precipitate was filtered and dried to afford the desired product.

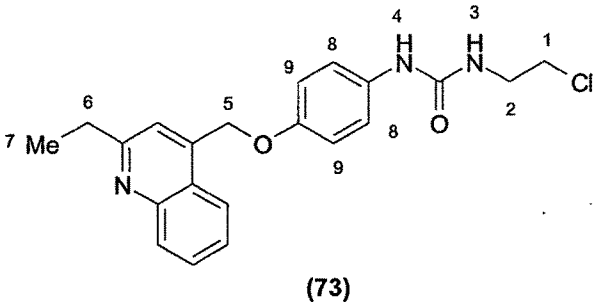
To improve the yield of compound (**87**), the method described above needed some modifications. The conventional method yielded only 30-40 % of the product. The low yield was due to very poor solubility of 4-aminophenol (**68**) in the reaction media i.e.

benzene. To overcome the solubility problem, THF was used to suspend 4-aminophenol **(68)**. The solubility of 4-aminophenol was poor even in THF, hence the reaction mixture was refluxed in order to ensure the completion of the reaction. After refluxing for 3 hours, the reaction mixture showed presence of minute quantities of 4-aminophenol which was removed by acidifying the reaction mixture with concentrated hydrochloric acid. It was observed that the product, 1-(2-chloroethyl)-3-(4-hydroxyphenyl)urea **(87)**, also showed some solubility in water. Hence, the reaction mass was suspended in minimum quantity of ice-water and the solid so obtained was filtered quickly.

IR spectra of these urea derivatives showed strong peaks around 3300 cm^{-1} for N-H stretching, 1640 cm^{-1} for C=O stretching (Amide I) and 1590 cm^{-1} for N-H deformation (Amide II) vibrations.

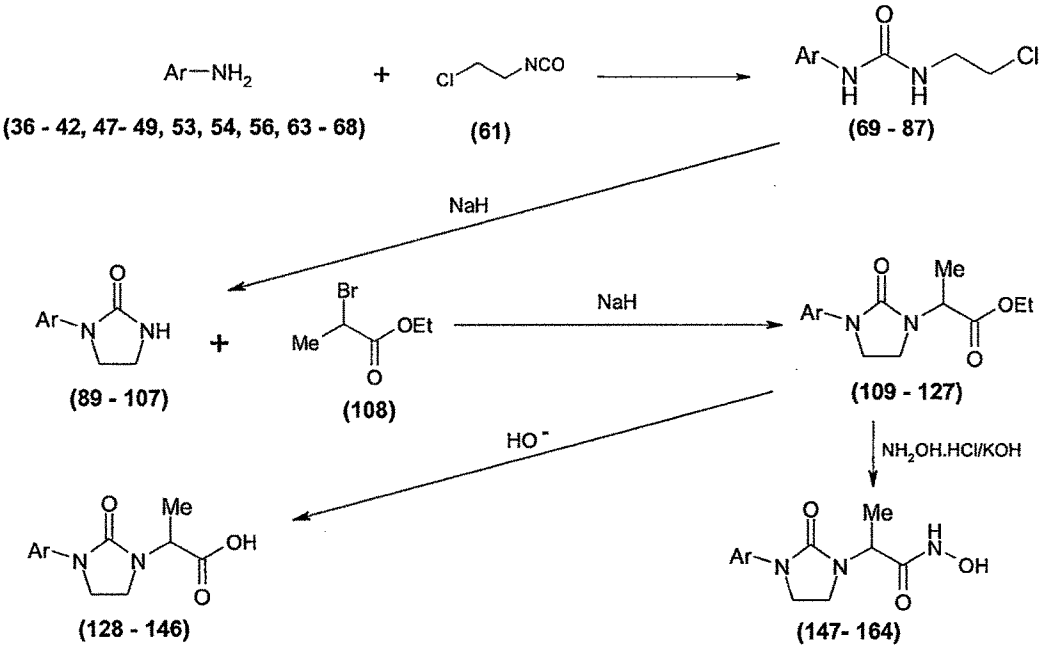
In PMR spectra, the proton attached to the aryl nitrogen appeared at around δ 8.0 as broad singlet and the other N*H* came at δ 5.5-6.4. This proton (-N*H*-CH_2-) showed splitting in some cases **(71, 73-76, 86, 87)** at 400 MHz. It was observed that these protons were readily exchanged in D_2O. The -CH_2Cl protons came at around δ 3.6 and -NHC*H*$_2$ protons were observed at δ 3.5.

PMR spectrum of the compound **(73)** showed aromatic protons at δ 8.20-8.22 (m, 1H), 8.08-8.10 (m, 1H), 7.98-8.00 (d, 1H), 7.70-7.74 (m, 1H), 7.52-7.59 (m, 2H), 7.32-7.36 (d, 2H; 8-C*H*) and 6.94-6.98 (d, 2H; 9-C*H*). The signal for (4-N*H*) probably got



(73)

merged with one of the aromatic signals. Among the aliphatic signals, a triplet at δ 6.24-6.27 was due to (3-N*H*), while multiplets at δ 3.62-3.65 and 3.51-3.55 were due to (1-CH_2) and (2-CH_2) signals, respectively. The (5-CH_2) protons appeared as singlet at δ 5.15 ppm. The methylene protons (6-CH_2) and the methyl protons (7-CH_3) appeared at δ 2.99-3.05 (q, 2H, J = 7.6 Hz) and 1.37-1.41 (t, 3H, J = 7.6 Hz), respectively.



Ar

(36, 69, 89, 109, 128, 147) =

(37, 70, 90, 110, 129, 148) =

(38, 71, 91, 111, 130, 149) =

(39, 72, 92, 112, 131, 150) =

(40, 73, 93, 113, 132, 151) =

(41, 74, 94, 114, 133, -) =

(42, 75, 95, 115, 134, 152) =

(47, 76, 96, 116, 135, 153) =

(48, 77, 97, 117, 136, 154) =

(49, 78, 98, 118, 137, 155) =

(53, 79, 99, 119, 138, 156) =

(54, 80, 100, 120, 139, 157) =

(56, 81, 101, 121, 140, 158) =

(63, 82, 102, 122, 141, 159) =

(64, 83, 103, 123, 142, 160) =

(65, 84, 104, 124, 143, 161) =

(66, 85, 105, 125, 144, 162) =

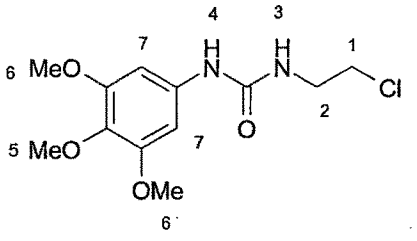
(67, 86, 106, 126, 145, 163) =

(68, 87) =

(-, 88, 107, 127, 146, 164) =

Scheme-10

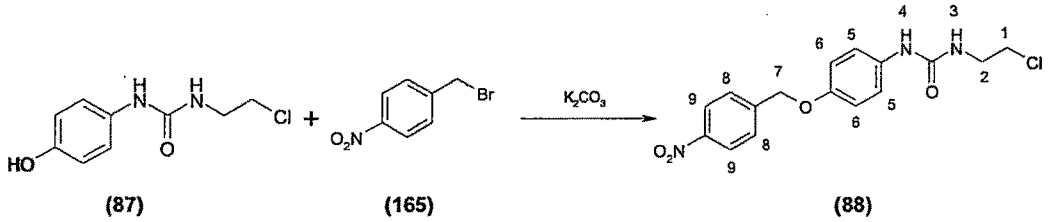
For compound (85), PMR spectrum showed a peak at δ 6.8 as singlet for (7-C*H*). The broad singlet at δ 8.6 was due to (4-N*H*), triplet at 6.38-6.40 for (3-N*H*) and



(85)

singlet at 3.73 for (6-OCH_3) for six protons. The other methoxy group (5-OCH_3) appeared as singlet at δ 3.64. The multiplets at δ 3.68-3.72 and 3.43-3.49 were due to (1-CH_2) and (2-CH_2), respectively.

In order to synthesize compound (88) Scheme-11 was employed. In this scheme, 4-nitrobenzyl bromide (165) was reacted with 1-(2-chloroethyl)-3-(4-hydroxyphenyl)urea (87) in DMF in the presence of potassium carbonate. The most important factor in this reaction was maintenance of temperature (20 °C) throughout the reaction. If the temperature was lower than 20 °C, the reaction rate was slowed and if it was higher, side products were formed in the reaction. If the reaction was maintained at the said temperature, no side products could be observed in TLC in the isolated product.



(87) **(165)** **(88)**

Scheme-11

IR spectrum of the compound (88) showed a strong peak at 1629 cm^{-1} due to the stretching vibrations of C=O group of amide. The symmetric and asymmetric stretching vibrations of nitro group were observed at 1452 and 1344 cm^{-1}, respectively. PMR spectrum of this compound showed aromatic protons at δ 8.20-8.23 (d, 2H; 9-C*H*), 7.61-7.64 (d, 2H; 8-C*H*), 7.30-7.32 (d, 2H; 5-C*H*) and 6.85-6.87 (d, 2H; 6-C*H*). The protons at (1-CH_2) and (2-CH_2) appeared as multiplets at δ 3.62-3.65 and 3.51-3.55, respectively. The other methylene protons i.e. (7-CH_2) were observed as singlet at δ

5.14. The (4-N*H*) proton was observed at δ 8.15 as a broad singlet and the (3-N*H*) proton appeared as triplet at 6.22-6.24, coupling constant being equal to 5.8 Hz.

Spectral data of the urea derivatives **(69-88)** is given in Table-1.

Table 1. Spectral Data of urea derivatives (69-88) synthesized in Scheme-10 and Scheme-11

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
69	3292 (N-H stretching), 1653 (C=O stretching), 1599 (N-H deformation), 1242 (C-O stretching), 1178 (C-O stretching), 1006 (C-O stretching).	-
70	-	8.57-8.59 (m, 1H), 8.09-8.11 (m, 1H), 7.72-7.76 (m, 1H), 7.51-7.53 (m, 1H), 7.24-7.32 (m, 3H), 6.86-6.90 (m, 2H), 6.19-6.21 (t, 1H), 5.15 (s, 2H), 3.62-3.65 (m, 2H), 3.51-3.56 (m, 2H).
71	3309 (N-H stretching), 3034 (N-H stretching), 1639 (C=O stretching), 1573 (N-H deformation), 1236 (C-O stretching), 1174 (C-O stretching), 1041 (C-O stretching).	-
72	3325 (N-H stretching), 1641 (C=O stretching), 1602 (N-H deformation), 1236 (C-O stretching), 1172 (C-O stretching), 1018 (C-O stretching).	8.11-8.13 (m, 1H), 7.91-7.93 (m, 1H), 7.69-7.73 (m, 1H), 7.51-7.55 (m, 1H), 7.41 (s, 1H), 7.22-7.26 (m, 2H), 6.97-7.0 (m, 2H), 6.77 (bs, 1H), 5.47 (s, 2H), 5.38-5.41 (t, 1H), 3.62-3.65 (m, 2H), 3.55-3.59 (m, 2H), 2.84-2.86 (d, 2H), 2.17-2.21 (m, 1H), 0.94-0.96 (d, 6H).
73	3329 (N-H stretching), 1633 (C=O stretching), 1610 (N-H deformation), 1251 (C-O stretching), 1170 (C-O stretching), 1020 (C-O stretching).	8.20-8.22 (m, 1H), 8.08-8.10 (m, 1H), 7.98-8.00 (m, 1H), 7.70-7.74 (m, 1H), 7.52-7.59 (m, 2H), 7.32-7.36 (d, 2H), 6.94-6.98 (d, 2H), 6.24-6.27 (t, 1H), 5.49 (s, 2H), 3.62-3.65 (m, 2H), 3.52-3.56 (m, 2H), 2.99-3.05 (q, 2H, J = 7.61 Hz), 1.37-1.41 (t, 3H, J = 7.62 Hz).
74	-	8.24-8.26 (m, 1H), 8.15-8.17 (m, 2H), 8.07 (s, 1H), 8.01-8.03 (m, 1H), 7.75-7.80 (m, 3H), 7.58-7.60 (m, 1H), 7.46-7.56 (m, 3H), 7.35-7.37 (m, 2H), 6.24-6.26 (t, 1H), 5.45 (s, 2H), 3.63-3.65 (m, 2H), 3.52-3.56 (m, 2H).

75	-	8.04-8.06 (m, 2H), 7.84-7.90 (m, 2H), 7.51-7.57 (m, 3H), 7.46-7.50 (m, 1H), 7.31-7.35 (m, 2H), 6.93-6.99 (m, 2H), 6.15-6.18 (t, 1H) 5.44 (s, 2H), 3.64-3.66 (m, 2H), 3.53-3.57 (m, 2H).
76	3383 (N-H stretching), 1697 (C=O stretching), 1587 (N-H deformation).	-
77	3379 (N-H stretching), 1703 (C=O stretching), 1606 (N-H deformation), 1251 (C-O stretching), 1174 (C-O stretching).	-
78	3450 (N-H stretching), 1639 (C=O stretching), 1606 (N-H deformation), 1246 (C-O stretching), 1176 (C-O stretching), 1035 (C-O stretching).	-
80	-	7.63-7.60 (m, 2H), 7.17-7.19 (m, 2H), 7.15 (s, 1H), 6.98 (bs, 1H), 3.61-3.65 (m, 2H), 3.47-3.49 (m, 2H), 2.36 (s, 3H).
81	3304 (N-H stretching), 1637 (C=O stretching), 1604 (N-H deformation), 1253 (C-O stretching), 1033 (C-O stretching), 819, 744.	-
82	3323 (N-H stretching), 1639 (C=O stretching), 1596 (N-H deformation).	7.30-7.33 (m, 4H), 7.10-7.14 (m, 1H), 6.55 (bs, 1H), 5.30 (bs, 1H), 3.65-3.68 (m, 2H), 3.62-3.65 (m, 2H), 3.58-3.62 (m, 2H).
83	3301 (N-H stretching), 1629 (C=O stretching), 1596 (N-H deformation), 1238 (C-O stretching), 1037 (C-O stretching).	8.00 (bs, 1H), 7.26-7.30 (d, 2H), 6.78-6.81 (d, 2H), 6.16 (bs, 1H), 3.76 (s, 3H), 3.62-3.65 (m, 2H), 3.52-3.56 (m, 2H).
84	3299 (N-H stretching), 1627 (C=O stretching), 1596 (N-H deformation), 1267 (C-O stretching), 1172 (C-O stretching), 1032 (C-O stretching).	6.99-7.00 (d, 1H, J = 2 Hz), 6.79-6.81 (d, 1H, J = 8.4 Hz), 6.71-6.74 (dd, 1H, J = 2 Hz & 8.4 Hz), 5.45 (bs, 1H), 3.86 (s, 6H), 3.63-3.65 (m, 2H), 3.55-3.59 (m, 2H).
85	3367 (N-H stretching), 3307 (N-H stretching), 1647 (C=O stretching), 1596 (N-H deformation), 1232 (C-O stretching), 1172 (C-O stretching), 1130 (C-O stretching).	8.65 (bs, 1H), 6.8 (s, 2H), 6.38-6.40 (t, 1H), 3.73 (s, 6H), 3.68-3.72 (m, 2H), 3.64 (s, 3H), 3.43-3.49 (m, 2H).

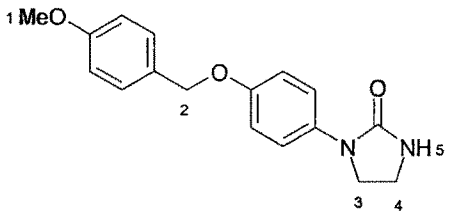
86	3310 (N-H stretching), 1639 (C=O stretching), 1600 (N-H deformation), 1236 (C-O stretching), 1006 (C-O stretching).	8.46 (bs, 1H), 7.40-7.44 (m, 2H), 7.36-7.38 (m, 2H), 7.31-7.33 (m, 1H), 7.27-7.29 (m, 2H), 6.88-6.90 (m, 2H), 6.29-6.33 (t, 1H), 5.03 (s, 2H), 3.62-3.65 (m, 2H), 3.35-3.41 (m, 2H).
87	3307 (N-H stretching), 3031 (N-H stretching), 1635 (C=O stretching), 1585 (N-H deformation), 1508, 1465, 1238, 835.	-
88	3301 (N-H stretching), 1629 (C=O stretching), 1595 (N-H deformation), 1452 (asym. C-NO_2 stretching), 1344 (sym. C-NO_2 stretching), 1244 (C-O stretching), 1174 (C-O stretching), 1047 (C-O stretching).	8.20-8.23 (d, 2H), 8.15 (bs, 1H), 7.61-7.64 (d, 2H), 7.30-7.32 (d, 2H), 6.85-6.87 (d, 2H), 6.22-6.24 (t, 1H), 5.14 (s, 2H), 3.62-3.65 (m, 2H), 3.51-3.55 (m, 2H).

Shia *et al* [150] and Chern *et al* [151] have reported the synthesis of pyridylimidazolidin-2-ones from *N*-(2-chloroethyl)-*N'*-pyridyl urea by reacting the linear compounds with sodium hydride in DMF. In the course of this work, the solvent for the cyclization reaction was changed from DMF to THF. Only those compounds, which remained insoluble in THF, were dissolved in DMF. Sodium hydride (60 % suspension in mineral oil) was washed with dry benzene/petroleum ether to remove the oil present in it before using it in the reaction. For analytical purposes, small quantities of the synthesized 1-arylimidazolidin-2-ones were crystallized from a mixture of ethyl acetate and n-hexane.

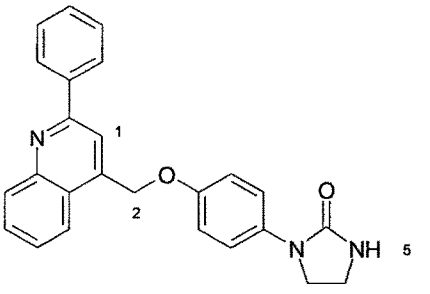
IR spectra of these compounds showed peaks at around 3300 cm^{-1} for N-H stretching, 1680 cm^{-1} for C=O stretching (Amide I) and at around 1590 cm^{-1} for N-H deformation (Amide II). The PMR spectra showed a broad singlet at δ 4.7-6.0 ppm for N*H*. The CH_2-CH_2 protons of the imidazolidinone rings were observed at around δ 3.7 and 3.3 as multiplets.

The aromatic protons of compound (89) appeared at δ 7.40-7.46 (m, 2H), 7.33-7.38 (m, 2H), 7.21-7.23 (m, 1H) and 6.85-6.93 (m, 3H). The broad singlet at δ 7.9 was due to (5-N*H*), singlet at 4.96 was due to (2-CH_2) and multiplets at 3.74-3.84 and at 3.30-3.35 were due to (3/4-CH_2 + 1-CH_3) for five protons and (3/4-CH_2), respectively.

The aromatic protons of compound (**94**) appeared at δ 8.22-8.24 (m, 1H), 8.15-8.17 (m, 2H), singlet at 8.04 due to (1-C*H*), 7.97-7.99 (m, 1H), 7.74-7.78 (m, 1H), 7.44-



(89)



(94)

7.60 (m, 6H) and 7.03-7.07 (m, 2H). The broad singlet at δ 4.7 was due to (5-N*H*), singlet at 5.57 was due to (2-CH_2) and multiplets at δ 3.89-3.93 and at 3.30-3.35 were due to (3/4-CH_2) and (4/3-CH_2).

IR and PMR spectral data of 2-imidazolidinones (**89-107**) is given in Table-2.

Table 2. Spectral Data of 2-imidazolidinone derivatives (89-107) synthesized in Scheme-10

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
89	3265 (N-H stretching), 1681 (C=O stretching), 1246 (C-O stretching), 1020 (C-O stretching).	7.91 (bs, 1H), 7.40-7.46 (m, 2H), 7.33-7.38 (m, 2H), 7.21-7.23 (m, 1H), 6.85-6.93 (m, 3H), 4.96 (s, 2H), 3.74-3.84 (m, 5H), 3.30-3.35 (m, 2H).
90	-	8.58-8.60 (m, 1H), 7.68-7.72 (m, 1H), 7.50-7.52 (m, 1H), 7.40-7.44 (m, 2H), 7.20-7.23 (m, 1H), 6.95-6.99 (m, 2H), 5.19 (s, 2H), 4.95 (bs, 1H), 3.87-3.91 (m, 2H), 3.53-3.57 (m, 2H).
91	3257 (N-H stretching), 1681 (C=O stretching), 1246 (C-O stretching), 1153 (C-O stretching), 1016 (C-O stretching).	-
92	3242 (N-H stretching), 1685 (C=O stretching), 1606 (N-H deformation), 1240 (C-O stretching), 1024 (C-O stretching).	8.00-8.04 (m, 2H), 7.80 (s, 1H), 7.69-7.73(m, 1H), 7.54-7.57 (m, 1H), 7.45-7.48 (m, 2H), 7.01-7.03 (m, 2H), 6.44 (bs, 1H), 5.51 (s, 2H), 3.85-3.89 (m, 2H), 3.48-3.52 (m, 2H), 2.82-2.84 (d, 2H), 2.14-2.21 (m, 1H), 0.95-0.97 (d, 6H).
93	3209 (N-H stretching), 2964 (aromatic C-H stretching), 1701 (C=O stretching), 1512, 1487, 1267 (C-O stretching), 1188 (C-O stretching), 1022 (C-O stretching), 825.	-

94	-	8.22-8.24 (m, 1H), 8.15-8.17 (m, 2H), 8.04 (s, 1H), 7.97-7.99 (m, 1H), 7.74-7.78 (m, 1H), 7.44-7.60 (m, 6H), 7.03-7.07 (m, 2H), 5.57 (s, 2H), 4.72 (bs, 1H), 3.89-3.93 (m, 2H), 3.54-3.58 (m, 2H).
95	-	8.04-8.07 (m, 1H), 7.87-7.91 (m, 2H), 7.59-7.61 (m, 1H), 7.52-7.55 (m, 2H), 7.44-7.49 (m, 3H), 6.99-7.02 (m, 2H), 6.29 (bs, 1H), 5.46 (s, 2H), 3.85-3.89 (m, 2H), 3.49-3.53 (m, 2H).
96	3250 (N-H stretching), 1678 (C=O stretching).	-
97	3097 (N-H stretching), 1680 (C=O stretching), 1255 (C-O stretching), 1174 (C-O stretching), 1030 (C-O stretching).	-
98	3209 (N-H stretching), 1697 (C=O stretching), 1247 (C-O stretching), 1182 (C-O stretching), 1031 (C-O stretching).	-
99	3223 (N-H stretching), 1691 (C=O stretching).	-
100	3236 (N-H stretching), 1685 (C=O stretching).	-
101	3265 (N-H stretching), 1685 (C=O stretching), 1608 (N-H deformation).	-
102	3259 (N-H stretching), 1683 (C=O stretching), 1598 (N-H deformation).	7.53-7.55 (m, 2H), 7.32-7.36 (m, 2H), 7.04-7.07 (m, 1H), 4.95 (bs, 1H), 3.94-3.97 (m, 2H), 3.56-3.60 (m, 2H).
103	3257 (N-H stretching), 1681 (C=O stretching), 1249 (C-O stretching), 1182 (C-O stretching), 1035 (C-O stretching).	7.41-7.44 (d, 2H), 6.85-6.87 (d, 2H), 6.05 (bs, 1H), 3.85-3.89 (m, 2H), 3.78 (s, 3H), 3.50-3.54 (m, 2H).
104	3361 (N-H stretching), 1697 (C=O stretching), 1249 (C-O stretching), 1195 (C-O stretching), 1020 (C-O stretching).	7.51-7.50 (d, 1H, J = 2.5 Hz), 6.81-6.84 (d, 1H, J = 8.7 Hz), 6.70-6.73 (dd, 1H, J = 2.5 Hz & 8.7 Hz), 5.15 (bs, 1H), 3.89-3.93 (m, 5H), 3.86 (s, 3H), 3.54-3.58 (m, 2H).
105	3371 (N-H stretching), 1697 (C=O stretching), 1271 (C-O stretching), 1126 (C-O stretching), 1076 (C-O stretching).	6.92 (bs, 1H), 6.88 (s, 2H), 3.82-3.86 (m, 2H), 3.74 (s, 6H), 3.60 (s, 3H), 3.35-3.39 (m, 2H).

106	3259 (N-H stretching), 1681 (C=O stretching), 1245 (C-O stretching), 1150 (C-O stretching), 1004 (C-O stretching).	7.40-7.48 (m, 4H), 7.35-7.39 (m, 2H), 7.29-7.33 (m, 1H), 6.91-6.94 (m, 2H), 6.29 (bs, 1H), 5.04 (s, 2H), 3.83-3.89 (m, 2H), 3.47-3.53 (m, 2H).
107	3273 (N-H stretching), 2929 (aromatic C-H stretching), 1693 (C=O stretching), 1583 (N-H deformation), 1514, 1433 (asym. C-NO_2 stretching), 1350 (sym. C-NO_2 stretching), 1257, 1232 (C-O stretching), 1186 (C-O stretching), 1051 (C-O stretching), 827.	-

In the next step, 2-imidazolidinone derivatives (**89-107**) were converted to ester derivatives (**109-127**) using ethyl 2-bromopropionate (**108**) in presence of a strong base like sodium hydride.

It was observed that the reaction depended on the quality of sodium hydride used. As sodium hydride is prone to degradation in presence of moisture, it was stored in inert atmosphere in a wax-sealed container. It was observed that in spite of all the precautions, sometimes (especially in the monsoon) because of the poor quality of sodium hydride the reaction either did not go at all or some amount of the unreacted starting material remained in the reaction mixture. In those cases either the reaction was discarded or purified by column chromatography. Also, sodium hydride was washed repeatedly with dry benzene/petroleum ether to remove the mineral oil present in it. In some cases if the washings were not proper the esters isolated could not be solidified and/or crystallized due to the presence of traces of mineral oil. As the presence of mineral oil impurity in these oily esters did not pose any problem in the further course of reactions, no attempts were made to purify the esters or synthesize them again in high purity.

THF was preferred as a solvent over DMF because of its easy removal from the reaction mixture. But, most of the cyclic derivatives (**89-93, 96-98, 102, 104, 106, 107**) were not soluble in dry THF. For these compounds the reaction was carried out in refluxing conditions in THF or in DMF. It was observed that if an imidazolidinone was soluble in THF and the reaction was carried out in refluxing conditions to decrease the duration of the reaction, a number of side products were obtained and the ester so

formed was difficult to purify. DMF was used as the solvent of choice for those compounds which did not dissolve in hot THF.

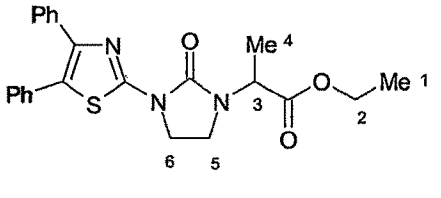
It was observed that compounds (**109, 123, 124**) were low melting as they got solidified when kept in refrigerator and remained oily at RT.

In the IR spectra of these esters, peaks at around 1730 cm^{-1} were observed due to C=O stretching of the ester group and 1690 cm^{-1} due to C=O stretching of the amide group. It is also notable that the peaks at around 1590 cm^{-1} which were present in the starting cyclic compounds due to N-H deformation were absent in these ester derivatives.

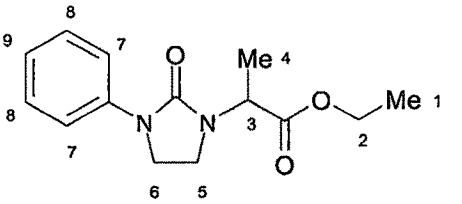
PMR spectra of these compounds showed the presence of three protons at δ 1.3 as doublet with coupling constant of 7.1 Hz for CH-C*H*$_3$ protons and δ 1.5 as triplet with coupling constant equal to 7.5 Hz for CH$_2$-C*H*$_3$ protons. The C*H*$_2$-CH$_3$ protons came at δ 4.2 ppm, in most of the cases as multiplet (**110, 122-124, 126**) and in two cases as quartet (**125**) with coupling constant equal to 7.1 Hz. In case of compounds (**117, 119**) these two protons merged with the C*H*$_2$ protons of the imidazolidinone ring. The protons of C*H*-CH$_3$ group were observed at δ 4.7 as quartet with coupling constant equal to 7.5 Hz.

The aromatic protons of compound (**119**) appeared at δ 7.40-7.43 (m, 2H), 7.31-7.38 (m, 3H) and 7.24-7.30 (m, 5H). The triplet at δ 1.18-1.21 was due to (1-C*H*$_3$) and the doublet at 1.41-1.43 was due to (4-C*H*$_3$). The proton at (3-C*H*) appeared at δ 4.53-4.58, the multiplet at 4.14-4.19 was due to (2-C*H*$_2$ + 1 proton of 5/6 C*H*$_2$) and multiplets at 4.03-4.12 and 3.33-3.70 were due to (1 proton of 5/6 C*H*$_2$) and (2 protons of 5/6 C*H*$_2$), respectively in the PMR spectrum.

PMR spectrum of compound (**122**) showed a triplet at δ 1.26-1.29 due to (1-C*H*$_3$), a multiplet at 4.16-4.22 due to (2-C*H*$_2$), a quartet at 4.71-4.77 due to (3-C*H*) and a doublet at 1.46-1.48 due to (4-C*H*$_3$). The multiplets at δ 3.80-3.92 for 1 proton, 3.64-3.70 for



(119)



(122)

one proton and 3.50-3.56 for 2 protons were due to (5-C*H*$_2$) and (6-C*H*$_2$). The aromatic

protons (7-C*H*) appeared as multiplet at δ 7.54-7.56, protons (8-C*H*) appeared as multiplet at 7.30-7.34 and the (9-C*H*) proton was observed at 7.03-7.05 as multiplet.

IR and PMR spectra of the esters (110-127) are described in Table-3.

Table 3. Spectral Data of ester derivatives (110-127) synthesized in Scheme-10

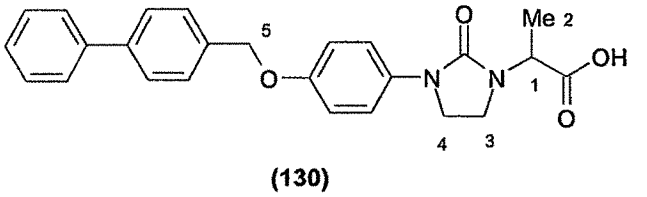
Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
110	-	8.56-8.60 (m, 1H), 7.68-7.72 (m, 1H), 7.50-7.52 (m, 1H), 7.42-7.46 (m, 2H), 7.20-7.22 (m, 1H), 6.94-6.98 (m, 2H), 5.19 (s, 2H), 4.69-4.75 (q, 1H, *J* = 7.51 Hz), 4.16-4.21 (m, 2H), 3.76-3.86 (m, 2H), 3.61-3.68 (m, 1H), 3.48-3.54 (m, 1H), 1.45-1.47 (d, 3H, *J* = 7.48 Hz), 1.25-1.29 (t, 3H).
111	1739 (C=O stretching of ester), 1689 (C=O stretching of imidazolidinone ring), 1242 (C-O stretching), 1182 (C-O stretching), 1014 (C-O stretching).	-
112	1739 (C=O stretching of ester), 1689 (C=O stretching of imidazolidinone ring), 1245 (C-O stretching), 1182 (C-O stretching), 1076 (C-O stretching).	-
113	2926 (aromatic C-H stretching), 1739 (C=O stretching of ester), 1701 (C=O stretching of imidazolidinone ring), 1518, 1437, 1280, 1242 (C-O stretching), 1180 (C-O stretching), 1020 (C-O stretching), 835, 763.	-
117	1741 (C=O stretching of ester), 1712 (C=O stretching of imidazolidinone ring), 1255 (C-O stretching), 1180 (C-O stretching), 1030 (C-O stretching).	7.83-8.87 (d, 2H), 6.695-6.98 (d, 2H), 4.72-4.77 (q, 1H, *J* = 7.49 Hz), 4.22-4.32 (m, 1H), 4.20-4.17 (m, 3H), 3.85-3.80 (m, 4H), 3.66-3.72 (m, 1H), 1.53-1.51 (d, 2H, *J* = 7.52 Hz), 1.27-1.30 (t, 3H).
119	-	7.40-7.43 (m, 2H), 7.31-7.38 (m, 3H), 7.24-7.30 (m, 5H), 4.53-4.58 (q, 1H), 4.14-4.19 (m, 3H), 4.03-4.12 (m, 1H), 3.33-3.70 (m, 2H), 1.41-1.43 (d, 3H), 1.18-1.21 (t, 3H).
120	1735 (C=O stretching of ester), 1716 (C=O stretching of imidazolidinone ring), 1514, 1421, 1267, 1197, 1022, 825, 742.	-

121	1732 (C=O stretching of ester), 1701 (C=O stretching of imidazolidinone ring), 1273 (C-O stretching), 1199 (C-O stretching), 1031 (C-O stretching).	-
122	1747 (C=O stretching of ester), 1699 (C=O stretching of imidazolidinone ring).	7.54-7.56 (m, 2H), 7.30-7.34 (m, 2H), 7.03-7.05 (m, 1H), 4.71-4.77 (q, 1H, J = 7.49 Hz), 4.16-4.22 (m, 2H), 3.80-3.92 (m, 2H), 3.64-3.70 (m, 1H), 3.50-3.56 (m, 1H), 1.46-1.48 (d, 3H, J = 7.48 Hz), 1.26-1.29 (t, 3H).
123	1737 (C=O stretching of ester), 1699 (C=O stretching of imidazolidinone ring), 1247 (C-O stretching), 1190 (C-O stretching), 1047 (C-O stretching).	7.36-7.38 (d, 2H), 6.79-6.82 (d, 2H), 4.64-4.66 (q, 1H, J = 7.49 Hz), 4.09-4.15 (m, 2H), 3.70-3.80 (m, 5H), 3.55-3.61 (m, 1H), 3.43-3.47 (m, 1H), 1.38-1.40 (d, 3H, J = 7.52 Hz), 1.19-1.22 (t, 3H).
124	1731 (C=O stretching of ester), 1681 (C=O stretching of imidazolidinone ring), 1250 (C-O stretching), 1139 (C-O stretching), 1076 (C-O stretching).	7.65-7.66 (d, 1H, J = 2.5 Hz), 6.80-6.82 (d, 1H, J = 8.7 Hz), 6.63-6.66 (dd, 1H, J = 2.5 Hz & 8.7 Hz), 4.70-4.75 (q, 1H, J = 7.49 Hz), 4.17-4.22 (m, 2H), 3.87-3.91 (m, 4H), 3.85 (s, 3H), 3.79-3.82 (m, 1H), 3.65-3.69 (m, 1H), 3.53-3.65 (m, 1H), 1.46-1.48 (d, 3H, J = 7.48 Hz), 1.26-1.30 (t, 3H, J = 7.14 Hz).
125	1739 (C=O stretching of ester), 1697 (C=O stretching of imidazolidinone ring), 1271 (C-O stretching), 1178 (C-O stretching), 1072 (C-O stretching).	6.85 (s, 2H), 4.69-4.75 (q, 1H, J = 7.49 Hz), 4.16-4.22 (q, 2H, J = 7.14 Hz), 3.88-3.92 (m, 8H), 3.86 (s, 3H), 3.79-3.84 (m, 1H), 3.58-3.74 (m, 1H), 1.47-1.48 (d, 3H, J = 7.48 Hz), 1.26-1.30 (t, 3H, J = 7.16 Hz).
126	1732 (C=O stretching of ester), 1685 (C=O stretching of imidazolidinone ring), 1242 (C-O stretching), 1008 (C-O stretching).	7.45-7.48 (m, 4H), 7.41-7.42 (m, 2H), 7.33-7.35 (m, 1H), 6.95-6.99 (m, 2H), 5.06 (s, 2H), 4.71-4.77 (q, 1H , J = 7.46 Hz), 4.18-4.24 (m, 2H), 3.82-3.88 (m, 2H), 3.66-3.70 (m, 1H), 3.51-3.56 (m, 1H), 1.47-1.49 (d, 3H , J = 7.60 Hz), 1.28-1.31 (t, 3H).
127	1732 (C=O stretching of ester), 1693 (C=O stretching of imidazolidinone ring), 1487 (asym. C-NO_2 stretching), 1352 (sym. C-NO_2 stretching), 1272 (C-O stretching), 1197 (C-O stretching), 1047 (C-O stretching).	-

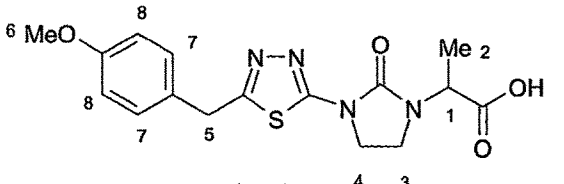
In order to have zinc binding ligands in the targeted molecules, it was proposed to prepare carboxylic acid derivatives. To achieve this, the esters (**109-127**) were hydrolyzed in basic medium to prepare the corresponding acids (**128-146**). Lithium hydroxide or sodium hydroxide was used as the base in aqueous medium in this reaction. In the work up, pH of the reaction mixture was adjusted to 2 in all cases except for compounds (**129, 131-133**). For these compounds the pH was adjusted to 4. The yield of this reaction was around 75 % in most of the cases. Compounds (**135, 139, 140, 142, 146**) were isolated in around 50 % yields while compounds (**138, 144, 145**) were isolated in 95 % yields.

IR spectra of these compounds showed C=O stretching of acid group at around 1750 cm^{-1} and C=O stretching of the amide group at around 1685 cm^{-1}. The O-H stretching vibrations appeared at around 3440 cm^{-1} . The mass spectra showed $(M+H)^+$ peaks for all the compounds. Some of the compounds (**133, 136, 140**) showed the presence of $(M\text{-}COOH)^+$ peak also, as expected. The other peaks observed were $(M+Na)^+$ peaks . In case of compound (**134**), $(M+Na)^+$ peak was obtained as the base peak.

PMR spectrum of compound (**130**) showed aromatic protons at δ 7.56-7.61 (m, 4H), 7.42-7.50 (m, 6H), 7.32-7.36 (m, 1H) and 6.93-6.96 (m, 2H). Among the aliphatic protons, the proton (1-C*H*) was observed at δ 4.56-4.60 as quartet with coupling constant of 7.4 Hz, three protons (2-CH_3) appeared at 1.43-1.45 as doublet, the coupling constant being equal to 7.4 Hz and (5-CH_2) protons were observed at 5.07 as singlet. The multiplets at δ 3.76-3.83 for two protons, 3.65-3.67 for one proton and 3.49-3.50 for one proton accounted for four protons of (3-CH_2) and (4-CH_2).

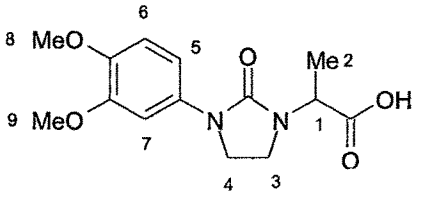


(130)



(137)

The aromatic protons of compound (137) in PMR spectrum appeared at δ 7.20-7.22 as doublet for (7-C*H*) and (8-C*H*) protons were observed at 6.87-6.89 as doublet. The proton (1-C*H*) was observed at δ 4.39-4.44 as quartet (J = 7.4 Hz), the protons (2-CH_3) appeared at 1.36-1.37 as doublet (J = 7.5 Hz), two protons (5-CH_2) were observed at 4.17 as singlet and the singlet at 3.71 was due to (6-OCH_3). The multiplets at δ 4.08-4.13 for one proton, 4.01-4.07 for one proton and 3.60-3.68 for two protons were due to protons (3- CH_2) and (4- CH_2).



(143)

PMR spectrum of compound (143) showed a doublet at δ 7.63-7.64 (J = 2.5 Hz) for the single proton (7-C*H*). The proton at (6-C*H*) was observed at 6.81-6.83 as doublet, coupling constant being equal to 8.72 Hz and the proton at (5-C*H*) appeared at 6.66-6.69 as double doublet with coupling constants equal to 2.5 Hz and 8.7 Hz. The single proton (1-C*H*) appeared at δ 4.63-4.69 as quartet (J = 7.5 Hz), (2-CH_3) protons appeared at 1.46-1.48 as doublet (J = 7.5 Hz) and one of the two methoxy protons (8-OCH_3/9-OCH_3) came at 3.87 as singlet. The other methoxy protons (9-OCH_3/8-OCH_3) were merged with one of the protons of (3-CH_2/4-CH_2). The merged signal was obtained as multiplet at δ 3.81-3.86. The other three protons of (3-CH_2 and 4-CH_2) appeared at δ 3.77-3.79 as multiplet for one proton and 3.50-3.56 as multiplet for two protons.

The spectral data of the acids (128-146) is given in Table-4.

Table 4. Spectral Data of acids (128-146) synthesized in Scheme-10

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
128	1749 (C=O stretching of acid), 1658 (C=O stretching of imidazolidinone ring), 1244 (C-O stretching), 1180 (C-O stretching), 1008 (C-O stretching).	7.42-7.45 (m, 2H), 7.32-7.35 (m, 2H), 6.88-6.94 (m, 4H), 4.95 (s, 2H), 4.60-4.63 (q, 1H, J = 7.52 Hz), 3.80-3.86 (m, 5H), 3.65-3.69 (m, 1H), 3.51-3.55 (m, 1H), 1.45-1.47 (d, 3H, J = 7.48 Hz).

129	3444 (O-H stretching), 1752 (C=O stretching of acid), 1652 (C=O stretching of imidazolidinone ring), 1250 (C-O stretching), 1134 (C-O stretching), 1027 (C-O stretching).	8.57-8.58 (m, 1H), 7.71-7.75 (m, 1H), 7.51-7.52 (m, 1H), 7.42-7.46 (m, 2H), 7.23-7.26 (m, 1H), 6.93-6.96 (m, 2H), 5.17 (s, 2H), 4.60-4.65 (q, 1H, J = 7.39 Hz), 3.77-3.85 (m, 2H), 3.65-3.68 (m, 1H), 3.50-3.54 (m, 1H), 1.45-1.47 (d, 3H, J = 7.48 Hz).
130	3446 (O-H stretching), 1734 (C=O stretching of acid), 1652 (C=O stretching of imidazolidinone ring), 1241 (C-O stretching), 1014 (C-O stretching).	7.56-7.61 (m, 4H), 7.42-7.50 (m, 6H), 7.32-7.36 (m, 1H), 6.93-6.96 (m, 2H), 5.07 (s, 2H), 4.56-4.60 (q, 1H, J = 7.44 Hz), 3.76-3.83 (m, 2H), 3.65-3.67 (m, 1H), 3.49-3.50 (m, 1H), 1.43-1.45 (d, 3H, J = 7.44 Hz).
131	3483 (O-H stretching), 1748 (C=O stretching of acid), 1652 (C=O stretching of imidazolidinone ring), 1248 (C-O stretching), 1075 (C-O stretching).	8.02-8.04 (m, 1H), 7.78-7.82 (m, 1H), 7.62-7.66 (m, 1H), 7.57 (s, 1H), 7.43-7.52 (m, 3H), 7.01-7.04 (m, 2H), 5.56 (s, 2H), 4.64-4.70 (q, 1H, J = 7.50 Hz), 3.82-3.90 (m, 2H), 3.68-3.72 (m, 1H), 3.52-3.56 (m, 1H), 2.90-2.99 (m, 2H), 2.24-2.28 (m, 1H), 1.47-1.49 (d, 3H, J = 7.52 Hz), 0.98 -1.00 (d, 6H).
132	3446 (O-H stretching), 1730 (C=O stretching of acid), 1637 (C=O stretching of imidazolidinone ring), 1242 (C-O stretching).	8.25-8.27 (m, 1H), 7.99-8.03 (m, 2H), 7.84-7.88 (m, 1H), 7.67 (s, 1H), 7.51-7.55 (m, 2H), 7.08-7.11 (m, 2H), 5.74 (s, 2H), 4.58-4.62 (q, 1H, J = 7.48 Hz), 3.81-3.91 (m, 2H), 3.65-3.71 (m, 1H), 3.51-3.58 (m, 1H), 3.42-3.46 (q, 2H, J = 7.6 Hz), 1.52-1.55 (t, 3H, J = 7.6 Hz), 1.46-1.48 (d, 3H, J = 7.5 Hz).
133	3442 (O-H stretching), 1751 (C=O stretching of acid), 1652 (C=O stretching of imidazolidinone ring), 1237 (C-O stretching), 1181 (C-O stretching), 1076 (C-O stretching).	8.36-8.38 (m, 2H), 8.15-8.17 (m, 2H), 8.05 (s, 1H), 7.97-7.99 (m, 1H), 7.76-7.80 (m, 2H), 7.46-7.55 (m, 4H), 7.02-7.06 (m, 2H), 5.57 (s, 2H), 4.66-4.71 (q, 1H), 3.81-3.86 (m, 2H), 3.60-3.66 (m, 1H), 3.50-3.55 (m, 1H), 1.49-1.51 (d, 3H).
134	1728 (C=O stretching of acid), 1635 (C=O stretching of imidazolidinone ring), 1276 (C-O stretching), 1170 (C-O stretching).	7.84-7.87 (m, 1H), 7.84-7.91 (m, 2H), 7.59-7.60 (m, 1H), 7.54-7.57 (m, 2H), 7.45-7.53 (m, 3H), 7.00-7.03 (m, 2H), 5.47 (s, 2H), 4.62-4.66 (q, 1H, J = 7.52 Hz), 3.78-3.88 (m, 2H), 3.65-3.71 (m, 1H), 3.50-3.56 (m, 1H), 1.47-1.48 (d, 2H, J = 7.48 Hz).

135	-	7.24-7.32 (m, 5H), 4.67-4.70 (q, 1H), 4.31 (s, 2H), 4.19-4.23 (m, 1H), 4.09-4.16 (m, 1H), 3.72-3.78 (m, 1H), 3.60-3.64 (m, 1H), 1.49-1.51 (d, 3H).
136	3446 (O-H stretching), 1746 (C=O stretching of acid), 1687 (C=O stretching of imidazolidinone ring), 1276 (C-O stretching), 1174 (C-O stretching), 1028 (C-O stretching).	8.07-8.09 (d, 2H, J = 7.92 Hz), 7.53-7.56 (d, 2H, J = 7.89 Hz), 4.44-4.52 (q, 1H, J = 7.43 Hz), 4.05-4.17 (m, 2H), 3.80 (s, 3H), 3.63-3.68 (m, 2H), 1.40-1.43 (d, 3H, J = 7.44 Hz).
137	-	7.20-7.22 (d, 2H), 6.87-6.89 (d, 2H), 4.39-4.44 (q, 1H), 4.17 (s, 2H), 4.08-4.13 (m, 1H), 4.01-4.07 (m, 1H), 3.71 (s, 3H), 3.60-3.68 (m, 2H), 1.36-1.37 (d, 3H).
138	1745 (C=O stretching of acid), 1718 (C=O stretching of imidazolidinone ring).	7.48-7.50 (m, 2H), 7.26-7.30 (m, 8H), 4.62-4.66 (q, 1H, *J* = 7.37 Hz), 4.26-4.31 (m, 1H), 4.17-4.20 (m, 1H), 3.76-3.81 (m, 1H), 3.67-3.70 (m, 1H), 1.52-1.54 (d, 3H, *J* = 7.40 Hz).
139	-	7.76-7.79 (d, 2H, *J* = 7.98 Hz), 7.47 (s, 1H), 7.19-7.22 (d, 2H, *J* = 7.95 Hz), 4.42-4.47 (q, 1H, *J* = 7.38 Hz), 4.05-4.18 (m, 2H), 3.60-3.67 (m, 2H), 2.31 (s, 3H), 1.38-1.41 (d, 3H, *J* = 7.38 Hz).
140	-	7.42-7.44 (d, 2H), 7.26-7.28 (d, 2H), 7.12-7.14 (d, 2H), 6.78-6.80 (d, 2H), 4.68-4.72 (q, 1H, *J* = 6.84 Hz), 3.99 (s, 2H), 3.80-3.84 (m, 2H), 3.77 (s, 3H), 3.62-3.66 (m, 1H), 3.51-3.55 (m, 1H), 1.50-1.52 (d, 3H, *J* = 6.72 Hz).
141	1753 (C=O stretching of acid), 1658 (C=O stretching of imidazolidinone ring).	7.52-7.56 (m, 2H), 7.31-7.35 (m, 2H), 7.04-7.07 (m, 1H), 4.69-4.74 (q, 1H, *J* = 7.49 Hz), 3.85-3.92 (m, 2H), 3.62-3.70 (m, 1H), 3.53-3.59 (m, 1H), 1.51-1.54 (d, 3H, *J* = 7.6 Hz).
142	1741 (C=O stretching of acid), 1654 (C=O stretching of imidazolidinone ring), 1251 (C-O stretching), 1178 (C-O stretching), 1033 (C-O stretching).	12.8 (bs, 1H), 7.48-7.50 (d, 2H), 6.92-6.95 (d, 2H), 4.34-4.38 (q, 1H, *J* = 7.48 Hz), 3.78-3.81 (m, 1H), 3.71-3.76 (m, 1H), 3.70 (s, 3H), 3.43-3.49 (m, 2H), 1.34-1.36 (d, 3H, *J* = 7.4 Hz).

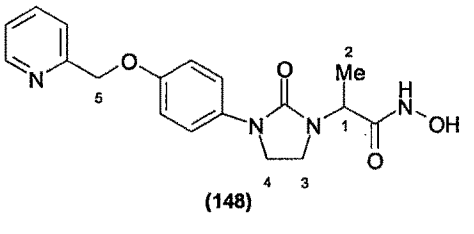
143	1745 (C=O stretching of acid), 1652 (C=O stretching of imidazolidinone ring), 1284 (C-O stretching), 1193 (C-O stretching), 1024 (C-O stretching).	7.63-7.64 (d, 1H, *J* = 2.5 Hz), 6.81-6.83 (d, 1H, *J* = 8.7 Hz), 6.66-6.69 (dd, 1H, *J* = 2.5 Hz & 8.7 Hz), 4.63-4.69 (q, 1H, *J* = 7.50 Hz), 3.87 (s, 3H), 3.81-3.86 (m, 4H), 3.77-3.79 (m, 1H), 3.50-3.56 (m, 2H), 1.46-1.48 (d, 3H, *J* = 7.52 Hz).
144	1753 (C=O stretching of acid), 1654 (C=O stretching of imidazolidinone ring), 1236 (C-O stretching), 1124 (C-O stretching).	6.80 (s, 2H), 4.68-4.74 (q, 1H, *J* = 7.49 Hz), 3.88-3.92 (m, 8H), 3.86 (s, 3H), 3.81-3.83 (m, 1H), 3.67-3.76 (m, 1H), 1.50 -1.52 (d, 3H, *J* = 7.52 Hz).
145	1751 (C=O stretching of acid), 1666 (C=O stretching of imidazolidinone ring), 1255 (C-O stretching), 1184 (C-O stretching), 1053 (C-O stretching).	7.43-7.58 (m, 4H), 7.36-7.41 (m, 2H), 7.31-7.33 (m, 1H), 7.03-7.06 (m, 2H), 5.04 (s, 2H), 4.62-4.68 (q, 1H, *J* = 7.48 Hz), 3.90-3.98 (m, 2H), 3.62-3.66 (m, 1H), 3.54-3.58 (m, 1H), 1.51-1.53 (d, 3H, *J* = 7.48 Hz).
146	1724 (C=O stretching of acid), 1695 (C=O stretching of imidazolidinone ring), 1433 (asym. C-NO_2 stretching), 1352 (sym. C-NO_2 stretching), 1251 (C-O stretching).	8.22-8.24 (d, 2H), 7.61-7.66 (d, 2H), 7.46-7.48 (d, 2H), 6.92-6.94 (d, 2H), 5.16 (s, 2H), 4.64-4.69 (q, 1H, *J* = 7.49 Hz), 3.80-3.88 (m, 2H), 3.73-3.78 (m, 1H), 3.49-3.55 (m, 1H), 1.46-1.48 (d, 3H, *J* = 7.52 Hz).

To prepare hydroxamates (**147-164**) as zinc binding ligands the esters (**109-127**) were also reacted with hydroxylamine hydrochloride. It was observed that some of the esters (**111, 115-120**) were not freely soluble in methanol. In those cases, the reaction mixture was heated to reflux until the completion of the reaction. After the reaction was over, the reaction mixture was filtered to remove potassium chloride, a by-product of the reaction, diluted with water and neutralized by adding 10 % hydrochloric acid to adjust the pH to 5.5-6.0 in order to obtain the desired hydroxamates.

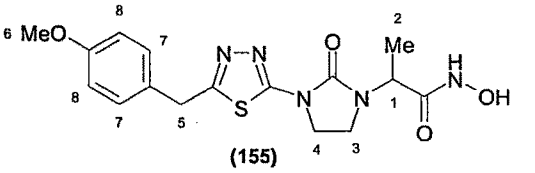
It was observed that a milder base like pyridine or potassium carbonate did not yield the required hydroxamates even after refluxing the reaction mixture overnight. The use of strong base caused hydrolysis of esters to afford mixtures of hydroxamates and free acids, which were difficult to purify as they were inseparable on TLC. The problem was solved by taking excess of hydroxylamine hydrochloride (about 100 times more than the esters on molar basis) to obtain pure hydroxamates.

IR spectra of these hydroxamates showed a broad peak at around 3440 cm^{-1} for the free OH group. The peaks due to the stretching vibrations of C=O group of imidazolidinone ring and the C=O group of hydroxamic acid merged with each other and came at around 1680 cm^{-1}. PMR spectra of some of the hydroxamic acids (**159-164**) showed two broad singlets at around δ 8.6 and 10.6 due to the protons of N*H* and O*H*, respectively. The mass spectra of all the hydroxamic acids showed $(M-14)^+$ as the base peak. Probably, in presence of moisture inside the ionizer, the hydroxamic acids got degraded into the corresponding carboxylic acids. Hence, the base peaks were that of protonated carboxylic acids. Apart from this peak, all the hydroxamic acids showed $(M-CONHOH)^+$ peak as expected. $(M+H)^+$ peaks were obtained for compounds (**156, 157**) and $(M-H)^+$ peak for compound (**152**). Compounds (**147, 148**) showed the presence of $(M+NH_4)^+$ peaks.

PMR spectrum of compound (**148**) showed aromatic protons at δ 8.58-8.59 (m, 1H), 7.71-7.75 (m, 1H), 7.51-7.53 (m, 1H), 7.41-7.44 (m, 2H), 7.23-7.26 (m, 1H) and 6.94-6.96 (m, 2H). The proton (1-C*H*) appeared at δ 4.61-4.65 and the protons (2-CH_3) appeared at δ 1.45-1.47 as doublet. The multiplets at δ 3.77-3.90 for two protons, 3.64-3.68 for one proton and 3.51-3.55 for one proton were due to (3-CH_2) and (4-CH_2). The methylene protons (5-CH_2) appeared as singlet at δ 5.17.



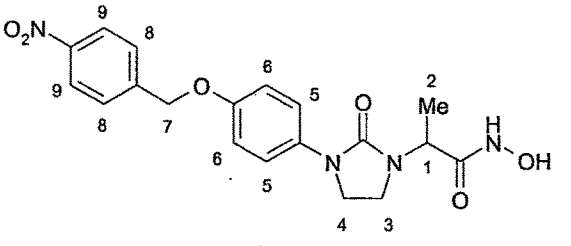
(148)



(155)

In the PMR spectrum of compound (**155**), it was observed that the (7-C*H*) protons appeared at δ 7.37-7.44 as doublet and (8-C*H*) protons appeared at 6.73-6.88 as doublet. The single proton (1-C*H*) was obtained as quartet at δ 4.27-4.32 and the three protons (2-CH_3) were obtained as doublet at 1.65-1.67. The protons of the methoxy group (6-OCH_3) were observed at δ 3.71 as a singlet. The other singlet obtained at δ 4.40 was due to (5-CH_2). The protons (3-CH_2) and (4-CH_2) came as multiplets at δ 4.27-4.32 for one proton, 4.22-4.26 for one proton and 3.53-3.63 for two protons.

The aromatic protons of compound (**164**) in the PMR spectrum appeared at δ 8.23-8.25 (d, 2H; 9-C*H*), 7.68-7.70 (d, 2H; 8-C*H*), 7.44-7.46 (d, 2H; 5-C*H*) and 6.97-7.00 (d, 2H; 6-C*H*). The proton (1-C*H*) was seen at δ 4.26-4.30 as quartet, the coupling constant being equal to 7.2 Hz and the protons (2-CH_3) were observed at 1.25-1.27 as doublet, the coupling constant being equal to 7.2 Hz. The multiplets at δ 3.70-3.77 and 3.54-3.60 were due to (3-CH_2 and 4-CH_2). A singlet at δ 5.23 was observed for (7-CH_2).



(164)

Detailed spectral data of the hydroxamates (**147-164**) is given in Table-5.

Table 5. Spectral Data of hydroxamic acids (147-164) synthesized in Scheme-10

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
147	3448 (O-H stretching), 1695 (C=O stretching), 1245 (C-O stretching), 1175 (C-O stretching), 1007 (C-O stretching).	7.41-7.45 (m, 2H), 7.33-7.35 (m, 2H), 6.89-6.94 (m, 4H), 4.96 (s, 2H), 4.63-4.66 (q, 1H, *J* = 7.48 Hz), 3.79-3.82 (m, 5H), 3.65-3.69 (m, 1H), 3.48-3.52 (m, 1H), 1.46-1.48 (d, 3H, *J* = 7.56 Hz).
148	3448 (O-H stretching), 1684 (C=O stretching), 1248 (C-O stretching), 1056 (C-O stretching).	8.58-8.59 (m, 1H), 7.71-7.75 (m, 1H), 7.51-7.53 (m, 1H), 7.41-7.44 (m, 2H), 7.23-7.26 (m, 1H), 6.94-6.96 (m, 2H), 5.17 (s, 2H), 4.61-4.65 (q, 1H), 3.77-3.90 (m, 2H), 3.64-3.68 (m, 1H), 3.51-3.55 (m, 1H), 1.45-1.47 (d, 3H).
149	3493 (O-H stretching), 1684 (C=O stretching), 1242 (C-O stretching), 1014 (C-O stretching).	7.59-7.62 (m, 4H), 7.49-7.51 (m, 2H), 7.42-7.47 (m, 4H), 7.33-7.36 (m, 1H), 6.95-6.97 (m, 2H), 5.09 (s, 2H), 4.62-4.66 (q, 1H, *J* = 7.48 Hz), 3.79-3.86 (m, 2H), 3.66-3.68 (m, 1H), 3.52-3.56 (m, 1H), 1.46-1.48 (d, 3H, *J* = 7.48 Hz).
150	3440 (O-H stretching), 1684 (C=O stretching), 1623 (C=N stretching), 1241 (C-O stretching), 1076 (C-O stretching).	8.17-8.19 (m, 1H), 7.92-7.94 (m, 1H), 7.70-7.73 (m, 1H), 7.52-7.55 (m, 1H), 7.39-7.45 (m, 3H), 6.98-7.02 (m, 2H), 5.49 (s, 2H), 4.71-4.68 (q, 1H, *J* = 7.28 Hz), 3.88-3.92 (m, 1H), 3.80-3.84 (m, 1H, 3.67-3.70 (m, 1H), 3.52-3.57 (m, 1H), 2.86-2.87 (d, 2H, *J* = 6.48 Hz), 2.16-2.21 (m, 1H), 1.50-1.52 (d, 3H, *J* = 7.32 Hz), 0.95-0.96 (d, 6H).

151	3444 (O-H stretching), 1684 (C=O stretching), 1254 (C-O stretching), 1018 (C-O stretching).	8.04-8.06 (m, 1H), 7.94-7.96 (m, 1H), 7.68-7.72 (m, 1H), 7.48-7.54 (m, 4H), 7.00-7.21 (m, 2H), 5.47 (s, 2H), 4.53-4.57 (q, 1H), 3.81-3.77 (m, 2H), 3.65-3.68 (m, 2H), 2.96-3.01 (q, 2H), 1.36-1.40 (m, 6H).
152	3446 (O-H stretching), 1684 (C=O stretching), 1277 (C-O stretching).	8.03-8.05 (m, 1H), 7.83-7.89 (m, 2H), 7.43-7.58 (m, 6H), 6.98-7.01 (m, 2H), 5.44 (s, 2H), 4.57-4.61 (q, 1H), 3.80-3.83 (m, 2H), 3.64-3.68 (m, 2H), 1.44-1.45 (d, 3H).
153	3244 (N-H stretching), 1660 (C=O stretching).	10.65 (bs, 1H), 9.06 (bs, 1H), 7.24-7.76 (m, 5H), 4.30-4.36 (m, 3H), 3.96-4.07 (m, 2H), 3.59-3.67 (m, 2H), 1.22-1.25 (d, 3H).
154	3446 (O-H stretching), 3142 (N-H stretching), 1687 (C=O stretching), 1602 (C=N stretching), 1255 (C-O stretching), 1180 (C-O stretching).	7.79-7.82 (d, 2H, J = 8.79 Hz), 7.03-7.06 (d, 2H, J = 8.82 Hz), 4.45-4.50 (q, 1H, J = 7.30 Hz), 4.07-4.18 (m, 2H), 3.80 (s, 3H), 3.59-3.64 (m, 2H), 1.32-1.34 (d, 3H, J = 7.26 Hz).
155	3421 (O-H stretching), 1652 (C=O stretching), 1247 (C-O stretching), 1176 (C-O stretching), 1030 (C-O stretching).	7.37-7.44 (d, 2H), 6.73-6.88 (d, 2H), 4.61-4.67 (q, 1H), 4.40 (s, 2H), 4.27-4.32 (m, 1H), 4.22-4.26 (m, 1H), 3.71 (s, 3H), 3.53-3.63 (m, 2H), 1.65-1.67 (d, 3H).
156	3423 (O-H stretching), 1697 (C=O stretching).	7.49-7.51 (m, 2H), 7.20-7.25 (m, 8H), 5.25-5.29 (q, 1H, J = 7.27 Hz), 4.34-4.37 (m, 1H), 4.01-4.04 (m, 1H), 3.32-3.35 (m, 2H), 2.04-2.10 (m, 2H), 1.25-1.27 (d, 3H, J = 7.30Hz).
157	3215 (N-H stretching), 1683 (C=O stretching).	7.77-7.79 (d, 2H), 7.48 (s, 1H), 7.20-7.22 (d, 2H), 4.53-4.58 (q, 1H), 4.32-4.37 (m, 1H), 4.12-4.20 (m, 1H), 3.65-3.80 (m, 2H), 2.30 (s, 3H), 1.39-1.41 (d, 3H).
158	-	7.52-7.55 (d, 2H), 7.33-7.35 (d, 2H), 7.21-7.23 (d, 2H), 6.85-6.87 (d, 2H), 4.65-4.69 (q, 1H, J = 7.40 Hz), 4.06 (s, 2H), 3.94-3.96 (m, 1H), 3.83-3.86 (m, 4H), 3.75-3.78 (m, 1H), 3.61-3.64 (m, 1H), 1.49-1.51 (d, 3H, J =7.36 Hz).
159	3232 (N-H stretching), 1654 (C=O stretching).	10.70 (bs, 1H), 8.92 (bs, 1H), 7.60-7.62 (m, 2H), 7.35-7.39 (m, 2H), 7.03-7.07 (m, 1H), 4.37-4.42 (q, 1H, J = 7.18 Hz), 3.80-3.89 (m, 2H), 3.63-3.69 (m, 1H), 3.55-3.61 (m, 1H), 1.34-1.35 (d, 3H, J = 7.20 Hz).
160	3228 (N-H stretching), 1654 (C=O stretching), 1242 (C-O stretching), 1022 (C-O stretching).	10.40 (bs, 1H), 8.70 (bs, 1H), 7.41-7.43 (d, 2H), 6.85-6.87 (d, 2H), 4.50-4.54 (q, 1H), 3.81-3.87 (m, 2H), 3.78 (s, 3H), 3.70-3.75 (m, 2H), 1.40-1.42 (d, 3H).
161	3234 (N-H stretching), 1666 (C=O stretching), 1250 (C-O stretching), 1029 (C-O stretching).	10.10 (bs, 1H), 8.62 (bs, 1H), 7.26-7.47 (m, 1H), 6.66-6.80 (m, 2H), 4.50-4.54 (q, 1H), 3.53-3.87 (m, 10H), 1.40-1.42 (d, 3H).

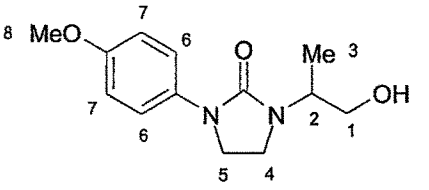
162	3259 (N-H stretching), 1660 (C=O stretching), 1589, 1514, 1433, 1276 (C-O stretching), 1128 (C-O stretching), 1004 (C-O stretching).	10.60 (bs, 1H), 8.68 (bs, 1H), 6.85 (s, 2H), 4.50-4.55 (q, 1H), 3.69-3.89 (m, 11H), 3.45-3.58 (m, 2H), 1.41-1.42 (d, 3H).
163	3197 (N-H stretching), 1664 (C=O stretching), 1260 (C-O stretching), 1039 (C-O stretching).	10.70 (bs, 1H), 8.90 (bs, 1H), 7.48-7.52 (m, 4H), 7.42-7.46 (m, 2H), 7.35-7.39 (m, 1H), 7.02-7.04 (m, 2H), 4.35-4.40 (q, 1H, *J* = 7.08 Hz), 3.78-3.87 (m, 2H), 3.62-3.68 (m, 1H), 3.51-3.58 (m, 1H), 1.32-1.34 (d, 3H, *J* = 7.16 Hz).
164	3232 (N-H stretching), 1670 (C=O stretching), 1515, 1483, 1436 (asym. C-NO_2 stretching), 1346 (sym. C-NO_2 stretching), 1249 (C-O stretching), 1058 (C-O stretching).	10.60 (bs, 1H), 8.80 (bs, 1H), 8.23-8.25 (d, 2H), 7.68-7.70 (d, 2H), 7.44-7.46 (d, 2H), 6.97-7.00 (d, 2H), 5.23 (s, 2H), 4.26-4.30 (q, 1H, *J* = 7.16 Hz), 3.70-3.77 (m, 2H), 3.54-3.60 (m, 2H), 1.25-1.27 (d, 3H, *J* = 7.20 Hz).

Thiol group possessing compounds were synthesized as per Scheme-12. The starting materials used were the ester derivatives (**110, 123, 125-127**) that were prepared in Scheme-10. In the first step the esters were reduced to the corresponding alcohols using sodium borohydride. As discussed earlier, sodium borohydride not being a reagent of choice for this reaction, the reaction takes longer time than usual.

IR spectra of these compounds, showed broad strong peaks at around 3340 cm^{-1} for the stretching of O-H of primary alcohols. The C=O stretching of the imidazolidinone ring was observed at around 1680 cm^{-1}. PMR spectra of these compounds showed the presence of CH_2-OH protons at around δ 3.6 ppm as multiplet.

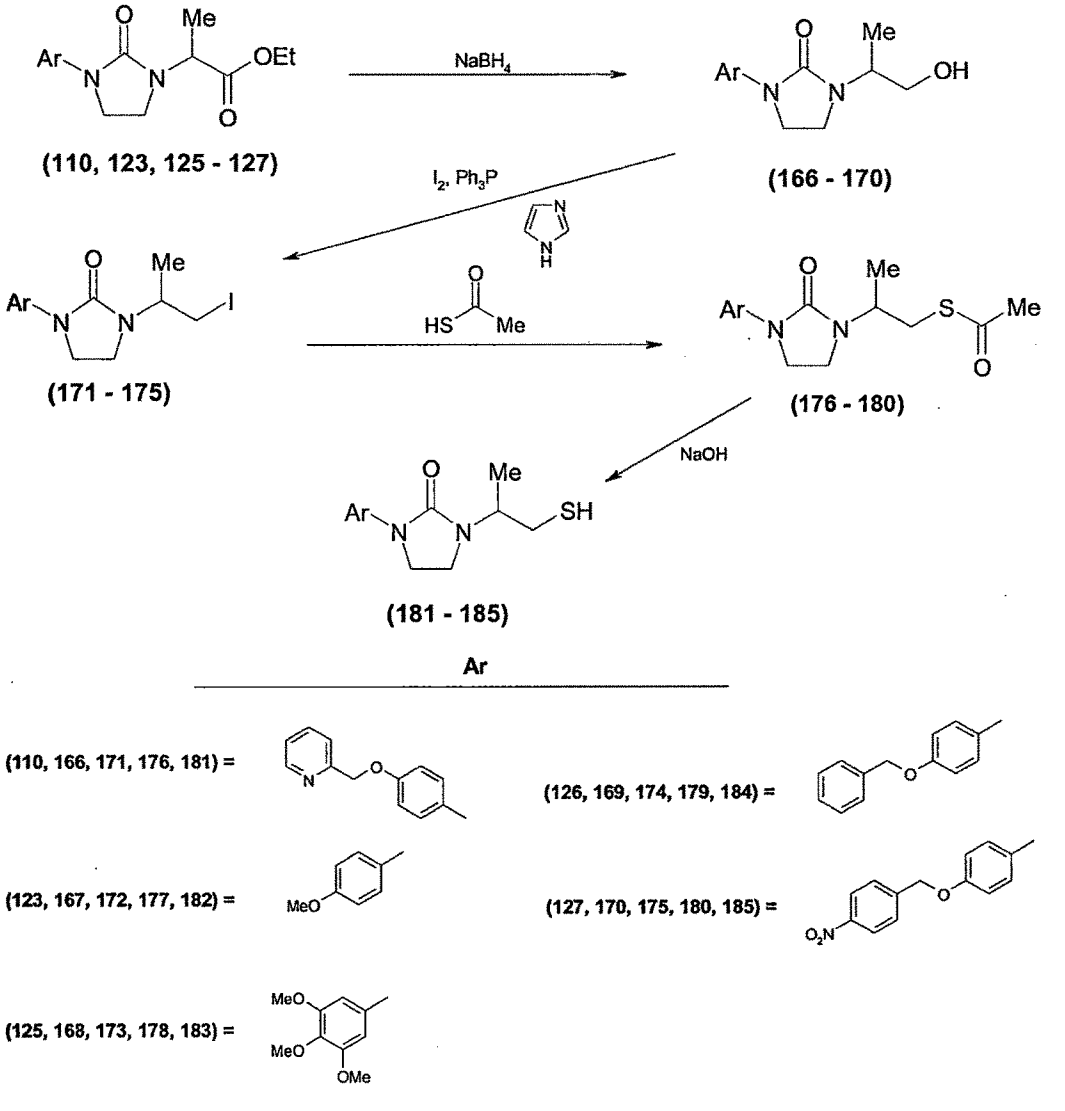
IR spectrum of compound (**166**) showed the O-H stretching vibrations at 3371 cm^{-1} and C=O stretchings of the imidazolidinone ring were observed at 1664 cm^{-1}. The C-O stretching vibrations of the ether group of the compound were observed at 1251 (aryl C-O) and 1033 cm^{-1} (alkyl C-O).

IR spectrum of compound (**167**) showed O-H stretching of the alcohol at 3358 and C=O stretching at 1664 cm^{-1}. The C-O stretching of the ether moiety appeared at 1251 and 1033 cm^{-1}. PMR spectrum of the compound (**167**) showed aromatic protons at δ 7.38-7.42 (d, 2H) and 6.86-6.89 (d, 2H) for (6-C*H*) and (7-C*H*), respectively. The single proton (2-C*H*) appeared at δ 4.00-4.05 as multiplet and the (3-CH_3) protons were



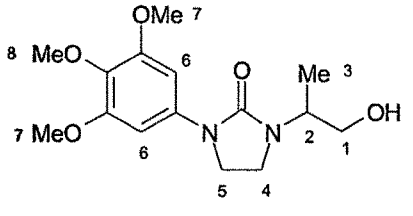
(167)

observed at as doublet at δ 1.18-1.20. The methylene protons (1-CH_2) got merged with (8-OCH_3) as multiplet at δ 3.79-3.81. The other multiplets at δ 3.74-3.78 for one proton, 3.70-3.72 for one proton and 3.50-3.64 for two protons accounted for four protons (3-CH_2) and (4-CH_2).

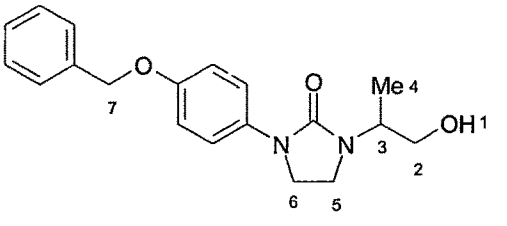


Scheme-12

The O-H stretching vibration of compound (**168**) was observed at 3450 cm^{-1} in its IR spectrum. The C=O stretching of imidazolidinone ring appeared at 1687 and the C-O stretching of ether group came at 1238, 1128 and 1028 cm^{-1}. The PMR spectrum of compound (**168**) showed the presence of aromatic protons (6-C*H*) at δ 6.81 as singlet. The methoxy protons (7-OCH_3) were observed at δ 3.86 as singlet. The other methoxy protons (8-OCH_3) were merged with two protons of imidazolidinone ring (4/5-CH_2) and came as multiplet at δ 3.79-3.81. The other two ring protons (4/5-CH_2) were observed at δ 3.71-3.75 as multiplet (one proton) and 3.61-3.66 as multiplet (one proton). The multiplet at δ 3.46-3.54 accounted for (1-CH_2) and the doublet at 1.19-1.20 appeared due to the methyl protons (3-CH_3). The single proton (2-C*H*) was observed at δ 4.20-4.25 as multiplet.



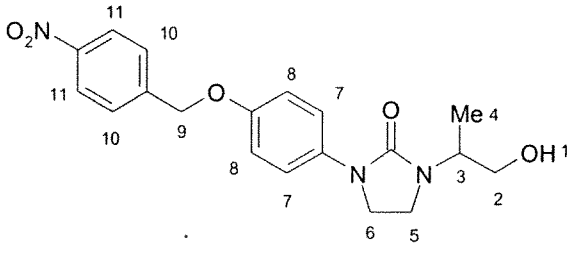
(**168**)



(**169**)

The IR spectrum of compound (**169**) showed O-H stretching at 3373 cm^{-1} and C=O stretching at 1662 cm^{-1}. The C-O stretching peaks due to the presence of ether group was observed at 1245 and 1053 cm^{-1}. The PMR spectrum of compound (**169**) showed the presence of aromatic protons at δ 7.43-7.46 (m, 4H), 7.36-7.40 (m, 2H), 7.30-7.33 (m, 1H) and 6.95-6.98 (m, 2H). The alcoholic proton (1-O*H*) was observed at 4.74 as broad singlet. The multiplet at δ 3.70-3.74 was due to (5/6-CH_2). Another multiplet at δ 3.39-3.42 accounted for four protons (2-CH_2 and 5/6-CH_2). The methylene protons of benzyloxy group (7-CH_2) were observed at δ 5.06 as singlet. The methyl protons (4-CH_3) appeared at δ 1.03-1.05 as doublet and the proton of (3-C*H*) appeared at 3.86-3.91 as multiplet.

IR spectrum of compound (**170**) showed O-H stretching at 3411 cm^{-1} and the C=O stretching at 1685 cm^{-1}. The asymmetric and symmetric C-NO_2 stretchings were observed at 1433 and 1350 cm^{-1}, respectively. The C-O stretching of the ether group appeared at 1247 and 1026 cm^{-1}. PMR spectrum of this compound showed aromatic protons at δ 8.22-8.24 (d, 2H, J = 8.60 Hz; 11-C*H*), 7.62-7.64 (d, 2H, J = 8.48 Hz; 10-C*H*), 7.45-7.47 (d, 2H, J = 9.00 Hz; 7-C*H*) and 6.92-6.94 (d, 2H, J = 9.00 Hz; 8-C*H*).



(170)

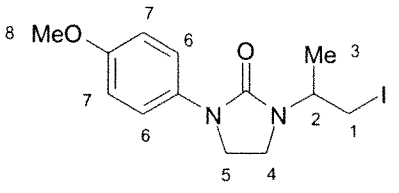
The singlet at δ 5.17 came due to (9-C*H*$_2$). The multiplets at δ 3.73-3.82 and 3.44-3.62 accounted for (5/6-C*H*$_2$) and (2-C*H*$_2$ and 6/5-C*H*$_2$), respectively. The alcoholic proton appeared as broad singlet at δ 4.26. Other signals were at δ 1.15-1.17 (d, 3H; 4-C*H*$_3$) and 4.05-4.10 (m, 1H; 3-C*H*).

Alcohols were converted to thiols in a one step process by Frank *et al* [152]. Their method involved the synthesis of isothiouronium salts by reacting alcohols with thiourea in presence of hydrobromic acid. Without isolating, the isothiouronium salts were hydrolyzed to the corresponding thiols by sodium hydroxide. According to the reported[152] procedure, alcohols (**166-170**) were refluxed with thiourea in presence of hydrobromic acid for nine hours. The reaction mixture showed formation of many impurities on TLC and the subsequent hydrolysis product could not be identified in the reaction mixture among so many impurities. This reaction did not work, probably due to the cleavage of imidazolidinone ring in presence of acid.

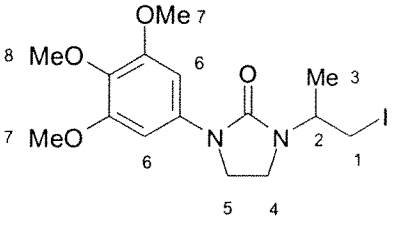
Hence, the alcohols (**166-170**) were converted to the corresponding iodo compounds (**171-175**) as described in the literature[153]. The alcohols were dissolved in DCM and iodine, triphenyl phosphine and imidazole were added to the above solution at RT. The reaction got completed within 1 hour.

Compound (**171**) could not be purified from the reaction mixture containing triphenylphosphine oxide, by column chromatography or crystallization, as the desired product and the side product (i.e. triphenylphosphine oxide) had the same R_f value in three mobile phases namely, ethyl acetate in n-hexane, acetone in n-hexane and pure chloroform. Hence, this impure compound could not be purified and used as such in the next step. Other iodo derivatives (**172-175**) could be isolated in pure form.

The IR spectrum of compound (**172**) showed C=O stretching at 1681 and C-O stretchings at 1244, 1157 and 1029 cm^{-1}. The PMR spectrum showed aromatic protons as doublets at δ 7.42-7.45 and 6.87-6.89 for (6-C*H*) and (7-C*H*), respectively. The multiplet



(172)

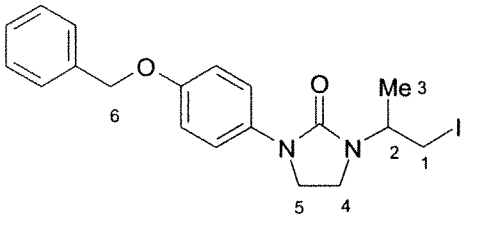


(173)

at δ 3.57-3.68 appeared due to (4/5-C*H*$_2$), the multiplets at δ 3.51-3.55 for one proton and 3.45-3.49 for one proton accounted for (4/5-C*H*$_2$). The signal due to the methoxy protons (8-OC*H*$_3$) merged with that of the methylene protons (1-C*H*$_2$) which appeared at δ 3.81-3.87 as multiplet. The methyl protons (3-C*H*$_3$) appeared at δ 1.31-1.32 as doublet. Methine proton (2-C*H*) was observed at δ 4.17-4.22 as multiplet.

The IR spectrum of compound (**173**) showed peaks at 1238, 1122 and 1002 cm^{-1} for the C-O stretching of the ether linkage present in the compound. The C=O stretching of imidazolidinone ring appeared at 1701 cm^{-1}. PMR spectrum of this compound (**173**) showed the presence of (3-C*H*$_3$) at δ 1.34-1.36 as doublet and (2-C*H*) at 4.19-4.21 as multiplet. The methylene protons (1-C*H*$_2$) merged with the signals of methoxy protons (7-OC*H*$_3$ and 8-OC*H*$_3$). The signals for these protons were observed at δ 3.86-3.89 as multiplet for seven protons and 3.81-3.84 as multiplet for four protons. Four protons of the imidazolidinone ring (4-C*H*$_2$) and (5-C*H*$_2$) appeared as multiplets at δ 3.46-3.56 for two protons, 3.35-3.39 for one proton and 3.25-3.30 for one proton. The aromatic protons (6-C*H*) appeared as singlet at δ 6.85.

The IR spectrum of compound (**174**) showed a strong peak at 1689 cm^{-1} due to C=O stretching of the imidazolidinone ring. The C-O stretching peaks of ether group



(174)

were observed at 1251, 1190 and 1045 cm^{-1}. PMR spectrum of this compound showed aromatic protons at δ 7.31-7.45 (m, 7H) and 6.93-6.97 (m, 2H). The methylene protons of benzyloxy group (6-C*H*$_2$) were observed at δ 5.04 as singlet. Multiplets at δ 3.75-3.83 and 3.48-3.56 appeared due to (1-C*H*$_2$) and (4/5-CH$_2$). The other two protons (5/4-

CH_2) of the ring came as multiplets at δ 3.38-3.46 (one proton) and 3.32-3.36 (one proton). The methine proton was observed at δ 4.16-4.21 as multiplet. The methyl protons (3-CH_3) appeared at δ 1.32-1.36 as doublet.

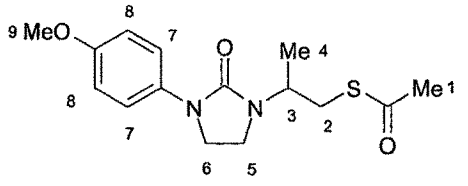
IR spectrum of compound (**175**) showed C=O stretching at 1687 cm^{-1} and C-O stretching at 1238, 1186 and 1028 cm^{-1}. Two strong peaks at 1433 and 1346 cm^{-1} appeared due to asymmetric and symmetric stretchings of nitro group.

The thioacetate derivatives (**176-180**) were prepared from iodo derivatives (**171-175**) using a biphasic system. Chloroform was used as the organic phase and tetrabutyl ammonium bromide was used as the phase transfer catalyst (PTC). Thiolacetic acid was dissolved in aqueous sodium bicarbonate solution. Prior to this, the reaction was tried in different solvents like THF, dioxane and DMF taking potassium carbonate as the base. Heating the reaction mixture even for overnight did not result into formation of the product. Using pure thiolacetic acid as solvent as potassium carbonate as base did not yield satisfactory results under various temperature conditions. The reaction was also tried in microwave oven (Sharp, 1100 W) in DMF in presence of potassium carbonate yielding unsatisfactory results.

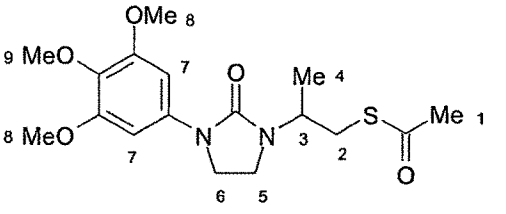
IR spectra of these thioacetates revealed that the stretching vibrations of C=O group of the imidazolidinone ring and C=O of thioacetate group merged together and appeared at 1685 cm^{-1}. PMR spectra of these compounds showed a characteristic singlet for three protons at δ 2.3 for S-C(=O)CH_3 group along with the other signals of the protons in the molecules.

The TLC of compound (**176**) showed a single spot in 50 % ethyl acetate in n-hexane as mobile phase. But in a more non-polar system, 20 % ethyl acetate in n-hexane when the same TLC was run for three consecutive times, it showed two distinct products. One had R_f value of 0.48 and another 0.52. The lower spot matched with that of triphenyl phosphine oxide. The compound was isolated as oil and no efforts were made to purify it.

IR spectrum of compound (**177**) showed a strong peak at 1685 cm^{-1} due to the stretching vibrations of C=O group. Both the C=O groups of imidazolidinone ring and



(177)

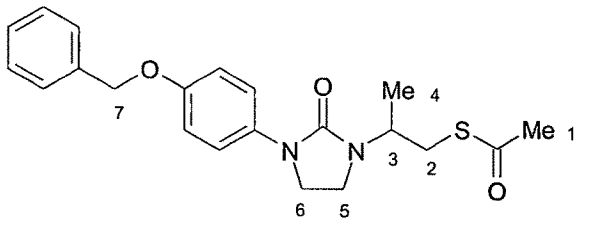


(178)

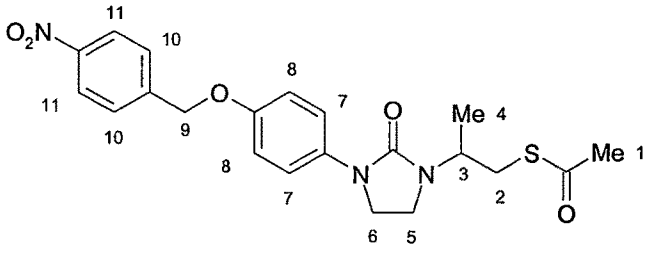
the thioacetate moiety merged together. The peaks at 1253 and 1029 cm^{-1} appeared due to the stretching vibrations of C-O group. PMR spectrum of this compound (177) showed aromatic protons at δ 7.41-7.45 (d, 2H) and 6.85-6.89 (d, 2H) for (7-C*H*) and (8-C*H*), respectively. The methoxy protons (9-OCH_3) merged with the imidazolidinone ring protons (5/6-CH_2) and appeared at δ 3.74-3.83 as multiplet. The other two ring protons (6/5-CH_2) were observed at 3.35-3.45 as multiplet. The multiplets at δ 4.16-4.22 and 3.09-3.15 were due to (3-C*H*) and (2-CH_2), respectively. The methyl protons (1-CH_3) and (4-CH_3) were observed at δ 2.33 as singlet and 1.31-1.32 as doublet, respectively.

IR spectrum of compound (178) showed a strong peak at 1685 cm^{-1} due to the stretching vibrations of C=O group. The C-O group stretchings were observed at 1232, 1128 and 1006 cm^{-1}. PMR of this compound showed methoxy protons (8-OCH_3) at δ 3.86 as singlet. The signal due to the third methoxy protons was merged with that of the ring protons (5/6-CH_2) and was observed as multiplet at δ 3.74-3.83. The multiplets at δ 4.16-4.22, 3.35-3.45 and 3.09-3.15 appeared due to (3-C*H*), (5/6-CH_2) and (2-CH_2), respectively. The methyl protons (1-CH_3) and (4-CH_3) were observed as singlet at δ 2.33 and doublet at 1.31-1.32, respectively. The aromatic protons (7-C*H*) were observed at 6.84 as singlet.

IR spectrum of compound (179) showed strong peak at 1685 cm^{-1} due to the stretching of C=O group. The stretchings of C-O group were observed at 1276 and 1251 cm^{-1}. PMR spectrum of this compound showed aromatic protons at δ 7.42-7.44 (m, 4H), 7.37-7.41 (m, 2H), 7.32-7.35 (m, 1H) and 6.93-6.96 (m, 2H). The singlets at δ 5.04 and 2.32 appeared due to (7-CH_2) and (1-CH_3). The multiplets at δ 4.14-4.23 and 3.05-3.14 were observed due to (3-C*H*) and (2-CH_2), respectively. The ring protons were observed at δ 3.71-3.77 and 3.40-3.49 due to (5-CH_2 and 6-CH_2) as multiplets. The methyl protons of (4-CH_3) appeared at δ 1.25-1.27 as doublet.



(179)



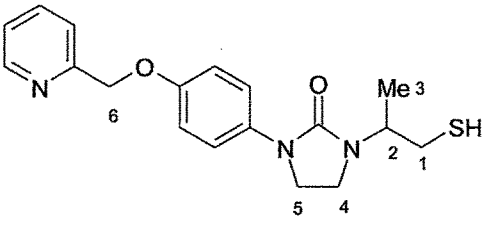
(180)

IR spectrum of compound (180), showed a strong peak at 1687 cm^{-1} due to stretchings of C=O group of imidazolidinone ring as well as thioacetate moiety. The peaks at 1431 and 1350 cm^{-1} are due to nitro group asymmetric and symmetric stretching vibrations. The PMR spectra of compound (180) showed aromatic protons at δ 8.22-8.24 (d, 2H; 11-C*H*), 7.61-7.64 (d, 2H; 10-C*H*), 7.44-7.46 (d, 2H; 7-C*H*) and 6.92-6.94 (d, 2H; 8-C*H*). Among the aliphatic protons, (1-CH_3) protons were observed as singlet at δ 2.32. The other methyl group (4-CH_3) appeared at δ 1.24-1.25 as doublet. The single proton (3-C*H*) was observed at δ 4.13-4.18 as a multiplet. The methylene protons (2-CH_2 and 9-CH_2) were seen at δ 3.08-3.10 as multiplet and 5.17 as singlet, respectively. The multiplets at δ 3.75-3.79 and 3.24-3.28 were due to (5-CH_2 and 6-CH_2).

In the next step, thioacetate derivatives (176-180) were hydrolyzed in basic conditions to the corresponding thiols (181-185). The reaction was carried out in an inert atmosphere. Nitrogen gas was bubbled through the reaction mixture continuously during the course of this reaction. In case of compound (181), it was observed that after the reaction was over, pure compound precipitated out in the reaction mixture. The compound was filtered and washed with diisopropyl ether in order to remove minor non-polar impurities.

IR spectra of thiols showed the stretching vibrations of C=O group of imidazolidinone ring at around 1680 cm^{-1}. PMR spectra of these compounds showed the presence of CH_2-SH protons as multiplet at around δ 2.9.

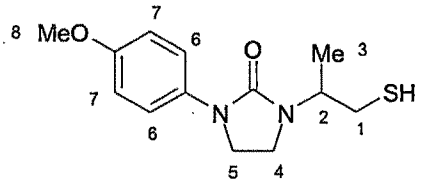
PMR spectrum of compound (**181**), showed aromatic protons at δ 8.57-8.58 (m, 1H), 7.66-7.71 (m, 1H), 7.46-7.51 (m, 1H), 7.37-7.39 (m, 2H), 7.19-7.22 (m, 1H) and 6.88-6.91 (m, 2H). The methyl protons (3-C*H*$_3$) were observed at δ 1.24-1.25 as doublet. The methine proton (2-C*H*) appeared at δ 4.29-4.35 as multiplet. The methylene protons (1-C*H*$_2$ and 6-C*H*$_2$) were observed at δ 3.35-3.40 as multiplet



(181)

and 5.15 as singlet, respectively. The multiplets at δ 3.65-3.69 and 3.35-3.40 were due (4-C*H*$_2$ and 5-C*H*$_2$).

IR spectrum of compound (**182**) showed a strong peak at 1676 cm^{-1} due to C=O stretching. The C-O stretching peaks were observed at 1247, 1180 and 1030 cm^{-1}. PMR

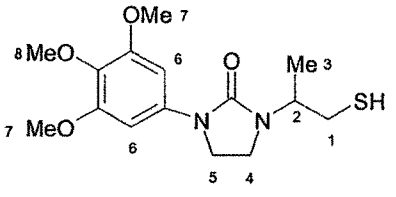


(182)

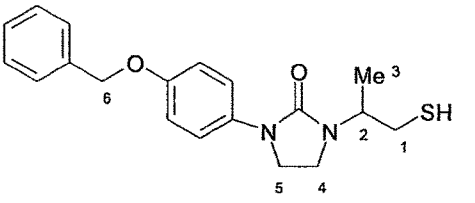
spectrum of this compound showed aromatic protons at δ 7.37-7.45 as doublet and 6.80-6.88 as doublet due to presence of (6-C*H*) and (7-C*H*), respectively. The signals of methoxy protons (8-OC*H*$_3$) and (4/5-C*H*$_2$) merged together and were observed at δ 3.71-3.81 as multiplet. The other two ring protons (4/5-C*H*$_2$) came as multiplet at δ 3.38-3.44. The methine proton (2-C*H*) and the methylene protons (1-C*H*$_2$) appeared at δ 4.28-4.33 as multiplet and 2.85-2.97 as multiplet, respectively. The methyl protons (3-C*H*$_3$) were observed at δ 1.24-1.26 as doublet.

IR spectrum of compound (**183**) showed C=O stretching at 1687 cm^{-1}. The C-O stretchings of the ether group were observed at 1236, 1128 and 1006 cm^{-1}. PMR spectrum of this compound showed aromatic protons (6-C*H*) at δ 6.84 as singlet. The signals

due to methoxy protons (7-OCH_3 and 8-OCH_3) merged with one proton of (4/5-CH_2)



(183)

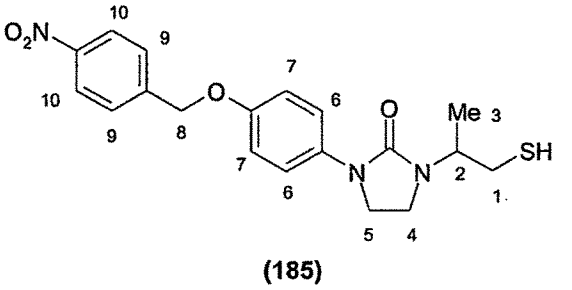


(184)

and were observed as multiplets at δ 3.80-3.86 and 3.75-3.79, respectively. The other two protons of the ring (4/5-CH_2) appeared as multiplet at δ 3.64-3.72. The methyl protons (3-CH_3) were observed as doublet at δ 1.24-1.27. The multiplets at δ 4.29-4.38 and 2.90-2.95 were due to (2-C*H*) and (1-CH_2), respectively.

IR spectrum of compound (**184**) showed C=O stretching of imidazolidinone ring at 1676 cm^{-1}. The peaks at 1245 and 1047 cm^{-1} are due to aryl C-O stretching and alkyl C-O stretching of the arylalkyl ether group present in the molecule. PMR spectrum of compound (**184**) showed the presence of nine aromatic protons at δ 7.41-7.44 (m, 4H), 7.30-7.38 (m, 3H) and 6.92-6.94 (m, 2H). The singlet at δ 5.03 was due to (6-CH_2). The methine proton (2-C*H*) appeared at δ 4.25-4.31 as multiplet. The multiplet at δ 2.84-2.95 is due to the presence (1-CH_2) in the molecule. The methyl protons (3-CH_3) appeared at δ 1.21-1.23 as doublet. The multiplets at δ 3.72-3.80 and at 3.37-3.43 for two protons each were due to the four protons of the imidazolidinone ring i.e. (4- CH_2 and 5-CH_2).

IR spectrum of the compound (**185**) showed two strong peaks at 1431 and 1348 cm^{-1} due to nitro stretching. The C=O stretching was observed at 1685 cm^{-1} and C-O stretchings were seen at 1249 cm^{-1}. PMR spectrum of this compound showed aromatic protons at δ 8.20-8.24 (d, 2H; 10-C*H*), 7.61-7.65 (d, 2H; 9-C*H*), 7.41-7.46 (d, 2H; 6-C*H*) and 6.87-6.94 (d, 2H; 7-C*H*). The methylene protons (8-CH_2) were observed at δ 5.17 as singlet. The multiplets at δ 3.75-3.79 and 3.24-3.28 were due to the ring



(185)

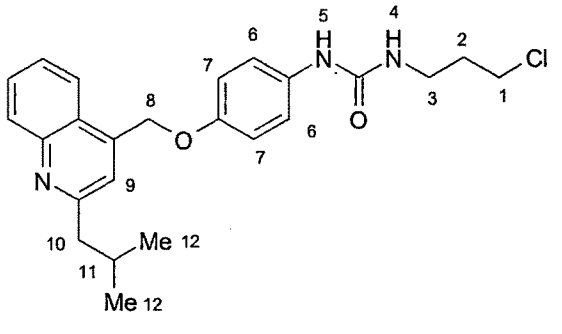
protons (4/5-C*H*$_2$ and 5/4-C*H*$_2$). The other multiplet at δ 2.86-2.90 was observed due to (1-C*H*$_2$). The methyl protons (3-C*H*$_3$) and the methine proton (2-C*H*) appeared at δ 1.24-1.25 as doublet and 4.13-4.18 as multiplet, respectively.

3.1.4 Synthesis of Tetrahydropyrimidin-2(1*H*)-one Derivatives

After preparing the five-membered imidazolidinone derivatives, it was planned to increase the ring size of the central ring to a six-membered structure. A synthetic strategy similar to Scheme-10 was devised (Scheme-13). The amines (**36-42, 47, 49, 53, 54, 63-65, 67**) were reacted with 3-chloropropionyl isocyanate (**62**) in the first step of Scheme-13 to obtain 1-aryl-3-chloropropylurea derivatives (**186-200**). These reactions were carried out in benzene and the solids so precipitated out in the reaction mixture were isolated as pure products.

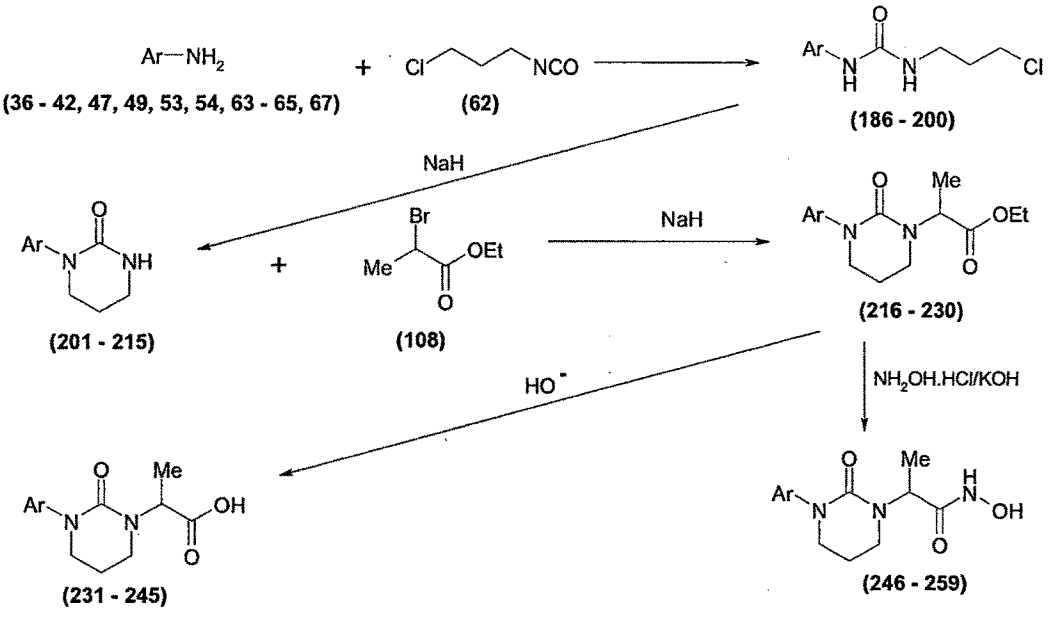
The urea derivatives showed C=O stretching vibrations of amide group (Amide I) at around 1640 cm^{-1} in their IR spectrum. The N-H deformation peaks (Amide II) were observed at 1595 cm^{-1}. The stretching vibrations of N-H group were observed near to 3300 cm^{-1}. The PMR spectra showed the presence of CH$_2$-C*H*$_2$-CH$_2$ protons at around δ 2.0 as multiplets.

The PMR spectrum of compound (**189**) showed aromatic protons at δ 8.14-8.15 (m, 1H), 8.00-8.03 (m, 2H), 7.68-7.72 (m, 1H), 7.52 (s, 1H; 9-C*H*), 7.32-7.34 (d, 2H; 6-C*H*) and 6.93-6.95 (d, 2H; 7-C*H*). The protons (5-N*H*) and (4-N*H*) attached to nitrogen atoms were observed at δ 7.45 as broad singlet and 6.09-6.12 as triplet, respectively. Methyl protons of (12-C*H*$_3$) appeared as doublet at δ 0.95-0.96. The methylene protons of (1-C*H*$_2$, 2-C*H*$_2$, 3-C*H*$_2$, 8-C*H*$_2$ and 10-C*H*$_2$) were observed at δ 3.61



(189)

-3.65 (m, 2H), 1.92-1.99 (m, 2H), 3.29-3.33 (m, 2H), 5.48 (s, 2H) and 2.81-2.83 (d, 2H), respectively. The methine proton (11-C*H*) was seen at δ 2.81-2.83 as multiplet.



Ar

(36, 186, 201, 216, 231, 246) =

(37, 187, 202, 217, 232, 247) =

(38, 188, 203, 218, 233, 248) =

(39, 189, 204, 219, 234, 249) =

(40, 190, 205, 220, 235, 250) =

(41, 191, 206, 221, 236, 251) =

(42, 192, 207, 222, 237, 252) =

(47, 193, 208, 223, 238, -) =

(49, 194, 209, 224, 239, 253) =

(53, 195, 210, 225, 240, 254) =

(54, 196, 211, 226, 241, 255) =

(63, 197, 212, 227, 242, 256) =

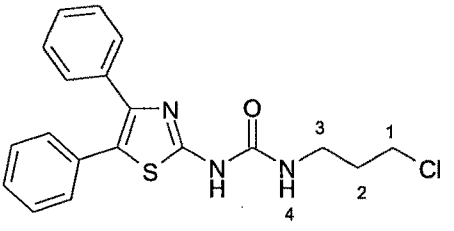
(64, 198, 213, 228, 243, 257) =

(65, 199, 214, 229, 244, 258) =

(67, 200, 215, 230, 245, 259) =

Scheme-13

Ten aromatic protons of compound (**195**) were observed together at δ 7.26-7.37 as multiplet in its PMR spectrum. The (4-N*H*) proton appeared as broad singlet at δ 6.72. The multiplets at δ 3.80-3.84, 3.26-3.33 and 1.90-2.01 were due to (1-CH_2), (3-CH_2)



(195)

and (2-CH_2), respectively.

Spectral data of the urea derivatives (**186-200**) is given in Table-6.

Table 6. Spectral Data of urea derivatives (186-200) synthesized in Scheme-13

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
186	3317 (N-H stretching), 1635 (C=O stretching), 1242 (C-O stretching), 1178 (C-O stretching), 1031 (C-O stretching).	-
187	3312 (N-H stretching), 1648 (C=O stretching), 1596 (N-H deformation), 1252 (C-O stretching), 1048 (C-O stretching).	8.49-8.59 (m, 1H), 7.69-7.74 (m, 1H), 7.49-7.51 (m, 1H), 7.22-7.25 (m, 1H), 7.15-7.19 (d, 2H), 6.92-6.95 (d, 2H), 6.51 (bs, 1H), 5.17 (s, 2H), 5.01-5.03 (t, 1H), 3.55-3.58 (m, 2H), 3.34-3.39 (m, 2H), 1.94-2.00 (m, 2H).
189	3358 (N-H stretching), 3292 (N-H stretching), 1637 (C=O stretching), 1600 (N-H deformation), 1236 (C-O stretching), 1170 (C-O stretching), 1070 (C-O stretching).	8.14-815 (m, 1H), 8.00-8.03 (m, 2H), 7.68-7.72 (m, 1H), 7.52 (s, 1H), 7.45 (bs, 1H), 7.32-7.34 (d, 2H), 6.93-6.95 (d, 2H), 6.09-6.12 (t, 1H), 5.48 (s, 2H), 3.61-3.65 (m, 2H), 3.29-3.33 (m, 2H), 2.81-2.83 (d, 2H), 2.19-2.23 (m, 1H), 1.92-1.99 (m, 2H), 0.95-0.96 (d, 6H).
190	3313 (N-H stretching), 1635 (C=O stretching), 1606 (N-H deformation), 1244 (C-O stretching), 1172 (C-O stretching), 1020 (C-O stretching).	-
191	3316 (N-H stretching), 1640 (C=O stretching), 1592 (N-H deformation), 1252 (C-O stretching), 1052 (C-O stretching).	8.16-8.19 (m, 2H), 7.98-8.06 (m, 3H), 7.73-7.77 (m, 1H), 7.44-7.60 (m, 4H), 7.32-7.36 (d, 2H), 6.96-6.99 (d, 2H), 5.98-6.01 (t, 1H), 5.55 (s, 2H), 3.61-3.64 (m, 2H), 3.32-3.37 (m, 2H), 1.94-2.01 (m, 2H).

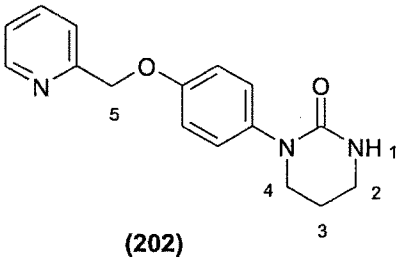
192	3309 (N-H stretching), 1639 (C=O stretching), 1249 (C-O stretching), 1024 (C-O stretching).	-
194	3215 (N-H stretching), 1685 (C=O stretching), 1253 (C-O stretching), 1174 (C-O stretching), 1031 (C-O stretching).	-
195	-	7.26-7.37 (m, 10H), 6.72 (bs, 1H), 3.80-3.84 (m, 2H), 3.26-3.33 (m, 2H), 1.90-2.01 (m, 2H).
197	3323 (N-H stretching), 1635 (C=O stretching), 1593 (N-H deformation).	8.04 (bs, 1H), 7.37-7.39 (m, 2H), 7.19-7.24 (m, 3H), 6.05 (bs, 1H), 3.61-3.65 (m, 2H), 3.33-3.38 (m, 2H), 1.95-2.01 (m, 2H).
198	3309 (N-H stretching), 1627 (C=O stretching), 1596 (N-H deformation), 1238 (C-O stretching), 1039 (C-O stretching).	7.68 (bs, 1H), 7.24-7.28 (d, 2H), 6.77-6.81 (d, 2H), 5.82 (bs, 1H), 3.76 (s, 3H), 3.60-3.63 (m, 2H), 3.32-3.37 (m, 2H), 1.94-2.01 (m, 2H).
199	3309 (N-H stretching), 1627 (C=O stretching), 1604 (N-H deformation), 1240 (C-O stretching), 1168 (C-O stretching), 1024 (C-O stretching).	-
200	3310 (N-H stretching), 1638 (C=O stretching), 1598 (N-H deformation), 1248 (C-O stretching), 1036 (C-O stretching).	7.92 (bs, 1H), 7.26-7.53 (m, 7H), 6.84-6.86 (m, 2H), 5.00 (bs, 1H), 3.60-3.63 (m, 2H), 3.32-3.35 (m, 2H), 1.93-2.01 (m, 2H).

In the next step, these linear urea derivatives (**186-200**) were cyclized by sodium hydride to prepare the cyclic tetrahydropyrimidin-2(1*H*)-one derivatives (**201-215**). The reaction conditions were kept exactly the same as given for the preparation of cyclic imidazolidinone derivatives (**89-107**).

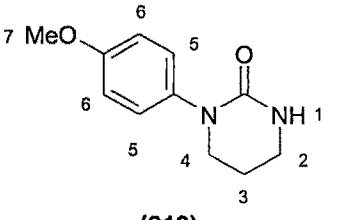
IR spectra of these compounds showed N-H stretching at around 3250 cm^{-1} and N-H deformation (Amide II) at around 1600 cm^{-1}. The C=O stretching vibrations were observed at around 1670 cm^{-1}. PMR spectra of these cyclic compounds did not show the presence of PhN*H*C=O proton which was observed in case of linear urea derivatives at around δ 7.5 ppm as broad singlet.

IR spectrum of compound (**202**) showed moderate intensity peak at 3223 cm^{-1} due to the stretchings of N-H group. The stretching vibrations of C=O group of

tetrahydropyrimidine ring resulted in a sharp peak at 1670 cm^{-1}. The C-O stretchings of ether linkage could be seen at 1249, 1179 and 1039 cm^{-1}. PMR spectrum of this compound (202) showed aromatic protons at δ 8.58-8.59 (m, 1H), 7.68-7.73 (m, 1H), 7.50-7.52 (m, 1H), 7.18-7.23 (m, 3H) and 6.94-6.97 (m, 2H). The methylene protons



(202)



(213)

(5-CH_2) appeared at δ 5.19 as singlet. The multiplets at δ 3.62-3.65, 3.40-3.43 and 2.04-2.17 were due to (2-CH_2/4-CH_2), (4-CH_2/2-CH_2) and (3-CH_2), respectively. The NH proton (1-N*H*) was observed at δ 4.87 as broad singlet.

PMR spectrum of compound (213) showed aromatic protons at δ 7.18-7.21 (d, 2H) and 6.86-6.89 (d, 2H) due to (5-C*H*) and (6-C*H*), respectively. The multiplets at δ 3.61-3.64 and 3.39-3.42 were due to the presence (2-CH_2/4-CH_2) and (4-CH_2/2-CH_2), respectively. The methylene protons (3-CH_2) appeared at δ 2.04-2.10 as multiplet. The NH proton (1-N*H*) was observed at δ 5.12 as broad singlet and the methoxy protons (7-OCH_3) appeared at 3.79 as singlet.

Spectral data of the cyclized products (201-215) is given in Table-7.

Table 7. Spectral Data of tetrahydropyrimidin-2(1*H*)-one derivatives (201-215) synthesized in Scheme-13

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
201	3217 (N-H stretching), 1647 (C=O stretching), 1585 (N-H deformation), 1244 (C-O stretching), 1174 (C-O stretching), 1030 (C-O stretching).	7.33-7.35 (d, 2H), 7.14-7.16 (d, 2H), 6.88-6.90 (m, 4H), 6.27 (bs, 1H), 4.96 (s, 2H), 3.79 (s, 3H), 3.58-3.61 (m, 2H), 3.30-3.330 (m, 2H), 2.00-2.02 (m, 2H).
202	3223 (N-H stretching), 1670 (C=O stretching), 1249 (C-O stretching), 1179 (C-O stretching), 1039 (C-O stretching).	8.58-8.59 (m, 1H), 7.68-7.73 (m, 1H), 7.50-7.52 (m, 1H), 7.18-7.23 (m, 3H), 6.94-6.97 (m, 2H), 5.19 (s, 2H), 4.87 (bs, 1H), 3.62-3.65 (m, 2H), 3.40-3.43 (m, 2H), 2.04-2.17 (m, 2H).

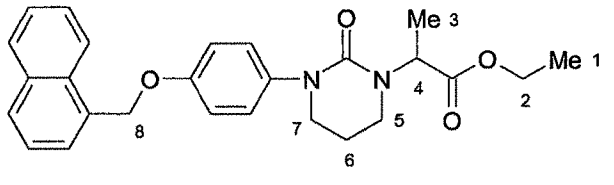
203	3221 (N-H stretching), 1645 (C=O stretching), 1242 (C-O stretching), 1033 (C-O stretching).	-
204	3225 (N-H stretching), 1671 (C=O stretching), 1241 (C-O stretching), 1182 (C-O stretching), 1045 (C-O stretching).	8.07-8.09 (m, 1H), 7.95-7.98 (m, 1H), 7.69-7.73 (m, 1H), 7.52-7.56 (m, 2H), 7.48 (s, 1H), 7.23-7.25 (m, 1H), 7.00-7.06 (m, 2H), 5.56 (s, 2H), 3.83-3.87 (m, 2H), 3.63-3.66 (m, 1H), 3.40-3.41 (m, 1H), 2.84-2.85 (d, 2H), 2.15-2.23 (m, 2H), 2.06-2.09 (m, 1H), 0.95-0.97 (d, 6H).
205	3213 (N-H stretching), 1658 (C=O stretching), 1606 (N-H deformation), 1244 (C-O stretching), 1174 (C-O stretching).	-
206	3223 (N-H stretching), 1670 (C=O stretching), 1249 (C-O stretching), 1179 (C-O stretching), 1039 (C-O stretching).	8.17-8.19 (m, 3H), 8.08 (s, 1H), 8.02-8.04 (m, 1H), 7.75-7.78 (m, 1H), 7.45-7.61 (m, 4H), 7.24-7.26 (m, 2H), 7.05-7.07 (m, 2H), 5.78 (bs, 1H), 5.59 (s, 2H), 3.63-3.66 (m, 2H), 3.37-3.41 (m, 2H), 2.04-2.09 (m, 2H).
207	-	8.02-8.04 (m, 1H), 7.85-7.91 (m, 2H), 7.69-7.71 (m, 1H), 7.54-7.59 (m, 2H), 7.50-7.52 (m, 1H), 7.20-7.24 (m, 2H), 6.98-7.02 (m, 2H), 5.92 (bs, 1H), 5.47 (s, 2H), 3.61-3.65 (m, 2H), 3.36-3.40 (m, 2H), 2.03-2.09 (m, 2H).
208	3207 (N-H stretching), 1676 (C=O stretching).	7.28-7.30 (m, 4H), 7.22-7.25 (m, 1H), 5.48 (bs, 1H), 4.29 (s, 2H), 4.18-4.21 (m, 2H), 3.39-3.42 (m, 2H), 2.08-2.14 (m, 2H).
210	3230 (N-H stretching), 1676 (C=O stretching).	-
211	3227 (N-H stretching), 1681 (C=O stretching).	-
212	3220 (N-H stretching), 2923 (aromatic C-H stretching), 1651 (C=O stretching).	7.28-7.36 (m, 4H), 7.14-7.19 (m, 1H), 5.19 (bs, 1H), 3.67-3.70 (m, 2H), 3.40-3.43 (m, 2H), 2.05-2.11 (m, 2H).
213	3213 (N-H stretching), 1664 (C=O stretching), 1249 (C-O stretching), 1170 (C-O stretching), 1029 (C-O stretching).	7.18-7.21 (d, 2H), 6.86-6.89 (d, 2H), 5.12 (bs, 1H), 3.79 (s, 3H), 3.61-3.64 (m, 2H), 3.39-3.42 (m, 2H), 2.04-2.10 (m, 2H).
214	3209 (N-H stretching), 1664 (C=O stretching), 1593 (N-H deformation), 1244 (C-O stretching), 1172 (C-O stretching), 1024 (C-O stretching).	-

215	3222 (N-H stretching), 1666 (C=O stretching), 1248 (C-O stretching), 1178 (C-O stretching), 1036 (C-O stretching).	7.35-7.42 (m, 4H), 7.28-7.32 (m, 1H), 7.16-7.19 (d, 2H), 6.89-6.93 (d, 2H), 6.01 (bs, 1H), 5.04 (s, 2H), 3.60-3.63 (m, 2H), 3.34-3.37 (m, 2H), 2.01-2.07 (m, 2H).

Tetrahydropyrimidin-2(1*H*)-ones (**201-215**) were treated with ethyl 2-bromopropionate (**108**) in presence of a strong base like sodium hydride to synthesize the corresponding ester derivatives (**216-230**).

IR spectra of these ester derivatives showed C=O stretchings at around 1685 and 1735 cm^{-1} due to the amide and the ester moieties. The N-H stretching and deformation peaks at around 3350 and 1500 cm^{-1} were absent the IR spectra of these compounds. PMR spectra of these compounds showed triplet for three protons at around δ 1.3 ppm for CH_2CH_3 protons and multiplet for 2 protons at around δ 4.2 for CH_2CH_3 protons along with other signals of the molecule.

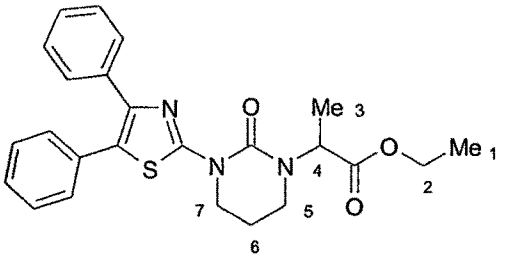
PMR spectrum of compound (**222**) showed the presence of eleven aromatic protons at δ 7.94-7.97 (m, 1H), 7.80-7.83 (m, 1H), 7.63-7.71(m, 1H), 7.45-7.52 (m, 2H), 7.25-7.31 (m, 1H), 7.13-7.18 (m, 2H), 6.95-6.98 (m, 1H) and 6.75-6.78 (m, 2H). The methyl protons (1-CH_3) and (3-CH_3) appeared at δ 1.19-1.22 as triplet and 1.36-1.38 as



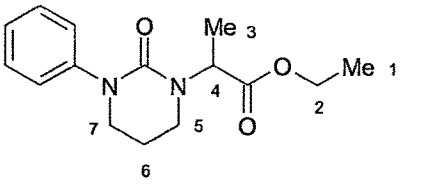
(222)

doublet, respectively. The singlet at δ 5.39 was due to (8-CH_2) and the quartet at 4.45-4.49 due to (4-CH). The methylene protons (2-CH_2 and 6-CH_2) came as multiplets at δ 4.07-4.15 and at 2.05-2.13, respectively. The multiplets at δ 3.57-3.60 for two protons and δ 3.30-3.34 for another two protons were due to (5-CH_2/7-CH_2) and (7-CH_2/5-CH_2).

PMR spectrum of compound (**225**) showed aromatic protons at δ 7.51-7.53 (m, 2H), 7.32-7.35 (m, 2H) and 7.26-7.30 (m, 6H). The methyl protons (1-CH_3 and 3-CH_3) were observed at δ 1.26-1.30 as triplet and 1.48-1.50 (d, J = 7.6 Hz), respectively. The methylene protons (6-CH_2) appeared at δ 2.12-2.23 as multiplet. The multiplets at δ 4.19-4.24 for three protons accounted for (2-CH_2) and one proton of (5/7-CH_2). The other three protons (5-CH_2 and 7-CH_2) appeared at δ 4.39-4.45 (m, 1H) and 4.09-4.18 (m, 2H).



(225)



(227)

The methine proton (4-C*H*) was observed at δ 5.23-5.28 as quartet, having a coupling constant equal to 7.5 Hz.

IR spectrum of compound (**227**) showed C=O stretchings of the ester group at 1737 cm^{-1} and that of the tetrahydropyrimidin-2(1*H*)-one ring at 1647 cm^{-1}. In the PMR spectrum of compound (**227**), the aromatic protons were observed at δ 7.27-7.36 (m, 4H) and 7.13-7.19 (m, 1H). The methyl protons (1-CH_3) and (3-CH_3) were observed at δ 1.26-1.29 as triplet and at 1.44-1.46 as doublet, respectively. The quartet at δ 5.14-5.18 was due to (4-C*H*). The methylene protons (2-CH_2) and (6-CH_2) appeared at δ 4.16-4.19 and 2.06-2.13 as multiplets. respectively. The (7-CH_2) and (5-CH_2) protons appeared as multiplets at δ 3.68-3.73 and 3.39-3.44.

Formation of these ester intermediates (**216-230**) were monitored by TLC. Some of them were characterized on the basis of their spectral data as given in Table-8.

Table 8. Spectral Data of ester derivatives (216-230) synthesized in Scheme-13

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
216	1737 (C=O stretching of ester), 1645 (C=O stretching of ring), 1249 (C-O stretching), 1180 (C-O stretching), 1026 (C-O stretching).	-
218	1735 (C=O stretching of ester), 1645 (C=O stretching of ring), 1240 (C-O stretching), 1188 (C-O stretching), 1016 (C-O stretching).	-

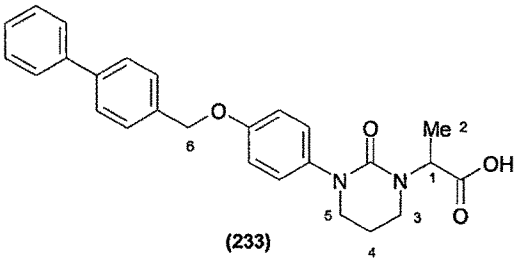
222	-	7.94-7.97 (m, 1H), 7.80-7.83 (m, 1H), 7.63-7.71(m, 1H), 7.45-7.52 (m, 2H), 7.25-7.31 (m, 1H), 7.13-7.18 (m, 2H), 6.95-6.98 (m, 1H), 6.75-6.78 (m, 2H), 5.39 (s, 2H), 4.45-4.49 (q, 1H), 4.07-4.15 (m, 2H), 3.57-3.60 (m, 2H), 3.30-3.34 (m, 2H), 2.05-2.13 (m, 2H), 1.36-1.38 (d, 3H), 1.19-1.22 (t, 3H).
225	-	7.51-7.53 (m, 2H), 7.32-7.35 (m, 2H), 7.26-7.30 (m, 6H), 7.23-7.25 (m, 2H), 5.23-5.28 (q, 1H, J = 7.5 Hz), 4.39-4.45 (m, 1H), 4.19-4.24 (m, 3H), 4.09-4.18 (m, 2H), 2.12-2.23 (m, 2H), 1.48-1.50 (d, 3H, J = 7.6 Hz), 1.26-1.30 (t, 3H).
227	1737 (C=O stretching of ester), 1647 (C=O stretching of ring).	7.27-7.36 (m, 4H), 7.13-7.19 (m, 1H), 5.14-5.18 (q, 1H, J = 7.44 Hz), 4.16-4.19 (m, 2H), 3.68-3.73 (m, 2H), 3.39-3.44 (m, 2H), 2.06-2.13 (m, 2H), 1.44-1.46 (d, 3H, J = 7.40 Hz), 1.26-1.29 (t, 3H).
228	1733 (C=O stretching of ester), 1629 (C=O stretching of ring), 1248 (C-O stretching), 1178 (C-O stretching), 1035 (C-O stretching).	7.17-7.19 (d, 2H), 6.84-6.87 (d, 2H), 5.15-5.21 (q, 1H, J = 7.44 Hz), 4.13-4.21 (m, 2H), 3.78 (s, 3H), 3.63-3.66 (m, 2H), 3.37-3.41 (m, 2H), 2.08-2.18 (m, 2H), 1.43-1.44 (d, 3H, J = 7.40 Hz), 1.25-1.29 (t, 3H).

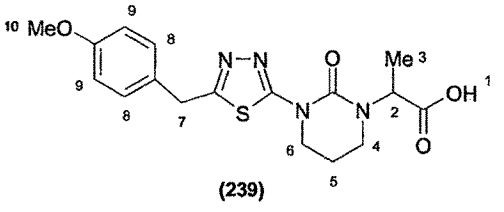
The ester derivatives (**216-230**) were hydrolyzed to the corresponding carboxylic acids (**231-245**) in basic medium. Sodium hydroxide or lithium hydroxide was used for these reactions and the reaction mixture was acidified to afford the desired acids.

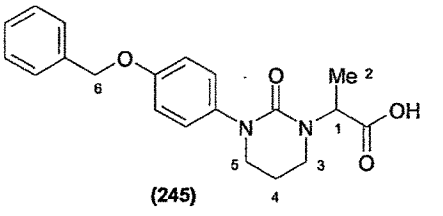
IR spectra of these compounds showed the presence of acidic functionality by the presence of a sharp peak at around 1740 cm^{-1} due to the stretching vibrations of C=O group of the acid moiety. The peak at around 1685 cm^{-1} is indicative of C=O stretching of the tetrahydropyrimidin-2(1*H*)-one ring. The O-H stretchings of the molecules were observed at around 3440 cm^{-1}. The mass spectra of these acids showed $(M+H)^+$ peaks as the base peaks. For compounds (**232, 236, 245**) another important peak was $(M-COOH)^+$ peak. Apart from these, compounds (**232, 237**) showed $(M+Na)^+$ and $(M+K)^+$ peaks as well.

PMR spectrum of compound (**233**) showed the aromatic protons at δ 7.58-7.61 (m, 4H), 7.49-7.51 (m, 2H), 7.42-7.46 (m, 2H), 7.33-7.38 (m, 1H), 7.18-7.20 (m, 2H) and 6.96-6.94 (m, 2H). The methylene protons (6-CH_2) and the methine proton (1-C*H*) merged together and appeared as multiplet at δ 5.06-5.10. The methyl protons (2-CH_3) and methylene protons (4-CH_2) were observed at δ 1.44-1.46 as doublet and 2.10-2.19

as multiplet, respectively. The multiplet at δ 3.63-3.66 was due to either (3-CH_2 or 5-CH_2). Similarly, the multiplet at 3.38-3.44 was due to either (5-CH_2 or 3-CH_2).







PMR spectrum of compound **(239)** showed the presence of (1-O*H*) proton at δ 12.78 as a broad singlet. The aromatic protons were observed at δ 7.19-7.21 (d, 2H) and 6.86-6.88 (d, 2H) due to (8-C*H*) and (9-C*H*), respectively. The quartet at δ 4.68-4.74, (J = 7.2 Hz) and doublet at 1.32-1.34, (J = 7.6 Hz) were due to (2-C*H*) and (3-CH_3), respectively. The singlets at δ 4.18 and 3.81 were due to the methylene protons of (7-CH_2) and methyl protons of (10-OCH_3), respectively. The multiplet at δ 2.00-2.04 appeared due to (5-CH_2). The other four protons of tetrahydropyrimidin-2(1*H*)-one ring, i.e. (4-CH_2) and (6-CH_2) appeared as multiplets at δ 4.10-4.13 for one proton, 3.95-3.99 for one proton and 3.15-3.18 for two protons.

PMR spectrum of compound **(245)** showed the presence of nine aromatic protons at δ 7.38-7.43 (m, 4H), 7.30-7.33 (m, 1H), 7.15-7.18 (d, 2H) and 6.90-6.92 (d, 2H). The signal due to (6-CH_2) and (1-C*H*) merged together at δ 5.03-5.05 as multiplet. The multiplet at δ 2.09-2.15 was due to (4-CH_2). The other two multiplets at δ 3.62-3.65 and 3.37-3.42 appeared due to (3-CH_2 and 5-CH_2). The methyl protons (2-CH_3) were observed at δ 1.41-1.43.

Spectral data of the acids **(231-245)** is given in Table-9.

Table 9. Spectral Data of acids (231-245) synthesized in Scheme-13

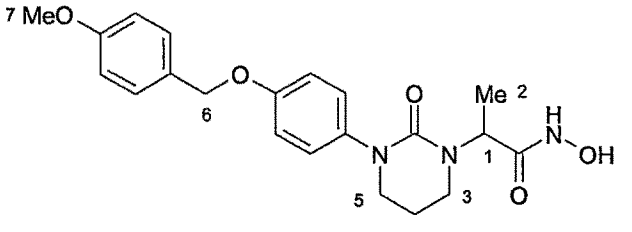
Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
231	3446 (O-H stretching), 1737 (C=O stretching of acid), 1685 (C=O stretching of ring), 1251 (C-O stretching), 1174 (C-O stretching), 1029 (C-O stretching).	7.33-7.35 (d, 2H), 7.14-7.16 (d, 2H), 6.88-6.91 (m, 4H), 4.96-5.01 (m, 3H), 3.80 (s, 3H), 3.60-3.65 (m, 2H), 3.40-3.43 (m, 2H), 2.09-2.17 (m, 2H), 1.40-1.42 (d, 3H).
232	3446 (O-H stretching), 1730 (C=O stretching of acid), 1652 (C=O stretching of ring), 1249 (C-O stretching), 1178 (C-O stretching), 1021 (C-O stretching).	8.57-8.58 (m, 1H), 7.69-7.72 (m, 1H), 7.50-7.52 (m, 1H), 7.24-7.27 (m, 1H), 7.16-7.18 (d, 2H), 6.91-6.94 (d, 2H), 5.17 (s, 2H), 5.03-5.08 (q, 1H, J = 7.41 Hz), 3.62-3.65 (m, 2H), 3.40-3.45 (m, 2H), 2.00-2.08 (m, 2H), 1.42-1.43 (d, 3H, J = 7.40 Hz).
233	1743 (C=O stretching of acid), 1641 (C=O stretching of ring), 1242 (C-O stretching), 1180 (C-O stretching), 1026 (C-O stretching).	7.58-7.61 (m, 4H), 7.49-7.51 (d, 2H), 7.42-7.46 (m, 2H), 7.33-7.38 (m, 1H), 7.18-7.20 (m, 2H), 6.96-6.94 (m, 2H), 5.06-5.10 (m, 3H), 3.63-3.66 (m, 2H), 3.38-3.44 (m, 2H), 2.10-2.19 (m, 2H), 1.44-1.46 (d, 3H).
234	3445 (O-H stretching), 1734 (C=O stretching of acid), 1652 (C=O stretching of ring), 1242 (C-O stretching), 1178 (C-O stretching), 1026 (C-O stretching).	8.11-8.13 (m, 1H), 7.91-7.93 (m, 1H), 7.68-7.72 (m, 1H), 7.55-7.52 (m, 1H), 7.41 (s, 1H), 7.20-7.22 (d, 2H), 7.01-7.03 (d, 2H), 5.50 (s, 2H), 4.71-4.74 (q, 1H, J = 7.24 Hz), 3.64-3.67 (m, 2H), 3.41-3.44 (m, 2H), 2.84-2.86 (d, 2H), 2.14-2.22 (m, 3H), 1.51-1.53 (d, 3H, J = 7.28 Hz), 0.95-0.97 (d, 6H).
235	3448 (O-H stretching), 1723 (C=O stretching of acid), 1652 (C=O stretching of ring), 1248 (C-O stretching), 1182 (C-O stretching), 1036 (C-O stretching).	8.03-8.05 (m, 1H), 7.67-7.71 (m, 2H), 7.54-7.56 (m, 1H), 7.45-7.49 (m, 2H), 7.23-7.26 (m, 1H), 6.90-7.03 (m, 2H), 5.34 (s, 2H), 4.75-4.79 (q, 1H, J = 7.45 Hz), 3.48-3.51 (m, 2H), 3.37-3.42 (m, 2H), 3.26-3.23 (m, 2H), 1.93-2.03 (m, 2H), 1.32-1.36 (t, 3H, J = 7.48 Hz).
236	3412 (O-H stretching), 1734 (C=O stretching of acid), 1639 (C=O stretching of ring), 1602 (C=N stretching), 1298 (C-O stretching), 1182 (C-O stretching), 1028 (C-O stretching).	8.17-8.23 (m, 2H), 8.10 (s, 1H), 8.04-8.06 (m, 1H), 7.80-7.86 (m, 2H), 7.61-7.65 (m, 1H), 7.46-7.56 (m, 3H), 7.22-7.24 (d, 2H), 7.04-7.06 (d, 2H), 5.60 (s, 2H), 5.02-5.08 (q, 1H, J = 7.29 Hz), 3.64-3.67 (m, 2H), 3.42-3.46 (m, 2H), 2.06-2.12 (m, 2H), 1.42-1.44 (d, 3H, J = 7.40 Hz).
237	1737 (C=O stretching of acid), 1643 (C=O stretching of ring), 1296 (C-O stretching), 1180 (C-O stretching), 1024 (C-O stretching).	8.02-8.05 (m, 1H), 7.85-7.91 (m, 2H), 7.55-7.61 (m, 2H), 7.45-7.52 (m, 2H), 7.20-7.22 (d, 2H), 6.99-7.01 (d, 2H), 5.47 (s, 2H), 5.04-5.08 (q, 1H, J = 7.44 Hz), 3.62-3.65 (m, 2H), 3.40-3.45 (m, 2H), 2.11-2.18 (m, 2H), 1.43-1.44 (d, 3H, J = 7.40 Hz).

238	3423 (O-H stretching), 1734 (C=O stretching of acid), 1654 (C=O stretching of ring),	7.20-7.33 (m, 5H), 5.06-5.11 (q, 1H, J = 7.44 Hz), 4.28 (s, 2H), 4.01-4.08 (m, 2H), 3.33-3.43 (m, 2H), 2.07-2.19 (m, 2H), 1.46-1.48 (d, 3H, J = 7.40 Hz).
239	3367 (O-H stretching), 1730 (C=O stretching of acid), 1649 (C=O stretching of ring), 1247 (C-O stretching), 1178 (C-O stretching), 1030 (C-O stretching).	12.78 (bs, 1H), 7.19-7.21 (d, 2H), 6.86-6.88 (d, 2H), 4.68-4.74 (q, 1H, J = 7.20 Hz), 4.18 (s, 2H), 4.10-4.13 (m, 1H), 3.95-3.99 (m, 1H), 3.81 (s, 3H), 3.15-3.18 (m, 2H), 2.00-2.04 (m, 2H), 1.32-1.34 (d, 3H, J = 7.60 Hz).
240	1751 (C=O stretching of acid), 1718 (C=O stretching of ring).	7.51-7.53 (m, 2H), 7.35-7.32 (m, 2H), 7.23-7.29 (m, 6H), 5.22-5.17 (q, 1H, J = 7.37 Hz), 4.42-4.45 (m, 1H), 4.11-4.13 (m, 1H), 3.41-3.44 (m, 2H), 2.15-2.20 (m, 2H), 1.52-1.54 (d, 3H, J = 7.36 Hz).
241	3438 (O-H stretching), 1735 (C=O stretching of acid), 1649 (C=O stretching of ring).	7.76-7.79 (d, 2H, J = 8.05 Hz), 7.36 (s, 1H), 7.17-7.20 (d, 2H, J = 8.00 Hz), 4.61-4.64 (q, 1H, J = 7.35 Hz), 4.14-4.19 (m, 1H), 4.03-4.09 (m, 1H), 3.41-3.47 (m, 1H), 3.18-3.24 (m, 1H), 2.30 (s, 3H), 1.97-2.09 (m, 2H), 1.21-1.23 (d, 3H, J = 7.33 Hz).
242	1743 (C=O stretching of acid), 1643 (C=O stretching of ring).	7.34-7.37 (m, 2H), 7.26-7.28 (m, 2H), 7.19-7.22 (m, 1H), 4.80-4.85 (q, 1H, J = 7.33 Hz), 3.67-3.70 (m, 2H), 3.40-3.46 (m, 2H), 2.11-2.19 (m, 2H), 1.49-1.51 (d, 3H, J = 7.32 Hz).
243	1737 (C=O stretching of acid), 1620 (C=O stretching of ring), 1299 (C-O stretching), 1172 (C-O stretching), 1033 (C-O stretching).	12.00 (bs, 1H), 7.14-7.18 (d, 2H), 6.81-6.85 (d, 2H), 5.00-5.05 (q, 1H, J = 7.40 Hz), 3.77 (s, 3H), 3.62-3.65 (m, 2H), 3.35-3.44 (m, 2H), 2.05-2.21 (m, 2H), 1.41-1.43 (d, 3H, J = 7.40 Hz).
244	3443 (O-H stretching), 1730 (C=O stretching of acid), 1650 (C=O stretching of ring), 1244 (C-O stretching), 1172 (C-O stretching), 1028 (C-O stretching).	6.84-6.87(m, 2H), 6.70-6.74 (m, 1H), 4.74-4.82 (q, 1H, J = 7.30 Hz), 3.71 (s, 6H), 3.54-3.57 (m, 2H), 3.28-3.31 (m, 2H), 1.94-2.07 (m, 2H), 1.27-1.30 (d, 3H, J = 7.34 Hz).
245	1743 (C=O stretching of acid), 1643 (C=O stretching of ring), 1298 (C-O stretching), 1174 (C-O stretching), 1026 (C-O stretching).	7.38-7.43 (m, 4H), 7.30-7.33 (m, 1H), 7.15-7.18 (dd, 2H), 6.90-6.92 (dd, 2H), 5.03-5.05 (m, 3H), 3.62-3.65 (m, 2H), 3.37-3.42 (m, 2H), 2.09-2.15 (m, 2H), 1.41-1.43 (d, 3H).

Next, the esters (216-230) in scheme-13 were converted to hydroxamic acids (246-259). The procedure followed was exactly similar as that described for the preparation of hydroxamates of imidazolidinones.

In the IR spectra of these hydroxamates, peak at around 3440 cm^{-1} was observed due to the stretching vibrations of O-H group of the NHOH moiety. The stretching of C=O group of tetrahydropyrimidine ring and that of the C=O group of hydroxamate moiety merged and appeared together at around 1650 cm^{-1}. In the PMR spectra, the protons of N*H* and O*H* of hydroxamate moiety (in case of compounds **248, 250** and **257**) appeared as broad singlets at δ 10.1 and 8.5, respectively. The mass spectra of these hydroxamic acids showed $(M-14)^+$ peak as the base peak. This might be due to rearrangement of the hydroxamic acids to the corresponding carboxylic acids inside the mass spectrometer. Another important peak $(M-CONHOH)^+$ was also observed for all these hydroxamic acids. For compound (**248**), peak due to the presence of $(M-NHOH)^+$ fragment was also observed. $(M+H)^+$ peak was present in case of compounds (**250, 253, 254**) and $(M-H)^+$ peak for compounds (**246, 247, 252**). The peak due to $(M+Na)^+$ was observed for compounds (**247, 248, 252**) and $(M+K)^+$ for compound (**248**).

PMR spectrum of compound (**246**) showed aromatic protons at δ 7.33-7.35 (d, 2H), 7.15-7.17 (d, 2H) and 6.89-6.91 (m, 4H). Among the aliphatic protons, (2-C*H*$_3$) and (1-C*H*) protons were observed at δ 1.42-1.44 as doublet (J = 7.4 Hz) and 5.01-5.05 as

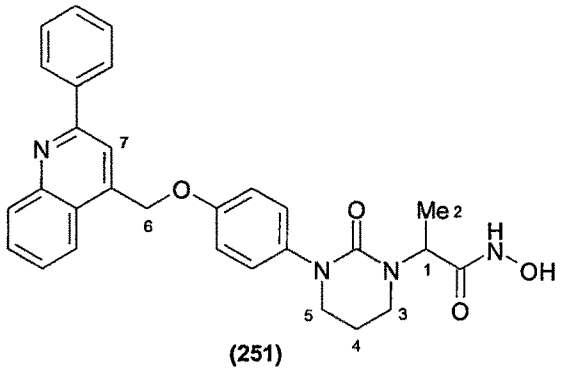


(246)

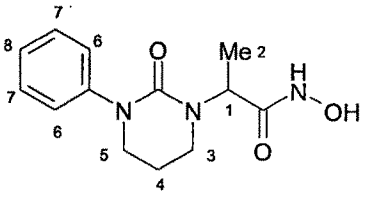
quartet (J = 7.4 Hz), respectively. The methylene protons (4-C*H*$_2$ and 6-C*H*$_2$) appeared at δ 2.10-2.16 as multiplet and 4.96 as singlet, respectively. The singlet at δ 3.81 was due to the presence (7-OC*H*$_3$). The multiplets at δ 3.62-3.65 and 3.47-3.40 were due to (3-C*H*$_2$ and 5-C*H*$_2$).

In the PMR spectrum of compound (**251**), the aromatic protons appeared at δ 8.17-8.19 (m, 2H), 8.08 (s, 1H; 7-C*H*), 8.03-8.05 (m, 2H), 7.75-7.79 (m, 1H), 7.58-7.62

(m, 1H), 7.52-7.55 (m, 2H), 7.45-7.49 (m, 1H), 7.22-7.25 (d, 2H) and 7.04-7.07 (d, 2H). The singlet at δ 5.60 was due to (6-C*H*$_2$). The protons (1-C*H*) and (2-C*H*$_3$) appeared as quartet at δ 5.03-5.06 and doublet at 1.37-1.39, respectively. The multiplet at δ 2.07-2.16 was due to (4-C*H*$_2$) while the multiplets at 3.62-3.68 and 3.39-3.46 were due to (3-C*H*$_2$) and (4-C*H*$_2$).



(251)



(256)

In the PMR spectrum of compound **(256)**, the aromatic protons were observed at δ 7.33-7.37 (m, 2H; 6-C*H*), 7.26-7.28 (m, 2H; 7-C*H*) and 7.19-7.22 (m, 1H; 8-C*H*). The methyl protons (2-C*H*$_3$) appeared at δ 1.49-1.51 as doublet with coupling constant equal to 7.4 Hz. The quartet at δ 4.80-4.86 with coupling constant of 7.2 Hz, was due to (1-C*H*). Multiplets appeared at δ 3.67-3.72, 3.40-3.44 and 2.13-2.19 due to (3-C*H*$_2$/5-C*H*$_2$), (5-C*H*$_2$/3-C*H*$_2$) and (4-C*H*$_2$), respectively.

Spectral data of the hydroxamic acids **(246-259)** is given in Table-10.

Table 10. Spectral Data of hydroxamates (246-259) synthesized in Scheme-13

Compound No.	IR Peaks (cm^{-1})	PMR Peaks (δ)
246	3446 (O-H stretching), 1652 (C=O stretching), 1263 (C-O stretching), 1177 (C-O stretching), 1028 (C-O stretching).	7.33-7.35 (d, 2H), 7.15-7.17 (d, 2H), 6.89-6.91 (m, 4H), 5.01-5.05 (q, 1H, *J* = 7.40 Hz), 4.96 (s, 2H), 3.81 (s, 3H), 3.62-3.65 (m, 2H), 3.47-3.40 (m, 2H), 2.10-2.16 (m, 2H), 1.42-1.44 (d, 3H, *J* = 7.36 Hz).
247	3446 (O-H stretching), 1652 (C=O stretching), 1250 (C-O stretching), 1177 (C-O stretching), 1052 (C-O stretching).	8.56-8.57 (m, 1H), 7.72-7.76 (m, 1H), 7.49-7.51 (m, 1H), 7.25-7.28 (m, 1H), 7.15-7.17 (d, 2H), 6.92-6.94 (d, 2H), 5.14 (s, 2H), 4.96-4.99 (q, 1H, *J* = 7.44 Hz), 3.61-3.70 (m, 2H), 3.37-3.48 (m, 2H), 2.05-2.15 (m, 2H), 1.41-1.43 (d, 3H, *J* = 7.40 Hz).

248	1643 (C=O stretching), 1242 (C-O stretching), 1172 (C-O stretching), 1029 (C-O stretching),	10.09 (bs, 1H), 8.61 (bs, 1H), 7.63-7.58 (m, 4H), 7.49-7.51 (m, 2H), 7.42-7.46 (m, 2H), 7.33-7.37 (m, 1H), 7.17-7.20 (d, 2H), 6.92-6.97 (d, 2H), 5.10 (s, 2H), 4.99-4.95 (q, 1H, J = 7.2 Hz), 3.60-3.63 (m, 2H), 3.39-3.45 (m, 2H), 2.06-2.16 (m, 2H), 1.38-1.37 (d, 3H, J = 7.2 Hz).
249	3448 (O-H stretching), 1652 (C=O stretching), 1246 (C-O stretching), 1180 (C-O stretching).	8.11-8.13 (m, 1H), 7.89-7.91 (m, 1H), 7.68-7.72 (m, 1H), 7.49-7.53 (m, 1H), 7.40 (s, 1H), 7.18-7.20 (d, 2H), 6.97-6.99 (d, 2H), 5.45 (s, 2H), 4.69-4.73 (q, 1H), 3.60-3.63 (m, 2H), 3.36-3.40 (m, 2H), 2.83-2.85 (d, 2H), 2.09-2.231 (m, 3H), 1.46-1.47 (d, 3H), 0.94-0.96 (d, 6H).
250	-	10.47 (bs, 1H), 8.78 (bs, 1H), 8.24-8.26 (m, 1H), 8.03-8.07 (m, 2H), 7.88-7.91 (m, 1H), 7.42 (s, 1H), 7.26-7.28 (d, 2H), 7.06-7.08 (d, 2H), 5.75 (s, 2H), 5.06-5.11 (q, 1H, J = 7.40 Hz), 3.66-3.69 (m, 2H), 3.49-3.55 (m, 2H), 3.37-3.40 (m, 2H), 2.11-2.21 (m, 2H), 1.55-1.58 (t, 3H), 1.43-1.45 (d, 3H, J = 7.40 Hz).
251	3414 (O-H stretching), 3203 (N-H stretching), 1680 (C=O stretching), 1602 (C=N stretching), 1238 (C-O stretching), 1182 (C-O stretching), 1028 (C-O stretching).	8.17-8.19 (m, 2H), 8.08 (s, 1H), 8.03-8.05 (m, 2H), 7.75-7.79 (m, 1H), 7.58-7.62 (m, 1H), 7.52-7.55 (m, 2H), 7.45-7.49 (m, 1H), 7.22-7.25 (d, 2H), 7.04-7.07 (d, 2H), 5.60 (s, 2H), 5.03-5.06 (q, 1H, J = 7.48 Hz), 3.62-3.68 (m, 2H), 3.39-3.46 (m, 2H), 2.07-2.16 (m, 2H), 1.37-1.39 (d, 3H, J = 7.24 Hz).
252	3440 (O-H stretching), 1652 (C=O stretching), 1221 (C-O stretching), 1169 (C-O stretching).	8.02-8.04 (m, 1H), 7.85-7.91 (m, 2H), 7.58-7.60 (m, 2H), 7.52-7.55 (m, 2H), 7.50-7.46 (m, 1H), 7.20-7.22 (d, 2H), 7.00-7.02 (d, 2H), 5.47 (s, 2H), 5.07-5.13 (q, 1H, J = 7.39 Hz), 3.65-3.72 (m, 2H), 3.36-3.45 (m, 2H), 2.17-2.21 (m, 1H), 2.07-2.12 (m, 1H), 1.44-1.45 (d, 3H, J = 7.44 Hz).
253	3254 (N-H stretching), 1651 (C=O stretching), 1247 (C-O stretching), 1178 (C-O stretching), 1030 (C-O stretching).	7.18-7.21 (d, 2H), 6.81-6.84 (d, 2H), 4.97-5.02 (q, 1H, J = 7.28 Hz), 4.20 (s, 2H), 4.01-4.06 (m, 2H), 3.7 (s, 3H), 3.39-3.45 (m, 2H), 2.10-2.20 (m, 2H), 1.43-1.45 (d, 3H, J = 7.36 Hz).
254	3414 (O-H stretching), 1647 (C=O stretching).	7.49-7.51 (m, 2H), 7.20-7.25 (m, 8H), 5.36-5.40 (q, 1H), 4.34-4.37 (m, 1H), 4.03-40.6 (m, 1H), 3.34-3.39 (m, 2H), 1.95-2.05 (m, 2H), 1.37-1.40 (d, 3H).
255	3091 (N-H stretching), 1631 (C=O stretching).	7.77-7.80 (d, 2H, J = 8.03 Hz), 7.42 (s, 1H), 7.18-7.21 (d, 2H, J = 7.99 Hz), 4.77-4.84 (q, 1H, J = 7.25 Hz), 4.00-4.09 (m, 2H), 3.34-3.37 (m, 2H), 2.30 (s, 3H), 2.01-2.08 (m, 2H), 1.34-1.36 (d, 3H, J = 7.31 Hz).

256	3213 (N-H stretching), 1670 (C=O stretching).	7.33-7.37 (m, 2H), 7.26-7.28 (m, 2H), 7.19-7.22 (m, 1H), 4.80-4.86 (q, 1H, J = 7.22 Hz), 3.67-3.72 (m, 2H), 3.40-3.44 (m, 2H), 2.13-2.19 (m, 2H), 1.49-1.51 (d, 3H, J = 7.36 Hz).
257	3119 (N-H stretching), 1687 (C=O stretching), 1251 (C-O stretching), 1172 (C-O stretching), 1033 (C-O stretching).	9.80 (bs, 1H), 8.55 (bs, 1H), 7.15-7.20 (d, 2H), 6.84-6.87 (d, 2H), 4.95-4.98 (q, 1H, J = 6.88 Hz), 3.79 (s, 3H), 3.59-3.62 (m, 2H), 3.39-3.44 (m, 2H), 2.02-2.12 (m, 2H), 1.37-1.39 (d, 3H, J = 6.92 Hz).
258	-	6.83-6.86 (m, 2H), 6.70-6.74 (m, 1H), 4.79-4.84 (q, 1H, J = 7.30 Hz), 3.70 (s, 6H), 3.52-3.55 (m, 2H), 3.20-3.25 (m, 2H, 1.89-1.99 (m, 2H), 1.20-1.22 (d, 3H, J = 7.16 Hz).
259	3059 (N-H stretching), 1693 (C=O stretching), 1242 (C-O stretching), 1174 (C-O stretching), 1026 (C-O stretching).	7.31-7.42 (m, 5H), 7.15-7.18 (m, 2H), 6.90-6.92 (m, 2H), 5.03 (s, 2H), 4.38-4.42 (m, 1H), 3.59-3.62 (m, 2H), 3.39-3.41 (m, 2H), 2.07-2.17 (m, 2H), 1.40-1.43 (m, 3H).

3.2 Biological Studies

In vitro biological studies were performed to evaluate the TACE inhibitory activities of the synthesized final compounds (e.g. G, H and L as in Scheme-1). Human monocytic acute leukemia (THP-1) cells were chosen for expressing TNF converting enzyme. The cells were grown and cell lysate was prepared according to the literature procedure[154]. This cell lysate was stored at -70 °C and used as the source of TACE in the enzyme inhibition studies as and when required in a span of seven days.

To assess the TACE inhibitory activity of the synthesized compounds, Innozyme™ TACE activity ELISA kit was procured from Calbiochem, USA (Catalog No. CBA042). The method followed for the assay was as given in the protocol supplied by the manufacturer[155].

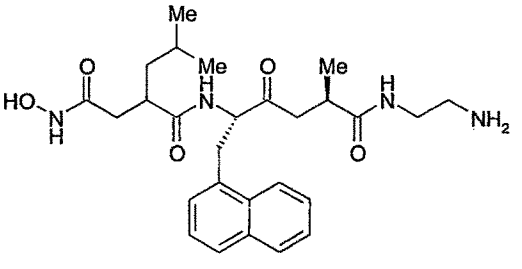
The kit contains 96 well plate and the wells are pre-coated with a monoclonal antibody specific for human TACE that captures the enzyme from the cell lysate. The diluted cell lysate was added to the wells and incubated for 1 hour at 25 °C. After the enzyme was attached to the antibody, the wells were washed to discard the unbound enzyme and inhibitors (synthesized compounds) were added to the designated wells. In one of the wells no inhibitor was added which was regarded as blank and in one of the wells TAPI-1, a well known TACE inhibitor was added. The wells were again incubated for 2 hours at 25 °C. In the presence of inhibitors, the enzyme would bind to

the inhibitor and there would be decrease in the concentration of the enzyme that was previously bound to the antibody. Upon addition of an internal fluorescent substrate (MCA-KPLGL-Dpa-AR-NH2), the free enzyme would cleave the scissile amide bond of the substrate. Fluorescence intensity of the cleaved product, MCA-KPLG was measured at an excitation wavelength of 355 nm and emission wavelength of 405 nm. The fluorescence intensity is indirectly related to the inhibitory activity of the test compounds. The inhibitory activity of a test compound in a particular concentration was calculated from the following equation:

% Inhibition = [1 - (Fluorescence intensity of test/Fluorescence intensity of blank)] x 100

[The blank well contains solvent (DMSO) and the substrate]

The TACE inhibitory activity of some of the selected compounds only was performed and the data has been given in Table-11. TAPI-1, a well known inhibitor of TACE and MMP[156], was used as the positive control in the study.



TAPI-1

From the activity data, the structure-activity relationship of this series of compounds is derived. It was noted that the five-membered 2-imidazolidinone ring is more favored in the central part of the molecule rather than the six-membered tetrahydropyrimidin-2(1*H*)-one ring. TACE inhibition was found out to be 35 % for compound (**151**) at 0.1 μM while for compound (**250**) the inhibition was only 14 % in the same concentration. Similarly, TACE inhibition was found out to be 38 % for compound (**131**) at 2.5 μM concentration and for compound (**234**) it was only 9 % in the same concentration. In the same manner, compound (**148**) showed an inhibition of 24 % at 0.1 μM concentration while for compound (**247**) it was 12 %. The same observation was noted for compounds (**147**) and (**246**) as well. Compound (**147**) showed an inhibition of 25 % at 2.5 μM concentration in comparison to compound (**246**) which showed only 9 % inhibition. Compounds (**163**) and (**259**) were almost equally active, showing 27 % and 24 % inhibition of TACE respectively, at 2.5 μM concentration.

Table-11. TACE Inhibitory activity of selected compounds

Compound No.	% Inhibition at Conc. (μM/L)	
	0.1	2.5
129	9	-
130	-	27
131	20	38
132	24	39.5
133	12	21
140	15	-
141	-	0
143	-	0
144	-	1
147	12	25
148	24	-
150	34	-
151	35	-
152	-	25
158	18	-
163	-	27
164	-	32
181	12	-
232	9	-
233	-	21
234	-	9
236	12	22
246	-	9
247	12	25
250	14	27
251	9	21
252	15	-
259	-	24
TAPI-1* (Positive Control)	22 (Lit.[156] 25)	-

- : Evaluation not performed in this concentration

* The Inhibition of TACE by TAPI-1 was determeined at 25 μM
The data shown here is obtained after averaging two readings

From the activity data, the structure-activity relationship of this series of compounds is derived. It was noted that the five-membered 2-imidazolidinone ring is more favored in the central part of the molecule rather than the six-membered tetrahydropyrimidin-2(1*H*)-one ring. TACE inhibition was found out to be 35 % for compound (**151**) at 0.1 μM while for compound (**250**) the inhibition was only 14 % in the same concentration. Similarly, TACE inhibition was found out to be 38 % for compound (**131**) at 2.5 μM concentration and for compound (**234**) it was only 9 % in the same concentration. In the same manner, compound (**148**) showed an inhibition of 24 % at 0.1 μM concentration while for compound (**247**) it was 12 %. The same observation was noted for compounds (**147**) and (**246**) as well. Compound (**147**) showed an inhibition of 25 % at 2.5 μM concentration in comparison to compound (**246**) which showed only 9 % inhibition. Compounds (**163**) and (**259**) were almost equally active, showing 27 % and 24 % inhibition of TACE respectively, at 2.5 μM concentration.

Compound (**232**) bearing carboxylic acid as the zinc binding group has shown activity in the same range in comparison to compound (**247**) at 0.1 μM concentration (9 % and 12 %, respectively). Compound (**140**) having carboxylate moiety has shown 15 % inhibition of the enzyme, while compound (**158**) having hydroxamate moiety has shown 18 % inhibition at 0.1 μM concentration. In these cases, it was observed that the hydroxamates were marginally more active than the corresponding caroxylates. Compound (**129**) bearing carboxylate moiety showed 9 % inhibition at 0.1 μM concentration while compound (**148**), having hydroxamate moiety showed 24 % inhibition in the same concentration. Compound (**181**) possessing the thiol group as the zinc binding motif has shown 12 % inhibition in the same concentration. Similarly, it was noted from the activities of compounds (**132**) and (**151**), that the hydroxamates were more active than carboxylates (24 and 35 % inhibition, respectively). The same observation was also made from the activities of compounds (**131**) and (**150**) (TACE inhibitory activities were 20 % and 34 %, respectively). From these observations, it could be concluded that although compounds bearing carboxylates and thiol as the zinc binding groups are active, but hydroxamate has higher inhibitory activity over the previous two ligands.

It was observed that the compounds having small P1' groups are not active against TACE (e. g. compounds (**141**) and (**143**)). Also compound (**144**) bearing 3,4,5-trimethoxyphenyl P1' group showed only 1 % inhibition of the enzyme. This result

validated the report that compounds ought to bear a bulky aromatic substitution at P1' position to be active against TACE.

The compound (**158**) having thioether linkage at P1' position is more active than the compound (**147**) bearing ether linkage in the same position, at 0.1 μM concentration (18 % inhibition by **158** in comparison to 12 % inhibition by **147**). This fact might be considered while designing newer TACE inhibitors in future.

The overall activity pattern of the compounds clearly shows that heterocyclic quinolinyl or pyridinyl ring at P1' position is a preferred ring system than simple phenyl or substituted phenyl ring. It has also been indicated from the above activity data that ethyl group is the group of choice at 2-position of quinolinyl ring. The phenyl ring at this position is not favored from the SAR point-of-view. Among the compounds tested, **151** has shown the highest activity (35 % inhibition at 0.1 μM concentration). Compound (**150**) which has shown 34 % inhibition of TACE at 0.1 μM concentration is also a very promising compound.

In this thesis, novel 2-imidazolidinones and tetrahydropyrimidin-2-(1*H*)-ones were synthesized and evaluated for their TACE inhibitory activity. Most of the synthesized compounds showed moderate to high TACE inhibitory activity. This piece of work has provided some important leads in the form of compounds (**131, 132, 148, 151** and **150**) as potential TACE inhibitors. These leads need to be exploited further in order to broaden the scope of the work.