Research Article

# Calcium Chloride Dihydrate: An Efficient Catalyst for the Synthesis of Hexahydropyrimidine Derivatives

Aman Hussain, Shivani Verma*, Sunita Bhandari and Virendra Kasana

Organic Synthesis Laboratory, Department of Chemistry, CBSH, G. B. Pant University of Agriculture and Technology, Pantnagar-263145, U. S. Nagar, Uttarakhand, India

**Abstract**

One pot three component methodology has been developed for the synthesis of hexahydropyrimidine derivatives by using ethyl/methyl acetoacetate, aniline and formaldehyde (1:2:3 ratio) as starting materials in the presence of calcium chloride dihydrate as catalyst (10 mol%) under solvent free condition at room temperature with good to excellent yield (70-95%) and short reaction time. Calcium chloride dihydrate as a catalyst offers simple, efficient and economical method for this reaction. All the compounds were characterized by FT-IR and $^{1}$HNMR data.

**Keywords:** Hexahydropyrimidine, solvent free, catalyst, calcium chloride dihydrate, FT-IR, Proton NMR

***Correspondence**

Author: Shivani Verma

Email: shivaniverma407@gmail.com

## Introduction

Hexahydropyrimidines are heterocyclic compounds found in many natural products as pharmaceutical agents [1]. It has been reported that these derivatives having diverse biological activities including anti-inflammatory [2], leishmanicidal [3], anticonvulsant [4], antifolate [5], hepatitis B virus inhibitor [6], antimicrobial [7], anti-rubella [8], anxiolytic [9], anti-HIV [10], cytotoxic [11], anticancer [12], antibacterial [13], antifungal [14-15] and antiviral [16]. Several derivatives of hexahydropyrimidine are used as polymers stabilizers [17].

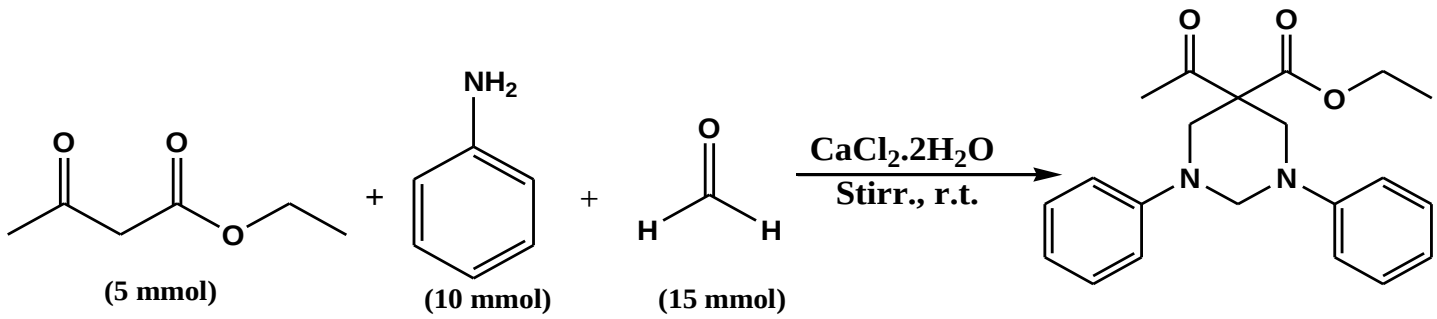
Hexahydropyrimidine derivatives have been prepared by the reaction of 1,3- dicarbonyl compound, aromatic amine and formaldehyde in 1:2:3 ratio. Various methods have been reported for the synthesis of hexahydropyrimidine derivatives such as $FeCl_3$ in the presence of DCM as a solvent [18-19], para-toluene sulfonic acid [20], indium triflate [21], superparamagnetic $Fe_3O_4$ [22], Clay-sulphonated PVA polymer [23], Dy/chitosan [24], microwave [25] and in acidic solvent [26]. Reported methods have suffers long reaction time, drastic condition and low yield. Now days, due to their significant biologically activity, a new methodology of hexahydropyrimidines synthesis with less time and high yield have received a great deal of attention.

## Experimental Details

All the chemicals were purchased from hi-media and were used without further purification. $^{1}$H NMR spectra were recorded on 400 MHz JEOL JNM ECS400 and BRUKER AVANCE DRX-500 MHz spectrophotometer using $CDCl_3$ as a solvent and TMS as an internal standard. FT-IR spectra were recorded on BRUKER (Alpha) FT-IR spectrometer. The purity of products and reaction progress were checked using solvent system hexane: ethyl acetate in varying composition depending on the polarity of the constituents of reaction mixture and visualized using iodine vapors.

### *General Procedure for the synthesis of hexahydropyrimidine derivatives*

In a round bottom flask ethyl/methyl acetoacetate (5 mmol), aniline (10 mmol), formaldehyde 40% (15 mmol) and calcium chloride dihydrate (10 mol%) as a catalyst were taken (**Scheme 1**). The reaction mixture was magnetically stirred at room temperature. After some time of stirring the reaction mixture was converted into solid state. The completion of the reaction was monitored by TLC using hexane: ethyl acetate (95:5) as mobile phase. The crude solid was obtained and washed with hexane then dissolved in ethyl acetate and transferred into separating funnel. The solution was washed three times with water to remove calcium chloride dihydrate and other impurities. The solvent was removed by evaporating it under reduced pressure. The obtained product was recrystallized from hot ethanol to get the pure product.




**Scheme 1** Synthesis of hexahydropyrimidine

## Result and Discussion

Reaction conditions were standardized by taking ethyl/methyl acetoacetate (5 mmol), aniline (10 mmol) and formaldehyde 40% (15 mmol) as starting material and calcium chloride dihydrate as a catalyst in round bottom flask (**Table 1**). This reaction carried out at room temperature took longer time (40 min) and afforded 35% yield in the absence of catalyst but at reflux condition it took 26 min and afforded 56% yield. The same reaction carried out in the presence of calcium chloride dihydrate (2 mol%) as catalyst took 15 min and afforded 85% yield but by taking 5 mol% catalyst afforded 89% of yield. With increase the concentration of catalyst from 10-20 mol%, it has been found that there was no comparable difference in the product yield. This clearly shows the importance of catalyst. In our approach, the stoichiometric ratio of 1:2:3 (ethyl/methyl acetoacetate: amine: formaldehyde) in the presence of calcium chloride dihydrate 10 mol% as catalyst with stirring at room temperature in solvent free condition was found to be the optimum condition for the maximum yield of hexahydropyrimidine.

**Table 1** Standardization of reaction conditions for the synthesis of hexahydropyrimidine

| Entry | Condition | Mol% | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | Without catalyst, room temp | - | 40 | 35 |
| 2 | Without catalyst, reflux | - | 26 | 56 |
| 3 | $CaCl_2.2H_2O$, room temp | 2 | 15 | 85 |
| 4 | $CaCl_2.2H_2O$, room temp | 5 | 9 | 89 |
| 5 | $CaCl_2.2H_2O$, room temp | 10 | 4 | 92 |
| 6 | $CaCl_2.2H_2O$, $50^0C$ | 10 | 4 | 93 |
| 7 | $CaCl_2.2H_2O$, room temp | 20 | 5 | 92 |

The same amount of catalyst was used to synthesize all the derivatives of hexahydropyrimidine by taking substituted aniline derivatives (**Table 2**). The percent yield, melting point, color and time taken for completion of reaction are presented in Table 2. All the reactions were completed within 4-115 minutes. Perusal of Table 2 it has been found that there is not much difference in the yield of reaction with different substituted aniline (electron donating and electron with drawing group).

The plausible mechanism of the multicomponent reaction leading to formation of hexahydropyrimidine from ethylacetoacetate, aniline and formaldehyde catalysed by $CaCl_2.2H_2O$ is proposed in **Figure 1**. The ethyl acetoacetate undergoes alpha amino methylation reaction twice in succession on the same alpha carbon of carbonyl group catalyzed by $CaCl_2.2H_2O$. Substituted propane 1,3 di-amine thus form gives condensation reaction with formaldehyde resulting in desired hexahydropyrimidine. $CaCl_2.2H_2O$ because of its acidic nature facilitated in enolization steps of ethyl acetoacetate.

### *Spectral analysis*

**[H-01] 5-acetyl-1,3-diphenyl-hexahydropyrimidine-5-ethyl ester: FTIR KBr ($cm^{-1}$),** 2981 (CH), 1709 (RCOOR), 1594 (C=C), 1224 (N-C); **$^1$H NMR ($CDCl_3$, TMS, 500MHz):** δ 7.23-6.8 (m, 10H, Ar-H), 4.18 (d, 2H, $NCH_2$), 1.29 (t,3H,- CH3), 2.14 (m, 2H,-CH2), 2.24 (s, 3H, O=C-O-$CH_3$), 3.76 (s, 3H, O=C-$CH_3$), 4.14 (d, 2H, N-$CH_2$), 4.16 (d, 2H, N-$CH_2$).

**[H-02] 5-acetyl-1,3-bis(2-chlorophenyl)-hexahydropyrimidine-5-ethyl ester: FTIR KBr ($cm^{-1}$),** 3419 (CH), 1710 (RCOOR), 1502 (C=C), 1031 (C-N), 739 (C-Cl); **$^1$H NMR ($CDCl_3$, TMS, 400MHz):** δ 7.24-6.6 (m, 8H, Ar-H), 4.18 (d, 2H, $NCH_2$), 2.24 (s, 3H, O=C-O-$CH_3$), 3.76 (s, 3H, O=C-$CH_3$), 4.14 (d, 2H, N-$CH_2$), 4.16 (d, 2H, N-$CH_2$).

**Table 2** Synthesis of different derivatives of hexahydropyrimidine

| S. No. | Compound code | IUPAC Name | Per cent yield (%) | Colour | M.P $^0$C | Time in min. |
|---|---|---|---|---|---|---|
| 1 | H-01 | 5-acetyl-1,3-diphenyl-hexahydropyrimidine- 5-ethyl ester | 70 | Orange | 109 | 4 |
| 2 | H-02 | 5-acetyl-1,3-bis(2-chlorophenyl)-hexahydropyrimidine-5- ethyl ester | 70 | Red | 85 | 5 |
| 3 | H-03 | 5-acetyl-1,3bis(4-fluorop-henyl)-hexahydropyrimidine-5-ethyl ester | 70 | White | 121 | 5 |
| 4 | H-04 | 5-acetyl-1,3-bis(2-chlorophenyl)-hexahydropyrimidine-5- methyl ester | 70 | Yellow | 155 | 5 |
| 5 | H-05 | 5-acetyl-1,3-bis(2,4-dimethylphenyl)-hexahydropyrimidine-5-ethyl ester | 75 | Yellow | 178 | 115 |
| 6 | H-06 | 5-acetyl-1,3-bis(4-hydroxyphenyl)-hexahydropyrimidine-5-ethyl ester | 80 | Black | 5 | 4 |
| 7 | H-07 | 5-acetyl-1,3-diphenyl-hexahydropyrimidine-5-methyl ester | 70 | Red | 122 | 90 |
| 8 | H-08 | 5-acetyl-1,3-bis(4-fluorophenyl)-hexahydropyrimidine-5-methyl ester | 70 | Red | 124 | 5 |
| 9 | H-10 | 5-acetyl-1,3-bis(2,4-dimethylphenyl)-hexahydropyrimidine-5-methyl ester | 80 | Yellow | 182 | 110 |
| 11 | H-11 | 5-acetyl-1,3-bis(4-hydroxyphenyl)- hexahydropyrimidine -5-methyl ester | 80 | Black | 101 | 4 |
| 12 | H-12 | 9,9-dimethyl-1,3-diphenyl-1,3-diazaspiro (5.5) undecane-7,11-dione | 70 | Red | 180 | 4 |

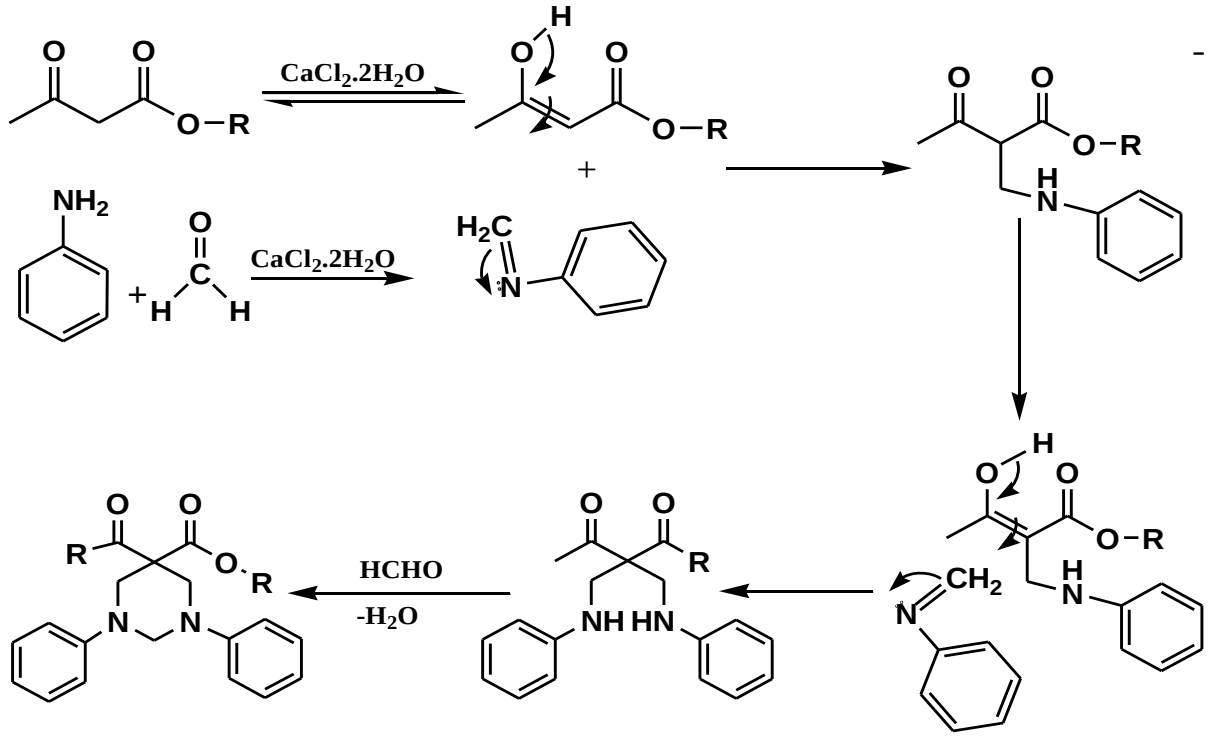



**Figure 1** Plausible mechanism for the formation of hexahydropyrimidine

**[H-03] 5-acetyl-1,3-bis(4-fluorophenyl)-hexahydropyrimidine-5-ethyl ester: FTIR KBr (cm$^{-1}$),** 1739 (RCOOR), 1503 (C=C), 1010 (C-F); **$^1$H NMR (CDCl$_3$, TMS, 400MHz):** δ 7.24 (dd, 2H,Ar-H), 6.98 (dd, 2H,Ar-H), 6.60 (dd, 2H,Ar-H), 2.24 (s, 3H, O=C-O-CH$_3$), 3.76 (s, 3H, O=C-CH$_3$), 4.14 (d, 2H, N-CH$_2$), 4.16 (d, 2H, N-CH$_2$).

**[H-04] 5-acetyl-1,3-bis(2-chlorophenyl)-hexahydropyrimidine-5-methyl ester: FTIR KBr (cm$^{-1}$),** 2948 (CH), 1653 (RCOOR), 1585 (C=C), 786 (C-Cl); **$^1$H NMR (CDCl$_3$, TMS, 400MHz):** δ 7.24-6.6 (m, 8H, Ar-H), 4.18 (d, 2H, NCH$_2$), 2.24 (s, 3H, O=C-O-CH$_3$), 3.76 (s, 3H, O=C-CH$_3$), 4.14 (d, 2H, N-CH$_2$), 4.16 (d, 2H, N-CH$_2$).

**[H-05] 5-acetyl-1,3-bis(2,4-dimethylphenyl)-hexahydropyrimidine-5-ethyl ester: FTIR KBr ($cm^{-1}$), 2978 (CH),** 1711 (RCOOR), 1616 (C=C), 765 (N-C)

**[H-06] 5-acetyl-1,3-bis(4-hydroxyphenyl)-hexahydropyrimidine-5-ethyl ester: FTIR KBr ($cm^{-1}$),** 3224 (OH), 2984 (CH), 1711 (RCOOR), (C=O), 1509 (C=C), 1222 (N-C)

**[H-07] 5-acetyl-1,3-diphenyl-hexahydropyrimidine-5-methyl ester: FTIR KBr ($cm^{-1}$),** 2982 (C-H), 1710 (RCOOR), 1591 (C=O), 1507 (C=C); **$^1$H NMR ($CDCl_3$, TMS, 400MHz):** δ 7.24-6.6 (m, 10H, Ar-H), 4.18 (d, 2H, $NCH_2$)2.24 (s, 3H, O=C-O-$CH_3$), 3.76 (s, 3H, O=C-$CH_3$), 4.14 (d, 2H, N-$CH_2$), 4.16 (d, 2H, N-$CH_2$).

**[H-08] 5-acetyl-1,3-bis(4-fulorophenyl)-1,3-hexahydropyrimidine-5-methyl ester: FTIR KBr ($cm^{-1}$),** 2952 (C-H), 1710 (RCOOR), 1574 (C=O), 1504 (C=C), 823 (C-F)

**[H-10] 5-acetyl-1,3-bis(2,4-dimethylphenyl)-1,3-hexahydropyrimidine-5-methyl ester: FTIR KBr ($cm^{-1}$),** 1743 (RCOOR), 1650 (C=O), 1514 (C=C)

**[H-11] 5-acetyl-1,3-bis(4-hydroxypenyl)-1,3- hexahydropyrimidine -5-methyl ester: FTIR KBr ($cm^{-1}$),** 3333 (OH), 1771 (RCOOR), 1642 (C=O), 1544 (C=C)

**[H-12] 9,9-dimethyl-1,3-diphenyl-1,3-diazaspiro (5.5) undecane-7,11-dione: FTIR KBr ($cm^{-1}$),** 1646 (C=O), 1536 (C=C)

## Conclusion

In summary, we have developed a new methodology for the synthesis of hexahydropyrimidine derivatives with highly efficient and green protocol via multicomponent reactions by using calcium chloride dihydrate as a catalyst. This method is simple, energy saving, and cost effective.

## Acknowledgement

We are thankful to G. B. P. U. A. & T. Pantnagar for providing Lab facilities, FT-IR spectra, IIT Ropar for providing $^1$HNMR and $^{13}$CNMR spectra.

## References

[1] I.A. Perillo, M.B. García, J.A. Bisceglia L.R. Orelli, J. Heterocyclic Chem., 2002, 39, 655.
[2] I. A. Shehata, R.A. Glennon, J. Heterocyclic Chem. 1987, 24, 1291.
[3] V.J. Ram, N. Haque, J. Cheminform, 1995, 26.
[4] U. Çaliş, M. Köksal, Drug Res., 2001, 51, 523.
[5] P. Prabakaran, J.J. Robert, P. Thomas Muthiah, G. Bocelli, L. Righi, Acta Cryst. C, 2001, 57,459.
[6] R. Kumar, M. Nath, D.L.J. Tyrrell, J. Med. Chem. 2002, 45, 2032.
[7] E. Gossnitzer, G. Feierl, U. Wagner, Eur. J. Pharm. Sci., 2002, 15, 49.
[8] R. Saladino, U. Ciambecchini, G. Maga, P. Mastromarino, C. Conti, M. Botta, Bioorg. Med. Chem. 2002, 10, 2143.
[9] E. Wagner, L. Becan, E. Nowakowska, Bioorg. Med. Chem., 2004, 12, 265.
[10] M. Sechi, L. Sannia, F. Carta, M. Palomba, R. Dallocchio, A. Dessì, M. Derudas, Z. Zawahir, N. Neamati, Antivir. Chem. Chem. 2005, 16, 41.
[11] O. C. Agbaje, O.O. Fadeyi, S.A. Fadeyi, L.E. Myles, C.O. Okoro, Bioorg. Med. Chem. Lett, 2011, 21, 989.
[12] S. Nishida, H. Maruoka, Y. Yoshimura, T. Goto, R. Tomita, E. Masumoto, F. Okabe, K. Yamagata, T. Fujioka, J. Heterocyclic Chem. 2012, 49, 303.
[13] N.D. Gaikwad, S.V. Patil, V.D. Bobade, J. Heterocyclic Chem. 2013, 50, 519.
[14] M. Brahmayya, B. Venkateswararao, D. Krishnarao, S. Durgarao, U.V. Prasad, T. Damodharam, R. Mishra, J. Pharm Res. 2013, 7, 516.
[15] L.L. Martin, L. Davis, J.T. Klein, P. Nemoto, G.E. Olsen, G.M. Bores, F. Camacho, W.W. Petko, D.K. Rush, D. Selk, C.P. Smith, Bioorg. Med. Chem.Lett, 1997, 7, 157.
[16] J.Y. Hwang, H.Y. Kim, S. Jo, E. Park, J. Choi, S. Kong, D.S. Park, J.M. Heo, J.S. Lee, Y. Ko, I. Choi, Eur. J. Med. Chem., 2013, 70, 315.

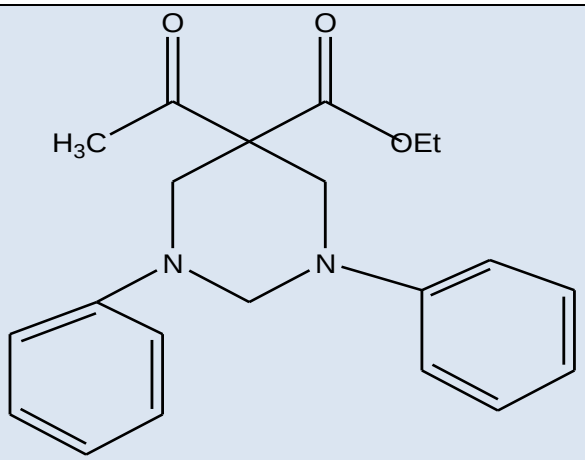
[17] M. Mayr, K. Wurst, K. H. Ongania, M.R. Buchmeiser, Chem. Eur. J., 2004, 10, 1256.
[18] C. Mukhopadhyay, S. Rana, R.J. Butcher, Tetrahedron Lett., 2011, 52, 4153.
[19] A. Saleh, M. Morton, J. D'Angelo, Syn. Comm., 2014, 44, 2715.
[20] H. F. Zohdi, N.M. Rateb, S.M. Elnagdy, Eur J. Med. Chem., 2011, 46, 5636.
[21] A. Dandia, A. K. Jain, S. Sharma, Tetrahedron Lett., 2012, 53, 5270.
[22] F. Janati, M.M. Heravi, A. Mirshokraie, J. Chem. 2013, 2012.
[23] A. Nayak, 2014. Synthesis, characterization and catalytic application of clay-sulphonated PVA based composite materials (Doctoral dissertation).
[24] N. Ahmed, S. Tarannum, Z.N. Siddiqui, RSC Adv., 2015, 5, 50691.
[25] M.I.P. Reis, V.R. Campos, J.A. Resende, F.C. Silva, V.F. Ferreira, Beilstein J. Org Chem, 2015, 11, 1235.
[26] N.N. Gibadullina, D.R. Latypova, V.A. Vakhitov, D.V. Khasanova, L.F. Zainullina, Y.V. Vakhitova, A.N. Lobov, B.I. Ugrak, Y.V. Tomilov, V.A. Dokichev, J. Flu. Chem., 2018, 211, 94.



Publication History
Received 04th Aug 2018
Revised 28th Sep 2018
Accepted 12th Oct 2018
Online 30th Oct 2018

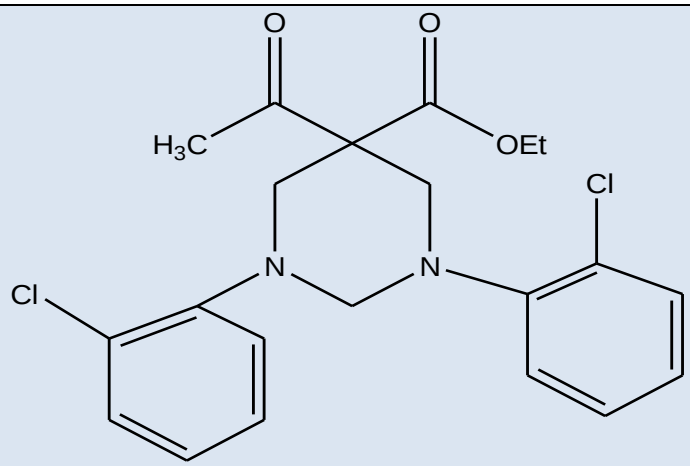
# Supporting Materials

**Hexahydropyrimidine**



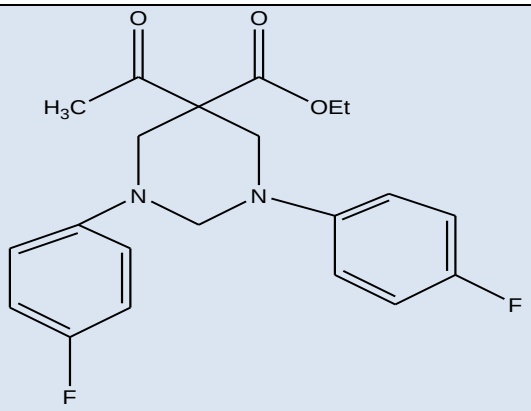

**PRODUCT CODE : H-01**

**IR KBr,** 2981 (CH), 1709 (RCOOR), 1594 (C=C), 1224 (N-C)
**$^1$H NMR (CDCl$_3$, TMS, 500MHz):** δ 7.23-6.8 (m, 10H, Ar-H), 4.18 (d,2H, NCH$_2$), 1.29 (t,3H,- CH3), 2.14 (m, 2H,-CH2), 2.24 (s, 3H, O=C-O-CH$_3$), 3.76 (s, 3H, O=C-CH$_3$), 4.14 (d, 2H, N-CH$_2$), 4.16 (d, 2H, N-CH$_2$)



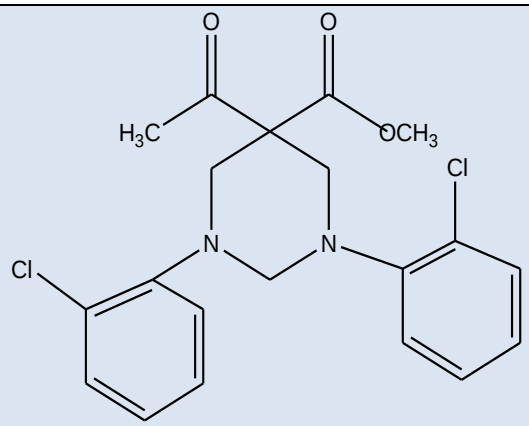

**PRODUCT CODE : H-02**

**IR KBr,** 3419 (CH), 1710 (RCOOR), 1502 (C=C), 1031 (C-N), 739 (C-Cl)
**$^1$H NMR** (CDCl$_3$, TMS, 400MHz): δ 7.24-6.6 (m, 8H, Ar-H), 4.18 (d, 2H, NCH$_2$), 2.24 (s, 3H, O=C-O-CH$_3$), 3.76 (s, 3H, O=C-CH$_3$), 4.14 (d, 2H, N-CH$_2$), 4.16 (d, 2H, N-CH$_2$)



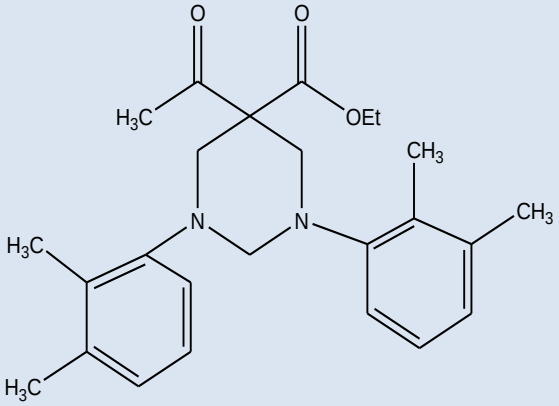
**PRODUCT CODE : H-03**

**IR KBr,** 1739 (RCOOR), 1503 (C=C), 1010 (C-F)
**$^1$H NMR ($CDCl_3$, TMS, 400MHz):** δ 7.24 (dd, 2H,Ar-H), 6.98 (dd, 2H,Ar-H), 6.60 (dd, 2H,Ar-H), 2.24 (s, 3H, O=C-O-$CH_3$), 3.76 (s, 3H, O=C-$CH_3$), 4.14 (d, 2H, N-$CH_2$), 4.16 (d, 2H, N-$CH_2$)



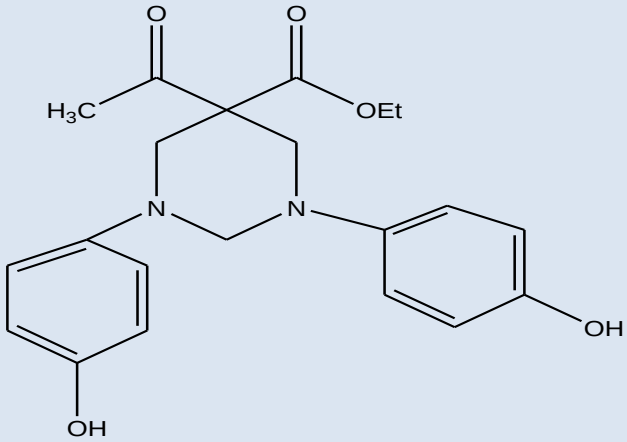
**PRODUCT CODE : H-04**

**IR KBr,** 2948 (CH), 1653 (RCOOR), 1585 (C=C), 786 (C-Cl)
**$^1$H NMR ($CDCl_3$, TMS, 400MHz):** δ 7.24-6.6 (m, 8H, Ar-H), 4.18 (d, 2H, $NCH_2$), 2.24 (s, 3H, O=C-O-$CH_3$), 3.76 (s, 3H, O=C-$CH_3$), 4.14 (d, 2H, N-$CH_2$), 4.16 (d, 2H, N-$CH_2$)



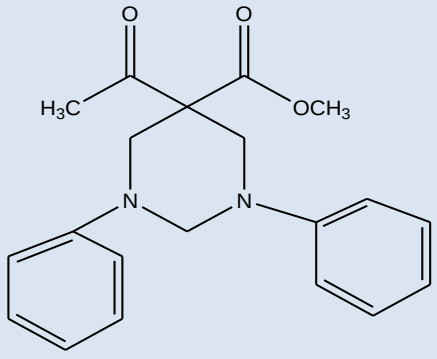
**PRODUCT CODE : H-005**

**IR KBr,** 2978 (CH), 1711 (RCOOR), 1616 (C=C), 765 (N-C



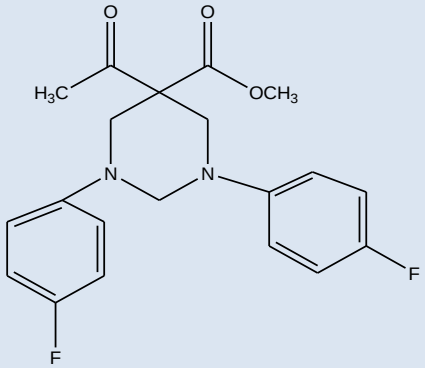
**PRODUCT CODE : H-06**

**IR KBr,** 3224 (OH), 2984 (CH), 1711 (RCOOR), (C=O), 1509 (C=C), 1222 (N-C)



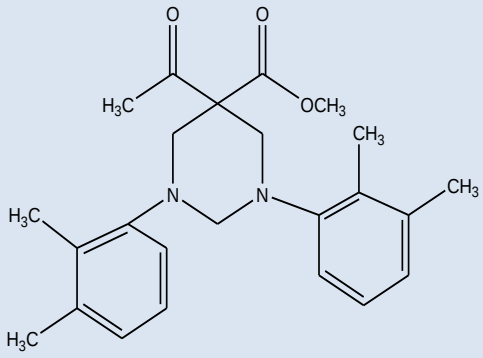
**PRODUCT CODE : H-07**

**IR KBr,** 2982 (C-H), 1710 (RCOOR), 1591 (C=O), 1507 (C=C)



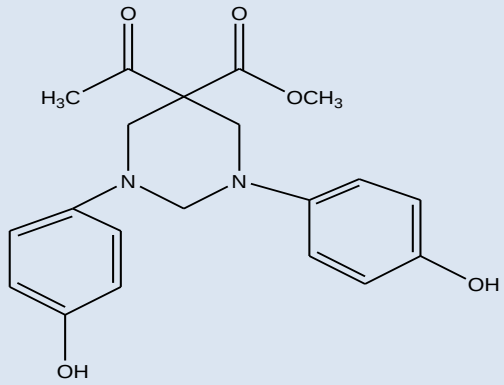
**PRODUCT CODE : H-08**

**IR KBr,** 2952 (C-H), 1710 (RCOOR), 1574 (C=O), 1504 (C=C), 823 (C-F)



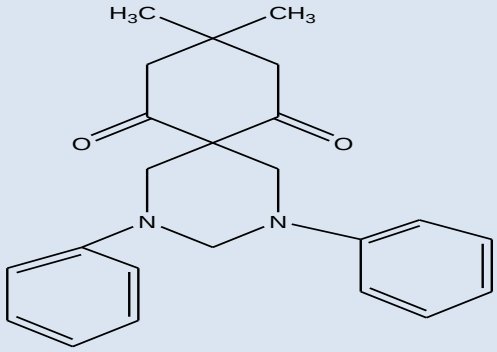
**PRODUCT CODE : H-10**

**IR KBr,** 1743 (RCOOR), 1650 (C=O), 1514 (C=C)



**PRODUCT CODE : H-11**

**IR KBr,** 3333 (OH), 1771 (RCOOR), 1642 (C=O), 1544 (C=C)



**PRODUCT CODE : H-12**

**IR KBr,** 1646 (C=O), 1536 (C=C)

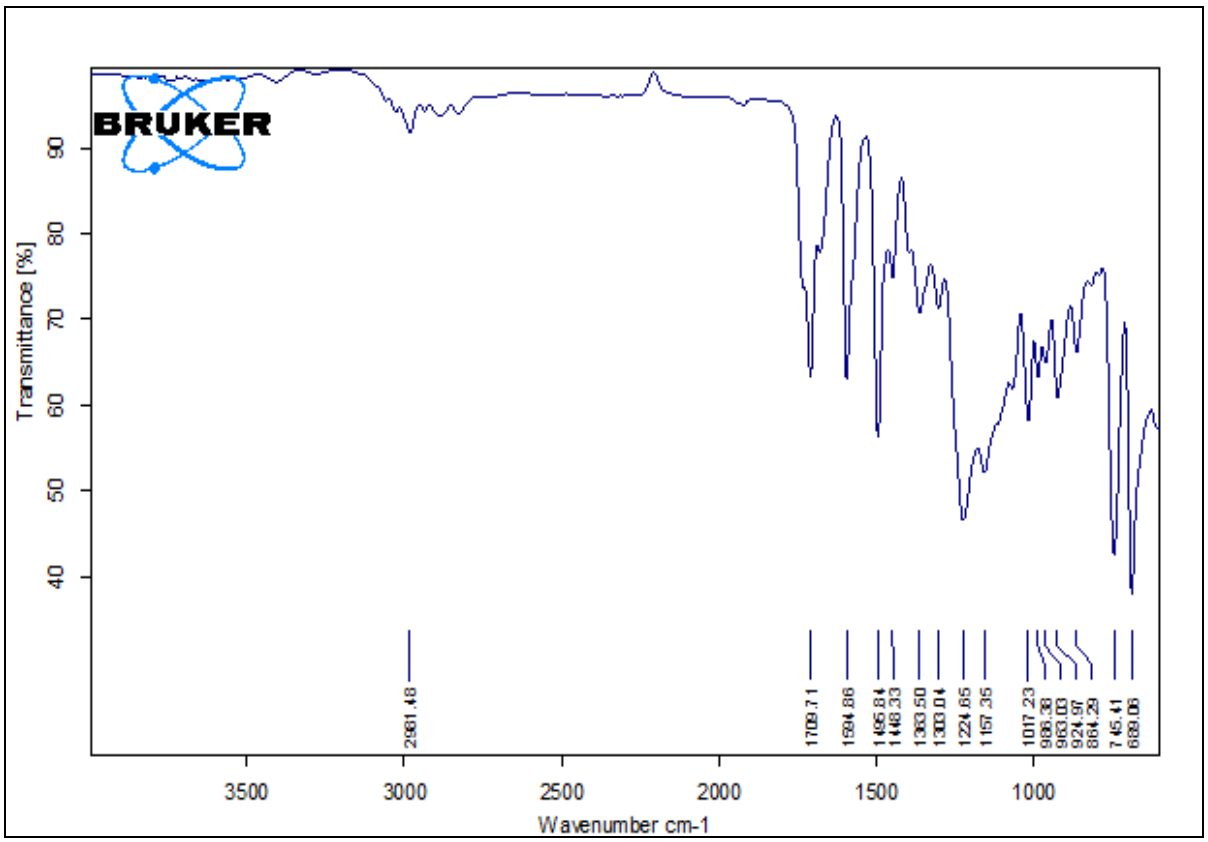



**Figure** FT-IR spectra of H-01

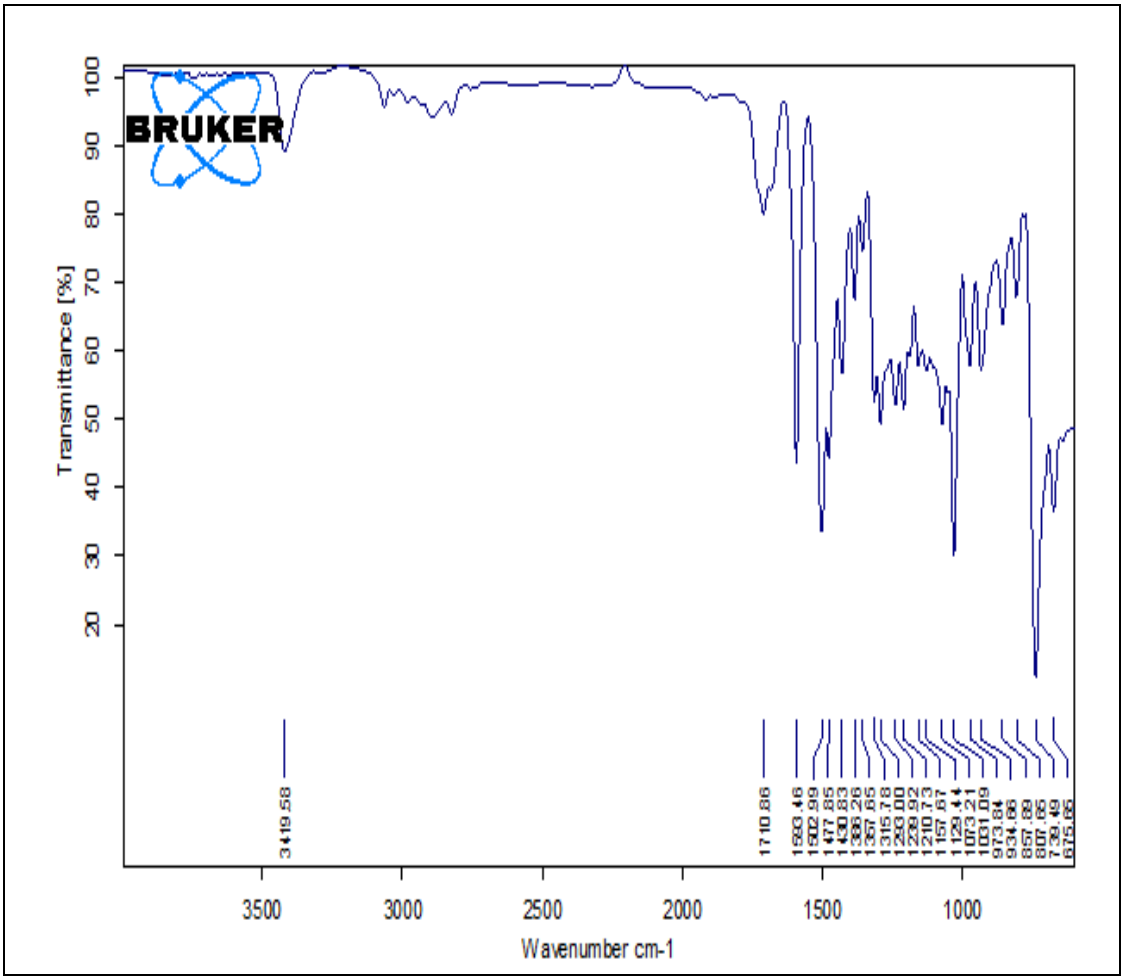



**Figure** FT-IR spectra of H-02

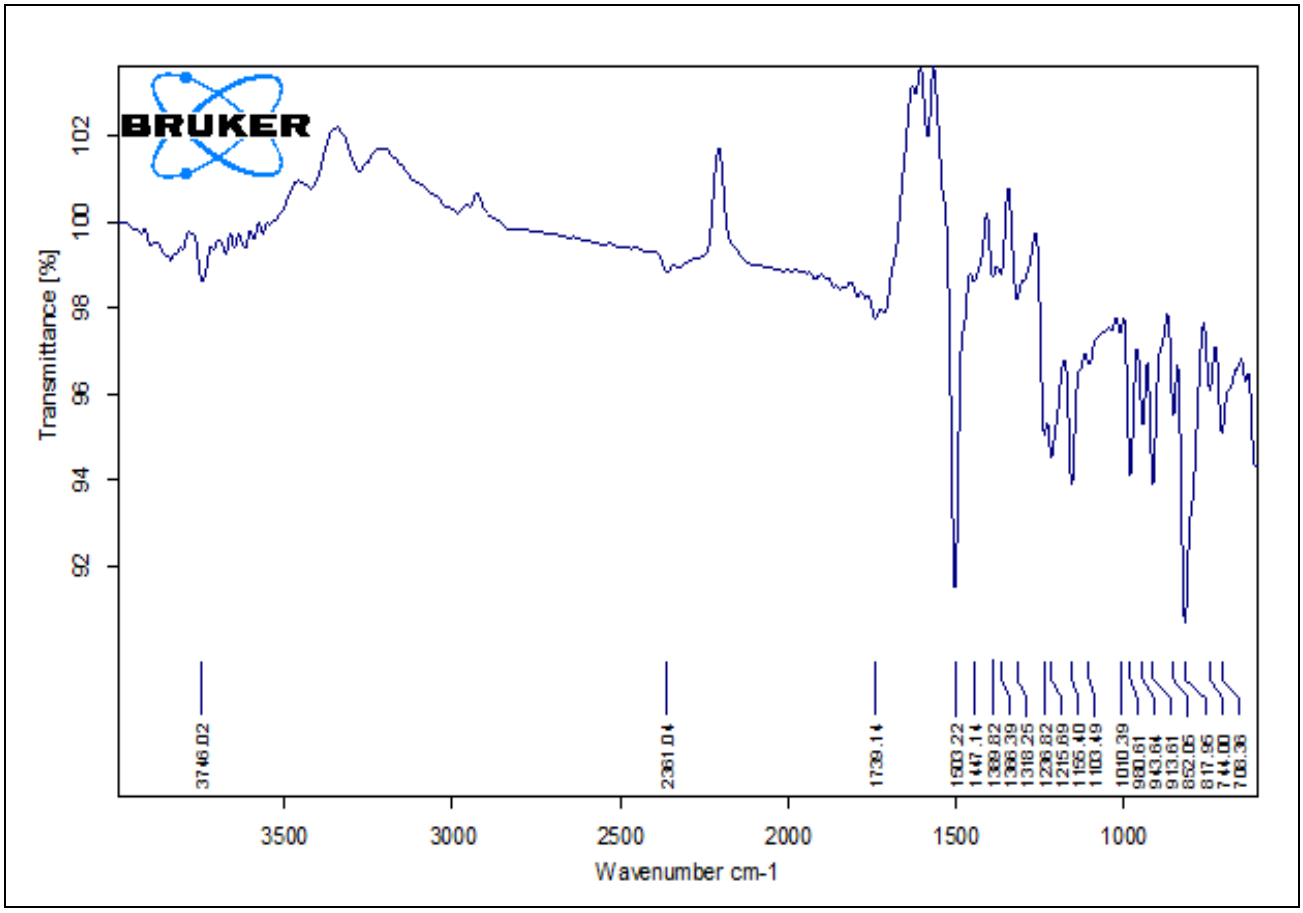



**Figure** FT-IR spectra of H-03

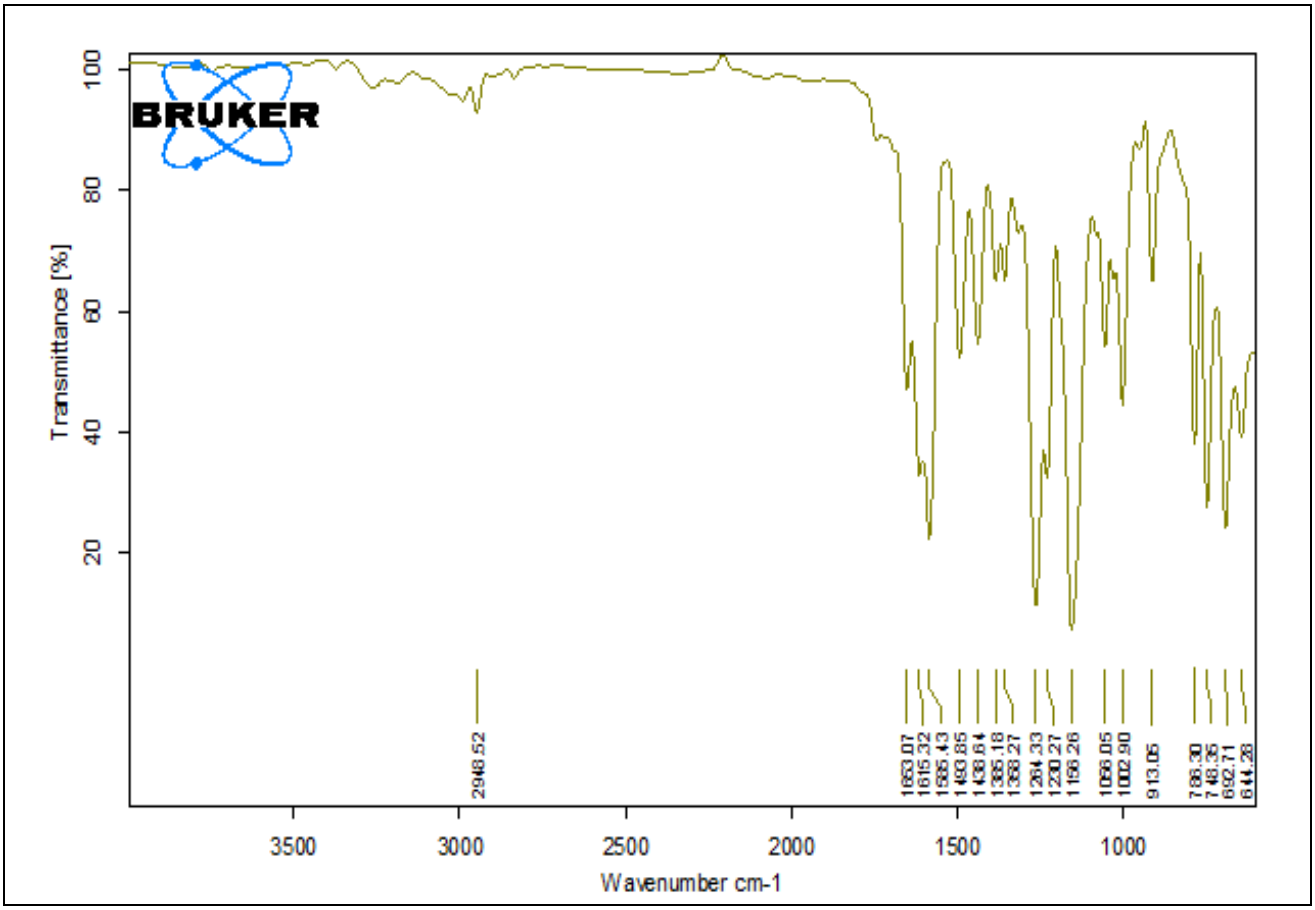



**Figure** FT-IR spectra of H-04

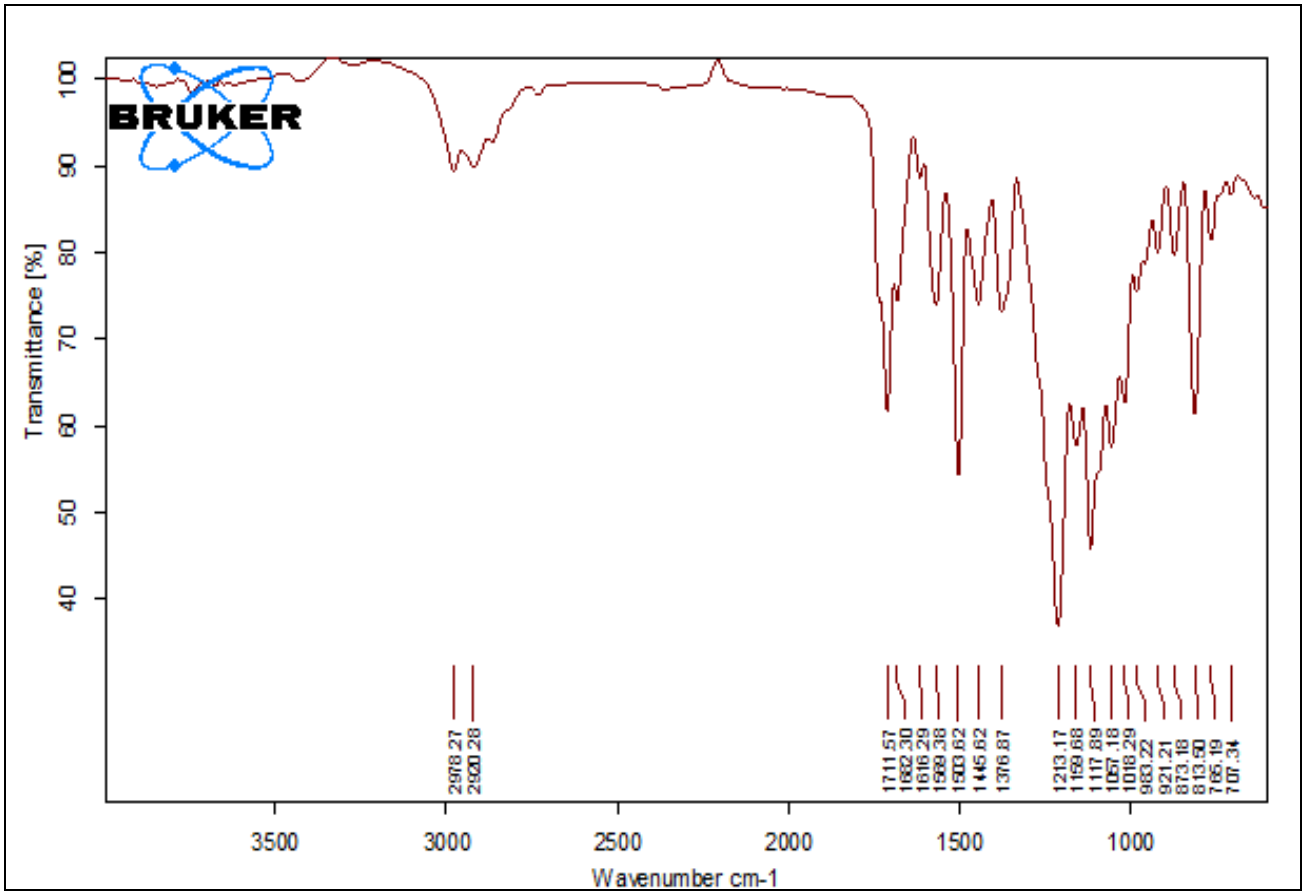



**Figure** FT-IR spectra of H-05

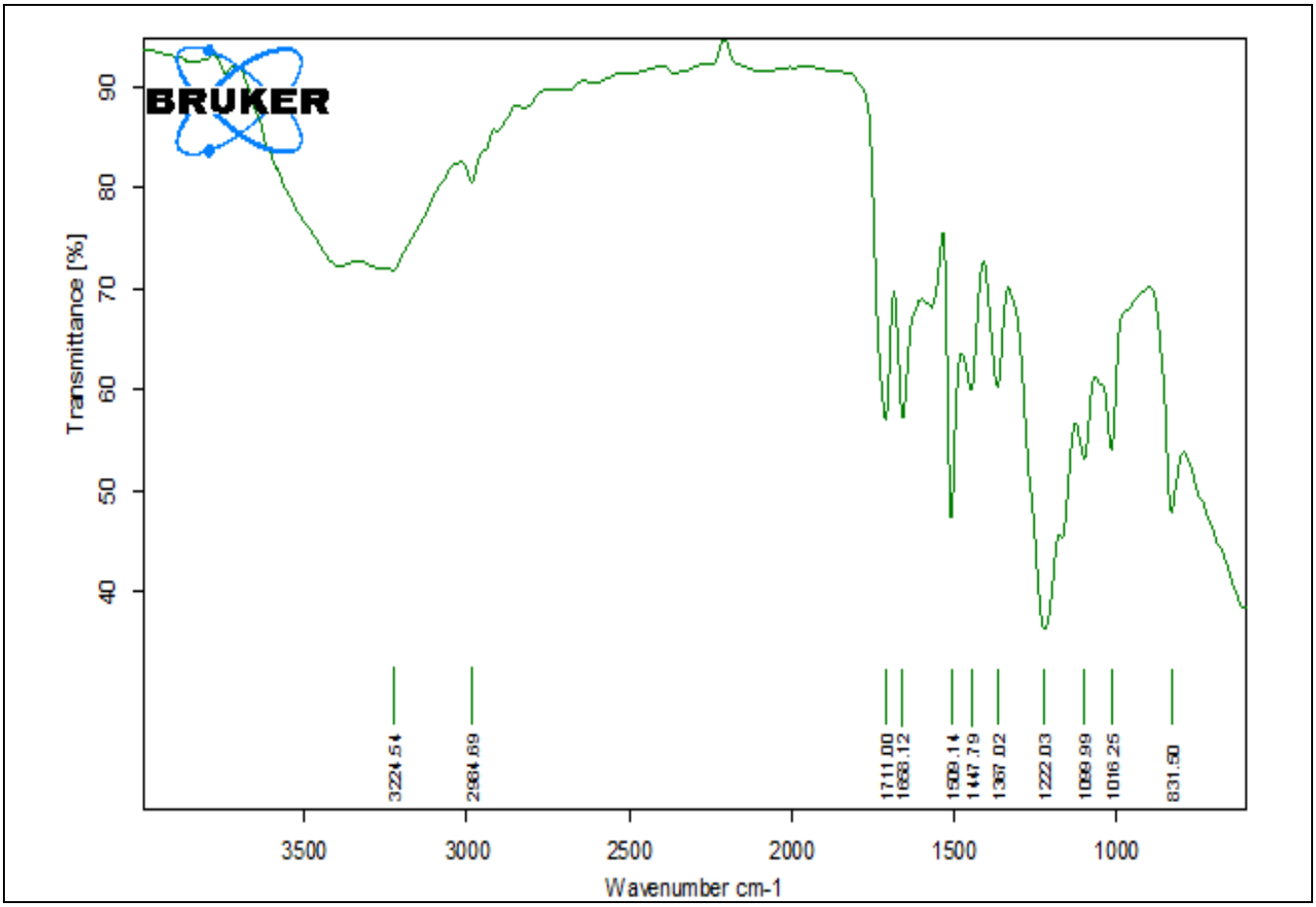



**Figure** FT-IR spectra of H-06

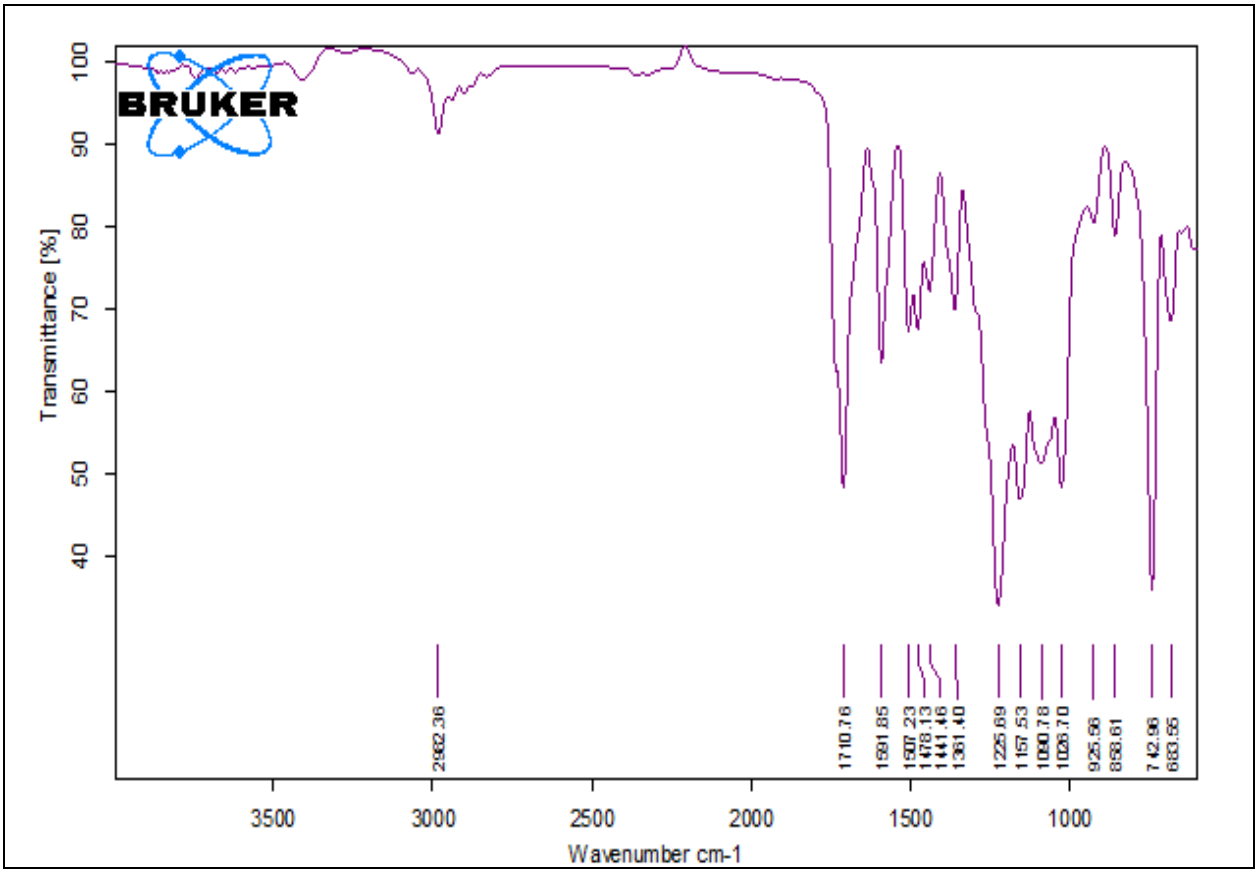



**Figure** FT-IR Spectra of H-07

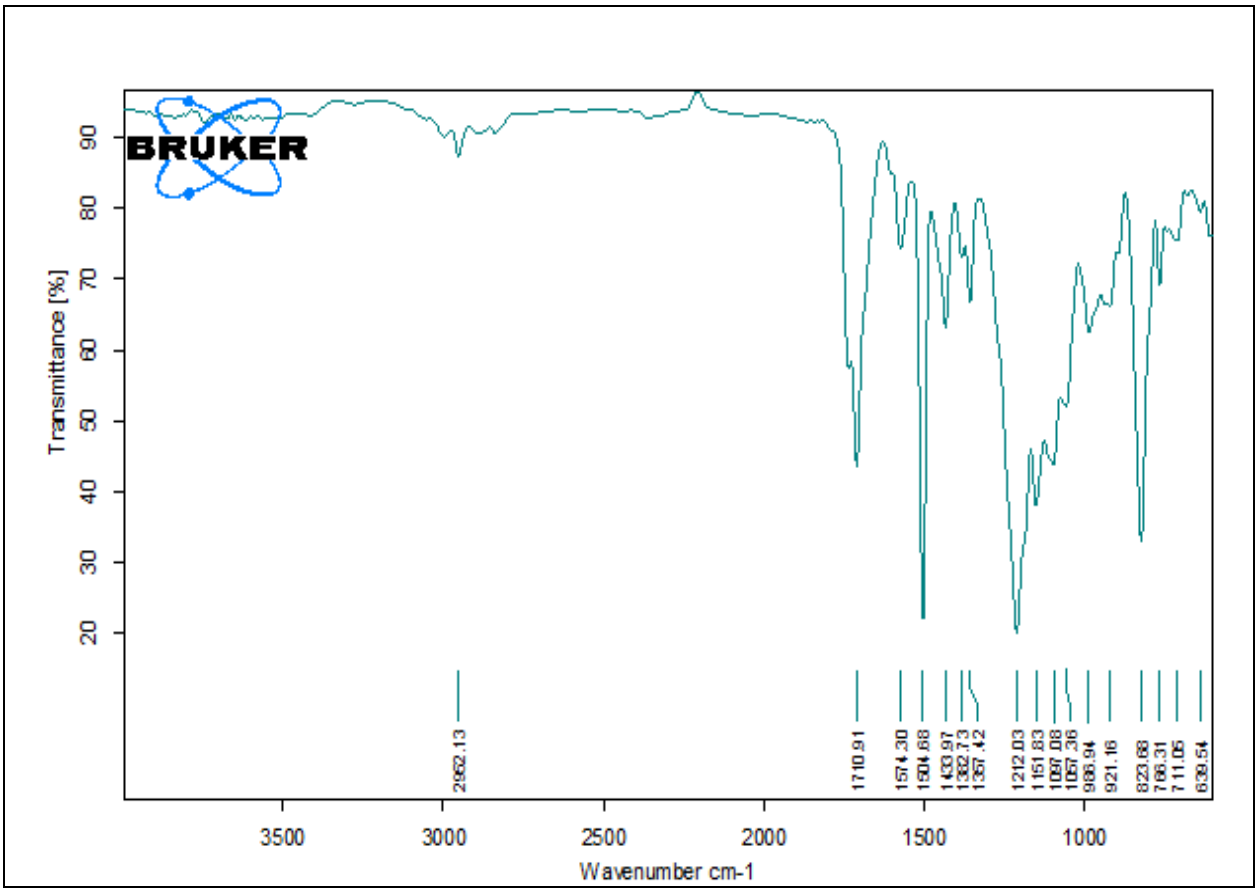



**Figure** FT-IR Spectra of H-08

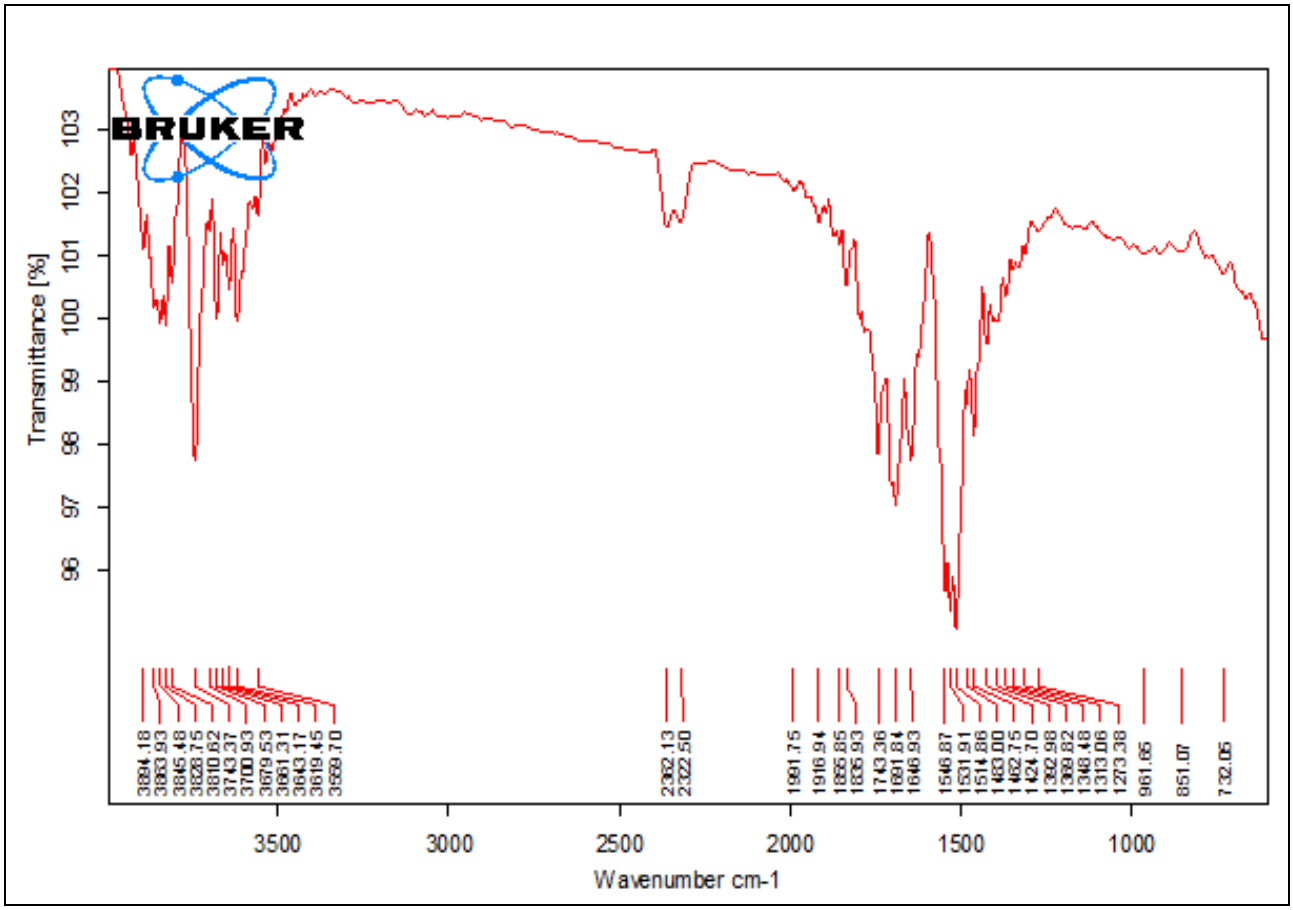



**Figure** FT-IR spectra of H-10

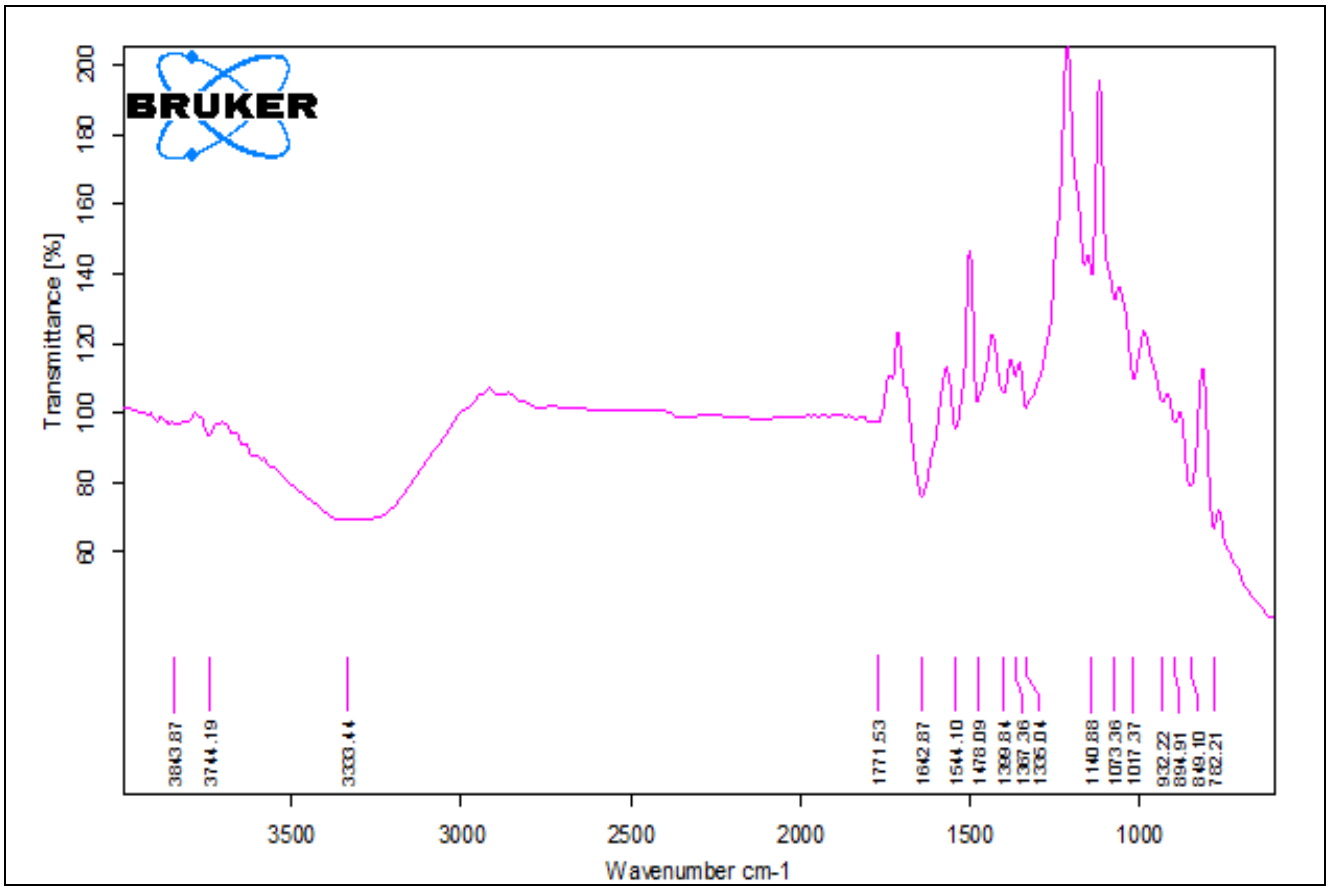



**Figure** FT-IR spectra of H-11

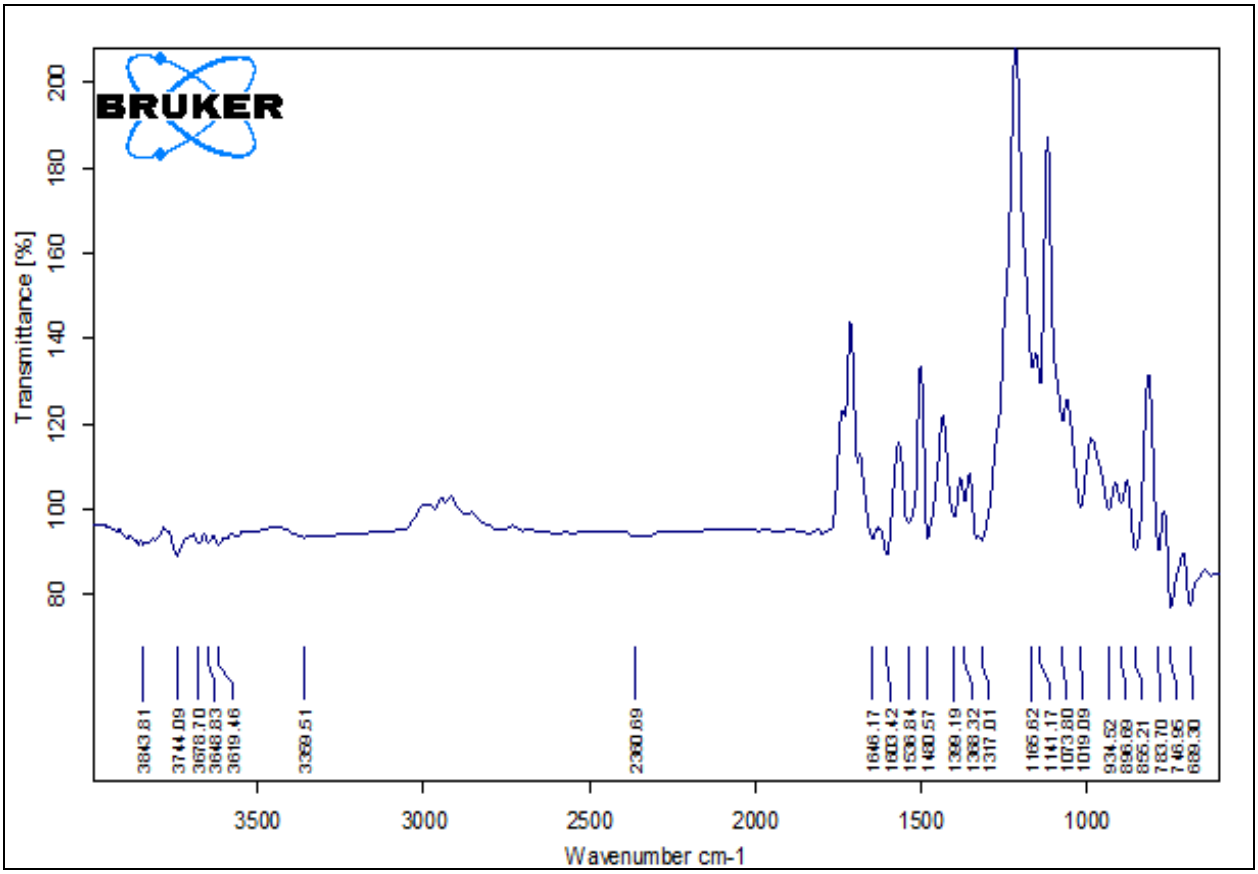



**Figure** FT-IR spectra of H-12

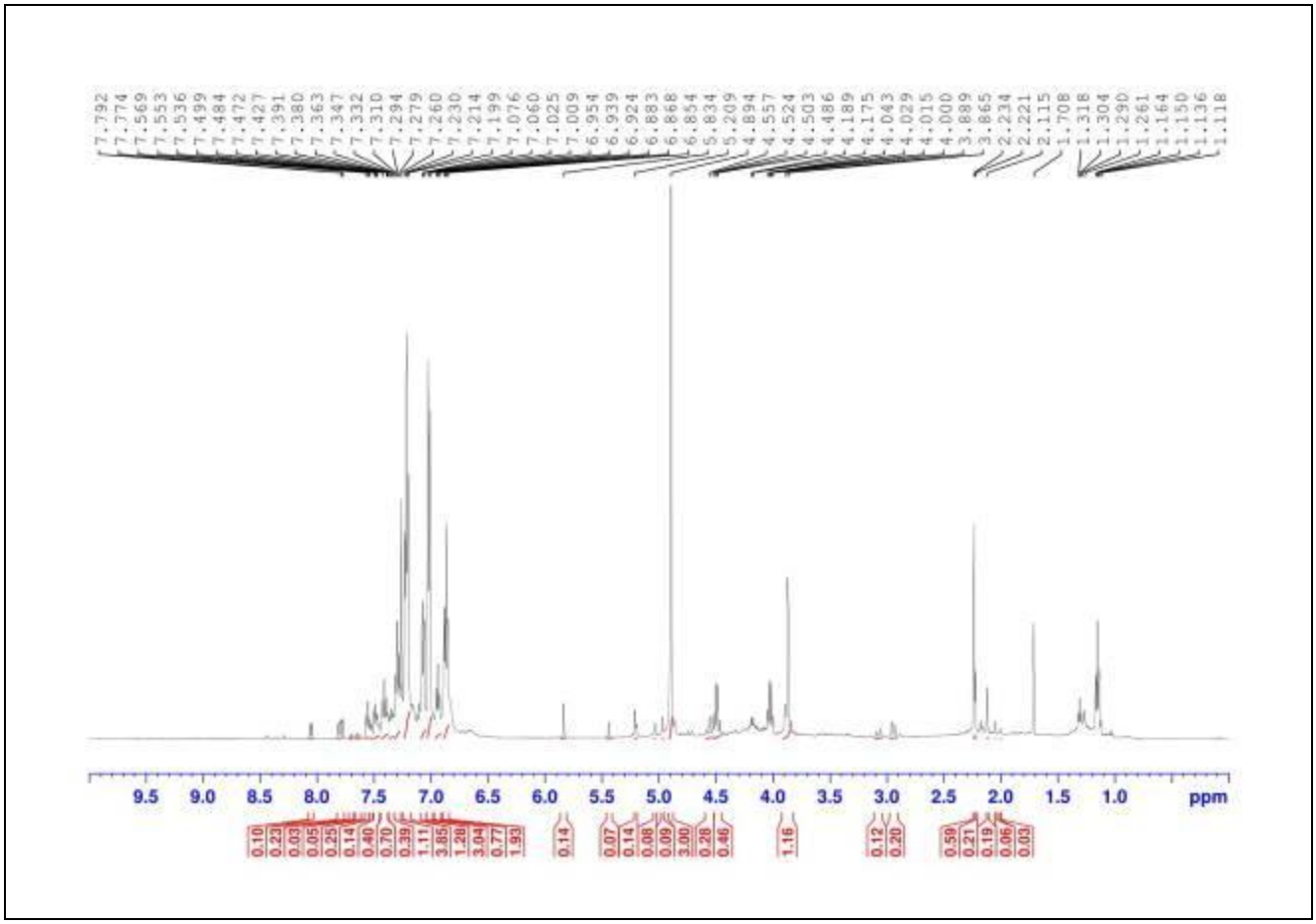



**Figure** HNMR of H-01

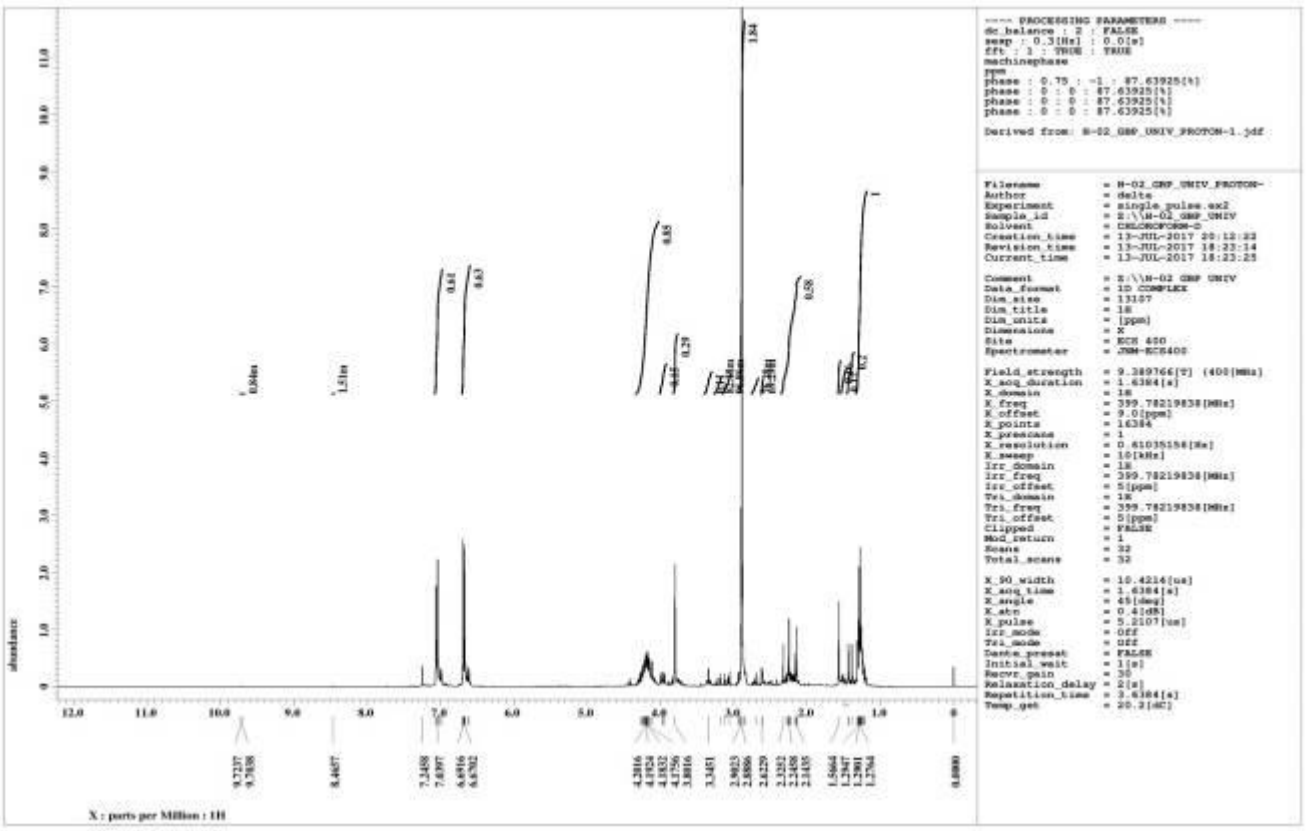


**Figure** HNMR of H-02

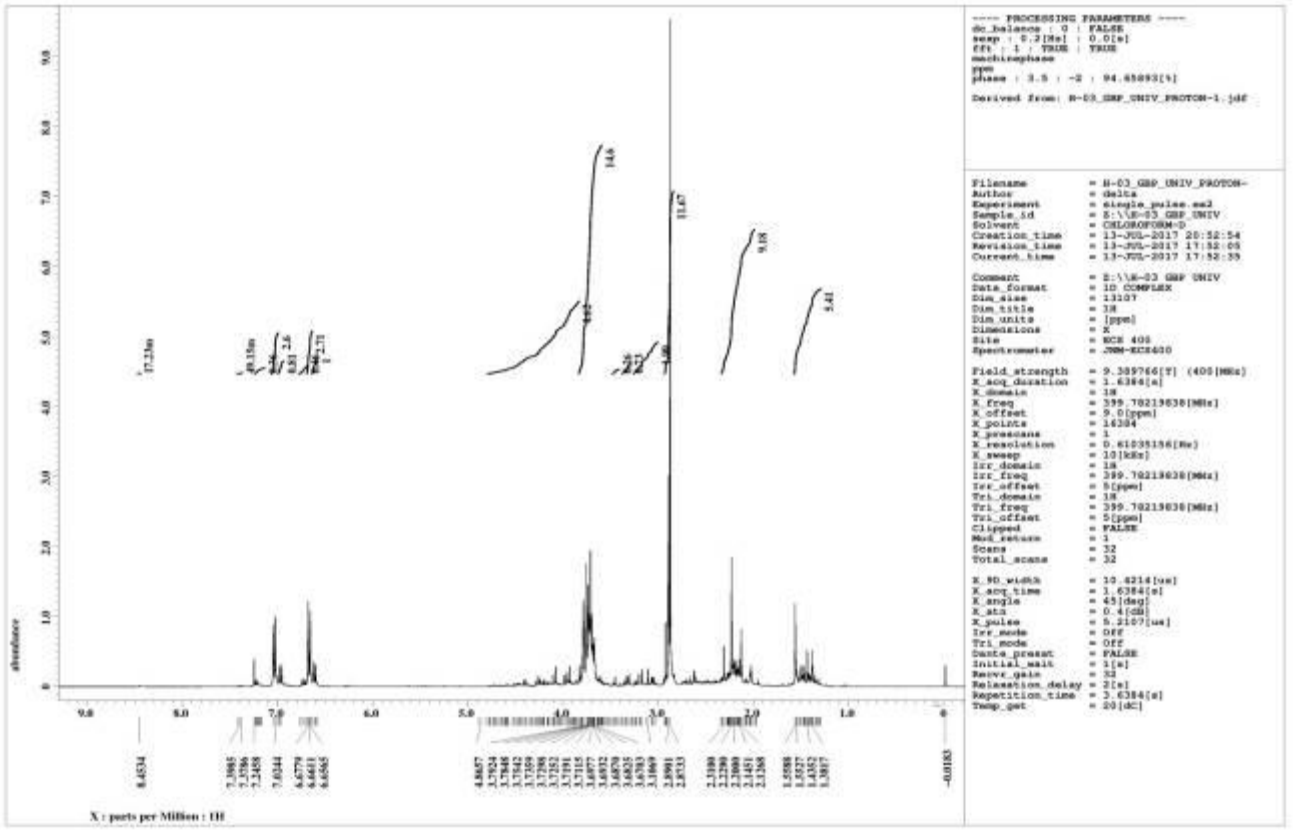


**Figure** 1HNMR spectra of H-03

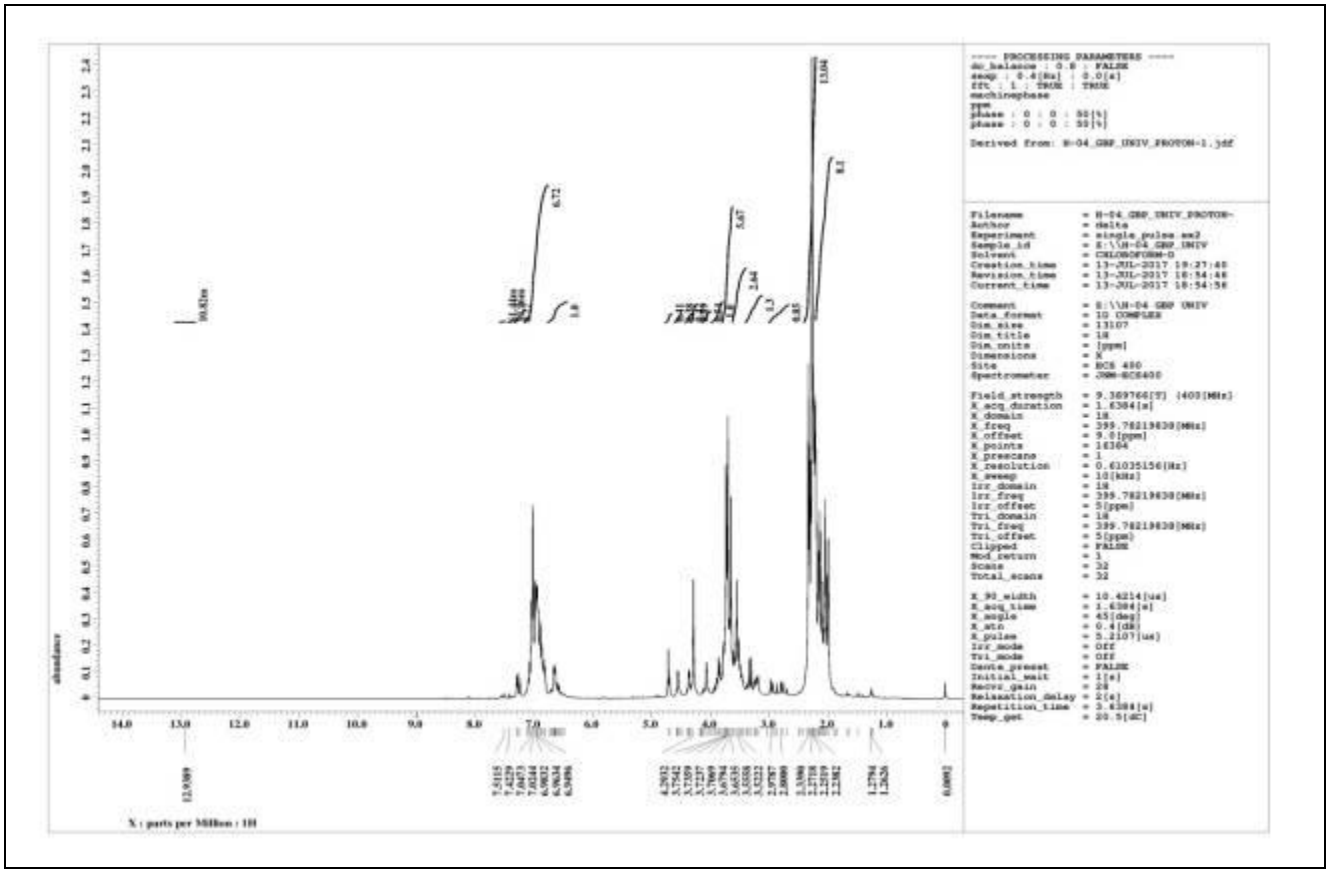


**Figure** 1HNMR spectra of H-04

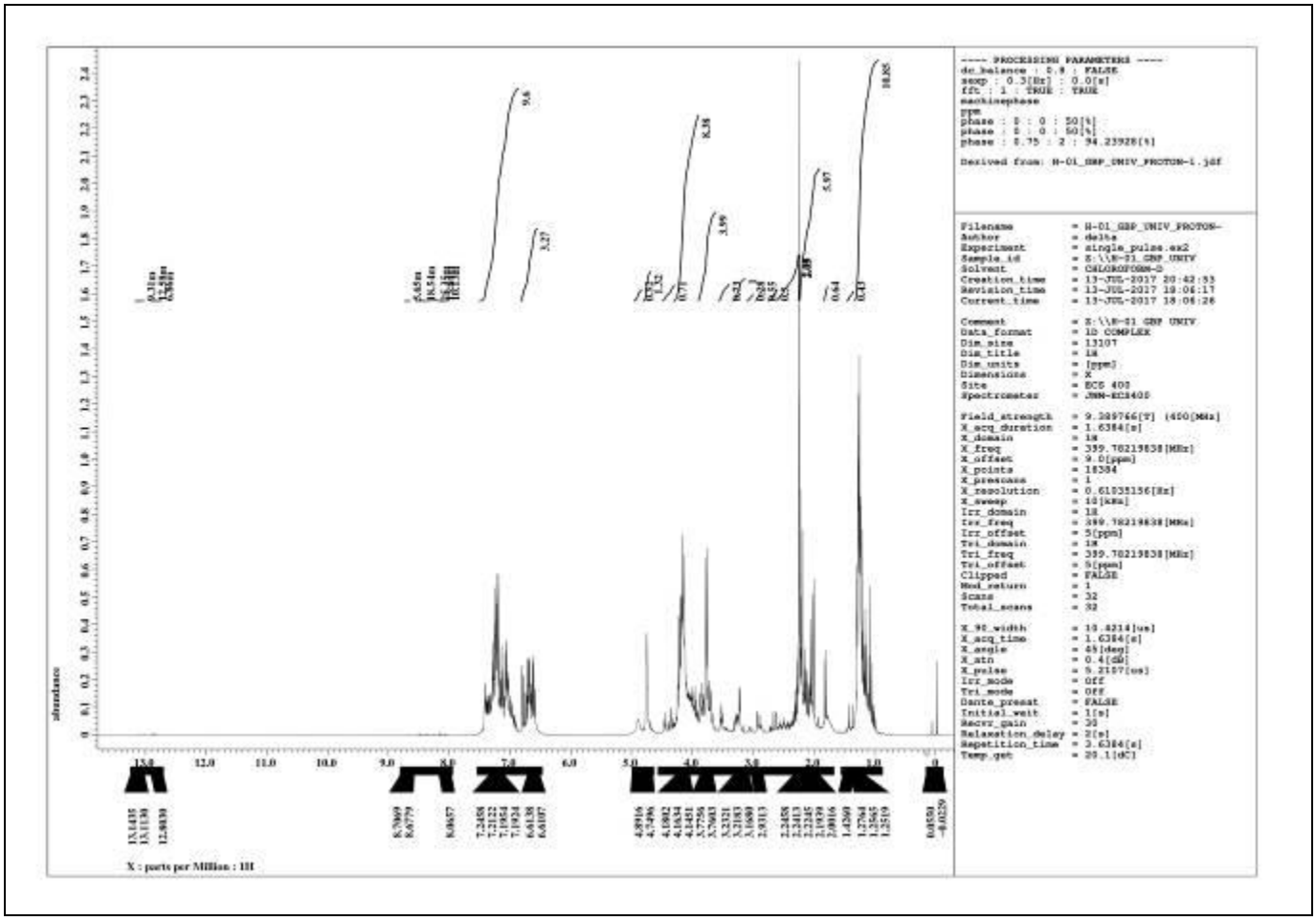


**Figure** FT-IR Spectra of H-07