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IJPBS |Volume 3| Issue 4 |OCT-DEC|2013|270-277

Research Article
Pharmaceutical Sciences

ONE POT SYNTHESIS OF TRI AND TETRA SUBSTITUTED IMIDAZOLE DERIVATIVES

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ABSTRACT

Imidazole ring is a constituent of several important natural products including purine, histamine, nucleic acids. Imidazole and its derivatives improve the pharmacokinetic properties of lead molecules and thus remedy for solubility and bioavailability related problems. This work mainly describes simple and low economic and less time consuming procedures were followed in the synthesis of tri and tetra substituted derivatives have wide range applications in the field of medicinal chemistry. The procedures which were used in the synthesis have given good yield values. Spectroscopic methods like ^{1}HNMR, ^{13}CNMR, ESI-MASS and IR were used to characterization of synthesized products.

KEY WORDS

Imidazole, Benzil, Heterocyclic ring.

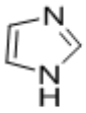
INTRODUCTION

In the field of five membered heterocyclic ring systems, imidazole nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents[1]. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, β-lactamase inhibitors, 20-HETE (20-Hydroxy-5, 8, 11, 14-eicosatetraenoic acid) synthase inhibitors, carboxy peptidase inhibitors, heme oxygenase inhibitors, anti-malarial drugs[2]. This group presents in antiaging agents, anticoagulants, anti inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and inhibit the accumulation of methylated sterols which destroys the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters.

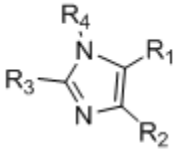
Among many heterocyclic units, imidazole ring behaves as an excellent hydrogen bond donor moiety in synthetic anion receptor systems, and the acidity of NH proton of the imidazole can be tuned by changing the electronic properties of imidazole substituent's. On the other hand presence of a donor pyridine -like nitrogen atom with in the ring, capable of selective binding cationic species also converts the imidazole derivatives in to excellent metal ion sensors. In this sense binding properties of imidazole core may be modulated by its derivatives bearing multiple binding sites[3].

Imidazole (1,3-di aza 2,4 cyclo pentadiene) is a planar 5 membered heterocyclic ring system with 3C 2N atom in 1 and 3 positions. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It is a highly polar compound, as evidenced by a calculated

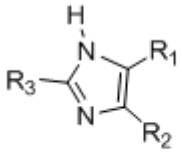
dipole of 3.61D, and is entirely soluble in water [4]. The incorporation of heterocyclic rings such as imidazoles and substituted imidazoles is an important strategy in drug discovery. The high therapeutic value of related drugs encouraged the medicinal chemist to synthesize the large number of novel chemotherapeutic agents.



IMIDAZOLE



TETRA SUBSTITUTED IMIDAZOLE



TRI SUBSTITUTED IMIDAZOLE

Substituted imidazoles are synthesized to improve the pharmacokinetic and pharmaco-dynamic profile of drugs.

Advantages of one pot synthesis:

- Imidazoles are synthesized in one step.
- Time consumption is less.
- Economical process.
- 1,2,4,5 and 2,4,5 positions of imidazole ring can be substituted in single step [8].
- Pure compounds can be obtained.

Materials and Methods:

All moisture sensitive reactions were performed under a nitrogen atmosphere using dried glass wares. Solvents were dried over standard drying agents and freshly distilled prior to use. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 ^{0}C in vacuo.

NMR spectra were recorded on Varian Gemini FT-200 MHz, Unity-400 MHz (21 ^{0}C) and Inova-500 MHz (30^{0}C) spectrometers, with 7–10 mM solutions in appropriate solvents using TMS as the internal standard.^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system, and FAB MS were measured using VG AUTOSPEC mass spectrometers at 5 or 7 K resolution, using per fluoro kerosene as an internal reference.

General procedure: Following general procedure is used to synthesize the imidazole derivatives.

To benzil (1eq in 10 ml acetic acid) substituted aromatic aldehyde was added. To the above mixture ammonium acetate (1eq)) was added. And finally amine (1.2eq) was added to the reaction mixture and all the ingredients are mixed thoroughly. The reaction mixture was kept at 120^{o}c reflux for 24 hr under stirring. Then reaction mixture was azeotroped with dry CH_2Cl_2 (Dichloro methane) to remove acetic acid from the reaction mixture. The crude compound was purified by column chromatography [5, 6, 7]. The following general reaction used in synthesis of tri and tetra substituted imidazoline derivates has showed below. The reactants and products were listed in **Table 1 and 2**.

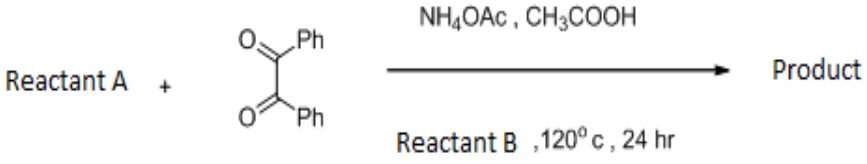


Table1: List of Reactants and Products of One Pot Synthetic Procedure.

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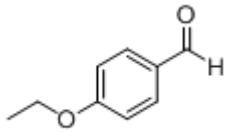
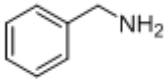
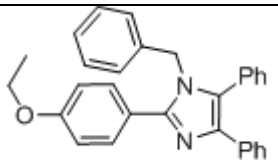
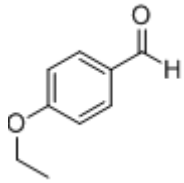
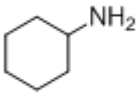
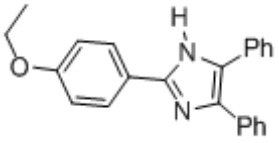
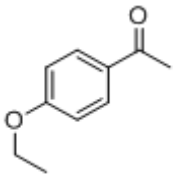
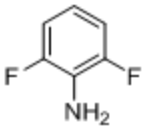
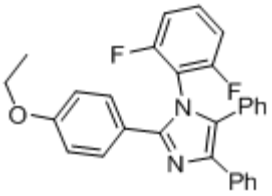
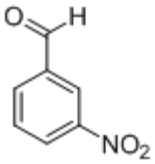
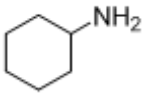
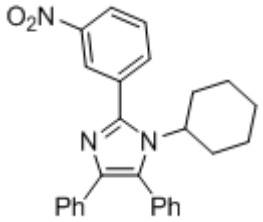
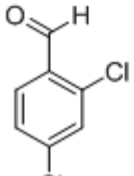
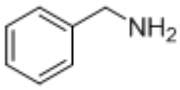
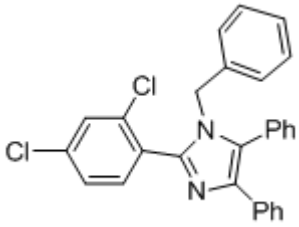
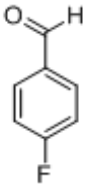
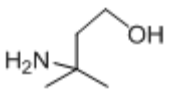
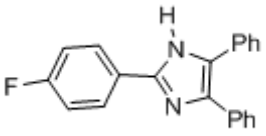
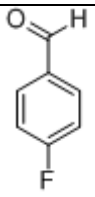
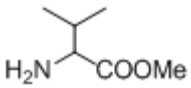
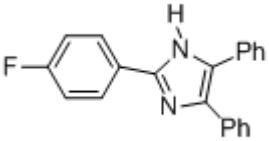
		 (1)
		 (2)
		 (3)
		 (4)
		 (5)
		 (6)
		 (7)

Table 2: List of Reactants and Products of One Pot Synthetic Procedure.

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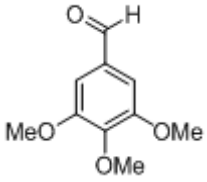
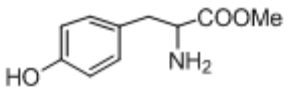
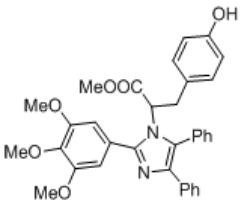
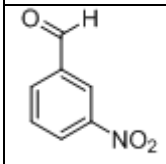
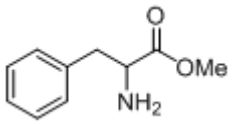
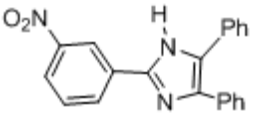
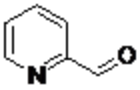
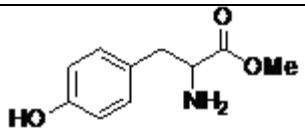
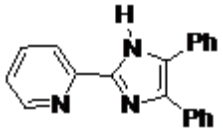
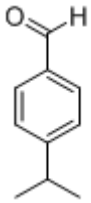
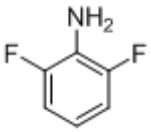
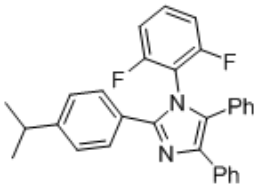
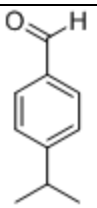
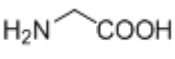
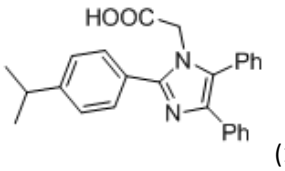
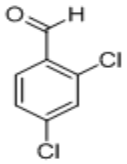
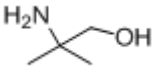
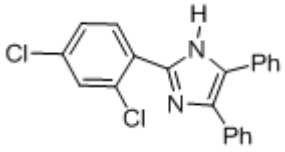
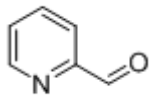
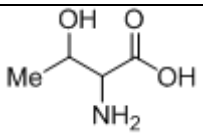
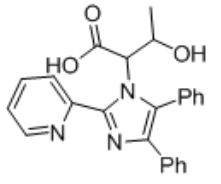
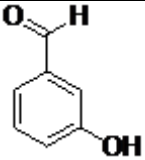
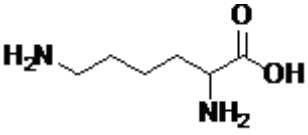
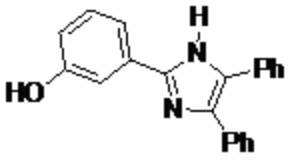
		 (8)
		 (9)
		 (10)
		 (11)
		 (12)
		 (13)
		 (14)
		 (15)

Spectral data of synthesized imidazoline derivatives:

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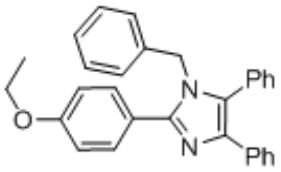


Compound (1)

R*f* : 0.5 in 10%v/v of ethyl acetate in petroleum ether
Yield: 65%

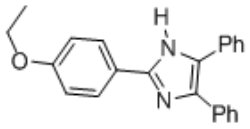
^{1}H NMR (300MHz, $CDCl_3$): δ 7.571 (d, 4H, *J* =7.932 Hz); 7.323 (m, 4H); 7.197 (m, 7H); 6.913 (d, 2H, *J* =8.6870 Hz); 6.812 (m, 2H); 5.080 (s, 2H); 4.055 (dd, 2H, *J* = 6.987 Hz); 1.414 (t, 3H, *J* = 6.987 Hz).

^{13}C NMR (75MHz, $CDCl_3$): 144.675, 123.001, 122.885, 119.743, 116.339, 115.612, 114.943, 113.983, 112.528, 111.859, 108.397, 99.727, 97.226, 48.700, 48.584, 33.427, 14.924.

ESI-Ms: 431 **(M+H$^+$)**

IR (neat): ν $_{max}$ 1456.62, 1176.86, 1042.59, 968.24, 919.29, 837.10, 771.28, 698.72 cm^{-1}

2-(4-Ethoxyphenyl), 4-5, di phenyl 1H-imidazole



Compound (2)

R*f* : 0.5 in 10%v/v of ethyl acetate in petroleum ether
Yield: 55%

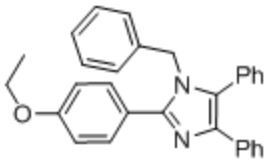
^{1}H NMR (300MHz, $CDCl_3$): δ **7.**826 (d, 2H, *J* = 8.498 Hz); 7.546 (d, 4H, *J* =6.798 Hz); 7.349 (m, 6H); 6.954 (m, 2H, *J* = 8.687 Hz); 4.103 (dd, 2H, *J* = 6.987 Hz); 1.457 (t, 3H, *J* =6.987 Hz)

^{13}C NMR (75MHz, $CDCl_3$): 132.623, 131.165, 128.621, 127.841, 127.257, 126.988, 126.711, 122.198, 114.682, 63.523, 29.677, 14.754.

ESI-Ms: 341 **(M+H)$^+$**

IR (neat): ν $_{max}$ 3616.55, 1497.03, 1177.26, 1116.05, 917.97, 836.14, 759.05, 695.42 cm^{-1}.

Synthesis of 1-(2, 6-difluorophenyl)-20(4-etoxyphenyl)-4, 5-diphenyl-1H-imidazole:



Compound (3)

R*f* : 0.6 in 20%v/v of ethyl acetate in petroleum ether
Yield: 72%

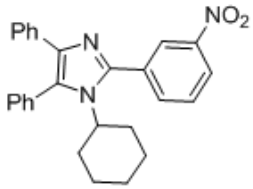
^{1}H NMR (300MHz, $CDCl_3$): δ 7.440 (d, 6H, *J* =9.065 Hz); 7.269 (d, 2H, *J* =6.778 Hz); 7.244 (m,3H); 6.843 (9m, 5H); 4.012 (dd, 2H, *J* =7.554 Hz): 1.37 (t, 3H, *J* =6.798 Hz).

^{13}C NMR (75MHz, $CDCl_3$): 119.344, 116.310, 115.990, 114.740, 113.750, 112.557, 111.888, 107.728, 99.786, 97.25, 96.935, 48.642, 33.456.

ESI-MS: 453 **(M +H)$^+$**

IR (neat): ν $_{max}$ 1514.90, 1247.11, 1176.31, 1044.07, 1009.32, 777.16, 697.20 cm^{-1}

Synthesis of 1-cyclohexyl-2-3(-nitro phenyl) 4-5-diphenyl-1H-imidazole:



Compound (4)

R*f* : 0.5 in 20% v/v of ethyl acetate in petroleum ether
Yield: 62%

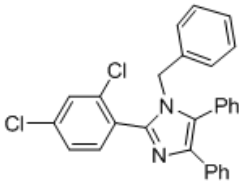
^{1}H NMR (300MHz, $CDCl_3$): δ 8.522 (m, 1H); 8.348 (d, 1H, *J* =8.309 Hz); 8.029 (d, 1H, *J* =7.554 Hz); 7.689 (m, 1H); 7.264 (s, 3H); 7.145 (m, 1H); 1.895 (m, 3H); 1.256 (s, 3H).

^{13}C NMR (75MHz, $CDCl_3$): 167.533, 164.472, 158.042, 155.337, 153.559, 151.379, 149.513, 148.565, 147.479, 145.832, 143.091, 78.299, 53.266, 49.155, 45.15.

ESI-MS: 424 **(M+H)$^+$**

IR (neat): ν $_{max}$ 1530.84, 1453.40, 1347.65, 1169.05, 1078.23, 904.84, 765.69, 700.90 cm^{-1}

Synthesis of 1-benzyl-2-(2, 4-dichlorophenyl) 4, 5-diphenyl1-H-imidazole:



Compound (5)

R*f* : 0.5 in 20% v/v of ethyl acetate in petroleum ether
Yield: 57%

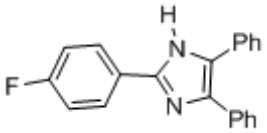
^{1}H NMR (300MHz, $CDCl_3$): δ 7.558 (m, 2H); 7.493 (d, 1H, *J* =8.312 Hz); 7.397 (m, 4H);
7.299 (m, 4H); 7.226 (m, 3H); 7.123 (m, 2H); 6.632 (m, 2H); 4.910 (s, 2H).

^{13}C NMR (75MHz, $CDCl_3$): 157.510, 155.585, 153.114, 150.242, 149.389, 148.434, 147.858, 146.757, 145.958, 67.707.

ESI-MS: 455 **$(M+H)^+$**

IR (neat): ν $_{max}$ 1599.42, 1448.02, 1222.58, 1103.79, 1026.79, 967.18, 752.81, 697.74 cm^{-1}.

Synthesis of 2-(4-fluorophenyl)-4, 5-diphenyl1-H-imidazole:



Compound (6)

R*f* : 0.5 in 20% v/v of ethyl acetate in petroleum ether
Yield: 60%

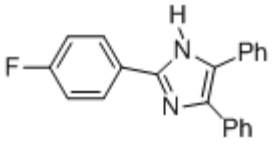
^{1}H NMR (300MHz, $CDCl_3$): δ 7.895 (dd, 2H, *J* =7.324 Hz); 7.551 (d, 6H, *J* =6.978 Hz); 7.337 (m, 5H); 7.145 (m,3H).

^{13}C NMR (75MHz, $CDCl_3$): 143.025, 130.550, 130.425, 129.371, 129.262, 128.795, 128.736, 128.404, 127.350, 120.140, 116.388, 116.087.

ESI-MS: 315 **$(M+H)^+$**

IR (neat): **ν $_{max}$** 3449.96, 1515.67, 1461.54, 1229.60, 838.23, 767.38, 733.44, 694.52 cm^{-1}.

Synthesis of 2-(4-fluorophenyl)-4, 5-diphenyl-1H-imidazole:



Compound (7)

R*f* : 0.5 in 25% v/v of ethyl acetate in petroleum ether
Yield: 65%

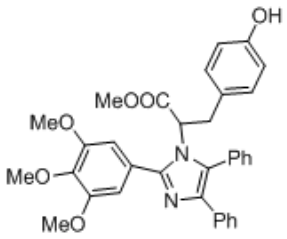
^{1}H NMR (300MHz, $CDCl_3$):

^{13}C NMR (75MHz, $CDCl_3$):

ESI-MS: 315 **$(M+H)^+$**

IR (neat): ν $_{max}$ 3447.27, 1516.36, 1463.39, 1235.19, 995.90, 822.27, 760.91 cm^{-1}.

Synthesis of methyl-2-(4, 5-diphenyl-2-(3, 4, 5 trimethoxy phenyl)1-H-imidazolyl)3-(4-hydroxyphenyl) propanoate:



Compound (8)

R*f* : 0.5 in 25% v/v of ethyl acetate in petroleum ether
Yield: 40%

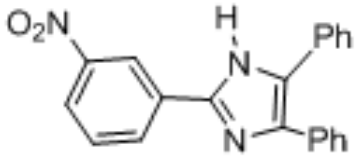
^{1}H NMR (300MHz, $CDCl_3$): δ 7.480 (m, 4H); 7.347 (m, 2H); 7.156 (m.2H); 6.941 (m, 2H); 6.729 (m, 3H); 6.595 (m, 2H); 6.476 (s, 1H); 6.027 (d, 1H, *J* =7.645 Hz); 4.886 (m, 1H); 3.831-3.666 (s,12H); 2.092 (d, 2H, *J* =3.826 Hz).

^{13}C NMR (75MHz, $CDCl_3$): 149.447, 147.691, 132.951, 132.071, 126.441, 114.828, 108.931, 106.795, 105.386, 103.967, 92.267, 83.920, 37.943, 33.037, 30.559, 29.932, 14,208, 12.218.

ESI-MS: 565 **$(M+H)^+$**

IR (neat): ν $_{max}$ 1741.73, 1695.12, 1516.02, 1461.22, 112.90, 1000.75, 833.43, 751.44, 692.45 cm^{-1}

Synthesis of 2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole:



Compound (9)

R*f*: 0.4 in 25% v/v of ethyl acetate in petroleum ether
Yield: 48%

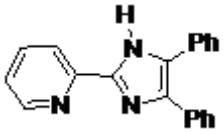
^{1}H NMR (300MHz, $CDCl_3$):

^{13}C NMR (75MHz, $CDCl_3$):

ESI-MS: 342 **$(M+H)^+$**

IR (neat): ν $_{max}$ 3566.84, 1648.66,1 517.87, 1462.85, 1396.17, 973.09, 769.59, 678.31 cm^{-1}

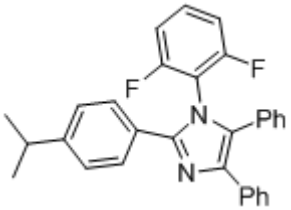
Synthesis of 2-(4,5-diphenyl-1H-imidazo-2-yl)pyridine:



Compound (10)

R*f* : 0.3in 25% v/v of ethyl acetate in petroleum ether
Yield: 40%
^{1}H NMR (300MHz, CDCl$_3$): δ 7.974 (d, 1H, *J* =8.674 Hz); 7.641 (m, 2H); 7.513 (m, 5H); 7.123 (m, 2H); 7.018 (m, 2H); 6.840 (d, 1H, *J* =7.632 Hz); 6.735 (dd, 2H, *J* =3.216 Hz).
^{13}C NMR (75MHz, CDCl$_3$): 134.899, 131.919, 130.863, 129.830, 128.827, 128.303, 127.925, 127.750, 127.424, 126.375, 126.179, 125.679 cm^{-1}.
ESI-MS: 298 **(M+H)$^+$**
IR (neat): ν $_{max}$ 3287.48, 1512.84, 1292.56, 1169.99, 965.17, 916.48, 839.25, 763.29, 696.722 cm^{-1}

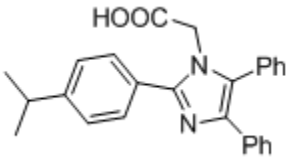
Synthesis of 1-(2,6-difluorophenyl)-2-(4-isopropylphenyl)4,5-diphenyl-1H-imidazole:



Compound (11)

R*f* : 0.3 in 25% v/v of ethyl acetate in petroleum ether
Yield: 40%
^{1}H NMR (300MHz, CDCl$_3$): δ 7.832 (d, 2H, *J* =8.309 Hz); 7.535 (d, 5H, *J* =6.798 Hz); 7.339 (m, 10H); 2.985 (m, 1H); 1.281 (s, 6H).
^{13}C NMR (75MHz, CDCl$_3$): 130.601, 129.852, 128.693, 128.253, 128.043, 127.954, 127.164, 22.596, 20.277.
ESI-MS: 339 **(M-110)$^+$**
IR (neat): ν$_{max}$ 1462.39, 839.41, 765.44, 692.37 cm^{-1}.

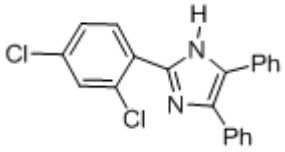
Synthesis of 2-(2-(4-isopropylphenyl-1H-imidazol-1-yl) acetic acid:



Compound (12)

R*f* : 0.4 in 25% v/v of ethyl acetate in petroleum ether
Yield: 50%
^{1}H NMR(300MHz, CDCl$_3$): δ 7.500 (m, 2H); 7.407(m, 5H); 7.311 (m, 6H); 7.118 (s,1H); 6.597 (s, 1H); 4.195 (s, 1H); 2.016 (s, 2H); 1.258 (m, 6H).
^{13}C NMR (75MHz, CDCl$_3$): 149.134, 132.054, 129.605, 129.415, 129.378, 128.562, 127.877, 127.520, 126.762, 126.332, 125.267, 33.752, 33.424, 23.313.
ESI-MS: 339 **(M-56)$^+$**
IR (neat): ν $_{max}$ 1741.01, 1461.57, 1270.50, 966.99, 916.96, 840.69, 762.73, 696.53. cm^{-1}

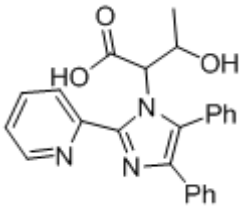
Synthesis of 2-(2, 4-dichlorophenyl) 4,5-diphenyl1H-imidazole:



Compound (13)

R*f* : 0.4 in 25% v/v of ethyl acetate in petroleum ether
Yield: 78%
^{1}H NMR (300MHz, CDCl$_3$): δ
^{13}C NMR (75MHz, CDCl$_3$): 134.181, 131.184, 129.604, 129.430, 129.427, 128.180, 127.308, 127.190, 126.839, 126.161.
ESI-MS: 365 **(M+H)$^+$**
IR (neat): ν $_{max}$ 3442.56, 1469.17, 1240.59, 1052.62, 970.93, 813.66, 761.12, 695.98 cm^{-1}

Synthesis of 2-(4, 5-diphenyl-2-pyridin-2-yl) 1H-imidazol-1-yl)3-hydroxy butyricacid:

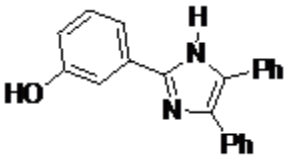


Compound (14)

R*f* : 0.5 in 25% v/v of ethyl acetate in petroleum ether
Yield: 50%
^{1}H NMR (300MHz, CDCl$_3$): δ 7.462 (m, 6H); 7.296 (m, 8H), 2.751 (s, 1H); 2.336 (s, 2H); 1.256 (s, 3H).
^{13}C NMR (75MHz, CDCl$_3$): 149.262, 131.744, 130.135, 129.138, 128.592, 127.960, 127.276**,** 126.747, 21.772, 20.711, 12.289.
ESI-MS: 249 **(M-149)$^+$**

IR (neat): ν $_{max}$ 3617.13, 1668.06, 1241.63, 1071.06, 1028.45, 916.89, 958.33, 697.34cm^{-1}.

Synthesis of 2-amino-6-(2-(3-hydroxyphenyl) 4,5-diphenyl-1H-imidazol-1-yl) hexanoic acid:



Compound (15)

R*f* : 0.6 in 25% v/v of ethyl acetate in petroleum ether
Yield: 60%

^{1}H NMR (300MHz, CDCl$_3$): δ **7**.457 (m, 5H); 7.320 (m, 5H); 7.171 (m, 2H); 6.798 (m, 2H); 4.77 (bs, 1H).

^{13}C NMR (75MHz, CDCl$_3$): 131.339, 130.601, 129.208, 128.963, 128.253, 127.954, 127.169, 127.044.

ESI-MS: 313 **(M-127)$^{+}$**

IR (neat): ν $_{max}$ 3617.72, 3059.48, 1232.35, 1037.63, 967.74, 875.71, 761.92, 696.79 cm^{-1}.

CONCLUSION

In the present study tri and tetra substituted imidazoline derivatives were successfully synthesized and characterized by using several analytical techniques and Thin layer chromatography. One step procedure which was used for the synthesis has given very good yield values so it can be applied for the bulk synthesis.

REFERENCES

1. Hayes, J. F.; Mitchell, M. B.; Wicks, C.; *Heterocycles.* 1994, *38*, 57.
2. Williams, D. A.; Lenke, T. L.; *Foyes principles of medicinal chemistry.* 2002, *5*, 36.
3. Pettit, G. R.; Kanano, Y.; Dfrense, C.; Cerny, R. L.; Herald, C. L.; Schmidt, J. M.; *J.org.chem.* 1969, *54*, 6005.
4. Williamson, M. P.; *Biochem.J.* 1994, *297*, 249-260.
5. Hirano, K.; Urban S.; Wang C.; Glorius, F.A.; Modular synthesis of highly substituted imidazlium salts, *org let*., 1991, *11*, 1019-1022.
6. Hirschbein, B. L.; Whitesides, G. M.; *J.Am.Chem.Soc.* 1982, *104*, 958.
7. Sarshar, S.; Siev, D.; Mjalli, M. M.; *TetrahedronLett.* 1996, *37*, 835.
8. Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L.; *J.Mol.catal.A.chem.* 2007, *66*, 109.
9. Laszlo, S. E.; Hacker, C.; Li, B.; *Med.Chem.Lett.*1999, *9*, 641.
10. Dupont, J.; De souza, R. F.; Suarez, P. A.Z.; *Chem. Rev*. 2002, *102*, 3667.

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