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Efficient One-Pot Asymmetric Synthesis of Novel Chiral Tetrahydropyridines Catalyzed by Benzyltriethylammonium Tetrathiomolybdate–Fe (III) Chloride

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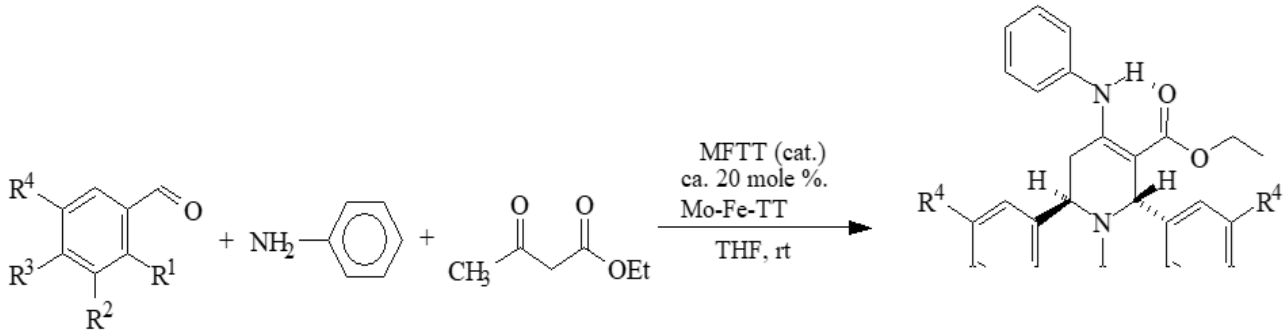

***Abstract*-- Immobilized benzyltriethylammonium tetrathiomolybdate, in the presence of co-catalyst Fe(III) chloride, has been found to efficiently catalyze the one-pot reaction of ternary mixture of arylaldehyde, arylamine and ethylacetoacetate to afford novel ethyl (2*S*, 6*R*) 1,2,6-triaryl-4-(arylamino)-1,2,5,6-tetrahydropyridine-3-carboxylates. This stereospecific reaction proceeds smoothly at room- temperature. The reaction seems to proceed via double Mannich type reaction, intramolecularrearrangement and annulation. The products are obtained in good yield (65 – 89%).**

***Keywords*-- Asymmetric synthesis, benzyltriethylammoniumtetrathiomolybdate, Fe(III) chloride, stereospecific double Mannich type –annulation reaction.**

I. Introduction

1,2,5,6-Tetrahydropyridineconstitutes the core nucleus of a small group of naturally occurring bioactive alkaloids.[1] The products derived from 1,2,5,6-tetrahydropyridine have been reported as potential $5HT_1A$ receptors and are useful in the management of neurodisorders[2] including Alzheimer's disease,[3] and symptoms of senile cognitive decline.[4] Some compounds derived from this nucleus have also been found to exhibit insecticidal,[5] acaricidal,[5] muscarinic[6] and antiaschemic properties.[7] Moreover, 2,6-disubstituted tetrahydropyridine derivatives serve as valuable substrates for the construction of polysubstituted piperidines. For obvious reasons, 2,6-disubstituted tetrahydropyridines have remained the target compounds of several syntheses.

Traditionally, 1,2,5,6-tetrahydropyridines are obtained by partial reduction of corresponding pyridinium salts or 4-piperidone derivatives.[8]Substituted tetrahydropyridines, especially the products possessing 1-aryl function, are difficult to prepare[9] and several strategies have been followed for their synthesis. They are mostly constructed via the formation of iminium ion intermediate,[10] phosphine catalyzed (4+2)π electron electrocyclic annulation,[11] acid catalyzed cyclisation of ene derivatives,[12] base catalyzed aza [2,3]-Wittig rearrangement,[13]aza-Diel's-Alder reaction, [14]enyne cross metathesis and intramolecular allyl silane-nitrone cycloaddition.[16]Although, most of the known syntheses are quite attractive, majority of these syntheses are fraught with one or the other drawbacks, such as multistage processes and operational difficulty, use of expensive substrates and reagents, specialized reaction conditions, difficult stereochemical control and poor yield. Therefore, there is enough scope for the development of simple, efficient and environmentally benign processes for the preparation of pharmacologically important polysubstituted 1,2,5,6-tetrahydropyridines.

Molybdenum is an important constituent of naturally occurring enzymes such as milk xanthine oxidase[17] and liver sulfite oxidase,[18] where it occurs as oxo-complex and is linked to sulfur atoms of side chain protein.[16] The nitrogenases of some microorganisms such as *Clostridium pasteurianum and Azobacter vinelandii* contain Fe-Mo proteins.[19]

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These enzymes play a key role in the bio-redox reactions. It is established that Fe-Mo-Co and cofactor are not interchangeable and possess cluster structures.[20] The metal bridging and terminal ligation by sulfides, in these enzymes, leads to double cubane structure.[21] Earlier, extensive studies on the use of benzyltriethylammoniumtetrathiomolybdate as a sulfur transfer reagent to various substrates, including alkyl halides and tosylates,[22] alcohols,[23] thiocyanates,[24] azides[25] and amides[26] have been carried out. However, its utility in the synthesis of nitrogen heterocycles has not been explored. We opined that the reagent, in combination with Fe(III) ions, may act in a fashion similar to naturally occurring nitrogenases and prove useful in the synthesis of nitrogen heterocycles. Indeed, for the first time, we have found that the reagent is highly efficient in catalyzing the otherwise difficult to form nitrogen heterocycles. In this paper we report a simple, elegant and stereospecific one-pot synthesis of novel ethy1,2,6-triaryl-4-(arylamino)-1,2,5,6-tetrahydropyridine-3-carboxylates from easily accessible arylaldehydes, arylamines and ethylacetoacetate, using immobilized benzyltriethylammonium tetrathiomolybdate as catalyst,in the presence of Fe(III) chloride,under ambient reaction conditions.

II. Preperation Of The Catalyst

Benzyltriethylammoniumtetrathiomolybdate was repared according to the known procedure of Ramesha and Chandrasekran.[22] The orange-red crystals of the product (5% w/w), in dry acetonitrile was adsorbed on silica gel and the solvent removed under vacuum. The solid residue was then stirred with anhydrous Fe(III)chloride (5% w/w) solution, in acetonitrile. The catalyst mixture (coded MFTT) was again dried in vacuum and preserved, in a desiccator, under anhydrous conditions.

III. Experimental Section

The aldehyde **1a-1k**, aniline and ethylacetoacetate (2:2: 1 mol) were dissolved in THF and Mo(IV)-Fe(III) catalyst mixture, taken in proportion by the weight of aldehydes, such that the concentration of the catalyst did not exceed ca. 20 mole percent, was added to the reaction mixture. The reaction mixture was stirred at room temperature and monitored by TLC. On completion of the reaction (40-48 hrs), the product mixture was filtered. The organic solution was diluted with water and extracted with ethylacetate.

After usual work up and concentration the product **2a-2k** (Scheme 1) separated out as crystalline material in 65-89% yield (Table 1).

TABLE 1
Percentage yield of 2a-2k

Compd.	Percent yield	Compd.	Percent yield
2a	89	**2g**	86
2b	82	**2h**	56
2c	78	**2i**	80
2d	70	**2j**	84
2e	71	**2k**	87
2f	65	--	--

IV. Results And Discussion

The products **2a–2k**were recrystallized from hot ethylacetate and analyzed by spectral methods (HRMS, IR,^{1}H-NMR, ^{13}C-NMR and DEPT 135^{0}) and elemental analysis.[27] The IR spectra of **2a–2k**exhibited characteristic absorption bands at υ_{max} 1652 -1698 (conjugated C=O), 2878-2973 (C-N), 1589, 1449 (C=C)cm^{-1}, in addition to other aromatic absorption bands. The ^{1}H-NMR spectra of the compounds, besides displaying the expected aromatic proton resonance signals, exhibited the characteristic resonance signals at δ 1.4 (t, J = 7.2 Hz, 3H), for ester methyl, and a broad resonance signal near δ10.30, attributable to the hydrogen bonded proton of secondary amino group at C-4.The diastereotopic methylene protons at C-5 displayed two double doublets at δ2.76-2.84 (dd, J =7.1, 2.2 Hz, 2H). The double doublet at δ 6.35 (dd, J = 6.7, 2.0 Hz, 1H) was attributable to the axial proton at C-6. This placed the phenyl group at C-6 in equatorial position. The single proton singlet at δ5.14 was assigned to the proton geminal to the phenyl group at C-2. ^{13}C-NMR and DEPT 135^{o} spectra displayed the ethoxy and ring methylene resonance signals near δ59.9 and 32.8, respectively. The resonance signals due to the double bond carbons of the tetrahydropyridine ring were observed at δ97.6 (C-3) and 155.10 (C-4), whileas the signals due to C-2 and C-6 were displayed at δ45.8-55.6 and 47.6-57.7, respectively.

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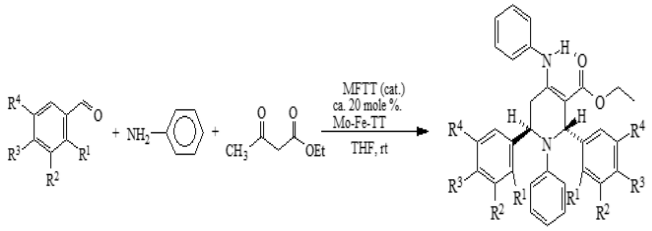
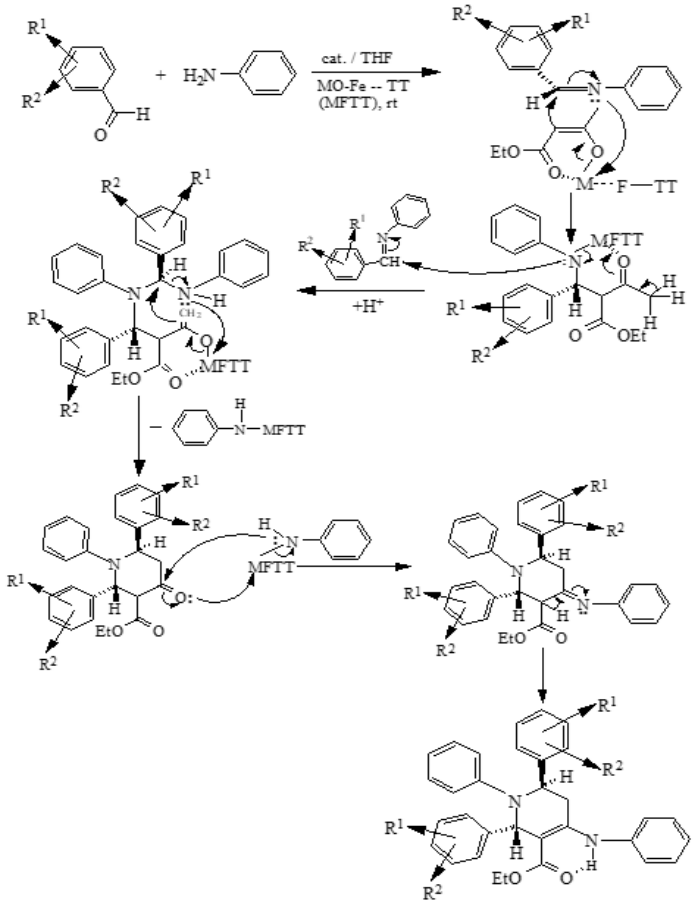


2a-2k

	R^1	R^2	R^3	R^4
1a	H	H	H	H
1b	H	H	OCH_3	H
1c	H	H	Cl	H
1d	Cl	H	H	H
1e	H	H	Br	H
1f	H	OCH_3	OH	H
1g	H	OCH_3	OCH_3	H
1h	H	OC_2H_5	OH	H
1i	Cl	Cl	H	H
1j	H	O-CH_2-O		H
1k	H	OCH_3	OCH_3	OCH_3

Scheme 1: Preparation of 1,2,6-triaryl-1,2,5,6-tetrahydropyridines

A peculiarity in the ^{1}H-NMR spectra of **2a** – **2k** was the presence of two clearly distinct but closely placed quartets, separated by 0.11 ppm, centered at δ 4.31 (q, J = 7.2 Hz) and 4.42 (q, J = 7.1 Hz) and integrating together for two protons, due to the methylene protons of the ester function placed at C-3. This could be explained as a combined effect of the conformational constraints of the tetrahydropyridine ring, hydrogen bonding between the secondary amino group at C-4 and the ester carbonyl at C-3and the magnetic anisotropy caused by the nearby carbonyl oxygen. Such a situation may arise when the tetrahydropyridine ring acquires *quasi* chair or distorted boat conformation and the ester carbonyl and the ring double bondare in *S*-cis configuration.



MFTT = *Catalyst* (Benzyltriethylammonium-tetrathiomolybdate-Fe(III) chloride-SiO_2

Scheme 2: Probable Mechanism for the formation of 1,2,6-triaryl-1,2,5,6-tetrahydropyridines.

The compounds were thus characterized as ethyl (2*S*, 6*R)-1*, 2, 6-triaryl-4-(phenylamino)-1, 2, 5, 6-tetrahydropyridine-3-carboxylates.

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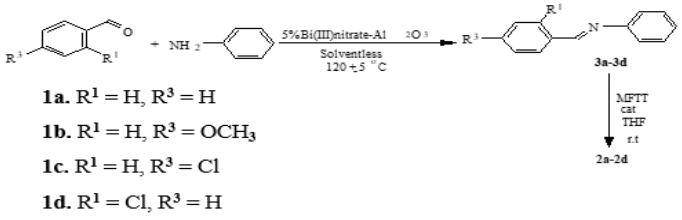
Although, compounds **2a** – **2k** possess two chiral centers at C-2 and C-6, due to internal compensation, the products were obtained in optically inactive form. The structure of **2a-2k** and stereochemistry of the substituents on tetrahydropyridine ring was confirmed by X-ray studies of **2a**[28,29] and comparison of their spectra. Fig.1 shows the ORTEP diagram of **2a**. The tetrahydropyridine ring adopts a distorted boat conformation with atoms C1 and C4 forming the apex. The C2-C3 distance of 1.372(4) Å corresponds to a normal C-C double bond. All other distances in the ring system correspond to $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-$N(sp^3)$ distances. There is a strong intramolecular H-bond between N2-H…O1, in which the H…O1 distance is 2.004(1) Å. The other crystallographic data are given in table 2.

The mechanism of the reaction may be rationalized as involving the condensation of arylaldehyde and arylamine to form Schiffs' base which may undergo stereospecific double Mannich-type addition by enolised six membered metal-ion-ethylacetoacetate complex (scheme 2) to form an intermediate carrying one tertiary and one secondary amino group. The intramolecular rearrangement and subsequent annulation followed by dehydration with released arylamine may lead to the formation of the compounds **2a – 2k**.

In order to substantiate the proposed mechanism, initially we prepared Schiffs' base by solid- supported reactions of arylaldehyde **1a-1d** and aniline, using the catalyst 5% Bi(III) nitrate adsorbed on neutral alumina[30] (scheme 3). The Schiffs' base **3a** – **3d** were then reacted with ethylacetoacetate (2:1 mole) as described above. The reactions were complete in 48 hrs. and afforded **2a** – **2d** whose identity was confirmed by co-tlc and m.m.p with authentic samples. Next, we also carried out the above reactions in the presence of neat benzyltriethylammoniumtetrathiomolybdate, neat Fe(III) chloride and their mixture without using silica gel. The results were disappointing with low yield of desired products and formation of several side products.

In conclusion, we have for the first time used benzyltriethylammoniumtetrathiomolybdate-Fe(III) chloride as a catalyst in the synthesis of polysubstituted tetrahydropyridine and have found that the immobilized catalyst promotes the one-pot stereospecific double Mannich-type reaction-rearrangement-annulation reaction leading to high yield of N-substituted products from readily available substrate. The essence of this procedure is that it is simple, efficient, environmentally benign and highly stereo-controlled and does not need any specialized reaction conditions. Further work on the utility of the new catalyst mixture in the synthesis of heterocyclic compounds is in progress.



1a. $R^1 = H$, $R^3 = H$
1b. $R^1 = H$, $R^3 = OCH_3$
1c. $R^1 = H$, $R^3 = Cl$
1d. $R^1 = Cl$, $R^3 = H$

Scheme 3: Preparation of 2a-2d from Schiff's base

Acknowledgement: The authors want to acknowledge IIIM Jammu for providing research and analytic facilities.

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[27] Spectral data of 2a-2k

(2a): Colorless crystals, m.p. 175.1°C. IR(KBr) : υ_{max}cm^{-1} 3047, 2973, 1653, 1589, 1500, 1449, 1373, 1328, 1256, 1171, 1071, 944, 750.^{1}H-NMR(200 MHz, $CDCl_3$):δ 1.45 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$). 2.76 (dd, *J*=2.38, 7.1 Hz, 1H, H_a-5), 2.82 (d, *J*=2.8, 1H, H_e-5), 4.22, 4.33 (q, each, *J*=7.1 Hz, integ.together, 2H, CO_2CH_2-), 4.47 (dd, 1H, *J*=3.0, 7.1 Hz, H-6), 5.14 (s, 1H, H-2), 6.59 (m, 4H, H-Ar), 7.01-7.36 (m, 16H), 10.30 (s br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 13.86($CO_2CH_2CH_3$), 32.6(C-5), 55.5(C-2), 57.2(C-6), 60.1(CO_2CH_2-), 97.6(C-3), 111.9(C-8, C-12), 115.1(C-14. C-18), 115.3(C-16), 124.8(C-22), 125.12(C-17),125.2(C-15), 125.3(C-10), 125.4(C-21), 126.6(C-29, C-28), 127.6(C-20), 127.7(C-23), 127.8(C-24, C-30, C-26), 127.9(C-28, C-9, C-11), 136.9(C-25), 137.0(C-19), 143.06(C-13), 146.0(C-7), 155.1(C-4), 167.8(C=O). MS: *m/z* (rel. int) 474.6041 (100)(M^+) (calc. for $C_{32}H_{30}N_2O_2$, 474.6059), 446(32), 402(53), 293(33), 221(51), 201(43), 181(69), 129(67), 92(59). Anal. Calc. for $C_{32}H_{30}N_2O_2$. C ,80.984, H ,6.371, N, 5.902. Found: C, 80.89, H, 6.45, N, 5.91.

(2b) : Colorless crystals m.p. 110°C. IR(KBr):υ_{max}cm^{-1} 3065, 2916, 1659, 1587, 1543, 1536, 1464, 1536, 1464, 1413, 1373, 1238, 1185, 1108, 1069, 1027, 794.^{1}H-NMR(200 MHz, $CDCl_3$):δ 1.42(t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.82(dd, *J*=5.4, 2.4 Hz, 2H, H-5x2), 3.75 (s, 3H, OCH_3), 3.78(s, 3H, OCH_3), 4.24, 4.35(q, each,*J*=7.1 Hz,2H, CO_2CH_2-), 5.10(s, 1H, H-2), 4.48(s, *J*=5.4, 2.4 Hz, H-6), 6.75 (m, 5H, H-Ph) 6.84(d, *J*=8.4 Hz, 4H, H-3′, H-5′ x 2), 7.05(m, 5H,NH-Ph), 7.15(d, *J*=8.3 Hz, 4H, H-2′, H-6′ x 2), 10.31(s, br, 1H, NH).^{13}C-NMR :δ_C 13.85($CO_2CH_2CH_3$), 32.8(C-5), 55.6(C-2), 55.9(2xOMe), 57.3(C-6), 60.1(CO_2CH_2-), 97.8(C-3), 112.1(C-8, C-12), 114.9(C-16), 115.0(C-17, C-29), 155.2(C-21, C-23), 115.6(C-14, C-18), 125.0(C-10), 125.3(C-15, C-17), 128.0(C-9, C-11), 129.1(C-20, C-24), 129.2(C-26, C-30), 130.5(C-19, C-25), 143.8(C-13), 146.1(C-7), 155.1(C-4), 159.9(C-28), 160.0(C-22), 167.8(C=O).MS: m/z (rel. int) 534.6580 (100)(M^+) (calc. for $C_{34}H_{34}NO_4$, 534.6588), 506(33), 462(52), 323(45), 251(60), 211(61), 159(67), 108(42), 92(56), 83(67).Anal. Calc. for $C_{34}H_{34}N_2O_4$,C, 76.381, H, 6.410, N, 5.240. Found: C, 76.30, H, 6.32, N, 5.20.

(2c): Fawn (Light pink) Color, m.p. 212°C. IR : υ_{max}cm^{-1} 3047, 2984, 1698 (CO_2Et), 1618, 1597, 1500, 1399, 1369, 1327, 1257, 1174, 1067, 1012, 859, 747.^{1}H-NMR (200 MHz, $CDCl_3$):δ 1.41(t, *J*=7.0Hz, 3H), 2.78(dd, *J*=9.0 Hz, 2.4 Hz, 2H,H-5 x 2), 4.30, 4.41 (q, each,*J*=7.0 Hz, 2H, -CO_2CH_2-), 5.24(s, 1H, H-2), 6.38(d, *J= 5.06,*1H, H-6), 6.48(4H, d, *J* =8Hz,4H,H-3′, H-5′ x 2), 7.06(d, *J*=7.62, 4H, H-2′, H-6′), 7.17(m, 10H, N-Ph x 2), 10.29(sbr, 1H, NH).^{13}C-NMR (50 MHz, $CDCl_3$):δ_C13.8(CO_2CH_2CH3), 40.2(C-5) 53.3(C-2), 56.7(C-6), 59.9(CO_2CH_2), 98.6(C-3), 113.8(C-14, C-18), 115.3(C-8, C-12), 118.0(C-16), 118.5(C-10), 128.6(C-9, C-11), 129.0(C-21, C-23, C-27, C-29), 129.7(C-15, C-17), 130.1(C-20, C-24, C-26, C-30), 133.1(C-22, C-28), 136.3(C-19, C-25), 144.9(C-13), 146.5(C-7), 154.8(C-4), 165.3(C=O).MS: m/z (rel. int) 534.4964 (100)(M^+) (calc. for $C_{32}H_{28}Cl_2N_2O_2$, 543.4956), 515(36), 471(57), 327(63), 255(57), 215(64), 235(52), 163(55), 112(56).Anal.Calc. for $C_{32}H_{28}Cl_2N_2O_2$: C, 70.70, H, 5.19, N = 5.15.Found : C, 70.76, H, 5.22, N, 5.12.

(2d): Light yellow (Lemon). m.p. 181.3°C. IR(KBr): υ_{max} cm^{-1}: 2984, 2371(C-N), 1679(CO_2Et), 1636, 1592, 1498, 1542, 1466, 1440, 1365, 1286, 1245, 1035, 758.^{1}H-NMR (200 MHz, $CDCl_3$):δ1.13(q, *J*=7.05 Hz, 3H), 2.75(dd, *J*=7.12, 2.4 Hz, H_a-5),3.13(d, *J*=2.4, H_e-5), 4.10, 4.21(q, each, *J*=7.0, 2H, $CO_2C\underline{H}_2$), 4.61(dd, *J*=4.6, 2.30 Hz, H-6), 5.30(s, 1H, H-2), 6.63(4H, d, *J*=6.62 Hz, H-3′, H-5′ x 2), 7.25(m, 10H, 2 x Ph), 7.14(2H, d, J=6.92, H-4′ x 2), 7.88(2H, d, J=6.3, H-6′ x 2). 10.21(1H, br, s, 1H, NH).^{13}C-NMR: δ_C 13.7(OCH_2CH_3), 40.1(C-5), 45.8(C-2), 47.6(C-6), 60.2(CO_2CH_2-), 98.0(C-3), 114.0(C-14, C-18), 115.1(C-8, C-12), 118.3(C-16), 118.4(C-10), 127.6(C-24, C-30), 127.8(C-23, C-29), 128.6(C-22, C-28), 129.2(C-21, C-27), 129.4(C-9, C-11), 129.6(C-15, C-17), 133.8(C-14, C-26), 139.3(C-19, C-25), 144.7(C-13), 146.7(C-7), 154.9(C-4), 167.3(C=O). MS: m/z (rel. Int) 543.4950 (100)(M^+), (cal. for $C_{32}H_{28}Cl_2N_2O_2$, 543.4956), 515(33), 471(62), 327(59), 255(47), 215(59), 235(44), 163(51), 112(49). Anal. Calc. for $C_{32}H_{28}Cl_2N_2O_2$ (543.4956) : C, 70.719, H, 5.193, N, 5.154. Found : C, 70.76, H, 5.14, N, 5.12.

(2e) : Colorless crystals m.p. 187°C. IR(KBr) : υ_{max}cm^{-1}3047, 2984, 1695, 1618, 1596, 399, 1387, 1350, 1150, 1055, 920, 75 cm^{-1}.^{1}H-NMR(200 MHz, $CDCl_3$):δ1.42(t, *J*=7.0 Hz, 3H), 2.78(dd, *J*=8.9, 2.4 Hz, 2H, H-5 x 2), 4.23, 4.34(q, each, *J*=7.0 Hz, 2H, -CO_2CH_2), 5.28(s, 1H, H-2), 6.38(d, *J*=5.16, 1H, H-6), 6.85(d, *J*=8.6 Hz, 4H, H-3′, H-5′ x 2), 6.88(m, 5H, N-Ph), 7.17(m, 5H, NH-Ph), 7.27(d, J=8.6 Hz, H-2′, H-6′ x 2), 10.30(s, br, NH).^{13}C-NMR:δ_C 13.8(OCH_2CH_3), 39.4(C-5), 53.4(C-2), 56.9(C-6), 59.9(CO_2CH_2-), 98.7(C-3), 114.0(C-14,C-18), 115.4(C-8, C-12), 118.2(C-16), 118.7(C-10), 120.9(C-22, C-28), 128.7(C-9, C-11), 129.8(C-15, C-17), 130.8(C-20, C-24, C-26, C-30), 132.6(C-21, C-29, C-23, C-27), 136.2(C-19, C-25), 145.1(C-13), 146.4(C-7), 154.8(C-4), 165.3(C=O).MS: m/z(rel. int.) 630.3979, 632.3989(100)(M^+)(calc. for $C_{32}H_{28}Br_2N_2O_2$, 632.3982), 604(32), 560(49), 372(46), 300(49), 280(56), 260(56), 208(71), 157(59), 92(65). Anal.Calc. for $C_{32}H_{28}Br_2N_2O_2$: C, 60.77, H, 4.46, N, 4.43.Found: C, 60.65, H, 4.52, N, 4.48.

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(2f) : Colorless crystal, m.p. 162°C, IR(KBr) : υ_{max} 3510, 3235, 2994, 2931, 1644, 1595, 1508, 1424, 1372, 1260, 1115, 1071, 1036, 786. ^{1}H-NMR(200 MHz, $CDCl_3$): 1.45(t, *J*=7.1 Hz, 3H, CO_2CH_2-CH_3),2.78(dd, *J*=5.3, 2.4 Hz, 2H, H-5 x 2), 3.72(s, 3H, OCH_3), 3.82(s, 3H, OCH_3), 4.31, 4.42(q, each„*J*=7.1 Hz, 2H, CO_2CH_2-), 5.05(s, br, 1H, H-5), 5.65(s, br, 2H, 2 x OH), 6.34(dd, *J*=6.34, 2.0, 1H, H-6), 6.55(dd, *J*=8.5, H-3′ x 2), 6.66(d, *J*=2.0 Hz, H-2′ x 2), 6.77(m, 5H, N-Ph), 6.98(m, 5H, NH-Ph), 7.08(d, *J*=8.3 Hz, 2H, H-6′ x 2), 10.32(sbr, 1H, NH).^{13}C-NMR: δ_C 13.8(-$CO_2CH_2CH_3$), 37.33(C-5), 53.57(C-2), 56.51(CH_3 x 2), 57.30(C-6), 59.91 (CO_2CH_2), 98.32(C-3), 112.29(C-8,C-12), 112.93(C-24), 113.10(C-26), 115.11(C-14, C-18), 117.62(C-21, C-29), 117.92(C-16), 120.10(C-20, C-30),128.03(C-9, C-11), 128.60(C-15, C-17), 130.8(C-25), 131.1 (C-19),142.31(C-22), 125.16(C-10), 142.73 (C-28) 145.11(C-3), 146.12(C-7), 152.41 (C-4) ,58.7(C-23), 159.2(C-27), 167.81(CO). MS: m/z (rel. int.566.6586(100)(M^+) (cal. for $C_{34}H_{34}N_2O_6$, 566.6576), 538(30), 494(52), 339(42), 267(49), 247(41), 227(69), 175(57), 124(55), 108(65). Anal. Calc.for $C_{34}H_{34}N_2O_6$ (566.6576)C,72.06, H,6.04, N, 4.94. Found : C, 72.04, H, 6.06, N, 4.98.

(2g) : Colorless, m.p. 161°C. IR(KBr) : υ_{max}cm^{-1} 3068, 2913, 1659, 1589, 1545, 1534, 1464, 1413, 1373, 1236, 1183, 1101, 1069, 1027, 794.^{1}H-NMR (200MHz, $CDCl_3$):δ 1.45 (t,„*J* =7.1Hz, 3H, $CO_2CH_2CH_3$), 2.84(dd, *J*=2.4, 5.4 Hz, 2H,H-5 x 2), 3.73-3.80 (s x 4, 12 H, OCH_3 x 4), 4.31, 4.42(q, each„*J*=7.1 Hz, 2H, CO_2CH_2-),, 5.07(s, 1H, H-2), 6.38(ddd,*J*=8.0, 3.2, 2.1 Hz, H-6, H-4′ x 2), 6.57 (ddd„*J*=8.2, 2.5 Hz, 4H, H-5′, H-6′ x 2), 6.75(m, 4H, NH-Ph x 4), 7.05(m, 6H, NH-Ph), 10.32(s br, 1H, NH).^{13}C-NMR : δ_C 13.80(CO_2CH_2CH3),40.92(C-5), 45.81(C-2), 47.92(C-6), 56.32(OCH_3), 59.9(CO_2CH_2), 97.9(C-3), 115.30(C-8, C-12), 115.8(C-20, C-21), 115.9(C-23, C-20), 116.1(C-14, C-18), 118.2(C-16), 118.5(C-10), 121.5(C-24), 121.63(C-20), 129.10(C-9, C-11), 129.50(C-15, C-17), 138.5(C-19, C-25), 144.5(C-13), 145.3(C-21, C-27), 146.5(C-22, C-28), 152.4(C-4), 167.5(C=O). MS: m/z(rel.int) 594.7125(100) (M^+) (calc. for $C_{36}H_{38}N_2O_6$, 594. 7116), 566(34),522(32),353(42), 281(67),241(70), 89(71), 138(42), 92(76). Anal. Calc.forC_{36} H_{38} N_2 O_6, C,72.70, H, 6.44, N, 4.71. Found : C, 72.75, H, 6.38, N, 4.69.

(2h) : Colorless crystals, m.p. 194.6 °C. IR(KBr) : υ_{max}cm^{-1} 3427, 3354(NH), 3290, 2973, 1695, 1593, 1503, 1420, 1371, 1263, 1229, 1115, 1039, 792.^{1}H-NMR(200 MHz, $CDCl_3$):δ 1.33(t, *J*=7.0 Hz, 3H, CO_2Et), 1.37(t, *J*=7.1 Hz,6H, OCH_2CH_3), 2.31(dd, *J*=7.1, 2.5 Hz, 1H, H_a-5), 2.76(dd, *J*=6.9 Hz, 1H,H_e-5), 3.90(q, *J*=7.1 Hz, 2H, CO_2CH_2), 4.39(q, *J*=7.1Hz, 2H, OCH_2H_3), 4.29, 4.40(q, each„*J*=7.1Hz,2H,CO_2CH_2), 5.01(1H, dd, *J*= 2.4 Hz, H-6), 5.50(s, 1H, H-2), 6.33(br s, 2H, 2 x OH), 6.36(d, *J*=9.1 Hz, 2H, H-5 x 2), 6.67(dd, *J*=9.1, 2.0, 2H, H-6 x 2), 6.73(dd, *J*=2.0 Hz, 2H, H-2′ x 2), 6.83(m, 4H, Ph), 7.07(m, 6H,Ph x 2), 10.31(br s, 1H, NH).^{13}C-NMRCDCl$_3$) : δ_C 13.86 ($CO_2CH_2CH_3$), 14.10(OCH_2CH_3 x 2), 32.86(C-5), 55.0(C-2), 56.9(C-6), 60.0(CO_2CH_2-), 64.3(OCH_2- 2), 97.9(C-3), 112.3(C-8, C-12), 112.9(C-24), 113.01(C-26), 115.0(C-16), 115.3(C-14, C-18), 117.2(C-21), 1174(C-29), 121.1(C-20, C-30), 125.0(C-10), 125.9(C-15,C-17), 128.1(C-9, C-11), 130.4(C-19, C-25), 140.8(C-23, C-27), 144.7(C-22, C-28), 144.9(C-13), 146.2(C-7), 155.2(C-4), 167.80(CO). MS : m/z (rel. int) 594.7124(100)(M^+) (Calc.for $C_{36}H_{38}N_2O_6$, 594.7116), 566(33), 538(55), 522(45), 353(41), 281(52), 261(56), 241(71), 189(58), 138(32), 110(49).Anal. Calc.$C_{36}H_{38}N_2O_6$ C, 72.70, H,6.44, N, 4.71. Found: C, 72.72, H, 6.46, N, 4.68.

(2i) : Colorless crystals, m.p. 172°C. IR(KBr) : υ_{max}cm^{-1}3058, 2973, 1646, 1590, 1501, 1446, 1403, 1365, 1324, 1233, 1170, 1066, 1044, 744.^{1}H-NMR($CDCl_3$, 200 MHz):δ 1.31(t, *J*=7.1 Hz, 3H, CO_2CH_2-CH_3), 2.83(d„*J*=5.38 Hz, 3.61, 2H,H-5 x 2). 4.14, 4.25 (q, each„*J*=7.2 Hz, 2H, CO_2CH_2), 5.33(s, 1H, H-2), 6.36(dd, *J*=3.4 Hz, 1H, H-6), 6.42(dd, *J*=7.8, 1.2 Hz,H-4′, H-5′ x 2), 7.10(m, 10H, N-Ph x 2), 7.32(dd, J=7.83, 1.2 Hz, H-6′), 10.07(s br, 1H,NH).^{13}C-NMR: δ_C 13.88 ($CO_2CH_2\underline{C}H_3$), 39.5(C-5), 44.2(C-2), 47.6(C-6), 59.8(CO_2CH_2-), 98.3(C-3), 113.6(C-14, C-18),115.4(C-8, C-12), 118.7(C-10), 118.8(C-16), 127.8(C-24, C-30), 128.3(C-23, C-29), 128.9(C-9, C-11), 129.0(C-22, C-28), 129.9(C-15, C-17), 134.2 (C-20, C-26), 135.1(C-21, C-27), 139.3(C-19, C-25), 144.8-13), 146.5(C-7),154.9(C-4), 165.2(C=O). MS: m/z (rel. Int) 612.3860(100)(M^+), 620 (calc. for $C_{32}H_{26}Cl_4N_2O_2$, 612.3853), 584(34), 540(55), 362(62), 290(43), 270(32), 250(42), 198(38), 147(62), 92(72). Anal calc. for $C_{32}H_{26}Cl_4N_2O_2$,C, 62.76, H, 4.279, N, 4.574.Found : C, 62.84, H, 4.23, N, 4.52.

(2j) : Colorless crystals, m.p. 157 °C. IR (KBr:υ_{max} cm^{-1} 3255, 3194, 2826, 1656, 1598, 1505, 1454, 1410, 1350, 1249, 1131, 1064, 1008, 796.^{1}H-NMR($CDCl_3$, 200 MHz): δ 1.44(t, *J*=7.0 Hz, 3H, $CO_2C\underline{H}_3$), 2.76(dd, *J*=6.9, 2.2 Hz, H-5 x 2), 4.30, 4.41(q, each„*J*=7.1 Hz, 2H, CO_2CH_2), 5.02(s, 1H, H-2), 6.38(dd, *J*=6.8, 2.2 Hz, H-6), 6.40(dd, *J*=7.9, 2.1 Hz, 4H, H-2′, H-5′ x 2), 6.62(m, 5H, N-Ph), 6.66(dd, *J* = 7.8, 2.1 Hz, 2H, H-6 x 2), 7.11(m, 5H, NH-Ph), 10.30(s br, 1H, NH).^{13}C-NMR) : δ_C 13.8($CO_2CH_2CH_3$), 41.5(C-5), 53.8(C-2), 57.1(C-6), 59.8(CO_2CH_2-), 98.2(C-3), 99.8(OCH_2O, 31), 100.1(OCH_2O, 32), 113.7(C-14, C-18),115.1(C-26, C-30), 115.3(C-20, C-24), 115.4(C-8, C-12), 118.1(C-16), 118.9 (C-10), 121.9(C-23, C-26), 128.7(C-9, C-11), 129.9(C-15, C-17), 130.8(C-19, C-25), 144.8(C-13), 146.1(C-22), 146.5(C-7), 146.7(C-28), 147.3(C-21), 147.6(C-29),153.9(C-4), 165.5(C=O). MS: m/z(rel. Int) 562.6266 (100)(M^+)(calc. for $C_{34}H_{30}N_2O_6$, 562.6258), 534, 532(46), 490(54), 337(64), 307(72), 265(54), 235(60), 225(57), 195(67), 165(48), 92(72). Anal:Calc.for $C_{34}H_{30}N_2O_6$. C, 72.58, H, 5.37, N, 4.97. Found : C, 72.50, H, 5.45, N, 4.91.

(2k) : Colorless crystals m.p. 175 °C. IR(KBr) :υ_{max}cm^{-1} 3258, 3194, 2828, 1654, 1592, 1500, 1453, 1411, 1350, 1249, 1131, 1064, 1007, 794.^{1}H-NMR(200 MHz, $CDCl_3$): 1.43(t, *J*=7.1, 3H,$CO_2CH_2CH_3$), 2.78(dd, *J*=6.9, 2.2 Hz,H-5 x 2), 3.70(s, 6H, 2x OMe), 3.78(s, 6H, 2 x OMe), 3.84(s, 6H, 3 x OMe), 4.31,4.42(q, each„*J*=7.1 Hz, 2H, CO_2CH_2-), 5.01(s, 1H, H-2), 6.37(4H, H-2 x 2, H-6′ x 2), 6.40 (dd, *J*=6.1, 2.4, 1H, H-6), 6.64(m, 5H, N-Ph), 7.11(m, 5H, NH-Ph), 10.31(s br, 1H, NH).^{13}C-NMR : δ_C 13.7(OCH_2CH_3), 41.6(C-5), 54.3(C-2), 56.0(2 x OCH_3), 56.3(2 x OCH_3), 56.4(2 x OCH_3), 57.7(C-6), 59.9(OCH_2-), 98.7(C-3), 109.2(C-20, C-24, C-26, C-30), 113.9(C-14, C-18), 115.5(C-8, C-12), 118.1(C-16), 118.8(c-10), 128.6(C-9, C-11), 129.8(C-15, C-17), 130.9(C-19, C-25), 132.3(C-22, C-28), 144.9(C-13), 146.8(C-7), 148(C-23, C-27), 148.9(C-21, C-29), 153.8(C-4), 167.5(C=O). MS: m/z (rel. %) 654.7648(calcd. for $C_{38}H_{42}N_2O_8$ 654.7645) (100)(M^+), 626(32), 582(56), 383(41), 311(50), 271(70), 219(52), 168(30), 138(36). Anal.Calc. for $C_{38}H_{42}O_8$, C, 69.70, H, 6.46,N, 4.27.Found : C, 69.79, H, 6.40, N, 2.22.

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