A NEW SYNTHESIS OF 1,4-DIHYDROPYRIDINE DEREVATIVES FROM FORMYL FUROCHROMONE

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Abstract :Condensation of equimolar β-enaminoester **(2a-d)**, β-ketoester **(3a-c)** with formyl furochromone **(1)** yielded 1,4-dihydropyridine derivatives **(4a-l)**. Oxidation of 1,4-dihydropyridine derivatives **(4a-c)** afforded the corresponding pyridine derivatives **(5a-c)**. Reaction of compound **(1)** with β-enaminoester **(2a-d)** in the molar ratio (1:2) gave 1,4-dihydropyridine derivatives **(6a-d)**. Treatnent of formyl furochromone **(1)** with 3-aminocrotononitrile **(7)** in the molar ratio (1: 2) in an acid medium yielded 1,4-dihydropyridine derivatives **(11)**. It has been found that compound **(1)** react with nitroketenaminals **(12a-d)** to give 1,4-dihydropyridine (13a-d). Reduction of nitro-group on 1,4-dihydropyridine **(13a)** gave compound **(14a)**.

Keywords : formyl furochromone , β-enaminoester, β-ketoester, 3- aminocrotononitrile, nitroketenaminal.

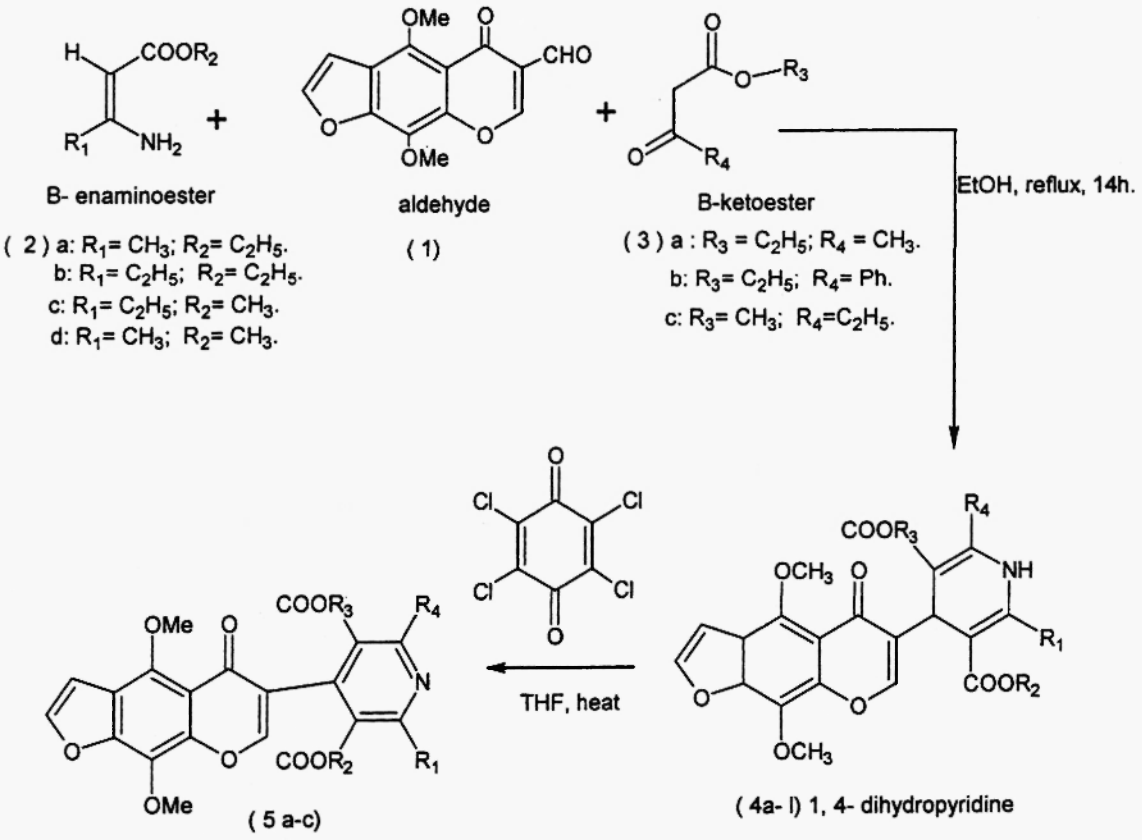
Introduction

The design of 1,4-dihydropyridine (DHP) calcium channel modulators has provided a significant challenge to medicinal chemists[1-4]. DHP calcium channel antagonists that have enhanced vascular selectivity such as felodipine, which exhibit a minimal inotropic effect are useful for the treatment of hypertension[5] and vasospasm[5]. In contrast, the calcium channel agonists Bay 8644 exhibits a positive inotropic effect by stimulating calcium entry into cardic muscle[6]. 1,4-Dihydropyridine blockers of L-type calcium channels are used extensively in the treatment of cardiovascular disorders as dilators of coronary arteries [7], We have found that, in addition to binding to calcium channels, some class of 1,4-Dihydropyridine has provided leads for novel antagonists[8] and agonist activities[4]. Based on these facts, it is of interest to synthesized new compounds in a trial to obtain 1,4-dihydropyridines derivatives. The 1,4-DHP compounds prepared but no pharmacological data reported

Results and Discussion

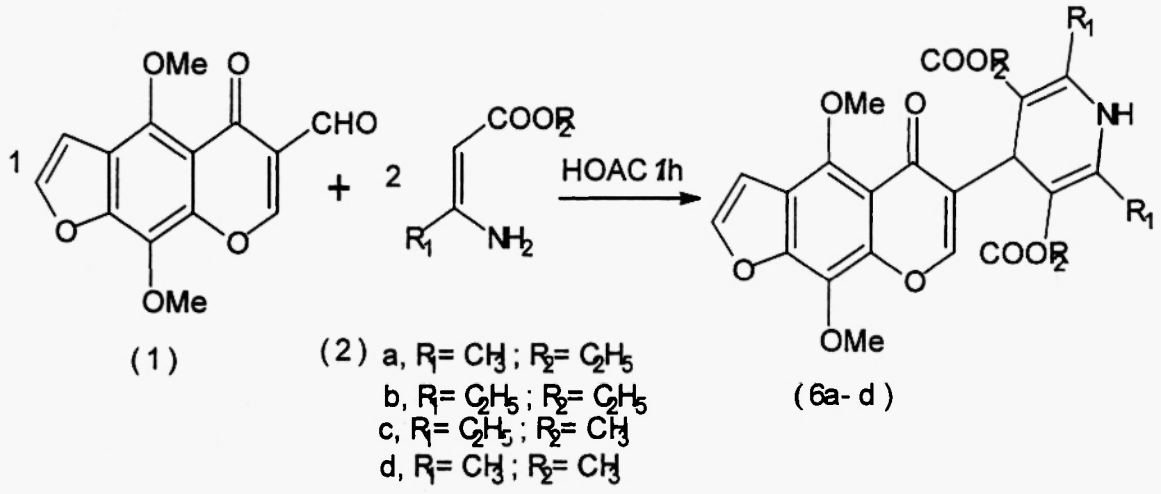
4(4,9-dimethoxy-*5H*-furo[3,2-g]chromen-5-one)-alkyl-1,4-dihydropyridine-3,5-dicarboxylate **(4a-l)** were prepared by a modified Hantzsch reaction. Also,

condensation of alkylaminocrotonoate **(2a-d)**, 4,9-dimethoxy-*5H*-furo[3,2-g]chrromen-5-one **(1)** and 3-keto ester derivatives**(3a-c)**, that were dissolved in ethanol and refluxed for 14h afforded the title compounds in 21- 69 % yields as illustrated in (scheme 1, method A). The IR spectrum of compounds**(4a-p)** showed the presence of 2CO(ester) groups, exchangeable NH groups in D_2O, while, The IR spectrum compounds**(4a-p)** showed the absence of (CHO) group, and the ^{1}HNMR spectrum afforded signals of exchangeable protons to CH_2CH_3, NH groups Oxidation of 1,4-dihydrpyridine **(4a-c)**, of the corresponding pyridine derivatives (5a-c) was carried using tetrachloro-1,4-benzoquinone (chloranil) in tetrahydrofuran (Scheme-1)[9]. The elemental analyses and spectrum data of compounds **(4a-l)** and **(5a-c)** were compatible with the suggested structures.



Scheme-1

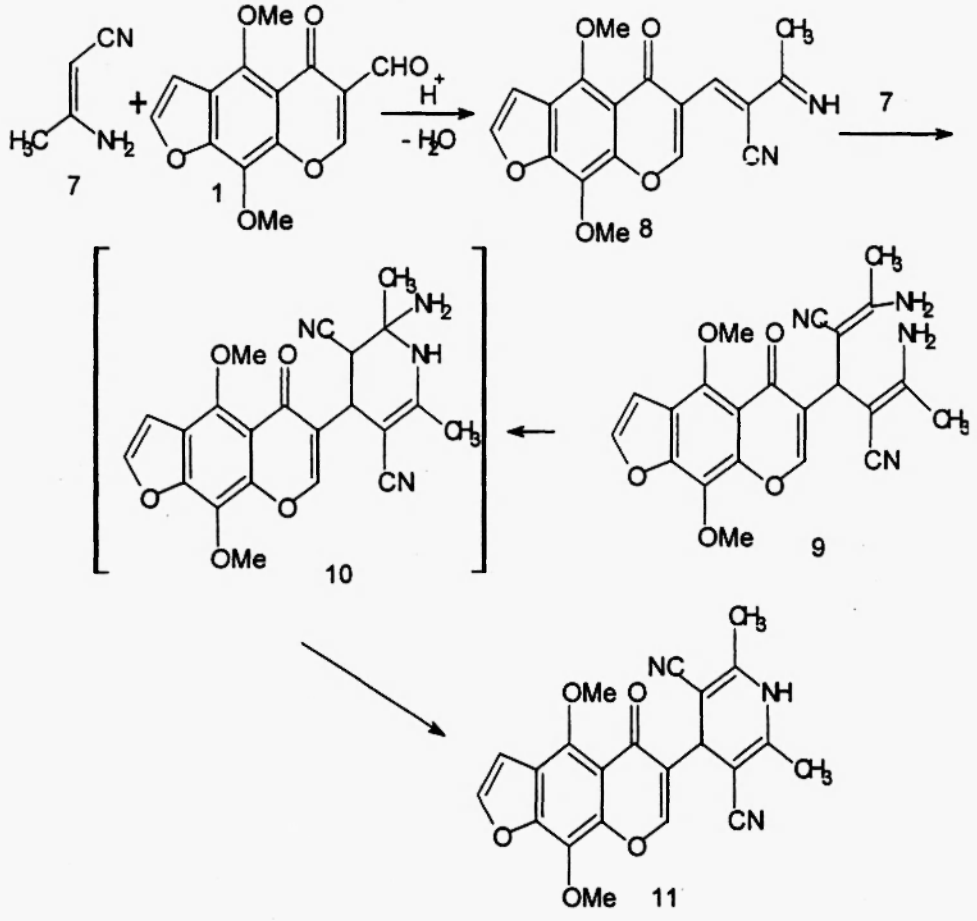
An approach to designing dihydropyridine that binding to L-type calcium channels has been described. 1,4-Dihydropyridine derivatives substituted with formyl furochromone group at 4-position, alkyl or aryl groups at 6-position were synthesized[10] . Combinations of methyl and ethyl esters were included at the 3- and 5-position. Method B to prepare 1,4- dihydropyridine derivatives **(6a-d)** by the reaction of formyl furochromone with enaminester are now reported. Aldehyde normally reacted with 3-aminocrotonate in the molar ratio 1: 2 in an acid medium to prepare 4(4,9-dimethoxy-*5H*-furo[3,2-g]chromen-5-one)-alkyl-1,4-dihydropyridine-3,5-alkan-1-one (Scheme-2), in 33-75%yield. In IR.spectrum of compound **(6a-d)** afforded bands to 2CO(ester), NH groups and the ^{1}HNMR spectrum appered a singlet of exchangeable protons to CH_2CH3, NH groups.



Scheme-2

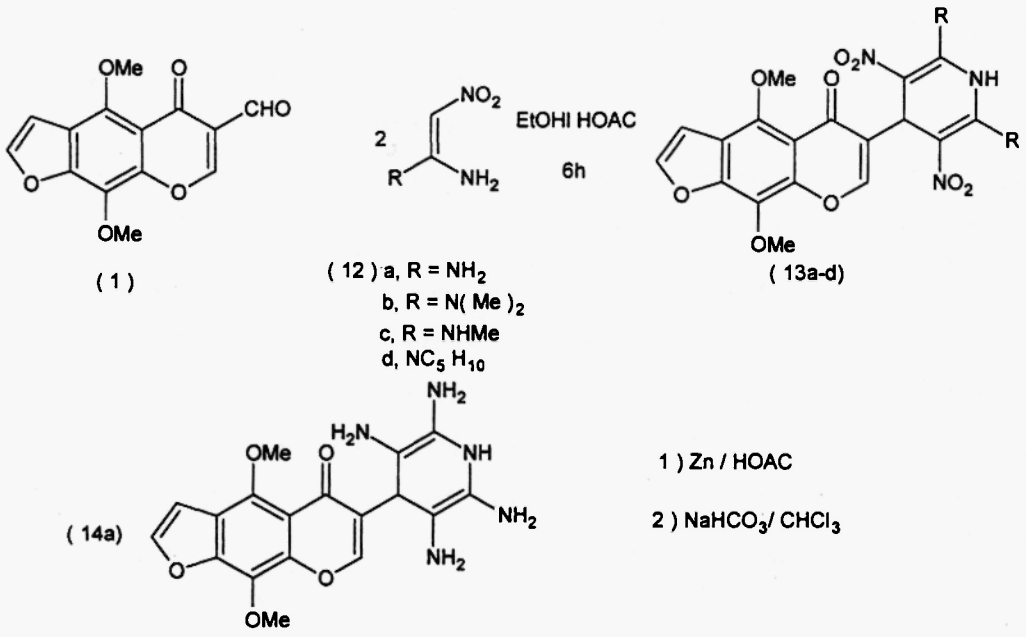
The first reported synthesis of 1,4-dihydropyridines **(11)** involved the condensation of β-enaminonitrile **(7)** and aromatic aldehyde **(1)**[11]. 1,4-dihydropyridines **(11)** have had widespread used in recent years in medicinal chemistry[12 -23] The synthesis of 1,4- dihydropyridines **(11)** takes place according to (Scheme-3) [23 , 24].The reaction of aldehyde **(1)** with enaminonitrile **(7)** yields the derivative **(8)** which in turn reacts with **(7)**, in acetic acid, to form the intermediate diamines **(9)**. The latter was isolated from the reaction of **(7)** with the aldehyde **(1)** in ethanol at room temperature. [25] The diamine **(9)** are readily converted into the 1,4- dihydropyridine (11) in acetic acid solution. Evidence for Scheme 3 was found by Ó Callaghan et al [24, 25] who isolated the dihydropyridine **(11)** by trapping the intermediate **(10)** using excess aldehyde **(1)** in the reaction mixture. Thus, a compound of 4-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-

g]chromen-6-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile **(11)** was prepared using Hantzsch reaction[12,26] that involved the condensation of aldehyde **(1)** with 3- aminocrotononitrile **(7)** is reported in the molar ratio 1: 2 in an acid medium (Scheme-3). The IR.spectrum of compound **(11)** showed a bands at 2220, 3320cm^{-1} corresponding of the CN, NH groups. This is in agreement with Eisner and et al [27].



Scheme-3

On the other hand; the synthesis of 1,4- dihydro- 3,5- dinitropyridine derivatives (13a-d) were carried out at the condensation of aldehyde **(1)** with primary/tertiary nitroketenaminals **(12a-d)**[28,29] in ethanol / AcoH (3:1) (Scheme-4). [1]. The assignment of structures **(13a-d)** were based on elemental analyses and spectrum data. This is in agreement with Troschütz and et al[30]. An aromatic nitro groups on C-3,5 side chain of a dihydropyridine **(13a)** could be reduced selectively using zinc/ acetic acid (Scheme-4) to yield compound **(14a).**



Scheme-4

Experimental

All melting points are uncorrect. Elemental analyses were performed by (Micro analytical analyses were within ± 0.4% of theoretical values), Micro-analyses were carried out by the Microanalytical laboratory of national research centre, Cairo, Egypt. The IR spectra were recorded on Jasco FTIR-300 Efouriertransform infra-red spectrometer and Perkin- elmer FTIR 1000 E spectrum using KBr wafer technique. ^{1}H-NMR spectra were performed on Jeol-EX-270 MHz ^{1}H-NMR spectra using TMS as an internal standered and spectra were taken in DMSO- d_6 or $CHCl_3$-d. The assignment of exchangeable protons (NH) was confirmed by addition of [D_2O]. Chemical- ionization (CI) mass spectrometry was determined on GC/MS finnigan mat SSQ 7000 Digital DEC3000. The purity of the synthesized compounds were tested by thin layer chromatography (TLC) :Merk Plates.

General procedure for the preparation of alkyl 1,4-dihydropyridine-3,5-dicarboxylate ester(4a-l):

Method (A)

Equimolar amounts (0.5 mmol) of the appropriate alkyl aminocrotonoate, namely, ethyl-3-aminobut-2-enoate; ethyl-3-aminopent-2-enoate; methyl -3-aminopent-2-enoate and methyl-3-aminobut-2-enoate **(2a-d)**, fomyl furochromone **(1)**, 3-ketoester,

namely ethyl 3-oxobutanoate; ethyl 3-oxo-3-phenylpropanoate; methyl 3-oxopentanoate and methyl 3- oxobutanoate (**3a**-d) derivatives were dissolved in 20 ml. of absolute ethanol was refluxed for 14 h. Removal of the solvent in vacuo afforded an oil- like residue which was purified by TLC silica gel using EtOAC: EtOH (95: 5) as eluent for all compounds.

4(4,9- Dimethoxy-5H-furo[3,2-g]chromen-5-one)- diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**). Mol. Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49, yield 33%, m.p.=211° C. IR (KBr) : ν 1780, 1778, 1640 cm^{-1}(3 CO) ,3260 cm^{-1} (NH).^{1}H-NMR($CDCl_3$): δ 1.28(t, 6H, *J= 6.5 Hz*, 3, 5- CH_2CH_3), 2.31(s, 6H, 2, 6-CH_3), 4.14(m, 4H, 3, 5-OCH_2), 4.05, 4.00 (2s, 6H, 4, 9-OCH_3), 4.60 (d, 1H, J = 5.9 Hz, 4-H), 5.66 (br., 1H, NH exchangable D_2O), 7.90, 7.14 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.11 (s, 1H, H_7). MS: m/z 498 (10%) , 252 (38%) , 246 (88%), 223 (63%), 208 (13%), 177 (32%), 165 (32%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) diethyl 2-methyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4b**). M.ol. Formula $C_{31}H_{29}NO_9$, M.Wt. = 559.56, yield 223%, m.p. 232°C. IR(KBr) : ν 1774, 1770, 1632 cm^{-1} (3CO), 3242 cm^{-1} (NH). ^{1}H-NMR($CDCl_3$): δ 1.26 (t, 6H, *J= 6.1 Hz*, 3, 5- CH_2CH_3), 2.22(s, 3H, 2-CH_3), 4.15(m, 4H, 3, 5-OCH_2), 4.00, 3.99 (2s, 6H, 4, 9-OCH_3), 4.56 (d, 1H, J = 5.6 Hz, 4-H), 5.64 (br., 1H, NH exchangable D_2O), 7.64 (m, 5H, 6- aromtic ring), 7.83, 7.11 (dd, 2H, $J_{H,H}$ = 2.3 Hz, $H_{2,3}$ furan), 8.05 (s, 1H, H_7). MS: m/z 560(11%) , 314 (22%), 253, (43%), 246 (91%), 238 (23%), 221 (22%), 216 (14%), 208 (21%), 164 (125%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) ethyl methyl-6-ethyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**4c**). Mol. Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49, yield 54%, m.p. 211°C .IR (KBr) : ν 1780, 1777, 1634 cm^{-1}(3CO) , 3246 cm^{-1} (NH). ^{1}H-NMR($CDCl_3$): δ1 .14(t, 3H, *J= 6.3 Hz*, 3- CH_2CH_3), 2.10 (s, 3H, 2- CH_3), 2.21 (t, 3H, 6-CH_2 CH_3) 4.15(m, 2H, 3-OCH_2), 4 .17 (s, 3H, 5-OCH_3) 4.03, 4.00 (2s, 6H, 4, 9-OCH_3), 4.54 (m, 2H, 6-CH_2), 4.76 (d, 1H, J = 5.3 Hz, 4-H), 5.25 (br., 1H, NH exchangable D_2O), 7.87, 7.01 (dd, 2H, $J_{H,H}$ = 2.2 Hz, $H_{2,3}$ furan), 8.01 (s, 1H, H_7). MS: m/z 498 (17%) , 254 (35%) , 246 (77%),216 (11%), 209 (23%), 191(19%),178 (42%),165 (26%) .

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) diethyl 2-ethyl- 6-methyl -1,4-dihydropyridine-3,5-dicarboxylate **(4d).** Mol. Formula $C_{27}H_{29}NO_9$, M.Wt = 511.52, yield 234%, m.p. 201°C. IR (KBr) : ν 1775, 1773, 1633 cm^{-1} (3CO) ,3245 cm^{-1} (NH).^{1}H-NMR($CDCl_3$): δ 1.11(t, 6H, *J= 6.0 Hz*, 3, 5- CH_2CH_3), 2.00 (s, 2H, 6-CH_3), 2.43 (m, 2H, 2-CH_2), 2.22(t, 3H, 2- CH_2 CH_3), 4.01(m, 4H, 3, 5-OCH_2), 3.99, 3.94 (2s, 6H, 4, 9-OCH_3), 4.53 (d, 1H, *J* = 5.5 Hz, 4-H), 5.04 (br., 1H, NH exchangable D_2O), 7.31 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.04 (s, 1H, H_7). MS: m/z 512 (21%) , 266 (40%), 246 (85%).,222 (53%), 216 (34%), 178 (20%), 164 (17%)...

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) diethyl 2-ethyl- 6-phenyl -1,4-dihydropyridine-3,5-dicarboxylate **(4e).** Mol. Formula $C_{32}H_{31}NO_9$, M.Wt = 573.59 yield 24%, m.p. 230°C.IR (KBr) : ν 1781, 1779, 1638 cm^{-1} (3CO) , 3260(NH).^{1}H-NMR($CDCl_3$): δ 1.20 (t, 6H, *J= 6.01 Hz*, 3, 5- CH_2CH_3), 2.22(t, 3H, 2- CH_2 CH_3), 2.13 (m, 3H, 2- CH_2), 4.21(m, 4H, 3, 5-OCH_2), 4.00, 9.97 (2s, 6H, 4, 9-OCH_3), 4.53 (d, 1H, *J* = 5.0 Hz, 4-H), 5.22 (br., 1H, NH exchangable D_2O), 7.64, 7.03 (m, 5H, 6- aromatic), 7.73, 7.01 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), , 8.04 (s, 1H, H_7). MS: m/z 574 (12%), 328 (37%), 254 (56%), 246 (78%), 222 (42%), 208 (32%), 165 (23%), 136 (9%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) ethyl methyl 2,6-diethyl -1,4-dihydropyradine-3,5-dicarboxylate **(4f).** Molecular Formula $C_{27}H_{29}NO_9$, M.Wt = 511.52 yield 64%, m.p. 188°C. IR: ν 1780, 1779, 1630 cm^{-1} (3CO), 3235cm^{-1} (NH).^{1}H-NMR ($CDCl_3$) : δ 1.02(t, 3H, *J= 6.7 Hz*, 3 - CH_2CH_3), 2.10 (t, 6H, 2, 6-CH_2CH3), 2.43 (m, 4H, 2, 6-CH_2), 4.22(m, 2H, 3- OCH_2), 4.17 (s, 3H, 5-OCH_3), 4.01, 3.98 (2s, 6H, 4, 9-OCH_3), 4.53 (d, 1H, *J* = 5.0 Hz, 4-H), 5.04 (br., 1H, NH exchangable D_2O),7.68, 7.11 (dd, 2H, $J_{H,H}$ = 2.0 Hz, $H_{2,3}$ furan), 8.02 (s, 1H, H_7). MS: m/z 512 (11%) , 268 (24%), 246 (80%),215 (52%), 222 (53%), 192 (32%), 165 (12%) .

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) ethyl methyl 2-ethyl-6-methyl -1,4-dihydropyridine-5,3-dicarboxylate **(4g).** Molecular Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49 yield 44%, m.p. 211°C. IR: ν 1780, 1776, 1629 cm^{-1} (3CO), 3265 cm^{-1} (NH).^{1}H-NMR: ($CDCl_3$) : δ 1.12 (t, 3H, *J= 6.0 Hz*, 5- CH_2CH_3), 2.12 (s, 3H, 6-CH_3), 2.21 (t, 3H, 2-CH_2CH3), 2.23 (m, 2H, 2-CH_2), 4.24(m, 2H, 5- OCH_2), 4.11 (s, 3H, 3-OCH_3), 4.01, 3.99 (2s, 6H, 4, 9-OCH_3), 4.53 (d, 1H, *J* = 5.3 Hz, 4-H), 5.54 (br., 1H, NH exchangable D_2O), 7.84, 7.10 (dd, 2H, $J_{H,H}$ = 2.1 Hz, $H_{2,3}$ furan), 8.03

(s, 1H, H_7). MS: m/z 498 (15%) , 254 (25%), 246 (88%), 222 (31%), 215 (33%), 208 (23%), 178 (22%), .

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) ethyl methyl 2-ethyl-6- phenyl- 1,4-dihydropyridine-5,3- dicarboxylate (**4h**).Molecular Formula $C_{31}H_{29}NO_7$, M.Wt = 559.56. yield 223%, m.p. 231°C. IR: ν 1779, 1777, 1637 cm^{-1} (3CO), 3235 cm^{-1} (NH).^{1}H-NMR: ($CDCl_3$): δ 1.22 (t, 3H, *J= 6.11 Hz* 5- CH_2CH_3), 2.19 (t, 3H, 2- CH_2 CH_3), 2.07 (m, 3H, 2- CH_2), 4.11(m, 4H, 5-OCH_2), 4.09 (s, 3H, 3-OCH_3), 4.03, 3.99 (2s, 6H, 4, 9-OCH_3), 4.53 (d, 1H, *J* = 5.5 Hz, 4-H), 5.22 (br., 1H, NH exchangable D_2O), 7.70, 7.12 (m, 5H, 6- aromatic), 7.73, 7.02 (dd, 2H, $J_{H,H}$ = 2.4 Hz, $H_{2,3}$ furan), 8.01 (s, 1H, H_7). MS: m/z 560 (13%), 528 (22%) , 315 (23%) , 246 (74%), 238 (23%), 184(18%), 165 (20%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) dimethyl 2,6- diethyl-1,4-dihydropyridine-3,5- dicarboxylate (**4i**).Molecular Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49 yield 43%, m.p. 200°C. IR: ν 1775, 1773, 1633 cm^{-1} (3CO),3330 cm^{-1} (NH).^{1}H-NMR: ($CDCl_3$) : δ 1.10 (t, 6H, *J= 5.21 Hz*, 2,6- CH_2CH_3), 2.23 (m, 4H, 2,6-CH_2), 4.30 (s, 6H, 3,5- OCH_3), 4.01, 4.00 (2s, 6H, 4, 9-OCH_3), 4.40 (d, 1H, *J* = 5.3 Hz, 4-H), 5.57 (br., 1H, NH exchangable D_2O), 7.64, 7.10 (dd, 2H, $J_{H,H}$ = 2.1 Hz, $H_{2,3}$ furan), 8.00 (s, 1H, H_7). MS: m/z 498 (15%), 466 (16%), 254 (35%), 246 (79%), 221(22%), 215 (45%), 191 (34%),164 (23%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) ethyl methyl 2,6-dimethyl-1,4-dihydropyridine-5,3- dicarboxylate (**4j**).Molecular Formula $C_{25}H_{25}NO_9$, M.Wt = 483.47 yield 64%, m.p. 211°C.IR: ν 1779, 1776, 1628 cm^{-1} (3CO), 3234 cm^{-1} (NH).^{1}H-NMR: ($CDCl_3$) : δ 1.13 (t, 3H, *J= 5.11 Hz*, 5- CH_2CH_3), 2.04 (s, 6H, 2,6-CH_3), 4.01, 4.00 (2s, 6H, 4, 9-OCH_3), 4.07 (m, 2H, 5- OCH_2), 4.11 (s, 3H, 3-OCH_3), 4.43 (d, 1H, *J* = 5.3 Hz, 4-H), 5.34 (br., 1H, NH exchangable D_2O), 7.78, 7.16 (dd, 2H, $J_{H,H}$ = 2.1 Hz, $H_{2,3}$ furan), 8.00 (s, 1H, H_7). MS: m/z 484 (21%), 438 (19%), 246 (83%), 240 (53%), 194 (33%),165 (24%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) 5-ethyl 3-methyl- 6-phenyl -1,4-dihydropyridine-3,5-dicarboxylate (**4k**).Molecular Formula $C_{30}H_{27}NO_9$, M.Wt = 545.54 yield 22%, m.p. 223°C. IR: ν 1779, 1775, 1629 cm^{-1} (3CO),3321cm^{-1}(NH).^{1}H-NMR: ($CDCl_3$): δ 1.28 (t, 6H, *J= 6.22 Hz* 5- CH_2CH_3), 2.07 (s, 3H, 2- CH_3), 4.00, 3.98 (2s, 6H, 4, 9-OCH_3), 4.18 (s, 3H, 3-OCH_3), 4.22(m, 2H, 5-OCH_2), 4.27 (d, 1H, *J* = 5.1 Hz, 4-H), 5.55 (br., 1H, NH exchangable D_2O), 7.72, 7.01 (m, 5H, 3-

aromatic), 7.81, 7.15 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.02 (s, 1H, H_7). MS: m/z 546 (11%), 500 (11%), 301 (24%), 246 (87), 222 (36%), 215 (37%), 181(31%), 152(21%).

4(4,9-Dimethoxy-5H-furo[3,2g] chromen-5-one) dimethyl 6-ethyl-2-methyl-1,4-dihydropyridine-3,5- dicarboxylate (4l).Molecular Formula $C_{25}H_{25}NO_9$, M.Wt = 483.47 yield 53%, m.p. 174°C.IR: ν 1780, 1778, 1630 cm^{-1} (3CO), 3254 cm^{-1} (NH).^{1}H-NMR: ($CDCl_3$) : δ 1.79 (t, 3H, *J= 5.22 Hz*, 6- CH_2CH_3), 2.50 (m, 3H, 6-CH_3), 4.00, 3.98 (2s, 6H, 4, 9-OCH_3), 4.61 (s, 6H, 3,5- OCH_3), 4.41 (d, 1H, *J* = 5.3 Hz, 4-H), 5.43 (br., 1H, NH exchangable D_2O), 7.70, 7.11 (dd, 2H, $J_{H,H}$ = 2.1 Hz, $H_{2,3}$ furan), 8.00 (s, 1H, H_7). MS: m/z 484 (23%), 452 (10%), 246 (89%), 240 (32%)., 221 (12%), 215 (31%), 191 (16%), 164 (23%).

Method (B):

(2mmol) of the appropriate alkyl aminocrotonoate (ethyl-3-aminobut-2-enoate; ethyl-3-aminopent-2-enoate; methyl 3-aminopent-2-enoate; methyl-3-aminobut-2-enoate) (2a-d), in 40 ml of glacial acetic acid was added to (1mmol) aldehyde (1).The solution was stirred and heated on a steam bath for 1hr and then poured into ice water and an orange oil separated. The H_2O was decanted and the oil was taken up in CH_2Cl_2, washed with H_2O,dried, and concentrated to give an oil which solidified on stirring with hexane to give (33- 75% yield) of (6a-d).

4(4,9-Dimethoxy-5H-furo[3,2-g]chromen-5-one) diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **(6a)**.Molecular Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49, yield 53%, m.p. 200°C . IR: ν 1677, 1668, 1627cm^{-1} (3CO) . ^{1}H NMR ($CDCl_3$): δ 1.29, 1.30 (t, 6H, *J* = 6.3 Hz, 3, 5-CH_2CH_3), 2.38 (s, 6H, 2,6- CH_3), 4.00, 3.98 (2s, 6H, 4,9-OCH_3), 4.22 (m, 2H, 3-OCH_2), 4.70 (d, 1H, *J* = 5.8 Hz, 4-H), 5.20 (2H, *J* =12.7 Hz, 5-OCH_2), 5.60 (br, 1H, NH exchangable D_2O), 7.70, 7.04 (2d, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.01 (s,1H, H_7). Ms : m/z 498 (22%), 252 (32%), 246 (75%), 221 (35%), 215(67%) ,191(56%), 164 (65%).

4(4,9-Dimethoxy-5H-furo[3,2-g]chromen-5-one) diethyl 2,6-diethyl-1,4-dihydropyridine -3,5-dicarboxylate **(6b).** Molecular Formula $C_{28}H_{31}NO_9$, M.Wt = 525.55, yield 33%, m.p. 210°C. IR: ν 1687, 1672, 1625cm^{-1} (3CO) .^{1}H NMR ($CDCl_3$): δ 1.29 (t, 6H, *J* = 6.8 Hz, 3 and 5-CH_2CH_3), 2.34 (t, 6H, 2,6- CH_3), 4.01, 4.00 (2s, 6H, 4,9-OCH_3), 4.05 (m, 4H, 2,6-CH_2), 4.22 (m, 4H, 3,5-OCH_2), 4.70 (d, 1H, *J* = 5.8 Hz, 4-H), 5.60 (br, 1H, NH exchangable D_2O), 7.90, 7.14 (2d, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$

furan), 8.11 (s,1H, H_7). Ms : m/z 526 (13%), 281 (23%), 246 (66%),.236(43%), 221 (58%), 215 (63%),192(77%).

4(4,9-Dimethoxy-5H-furo[3,2-g]chromen-5-one) dimethyl 2,6-diethyl-1,4-dihydropyridine-3,5-dicarboxylate(**6c**).Molecular Formula $C_{26}H_{27}NO_9$, M.Wt = 497.49, yield 59%, m.p. 211°C . IR: ν 1677,1671, 1623cm^{-1}(3CO) .^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H, 2 , 6-CH_3), 2.34, 2.38 (m, 4H, 2,6- CH_2), 4.01, 4.00 (2s, 6H, 4,9-OCH_3), 4.22 (s, 6H, 3, 5-OCH_3), 4.70 (d, 1H, J = 5.8 Hz, 4-H),), 5.60 (br, 1H, NH exchangable D_2O), 7.90, 7.14 (2d, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.11 (s,1H, H_7). Ms : m/z 498 (17%), 253 (45%),246 (87%),221 (26%), 215(53%) ,191(34%), 164 (51%).

4(4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one) dimethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(**6d**).Molecular Formula $C_{24}H_{23}NO_9$, M.Wt = 465.44, yield 75%, m.p. 202°C . IR: ν 1676,1668, 1626cm^{-1}(3CO) .^{1}H NMR ($CDCl_3$): δ 2.34 (s, 6H, 2,6- CH_3), 4.01, 4.00 (2s, 6H, 4,9-OCH_3), 4.22 (s, 6H, 3, 5-OCH_3), 4.70 (d, 1H, J = 5.4 Hz, 4-H),), 5.40 (br, 1H, NH exchangable D_2O), 7.70, 7.00 (2d, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.10 (s, 1H, H_7). Ms : m/z 466 (21%), 246 (88%), 224 (31%)..

General procedure of oxidation of 1,4-dihydropyridine- 3,5-dicarboxylate ester (5a-c):

Equimolar amounts (0.25 mmol) of the 1,4- dihydropyridine-3,5-dicarboxylate ester (5a-c) and tetrachloro-1,4- benzoquinone in tetrahydrofuran(2ml) were mixed and refluxed for up to 4h. The solvent was then evaporated, and products were purified by preparation TLC. Silica gel using, (20%Ethylacetate- 80% Petrolium ether 35-60) as eluent for all compounds

4-(4,9-Dimethoxy- 5- oxo- 5H- furo [3,2-g] chromene- 6- carbaldehyde)- diethyl 2,6-dimethyl pyridine- 3,5- dicarboxylate (**5a**).Molecular Formula $C_{26}H_{25}NO_9$, M.Wt = 495.48, yield 53%, m.p. 213°C . IR: ν 1677, 1774, 1628cm^{-1}(3CO) .^{1}H NMR ($CDCl_3$): δ 1.31 (2t, 6H, J = 6.8 Hz, 3, 5-CH_2CH_3), 2.34, 2.38 (2s, 6H, 2,6- CH_3), 4.14, 4.05 (2s, 6H, 4,9-OCH_3), 4.22 (m, 4H, 3,5-OCH_2), 4.70 (d, 1H, J = 5.8 Hz, 4-H), 7.81, 7.16 (**dd**, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.00 (s,1H, H_7). Ms : m/z 496 (13%), 252 (53), 245 (91%), 221(42%),215 (41%), 206 (23%),191 (45%), 163 (14%).

4-(4,9-Dimethoxy- 5H- furo [3,2-g] chromene- 5-one)- diethyl 2-methyl-6-phenyl pyridine - 3,5- dicarboxylate (**5b**).Molecular Formula $C_{31}H_{27}NO_9$, M.Wt = 557.56,

yield 53%, m.p. 230°C. IR: ν 1678, 1775, 1623cm^{-1}(3CO) .^{1}H NMR ($CDCl_3$): δ 1.29, 1.31 (2t,6H, *J* = 6.8 Hz, 3 , 5-CH_2CH_3), 2.36 (s, 3H, 2- CH_3), 4.14, 4.05 (2s, 6H, 4,9-OCH_3), 4.22 (m, 4H, 3,5-OCH_2), 4.60 (d, 1H, *J* = 5.3 Hz, 4-H), 7.90, 7.14 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.11 (s,1H, H_7); (5H, aromatic). Ms : m/z 558 (9%), 314 (41%), 286 ?(32%),245 (78%),235 (51%), 221(42%), 215 (26%), 191(12%),.

4-(4,9-Dimethoxy- 5H- furo [3,2-g] chromene- 5-one) ethyl methyl-2-ethyl-6-methyl pyridine - 5,3- dicarboxylate (5c).Molecular Formula $C_{26}H_{25}NO_9$, M.Wt = 495.48, yield 61%, m.p. 184°C. IR: ν 1674, 1671, 1623cm^{-1} (3CO) .^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, *J* = 6.8 Hz, 5-CH_2CH_3), 2.01(t, 3H, 2-CH_2CH_3), 2.28 (s, 3H, 6- CH_3), 4.14, 4.05 (2s, 6H, 4,9-OCH_3), 4.22 (m,2H, 5-OCH_2), 4.34 (s, 3H, 3-OCH_3), 4.55 (m, 2H, CH_2), 4.70 (d, 1H, *J* = 5.8 Hz, 4-H), 5.20 (2H, *J* =12.7 Hz, 5-OCH_2), 7.67, 7.03 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.11 (s,1H, H_7). Ms : m/z 496 (13%), 252 (33%), 245 (86%),221 (21%), 215 (47%),206 (21%), 176(11%), 191 (32%), 148(33%)

Procedure of 4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (11).

Refluxing of (1mmol) formyl furochromone (1) with (2mmol) 3-aminocrotononitrile (7) in (25ml) ethanol on water bath for 5h with 2 drops of TEA. The solvent was then evaporated, and products were purified by preparation TLC. Silica gel using, (20% Ethylacetate- 80% Petrolium ether 35-60) as eluent for compound (8).

Molecular formula $C_{22}H_{17}N_3O_5$, M.Wt = 403.39,. , yield 31%, m.p. 180°C IR: ν 2223cm^{-1}(2 CN), 3249cm^{-1}(NH) .^{1}H NMR ($CDCI_3$): δ 2.11 (s, 6H, 2,6- CH_3), 4.01, 3.99 (2s, 6H, 4,9-OCH_3), 4.63 (d, 1H, J = 5.0 Hz, 4-H), 5.24 (br, 1H, NH exchangable D_2O), 7.83, 7.01 (dd, 2H, $J_{H,H}$ = 2.3 Hz, $H_{2,3}$ furan), 8.00 (s,1H, H_7). Ms: m/z 404 (27%), 246 (76%), 221 (19%), 214(37%),160 (31%), 134 (23%), 108 (11%).

Procedure of 2- Amino- 1,4- dihydro- 3,5- dinitro- 6- methyl amino-4-phenylpyridine(**13 a-d**)**:**

(1mmol) aldehyde (1), and (2mmol) 2-nitroethylene-1,1-diamine, N,N-dimethyl-2-nitroethylene-1,1-diamine, N-methyl-2- nitroethen- 1,1- diamine , 2-nitro-1-piperidin-1-ylethylenamine (9a-d), in 9 ml ethanol and 3ml acetic acid were refluxed for 6h. The solvent was then evaporated, and products were purified by preparation TLC. Silica gel using, (20%Ethylacetate- 80% Petrolium ether 35-60) as eluent for compounds (13a-d).

4(-4,9-Dimethoxy-5H-furo[3,2-g]chromen-6-yl)N-methyl-3,5-dinitro-1,4-dihydro-pyridine-2,6-diamine (**13a**). Moleclar formula ,$C_{18}H_{15}N_5O_9$; M.Wt = 445.34, yield 21%, m.p. 184°C IR: ν 1623cm^{-1} (CO), 3245cm^{-1} (NH), 3461, 3459cm^{-1} (NH_2),^{1}H - NMR ($CDCl_3$): δ 4.14, 4.00 (2s, 6H, 4, 9-OCH_3), 4.71 (d, 1H, J = 5.8 Hz, 4-H), 5.59 (br, 1H, NH exchangable D_2O), 5.68 (br, 4H, NH_2 exchangable D_2O), 7.80, 7.04 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.01 (s,1H, H_7). Ms : m/z 446 (14%), 245 (90%), 200 (55%),221 (28%), 215 (55%), 200(68%),164 (40%), 110 (10).

4-(4,9-Dimethoxy-5H-furo[3,2-g]chromen-6-yl)N,N-dimethyl-3,5-dinitro-1,4-dihydropyridine-2,6-diamine (**13b**).Molecular formula:$C_{22}H_{23}N_5O_9$; M.Wt = 501.45, yield 29%, m.p. 200°C IR: ν 1628cm^{-1} (CO), 3223cm^{-1} (NH). ^{1}H NMR ($CDCl_3$): δ 2.34, 2.38 (ss, 12H, 1,1- 2CH_3), 4.01, 4.00(2s, 6H, 4, 9-OCH_3), 4.70 (d, 1H, J = 5.8 Hz, 4-H), 5.40 (br, 1H, NH exchangable D_2O), 7.87, 7.04 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.00 (s,1H, H_7). Ms : m/z 502 (11%), 245 (78%),221 (11%), 229 (28%), 214 (26%), 191(36%), 170 (72%).

4-(4,9-Dimethoxy-5H-furo[3,2-g]chromen-6-yl)N-methyl-3,5-dinitro-1,4-dihydropyridine-2,6-diamine (**13c**).Molecular formula:$C_{20}H_{19}N_5O_9$; M.Wt = 473.39, yield 23%, m.p. 194°C. IR: ν 1628cm^{-1}(CO) 3240cm^{-1} (3NH).^{1}H NMR ($CDCl_3$): δ 2.42, (2s, 6H, 2,6- CH_3), 4.00, 3.97 (2s, 6H, 4, 9-OCH_3), 4.62 (d, 1H, J = 5.8 Hz, 4-H), 5.25 , (br, 3H, 3NH exchangable D_2O), 7.75, 7.13 (dd, 2H, $J_{H,H}$ = 2.2 Hz, $H_{2,3}$ furan), 8.01 (s,1H, H_7). Ms : m/z 474 (11%), 246 (87%),228 (76%),220 (24%), 215 (43%), 170 (10%).

4-(4,9-Dimethoxy-5H-furo[3,2-g]chromen-6-yl) 3,5-dinitro-6-piperidin-4-yl-1,4-dihydropyridine-2-amine (**13d**).Molecular formula:$C_{28}H_{31}N_5O_9$; M.Wt = 581.57.39, yield 21%, m.p. 199°C. IR: ν 1626cm^{-1}(CO) 3245cm^{-1} (NH).^{1}H NMR ($CDCl_3$): δ 1.88 (m, 6H, piperidine), 2.45 (m, 4H, piperidine), 4.01, 3.99 (2s, 6H, 4, 9-OCH_3), 4.42 (d, 1H, J = 5.8 Hz, 4-H), 5.52 , (br, H, NH exchangable D_2O),7.83, 7.14 (dd, 2H, $J_{H,H}$ = 2.2 Hz, $H_{2,3}$ furan), 8.00 (s,1H, H_7). Ms : m/z 582 (9%), 498 (10%),415 (35%), 370 (34%), 324 (56%), 245. (68%),220 (76%), 214(27%),191 (32%), 81(92%).

Method for reduction of the Nitro- group on 1,4- Dihydropyridine derivative(10a) to affordedpyridine derivative(**14a**)**:**

Compound (14a) was prepared by the catalytic reduction of compound (13a) with zinc and acetic acid as described previously[30]. Compound (13a) (0.05m mol) was

dissolved in 1.5 ml of glacial acetic acid. Zn powder (0.15m mol) was added to the solution, and the reaction mixture was stirred with a magnetic stirring bar at room temperature. Six hours after the start of the reaction, another batch of zinc powder was added. At 9 hours reaction time, TLC(Silhca; petroleum ether 35-60- EtOAC= 80:20) analysis of the reaction mixture indicated that all starting material had been converted. The reaction mixture was diluted with 30 ml water and neutralized with saturated $NaHCO_3$ solution. The aqueous solution was extracted three time 15 ml of chloroform, and the organic phase was separated and dried over anhydrous MgSO4. The product was purified by preparation TLC of silica; petroleum ether 35- 60- EtOAC, 90:10 to yield 24% of a slightly yellow oil.

4(-4,9-dimethoxy-5H-furo[3,2-g]chromen-6-yl) N-methyl-3,5-dinitro - pyridine-2,6-diamine **(14a).** Moleclar formula: $C_{18}H_{19}N_5O_5$; M.Wt = 385.37, yield 25%, m.p. 196°C IR: ν 1623cm^{-1} (CO), 3260cm^{-1} (NH), 3476, 3481cm^{-1} (NH_2),^{1}H -NMR ($CDCl_3$): δ 4.00, 3.98 (2s, 6H, 5, 9-OCH_3), 4.53 (d, 1H, J = 5.6 Hz, 4-H), 5.59 (br, 5H,NH, NH_2 exchangable D_2O), 7.87, 7.01 (dd, 2H, $J_{H,H}$ = 2.5 Hz, $H_{2,3}$ furan), 8.00 (s,1H, H_7). Ms : m/z 386 (46%), 245 (81%), 221 (47%), 214 (39%), 198 (22%),140 (61%).

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