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Regioselective N-alkylation of some 2-(Substituted Phenyl) Imidazo[4,5-c] Pyridines: Synthesis and Structure Elucidation by NMR"

Hakan Göker and Seckin Özden

Abstract--- *Imidazopyridines can exist in a few tautomeric systems, as an instance, benzimidazole or purine consolidated frameworks. Regioselectivities have been resolved for N-alkylations of some 2-(substituted phenyl) imidazo [4,5-c] pyridines with benzyl bromides under important situations (K2CO3 in DMF). It became visible that N-five regioisomers were essentially framed. Their number one assignments were carried out -dimensional 1H-1H NOE (atomic over hauser effect spectroscopy [NOESY]) upgrades the various N-CH2 and protons on the C-4H and C-6H locations of the pyridine moiety. To check the NOESY facts, amalgamation of mixes 4b modified into done by using way of the unique approach. Correlative auxiliary data changed into given via second-HMBC spectra of the mixes.*

Keywords--- *Imidazo[4,5-c]Pyridine, Regioisomer, Nuclear Overhause Effect Spectroscopy NOESY.*

I. INTRODUCTION

Imidazopyridines are desirable hetereocycles for healing clinical professionals as their subsidiaries had been regarded to show some organic sporting events [1]. It was blanketed the distinguishing proof of a class ofimidazo [4,5-c]pyridines with severe enemy of pestivirus activity. Pestiviruses have an area, collectively with the flaviviruses and HCV, to the group of the Flaviviridae. Moreover, presentation of a fluorine iota in position 2 of the phenyl of 5-(4-bromobenzyl)- 2-phenyl-5H-imidazo[4,5-c]pyridine added approximately a compound with now not just enemy of pesti (cow-like viral the runs infection (BVDV) however also anti-HCV movement (Fig 1) [2,3].

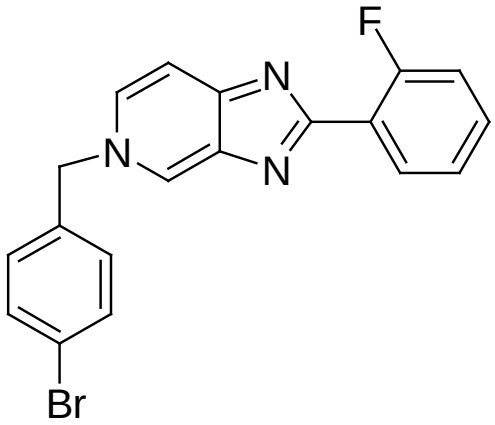

Fig 1.

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The NH association located in imidazopyridines is unequivocally acidic and pitifully number one. This accumulating widely recognized brief prototrophic tautomerism, which prompts concord mixes. Every one of the three possible structures and numbering of imidazo [4,5c] pyridines are delineated in Scheme 1. This relocation is not observed concurrently because the imidazole hydrogen is altered thru an alkyl company. That is the motive, N-alkylation motives association of regioisomer combination.In our in recent times published papers, we have characterised the union of some regio isomers of benzimidazoles [4] and imidazopyridines [5]. Their fundamental rationalization converted into performed via specific amalgamation and moreover 2nd-NMR facts complete of atomic overhauser effect spectroscopy (NOESY), and heteronuclear different bond relationship (HMBC) tests.

Expedited with the asset of the discoveries from the examination expressed above, we got the whole lot of the manner immediately all the way down to development and blend new bicyclic subsidiaries

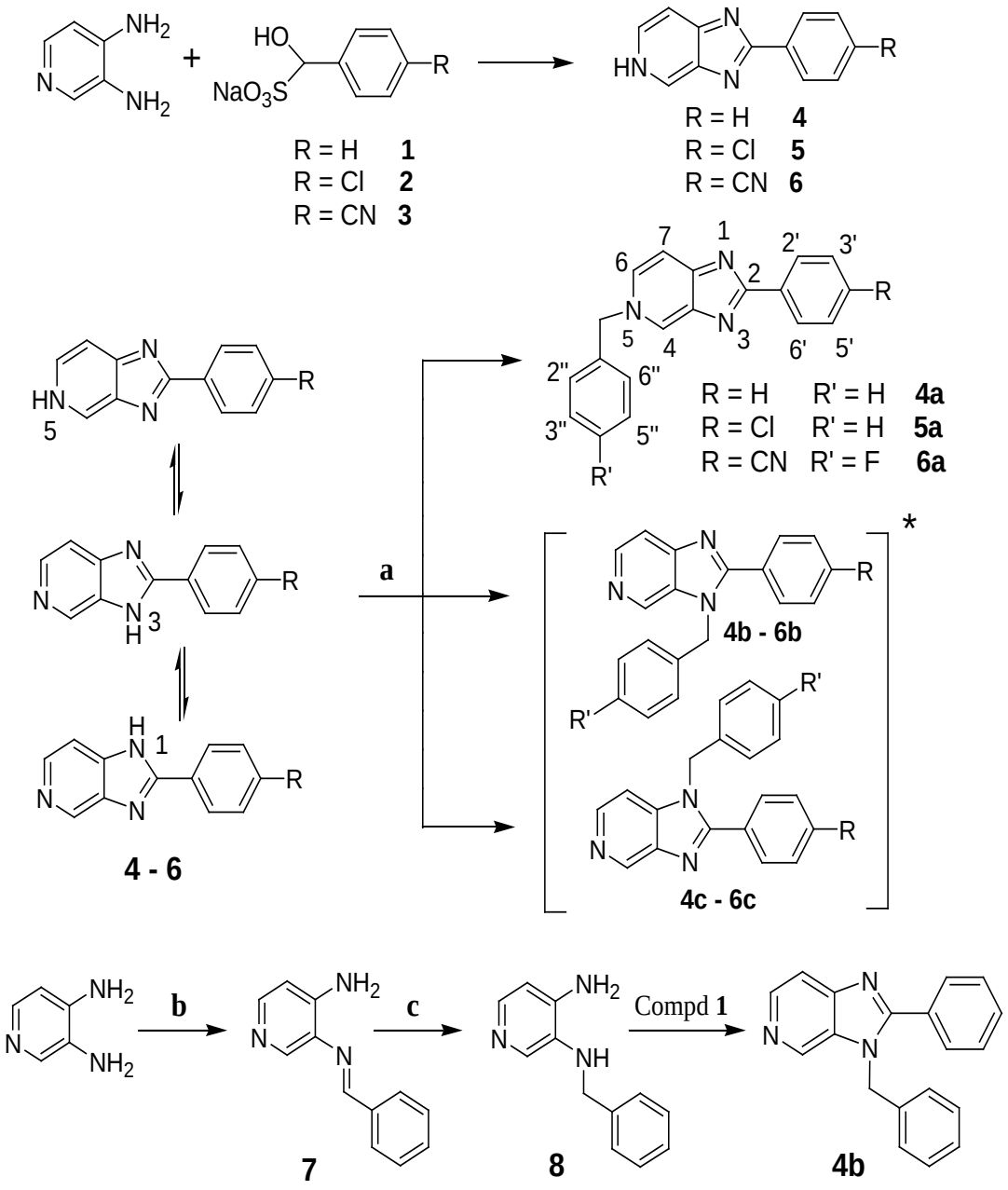
To have the option to be the buildup the given frameworks in Fig. 1 and test out their domestic grown amusement pastime. Other motivation in the back of this canvases became to interrupt down the selectivity of regioisomers shaping of the orchestrated mixes along those strains of the N-alkylation response.

II. RESULTS AND CONVERSATION

Focused mixes were readied the usage of the strategies noted in Scheme 1.Cyclization of related o-diamino-pyridines with sodium metabisulfite adduct of evaluating benzaldehydes (1-three) gave required imidazo [4,5c]pyridines4–6. In those dense systems, the nitrogen bears a hydrogen particle (N1,3) suggests up as a pyrrole-like N-iota; the others (N5) takes after a pyridine-like N-molecule. Hydrogen molecule related to nitrogen in the 1, three-include without problems tautomerise in numerous positions depicted as in mixes four-6.

Because of this tautomeric table paintings, every 1H and 13C-NMR spectra of unsubstituted analogs cannot be sufficient smooth. Its miles ordinary that, a few proton and carbon hints are showed up as full-size pinnacles or maybe more than one pivot carbon alerts are not substantive. Evacuation of NH proton then substitution of this nitrogen molecule can likewise forestall short tautomerism and purpose a detachable combination of regioisomers. While we have endeavored alkylation of 4-6 with related benzyl bromides under essential circumstances (K2CO3, DMF), alkylation had been for some time snared as explicitly N-five job.

Follow measure of 4b-6b and 4c-6cweredetected as N-3 and N-1 regioisomers, in my view, in their LC-MS chromatograms of4 - 6 (Fig 2), besides those regioisomers could not be segregated. That is the reason, we organized 4b by way of utilising particular regioisomer union machine, a number of the response eight and sodium metabisulfite adduct of benzaldehyde1. In LC-MS chromatogram of 4 series (Fig 2), at the equal time because the Rt estimations of 4c (N-1) (6.07 min) and 4b (N-three) (6.32 min) regioisomers are near every others, even as 4a (N-5) (four.0min) regioisomer is some distance an all-inclusive way from N-1 and N-3 pinnacles and the tallness area ofN-5is an over the top measure of greater outstanding than numerous isomers.



Reagents : * Could not be isolated a) Potassium carbonate / 4-Cl-benzyl bromide b) Benzaldehyde c) Sodium borohydride

Scheme 1: N^5-Benzylation of imidazo[4,5-*c*]pyridines4 - 6.

Henceforth, N-5regioisomer may be without issue isolated from N-3,1 as it develop as appeared in our analyses. 4b arranged by means of utilizing the particular methodology have develop as resolved to be identical Rt cost of 6.32 moment, inside the LC-MS chromatogram obtained during the blend reaction of 4series(Fig 2).Characterization of the individual isomeric product changed into chose through proclamation of second-NOESY upgrades a portion of the N-CH2 and H-4,6pyridine sweet-smelling protons. In NOESY spectra of compound 4a-6astrong relationships

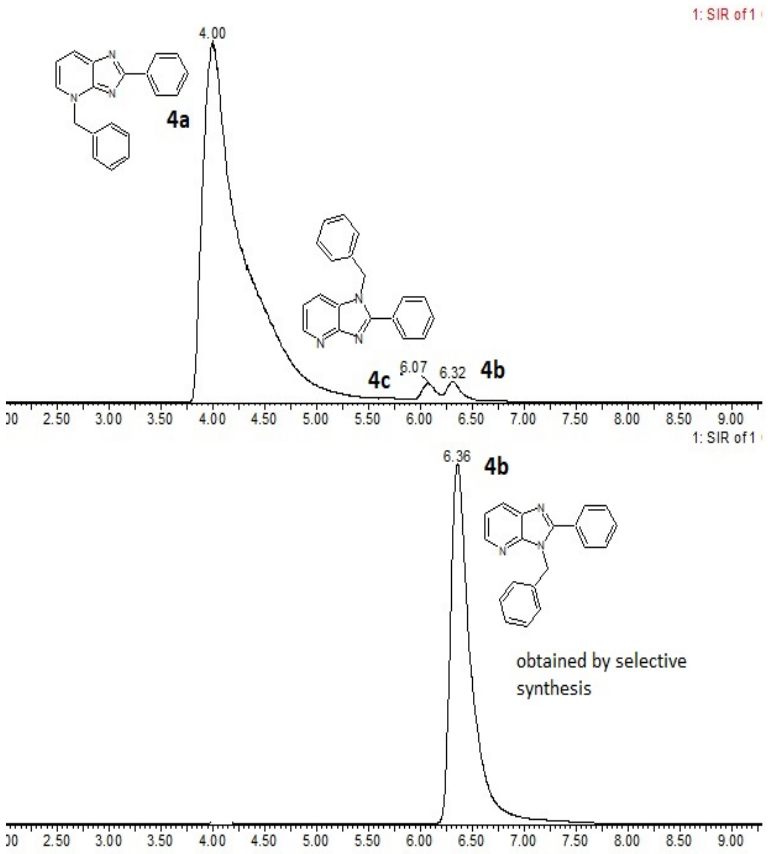
had been set a couple of the benzylic and H-4,6 protons (Fig3).Whereas, inside the NOESY range of 4b, there is ground-breaking NOE forms "a large number of the benzylic protons and best H-4, also right connections have been obvious some of the benzylic and H-2' as well as H-6', as envisioned (Fig 4). Those discovering gave us that, compound 4b is the N-3 regioisomer. Corresponding basic information develop to be outfitted through second-HMBC spectra of the incorporated mixes. Its miles suitable to decide the synthetic move rate (δppm) of C-3a and C-7a, by utilizing path in their connections with pyridine hydrogens in their HMBC spectra. At last, it ought to be available to decide one of a kind achievable correlations (whether or not N-CH2: C-3a or N-CH2: C-7a) for keeping separated of the regioisomers. The impacts have been gained in the HMBC spectra of 4a-6a, 4b gave the good profiles with every normal connection (Fig 5).The complete assignments of all orchestrated mixes were madeusing 1D and 2d NMR experiments including cozy, NOESY, gHSQC and gHMBC techniques. EXPERIMENTAL Uncorrected softening components have been estimated the utilization of a BüchiB-540capillary liquefying point of interest hardware. All NMR tests were carried out utilizing VARIAN (AGILENT) Mercury 400 MHz and 100 MHz for carbon. The NMR range improvement changed into led using Agilent VnmrJ adaptation three.2 modification.

The examples (five-15 mg) were composed in 0.7 ml of DMSO‑d6, CDCl3, and CD3OD. TMS got utilized as an internal standart. The fluid chromatography mass spectrometry (LC-MS) spectrawere taken on a Waters Micromass ZQ associated with Waters Alliance HPLC, the utilization of the ESI(+) approach with a C-18 segment (XTerra®, four.6 X 250 mm, 5 µm).Analytical circumstances of mass spectrometry were as follows: capillary voltage, 3.11 kV; cone voltage, 29V; supply temperature, 100oC; and desolvation temperature, 300oC.Elemental analyses were achieved with the helpful asset of LecoCHNS-932. 6 become prepared according to the lit. [6].Trendy union of sodium metabisulphite adduct of required benzaldehydes 1-threeAssociated benzaldehydes (7.5 mmol) altered into broke up in EtOH (25 mL) and sodium metabisulfite (zero.Eight g) (in 5 mL of water) changed into presented in parcels.

The reaction blend rise as mixed energetically and more prominent EtOH end up being included. The mix come to be spared in a fridge for some time. The white encourage, the got salts had been picked up by means of the utilization of filtration, dried and utilized for the further strides without purging and characterization. Popular combination of 4 - 5The total of sodium metabisulfite adduct of required benzaldehydes (2 mmol) and relating three, 4-diamino pyridine (2 mmol), in DMF (1 mL) had been warmed at 120oC, for 3-4 h. The response total have become cooled, filled water. The following encourage changed into amassed with the valuable asset of the utilization of filtration and dried."

2-Phenyl-3H-imidazo [4,5-c] pyridine, four

Prepared from 3, four-diaminopyridine (0.218 g) and 1 (zero.42g) as portrayed in exquisite methodology. White solid, yield 0.285 g, 73%, mp229oC. 1H NMR (400 MHz, DMSO-d6) δ 7.53-7.61 (m, 4H), 8.21-8.24(m,2H), 8.32(d,1H,J=5.6 Hz), 8.95(s,1H), 13.2(br. s). Exactly agreed with lit [7]. 13C NMR (100 MHz, DMSO-d6) δ 141.17, 130.5, 129.4, 128.9, 126.9. LC-MS (ESI +) m/e: 196 (M+H, 100%).



LC-MS chromatogram (ESI+ and SIR Techniques for m/e [M+H] 286 for 4a, 4c&4b at the endpoint of synthesis.

2-(4-Chlorophenyl)- 3H-imidazo[4,5-c]pyridine, 5

Preparedfrom3,4-diaminopyridine (0.218 g) and2 (0.488g) as depicted in General Method. White strong, yield 0.26 g, 57 %, mp> 300oC.1H NMR (400 MHz, DMSO-d6) δ 7.58(d,1H,J=5.2Hz), 7.65(d,2H,J=8.4Hz), 8.22(d,2H,J=8.4 Hz), 8.3(d,1H,J=5.6Hz), 8.95(s,1H), 13.35(br.s). 13C NMR (100 MHz, DMSO-d6) δ 141.16, 135.4, 129.2, 128.8. LC-MS (ESI +) m/e : 230 (M+H, 100%), 232(M+H+2, 32%).

General Synthesis of 4a - 6a

K2CO3 (1 mmol) was added to a suspension of the 4 - 6 (0.8 mmol) in DMF (0.5 mL) and mixed. After one hour, related benzyl bromide (0.8 mmol) was included. After medium-term mixing at RT, water was included and hasten was sifted.

5-Benzyl-2-phenyl-5H-imidazo [4,5-c] pyridine, 4a

Preparedfrom4 (0.156 g), benzylbromide (0.137 g) and K2CO3 (0.138g) as describedin GeneralMethod. Crude product (0.11g) was purified column chromatography by using CH2Cl2: MeOH (100: 6), white solid, yield 0.056 g, 24.5 %, mp221-223oC. 1H NMR (400 MHz, DMSO-d6) δ5.66(s, 2H), 7.34-7.48(m,8H), 7.73 (d,1H,J=6.8Hz), 8.19 (dd, 1H, J=6.8 and 1.2Hz), 8.35-8.37 (m,2H), 9.11 (d,1H,J=1.2Hz). Exactly agreed with lit [7]. 13C NMR (100 MHz, DMSO-d6) δ 171.0, 155.5, 145.3, 136.5, 134.8, 131.5, 131.0, 129.3, 128.95, 128.5, 128.4, 127.9, 127.6, 112.3, 61.2.LC-MS (ESI +) m/e: 286 (M+H, 100%).

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5-Benzyl-2-(4-chlorophenyl)- 5H-imidazo[4,5-c]pyridine, 5a

Prepared from5 (0.185 g), benzyl bromide (0.137g) and K2CO3 (0.138g) as described in General Method. Crude product (0.11g) was recrystallised from EtOAc, whites olid, yield 0.058 g, 31.5 %, mp212-214oC.1H NMR(400 MHz, CD3OD) δ 5.68 (s,2H), 7.36-7.5 (m,5H), 7.47 (d,2H,H-3'5'), 7.76 (d,1H,J=6.4Hz), 8.15 (dd,1H,J=6.4 and 1.6Hz), 8.26(d,2H, H-2',6'), 8.9(d,1H,J=1.6Hz). 13CNMR (100 MHz, CD3OD) δ 171.6, 156.7, 145.8, 137.3, 136.8, 133.7, 133.6, 132.9, 130.7, 130.4, 130.2, 129.95, 129.2, 113.8, 63.8. LC-MS (ESI +) m/e: 320(M+H, 100%), 322(M+H+2, 34%).

4-[5-(4-Fluorobenzyl)- 5H-imidazo[4,5-c]pyridin-2-yl]-benzonitrile, 6a

Prepared from6 (0.22 g), 4-fluorobenzyl bromide (0.189 g) and K2CO3 (0.138g) as described in General Method. Crude product (0.2g) was purified column chromatography by using CH2Cl2: MeOH (95: 5), white solid, yield 0.123 g, 37.4 %, mp225-227oC. 1H NMR (400 MHz, CD3OD) δ 5.7(s,2H,N-CH2),7.13-7.18(m,2H,H-3",5"),7.47-7.5(m,2H,H-2",6"), 7.82(m,3H,H-7,3',5'), 8.21(dd,1H,J=6.8 and 1.6Hz,H-6), 8.44(d,2H,J=8.4Hz,H-2',6'), 8.98(d,1H,J=1.2Hz, H-4).COSY : [H-3",5" : H-2",6"], [H-7: H-6], [H-3',5' : H-2',6']. NOESY: [N-CH2: H-4,6,2",6"]. 13C NMR, HSQC, HMBC (400 MHz, CD3OD) δ 170.7(C-2), 164.6(d,J=246Hz,C-4"), 156.6(C-7a), 145.95(C-3a), 139.4 (C-1'), 133.9(C-4H), 133.7(C-6H), 133.7(C-3',5'- H), 132.85(d,J=3.2Hz,C-1"), 131.5(d,J=9Hz,J=2",6"- H), 129.8 (C-2',6'- H), 119.6(CN), 117.2(d,J=22Hz,C-3",5"- H), 114.5 (C-7H), 114.3(C-4'), 63.1(N-CH2).

3-(Benzylideneamino) pyridin-4-amine 7

A blend of 3, 4-diaminopyridine (0.545 g, 5 mmol) and benzaldehyde (0.53g, 5 mmol) in ethanol (20 mL), was warmed under reflux for 8h. Dissolvable was evacuated, decontamination by section chromatography utilizing CH2Cl2 and MeOH (93:7), gave 7 as unadulterated yellow shaded sleek fluid item, yield 71 %. 1H NMR (DMSO-d6) δ 5.99 (s,2H,NH2), 6.61(d,1H, J=5.6Hz,5-H), 7.49-7.5(m,3H), 7.91(d,1H,J=5.6Hz,H-6), 7.99-8.01(m,2H), 8.04(s,1H), 8.68(s,1H).13C-NMR (DMSO-d6) δ 158.0, 148.8, 147.6, 137.6, 136.3, 132.5, 131.2, 128.8, 128.6, 108.6. LC-MS (ESI +) m/e: 198 (M+H, 100).

N3-Benzylpyridine-3,4-diamine 8

"To an answer of 7 (0.49 g, 2.5 mmol) in ethanol (10 mL) was included sodium borohydride (0.11 g 2.9mmol) in divide. After fruition of the expansion, the response blend was warmed on water shower. After two hours same amount of sodium borohydride was included and mixed medium-term. At that point blend was cooled and water was included. Hasten was separated, washed with water, recrystallization from ethanol gave unadulterated 8. White strong, yield 67 %, mp 182-183°C; 1H NMR (DMSO-d6) δ 4.3(d,J=6Hz,CH2), 5.17(t,1H,J=6Hz,NH), 5.48(s,2H,NH2), 6.42(d,J=5.2 Hz,1H), 7.2-7.3(m,1H), 7.3-7.38(m,4H), 7.46(s,1H), 7.49(d,1H,J=5.2Hz). 13C NMR (DMSO-d6) δ 141.8, 139.9, 139.4, 131.6, 130.7, 128.3, 127.2, 126.7, 107.9, 46.76. LC-MS (ESI +) m/e: 200 (M+H, 100).

3-Benzyl-2-phenyl-3H-imidazo[4,5-c]pyridine, 4b The blend of 8 (0.2 g, 1 mmol) and sodium metabisulfite adduct of benzaldehydes (0.21g, 1 mmol) in DMF (1 mL) were warmed at 120oC for 3 h. The response blend was cooled, water was included. The subsequent hasten was gathered by filtration and dried (0.19 g). Crude product was

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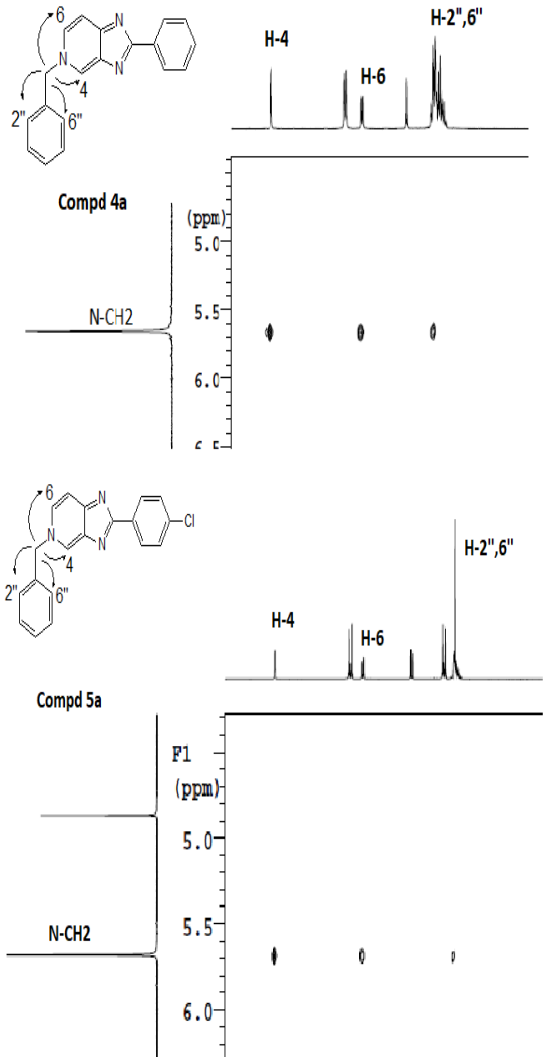
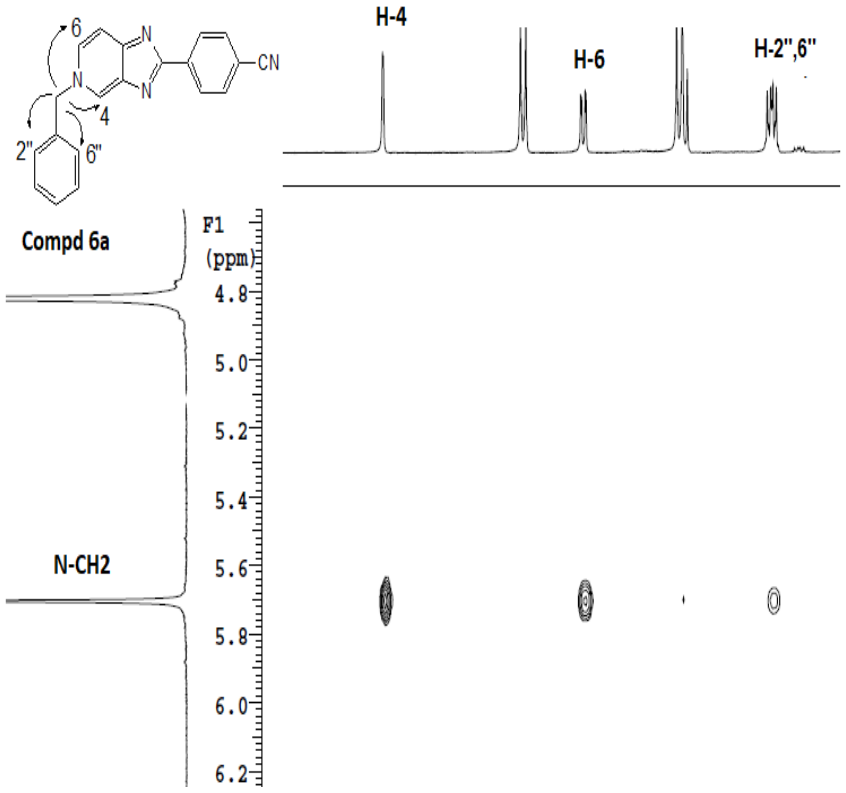
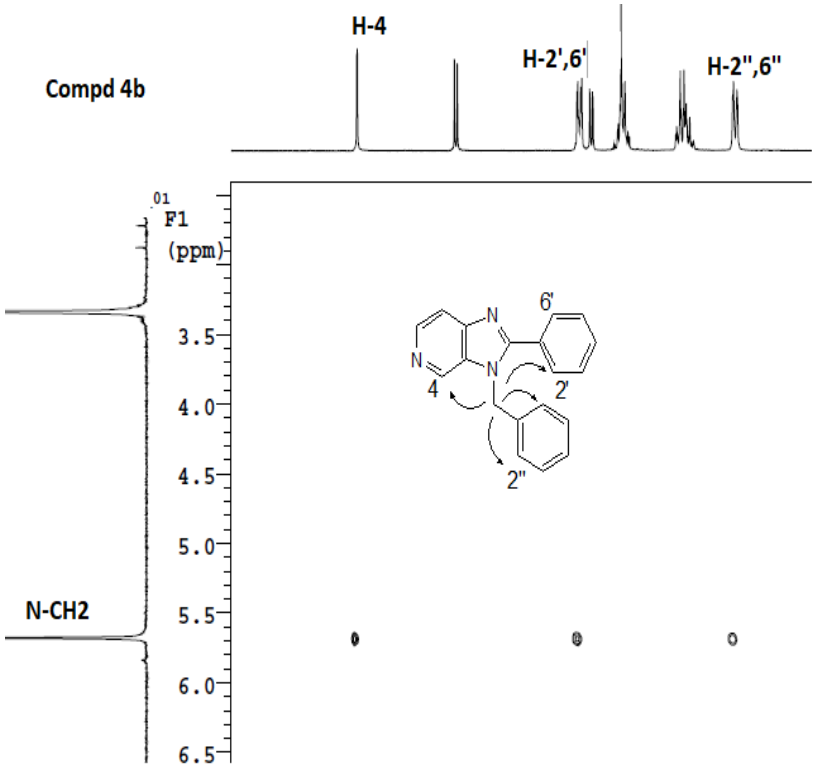
purified column chromatography by usingCH2Cl2 : MeOH (100 : 3), White yellowish solid, yield 0.12 g, 42 %, mp106-108oC.1H NMR (400 MHz, DMSO-d6) δ 5.65 (s,2H,N-CH2), 7.02 (m,2H,H-2",6"), 7.2-7.31 (m,3H,H-3",4",5"), 7.53-7.6 (m,3H,H-3',4',5'), 7.71 (dd,1H,J=5.6&1.2Hz,H-6), 7.76-7.78 (m,2H,H-2',6'), 8.36 (d,1H,J=5.6Hz,H-7), 8.84 (d, 1H,J=1.2Hz,H-4). COSY [H-3", 5'': H-2", 6"], [H-7: H-6], [H-3', 5': H-2',6']. NOESY : [N-CH2: H-4, 2',6', 2",6"].13C NMR, HSQC, HMBC(100 MHz, DMSO-d6) δ 155.9 (C-2), 147.2(C-7a), 141.76(C-7H), 136.4(C-1"), 134.6 (C-4H), 133.5(C-3a), 130.5, 129.3, 128.9, 128.85, 127.7 (C-2',6',3',4',5',3",4",5"- H), 129.23(C-1'), 126.3 (C-2",6"- H), 113.9(C-6H), 47.9(N-CH2). LC-MS (ESI +) m/e: 286 (M+H, 100%). Butt-centric Calcd. for C19H15N3C : 79.98, H : 5.30, N : 14.73. Found: C: 80.16, H: 5.59, N: 14.71.

NMR information given by Avineshet al [8] and Dubey et al [9] was seen as not the same as the spectra we recorded in CDCl3 at beneath. Interim, their spectra are not indistinguishable from every others. 1H NMR (400 MHz, CDCl3) δ 5.53 (s,2H,N-CH2), 7.1(m,2H), 7.26-7.35(m,3H), 7.47-7.55(m,3H,), 7.7-7.73(m,2H), 7.75 (dd,1H,J=5.6 and 1.2Hz), 8.47 (d,1H,J=5.6Hz), 8.63 (d,1H,J=1.2Hz). 13C NMR (100 MHz, CDCl3) δ 48.9, 114.6, 126.1, 128.3, 128.9, 129.0, 129.3, 129.4, 130.75, 133.67, 134.0, 135.5, 142.5, 148.2, 156.9."."





Partial NOESY Spectra of Compounds 4a, 5a and 6a Displaying go Peaks among N-CH2 and H-four, 6, 2'', 6''



Partial NOESY Spectrum of Compounds 4b showing Move Peaks among N-CH2 and H-four, 2',6', 2'',6''.

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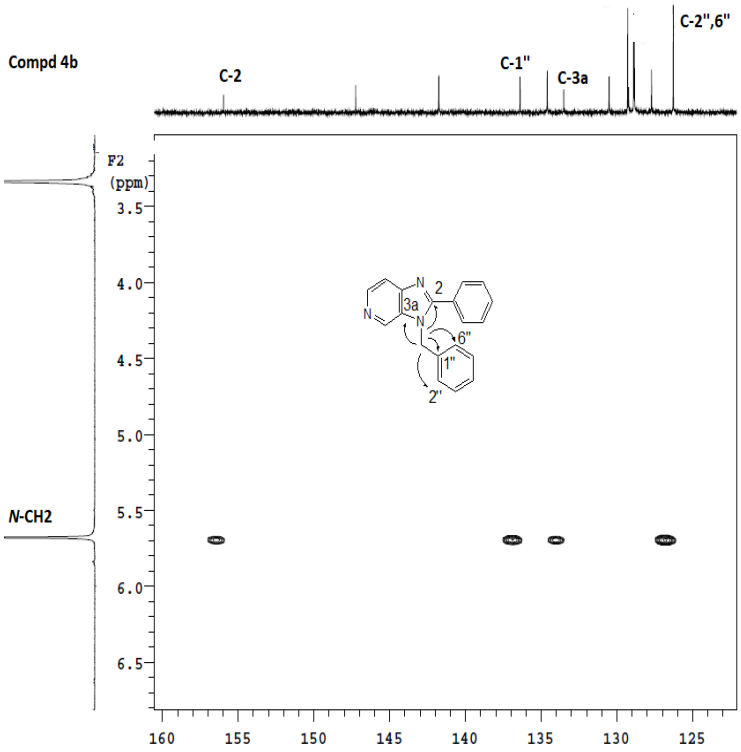

Partial gHMBC Spectrum of Compound 4b, Displaying Pass Peaks among N-CH2/C-2,C-3a,C-1'',C-2'',6''

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