



A novel, efficient and RH (II) catalysed one pot Aza-Diels-alder reaction for facile synthesis of Trihydroquinoline bearing INZ

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ABSTRACT:

Isoniazid(**1**) on condensation with different aromatic aldehyde(**2a-n**) gives Schiff's bases N-(substituted benzylidene) isonicotinohydrazide(**3a-n**). The Schiff base (**3a-n**) so formed on RH (II) Octanoate catalysed one pot cyclo-addition with Anthracene in MDC at room temperature for 12-14 Hrs have been found to yield the N-(2-(substituted phenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (**5a-n**). The synthesized cyclo-adduct were characterized by spectral analysis like IR, ¹HNMR, ¹³CNMR & Mass and elemental analysis. The synthetic details and characterization results are discussed.

KEY WORDS: Isoniazid; Aromatic aldehyde (Ar-CHO), Trihydroquinoline, RH (II) catalyst.

INTRODUCTION:

Heterocyclic compounds promote the life on earth¹. They are widely distributed in nature and essential to life as they play a role in the metabolism of living cells¹⁻². Quinoline is one of the heterocycles which exhibit various biological activities including antibacterial, antitumor, anti-inflammatory. Trihydroquinoline are a group of compounds possessing a wide spectrum of biological activities such as antimicrobial, anti-inflammatory. Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used therapeutic agents for the treatment of pain and inflammation. The widespread use of NSAIDs is connected with several adverse effects, mainly those related to the gastrointestinal tract such as ulcers and bleedings³. Much attention has recently been devoted to the development of NSAIDs bearing heteraryl pharmacophores, viz quinoline. These inhibitors are expected to retain potent anti-inflammatory activity and also have relative minimum side effects⁴. Isoniazid is effective in the treatment of TB patients but by the acetylation it decreased bioavailability and acquired INZ resistance⁵.

Considering the biological and therapeutic activities of trihydroquinoline and the upcoming resistance problem of Isoniazid, it is proposed to synthesize trihydroquinoline bearing isoniazid moiety in a single molecular framework which may be helpful to society to get pharmacologically more active compounds. In the present study a novel series of trihydroquinoline were synthesized and characterized by means of IR, ¹HNMR, ¹³CNMR, Mass spectral analysis and elemental analysis.

Experimental:

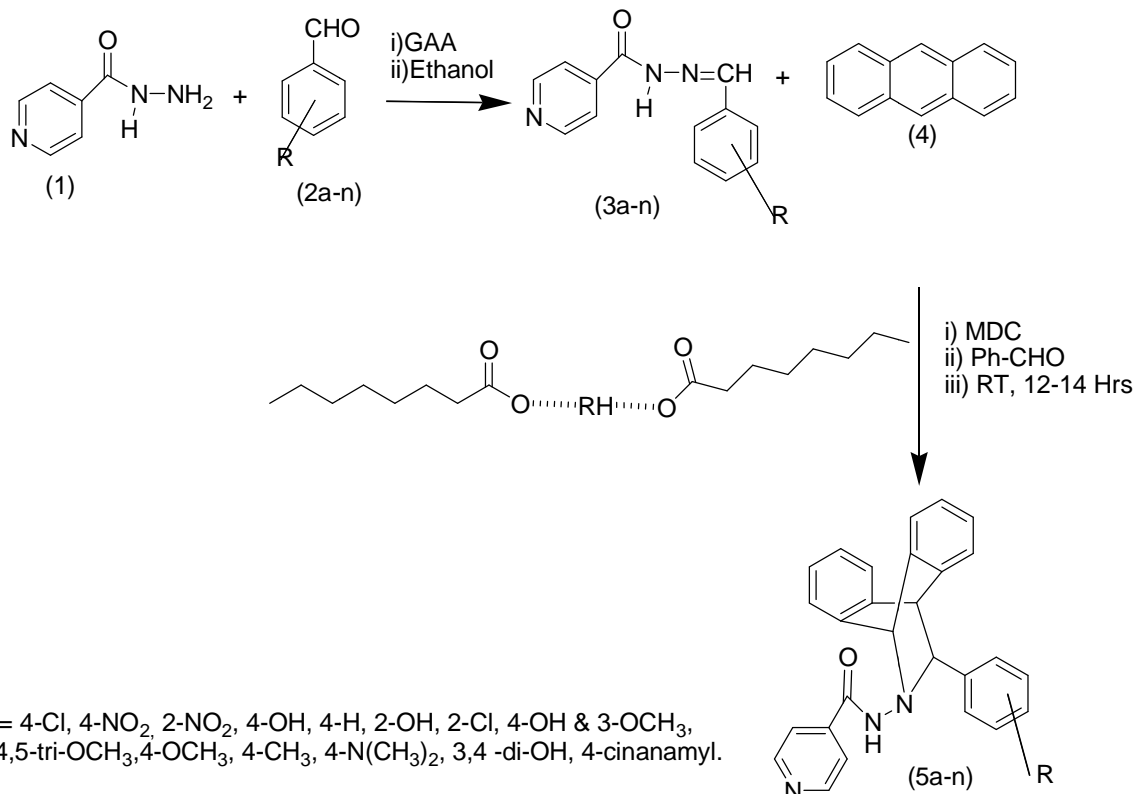
General procedure for N-(substituted benzylidene) isonicotinohydraide **3(a-n)**

Take equimolar mix of Isoniazid (**1**) (0.25 mol) and substituted aromatic aldehyde (**2a-n**) (0.25 mol) in appropriate volume of ethanol. Charged 2-3 drops of glacial acetic acid at room temperature. Then raise temperature of reaction mass upto reflux, reaction mass reflux for 60-90 minutes under continuous stirrings and progress of reaction check on TLC using ethyl acetate: hexane (5:5) as solvents. After completion of reaction, reaction mixture cool at room temperature and poured on ice-cold water. The precipitate product was filtered out through G1 sintered filtration assembly and recrystallized by alcohol.

General procedure for N-(2-(substituted phenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (**5a-n**)

Take equimolar mixture of N-(substituted benzylidene) isonicotinohydraide **3(a-n)** (0.1 mol) and Anthracene (**4**) (0.1 mol) in MDC (15 ml) at room temperature stir 30 min then charged Ph-CHO (0.05 mol %), then put rhodium octanoate catalyst (0.0005gm) then temperature maintain reaction mass for 12-14 hours under continuous stirring, check TLC using ethyl acetate: hexane (5:5) as solvents., after completion of reaction cool at room temperature slowly, charged methanol (5ml) for crystallisation then cool at 20°C stir 60 minutes filter the product through G1 sintered filtration assembly and recrystallized by alcohol.

Reaction scheme:





The chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra (In KBr pellets) were recorded on Bruker FT-IR spectrometer. ^1H NMR spectra were recorded on a Bruker DRX-300 and 400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on a Bruker DRX-75 and 100 MHz NMR in $\text{CDCl}_3/\text{DMSO-d}_6$ using tetramethylsilane (TMS) as an internal standard and chemical shifts are in δ (ppm). High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument. The purity of each of the compound was checked by thin-layer chromatography (TLC) using silica-gel, 60F₂₅₄ aluminium sheets as an adsorbent, and visualization was accomplished by iodine/ultraviolet light.

N-(2-(4-chlorophenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6a)

White needles (EtOH) (this compound was prepared by the reaction of compound 4a, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as a white solid); mp218–220 °C; IR (KBr) ν_{max} : 3,150, 3,012, 1,690, 1,425, and 610 cm^{-1} . ^1H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 7.06-7.34(m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.67 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ^{13}C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.5 (THQ ali. C), 122.8, 140.9, 149.8 (β , γ , α carbon of pyridine), 126.8, 128.7, 128.8, 129.4, 132.6, 136.4, 139.8, 144.0(aromatic ring carbons) 164.9(amide carbon). HRESIMS m/e (pos): 437.1295 [M^+] for $\text{C}_{27}\text{H}_{20}\text{ClN}_3\text{O}$.

N-(2-(4-nitrophenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6b)

Yellow needles (EtOH) (this compound was prepared by the reaction of compound 4b, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as a yellow solid); mp204–206 °C; IR (KBr) ν_{max} : 3,190, 3,010, 1,680, 1520, 1,420, and 1340 cm^{-1} . ^1H NMR (400 MHz, DMSO-d₆) δ = 4.48-4.66(d, 2H, trihydroquinoline (THQ) proton), 4.94(s, 1H, THQ proton), 7.14-7.60(m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.7 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ^{13}C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.5 (THQ ali. C), 122.8, 140.9, 149.8 (β , γ , α carbon of pyridine), 120.9, 126.8, 128.8, 128.9, 139.8, 144.0(aromatic ring carbons), 163.8(amide carbon). HRESIMS m/e (pos): 448.1535 [M^+] for $\text{C}_{27}\text{H}_{20}\text{N}_4\text{O}_3$.

N-(2-(2-nitrophenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6c)

Pale yellow needles (EtOH) (this compound was prepared by the reaction of compound 4c, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as pale yellow solid); mp210–212 °C; IR (KBr) ν_{max} : 3,190, 3,010, 1,680, 1540, 1,435, and 1360 cm^{-1} . ^1H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.66(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 7.19-8.14 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.9 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ^{13}C NMR (100 MHz, DMSO-d₆) δ = 37.9, 58.0, 61.9 (THQ ali. C), 122.8, 140.9, 149.8 (β , γ , α carbon of pyridine), 120.9, 126.8, 128.0, 128.8, 128.9, 132.3, 134.7, 139.8, 144.0(aromatic ring carbons), 164.8(amide carbon). HRESIMS m/e (pos): 448.1535 [M^+] for $\text{C}_{27}\text{H}_{20}\text{N}_4\text{O}_3$.



N-(2-(4-hydroxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6d)

Light brown needles (EtOH) (this compound was prepared by the reaction of compound 4d, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as light brown solid); mp238-240⁰C; IR (KBr) v_{max}: 3,332, 3,170, 3,010, 1,660, 1435, and 890 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.01 (s, 1H, OH), 5.04(s, 1H, THQ proton), 7.14-7.31 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.67 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 60.5 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 126.8, 128.7, 128.8, 129.4, 132.6, 136.4, 139.8, 144.0(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 419.1634 [M⁺] for C₂₇H₂₁ N₃O₂.

N-(2-(phenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6e)

Sharp white needles (EtOH) (this compound was prepared by the reaction of compound 4e, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as white solid); mp219-221⁰C; IR (KBr) v_{max}: 3,120, 2,990, 1,660, 1540, 1,435, and 1420 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.50-4.66(d, 2H, trihydroquinoline (THQ) proton), 5.01(s, 1H, THQ proton), 7.08-7.31 (m, 13H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.4 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.5 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 126.8, 128.0, 128.6, 128.8, 138.3, 139.8, 144.0(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 403.1634 [M⁺] for C₂₇H₂₁ N₃O.

N-(2-(2-hydroxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6f)

white needles (EtOH) (this compound was prepared by the reaction of compound 4f, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as light brown solid); mp240-242⁰C; IR (KBr) v_{max}: 3,350, 3,130, 3,025, 1,670, 1435, and 885 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.03 (s, 1H, OH), 5.07(s, 1H, THQ proton), 6.68-7.31 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.49 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 39.2, 58.0, 60.3 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 115.7, 121.2, 125.7, 126.8, 128.5, 128.8, 129.4, 139.8, 144.0(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 419.1634 [M⁺] for C₂₇H₂₁ N₃O₂.

N-(2-(2-chlorophenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6g)

White needles (EtOH) (this compound was prepared by the reaction of compound 4g, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as a white solid); mp221–223⁰C; IR (KBr) v_{max}: 3,170, 3,022, 1,680, 1,425, and 630 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 7.02-7.31(m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.61 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.4, 58.0, 61.4 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 126.7, 126.8, 128.5, 128.7, 128.8, 129.4, 138.3, 139.8, 144.0(aromatic ring carbons) 164.9(amide carbon). HRESIMS m/e (pos): 437.1295 [M⁺] for C₂₇H₂₀Cl N₃O.



N-(2-(3-methoxy-4-hydroxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6h) Light brown needles (EtOH) (this compound was prepared by the reaction of compound 4h, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as light brown solid); mp236-238⁰C; IR (KBr) v_{max}: 3,332, 3,170, 3,010, 2995, 1,660, 1435, and 890 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 3.73 (s, 3H, methoxy proton), 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.03 (s, 1H, OH), 5.04(s, 1H, THQ proton), 6.46-7.31 (m, 11H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.52 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.8 (THQ ali. C), 56.2 (methoxy C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 113.4, 116.7, 121.7, 126.8, 128.8, 131.9, 139.8, 144.0(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 449.5005 [M⁺] for C₂₈H₂₃N₃O₃.

N-(2-(3,4,5-trimethoxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6i) Light brown needles (EtOH) (this compound was prepared by the reaction of compound 4i, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as light brown solid); mp212-215⁰C; IR (KBr) v_{max}: 3,152, 3,070, 3,010, 2995, 1,650, 1435, and 870 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 3.73 (s, 9H, methoxy proton), 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 6.80-7.31 (m, 10H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.68 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 71.1 (THQ ali. C), 56.5 (methoxy C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 105.3, 126.8, 128.8, 132.6, 137.6, 139.8, 144.0, 150.6(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 493.2002 [M⁺] for C₃₀H₂₇N₃O₄.

N-(2-(4-methoxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6j) Light brown needles (EtOH) (this compound was prepared by the reaction of compound 4j, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as light brown solid); mp208-210⁰C; IR (KBr) v_{max}: 3,132, 3,030, 2995, 1,650, 1435, and 870 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 3.73 (s, 3H, methoxy), 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 6.72-7.31 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.90 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.5 (THQ ali. C), 55.9 (methoxy C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 114.1, 126.8, 128.8, 129.0, 130.6, 139.8, 144.0, 159.0(aromatic ring carbons), 164.9(amide carbon). HRESIMS m/e (pos): 433.1790[M⁺] for C₂₈H₂₃N₃O₂.

N-(2-(4-methylphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6k) white needles (EtOH) (this compound was prepared by the reaction of compound 4k, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as white solid); mp218-220⁰C; IR (KBr) v_{max}: 3,070, 3,010, 2995, 1,650 and 1435 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆) δ = 2.35 (s, 3H, methyl), 4.52-4.67(d, 2H, trihydroquinoline (THQ) proton), 5.04(s, 1H, THQ proton), 7.00-7.31 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.86 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (75 MHz, DMSO-d₆) δ = 24.3 (methyl C), 38.9, 58.0, 70.5 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 126.8, 127.9, 128.8, 128.9, 135.3,



136.7, 139.8 (aromatic ring carbons), 164.9 (amide carbon). HRESIMS m/e (pos): 417.1841 [M⁺] for C₂₈H₂₃N₃O₂.

N-(2-(4-dimethylaminophenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6l) white needles (EtOH) (this compound was prepared by the reaction of compound 4i, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as white solid); mp 213-214^oC; IR (KBr) v_{max}: 3,048, 2995, 2851, 1772, 1,606 and 1435 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆) δ = 2.85 (s, 6H, methyl), 4.52-4.67 (d, 2H, trihydroquinoline (THQ) proton), 5.04 (s, 1H, THQ proton), 6.54-7.31 (m, 12H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.43 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (75 MHz, DMSO-d₆) δ = 40.3 (methyl C), 38.9, 58.0, 70.5 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 114.1, 126.8, 128.8, 128.9, 139.8, 144.0, 147.9_{ss} (aromatic ring carbons), 164.9 (amide carbon). HRESIMS m/e (pos): 446.2107 [M⁺] for C₂₉H₂₆N₄O.

N-(2-(2,4-dihydroxyphenyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6m) sharp white needles (EtOH) (this compound was prepared by the reaction of compound 4m, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as sharp white solid); mp 258-261^oC; IR (KBr) v_{max}: 3,532, 3,170, 3,010, 1,710, 1435, and 880 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 4.52-4.67 (d, 2H, trihydroquinoline (THQ) proton), 5.02 (s, 2H, OH), 5.04 (s, 1H, THQ proton), 6.44-7.31 (m, 11H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.57 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 38.9, 58.0, 70.8 (THQ ali. C), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 115.0, 117.1, 122.0, 126.8, 128.8, 132.3, 139.8, 144.0, 145.6, 147.1 (aromatic ring carbons), 164.9 (amide carbon). HRESIMS m/e (pos): 435.1583 [M⁺] for C₂₇H₂₁N₃O₃.

N-(2-(Cinnamyl)-2,5-dihydroanthro [7,10b] azet-1(10bH)-yl) isonicotinamide (6n) white needles (EtOH) (this compound was prepared by the reaction of compound 4n, anthracene in p-Xylene in the presence of RH (II) catalyst. It was obtained as white solid); mp 243-244^oC; IR (KBr) v_{max}: 3,170, 3,010, 1,710, 1632 and 1435 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.91-2.16 (m, 2H, ali. -CH₂- proton), 3.42 (m, 1H, trihydroquinoline (THQ) proton), 4.13 (d, 1H, THQ proton), 5.04 (s, 1H, THQ proton), 6.06 (m, 1H, vinylic proton), 6.41 (d, 1H, vinylic proton), 7.14-7.31 (m, 13H, Ar- H), 7.96 (d, 2H, J=6Hz, Pyridine proton), 8.60 (s, 1H, NH), 9.06 (d, 2H, J=6Hz, Pyridine proton). ¹³C NMR (100 MHz, DMSO-d₆) δ = 31.8 (ali. Carbon), 36.9, 58.5, 67.3 (THQ ali. C), 123.2, 129.1 (vinylic carbon), 122.8, 140.9, 149.8 (β, γ, α carbon of pyridine), 126.4, 126.8, 128.0, 128.7, 128.8, 135.2, 139.8, 144.0 (aromatic ring carbons), 164.9 (amide carbon). HRESIMS m/e (pos): 443.1998 [M⁺] for C₃₀H₂₅N₃O.

RESULTS AND DISCUSSION

The RH (II) catalyzed one pot Aza-Diels Alder reaction of N-(substituted benzylidene) isonicotinohydrazide 3(a-n) with anthracene gives good to better yield trihydroquinoline product. The IR spectra of compound 5a – 5g should extra vibration at near about 1684 cm⁻¹ which are characteristics of carbonyl group present as an amido group. ¹H NMR & ¹³C NMR data of



synthesized compound confirm the formation of substituted Trihydroquinoline and Hres. Mass spectra confirmed the molecular mass of the synthesized derivatives.

Conclusion:

Substituted trihydroquinolinebearing Isoniazid moiety and their derivatives has been successfully and conveniently prepared by one pot Aza-dies–alder reaction which is the important class of heterocyclic compounds with a diverse pharmacological activity.

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