ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Synthesis and Characterization of Some New Quinolinic acid Derivatives

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Abstract

Preparation of some non-homogeneous cyclic compounds starting with Quinolic acid .A different N-heterocyclic substituted derivative of quinolone has been synthesized. The nitrogen atoms have been alkylated first to form N-carboxymethyl followed by cyclization reaction to form heterocyclic/substituted aryl groups. All the synthesized compounds have been identified using FT-IR, ^{1}H NMR spectrum.

Keywords: *Quinolinic acid, 1, 3-Oxazole, Imidazol, 1, 2, 4-Triazole, 1, 3, 4- thiadiazol, diazetidin, diazepines.*

Introduction

Heterocyclic play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocyclic [1]. Heterocyclic moieties can be found in large number of compounds which display industrial applications. The activity of the compounds is mainly dependent on their molecular structures [2-9]. As a consequence of development of systems useful for the meeting of molecules containing heterocyclic templates continues to be a focus for the attention of both the educational and industrial communities.

The 1, 3-Oxazole and Imidazol units constitute an useful biological active compounds [10, 11]. Thiadiazole and 1, 3, 4-oxadiazol rings is also associated with wide ranging physiological activity [12, 19]. Quinolinic acid (QUIN), an internal metabolite of the kynurenine pathway, engages in numerous neurological disorders, including Huntington's disease, Alzheimer's disease, schizophrenia, HIV-related dementia (HAD) etc. Kinetic toxicity involves many mechanisms that attract different metabolic pathways and transcription factors. quinolic acid produces its poisonous effect through many mechanisms, primarily as a function of it as a catalyst for the future of NMDA, leading to a series of harmful effects, but also through fat peroxidation and congenital instability [20].

Materials and Methods

All chemicals were purchased from Sigma Aldrich, BDH, CDH and Merck. Fusion Point Measurements were performed by the open capillary method using the SMP30 melting point device reported non-certified. The FT-IR spectra (KBr disks) were recorded with the Shimadzu Iraffinity-1CE Shimadzu spectrometer. The 1HNMR spectra were recorded on a 400 MHz NMR spectrum device operating at a frequency of 400 MHz For ^{1}H measurements.

Synthesis of :(H1) Quinolinic Acid

To a combination of 25% potassium hydroxide (53.86 g. 0.96 mol) and quinoline (22.66 g 0.175 mol) at 90 ° C, 277.5 g 30% hydrogen peroxide (2.45 mol) is added over three hours and a quarter with constant stirring while maintaining a degree Heat 90 The reaction is left for another two hours with stirring. The reactants are distilled to remove 234 g of water to make the reactive materials weight in half of the original weight. The reactants are cooled to a temperature of 45. The concentrated sulfuric acid is gradually added until the acidic function becomes 3.5. The dough produced

from the thomium sulphate is cooled to 10 degrees, left half an hour, shaved and washed with 5 ml cold water. The concentrated sulfuric acid is added to the filtrate until it becomes Acid function. The resulting dough is left for half an hour at 10 ° C and then filtered and washed with 20 ml cold water. The precipitate is dried at 55 ° C under pressure for 3 hours to obtain 6.19 g 97% purity from light yellow to dark white Yield: 41 %; m.p. 188-190; Color: White; $C_7H_5NO_4$ (m.w. 167.02). IR (v, cm $^{-1}$): 2837-3415 broad (OH carboxyl), 1728(C=O carboxyl), 3032 (C-Har); ^{1}HNMR (400 MHz, DMSO-d6) δ(ppm): The ^{1}H-NMR (300 MHz, TMS, δ, ppm) the spectrum of H34 ;8.06-8.98 (m,3H,Ar-H),10.46(s,1H,COOH), 2.5 DMSO.

Synthesis of: 5H-Pyrido[2,3-e] [1,3] diaepine-5,7,9(6H,8H)-trione)- 7-thioxo-7,8-dihvrido [2,3-e][1,3]diazepine-5,9 (6H)-dione (H2-H3)

Compound (H1) (0.01 mole,1.67gram) dissolved with(0.01mole) urea and thiourea (0.6gram and 0.76gram) respectively in (20ml) of ethanol and then the mixture was refluxed for (6hrs), then the mixture was cooled to room temperature, the product was collected and recrystallized from absolute ethanol.

5H-Pyrido[2,3-e][1,3]diaepine-5,7,9(6H,8H)-trione(H2) Yield: 51%; m.p. 373-375°C; Color: leady; $C_8H_5N_3O_3$ (m.w.191.14) . IR (v, cm^{-1}) 1695 cm-1 (C=O $_{amid}$), 3251 cm-1 (NH), 3095cm-1 (C-Har). ^{1} H-NMR (300 MHz, DMSO-d6) δ(ppm):8.06-8.55 (m, 3H, Ar-H) and 9.99(s,1H,NH), 2.5 (DMSO).

7-thioxo-7,8-dihvrido[2,3-e][1,3]diazepine-5,9(6H)-dione(H3); Color: leady ; Yield:58%; m.p286-288°C; $C_8H_5N_3O_2S$ (m.w.207.21). IR (v, cm^{-1}): 3444 (NH), 3105 (C-H_{ar}), 1668 (C=O_{amid}): C=S (1249) .^{1} H-NMR (300 MHz, DMSO-d6) δ (ppm):8.12-8.74 (m, 3H, Ar-H) and 8.04(s, 1H, NH), 2.5 (DMSO).

Synthesis of;5,5-(pyridine-2,3diyl) bis (1,3,4-thiadiazol -2-amine)- 5,5-(pyridine-2,3diyl) bis(1,3,4-oxadiazol-2-amine)(H4-H5)

The compound (H1) (0.01mol, 0.91gm, 0.75gm) was mixed with thiosimecarbazide and simecarbazide using 10 ml of $POCl_3$ as solvent, and the reflex was increased for 36 hours. The mixture was slowly mixed with the continuous stirring. The acid mixture was mixed with potassium carbonate. Leave the mixture for the next day to settle. Collect the precipitate by filtration and wash with distilled water (50 mL) and recrystallize with appropriate solvent.

5,5-(pyridine-2,3diyl)bis(1,3,4-thiadiazol -2-amine)(H4) Color: black; Yield: 68%; $C_8H_5N_3O_2s$(m.w.207.01),m.p. Oily; IR (v, cm-1) 3481-3381 (NH_2), 3091 (C-Har), 1653(C=N). ^{1} H-NMR (300 MHz, DMSO-d6) δ (ppm):7.47-8.8 (m, 3H, Ar-H) and 7.21-7.44 (s, 2H, NH2), 2.5 (DMSO).

5,5-(pyridine-2,3diyl)bis(1,3,4-oxadiazol-2-amine)(H5) Color: black; Yield: 56%; C8H5N3O3 (m.w.191.14) ;m.p. Oily; IR (v, cm-1) 3523-3444 (NH_2), 3049 (C-Har), 1651(C=N); $C_8H_5N_3O_3$ (m.w.191.14). ^{1} H-NMR (300 MHz, DMSO-d6) δ(ppm):7.94-8.40 (m, 3H, Ar-H) and 7.53 (s,2H,NH_2), 2.5 (DMSO)

Synthesis of 6, 7-dihydropyrido [2, 3-d] pyridazine-5, 8-dione (H6)

In a round bottom flask containing (0.01mol1.67gm) of compound (H1), a mixture of hydrazine (0.01 mol, 0.32gm), (20ml) ethanol have been added. The mixture has been refluxed with stirring for5- 6 hrs. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Color: gray; Yield: 66%; m.p. 213-215°C;); $C_7H_5N_3O_2$ (m.w.163,13). IR (v, cm^{-1}) 3491 (NH), 3070 (C-H_{ar}), 1627(C=O_{amid}) . ^{1} H-NMR (300 MHz, DMSO-d6) δ (ppm): 8.38-8.86 (m, 3H, Ar-H) and 8-8.03(s,H,NH), 2.5 (DMSO).

Synthesis of: 7, 8-dihydro-[1, 2] diazeto [1, 2-a] pyrido [2,3-d]pyridazine-5,10-dione(H7)

In around bottom flask containing (0.01mol, 0.32gm) of compound (H8), a mixture of dichloroethane (0.01 mol, 0.989 gm) and ethanol (20 ml) have been added. The mixture refluxed for 5-6 hrs. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Yield: 90 %; m.p258-260 C; Color:brown; $C_9H_7N_3O_2$ (m.w.189.17) .IR (v, cm^{-1})1627 (C=O $_{amid}$), 1487 (C-N), 2885-2985 (C-H $_{aliph}$), 3035 (C-Har). ^{1} H-NMR (300 MHz, DMSO-d6) δ (ppm): 6.93-7.27 (m, 3H, Ar-H) and 3.37 (triplet, 2H, CH2-CH_2), 2.5 (DMSO).

Syntheses of: 2, 2-((Pyridine-2, 3-dicarbonyl) bis (azanediyl)) diacetic acid (H8)

Compound H1 (0.01mol) in (5ml) dioxane was added to a stirring solution of glycine

(1.4g, 0.02mol) and sodium hydroxide (20ml , 10% solution).

Then, the reaction mixture was stirring overnight and a few grams of crushed ice were added with stirring. After that, the solution was acidified with conc. HCl and the combined solution was concentrated in vacuo and the residual precipitate dissolved in ethanol. The inorganic salts were filtered .the remaining solution concentrated in vacuo. The remained crude oily

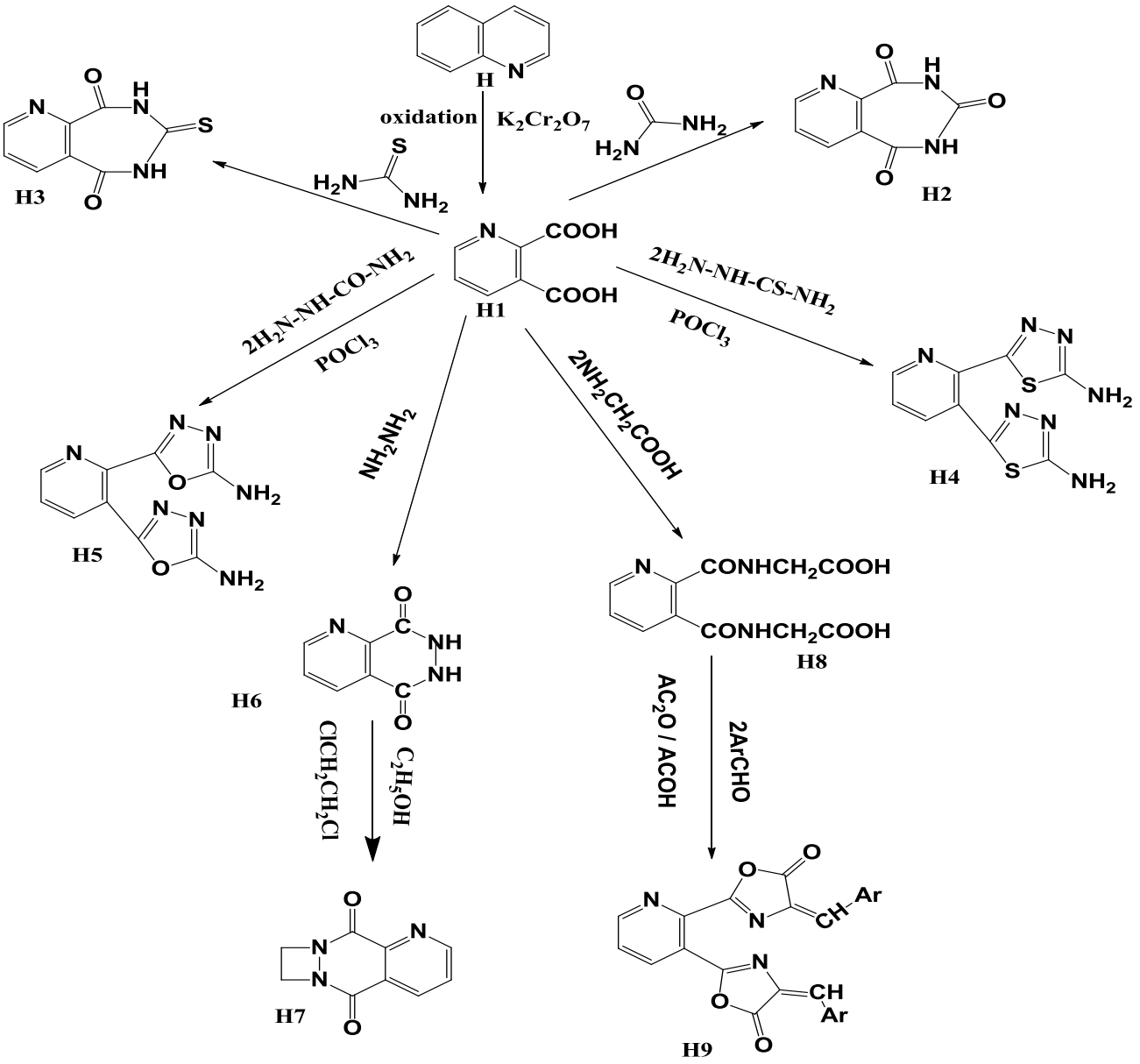
Yield: 70 %; m.p 220 ˚C; Color: Green; $C_{11}H_{11}N_3O_6$ (m .w.t 281.22), IR (v, cm $^{-1}$): 3837-3429 brod (OH carboxyl) 3419 (NH), 2837-2902 cm-1 (C-H $_{aliph}$), 1734 (C=O carboxyl), 1633 (C=O amid). ^{1} H-NMR (300 MHz, DMSO-d6) δ(ppm): 8.67-8.88(m, 3H, Ar-H) and 8.07(s, H,NH),11.05(s,1H,COOH),3.61(s,2H,CH_2C=O), 2.5 (DMSO).

Syntheses of (4E, 4E)-2, 2-(pyridine-2, 3-diyl) bis (4-(argiomethylene) oxazol-5(4H)-one) (H9)

Compound H8 (0.01 mol, 2.81gm) dissolved in acetic acid (10 ml) and acetic anhydride (40 ml) later aromatic aldehyde (4-bromo benzylaldehyde) (0.02 mol) was added and the refluxing was continued for (7 hrs). Then after evaporating the solvent under reduced pressure and recrystallized from absolute ethanol and filtered. Yield: 75 %; m.p258-260 C; Color: brown; $C_9H_7N_3O_2$ (m.w.189.17), IR (v, cm^{-1})1651 (C=O $_{amid}$), 1487 (C-N), 2852-2993 (C-H $_{aliph}$), 3035 (C-Har).^{1} H-NMR (300 MHz, DMSO-d6) δ(ppm): 7.45-9.12 (m, 3H, Ar-H) and 7.25(s,H,CH=C), 2.5 (DMSO).

Results and Discussion

The designated compounds were synthesized according to Scheme.



Scheme 1: the synthesis of compounds H1-H9

We prepared the quinolic acid H1 by oxidizing the quinolin H with hydrogen peroxide. The IR spectrum of the H1 indicated by appearance of broad band (2837-3415) cm-1 due to hydroxyl group of carboxylic derivatives, 1H-NMR spectrum of compound H1, show new signal at 10.46 ppm(s,1H,COOH), 8.06-8.98 (m,3H,Ar-H).The reaction of Quinolic H1 with urea gives 5H- Pyrido[2,3-e][1,3]diaepine-5,7,9(6H,8H)-trione (H2), the prepared compound have been identified by the absence of band of hydroxyl group of carboxylic acid in compound (H2) at(2837-3415)cm-1 and appearance of new sharp band at 1695 cm-1 refers to carbonyl of amid and 3251 cm-1 of (NH) group, consecutively in FT-IR spectrum, 1H-NMR spectrum of compound H2 ,show new signal at 9.99(s,1H,NH) , 8.06-8.55 (m, 3H, Ar-H).

Reaction of H1 with thiourea give 7-thioxo-7,8-dihvrido[2,3-e] [1,3] diazepine-5,9(6H)-dione (H3) which it has been identified by absence of band of hydroxyl group of carboxylic acid in compound (H1) at(2837-3415)cm^{-1} and appearance of new sharp band at 1668 cm^{-1} refers to carbonyl of amid and appear the new sharp band at 1249 cm^{-1} (C=S), and 3444 of (NH) group consecutively, ^{1}H-NMR spectrum of compound H3,show new signal at 8.04 ppm (s,1H,NH) and 8.12-8.74 ppm (m, 3H, Ar-H) .Reaction of H1with thiosemacarbazid gave 5,5-(pyridine-2,3diyl) bis(1,3,4-thiadiazol -2-amine) (H4) the compound have been identified by IR through the appearance of absorption band at due to the primary amine spectrum through the appearance of absorption band at(3381-3481) cm^{-1} due to the primary amine and absorption band at (1514) due to (C-N). Also the appearance of (C=N) imines absorption bands at (1653 cm^{-1}), ^{1}H-NMR spectrum of compound H4,show new signal at 7.21-7.44 ppm (s,2H,NH_2) and 7.47-8.8 ppm (m, 3H, Ar-H) .Reaction of H1 with semecarbazid gave 5,5-(pyridine-2,3diyl)bis(1,3,4-oxadiazol-2-amine) (H5).

It has been identified by IR spectrum through the appearance of absorption band at (3523 -3444) cm^{-1} due to the primary amine and absorption band at (1456) due to (C-N). Also the appearance of (C=N) imines absorption bands at (1651 cm^{-1}), ^{1}H-NMR spectrum of compound H5,show new signal at 7.53 ppm (s,2H,NH_2) and 7.94-8.40 (m, 3H, Ar-H). Reaction of H1 with hydrazine gave 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione(H6) , It has been identified by absence of band of hydroxyl group of carboxylic acid in compound (H1) at(2837-3415)cm^{-1} and appearance a new sharp band at1627 cm^{-1}, was assigned to a C=O stretching frequency of amide carbonyl and the absorption bands for the NH at 3491 cm^{-1} precipitate was recrystallized from ethanol, ^{1}H-NMR spectrum of compound H6,show new signal at 8-8.03 ppm (s, H,NH) ,8.38-8.86 ppm (m, 3H, Ar-H) and, 2.5 (DMSO). Reaction of H6 with dichloroethane gave 7,8-dihydro-[1,2] diazeto [1,2-a]pyrido[2,3-d]pyridazine-5, 10-dione (H7). It has been identified by the absence of NH band at 3491cm^{-1} and appearance of new band at1627 cm^{-1} ($C=O_{amid}$), 1487 cm^{-1} (C-N), (3035cm^{-1})refers to C-Har,(2985,2885cm^{-1}), ^{1}H-NMR spectrum of compound H7,show new signal 3.37 (triplet, 2H,CH_2-CH_2) and 6.93-7.27 (m, 3H, Ar-H), 2.5 (DMSO).

Reaction of H1 with glycine gave 2,2-((Pyridine-2,3-dicarbonyl) bis (azanediyl) diacetic acid (H8) The IR spectrum of the product indicated the absence of absorption of broad band (2837-3415) cm^{-1}due to hydroxyl group of carboxylic bands and the presence of a OH absorption band at 3837-3429cm-1 and showed two sharp absorption band, the first appears at 1734 cm-1 and is attributed to carbonyl function of the carboxylic acid and other, observed at 1633cm-1 , was assigned to a C=O stretching frequency corresponding to the amide carbonyl, ^{1}H-NMR spectrum of compound H8 ,show new signal at 11.05 ppm (s,1H,COOH),8.67-8.88 ppm (m, 3H, Ar-H) and 8.07(s, H,NH),3.61(s,2H,CH_2C=O) . The structures of compounds (H9) were identified by the absence of the characteristic OH stretching at (3837-3429) cm^{-1} and appear new signal at1651 ($C=O_{amid}$), (2852 and 2993) Cm^{-1} refers to C-H_{aliph} , ^{1}H-NMR spectrum of compound H9,show new signal at 7.25(s, H,CH=C) and 7.45-9.12 (m, 3H, Ar-H).

Conclusion

These compounds were prepared and diagnosed and found to be stable through high melting point and that the diazepine ring resulting from the closure of the ring Thiourea is the best proportion of the Yield, the seven membered (diazepine) ring produced by the closure of the ring of urea.

As well as the closure of thiosemecarbazid to product thiadiazo ring has a proportion of the Yield in which more than of the closure of the ring of semecarbazid to produce oxazole, also the closure in the thiosemecarbazid is easier.

The closure of hydrazine produces azitidine. Compound H9 is a Schiff base product from (4-bromo benzaldehyde) The Yield is acceptable.

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