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Synthesis of 2, 6-(substituded)pyridine Derivatives Using Amide and Imine Groups

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Abstract: A new 'two-armed' acyclic diamide $\mathbf{I_a}$ 2, 6-bis(1-ethanecarbozamido-2-amino)pyridine, and a new series of aromatic aldehyde schiff bases containing pyridine ring and amide bridge, $\mathbf{II_{a\text{-}f}}$, were prepared. The compounds were characterized by elemental analysis, IR, ^{1}HNMR and MS. The bioactivity half inhibitory concentration $C_{1/2}$ is given.

Keyword: Aromatic aldehyde Schiff bases, pyridine, amide bridge.

Pyridine derivatives are widely applied in medicine and agriculture, for example, used as anticancer drugs[1], anti-hypertension[2] and antifungal[3] reagents, pesticides[4], herbicides[4], plant growth reagents[4] etc.. Meanwhile, aromatic aldehyde Schiff bases have also attracted much attention due to their diverse biological activities, such as antimicrobial[5], antibacterial[6], antiviral[7], anticancer[8]activities etc.. Further, amide compounds are commonly used in medicine[9].

In view of above, we report herein the preparation of a new series of compounds bearing both pyridine and aromatic aldehyde Schiff bases with amide bridge, with the objective of obtaining new biologically active compounds. The synthesis route is shown in **Scheme**. The bioactivity has been investigated by microcalorimetry and characterized by half inhibitory concentration $C_{1/2}$.

2, 6-dimethylpyridinedicarboxylate and intermediate $\mathbf{I_b}$ was prepared as the literature[10] with stoichiometric yield 100%. High-dilution method and 5-fold excess of amine were employed to avoid polymeric/cyclic by-product when preparing the intermediate $\mathbf{I_a}$, in good yield (95%) and purity which has been confirmed by thin layer chromatography, as grey hygroscopic solid. $\mathbf{I_a}$: IR(KBr/cm^{-1}): 3442(NH_2),3293, 1667(amide I), 1539(amide II),1445,681; ^{1}HNMR(300MHz,$CDCl_3$, δppm): 8.85(br,2H),8.26(d,2H), 7.97(t,1H),5.55(br,4H),2.93(br,4H,-NH_2),2.22(br,4H); anal. for $C_{11}H_{17}N_5O_2$: calcd.: C: 52.58,H:6.82,N:27.87; found: C:52.39,H:6.93,N:28.15.

The general synthesis procedure of the compounds: to 15ml methanolic solution of 2.2mmol aromatic aldehyde, 1mmol intermediate in 15ml methanol was added under stirring. The mixture was refluxed for 4hs, then the precipitate was filtered out, washed with methanol, ether and dried in vacuum to gain the product.

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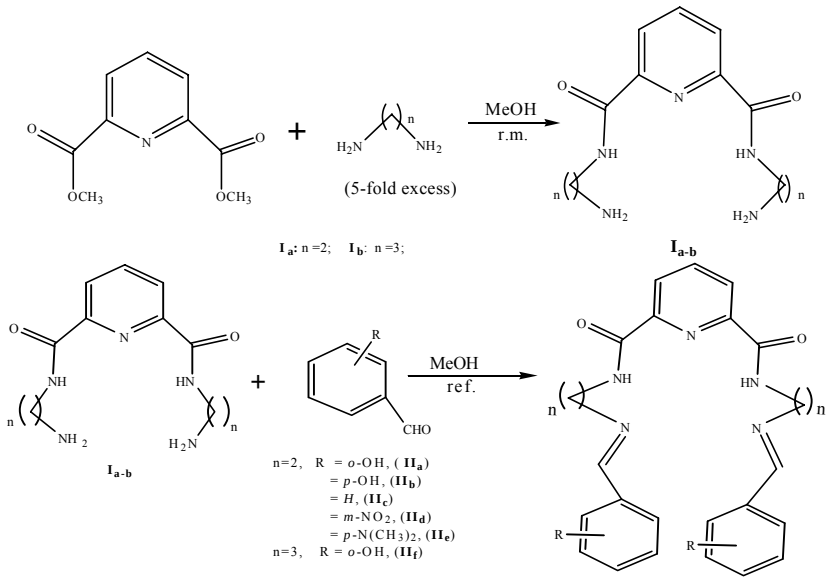
Scheme



Compound **II_a**: recrystallized from $CHCl_3$. Yield:89%;m.p.:191-193°C; MS(1.2v)m/z(%): 459(M,100); ^{1}HNMR(300MHz, $CDCl_3$, δppm): 13.56(2H,D_2O exchangable), 8.37(d,2H), 8.25(br,2H,amide), 8.01(t,1H), 7.33 (s,2H), 7.26(d,2H), 7.16(q,2H), 6.87(m,4H), 3.85 (t, 4H), 3.48(q,4H); IR(KBr/cm^{-1}): 3354,1676(amide I), 1633(C=N), 1535(amide II), 1492, 1272, 760,660; anal. for $C_{25}H_{25}N_5O_4$: calcd.: C:65.35,H:5.48,N:15.24; found: C:65.58,H: 5.27, N:15.11. $C_{1/2}$:226.906 μg/mL.

Compound **II_b**: recrystallized from ethanol. Yield:87%; m.p.:215-217°C; MS(666mv) *m/z*(%):459(M,30); ^{1}HNMR(300MHz,DMSO-d_6, δppm): 9.77(br,2H),9.39(br,2H,amide), 8.25(d, 2H), 8.22(s, 2H), 8.18(t, 1H),7.52(d, 4H), 6.78(d, 4H),3.72(t, 4H),3.60(q, 4H); IR (KBr/cm^{-1}): 3360, 3312,1649(amide I), 1600(C=N),1532(amide II), 1448, 1287, 830, 675; anal. for $C_{25}H_{25}N_5O_4$: calcd.: C:65.35, H:5.48, N:15.24; found: C:65.18,H: 5.69,N:15.45. $C_{1/2}$: 777.514μg/mL.

Compound **II_c**: recrystallized from ethanol. Yield:84%; m.p.:153-155°C;MS(104mv)m/z (%):427(M,50); ^{1}HNMR(300MHz,DMSO-d_6, δppm): 8.31(d,2H),8.27(br,2H,amide), 8.21(s,2H),8.02(t, 1H),7.64(d, 4H),7.39(br, 6H),3.76(br, 8H); IR(KBr/cm^{-1}): 3403, 1676 (amide I), 1653(C=N), 1530 (amide II), 1445, 1350, 735, 671, 645; anal. for $C_{25}H_{25}N_5O_2$: calcd.: C:70.24, H:5.89, N:16.38; found: C:70.43,H:5.72, N:16.49. $C_{1/2}$: ›1000μg/ml.

Compound **II_d**; recrystallized from 5:1ethanol/DMF (v/v). Yield:83%; m.p.:170-171°C; MS(47mv)*m/z*(%): 518(M+1,98); ^{1}HNMR(300MHz,DMSO-d_6, δppm): 9.41(br,2H, amide), 8.51(s, 2H), 8.41(d, 2H), 8.30(d, 2H), 8.19(s, 2H),8.11(d, 2H), 8.07(t, 1H), 7.67(q,H), 3.80(t,4H), 3.64(q,4H); IR(KBr/cm^{-1}): 3336, 3282, 1670(amide I), 1641(C=N),1541 (amide II), 1449, 1292, 843, 756, 695; anal. for $C_{25}H23N_7O_6$: calcd.:C:58.02,H:4.48,N:18.95; found: C:57.85, H:4.27, N:18.77. $C_{1/2}$: 538.39 μg/mL.

Compound **II_e**: recrystallized from 5:3 petroleum ether/ethanol (v/v). Yield:82%;m.p.: 131-132°C; MS(430mv)m/z(%): 514(M+1,100); ^{1}HNMR(300MHz,$CDCl_3$, δppm): 8.93 (br,2H,amide), 8.32(d, 2H), 8.14(d, 2H) 8.06(t, 1H),7.55(d, 4H),6.56(d, 4H), 3.72 (s,br,8H), 2.95(s,12H); IR(KBr/cm^{-1}): 3416,3278,1668(amide I), 1633(C=N), 1601, 1529 (amideII), 1366, 1182, 820, 685; anal. for $C_{29}H_{35}N_7O_2$: calcd.: C:67.81,H:6.87,N:19.09; found: C: 67.61, H:6.78, N:19.39. The structure has been confirmed by the X-ray crystal structure which will be reported in another paper. $C_{1/2}$: >1000μg/mL.

Compound **II_f**: recrystallized from 2:5 petroleum ether/acetone (v/v). Yield:81%; m.p.: 101-102°C; MS(47mv)*m/z*(%): 488(M+1,41); ^{1}HNMR(300MHz,$CDCl_3$, δppm): 13.59 (2H,D_2Oexchangable),8.34(d, 2H),8.20(br, 2H,amide),8.04(t, 1H),7.91(s, 2H),7.27(d,2H), 7.17(q,2H),6.83(m,4H),3.65(m,8H),2.09(m,4H); IR(KBr/cm^{-1}): 3299,1667(amideI),1635 (C=N),1582,1540(amide II), 1460, 1281, 756, 646; anal. for $C_{27}H_{29}N_5O_4$: calcd.: C:66.51, H:6.00,N:14.36; found: C:66.68, H:5.88, N:14.59. $C_{1/2}$: 213.21μg/mL.

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