SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME N-(3-HYDROXY-2-PYRIDYL) BENZAMIDES

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Abstract : N-(3-Hydroxy-2-pyridyl)benzamides 3(a-J) were synthesized under weak basic solution by reacting of 2-amino-3-pyridinol and an appropriate carboxylic acid chloride, obtained by reaction of carboxylic acids with thionyl chloride. The microbiological activity of these compounds was tested in vitro against Escherichia Coil (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and Staphylococcus aureus (PTCC 1119) bacteria. Compounds 3a, 3e and 3f were the active benzamide derivatives against the Ef and Sa bacteria with a MIC value of 128 μg/ml. Compound 3g was the active entry against Ec and Pa bacteria with a MIC value of 128 μg/.

Keywords: 3-Hydroxypyridyl, Benzamide, 2-Amino-3-pyridinol, Bacteria

Introduction

Benzoxazoles derivatives constitute important chemical classes of compounds having antibacterial and antifungal activities (1-8). Benzamide derivatives which are the possible metabolites of benzoxazolez posses various types of biological activities such as antihistaminic, antihelmintic antifungal and antibacterial activities (9,10). Biological activities of some N-(2-hydroxyphenyl)benzamides, phenylacetamides and furamides have been studied in depth recently. N-(2-Hydroxyphenyl)benzamides, which showed significant activity compared to phenylacetamides and furamides (10), have been synthesized by a simple nucleophilic reaction of 2-aminophenol with carboxylic acid chlorides under weak basic solution (10-12). However synthesis and especially microbiological activities of N-(3-hydroxy-2-pyridyl)benzamides were not studied well. Owing to the versatility of compounds containing pyridine moiety in biological activities (13) we have extended the reaction of 2-amino-3-pyridinol with different carboxylic acid chlorides in order to preparation of some new benzamide derivatives containing a hydroxypyridyl ring.

Experimental

Chemistry

All reagents commercially were available. Carboxylic acid chlorides were prepared by reaction of carboxylic acids with thionyl chloride in benzene at 80 °C for 1-2 h. Melting points were determined with an elctrothermal digital melting point apparatus. IR spectra were taken on a Galaxy series FT-IR 5000 spectrophotometer in potassium bromide pellets. ^{1}H NMR spectra were recorded at 25 °C on Bruker 500 MHz spectrometers with using Me_4Si (TMS) as an internal standard. Reaction courses and product mixtures were monitored by thin layer chromatography. **3i** and **3j** are known compounds.

General procedure for synthesis of N-(3-hydroxy-2-pyridyl)benzamides 3(a-j)
Appropriate aromatic carboxylic acid (1 mmol) and thionyl chloride (5 ml) was refluxed in benzene (5 ml) for 1-2 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled and the excess amount of thionyl chloride evaporated under reduced pressure to give the desired acid chloride. The prepared acid chloride was dissolved in ether (10 ml) and the solution added dropwise during 1 hour to a stirred, ice-cold mixture of 2-amino-3-pyridinol (1 mmol), sodium bicarbonate (1 mmol), diethyl ether (10 ml) and water (10 ml). The mixture was then stirred overnight at room temperature and flittered. The crude product was precipitated out from the filtrate, which recrystallized from a mixture of water and ethanol.

N^1-(3-hydroxy-2-pyridyl)-4-nitrobenzamide (3a)
Yield 65%, m.p. 193-195 °C
IR (KBr) : υ = 3100, 3060, 1690, 1610, 1110 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 7.26-7.35 (m, 4H, Ar-H), 8.21-8.38(m, 3H, Ar-H), 9.92 (bs, 1H, OH), 10.74 (bs, 1H, NH)
Anal. Calcd for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.47; N, 16.20%. Found: C, 55.70; H, 3.40; N, 16.32.

N^1-(3-hydroxy-2-pyridyl)-2-hydroxybenzamide (3b)
Yield 32%, m.p. 118-120°C
IR (KBr) : υ = 3231, 3101, 2351, 1663, 1541 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 7.80-6.91 (m, 7H, Ar-H), 9.90 (bs, 1H, OH), 11.40 (bs, 1H, NH)
Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.17%. Found: C, 62.49; H, 4.44; N, 12.38.

N^1-(3-hydroxy-2-pyridyl)-3,4,5-tri-methoxybenzamide (3c)
Yield 52%, m.p. 104-106 °C
IR (KBr) : υ = 3240, 2880, 1700, 1600, 1070 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 3.88 (s, 9H, 3 x O-CH_3), 6.05-7.99 (m, 5H, Ar-H), 9.84 (bs, 1H, OH), 10.67 (bs, 1H, NH)
Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.26; N, 9.21%. Found: C, 59.32; H, 5.00; N, 9.54.

N^1-(3-hydroxy-2-pyridyl)-3-chlorobenzamide (3d)
Yield 45%, m.p. 116-118 °C
IR (KBr) : υ = 3145, 1650, 1600, 1105 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 7.21-8.06 (m, 4H, Ar-H), 9.00-9.50 (m, 3, Ar-H), 9.82 (bs, 1H, OH), 10.58 (bs, 1H, NH)
Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.94; H, 3.62; N, 11.27%. Found: C, 57.75; H, 3.50; N, 11.40.

4-Chloro-N^1-(3-hydroxy-2-pyridyl)-3-nitrobenzamide (3e)
Yield 40%, m.p. 121-122°C
IR (KBr): υ = 3289, 1685, 1602, 1051
^{1}HNMR (DMSO-d_6): δ= 7.91-8.55 (m, 6H, Ar-H), 11.24 (bs, 1H, OH), 12.51 (bs, 1H, NH)
Anal. Calcd for $C_{12}H_8ClN_3O_4$: C, 49.06; H, 2.73; N, 14.31%. Found: C, 49.20; H, 2.96; N, 14.03.

N^1-(3-hydroxy-2-pyridyl)-3,5-di-nitrobenzamide (3f)
Yield 62%, m.p. 202-203 °C
IR (KBr) : υ = 3400, 3060, 1690, 1600, 1030 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 7.20-8.00 (m, 3H, Ar-H), 9-9.50 (m, 3H, Ar-H), 9.95 (bs, 1H, OH), 11.20 (bs, 1H, NH)
Anal. Calcd for $C_{12}H_8N_4O_6$: C, 47.37; H, 2.63; N, 18.42%. Found: C, 47.10; H, 2.39; N, 18.69.

N^1-(3-hydroxy-2-pyridyl)-4-t-butylbenzamide (3g)
Yield 40%, m.p. 136-137 °C
IR (KBr) : υ = 3480, 3300, 2940, 1600, 1020,740 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 1.32 (s, 9H, 3 x CH_3) 6.01-7.86 (m, 7H, Ar-H), 8.60 (bs, 1H, NH), 8.40 (bs, 1H, OH)
Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.67; N, 10.37%. Found: C, 69.86; H, 6.90; N, 10.39.

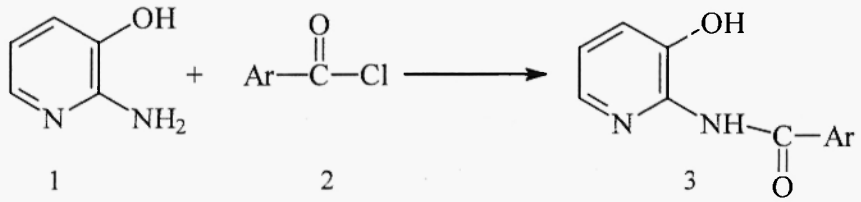
N^1-(3-hydroxy-2-pyridyl)-3-bromobenzamide (3h)
Yield 40%, Yield 40%, m.p. 230-232 °C
IR (KBr) : υ = 3260, 2920, 1685, 1600 cm^{-1}
^{1}HNMR (DMSO-d_6): δ= 7.75-8.30 (m, 7H, Ar-H) 11.35 (bs, 1H, OH), 13.35 (bs, 1H, NH)
1H, NH)
Anal. Calcd for $C_{12}H_9BrN_2O_2$: C, 49.15; H, 3.07; N, 9.56%. Found: C, 49.41; H, 3.25; N, 9.70.

Biological activities

Antibacterial effects were studied through applying broth dilution method, which is the most precise and reliable one for determining the sensitivity degree of microbes towards antibiotic (14). All compounds were dissolved in DMSO (25.6 mg/ml) and diluted with acetonitrile (256 μg/ml). Further dilution of the compounds in the test medium was carried out at the required concentration of a 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/ml with Muller-Hinton broth. The base medium used is Muller Hinton Broth (21 g/lit). A set of tubes containing only inoculated broth was kept as controls. It was determined that the solvent had no antimicrobial activity against any of the test microorganism. All compounds were tested for their in vitro grow inhibitory activity against different bacteria. The origins of bacterial structures were Escherichia Coil (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and Staphylococcus aureus (PTCC 1119). The cultures were obtained in Muller Hilton Broth for all bacteria after 18-24 h of incubation at 37 ± °C. After incubation for 18-24 h, the last tube with no grow of microorganism was recorded to represent the minimum inhibitory concentrations (MIC) in term of μg/ml. Every experiment in the antibacterial assay was replicated twice in order to define the MC values

Results and Discussions

The reaction of carboxylic acids with thionyl chloride gave the related acid chlorides. Further reaction of the acid chlorides with 2-amino-3-pyridinol afforded N-(3-hydroxy-2-pyridyl)benzamides **3(a-J)** as shown in Scheme-1.



1 2 3

a) Ar=4-nitrophenyl
b) Ar=2-hydroxy phenyl
c) Ar=3,4,5-trimethoxyphenyl
d) Ar=3-chlorophenyl
e) Ar=4-chloro-3-nitrophenyl
f) Ar=3,5-di-nitrophenyl
g) Ar=4-t-butylphenyl
h) 3-bromophenyl
i) 4-bromophenyl
j) 4-methylphenyl

Scheme-1

The ^{1}HNMR spectra of the synthesized compounds are simple and consist of the aromatic protons signals and two OH and NH proton signals. The aromatic protons including pyridine ring protons resonate as multiple signals at 6.05-9.4 ppm range depend on Ar group. However the ^{1}HNMR spectra of **3c** and **3g** show a singlet signal in the aliphatic region due to resonance of three OCH_3 or CH_3 groups. On the basis of ^{1}H NMR spectra the products **3(a-j)** are obtained as a result of nucleophilic attack on the NH_2 group. In ^{1}HNMR spectra of these compounds the OH and the NH protons resonate as a broad singlet signal at lower chemical shift, as compared to those of starting material, is in support of a nucleophilic attack on the NH_2 group.

The IR spectra of **3(a-j)** display two absorption bands at 1600-1700 cm^{-1} and 3100-3430 cm^{-1}, which are assigned to carbonyl and NH groups respectively, and are in support of the expected reactions.

All synthesized compounds were tested against the Escherichia Coil (PTCC 1338), Pseudomonas aeruginosa (PTCC 1074), Entrococcus faecalis (PTCC 1237) and Staphylococcus aureus (PTCC 1119) bacteria. **3a, 3f** and **3e** containing a strong electron withdrawing group showed antibacterial activity against the Ef and Sa bacteria with a MIC value of 128 μg/ml. Compound **3g** containing a bulky t-butyl group was active against the Ec and Pa bacteria with a MIC value of 128 μg/ml.

However other N-(3-hydroxy-2-pyridyl)benzamides were not effective against all four chosen bacteria.

Conclusions

In summary some N-(3-Hydroxy-2-pyridyl)benzamides were prepared from reaction of 2-amino-3-pyridinol and an appropriate carboxylic acid chloride. Some of these compounds were active against the Ef and Sa bacteria with a MIC value of 128 μg/ml.

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