IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
October 2017 Vol.:10, Issue:3

Synthesis and Potential Biological Activity Evaluations of Pyridine Amides Derivatives with Naphtho[2, 3-D] Imidazoles

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Dr. Shobha S. Borhade

Department of Drug Chemistry, S.M.B.S.T.College, Sangamner, Maharashtra, India.

Submission: 19 September 2017
Accepted: 29 September 2017
Published: 30 October 2017

Keywords: Synthesis, Spectral study, Antimicrobial and Antifungal Activity

ABSTRACT

Compounds with Naphtho [2,3-d] imidazole shows antibacterial and antifungal activity, here we have synthesized the compound with pyridine amides have potent antifungal and antibacterial activity and it is also active in plant pathogens. Pyridine derivatives exhibited promising biological activities. We have been synthesized different pyridine amides. The synthesized compounds were confirmed by IR, 1H NMR and Mass spectral analysis and they were evaluated for their antibacterial activities by disc diffusion method possessed weakly to moderately antifungal activities against *G. zeae*, *F. oxysporum*, and *C. mandshurica*. Most of the synthesized compounds exhibited similar activities as (or higher than) these of hymexozol on their corresponding fungus. The compounds were evaluated for antimicrobial activity against bacteria, *viz*. *Streptomyces* sp, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas* sp and antifungal activity against various fungi, *viz*. *Aspergillus niger*, *Penicillium* sp, and yeast *Candida albicans*.

INTRODUCTION

Heterocyclic compounds have largest area of research in organic chemistry. They are associated with a wide variety of physiological activities. Nitrogen heterocycles are present in nucleic acids, vitamins, proteins and other biological important systems[1]. Amides play a role for medicinal chemists. Carboxamide groups appear in more than 255 of known drugs[2]. Carboxamide is neutrally stable and has both hydrogen bond accepting and donating properties[3]. Variety of fused pyridines studied in the field of chemistry of heterocyclic compounds. [4,5]. They play a significant role in bioactive molecules[6,7.] Synthesis and reactivity of various furo[3,2-c] pyridines[6-16].Imidazole and its derivatives are of great significance due to their important roles in a biological system in enzymes, as a proton donor and or proton acceptors, coordination system ligands and the base charge transfer processes[17]. Imidazole derivatives possess a broad spectrum of pharmacological activities such as anticonvulsant[17,19], anti-parkinson[18,20], and mono-amino oxidase inhibitory activity[17,21].

Antibiotic resistance in microorganisms has become a critical health issue nowadays and has evolved to become a worldwide health threat. Antimicrobial resistance is an important concern for the public health authorities at the global level. However, in developing countries like India, recent hospital and some community-based data showed an increase in the burden of antimicrobial resistance. Research related to antimicrobial use, determinants and development of antimicrobial resistance, regional so now there is lots of research and study required to sustain and defeat new resistant strains of bacteria and fungus so nicotinamide derivatives, an important class of heterocyclic derivative has attracted more and more.

Attention in the field of antibacterial antifungal and pesticide also in continuation of our previous work in Naphtho [2,3-d] imidazole chemistry. We have now synthesized some novel heterocyclic compounds containing the N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl) moiety fused with a pyridine amides and tested their antimicrobial, antifungal activities.

MATERIALS AND METHODS

All used chemicals were purchased from Spectrochem and Alfa Acer Company. Melting points were determined on the open capillary tube. The NMR spectra's were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referred to the internal standard tetramethylsilane (TMS).The mass spectra were recorded on a JEOLJMS-D300 spectrometer

operating at 70eV. Reactions were monitored by thin layer chromatography using silica gel F254 aluminum sheets (ethyl acetate/ n-hexane, 3:1).

EXPERIMENTAL

Synthesis of Comp 2 (4-(1H-naphtho[2,3-d]imidazol-2-yl)aniline)

The synthetic strategy leading to the target compounds 1 are illustrated in scheme1. Synthesized by equimolar quantities (0.01mol) of 2,3 naphthalene diamine, *p*-aminobenzoic acid (0.01mol) in polyphosphoric acid (PPA) (20mL) was refluxed at 170ºC for 2 hrs. The mixture is cooled and diluted with water and quenched by 10% NaOH, an aqueous layer was extracted with EtOAc. The organic layer was separated dried over Na_2SO_4 and concentrated to afford the desired compound as brown colored free flow solid. Obtained compound was purified by column chromatography as 4-(1H-naphth o[2,3-d]imidazol-2-yl)aniline Yield 59%; MP 209-212^{o}C DM-259+1

General method of Synthesis of Comp (3a-3e)

N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl) isonicotinamide

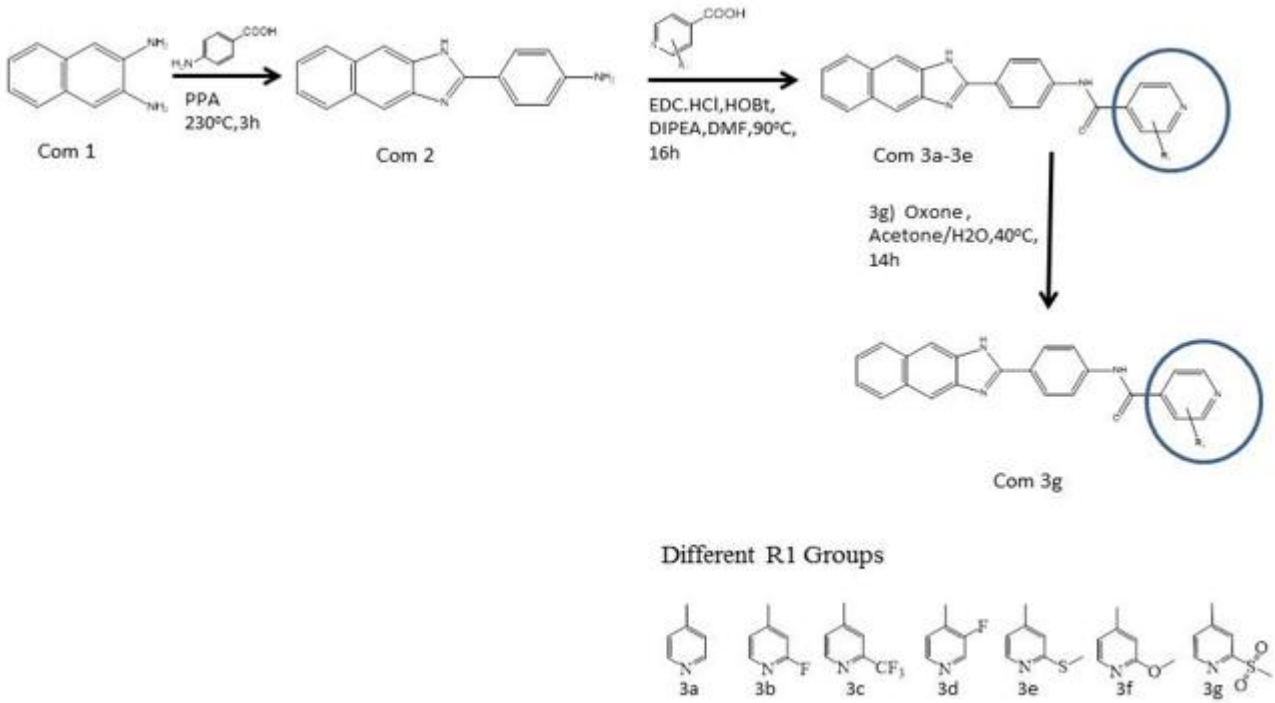
A compound 24-(1H-naphtho [2,3-d]imidazol-2-yl) aniline e (0.01mol) and was dissolved in DMF in two neck or single neck round bottom flask under nitrogen atmosphere and then added EDC. HCl (1.5 eq) followed by HOBt (1.5 eq) of and different isonicotinic acid (a – e) then base as DIPEA (3.0 eq) was added and reaction mix was refluxed for16 hr. Their action mixture was cooled, added ethyl acetate and washed with ice-cold water and brine sole (20X3) organic layer was separated washed again with brine, dried over Na_2SO_4 and concentrated and purified by column chromatography obtained solid was recrystallized from ether: pentane as the desired comp (3a-3e).

N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(methylsulfonyl) isonicotinamide

A compound 3eN- (4-(1H-naphtho [2,3-d]imidazol-2-yl) phenyl)-2-(methylthio) isonicotinamide (0.01mol) and was dissolved in Acetone in two neck or single neck round bottom flask under nitrogen atmosphere and then added oxone (2.5 eq) in H_2O and was stirred for16 hr. Their action mixture was concentrated & added ethyl acetate and washed with water and brine sole (20X3). The organic layer was separated washed again with

brine, dried over Na_2SO_4 and concentrated and purified by column chromatography obtained solid was recrystallized from DCM: pentane as the desired comp (3f).

Synthetic Scheme



RESULTS AND DISCUSSION

Spectral Data

4-(1H-naphtho [2,3-d]imidazol-2-yl) aniline(2)

Brown Solid, Yield 59%, M.P: 209-212ºC, ^{1}HNMR data (DMSO) δ(ppm) aromatic protons -7.31-7.33 (dd, 2H), 7.69-7.70 (dd, 2H), 6.70-6.61 (s, 2H), 7.95-7.93 (d, 4H), NH 12.56 (bs , 1H), NH_2 5.7 (s,2H) , MS: m/z 259(M^+)

3a-3e

N-(4-(1H-naphtho [2,3-d] imidazol-2-yl) phenyl)isonicotinamide(3a)

Off white solid, Yield 29%, M.P.: 221-223ºC, ^{1}HNMR data (DMSO) δ (ppm) aromatic protons -7.69-7.20 (dd, 2H), 7.70-7.75 (s, 2H), 8.11-8.15 (d, 2H), 8.01-8.10 (s, 4H), 8.15-8.21 (dd, 2H), 8.75-8.82 (dd, 2H), NH 12.56 (bs , 1H), NH 11.06 (bs , 1H),

MS: m/z 365(M+1)

N-(4-(1H-naphtho [2,3-d]imidazol-2-yl)phenyl)-2-fluoroisonicotinamide (3b)

Pale yellow solid, Yield 39%, M.P. 230-233ºC, ^{1}HNMR data (DMSO) δ (ppm) aromatic protons -7.39-7.30 (dd, 2H), 7.70-7.75 (s, 2H), 8.02-8.10 (d, 2H), 7.91-8.10 (s, 4H), 7.76-8.21 (s, 1H), 8.31 (d, 1H), 8.5 (d, 1H), NH 12.56 (bs , 1H), NH 10.86 (bs , 1H), MS: m/z 383(M+1)

N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(trifluoromethyl) isonicotinamide (3c)

Off white solid yield 62%, M.P. : 221-223ºC, ^{1}HNMR data (DMSO) δ (ppm) aromatic protons -7.39 (s, 2H), 7.78-7.79 (d, 2H),7.9(d, 2H), 8.01(s, 4H), 8.16(d, 1H), 8.36 (s,1H), 9.07 (d,1H), NH 9.13 (bs , 1H), NH 10.6 (bs , 1H), MS:m/z 433(M+1)

N-(4-(1H-naphtho [2,3-d]imidazol-2-yl)phenyl)-3-fluoroisonicotinamide (3d)

Off white solid, Yield 52%, M.P. :221-223ºC, ^{1}HNMR data (DMSO) δ (ppm) aromatic protons -7.38 (s, 2H), 7.74 (d, 2H),7.9 (dd, 2H), 8.0 (s, 4H), 8.3 (d, 1H), 8.6 (d,1H), 8.8 (s,1H), NH 13.06 (bs , 1H), NH 10.99 (bs , 1H), MS: m/z 383 (M+1)

N-(4-(1H-naphtho [2,3-d]imidazol-2-yl)phenyl)-2-(methylthio)isonicotinamide (3e)

Brown colour solid, Yield 50%, M.P.:200-203ºC, ^{1}HNMR data (DMSO) δ(ppm) aromatic protons -7.38 (s,2H), 7.75 (d,2H), 7.9 (dd,2H), 8.013 (s,4H), 7.35 (d, 1H), 8.6 (d,1H), 7.8 (s,1H), CH_3 S 2.5 (s , 3H), NH 13.06 (bs , 1H), NH 11.06 (bs , 1H) ,MS: m/z 412(M+1)

N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-methoxyisonicotinamide (3f)

White solid, Yield 79%, M.P.:230-233ºC,^{1}HNMR data (DMSO) δ (ppm)aromatic protons -7.35 (s, 2H), 7.70 (d,2H), 8.00 (dd, 2H), 8.10 (s, 4H), 7.26 (s, 1H), 8.16 (d,1H), 7.1(d,1 H), CH_3O 3.39 (s , 3H), NH 12.10 (bs , 1H), NH 11.10 (bs , 1H),

MS: m/z 395(M+1)

N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(methylsulfonyl)isonicotinamide (3g)

Off white yellowish solid, Yield 39% M.P.:222-223ºC,^{1}HNMR data (DMSO) δ (ppm) aromatic protons --7.38 (s, 2H), 7.75 (d, 2H), 7.91 (dd, 2H), 8.013 (s, 4H), 6.64 (d, 1H), 8.0

(d,1H), 9.07 (s,1H), CH_3S 3.39 (s , 3H), NH 12.06 (bs , 1H), NH 11.06 (bs , 1H), MS: m/z 443 (M+1)

Biological Evaluation:

Antimicrobial and Antifungal Activity

General method for the preparation of cultural media

The antimicrobial activities of some of the synthesized compounds were determined by the agar diffusion method, Nutrient agar (antibacterial activity) and sabouraud's dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121ºC and 15 Ibs for 20 min) and transferred to previously sterilized Petri dishes (9 cm in diameter). After solidification, Petri plates were inoculated with bacterial organisms in sterile nutrient agar medium at 45ºC, organisms in sterile sabouraud's dextrose agar medium at 45ºC in aseptic condition. Sterile Whatman filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 10µg/ml and 30µg/ml were placed in the organism-impregnated Petri plates under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic discs of streptomycin and fusidic acid (10µg /ml) as std were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 ± 1ºC for antibacterial activity and 48 h at 37±1ºC for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around each disc. The synthesized compounds were screened for both antifungal and antimicrobial activity by the zone of inhibition method. Antibacterial activity was observed for all the compounds using two strains of Gram (-ve) bacteria *Pseudomonas* sp and *Escherichia coli* (-ve). The concentrations taken were 10 µg/ml.for antifungal activity against *Aspergillus niger*, *Penicillium* spat same concentration 10 µg/ml. All above-synthesized nicotinamide compound shows moderate antifungal and antibacterial activity against respective stains. Some show little bit less than positive control and some shows higher.

Table 1 Antimicrobial activity of synthesized compound

Standard as streptomycin and Fusidic acid

	Antibacterial		**Antifungal**	
Compounds No.	*Pseudomonas* sp (+ve).	*Escherichia coli* (-ve).	*Aspergillus niger*	*Penicillium* sp
3a	2.0	1.5	1.6	1.9
3b	2.5	2.6	2.0	1.5
3c	2.4	2.3	2.1	1.8
3d	2.7	2.6	2.3	2.0
3e	2.1	2.3	2.5	3.1
3f	1.6	1.5	1.2	2.0
3g	2.6	2.5	2.6	2.9
Streptomycin	3.9	3.5	-	-
Fusidic acid	-	-	4.1	4.5

CONCLUSION

Synthesis of pyridine amides derivatives with naphtho[2, 3-d] imidazoles can be effective for antibacterial and antifungal activity.

ACKNOWLEDGMENT

The authors are grateful to the Principal of K.T.H.M. College, Nashik, and Principal of S.M.B.S.T. College, Sangamner, Ahmednagar.

REFERENCES

1. Rao V., Suresh M. ,(2010), Der Pharmacia Letter, 2, 393-402.
2. Ghose A., Viswanadhan V., Wendoloski J., Comb (1999), J. Chem., 1,55-68.
3. Christian A., Montalbetti., (2005), Tetrahedron, 61,10827-10852.
4. Sherman A.R., Bicyclic 5-6 systems: two heteroatoms 1:1, In; Katrizky A.R., Ramsden C.A., Seriven E.F., Taylor R.J., (2008), Comprehensive Heterocyclic Chemistry 10, 263-338.
5. Sherman A.R., Bicyclic 5-6 systems: two heteroatoms 1:1, In; Katrizky A.R., Ramsden C.A., Seriven E.F., Taylor R.J.,(1996), Comprehensive Heterocyclic Chemistry 7,167-227.

6. Kawakami K., Takahashi H., Ohki H., Kimura K. ,Miyauchi S., Miyauchi R., Takemura M., (2008), Chem. Pharm. Bull. 48, 1667-1672.
7. Ledoossal B., Boazard B. ,Coroneos E.,(1992), J. Med. Chem., 35, 98-200.
8. Bobosik V.,Krutosikova A., Jordis U., Montash C., Chem. 1995 ,126 , 747-752.
9. Krutosikova A., Sleziak R. ,Collect. Czech. (1996), Chem. Commun. 61, 1627-1636.
10. Gajdos P., Miklovic J. ,Krutosikova A. ,Khim.,(2006), Geterotsikl. Soed, 6, 823-831.
11. Mojumdar S.C., Miklovic J., Krutosikova D., Valigura Steward J.M.,Therm (2005), J. Anal. Cal. 281 , 211-215.
12. Budova M., Fojtikova K., Miklovic J., Mrazova B., Horvath A., Krutosikova A. ,(2006), Chem. Pap. 620, 231-236.
13. Bradiakova I., Pronayova N., Gatial A., Krutosikova A.,(2008), Chem. Pap., 2008 , 62 , 428-434.
14. Bradiakova I, Durcekova T., Pronayova N., Gatial A., Krutosikova A., (2009), Chem. Pap., 63, 586-591.
15. Tarabova D., Titis J., Pronayova N., Gatial A., Krutosikova (2010), ARKIVOC 9 , 269-281.
16. Hrasna M., Urgeova A., Krutosikova A., Nova Biotechnological et (2012), Chimica, 11 -1, 73-85.
17. Gregory H., Chang N., Lyotropic J.,(20060, Journal of Soft Mater 2, 889-891.
18. Abdul J., Kh Atia (2009), Molecules 14 ,2431-2446.
19. Sharba A.,(2005), Molecules 10 , 1153-1160.
20. Nguyen H., Destrade C.,(1997), Advanced Materials 9, 375-388.
21. Bowden K., Izadi J.,(1997), Journal of Medicinal Chemistry 32, 995-1000.
22. Amar A.E.,(2000), Indian J. Heterocyclic Chem.10, 49-58.
23. Attia A., Abdel-Salam O.A., Amr, A.E., Stibor I., Budesinsky M., Egypt.(2000), J. Chem. *43*, 187–201.
24. Nehad A.A., Amr A.E., Alhusien A.I., (2007), Monatsh. Chem. 138.
25. Bai G.H., Gregory S., Rev Phytopathol (2004), 42:135–161.
26. De Wolf E.D., Madden L.V., Lipps P.E. Phytopathol (2003), 93:428–435.
27. Komori T., Ujita S., Inoue T., Chem .Abstr. (2010) , 154: 64642.
28. Kozlevcar B., Leban I., Turel I., Segedin P, Petric M., Pohleven F., White Andrew J.P., Williams D.J., Sieler J., Polyhedron (1999) , 18: 755–762.559–567.
29. Hawkey P. M., Lewis D.A.(1994), Medical Bacteriology-A Practical Approach Oxford University Press., United Kingdom 181-194.
30. Jitender S.S., Rishi S.H., Vipin K., (2002), J. Ind. Inst. Sci., 82:177-182.
31. Kohara Y., Kubo K., Immamiya E., wada T., Inada Y., Naka T., (1996), J. Med. Chem., 39, 5228-5235.
32. Khyati A.P., Paresh S.O., Bhatt S.B., Parikh A.R., (2000), Ind. J.Chem., 39B, 716-718.
33. Nare B., Prichard R.K., Georges E., (1994), Bio. Chem. Pharmacol, 48: 2215-2222.
34. Shiva P.S., Surendra S.P., Krishna R., Virgil I.S., (1981), Chem. Rev., 81, 175-203.