EUROPEAN ACADEMIC RESEARCH, VOL. I, ISSUE 8/ NOVEMBER 2013
ISSN 2286-4822, www.euacademic.org
IMPACT FACTOR: 0.485 (GIF)
DRJI VALUE: 5.9 (B+)

Antibacterial and Antifungal Profile of 2-(2´-Pyridyl) Benzimidazole Derivatives

ARFA KAMIL
Department of Pharmaceutical Chemistry
Federal Urdu University of Arts Sciences and Technology
Gulshan-e- Iqbal Campus, Karachi
Pakistan
SHAMIM AKHTAR
Department of Pharmaceutical Chemistry
University of Karachi, Karachi
Pakistan
MEHWISH FARRUKH
Department of Pharmaceutical Chemistry
Federal Urdu University of Arts Sciences and Technology
Gulshan-e- Iqbal Campus, Karachi
Pakistan
SOHAIL HASSAN
Department of Pharmaceutical Chemistry
University of Karachi, Karachi
Pakistan
SARWAT JAHAN
Department of Pharmaceutical Chemistry
Federal Urdu University of Arts Sciences and Technology
Gulshan-e- Iqbal Campus, Karachi
Pakistan

Abstract:

Benzimidazoles are an important class of compounds with a wide spectrum of biological activity. The five membered heterocyclic moieties also confer for various biological activities. Hence a series of 2-(2´-pyridyl) benzimidazole derivatives have been synthesized and investigated their antibacterial and antifungal properties. The synthetic analogs were characterized by UV, IR and ^{1}H NMR spectral data.

Key words: Heterocycles, Antibacterial, Antifungal, Pharmacological activities.

Introduction

Heterocycles form by far the principal divisions of organic chemistry and are of enormous significance biologically and industrially. One prominent structural feature intrinsic to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Heterocycles are present in a wide variety of drugs, mostly vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, antimicrobial, antibacterial, antifungal, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals [1].

Several thousands of benzimidazole analogs have been synthesized and screened for pharmacological activity. They are of wide interest because of their diverse biological activity and clinical applications and have different activities as they can act as bacteriostats or bactericides, as well as fungicides [2-6], and they are present in numerous, antiparasitic, antitumoral and antiviral drugs [7-8], in the antiprotozoal activity [9]. It was shown that they have a moderate *in vitro* anti-HIV activity [10].

In this context, the aim of the present work is to investigate the quantitative effect of structural properties of the series of 2-(2´-pyridyl) benzimidazole derivatives on their antibacterial activity against Gram negative bacteria.

Materials and Method:

Agar well diffusion method

Media Preparation

Three types of media were used: Solid medium (Nutrient agar), Liquid medium (Nutrient broth), semi-solid medium (Soft agar). The medium was dissolved and autoclaved at 121 ^{o} C for 15 min then cooled up to 45 ^{o} C and poured 40-50 mL media in sterile 14 cm diameter petri dishes. The medium was then solidified and kept at room temperature to check the sterility of the prepared media. The broth was dissolved and dispensed approximately 3mL nutrient broth in screw capped test tubes and autoclaved at 121 ^{0} C for 15 minutes and then refrigerated.

Determination of Antifungal Activity

The compounds were tested for antifungal activity by Agar tube dilution method [11].Growth in the compound amended media was determined by measuring linear growth (mm) and growth inhibition calculated with reference to the negative control. The test compounds were evaluated for the antimicrobial activity by disc diffusion method. Different Gram negative and Gram-positive organisms were seeded over previously sterilized nutrient agar. The zones of inhibition were measured around the dried discs of Wattman containing l0µl of the test sample. Blank discs containing DMSO were used as control. The plates were incubated at 37°C for 24 hours. The formula used to determine % Inhibition of fungal growth

$$\% \text{ Inhibition} = 100 - \text{linear growth in test (mm)} / \text{linear growth in control (mm)} \times 100$$

General Method of Synthesis

2-(2´-pyridyl) benzimidazole (Ia) and corresponding substituted phenacyl halides in equimolar quantities (0.01mole) were dissolved in 15-20 mL acetone separately in conical flask and mixed together in a round bottom flask. The reaction mixture was stirred on magnetic stirrer for four hrs. and then refluxed on water bath for about 5 to 6 hrs. Completion of reaction was monitored by TLC. The resulting precipitates of products were filtered and washed with warm acetone to remove the unreacted starting material. The precipitates of each product were re-crystallized at least three times to ensure purity and to improve color and shape of crystals. The pure compounds were dried in vacuum desiccators over anhydrous calcium sulphate.

Results

The results were presented in the Table-1 and 2. It was observed that the synthetic analogs possess antibacterial and antifungal properties.

Table – 1: *In vitro* antibacterial activity of compound 2-(2´-pyridyl) benzimidazole and its derivatives against various strains of bacterial organisms

Name of Bacterial Strains	zone of inhibition (mm)												
	Imipenem	Parent **(Ia)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Escherichia coli	35	Nil	-	-	-	-	-	-	N.T	-	-	-	-
Bacillus. subtitlis	30	Nil	-	-	28	-	-	-	N.T	-	28	-	21
Staphylococcus aureus	30	Nil	-	-	26	-	-	-	N.T	-	26	-	-
Shigella flexenari	30	Nil	-	-	30	-	-	20	N.T	-	30	-	19
Pseudomonas. aureginosa	31	Nil	-	-	-	-	-	-	N.T	-	-	-	-
Salmonella. typhii	25	Nil	-	-	26	-	-	22	N.T	-	27	-	20

Activity Key:

- = No activity
13-15 (mm) = Low Activity
Above 18 (mm) = Significant Activity
9-12 (mm) = Non-significant
16-18 (mm) = Good Activity
N.T = not tested

Table – 2: *In vitro* antifungal activity of compound 2-(2´-pyridyl) benzimidazole and its derivatives against various strains of antifungal organisms

Name of Fungal Species	Std. drugs		Zone of inhibition (%)											
			Parent (Ia)	1	2	3	4	5	6	7	8	9	10	11
Candida albicans	Miconazole	110	0	0	0	0	0	0	0	N.T	0	0	0	0
Aspergillus flavus	Amphotericin B	24	0	0	45	50	0	20	60	N.T	50	0	70	57
Microsporum canis	Miconazole	97	0	0	65	70	0	30	0	N.T	60	0	75	70
Fusarium solani	Miconazole	85	0	0	75	70	0	50	40	N.T	65	0	60	65
Candida glabrata	Miconazole	100	0	0	0	0	0	0	0	N.T	0	0	0	0

Activity Key:

Below 30% inhibition = no activity
30-40 % inhibition = low activity
50-60% inhibition = moderate activity
60-70% inhibition = good activity
Above70% inhibition = significant activity
N.T = not tested

Discussion

Antibacterial Activity

Antibacterial activities of the new derivatives of 2-(2´-pyridyl) benzimidazole (Ia) by agar well diffusion method have been observed[12]. From the table, it was evident that the parent compound (Ia) exhibited no activity while some of its derivatives displayed encouraging antibacterial results when tested against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aureginosa, Salmonella typhii and Shigella flexenari.* The results indicated that compounds 3 and compound 9 showed highly significant activity against *Staphylococcus aureus*, while the same compounds exhibited significant activity against *Shigella flexenari, Staphylococcus aureus* and *Salmonella typhii.* Compound 6 showed significant activity against *Staphylococcus aureus* and *Salmonella typhi*

and the compound 11 exhibited significant activity against *Shigella flexenari, Pseudomonas aureginosa.*

The antibacterial results given by compound 3 and 9 were comparable. Compound 3 contained chloro group and compound 9 had phenyl group at *para* position in the phenyl moiety. It seemed that both these functional groups might be responsible to impart antibacterial activity to the parent molecule at the same level.

Antifungal Activity

The compound were screened against five fungal strains i.e., *Aspergillus flavis, Candida albican*, *Microsporum canis, Fusarium solani, Candida glabrata* at the concentration of 200µg/mL. The zone of inhibition was presented in percent in comparison to standard drugs i.e., Miconazole and Amphotericin B.

The results of antifungal bioassay were reported in Tables 1 and 2 which indicated that the parent nucleus did not possess any antifungal activity against the tested strains of fungi. While most of its derivatives produced good to moderate results and only one derivative (compound 2) significantly killed *Fusarium solani.* It was also found that all the derivatives showed no activity against *Candida albicans* and *Candida glabrata.* Compounds 2, 3, 5 6, 8, 10 and 11 showed lower to moderate antifungal activity.

Conclusion

The conclusion to be drawn from the present study is that the out of the eleven (11) derivatives of 2-(2´-pyridyl) benzimidazole four compounds showed activity against the tested antibacterial strains and seven (7) compounds showed antifungal activities.

BIBLIOGRAPHY

Akbay, A., I. Oren, A.O. Temiz, S.E. Aki, and I. Yalcin. 2003. "Synthesis and HIV-1 Reverse Transcriptase Inhibitor Activity of Some 2,5,6-Substituted Benzoxazole, Benzimidazole and Oxazolo(4,5-b) Pyridine Derivatives." *Arzneim.Forsch/Drug Res.* 53: 266-271. [10]

Ayhan K.G., and N. Altanlar. 2006. "Synthesis and Antifungal Properties of Some Benzimidazole Derivatives." *Turk. J. of Chem*. 30: 223-228. [6]

Blank H., and G. Rewbell. 1965. "Griseofulvin-containing medium for simplified diagnosis of dermatophytosis." *Archives of Dermatological Research* 92: 319-322. [11]

Boiani M., and M. Gonzalez. 2005. "Imidazole and Benzimidazole Derivatives as Chemotherapeutic Agents." *J. Med. Chem*. 5: 409-424. [7]

Carron R. A., J. M. Maran, L. Montero, Fernandozaigo, and A.A. Dominguez. 1987. "Synthesis, characterization and biological studies of tri- and diorganotin(IV) complexes with 2',4'-difluoro-4-hydroxy-[1,1']-biphenyl-3-carbolic acid: Crystal structure of $[(CH_3)_3Sn(C_{13}H_7O_3F_2)]$." *Plantes Medicinales Phytotherapic.* 21:195-202. [12]

Garuti L., M. Roberti, and C. Cermelli. 1999. "Synthesis and Antiviral Activity of Some N Benzenesulphonyl-benzimidazoles." *Bioorg. & Med. Chem. Lett.* 9: 2525-2530. [8]

Goker H., and M.S. Yildiz. 2000. "Synthesis and Potent Antimicrobial Activity of Some Novel N-(Alkyl)-2-Phenyl-1H-Benzimidazole-5-carboxamidines." *Molecules* 10: 1377-1386. [2]

Kazimierczuk Z., J.A. Upcroft, P. Gorska, A. Starosciak, and B.A. Laudy. 2002. "Synthesis, Antiprotozoal and Antibacterial Activitiy of Nitro- and Halogeno-Substituted Benzimidazole Derivatives." *Acta Biochimica Polonica* 49: 185-195. [9]

Nguyen P.T.M., O.J.D. Baldeck, and J.R.E. Marquis. 2005. "Antimicrobial Actions of Benzimidazole against Oral Streptococci." *Oral Microbiol. and Immunol*. 20: 93-99. [3]

Podunavac K., S.O. Leovac, J.V.M. Perišić, N.U. Rogan, and J. Balaz. 1999. "Complexes of Cobalt (II), Zinc (II) and Copper (II) with Some Newly Synthesized Benzimidazole Derivatives and their Antibacterial Activity." J. *Ser Chem Soc.* 64: 381-388. [4]

Podunavac K., and S.O.D. Cvetković. 2007. "Antibacterial Evaluation of Some Benzimidazole Derivatives and Their Zinc (II) Complexes." *J. Ser Chem Soc.* 75:459-466. [5]

Valverde M.G., and T. Torroba. 2005. "Sulfur-Nitrogen Heterocycles." *Molecules* 10: 318-320. [1]