Research Paper

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Synthesis of 6-Aryl Benzimidazo[1,2-C] Quinazoline Derivatives and Their Antimicrobial Evaluation

Pharma

KEYWORDS : 6-arylbenzimidazo[1,2-c]quinazoline, synthesis, antibacterial and antifungal screening.

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ABSTRACT

Benzimidazo[1,2-c]quinazoline is a fused heterocyclic ring structure which is said to have many pharmacological properties. In this current study we intended to synthesis few derivatives of 6-aryl benzimidazo [1,2-c]quinazoline and study their antimicrobial property against Escherichia coli, Salmonella paratyphi, Staphylococcus aureus, and Bacillus subtilis using ciprofloxacin as antibacterial standard, and against Aspergillus niger and Candida albicans using clotrimazole as antifungal standard. The intended derivatives were synthesized by heating the substituted acid chlorides with 2-(2-aminophenyl) benzimidazole.The structures of the synthesizedBenzimidazo[1,2-c]quinazoline were established by IR and 1H-NMR analysisand studied for antimicrobial activity by well diffusion method in the agar plate.The antimicrobial effectiveness was determined by measuring the zone of inhibition around well. The synthesized compounds were effective against Candida albicans species and showed very poor activity against the other studied organisms.

INTRODUCTION

Benzimidazole nucleus is the key building block for variety of compounds. This nucleus plays crucial roles in the function of number of biologically important molecules. Benzimidazoles are a group of molecules which have shown application in a variety of pharmacological targets and hence there is a growing interest over the past years for the synthesis of benzimidazole based heterocycles. Substituted benzimidazole derivatives have therapeutic values like antimicrobial (1,2), antioxidant (3), antiviral, antihypertensive, antiprotozoal, analgesic, anti-inflammatory (4), molluscicidal, antitumor (5,6,7) and antihyperglycemic (5).

These are few examples for benzimidazole-based polyheterocycles, exhibiting biological properties. Benzimidazo quinazolines, benzimidazo isoquinolines and benzimidazo[2,1-a]isoindolones were reported as potent antitumor agents. Benzimidazo[2,1-b]quinazolines are potent immuno-suppressors and benzimidazo[2,1-b]benzo[f]isoquinoline ring system is present in pharmacologically active compounds. Isoindolo[2,1-a] benzimidazoles are also known to be sedatives and tranquilizers (8).

Our aim in this study is to synthesis and evaluate antimicrobial property of few benzimidazo [1,2-c] quinazoline derivatives.

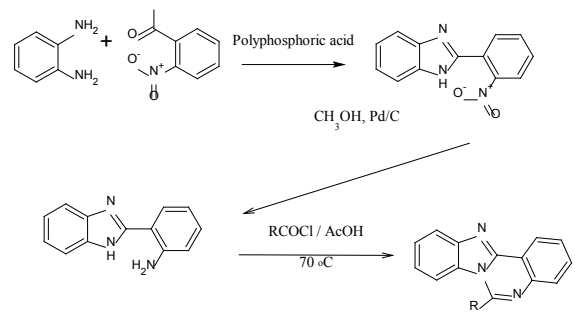
MATERIALS AND METHODS

All the chemicals required for the synthesis were purchased from Sigma Aldrich and stored according to the instructions specified.

In the presence of polyphosphoric acid, orthophenylene diamine was treated with 2-nitrobenzoic acid and was heated to 150°C for 16 hrs. After completion of reaction, the mixture was slowly basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was separated and dried over sodium sulphate and concentrated to residue stage. (2,8,9) The crude product obtained was then treated with palladium for reduction of nitro to amino group.

Synthesis of substituted 6-aryl benzimidazo[1,2-c]quinazolines:

Synthetic pathway followed is represented in Fig 1. To a stirred solution of 2-(2-aminophenyl) benzimidazole (100mg), substituted acid chloride (0.574mmol) in glacial acetic acid (2mL) was added and placed on water-bath at 60-70 °C for 16hr (10). After completion of reaction, glacial acetic acid was removed under high vacuum. The crude compound was purified by column chromatography. The desired product was eluted at gradient elution of 40-50% of hexane in ethyl acetate.



R = 2,4-dichlorophenyl; 3,5-dichlorophenyl; 2,6-dichlorophenyl

Fig . 1: Scheme for synthesis of benzimidazo[1,2-c]quinazoline

For all the obtained products, The mass spectra were recorded on a Agilent LC-MS, FT-IR spectra were recorded between 4000 cm-1 to 400 cm-1 wavenumbers. The 1H- nmr spectra were run on a Bruker AV III 500 spectrometer operating at 500 MHz using dimethyl sulfoxide-d6 as solvent and tetramethylsilane as internal standard.

Antimicrobial screening:

The screening was done by well diffusion method in agar plates. The derivatives were studied against *Escherichia coli, Salmonella paratyphi* (gram negative), *Staphylococcus aureus, Bacillus subtilis* (gram positive) bacterial strains using ciprofloxacin as standard. The antifungal activity was studied against *Candida albicans, Aspergillus niger* using clotrimazole as standard. Each of all the inoculated petri plates was divided into 4 equal quadrants. In each quadrant wells were made with the help of cork borer of 4 mm size. Using micropipette about 100 µg of test concentration and 10 µg of the standard concentration was added into their respective quadrant wells. The plates were then placed under room temperature for the diffusion to occur. After one hour the plates were incubated at 37°C for 24 hours (10). The zone of inhibition was observed, measured and reported.

RESULTS AND DISCUSSION

Synthesis of the compounds was done by treating 2-(2-aminophenyl) benzimidazole with substituted acid chlorides in presence of glacial acetic acid and obtained the products at the

percentage yield of about 60 - 72 %. The desired product was eluted by column chromatography using 40 – 50 % of hexane in ethyl acetate by gradient elution technique. Melting points of the compounds were determined using DSC technique and were found to be in the range of 225 – 249 °C. Characterization of the obtained products were done by IR, NMR and MS spectroscopy techniques and mentioned in Table 1. Characteristic IR peak for benzimidazoquinazoline ring structure was observed around the wave numbers 3050, 1450, 1050, 1500 cm-1. The halogen peaks were around 760 cm-1. The 1H NMR spectra also showed the aromatic protons of various environments, as multiplets in the range of δ 7.28-8.89 ppm. The compounds reflected their molecular mass in the ESI-MS spectra as a single peak.

Table 1: Spectral characterization data of the synthetic derivatives

	Yield (%)	FT-IR (cm^{-1})	^{1}H NMR (ppm)	MASS (m/z)
6-(2,4-dichlorophenyl)-benzimidazo[1,2-c] quinazoline	60.9	3070 - Aromaric C-H 1474 - C=N 1051 - C-N 785, 771 - C-Cl 1584, 1553, & 1527 - Aromatic C=C	8.06 - 8.12 (1H,m,Ar) 7.94 – 8.05 (3H,m,Ar) 7.82 – 7.72 (4H,m,Ar) 7.46 – 7.58 (3H,m,Ar)	362.44 (ES-)
6-(3,5-dichlorophenyl)-benzimidazo[1,2-c] quinazoline	71.83	3062 - Aromaric C-H 1491 - C=N 1055 - C-N 762, 749 - C-Cl 1593, 1549, & 1535 - Aromatic C=C	8.78 – 8.89 (1H,m,Ar) 8.12 – 8.19 (3H,m,Ar) 7.82 – 7.95 (1H,m,Ar) 7.71 – 7.84 (1H,m,Ar) 7.61 – 7.72 (1H,m,Ar) 7.42 – 7.58 (1H,m,Ar) 7.28 – 7.31 (3H,m,Ar)	364.10 (ES+)
6-(2,6-dichlorophenyl)-benzimidazo[1,2-c] quinazoline	64.9	3014 - Aromaric C-H 1448 - C=N 1086 - C-N 784,754 - C-Cl 1582, 1563 & 1495 - Aromatic C=C	7.98 – 8.06 (1H,m,Ar) 7.74 – 7.91 (3H,m,Ar) 7.64 – 7.78 (4H,m,Ar) 7.45 – 7.49 (3H,m,Ar)	362.39 (ES-)

The antimicrobial screening was done by well diffusion method. The dosage of standards and samples studied were 10µg/well and 100µg/well respectively. The size of zone of inhibition of samples was compared with that of the size of zone of inhibition of standard and the results are tabulated in Table 2.

All the three derivatives showed more than 50% zone of inhibition, compared with Clotrimazole, only against *Candida albicans*, whereas they showed less than 50 % zone of inhibition against all the other organisms studied. The MIC was determined by serial dilution method (11) for all the synthetic substances against *Candida albicans*.

Table 2: Zone of inhibition (measured in mm) of the synthetic compounds

Derivatives	E.coli	S.paratyphi	S.aureus	B.subtilis	C.albicans	A.niger
6-(2,4-dichlorophenyl)-benzimidazo[1,2-c]quinazoline	8	4	12	8	9	7
6-(3,5-dichlorophenyl)-benzimidazo[1,2-c]quinazoline	7	8	18	11	8	8
6-(2,6-dichlorophenyl)-benzimidazo[1,2-c]quinazoline	11	9	16	10	9	8
Ciprofloxacin	33	40	40	37	-	-
Clotrimazole	-	-	-	-	10	27

CONCLUSION

We conclude that 6-dichloroaryl benzimidazo[1,2-c] quinazoline derivatives were synthesized with a moderate yield and the derivatives synthesized showed good antifungal property against *Candida albicans*. *Aspergillus niger* and all the bacterial strains studied were less sensitive to the synthesized compounds. The MIC for the compounds was ranging between 125µg/ml to 250µg/ml.

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