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SYNTHESES, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME NOVEL BENZIMIDAZOLES

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Key words:
Benzimidazole, antibacterial activity, antifungal activity.

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ABSTRACT

Plan: *Present work aims to synthesize a series of new benimidazoles (SBS-a-m) with various substitutions at 2-o-amino phenyl position and to evaluate their in-vitro antibacterial and anti-fungal activity.*

Prologue: *Benzimidazole containing organic compounds forms a significant group of drugs which exhibit an array of biological activities ranging from antibacterial, antifungal, anti-inflammatory, analgesic, anthelmintic activities and so on.*

Methodology: *The starting material SBS was synthesized by microwave irradiation of o-phenylenediamine and anthranilic acid mixture in presence of polyphosphoric acid. SBS was further derivatized to Schiff bases (SBS-a-m) by reacting with various substituted aromatic aldehydes. The in-vitro antibacterial and anti-fungal activity was carried out by the agar diffusion method using Ampicillin and Miconazole nitrate respectively as standards at a concentration of 50µg/0.1ml.*

Outcome: *SBS-k was found to be most active on all the bacteria used and SBS-e showed good activity against both Gram-positive bacteria and moderate activity against both Gram-negative bacteria. No compound showed significant antifungal activity.*

INTRODUCTION

Benzimidazole is a well-known privileged structure in medicinal chemistry, having various biological activities. It is a benzannulated ring system wherein benzene ring is fused with a five member ring system having hetero atom at 1 and 3 positions. It possesses a wide spectrum of biological activities.

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Several substituted and condensed benzimidazoles have been reported to exhibit an array of biological activities which include antimicrobial[1-3], antiviral[4], antiprotozoal[5], anti-hypertensive[6], antiallergic[7], antioxidant, anti-allergic, analgesic, anti-inflammatory[8] activities and so on. Based upon the fact, the present investigation was planned substantial and interest has been shown in the synthesis and characterization of benzimidazole compounds in search of potential drugs.

By and large, in Pharmaceutical field new drugs are discovered by molecular modification of the lead compound of established pharmacological activity. In the current literature survey, it has been observed that drug designed by molecular modification is more rational and productive foundation of new drug, consequently the need to synthesize new molecule as potential medicinal agent is more relevant today.

So far various new benzimidazoles have been synthesized and screened for antimicrobial activity. The enthusiastic results prompted us to continue the investigation. So, an attempt was made to synthesize and screen some novel substituted benzimidazoles for antimicrobial activity. Hence the synthesis of 2-(o-amino) phenyl benzimidazole (SBS) was carried out. The SBS was further derivatized to various Schiff base SBS-a-m by reacting with various substituted aromatic aldehyde (a-m).

MATERIALS AND METHODS

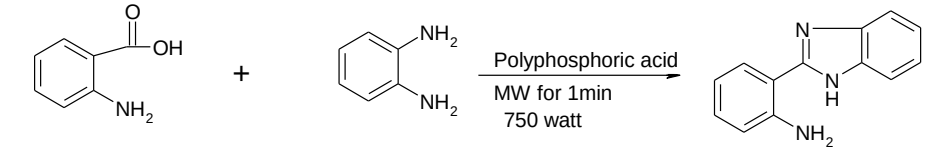
Drugs and Chemicals

The Anthranilic acid, orthophenyline diamine, standard Amoxicillin, Miconazole nitrate, solvents and other chemical used for the study were of analytical grade.

Experimental design

Step 1- Synthesis of 2-(o-amino) phenyl benzimidazole (SBS):

A mixture of anthranilic acid (13.7gm, 0.01mol), o-phenylenediamine (10.8gm, 0.01mol), and polyphosphoric acid (10gm) were properly mixed with a glass rod in a beaker and irradiated in microwave[9-10] oven for 1min at 750 watt. After irradiation, the mixture was cooled to room temperature and ice cold water (100ml) was poured into the mixture and then slowly neutralized with 40% NaOH to P^H 8. The solid obtained was collected by filtration, washed with hot water, dried and recrystallized from ethanol. Yield: 92.87 %. M.P.: 218ºC, IR (KBr):3422.07 (-NH_2); 3260.22 (-NH str); 3067.99(Ar-H str); 1672.37 (C=N); 1659.29 (-NH bend); 1512.05 (Ar C=C); 1172.84 (C-N); 1116.58 (C-C); 923.51 (Ar-H).

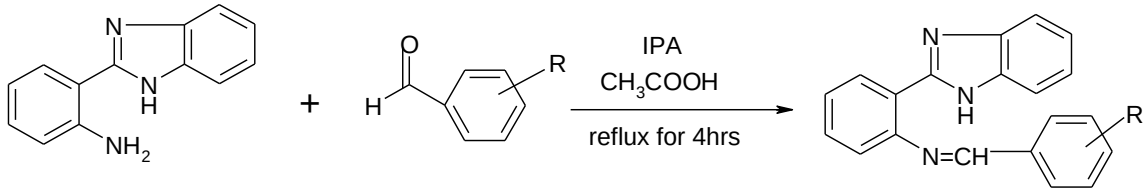


Anthranilic acid o-Phenylene diamine

2-(o-amino) phenyl benzimidazole

(SBS)

Step-II



(SBS) (a-m) (SBS-a-m)

2-(o-amino) phenyl benzimidazole

Various substituted aromatic aldehydes

	R		*R*		*R*		*R*
a	3,4,5-trimethoxy	e	2-chloro	h	4-methyl	k	4-chloro
b	3,4-dimethoxy	f	4-hydroxy	i	H	l	4-methoxy
c	2-nitro	g	4-hydroxy-3-methoxy	j	4-dimethyl amino	m	2-hydroxy
d	3-nitro	-		-	-	-	-

Step 2- Method for the syntheses of 2-[(o-substituted benzylidene) imino] phenyl benzimidazole (Schiff bases) SBS-a-m:

A mixture of the starting compound (SBS) (0.005 mol, 1.045gm) and the required aryl aldehyde (0.005 mol) in isopropanol (30 ml) and catalytic amount of glacial acetic acid (2-5 drops) and was refluxed for 4 hrs. The mixture was cooled to room temperature, the solid separated was filtered, washed with isopropanol and recrystallized with DMF: water mixture (8:2).

In-vitro Antimicrobial activity[1-5] *Antibacterial activity:* [5]

The antibacterial activity was carried out by the agar diffusion method. Here responses of organisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drug used was *Ampicillin* (Ranbaxy).

1. Microorganisms:

The four microorganisms used were *Staphylococcus aureus* (Gram-positive), *Bacillus subtilus* (Gram-positive), *Escherichia coli* (Gram-negative) and *Klebsiella pneumoniae* (Gram-negative).

3. Preparation of test solutions:

Each test compound was dissolved in DMSO to get a concentration of 500 μg/ml. This concentration was used for testing antibacterial activity.

4. Preparation of Nutrient agar media:

A mixture of known quantities of peptone, meat extract, sodium chloride, dextrose and agar was dissolved in 1000 ml of distilled water by heating. The pH was adjusted to 7.4, using a pH meter or by adding either acid or alkali. Finally the medium was sterilized by autoclaving at 121ºC for 15 minutes at 15 lb pressure per square inch. The autoclave was allowed to cool and then the mixture was removed from the autoclave and cooled to 40^0C-45ºC. To this, the fresh culture of bacteria was added and mixed well. Sterile petridishes were numbered and 30ml of media was poured into each petridish and then the media was allowed to solidify. A sterile borer was used to make wells, 5 wells in each petridish. 0.1 ml of test and standard solutions at a concentration of 50 µg/0.1ml and a control having only DMSO were poured into separate wells in each plate. Then the petridishes were covered and set aside for 1hr and then incubated at 37ºC for 24 hrs. Zones of inhibition were observed and measured and the average of three readings was recorded.

5. Preparation of Inoculum:

The suspensions of all the organisms were prepared as per standard procedure. A 24 h old subculture was used for the preparation of bacterial suspension. Suspensions of organisms were made in sterile isotonic solution of sodium chloride (0.9 % w/v).

Antifungal activity: [12-13]

The antifungal activity was carried out by the agar diffusion method. Here responses of organisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drug used in the present work was *Miconazole nitrate (Ranbaxy).*

Microorganisms: The two microorganisms used were *Candida albicans* and *Aspergillus niger*.

3. Preparation of test solutions:

Each test compound was dissolved in DMSO to get a concentration of 500 µg/ml. This concentration was used for testing antifungal activity.

Procedure:

A mixture of known quantities of glucose, peptone and agar-agar was dissolved in 1000 ml of distilled water by heating. The pH was adjusted to 7.4, using a pH meter or by adding either acid or alkali. Finally the medium was sterilized by autoclaving at 121ºC for 15 minutes at 15 lb pressure per square inch. The autoclave was allowed to cool and then the mixture was removed from the autoclave and cooled to 40-45ºC. To this mixture , fresh culture of fungi and Ampicillin at a concentration of 25µg/30ml of the culture medium (to prevent bacterial growth) were added.

Sterile petridishes were numbered and 30ml of media was poured into each petridish and then the media was allowed to solidify. A sterile borer was used to make wells, 5 wells in each petridish. 0.1 ml of test and standard solutions at a concentration of 50 μg/0.1ml and a control having only DMSO were poured into separate wells in each plate. The petridishes were covered and set aside for 1 h and incubated at 28ºC for 2 days. After incubation the results were analyzed by measuring the zones of inhibition. The results were interpreted by comparing with the standard miconazole nitrate. The average of three readings was recorded.

RESULTS

Physical data

Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC on silica gel plates. The solvent system used to carry out the TLC is Benzene: Chloroform at a ratio of 7:3.

Table-1: Physical data of compounds prepared

Compd.	*Molecular formula*	*M.W. (gm)*	*M.P. (°C)*	*R_f Value*	*Yield (%)*
SBS	$C_{13}H_{11}N_3$	209	218	0.65	92.87
SBS-a	$C_{23}H_{21}O_3N_3$	387	249	0.89	71.17
SBS-b	$C_{22}H_{19}O_2N_3$	357	242	0.71	68.35
SBS-c	$C_{20}H_{14}O_2N_4$	342	248	0.87	69.25
SBS-d	$C_{20}H_{14}O_2N_4$	342	254	0.76	61.18
SBS-e	$C_{20}H_{14}N_3Cl$	331	260	0.85	62.96
SBS-f	$C_{20}H_{15}O_2N_3$	313	250	0.68	66.16
SBS-g	$C_{21}H_{17}O_2N_3$	343	259	0.90	65.75
SBS-h	$C_{21}H_{17}N_3$	311	256	0.74	69.84
SBS-i	$C_{20}H_{15}N_3$	297	251	0.72	67.36
SBS-j	$C_{22}H_{20}N_4$	340	237	0.96	59.66
SBS-k	$C_{20}H_{14}N_3Cl$	331	265	0.81	64.35
SBS-l	$C_{21}H_{17}ON_3$	327	233	0.94	70.36
SBS-m	$C_{20}H_{15}O_2N_3$	313	246	0.78	63.66

Spectral data

IR spectra (cm^{-1}) were recorded in KBr on a Shimadzu FTIR-8700 spectrometer.^{1}H NMR (ppm) in DMSO using TMS as reference on Bruker 400 AMX. (Table 3 and Table 4) .

Table 2. IR Spectral data of compounds (KBr) cm^{-1}:

Compound Name	IR Spectral data($c.m^{-1}$)
SBS-a:	3448.22 (-NH str); 3101.56 (Ar-H str); 2801.51 (Ali-CH); 1684.46 (C=N); 1649.94 (N=CH); 1588.12 (Ar C=C); 1551.79 (-NH bend); 1331.94 (C-N); 1234.47 (C-C); 1134.53 (C-O); 846.31 (Ar-H bend).
SBS-b:	3430.52 (-NH str); 3089.99 (Ar-H str); 2983.97 (Ali-CH); 1683.97 (C=N); 1659.09 (N=CH); 1588.15 (-NH bend); 1513.71 (Ar C=C); 1349.09 (C-N); 1270.04 (C-C); 1156.81 (C-O); 884.95 (Ar-H bend).
SBS-c:	3423.67 (-NH str); 3112.18 (Ar-H str); 1686.95 (C=N); 1655.07 (N=CH); 1639.35 (Ar C=C); 1617. 44 (-NH bend); 1551.79 & 1381.34 (N-O); 1197.42 (C-N); 923.84 (C-C); 729.97 (Ar-H bend).
SBS-d:	3411.95 (-NH str); 3054.17 (Ar-H str); 1695.94 (C=N); 1684.46 (N=CH); 1611.78 (-NH bend); 1534.94 (N-O) 1512.53 (Ar C=C); 1352.95 (N-O); 1158.85 (C-N); 935.31 (C-C); 730.32 (Ar-H bend).
SBS-e:	3424.05 (-NH str); 3102.41 (Ar-H str); 1683.97 (C=N); 1649.09 (N=CH); 1610.08 (-NH bend); 1472.30 (Ar C=C); 1254.27 (C-N); 1173.57 (C-C); 833.04 (Ar-H bend); 564.78 (C-Cl).
SBS-f:	3639.62 (-OH); 3433.91 (-NH str); 3066.20 (Ar-H str); 1694.82 (C=N); 1685.72 (N=CH); 1601.96 (-NH bend); 1557.76 (Ar C=C); 1160.70 (C-N); 886.14 (C-C); 731.09 (Ar-H bend).
SBS-g:	3630.57 (-OH); 3448.80 (-NH str); 3094.17 (Ar-H str); 2801.51 (Ali-CH); 1670.25 (C=N); 1654.51 (N=CH); 1570.94 (-NH bend); 1534.94 (Ar C=C); 1300.28 (C-O); 1266.42 (C-N); 1154.78 (C-C); 733.15 (Ar-H bend).
SBS-h:	3432.07 (-NH str); 3067.99 (Ar-H str); 2926.28 (Ali-CH); 1654.51 (C=N); 1639.59 (N=CH); 1551.90 (-NH bend); 1522.53 (Ar C=C); 1163.09 (C-N); 889.97 (C-C); 731.40 (Ar-H bend).
SBS-i:	3431.33 (-NH str); 3126.02 (Ar-H str); 1698.90 (C=N); 1653.82 (N=CH); 1577.89 (-NH bend); 1514.44 (Ar C=C); 1163.22 (C-N); 885.29 (C-C); 730.28 (Ar-H bend).
SBS-j:	3422.32 (-NH str); 3101.56 (Ar-H str); 2825.81 (Ali-CH); 1653.83 (C=N); 1642.29 (N=CH); 1552.05 (-NH bend); 1508.82 (Ar C=C); 1302.55 (Ar C-N); 1221.23 (Ali C-N); 921.91 (C-C); 719.01 (Ar-H bend).
SBS-k:	3422.40 (-NH str); 3102.41 (Ar-H str); 1686.94 (C=N); 1654.42 (N=CH); 1571.90 (-NH bend); 1473.13 (Ar C=C); 1198.58 (C-N); 923.23 (C-C); 833.45 (Ar-H bend); 720.30 (C-Cl).
SBS-l:	3442.80 (-NH str); 3112.18 (Ar-H str); 2836.61 (Ali-CH); 1686.94 (C=N); 1640.54 (N=CH); 1610.08 (-NH bend); 1514.90 (Ar C=C); 1198.90 (C-N); 1031.72 (C-O); 924.84 (C-C); 729.82 (Ar-H bend).
SBS-m:	3630.96 (-OH); 3434.32 (-NH str); 3112.41 (Ar-H str); 1685.72 (C=N); 1638.80 (N=CH); 1601.48 (-NH bend); 1576.81 (Ar C=C); 1163.10 (C-N); 888.03 (C-C); 730.97 (Ar-H bend).

DISCUSSION

In recent years, reagents impregnated on mineral solid support and assisted by microwaves have gained popularity in the synthesis of various heterocyclic compounds like benzimidazoles, triazoles, quinolines, benzofurans, quinazolines etc. This could happen because of their enhanced selectivity, improved reaction rates, associated ease of manipulation and above all, the eco-friendliness of this method.

An array of methods has been established for the syntheses of benzimidazoles. Amongst the synthetic approaches described for benzimidazoles, important one is the synthesis of benzimidazole by microwave irradiation of substituted or unsubstituted o-phenylenediamine and an aldehyde or an acid in the presence of a dehydrating agent like polyphosphoric acid, p-TsOH, alumina- methane-sulfonic acid etc.

Table 3. ^{1}NMR (DMSO) data of compounds δ (ppm)

Compound name	*Spectral data (ppm)*
SBS:	4.49 (s, 2H, NH_2 at i); 6.51 (d,1H, CH at h); 6.98 (s, 2H, CH at f, g); 7.24 (d, 1H, CH at e); 7.45 (s, 2H, CH at b, c); 7.68 (d, 1H, CH at a); 7.82 (d, 1H, CH at d); 12.52 (s, 1H, NH at j).
SBS-j	3.01 (s, 6H, CH_3 at o, p); 6.49 (d, 1H, CH at h); 6.61(d, 2H, CH at m, n); 6.96 (s, 2H, CH at f, g); 7.21 (d, 1H, CH at e); 7.35 (d, 2H, CH at k, l); 7.43 (s, 2H, CH at b, c); 7.66 (d, 1H, CH at a); 7.78 (d, 1H, CH at d); 9.20 (s, 1H, N=CH at i); 12.48 (s, 1H, NH at j).
SBS-k:	6.50 (d, 1H, CH at h); 6.97 (s, 2H, CH at f, g); 7.22 (d, 1H, CH at e); 7.35 (d, 2H, CH at m, n); 7.44 (s, 2H, CH at b, c); 7.52 (d, 2H, CH at k, l); 7.67 (d, 1H, CH at a); 7.80 (d, 1H, CH at d); 9.21 (s, 1H, N=CH at i); 12.51 (s, 1H, NH at j).

Table-4 : *In-vitro* Antibacterial activity data

Comp. Code	R	ZONE OF INHIBITION (mm).*			
		S.aureus	*B.subtilis*	*E.coli*	*K. pneumoniae*
SBS-a	3',4',5'-Trimethoxy	04±0.23	05±0.34	NA	NA
SBS-b	3',4'-Dimethoxy	05±0.45	04±0.42	02±0.12	03±0.12
SBS-c	2'-Nitro	07±0.21	06±0.21	07±0.45	08±0.14
SBS-d	3'-Nitro	08±0.27	07±0.12	08±0.23	07±0.10
SBS-e	2'-Chloro	09±0.41	11±0.23	10±0.15	08±0.32
SBS-f	4'-Hydroxy	05±0.31	04±0.45	NA	NA
SBS-g	4'-Hydroxy,3'-methoxy	05±0.21	07±0.35	NA	NA
SBS-h	4'-Methyl	06±0.34	05±0.13	02±0.34	07±0.41
SBS-i	H	06±0.13	07±0.42	NA	NA
SBS-j	4'-Dimethyl amino	05±0.42	02±0.25	06±0.21	03±0.14
SBS-k	4'-Chloro	11±0.28	12±0.48	14±0.53	11±0.25
SBS-l	4'-Methoxy	05±0.41	08±0.16	NA	NA
SBS-m	2'-Hydroxy	06±0.32	03±0.32	03±0.15	04±0.14
Ampicillin	----------	11±0.42	13±0.42	16±0.43	12±0.45

Dose concentration: 50 µg / 0.1 ml, NA: No activity. Control: DMSO (Dimethyl sulfoxide). , Medium: Nutrient Agar. , Method: Agar diffusion method. *Note: - Zone of inhibition excludes bore size (4mm) and zone of inhibition of control (7mm).The zone of inhibition was obtained from the average of three readings.

Several substituted and condensed benzimidazoles have been reported to possess a wide range of biological and pharmacological activities including antimicrobial, anti-inflammatory, analgesic anthelmintic activities and so on.

Table 5: *In-vitro* Antifungal activity data

		*Zone of Inhibition (mm).**	
Comp. Code	*R*	*Aspergillus niger*	*Candida albicans*
SBS-a	3',4',5'-Trimethoxy	06	NA
SBS-b	3',4'-Dimethoxy	07	NA
SBS-c	2'-Nitro	10	01
SBS-d	3'-Nitro	11	NA
SBS-e	2'-Chloro	13	NA
SBS-f	4'-Hydroxy	06	03
SBS-g	4'-Hydroxy,3'-methoxy	03	NA
SBS-h	4'-Methyl	04	NA
SBS-i	H	06	NA
SBS-j	4'-Dimethyl amino	05	NA
SBS-k	4'-Chloro	14	03
SBS-l	4'-Methoxy	06	NA
SBS-m	2'-Hydroxy	06	02
Miconazole Nitrate	---------	19	16

Dose concentration: 50 µg/0.1 ml , NA : No activity., Control: DMSO (Dimethyl sulfoxide). Medium: Sabouraud'sAgar. Method: Agar diffusion method. , *Note: - Zone of inhibition excludes bore size (4mm) and zone of inhibition of control (8mm). The zone of inhibition was obtained from the average of three readings.

The synthesis of2-(o-amino) phenyl benzimidazole (SBS) was carried out by microwave irradiation of o-phenylenediamine and anthranilic acid in the presence of polyphosphoric acid for 1min at 750 watt. This involves the nucleophilic attack of the lone pair of electrons on the nitrogen of o-phenylenediamine on the carbonyl carbon of anthranilic acid followed by the loss of two molecules of water and cyclization. The presence of nitrogen in the compound (SBS) was confirmed by Lassaigne's test.

The melting point of anthranilic acid was found to be 137^0C and that ofo-phenylenediamine was found to be 102^0C whereas the melting point of 2-(o-amino) - phenyl benzimidazole (SBS) was found to be 218^0C. The R_f value of anthranilic acid was found to be 0.2 and that of o-phenylenediamine was found to be 0.3 whereas the R_f value of SBS was found to be 0.65. The difference in the R_f values also confirmed the formation of 2-(o-amino) phenyl benzimidazole.

The IR Spectrum of the compound **SBS** showed the absence of carboxyl peak as in anthranilic acid and appearance of (C=N) peak at 1672.37cm^{-1}, which in turn is absent in both anthranilic acid and o-phenylenediamine.

The compound SBS also showed distinct NH_2peaks at 3422.07cm^{-1}. The formation of Schiff bases were confirmed from the IR spectrum of the compounds. The presence of specific IR peaks at 1649 cm^{-1}; indicated the presence of N=CH- peak which was absent in compound SBS.. All these showed that, the new compounds were formed.

The title compounds (SBS-a-m) were screened for their antibacterial activity against two Gram-positive bacteria i.e. *Staphylococcus aureus*& *Bacillus subtilus* and two Gram-negative bacteria i.e. *Escherichia coli* &*Klebsiella pneumonia* using Ampicillin as standard, each at a concentration of 50 µg/0.1 ml, adapting agar diffusion method. The compounds were also screened for their antifungal activity against two pathogenic fungi i.e. *Candida albicans* and *Aspergillus niger* using miconazole nitrate as standard at a concentration of 50 µg/0.1 ml, adapting the same method. The results of antibacterial and antifungal activity were reported in Table 2 and Table 3.

CONCLUSION

In conclusion, from the antibacterial activity results, it was observed that both electron donating and electron withdrawing groups on the aldehydic phenyl ring of the compounds influenced the activity. But aldehydic phenyl ring containing electron withdrawing groups had shown more promising result. Among all the compounds tested, SBS-k with 4'-chloro substitution at R was found to be most active on all the bacteria used and SBS-e with 2'-chloro substitution showed good activity against both Gram-positive bacteria and moderate activity against both Gram-negative bacteria emloyed. The remaining compounds exhibited mild to moderate activities compared to the standard. The antifungal screening results also suggest that the test compounds showed mild to moderate activity against *A.niger* only but no significant activity against *C.albicans* compared to the standard employed.

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