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Synthesis and biological activity of some triazole-bearing benzimidazole derivatives

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Abstract: A number of *N*'-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol--1-yl)acetohydrazide and 4-aryl-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]--4*H*-1,2,4-triazole-3-thiol derivatives were synthesized by incorporating various aromatic and heterocyclic substituents on 2-methyl-1*H*-benzimidazole. The structures of all the synthesized compounds were elucidated based on their elemental analyses and spectral data. The *in vitro* activities of these compounds against bacteria and fungi were evaluated by the disc diffusion and the minimum inhibitory concentration (MIC) methods. Some of the synthesized derivatives were found to be as active as kanamycin (standard drug).

Keywords: benzimidazole; triazole; antimicrobial activity; ampicillin; kanamycin; amphotericin B.

INTRODUCTION

The benzimidazole nucleus, which is a useful structure for research and development of new pharmaceutical molecules, has received much attention in the last decade. Due to their antimicrobial activities, new benzimidazoles have been synthesized and investigated for medical applications. As resistance to antimicrobial drugs is widespread; there is an increase necessity for the identification of novel structures which could lead to the design of new, potent and less toxic antimicrobial agents. Numerous attempts have been made to develop new structural prototypes to search for more effective antimicrobials. The benzimidazoles still remain one of the most versatile classes of compounds against microbes and, therefore, are useful substructures for further molecular exploration. They exhibit a range of biological activities. Specifically, this ring system is present in numerous antioxidants,[1,2] antiparasitic,[3,4] antimicrobial,[5–8] anthelmintic,[9,10] antiproliferative,[11] anti-inflammatory,[12,13] anticonvulsant,[14] antineoplastic,[15,16] antihypertensive[17] anti HIV[18] agents. Owing to the immense importance and varied biological activities exhibited by the benzimidazoles, efforts

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have been made periodically to generate libraries of these compounds and screen them for their potential biological activities. In addition, it is well documented that the triazole nucleus is associated with a variety of pharmacological activities. It displays pronounced antimicrobial,[19,20] anti-inflammatory[21] and analgesic[22] activities. The effectiveness of the benzimidazole and triazole moieties towards various microbes prompted the synthesis of some new benzimidazole derivatives bearing the triazole nucleus and the screening of their potential biological activities. In continuation of studies on biologically active benzimidazole derivatives,[23–25] the results of the synthesis of some new benzimidazole derivatives having a triazole nucleus are reported herein.

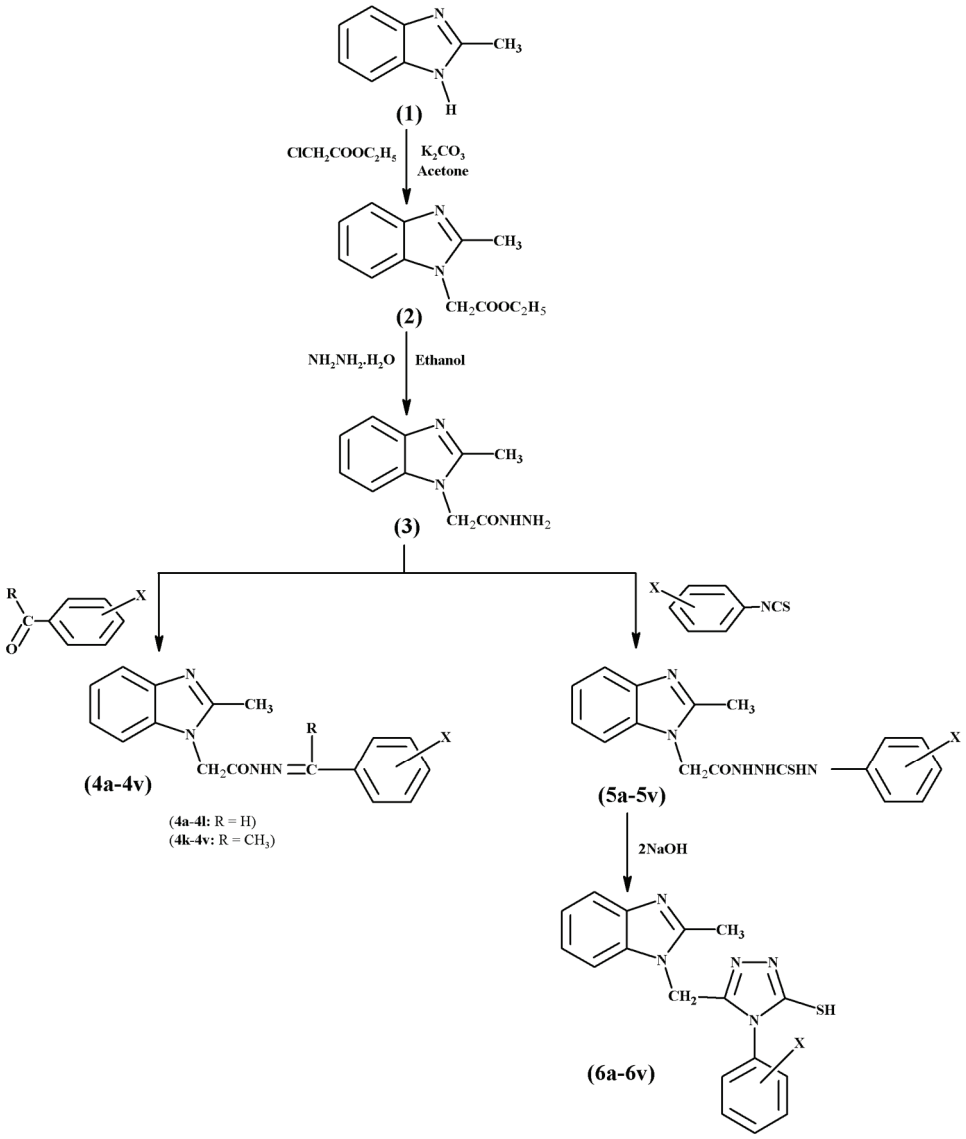
RESULTS AND DISCUSSION

Chemistry

The physical, analytical and spectral data are given in Supplementary material.

The key intermediate used for the synthesis of both series of the final compounds was 2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazide (**3**), which in turn was prepared by the reaction of 2-methyl-1*H*-benzimidazole (**1**) with ethyl chloroacetate in the presence of anhydrous potassium carbonate as a base,[23] followed by the reaction with hydrazine hydrate (Scheme 1).[24] The reaction of compound **3** with different arylaldehyde and acetophenones in absolute ethanol gave the desired *N*'-[(aryl)methylidene]-2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazides **4a**–**v**. The *N*-(aryl)-2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]hydrazinecarbothioamides **5a**–**k** were prepared by condensing compound **3** with appropriate phenyl isothiocyanates. Cyclization of compounds **5a**–**i** in 2 M NaOH solution under reflux finally gave the 4-(aryl)-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]-4*H*-1,2,4-triazole-3-thiols **6a**–**k**. The purity of the synthesized compounds was monitored by TLC and the structures of all the derivatives were supported by spectral data. The IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra are in agreement with the proposed structures. The structures of all the compounds were established based on analysis of the spectral data. The compounds **4a**–**v** showed the –CONH group band between 1657–1679 cm^{-1} in their IR spectra. The ^{1}H-NMR spectra of these compounds showed the signal of the –CONH proton between δ 9.00–9.27. In compounds **5a**–**k**, the appearance of a new band between 1220––1246 cm^{-1} showed the formation of thiosemicarbazide and the ^{1}H-NMR signal for the –NH– proton peak appeared between δ 7.04–9.03, depending on the type of substitution at the benzene ring. Compounds **6a**–**k** showed the –N–N– group band between 1253–1275 cm^{-1} and S–H group band between 2545–2562 cm^{-1}, which indicate the formation of the triazole ring. In the ^{1}H-NMR spectra of compounds **6a**–**k**, a sharp peak between δ 12.90–12.92 showed the presence of the C–SH proton and the –N–CH_2 proton signal appeared between δ 6.00–6.18. The

mass spectra of compounds **6a**–**k** exhibited molecular ion peaks at *m*/*z* 321, 351, 337, 355, 444 and 336 together with their fragmentation peaks, which indicated the formation of triazole derivatives.



Scheme 1. Reagents and conditions: *i*) $ClCH_2COOC_2H_5$/dry acetone, K_2CO_3; RT: 10 h, *ii*) $NH_2NH_2.H_2O$/dry methanol; RT: 4–5 h, *iii*) substituted arylaldehyde or actophenone/absolute ethanol; RT: 5 h, *iv*) substituted phenyl isothiocyanate/absolute ethanol; RT: 1 h and *v*) 2NaOH; RT: 4 h.

Antimicrobial evaluation

The *in vitro* antimicrobial activity against different strains of bacteria and fungi was screened using the disc diffusion and the minimum inhibitory concentration (MIC) methods. Ampicillin, nalidixic acid and kanamycin were used as the positive controls for the bacteria and amphotericin B for the fungi.

By comparing the antimicrobial activity of the synthesized compounds, it was found that the tested compounds were more effective against the Gram positive bacteria. It is believed that the strong lipophilic character of a molecule plays an essential role in producing antimicrobial effects. These properties are seen as an important parameters related to membrane permeation in biological systems. Many of the processes of drug disposition depend on the capability of a drug to cross membranes and hence there is a high correlation with measures of lipophilicity. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments, such as lipid bilayers of cells, while hydrophilic drugs (low partition coefficients) are found preferentially in hydrophilic compartments, such as blood serum. Hydrophobicity/lipophilicity play a major role in determining where drugs are distributed within the body after adsorption and as a consequence in how rapidly they are metabolized and excreted. In this context, the presence of a hydrophobic moiety would be important for such activity. Moreover, many of the proteins involved in drug disposition have hydrophobic binding sites, further adding to the importance of lipophilicity.

The lipophilicity of compounds, expressed as log *P*, represents the main predictor for activity. The octanol/water partition coefficient, *C*log *P*, being a measure of hydrophobicity/ lipophilicity was calculated using ChemDraw Ultra 11.0 software integrated with Cambridgesoft Software (Cambridgesoft Corporation).[26] The results obtained are given in Table I. The calculated values of log *P* for the *N*'-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazides **4a**–**v** were lower than for the corresponding 4-aryl-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]-4*H*-1,2,4-triazole-3-thiols **6a**–**k**. The lipophilic power of the compounds increased with increasing log *P*. The activity observed for compounds **6a**–**k**, having higher values of log *P* was slightly higher than that of the corresponding compounds **4a**–**v**, which shows that incorporation of triazole nucleus on benzimidazole derivatives did not favor antimicrobial activity.

Regarding the correlation of the antimicrobial activity of substituted benzimidazoles with the planarity of their molecules, the *ortho*-substitution in the benzene nucleus of the *N*'-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol-1--yl)acetohydrazides **4a**–**v**, *N*-aryl-2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]-hydrazinecarbothioamides **5a**–**k** and 4-aryl-5-[(2-methyl-1*H*-benzimidazol-1--yl)methyl]-4*H*-1,2,4-triazole-3-thiols **6a**–**k** generates steric hindrance, hence they were less active than the corresponding *para*-substituted derivatives, thereby showing a marginal steric effect. The molar refractivity (*MR*), which represents

the size and polarizability of a molecule describing steric effects, was calculated (using ChemDraw Ultra 11.0 software) to explain the activity behavior of the synthesized compounds. From Table I, it can be inferred that a slightly lower value of the molar refractivity favored the activity ratio.

TABLE I. Calculated log *P* and molar refractivity of compounds **4a**–**4v**, **5a**–**5k** and **6a**–**6k** (calculated from ACD/Labs software, v.12.0 (Advanced Chemistry Development, Inc.))

Compound	X	*C* log *P*	*MR*
4a	–	2.626	85.62
4b	2-CH_3	2.858	91.58
4c	2-CH_2CH_3	2.754	96.12
4d	2-$CH_2CH_2CH_3$	3.283	100.72
4e	2-OH	3.225	87.44
4f	4-OH	2.595	87.44
4g	2-OCH_3	2.415	92.87
4h	4-OCH_3	2.845	92.87
4i	2-Cl	2.739	90.23
4j	4-Cl	3.339	90.23
4k	4-NH_2	1.999	90.45
4l	–	3.485	89.72
4m	2-CH_3	3.984	95.62
4n	2-CH_2CH_3	4.513	100.21
4o	2-$CH_2CH_2CH_3$	5.042	104.81
4p	2-OH	2.818	91.53
4q	4-OH	2.818	91.53
4r	2-OCH_3	3.404	96.97
4s	4-OCH_3	3.404	96.97
4t	2-Cl	4.198	94.32
4u	4-Cl	4.198	94.32
4v	4-NH_2	2.258	94.54
5a	–	1.978	96.49
5b	2-CH_3	2.477	102.39
5c	2-CH_2CH_3	3.006	106.99
5d	2-$CH_2CH_2CH_3$	3.535	111.59
5e	2-OH	1.311	98.31
5f	4-OH	1.311	98.31
5g	2-OCH_3	1.897	103.74
5h	4-OCH_3	1.897	103.74
5i	2-Cl	2.691	101.10
5j	4-Cl	2.691	101.10
5k	4-NH_2	0.751	101.32
6a	–	3.455	93.15
6b	2-CH_3	3.954	99.05
6c	2-CH_2CH_3	4.483	103.65
6d	2-$CH_2CH_2CH_3$	5.012	108.25
6e	2-OH	3.160	94.97
6f	4-OH	3.160	94.97

TABLE I. Continued

Compound	X	*C* log *P*	*MR*
6g	2-OCH_3	3.434	100.4
6h	4-OCH_3	3.434	100.4
6i	2-Cl	4.171	97.76
6j	4-Cl	4.171	97.76
6k	4-NH_2	2.576	97.98

Considering the structure of the compounds that exhibit antimicrobial activity, substituted methylidene and triazole may play a role for the antimicrobial activity. From the results, which indicated that tested compounds were more active against Gram-positive bacteria than Gram-negative bacteria, it may be concluded that the antimicrobial activity of the compounds is related to cell wall structure of the bacteria. This is possible because the cell wall is essential for the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. Gram positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acids, but in contrast, Gram negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan surrounded by a second lipid membrane containing lipopolysachharides and lipoproteins. These differences in cell wall structure can produce differences in the antibacterial susceptibility and some antibiotics that can kill only Gram-positive bacteria are ineffective against Gram negative bacteria.[27]

Antibacterial activity

The results of the preliminary testing of the antibacterial activity of the final compounds are given in Table II. The results revealed that the majority of the synthesized compounds show varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-positive bacteria was higher than against the Gram-negative bacteria. The triazole derivatives **6a**–**k** displayed the lowest activity. Compounds **4a**, **4b**, **4e**, **4f**, **4k** and **4l** showed excellent activity against the Gram-positive bacteria. None of the compounds tested in this study displayed any effect against *Escherichia coli* and *Salmonella typhi* and only an insignificant effect against *Pseudomonas aeruginosa* (except compound **4a**, which showed the same activity as the standard drug against *P. aeruginosa*).

The values of the minimum inhibitory concentration (*MIC*) against the microorganism susceptible in the preliminary test are reported in Table III. The results showed significant inhibitory effects, with the majority of the compounds tested having *MIC* values of 2–16 μg mL^{-1}. This class of compounds presented high activity against *Staphylococcus aureus* and *Bacillus subtilis*, especially compounds **4a**, **4b**, **4f**, **4h**, **4j**, **4l**, **4s**, **4u**, **5f** and **5j** showed good antibacterial activity against these two microorganisms. For *Streptococcus mutans*, these compounds

were as active as the standard kanamycin (*MIC* = 4 μg mL^{-1}), but less active than ampicillin. Activity compared to ampicillin was also encountered for **4a**, **4f**, **4k**, and **4v** against *B.subtilis* and for **4a**, **4b**, **4f**, **4l**, **4s**, **4v** and **5j** against *P. aeruginosa*.

TABLE II. Inhibitory zone diameter of compounds against bacterial strains using the disc diffusion method (Sa – *S. aureus*, Bs – *B. subtilis*, Sm – *S. mutans*, Ec – *E. coli*, Pa – *P. aeruginosa* and St – *S. typhi*)

Compd.	Mean zone inhibition, mm[a]					
	Gram-positive bacteria			Gram-negative bacteria		
	Sa	Bs	Sm	Ec	Pa	St
4a	35	25	20	–[b]	18	–
4b	33	24	19	–	16	–
4d	28	23	18	–	17	–
4e	24	23	16	–	14	–
4f	35	25	19	–	17	–
4g	24	19	15	–	13	–
4h	33	28	18	–	16	–
4i	27	18	14	–	12	–
4j	30	25	20	–	16	–
4k	35	–	16	–	16	–
4l	33	23	19	–	16	–
4m	29	20	17	–	16	–
4p	22	20	16	–	15	–
4r	21	–	16	–	14	–
4s	28	24	18	–	17	–
4t	24	18	15	–	–	–
4u	28	22	18	–	17	–
4v	29	24	20	–	17	–
5a	24	18	–	–	10	–
5b	28	24	17	–	16	–
5d	25	21	17	–	14	–
5f	29	24	19	–	17	–
5g	18	20	–	–	–	–
5j	24	18	20	–	15	–
6b	20	18	12	–	10	–
6f	24	19	18	–	12	–
6h	21	18	18	–	16	–
Ampicillin[c]	38	28	22	20	NT[d]	NT
Nalidixic acid[c]	NT	NT	NT	28	18	20

[a]*n* = 3; [b]indicates no sensitivity or mean inhibition zone diameter less than 7 mm; [c]ampicillin (10 μg/disc) and nalidixic acid (30 μg/disc) used as positive reference, synthesized compounds, 300 μg/disc; [d]not tested

Antifungal activity

The *in vitro* antifungal activities of the derivatives of *N*'-(arylmethylidene)--2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazide (**4a**–**v**), *N*-aryl-2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]hydrazinecarbothioamide (**5a**–**k**) and 4-aryl-5-[(2-

-methyl-1*H*-benzimidazol-1-yl)methyl]-4*H*-1,2,4-triazole-3-thiol (**6a**–**k**) and of amphotericin B as a reference drug on three fungi species are given in Table IV. Some of the compounds tested were endowed with a good activity against *Candida albicans*. Of these, 2-(2-methyl-1*H*-benzimidazol-1-yl)-*N*'-(phenylmethylidene)acetohydrazide **4a** and *N*'-[1-(4-aminophenyl)ethylidene]-2-(2-methyl-1*H*--benzimidazol-1-yl)acetohydrazide (**4v**) were found to be the most potent, showing an *MIC* value 4 μg mL^{-1}, whereas the *MIC* value for compounds **4b**, **4f**, **4i**, **4k**, **4v** and **5a** was 8 μg mL^{-1} (Table III). Compounds with a *para*-substitution in the benzene ring (**4a**, **4b**, **4d**, **4f**, **4j**, **4k**, **4s**, **4u**, **5d** and **5j**) were also found to be potent against *Aspergillus flavus* (inhibition zone 18–22 mm) with medium activity. All the other tested compounds exhibited insignificant chemotherapeutical activity against the tested microorganism.

TABLE III. Antimicrobial activity of tested compounds expressed as *MIC* in μg mL^{-1} (Sa – *S. aureus*, Bs – *B. subtilis*, Sm – *S. mutans*, Pa – *P. aeruginosa* and Ca – *C. albicans*)

Compd.	Sa	Bs	Sm	Pa	Ca
4a	4	4	4	8	4
4b	8	8	4	8	8
4d	16	16	16	NT[a]	32
4e	16	16	16	16	NT
4f	4	4	4	8	8
4g	16	NT	32	16	32
4h	16	8	4	4	16
4i	8	8	16	16	8
4j	16	32	4	16	16
4k	4	4	8	16	8
4l	4	8	4	8	16
4m	8	16	8	NT	16
4p	NT	16	16	32	32
4r	16	32	16	16	16
4s	8	8	4	8	16
4t	16	NT	32	16	NT
4u	8	8	4	16	8
4v	8	4	4	8	4
5a	8	16	8	16	8
5b	8	16	8	32	16
5d	16	16	8	16	16
5f	4	8	4	NT	16
5g	32	32	64	32	16
5j	4	8	4	8	NT
6b	NT	NT	16	16	32
6f	8	16	16	16	NT
6h	8	16	32	32	32
Ampicillin	2	2	≤1	4	NT
Kanamycin	2	≤1	4	2	NT
Amphotericin B	NT	NT	NT	NT	2

[a]Not tested

TABLE IV. Inhibitory zone of compounds against fungal strains using the disc diffusion method (Ca – *C. albicans*, An – *A. niger* and Af – *A. flavus*)

Compd.	Mean zone of inhibition, mm (n = 3)		
	Ca	An	Af
4a	28	24	18
4b	24	23	20
4d	22	22	22
4e	20	20	–[a]
4f	24	22	22
4g	–	–	10
4h	25	10	12
4i	16	14	–
4j	18	23	20
4k	26	22	22
4l	24	20	17
4m	–	13	15
4p	18	17	10
4r	12	14	13
4s	18	24	18
4t	12	14	–
4u	18	18	18
4v	28	20	–
5a	18	–	12
5b	17	10	12
5d	15	22	20
5f	16	18	12
5g	12	12	10
5j	16	20	22
6b	17	14	10
6f	18	14	10
6h	18	16	15
Amphotericin B[b]	28	32	28

[a]No sensitivity or mean inhibition zone diameter lower than 7 mm; [b]amphotericin B (30μg/disc) used as positive reference; synthesized compounds: 300μg/disc

EXPERIMENTAL

All melting points were determined in an open capillary tube and are uncorrected. Infrared spectra were recorded in KBr on Perkin-Elmer RX1 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ solutions on a Bruker DRX-300 MHz spectrometer using TMS as an internal reference (chemical shift in δ / ppm). The mass spectra were recorded on a Jeol SX-102 instrument. Elemental analyses were realized using an Elementar Vario EL III elemental analyzer. Thin layer chromatography was performed on silica plates pre-coated with Merck Silica Gel 60 F254 and column chromatography with silica gel.

Synthesis of N'*-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazides* ***4a–v***

General procedure. An equimolar (0.001 mol) mixture of compound **3** and substituted arylaldehyde or substituted acetophenone in absolute ethanol (50 ml) containing 2–3 drops of

glacial acetic acid was refluxed for 5 h and the solvent removed. The separated solid was filtered and recrystallized from a suitable solvent to give compounds **4a**–**v**.

Synthesis of N-*aryl-2-[(2-methyl-1*H-*benzimidazol-1-yl)acetyl]hydrazinecarbothioamides* ***5a–k***

General procedure. To a boiling solution of compound **3** (0.001 mol) in absolute ethanol (30 ml) was added an appropriate substituted phenyl isothiocyanate (0.001 mol) and the reaction mixture was refluxed for 1 h, concentrated and cooled. The separated solid was filtered and recrystallized from an appropriate solvent to give **5a**–**k**.

*Synthesis of 4-aryl-5-[(2-methyl-1*H-*benzimidazol-1-yl)methyl]-4*H-*1,2,4-triazole-3-thiols* ***6a–k***

General procedure. A solution of compound **5** (0.001 mol) in 2 M NaOH (20 ml) was refluxed for 4 h, cooled, poured into ice cold water (50 ml) and neutralized with acetic acid. The precipitate was filtered, washed with water and recrystallized from an appropriate solvent to afford compounds **6a**–**k**.

Antimicrobial activity test

All the synthesized compounds **4a**–**v** and **6a**–**k** were screened for their *in vitro* antimicrobial activity against the standard strains: *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (MTCC 121), *Streptococcus mutans* (MTCC 890), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (MTCC 741) and *Salmonella typhi* (MTCC 733) and the fungi *Candida albicans* (MTCC 1637), *Aspergillus flavus* (AIIMS) and *Aspergillus niger* (AIIMS).

The preliminary antimicrobial activity was reported using the disc diffusion method.[28] In this method, paper discs (6 mm) containing specific amounts of an antimicrobial agent (300 μg for the synthesized compounds) were placed on the surface of an agar plate inoculated with a standardized suspension of the tested microorganisms. The plates were incubated at 35 °C for 24 and 48 h, respectively, for the bacteria and fungi. Amphotericin B (30 μg) for the fungi, ampicillin (10 μg) for the Gram-positive bacteria and nalidixic acid (30 μg) for the Gram-negative bacteria were used as standard drugs. Paper discs with only dimethyl sulfoxide (DMSO) were utilized as the negative control.

The twofold serial dilution technique[29,30] was followed to determine the *MIC* of the compounds against the microorganisms susceptible in the preliminary tests (Gram positive bacteria and fungi). The test compounds were dissolved in DMSO and then diluted with culture medium (Mueller–Hinton agar medium for the bacteria and Sabouraud liquid medium for the fungi), at the required final concentration, within the range 128–1.0 μg mL^{-1}. A plate for the bacteria and a tube for the fungi containing only culture medium and DMSO, in the same dilution as in the experiments, were used as negative controls.

The final amount applied was of 10^4 CFU/plate for the bacteria and 10^3 CFU/tube for the fungi. The *MIC* values were read after incubation at 35 °C for a period of 20 (bacteria) and 48 h (fungi). The lowest concentration of the test substance that completely inhibited growth of the microorganism was recorded as the *MIC*, expressed in μg mL^{-1}. Ampicillin and kanamycin for the bacteria and amphotericin B for the fungi were used as standard drugs. All experiments were performed in triplicate.

CONCLUSIONS

In conclusion, several benzimidazole derivatives were synthesized starting with 2-methylbenzimidazole. A microbiological study was undertaken to evaluate the effect of the synthesized compounds on different bacteria and fungal strains. With regards to the structure–activity relationship of the derivatives of

N'-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazide **4a**–**v**, *N*-aryl-2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]hydrazinecarbothioamide **5a**–**k** and 4-aryl-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]-4*H*-1,2,4-triazole-3-thiol **6a**–**k**, the group with a substituent on *para*-position exhibited enhanced antimicrobial activity in comparison to *ortho*-substitution on the same ring. Moreover, *para* substituted hydroxy and chloro derivatives produced activity equal to that of ampicillin for *S. aureus*. Similarly, in the case of the antifungal activity, *para* hydroxy and *para* chloro substituted derivatives were proved to be the most active compounds and their activity was equal to that of amphotericin B. These differences in activity depended on the substitution of different reactive group on the benzimidazole moiety. Based on the observations, it may be concluded that the order of inhibitory effect against S. *aureus* was influenced by the type of substitution present at *para* position, *i.e.*, the derivatives with chloro and hydroxyl groups showed maximum activity in comparison to those with a methyl group, which in turn were more reactive than the methoxy derivatives.

More extensive studies are required to confirm these preliminary results and studies involving the mechanism of action are necessary for a complete understanding of their antimicrobial activity, as well as structural modifications on the final investigated compounds to improve their biological activity.

SUPPLEMENTARY MATERIAL

The physical, analytical and spectral data of synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ НЕКИХ ТРИАЗОЛСКИХ ДЕРИВАТА КОЈИ САДРЖЕ БЕНЗИМИДАЗОЛНИ СТРУКТУРНИ СЕГМЕНТ

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Синтетисани су бројни деривати *N*'-(супституисани фенилметилиден)-2-(2-метил-1*H*-бензимидазол-1-ил)ацетохидразида и 4-(супституисани фенил)-5-[(2-метил-1*H*-бензимидазол-1-ил)метил]-4*H*-1,2,4-триазол-3-тиола који садрже различите ароматичне и хетероароматичне супституенте на 2-метил-1*H*-бензимидазолу. Структуре синтетисаних једињења утврђене су на основу елементалне анализе и спектралних података. Испитане су *in vitro* активности једињења према бактеријама и гљивама диск-дифузионом методом и методом минималних инхибиторних концентрација. Нека од испитиваних једињења активна су у истој мери као и стандардни лек канамицин.

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