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CHEMISTRY RESEARCH ARTICLE

Green Synthesis of Substituted- Phenyl-Azetidin/Thiazolidin-1-yl- Amino-Methyl-Benzimidazolyl Propanone by micro wave irradiation and screened for Antifungal activity

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ABSTRACT

Benzimidazole and their derivatives have gained popularity due to their applications in pharmaceutical chemistry. In this paper we have been discussed about the synthesis of Substituted-Phenyl-Azetidin/Thiazolidin-1-yl- Amino-Methyl-Benzimidazolyl Propanone by micro wave irradiation. Here, in this part a brief account on the biological activities of triazole and benzimidazoles has been presented. The antifungal activity of benzimidazole derivatives was carried out by using standard compound Streptomycin by cup-plate method against bacteria.

Keywords: benzimidazole, antifungal activity, micro wave irradiation.

1. INTRODUCTION

Benzimidazole and 1, 2, 4-triazole derivatives possess better biological activities. Recently the compounds 1H, 3H- thiazolo [3, 4-a] benzimidazoles, which have been found to possess HIV-I and reverse transcriptase inhibitors Fluconazole as a bis-triazole containing compound effective against fungal infections. Several substances structurally related to benzimidazole occur naturally inbiological systems. A derivative of this compound, 5-6-imethyl benzimidazole, constitute part of the vitamin B12 molecule purines, an important component of nucleic acid structures and nucleotides, bear a structural similarity to benzimidazole.

The application of microwave irradiation is used for carrying out chemical transformation which is pollution free and ecofriendly. The microwave assisted organic reactions occurs more rapidly, safely and with higher yields. The classical approach for synthesis of these derivatives involves refluxing for several hours in presence of solvents, which result in generation of aqueous and organic waste. Triazole and benzimidazole nucleus find importance in the field of drug discovery as antimicrobial agents.

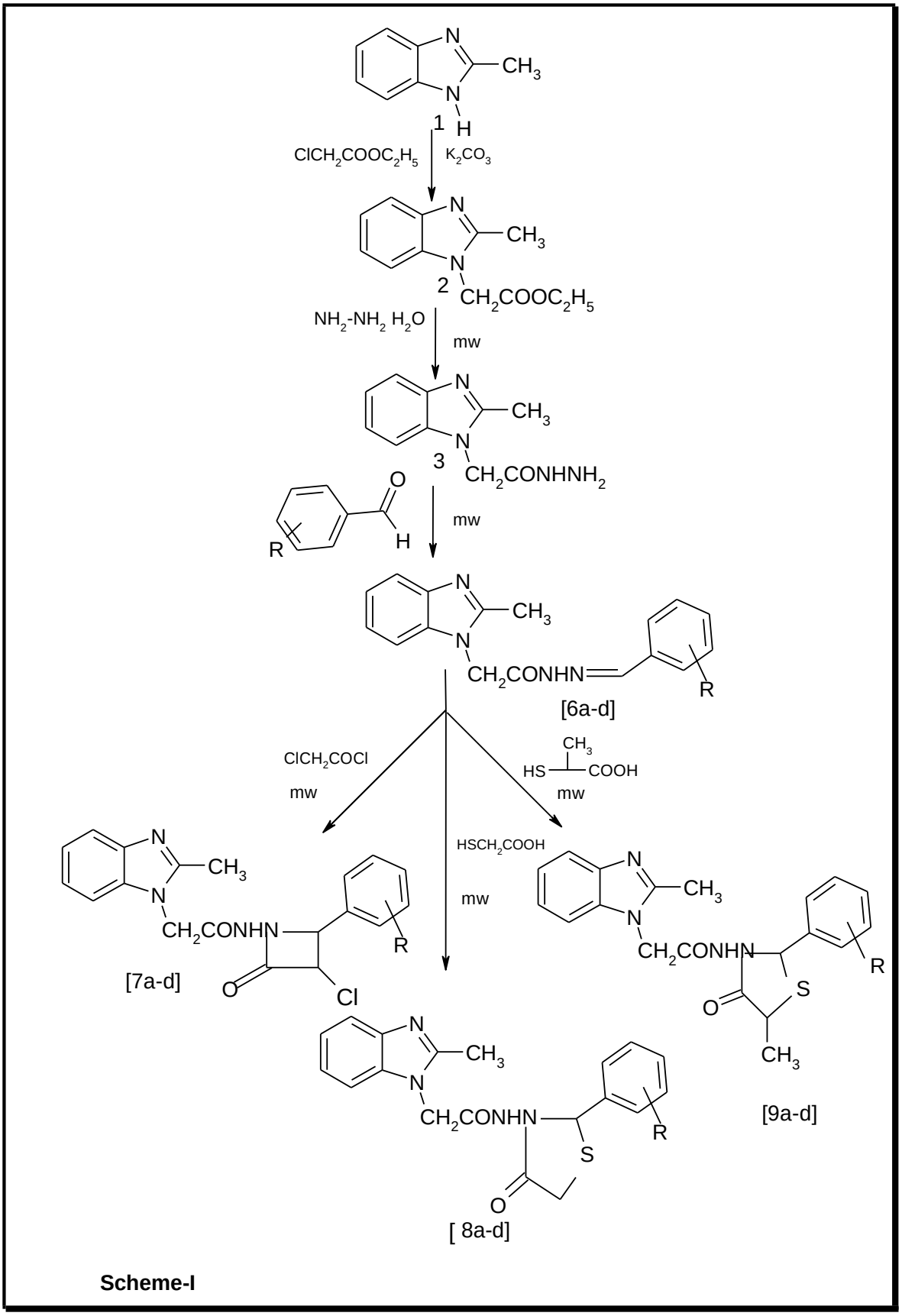
2. RESULTS AND DISCUSSIONS

The reaction of 2-methyl-1-H-benzimidazole 1 with ethylchloroacetate afforded ethyl-2-methyl benzimidazole-1-acetate (2). The formation of 2 has been ensured on the basis of its IR. The broad band at 1760 cm-1 indicates the presence of ester group. Compound 2 on reaction with hydrazine hydrate under microwave irradiation afforded ethyl-(2-methylbenzimidazole-2-yl) acetic acid hydrazide (3), The IR spectrum of 3 exhibited amide C=O at 1690 cm^{-1}. Condensation of compound 3 with aromatic aldehyde in absolute ethanol afforded the corresponding compound (6a-d). A typical experimental procedure entails mixing of compound 3 with different aromatic aldehydes in glass container and irradiated in a microwave oven for 2-3 minute with intermittent irradiation to afford (6a-d) in 85-90% yields. The IR spectra of 6 showed -NH band at 3133 cm^{-1} and a singlet at δ, 9.1 due to -NH proton. Compound 6 on reaction with chloroacetyl chloride in presence of triethylamine yielded compound (7a-d). In reactions are carried out in presence of benzene which takes about 12-14 hrs. Whereas by microwave method it is completed within 6-7 min. The structures of compounds 7a-d were confirmed on basis of IR and PMR. The IR spectrum of compound 7a-d showed bands at 1676 cm^{-1} and 1733 cm-1 due to amide group and azetidin ring C=O respectively.

Compound 6 on treatment with thioglycolic acid under microwave irradiation afforded the compound (8a-d). The structure of which have

been confirmed on the basis of IR band observed at 1725 cm-1 due to the cyclic C=O group of thiazolidione ring. Compound 6 on reaction with thiolactic acid in DMF as solvent yielded compounds (9a-d).

The IR spectrum of Compound 9a- d revealed band at 1702 cm^{-1} due to the thiazolidine ring C=O group. Reaction time, yield and physical and analytical data of the compounds are given in Table1 and 2 respectively.



Scheme-I

3. EXPERIMENTAL SECTION

Ethyl-2-methyl benzimidazole-1-acetate (2):
The compound **2** was prepared by N-alkylation of 2-methyl benzimidazole with ethyl chloroacetate using K2CO3 catalyst and characterized.

Ethyl-(2-methylbenzimidazole-2-yl) acetic acid hydrazide (3):
Ethyl-2-methyl benzimidazole-1-acetate (0.01mol) and hydrazine hydrate (0.01mol) in methanol was taken in glass container and irradiated in microwave oven to get desired solid product, filtered and recrystalized in methanol.

Synthesis of 3- (2-methylbenzimidazole-1-yl) acetic acid hydrazide Schiff's bases (Hydrazones) (6a-d):
Microwave method: A mixture of compound **3** (1.88gm, 0.01 mol) and the appropriate aldehydes (0.01mol) in ethanol was taken in flat bottomed flask and irradiated in microwave oven for 2 min. It was then diluted with ice cold water. The Schiff's base formed was filtered, dried and recrystallized from ethanol.

Synthesis of 3-Chloro-1-[[3-(2-methyl-1H-benzimidazol-1-yl)-2-oxopropyl] amino]-4-phenylazetidin-2-one (7a-d):

Microwave method: A mixture of compound **6a-d** (0.01 mole) and chloroacetyl chloride (0.01 mole) in a flat bottomed flask was added and mixture was irradiated in microwave oven for 2-3 minutes and the mixture triturated with ice water. The solid product thus obtained was filtered, dried and recrystallized from ethanol.

Synthesis of 3-[[3-(2-methyl-benzimidazo1yl)-2-oxopropyl] amino] phenyl-1, 3- thiazolidin-4-one of (8a-d):

Microwave method: A mixture Schiff's base **6a-d** (0.01mol) in DMF was taken in a flat bottomed flask, and thioglycolic acid (0.01mol) was added slowly. The mixture was irradiated in a microwave oven for about 6-7 minutes. It was then diluted with ice water. The solid product thus formed was filtered, dried and recrystallized from ethanol.

Synthesis of 5-[[3-(2-methyl-1H-benzimidazole-1-yl)-2-oxopropyl] amino]-2-phenyl-1,3-thiazolidin-4-one compound (9a-d):

Microwave method: A mixture Schiff's base **(6a-d)** (0.01mol) in DMF was taken in a flat bottomed flask, and thiolactic acid was added slowly. The mixture was irradiated in a microwave oven for about 6-7 minutes. It was then diluted with ice cold water. The solid product thus formed was filtered, dried and recrystallized from ethanol

Biological activity of Triazole and Imidazoles by Cup-plate method:

This method depends on the diffusion of an antibiotic through a cavity into the solidified agar layer in a Petri dish. About 15-20 ml of molten nutrient agar was poured into each of the sterile plates. With the help of sterile cork borer, the cups were punched and scooped out of the solidified agar. The agar plates so prepared were divided into different sets and each set of the plates was inoculated with the suspension of particular organism by spread plate technique.
The cups of inoculated plates were then filled with 0.1 ml of the test solution, and the plates were allowed to stay in their upright position for 2 hrs. Further, the plates were incubated at 37 oC and kept overnight. The zone of inhibition developed, was measured for test organism for the particular compound. The antifungal activity of triazole and benzimidazole derivatives was assayed using standard compound Flucanazole by disc diffusion method using two fungal species as *Aspergillus niger* and *Aspergillus flavus.*

Method of testing:
About 15-20 ml of PDA was poured into each of sterile plates. After solidifying the agar plates were inoculated with the suspension by spread plate technique. A good quality of paper absorbent disc of 6 mm. diameter saturated with respective chemicals placed on the surface of plate with the help of sterile forcep. The plates were incubated at 370C temperature for 24 hrs. The zone of inhibition developed and then measured for the particular compound with selected organism.
For comparison the standard, compound Flucanazole was used for screening under similar conditions and control of the solvent at the same time was also run to know the activity in blank. The zones of inhibition have been measured in mm. The antimicrobial screening data have been incorporated in **Table 3.**

Table-1: Solvent, reaction time and % yield of the products.

Entry	Conditions	Microwave method	
		Time(min)	Yield (%)
6a	MeOH	2	90
6b	MeOH	2	90
6c	MeOH	2	85
6d	MeOH	3	90
7a	TEA	5	70
7b	TEA	5	60
7c	TEA	6	70
7d	TEA	6	70
8a	DMF	6	65
8b	DMF	6	80
8c	DMF	6	80
8d	DMF	7	70
9a	DMF	6	80
9b	DMF	6	80
9c	DMF	6	75
9d	DMF	7	65

Table-2: Physical analytical data of the compounds.

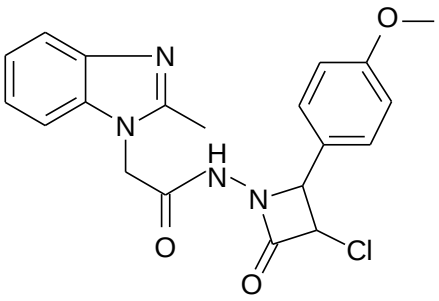
Entry	R	Molecular Formula	Melting point oC
6a	H	C17H16N4O	232
6b	p-OCH3	C18H18N4O2	167
6c	p-Cl	C17H15ClN4O	187
6d	m-NO2	C17H15N5O3	199
7a	H	C20H19ClN4O2	234
7b	p-OCH3	C21H21ClN4O3	220
7c	p-Cl	C21H21ClN4O2	190
7d	m-NO2	C20H18ClN5O4	215
8a	H	C20H20N4O2S	242
8b	p-OCH3	C21H22N4O3S	236
8c	p-Cl	C20H19N4O2SCl	250
8d	m-NO2	C20H29N5O4S	217
9a	H	C21H22N4O2S	240
9b	p-OCH3	C22H24N4O3S	210
9c	p-Cl	C21H22N4O2S	193
9d	m-NO2	C21H21N4O2SCl	160

Table-3: Zone of inhibition of tested compounds 7a, 8c, 8d and 9d.

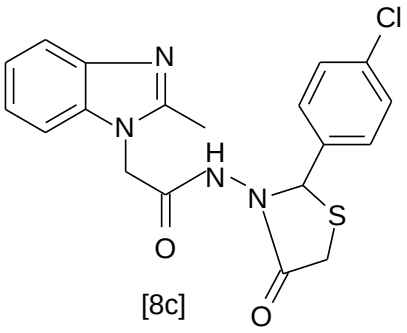
Entry	*S. typhi*	*S. Aureus*	Entry	*Aspergillus niger*	*Aspergillus flavus*
7a	18	16	6a	14	18
8c	27	20	6b	22	16
8d	21	18	6c	28	31

9d	20	29	6d	21	27
Standard (Streptomycin)	20.00	22.00	Standard (Fluconazole)	30.00	30.00
Control of the solvent (DMF)	10.00	12.00	Control of the solvent (DMF)	10.00	13.00

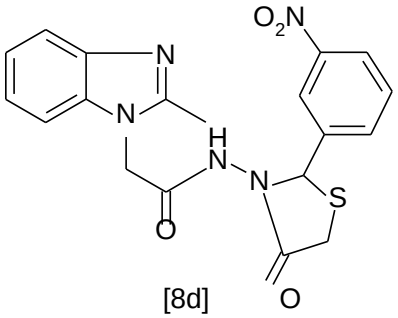
Antimicrobial screening results for compounds 7a, 8c, 8d and 9d.



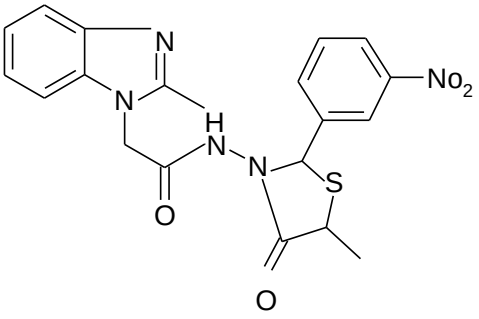
[7a]



[8c]

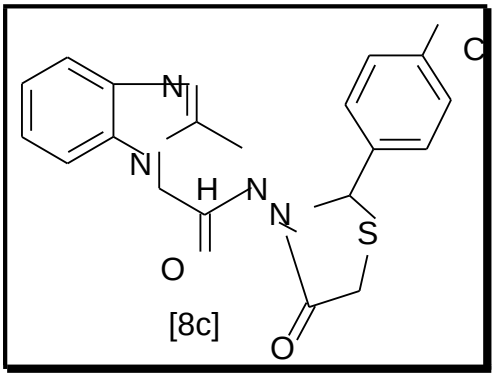


[8d]



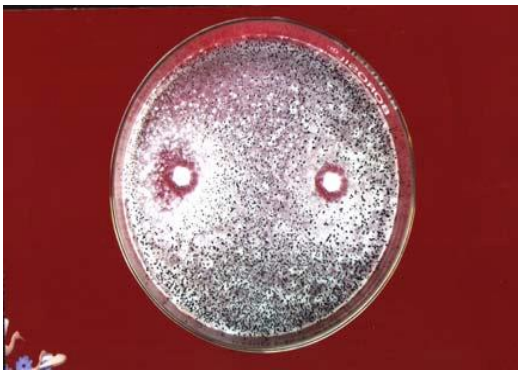
[9d]

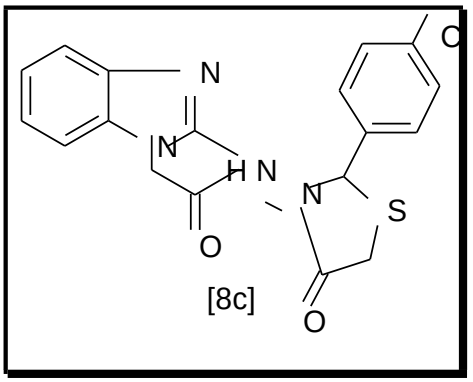
Zone of inhibition for tested compounds 8c (1) against *S.typhi* and *S. aureus*



[8c]

Zone of inhibition for tested compound 8c against *Aspergillus flavus*





Structure activity relationship

4. CONCLUSIONS

From scheme-1 we have concluded that the methodology is environmentally benign and further conformed by spectral data. Compound **8c** exhibited an excellent activity against *Salmonella typhi* where as other compound 9**d shows** moderate to good activity against S. *Aureus***.** Compound **8c** and **9d** shows moderate to good antifungal activity as compared with the standard can have medicinal value as drugs.

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