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Synthesis and antimicrobial activity of 2-(1*h*-benzimidazol -2-ylsulfanyl)-*n*-phenylacetamide

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ABSTRACT

In the present study, a series of substituted 2-(1*H*-benzimidazol-2-ylsulfanyl)-*N*-phenylacetamide was prepared. The synthesis of titled compounds from starting material unsubstituted 2-mercapto benzimidazoles was prepared from *o*-phenylenediamine and carbon disulfide in presence of KOH in single step. 2-mercapto Benzimidazole on reacting with *N*-substituted-α-chloroacetanilides yield different derivatives of Benzimidazole. The structure of new compounds prepared during present investigation have been authentically established by their IR, ^{1}H NMR and Mass spectral studies. The antibacterial and antifungal activities of thiadiazole derivatives also reported. Some of these derivatives exhibit significant antimicrobial activity.

Key words: 2-mercapto benzimidazoles, phenylacetamide, antibacterial, antifungal.

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INTRODUCTION:

During recent years there has been a large investigation on different classes of benzimidazoles compounds, many of which were found to possess an extensive spectrum of pharmacological activity such as anticonvulsant[1], antitumor[2], CNS depressants[3], herbicidal[4], antiviral[5] and anti-inflammatory activity[6], antifungal[7], antibacterial & antimycobacterium[8] etc. Generally, in pharmaceutical field new drugs are discovered by molecular modification of the lead compound of established activity. So an attempt was made to synthesize, new substituted benzimiazoles compounds as antimicrobial agents. Hence synthesis of different derivative of benzimiazoles was carried out along with other substituted aromatic amines.

MATERIALS AND METHODS:

The chemicals and reagents used in the present project were of AR grade and LR grade, purchased from Lancaster, Sigma, Qualigens, NR Chem., Rolex, S.D. Fine Chem. Ltd., Merck, Loba and Himedia. O-phenylenediamine, potassium hydroxide, carbon disulfide, *N*-substituted-α-chloroacetanilides, chloroacetylchloride, sodium acetate etc were used.

The completion of reactions was monitored by TLC technique using Silica gel-G (for TLC) using suitable solvent. Determination of melting point was done by open capillary tube method using paraffin bath and are uncorrected. Recrystallization was done by suitable solvent. The ^{1}H NMR of synthesized compounds were recorded in Bruker FT-NMR (400MHz & 200MHz) as TMS as internal standard and IR-spectra were recorded in Bruker alpha FT-IR using KBr pellets. The Mass spectra were recorded on Shimadzu LC-MS with ESI source.

Experimental:

Step-1: Preparation of 2-mercapto benzimidazole:

A mixture of 10.8gm (0.1mole) of *o*-phenylenediamine, 5.65 gm (0.1mole) of potassium hydroxide and 7.67 gm (0.1mole, 6.19ml) of carbon disulfide, 100ml of 95% ethanol and 15 ml of water in a 500ml round bottom flask heated under reflux for three hours. Then added 1-1.5 gm of charcoal cautiously and the mixture was further heated at the reflux for 10 minutes, the charcoal is removed by filtration. The filtrate was heated to 60-70^{0}C, 100ml of warm water is added, and acidified with dilute acetic acid with good stirring. The product separated as glistening white crystals, and the mixture is placed in a refrigerator for three hours to complete the crystallization. The product was collected on a Buckner funnel and dried over night at 40^{0}C. The dried product was recrystallized by ethanol the yield is 8.5gm (73%) melting point is 300-305^{0}C.

Step-2: General procedure for preparation of *N*-substituted–α-chloroacetanilides:-

The aromatic amines (0.05mole) were dissolved in a mixture of glacial acetic acid (25ml) and saturated solution of sodium acetate (25ml) and cooled to 5^0 C. To this, chloroacetylchloride (6.2ml. 0.075 mole) was added drop wise at 0-5^0 C under constant stirring. Then it was left at room temperature for 5-6 hr and the crude product that separated was filtered, washed with 50% acetic acid and cold water. It was recrystallized from suitable solvent.

Step-3: General procedure for the preparation of substituted 2-(1*H*-benzimidazol-2-ylsulfanyl)-*N*-phenylacetamide:

2-mercaptobenzimidazole (I) (1.50gm. 0.01 mole) was dissolved in aqueous potassium hydroxide solution (0.61gm in 10ml water) with stirring till a clear yellow solution was obtained. It was filtered to remove any suspended impurities. Then various aromatic *N*-substituted-α-chloroacetanilides (II) (0.011 mole) were added in small proportions with magnetic stirring at 50-60^0 C for ½ hr. Precipitate was filtered and washed with cold water to remove KCl and dry. Dried product (III) was recrystallized from aqueous ethanol.

RESULTS AND DISCUSSION

It is noteworthy that such a procedure for rapid preparation of various benzimidazoles affords advantages of short reaction time, moderate yields and simple workup. M_1 compound exhibited N-H absorption peak at 3245 cm^{-1} which is the normal place of absorption of N-H of benzimidazole moiety. The N-H of amide resonated at 3134 cm^{-1}. The aromatic C-H peak is notices 3069 cm^{-1} but aliphatic C-H at 2978 cm^{-1}. The C=O of the amide appeared at 1672 cm^{-1}. These data in confirmative with the structural propose of the synthesized compound.

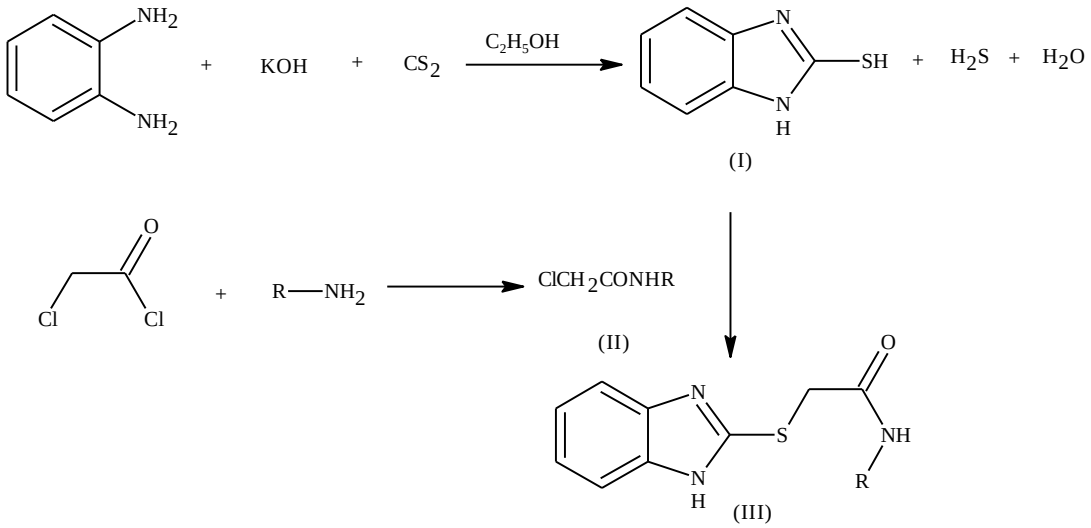
The ^{1}H NMR of this compound when recorded in DMSO-d6 gave DMSO peak at 3.4 δ, where as CH_2 protons of the side chain resonated at 4.5 δ. The H of N-H group which is sandwiched between two deshielding moieties one side is C=O other side phenyl ring gave an absorption peak at downfield due to deshielding effect at 10.5 δ. The H of N-H of benzimidazole moiety gave an absorption peak at 7.4 δ. The aromatic cluster is seen from 7.1 to 7.8 δ as multiplet. These ^{1}H NMR data are in confirmative with the structure of the molecule proposed under investigation. The IR spectrum of M_2 also gives N-H absorption peak at 3244cm^{-1} and 3152cm^{-1}. In these case the aromatic C-H peak is seen at 3082 cm^{-1} and aliphatic C-H peak is seen at 2975 cm^{-1}, C=O of amide absorbed at 1667 cm^{-1}. These are the expected concurrent data for proposed molecule.

The next analogue of the compound M_3 where in NO_2 substitution is carried out at the aniline moiety. In these cases N-H of benzimidazole gave an absorption peak at 3220 cm^{-1} and N-H of amide at 3167 cm^{-1}. The aromatic C-H peak found to be absorbed at 3096 cm^{-1} and 3043 cm^{-1}. The aliphatic C-H peak is found to be absorbed at 2917 cm^{-1}. The C=O of amide group gave absorption peak at 1677 cm^{-1}. These are the expected IR data for the molecule under investigation. These compound was taken for ^1H NMR measurement in DMSO-d6 solution in the strong absorption peak due to H of DMSO is seen resonated at 3.4 δ but CH_2 protons present in the side chain gave an absorption peak at 4.4 δ. The downfield shift of the H of N-H is found at 11.1 δ due to the strong deshielding effects of p-nitro aniline moiety and C=O attached to the both sides of N-H group. The H of N-H of benzimidazole moiety is seen at 7.5 δ. The multiplet of aromatic moiety is found from 7.1 δ to 8.4 δ. These are in confirmative which is proposed structure of the molecule under investigation.

In M_4 compound the IR data obtained are in resembling with the IR data found for the compounds already described. The H of N-H found at 3294 cm^{-1} and H of N-H of amide at 3199 cm^{-1}. The C=O of the amide at 1676 cm^{-1}. These are the data obtained resembling with expected data. The next compound M_5 taken for IR measurement is diflouroaniline substituted to benzimidazole derivatives. This compound produce IR measurement identical with the previous spectrum discuss. In this case also N-H, CH, C=O absorption peak appear at the places where they are expected to appear.

The synthesized all benzimidazole derivatives were screened for antibacterial activity using DMF as a solvent against the organisms, *S.aureus* and *E.coli*. And Antifungal activity using *Candida albicans*. By disc diffusion method on nutrient agar media. The Ampicillin was used as standard drug for antibacterial and Ketoconazole as standard for antifungal activity. M_1, M_2, M_4 and M_5 showed good activity at concentration 50µg/ml and at 100 µg/ml they possess good activity against *E.Coli* and *S .Aureus*. M_3 Shows good activity at 50 µg/ml but at 100 µg/ml it shows very good activity against *S.Aureus* when compared with Ampicillin.

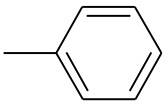
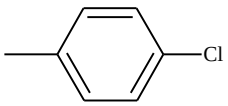
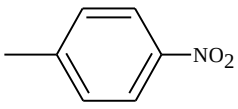
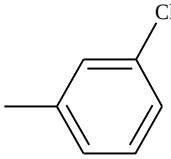
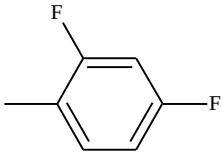
The same Compounds also screened for the antifungal activity against *Candida albicans* the compounds M_1, M_2, M_3, M_4 and M_5 Showed no growth at 250µg/ml and 500µg/ml against *C. albicans* when compared with the standard drug Ketoconazole. However the activities shown by all the compounds were less than that of the standard.



SCHEME 1

Where R= -C_6H_5, *P*-ClC_6H_4, *m*-ClC_6H_4, *P*-$NO_2C_6H_4$, 2, 4 di F-$C6H_3$

Table 1: Physicochemical parameters of benzimidazole derivatives.

Sr No.	Compound code	R	Molecular Formula	Molecular Weight	% yield	Melting point (^{0}C)
1	M_1		$C_{15}H_{13}N_3OS$	283.34	77	205-210
2	M_2		$C_{15}H_{12}ClN_3OS$	317.79	65	190-195
3	M_3		$C_{15}H_{12}N_4O_3S$	328.79	75	215-220
4	M_4		$C_{15}H_{11}ClN_3OS$	317.79	63	170-175
5	M_5		$C_{15}H_{11}F_2N_3OS$	319.32	60	175-178

Antimicrobial Activity[7-12]:

All the compounds synthesized in the present investigation were screened for their *in vitro* antibacterial activity by Cup plate Method. Antibacterial activities were tested against,

Staphylococcus aureus, and *Escherichia coli* which are representative types of gram positive and gram negative organisms respectively. The antibacterial activity of the compounds was assessed by disc diffusion method. The extent diameter of inhibition after 24hrs for antimicrobial activity was measured as the zone of inhibition in mm and the results were shown in **Table No-2.** Antifungal activity tested against *C. albicans* and extent diameter of inhibition after 48hrs of incubation at 30ºC. Ketoconazole as standard reference and obtained results were tabulated **Table-3**.

Table 2 Antibacterial activity data of synthesized benzimidazole

Sr. No	Compound	Concentration µg/ml	*E. coli* (mm)	*S. Aureus* (mm)
1.	M_1	50	11	13
		100	15	17
2.	M_2	50	13	15
		100	17	19
3.	M_3	50	17	19
		100	21	23
4.	M_4	50	13	15
		100	17	19
5.	M_5	50	13	15
		100	17	19
6.	Ampicillin	50	23	25
		100	25	25

Table 3 Antifungal activity data of synthesized benzimidazole

Sr. No	Compound	Concentration µg/ml	*Candida albicans*
1.	M_1	250	-
		500	-
2.	M_2	250	-
		500	-
3.	M_3	250	-
		500	-
4.	M_4	250	-
		500	-
5.	M_5	250	-
		500	-
6.	Ketoconazole	250	-
		500	-

Note: (-) No growth

The compounds were tested at two concentrations antibacterial activity namely 50µg/ml and 100µg/ml in DMF against gram positive and gram negative organisms. The zone of inhibition was compared with Ampicillin and antifungal activity is tested in Concentration 250 µg/ml and 500µg/ml Ketoconazole.

CONCLUSION:

In this work, the reaction of 2-mercaptobenzimidazole and various aromatic *N*-substituted-α-chloroacetanilides in presence of aq. KOH in the synthesis of benzimidazole derivatives is successfully carried out. The data obtained from IR, ^{1}H NMR and Mass data resembled with expected data. The data obtained in confirmative with the structural propose of the synthesized compound. Since some of the present new benzimidazole derivatives exhibit moderate antibacterial activity compared with the standard employed, it is desirable to determine their toxicity to decide on whether to go for further screening or not.

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