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Synthesis and Biological Evaluation of 2-Mercaptobenzimidazole Derivatives as Anti-inflammatory Agents

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Abstract: A series of 2-mercaptobenzimidazole derivatives (MB1–MB5) were synthesized by mannich reaction. The purity of synthesized compounds were determined by melting point and TLC and their structure was established by various analytical techniques such as IR and 1HNMR spectral studies. The newly synthesized compounds were screened for anti-inflammatory activities on carrageenan induced paw oedema in rats. Compounds MB1 and MB5 showed a significant anti-inflammatory activity when compared with standard drug indomethacin. The other compounds showed promising anti-inflammatory activity.

Keywords: 2-Mercaptobenzimidazole, Mannich Reaction, Anti-inflammatory

1. Introduction

Inflammation is a response of the tissue to an infection, irritation or foreign substance and is a part of the host defence mechanism. The inflammatory process involves a series of events that can be elicited by numerous stimuli (e.g. infectious agents, ischemia, antigen-antibody interaction and thermal or other physical injuries).

In recent years benzimidazole derivatives have attracted considerable interest because of their therapeutic and pharmacological properties. It is well known that benzimidazole derivatives possess antimicrobial [1], analgesic and anti-inflammatory activities [2], as well as proved to have activities against HIV and cancer [3, 4]. 2-mercaptobenzimidazole, one of the most important derivatives of benzimidazole exhibited a wide variety of interesting biological activities such as antimicrobial, antihistamine, neurotropic and analgesic activities. These observations have been guiding for the development of new 2-mercaptobenzimidazole derivatives that possess varied biological activities.

The success of NSAIDs in treatment of various inflammatory disorders validated inhibition of COX enzyme as a highly suitable target of anti-inflammatory therapies. However, the gastrointestinal toxicities associated with widespread use of NSAIDs proved to be a major problem during long term therapy [5]. Although COX-2 is concerned to be the main isoenzyme related to inflammation, most NSAIDs in the market today block both forms of COX isoenzymes. Side effects such as gastrointestinal pain have been associated with NSAID use due to the inhibition of COX-1 [6].

The identification of cyclooxygenase-2 (COX-2) and the subsequent introduction of the COX-2 selective inhibitor NSAIDs were thought to be a major breakthrough, with the expectation of a significant reduction in GI side effects [7]. The differential tissue distribution of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) provides a rationale for the development of selective COX-2 inhibitors as anti-inflammatory-analgesic agents that lack the GI side effects exhibited by traditional NSAIDs [8].

The initial postulate that a selective COX-2 inhibitor would reduce inflammation without causing gastric irritation was validated following the introduction of selective COX-2 inhibitors such as celecoxib and rofecoxib. However, it was subsequently observed that selective COX-2 inhibitors may alter the balance in the cyclooxygenase pathway resulting in a decrease in the level of the vasodilatory and anti-aggregatory prostacyclin (PGI2), relative to an increase in the level of the prothrombotic thromboxane A2 (TxA2), leading

to increased incidences of an adverse cardiovascular thrombotic event [9].

This limitation has led to the investigation of new 2-mercaptobenzimidazole derivatives with that more potent activity and less toxicity. Motivated by the aforementioned endings, it was designed to synthesize novel series of 2-mercaptobenzimidazole derivatives that would act as anti inflammatory agents.

2. Materials and Method

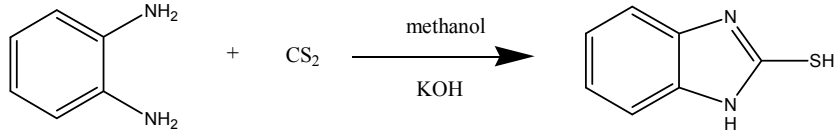
Starting materials and reagents used were procured from commercial suppliers. A melting point was determined by open-ended capillary tube on Veego electrical melting point apparatus and was uncorrected. The purity of the compounds were checked by TLC using Silica Gel as stationary phase and chloroform: methanol (9: 1) as eluent and the spots were visually detected in an Iodine chamber. The structure of synthesized compounds was determined by spectral analysis. The λ_{max} of synthesized compound was determined by using Shimadzu model 1700 spectrophotometer. IR spectra was recorded using KBr disc technique and ^{1}H NMR spectra in δ units (ppm) relative to an internal standard of tetramethylsilane on ^{1}H NMR in DMSO-d_6.

3. Chemistry

Synthesis of ketosulfones derivatives was done in three steps.

Step-1: Synthesis of 2-mercaptobenzimidazole

A mixture of o-phenylenediamine (0.01 mole), potassium hydroxide (0.01 mole) and carbon disulfide (0.01 mole), 100 ml of methanol and 15ml of water in a 500 ml round bottom flask and heated under reflux for 3 hours. The reaction mixture was then filtered. The filtrate was heated to 60-70ºC then 100 ml water was added, and then the mixture was acidified with dilute acetic acid with stirring. The mixture was then placed in the refrigerator for crystallization. The product was collected after filtration and dried. The product was recrystallized with ethanol [10].

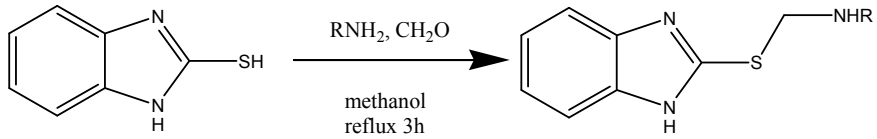


o-phenylene diamine carbon disulphide 2-mercaptobenzimidazole

Figure 1. *Scheme for synthesis of 2-mercaptobenzimidazole.*

Step-2: Synthesis of 2-mercaptobenzimidazole derivatives

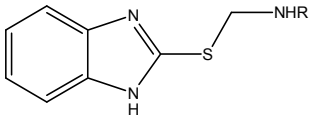
2-Mercaptobenzimidazole (0.01 mole) in 30 ml methanol, different amines (0.01 mole) and formaldehyde solution (1 ml) was refluxed for 3-4 hours. On cooling there action mixture was poured on crushed ice. Then it was kept in refrigerator overnight. The precipitated mannich base was filtered and recrystallized from ethanol [11].

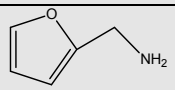
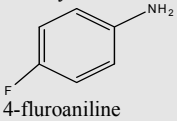
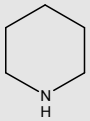
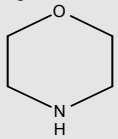
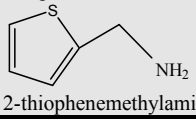


2-mercaptobenzimidazole MB 1-5

Figure 2. *Scheme for synthesis of 2-mercaptobenzimidazole derivatives.*

Table 1. *Synthesized compounds with their derivatives.*



S.No.	Compound code	RNH_2
1.	MB 1	 Furfurylamine
2.	MB 2	 4-fluroaniline
3.	MB 3	 Piperidine
4.	MB 4	 Morpholine
5.	MB 5	 2-thiophenemethylamine

2-[[(3-furanyl)-aminomethyl]-thio]-1H benzimidazole (MB-1).

Yield: 45%; m. p.: 160-163ºC; λ_{max}: 307; IR (abs): 2959cm^{-1}(C-H str), 3451cm^{-1}(N-H str), 1621cm^{-1}(N-H bend), 1039cm^{-1}(C-O-C str), 1466cm^{-1}(C=C str), 1226cm^{-1}(C-N str); ^{1}HNMR (DMSO-d_6) δ: 7.2-7.9 (m, Ar-CH, 4H), 5.2 (s, NH, 1H), 4.3 (d, CH_2, 2H), 4.0 (t, Ar-NH, 1H), 6.2-6.3 (d, Ar-CH, 3H).

2-[[(4-fluro-phenyl)-aminomethyl]-thio]-1H benzimidazole (MB-2).

Yield: 30%; m.p.: 155-157ºC; λ_{max}: 306; IR (abs): 2960cm^{-1}(C-H str), 3452cm^{-1}(N-H str), 1622cm^{-1}(N-H bend), 1465cm^{-1}(C=C str), 1418cm^{-1}(C-H bend), 1153(C-F str), 1271cm^{-1}(C-N str), 741cm^{-1}(C-H bend); ^{1}HNMR (DMSO-d_6)δ: 7.26-7.70(m, Ar-CH, 4H), 5.2(s, NH, 1H), 4.31(d, CH_2, 2H), 4.0(t, Ar-NH, 1H), 6.3-6.4(d, CH, 4H).

2-[[(1-piperidinyl)-aminomethyl]-thio]-1H benzimidazole (MB-3).

Yield: 80%; m.p.: 149-152ºC; λ_{max}: 305; IR (abs): 3417cm^{-1}(N-H str); 1622cm^{-1}(C=C str), 1508cm^{-1}(N-H bend), 1390cm^{-1}(C-N str), 749cm^{-1}(C-H bend); ^{1}HNMR (DMSO-d_6) δ: 7.2-7.9(m, Ar-CH, 4H), 5.2(s, NH, 1H), 4.31(s, CH_2, 2H), 1.2-2.6(m, CH_2, 5H).

2-[[(4-morphinyl)-aminomethyl]-thio]-1H benzimidazole (MB-4).

Yield: 83%; m.p.: 190-192ºC;λ_{max}: 304; IR (abs): 2960cm^{-1}(C-H str), 3452cm^{-1}(N-H str), 1283cm^{-1}(C-N str), 1624cm^{-1}(C=C str), 1508cm^{-1}(N-H bend), 1052cm^{-1}(C-O-C str), 751cm^{-1}(C-H bend); ^{1}HNMR (DMSO-d_6) δ: 7.2-7.9(m, Ar-CH, 4H), 5.2(s, NH, 1H), 2.4-3.9(m, CH_2, 2H), 4.0(s, CH_2, 2H).

2-[[(3-thiopheneyl)-aminomethyl]-thio]-1H benzimidazole (MB-5).

Yield: 77%; m.p.: 119-121ºC; λ_{max}: 306; IR (abs): 2959cm^{-1}(C-H str), 3451cm^{-1}(N-H str), 1621cm^{-1}(N-H bend), 1466cm^{-1}(C=C str), 1226cm^{-1}(C-N bend), 741cm^{-1}(C-H bend); ^{1}HNMR (DMSO-d_6) δ: 7.2-7.9(m, Ar-CH, 4H), 5.2(s, NH, 1H), 4.31(d, CH_2, 2H), 4.0(m, Ar-NH, 1H), 6.2-6.4(d, CH, 1H).

4. Carrageenan Induced Rat Paw-edema Method

All the synthesized compounds were evaluated for their anti-inflammatory activity by carrageenan induced paw edema method. The animals were divided into 7 groups of six animals each. Tween 80 suspension (0.5 % v/v) of test compounds was administered intraperitoneally at a dose of 20 mg/kg. The control group was given only 0.5 % v/v Tween 80 (0.5 ml) suspension. One group was administered Indomethacin as standard, intraperitoneally at a dose of 10 mg/kg. Thirty minutes after the administration of test compounds and indomethacin, 0.1 ml of carrageenan suspension (1 %, v/v in normal saline) was injected into the left hind paw subplantar region of control and test animals were used to induce the paw edema. The paw volume was measured immediately using a plethysmometer (initial paw volume), and thereafter the paw volume was measured every one hour for three hours. The anti-inflammatory activity was measured in terms of percentage inhibition of edema [12].

$$\%\text{Inhibition} = (1-V_t/V_c)*100$$

V_t and V_c is a edema volume in the rat treated with the test drug and control respectively.

Table 2. *Anti-inflammatory activity of synthesized compounds by carrageenan induced rat hind paw edema method.*

Groups	Dose (mg/kg)	Mean paw volume ± SEM			% inhibition
		Before carrageenan (V_0)	After 3 hrs (V_t)	V_t-V_0	
I (control)	---	0.415±0.013	0.72±0.027	0.305±0.192	---
II (std)	10	0.428±0.014	0.052±0.016	0.092±0.007*	69.83
III (MB-1)	20	0.0426±0.013	0.501±0.020	0.086±0.021*	65.85
IV (MB-2)	20	0.405±0.005	0.56±0.018	0.158±0.022*	48.19
V (MB-3)	20	0.415±0.008	0.556±0.018	0.156±0.015*	44.85
VI (MB-4)	20	0.423±0.012	0.59±0.030	0.170±0.030*	42.26
VII (MB-5)	20	0.413±0.009	0.58±0.016	0.171±0.024*	50.93

(Values are represent mean ± SEM; n= 6 albino rats per groups; *P<0.05 as compared with control group)

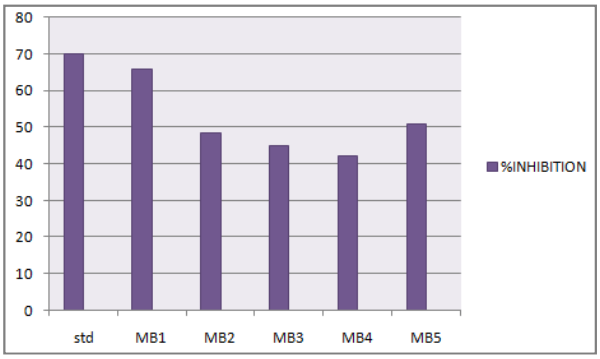


Figure 3. *Graph representing %inhibition of the compounds.*

5. Result and Discussion

The melting point of all compounds was observed different from ingredients melting point which confirmed the synthesis of product. The purity of synthesized compounds was checked by observing single spot on TLC plate. All synthesized compounds gave only single spot. It means all synthesized compounds were obtained in pure form. The UV λ_{max} of synthesized compounds was observed at range between 304-308 nm.

IR spectroscopy helps to identify the chemical structure of the compounds, like in the given data all the compounds

show the peak values of the representing group which is present in the compounds so all these 2-mercaptobenzimidazole derivatives show N-H stretch, C-C stretch (aromatic), C-N stretch, C-H bend, N-H bend, C-F stretch peaks with the absence of SH proton of 2-mercaptobenzimidazole confirmed the formation of 2-mercaptobenzimidazole derivatives.

NMR spectroscopical data also helps to confirm the presence of hydrogen bonds in the compound so here the NMR spectroscopy was done by using DMSO-d_6 as the solvent and tetra methyl silane as the internal standard and the chemical shift values (ppm) gave the much more conformation about the structural determination of the compounds.

After structural determination, the in-vivo testing of the synthesized compounds was also done by using carrageenan-induced rat hind paw edema method in which swiss albino rats were used for animal model, 1% carrageenan solution (for induction of inflammation in animals), indomethacin (NSAID) in a dose of 10mg/kg body weight, and for test compounds 20mg/kg body weight, method includes 7 groups on which this study was performed as control, standard, and 5 test compound groups. % inhibition values were represented as mean ± SEM.

The order of anti-inflammatory activity of the synthesized compounds is as follows:

MB1>MB5>MB2>MB3>MB4

Synthesized compound MB-1 and standard drug indomethacin showed 65.85% and 69.83% inhibition of paw edema respectively. Compound MB-1 showed maximum activity as compared to other compounds.

6. Conclusion

Synthesized compound MB-1 and standard drug indomethacin showed 65.85% and 69.83% inhibition of paw oedema respectively. Compound MB-1 showed maximum activity as compared to other compounds. The standard drug indomethacin is a COX-2 inhibitory anti-inflammatory agent so it can be concluded that compound MB-1 may also showed anti-inflammatory activity due to inhibition of COX-2 enzyme.

The findings of the present study revealed that the considerable variation of these effects were seen with each structural change, varying from agents that had less activity to those high potency, and significant change in potency resulted even from minor change in chemical structure. The study can be explored for further study in the development of novel anti-inflammatory agents containing 2-mercaptobenzimidazole nucleus.

Abbreviations

TLC-Thin Layer Chromatography
IR-Infra Red
NMR-Nuclear Magnetic Resonance
NSAIDs-Nonsteroidal anti-inflammatory drugs
COX-cyclooxygenase

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