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Synthesis, Characterization, and Preliminary Structure Activity Evaluation of Mannich Base Derivatives of 2-Mercaptobenzimidazole

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Abstract: The unceasing development of resistance to drugs requires the discovery of new bioactive compounds and the enhancement of pharmacological properties in small molecules. In this research, a series of twelve derivatives of 2-Mercaptobenzimidazole (AK1-AK12) were successfully prepared from formaldehyde, benzaldehyde, and 4-chlorobenzaldehyde as linkers, as well as from various secondary amines such as diethanolamine, 4-hydroxydiphenylamine, and a few fragments of drugs. The resulted compounds were prepared under mild acidic conditions in ethanol/methanol solvents, and good to excellent yields (68-92%) of the desired compounds were achieved. The prepared compounds were identified by thin layer chromatography, melting point measurements, and FT-IR and 1HNMR analyses, demonstrating the success of aminomethylation and the creation of new C-N/C-S bonds. The initial physicochemical studies of the prepared compounds showed that aromatic and medicinal Mannich base derivatives possessed relatively enhanced activities. Electron-withdrawing groups played a positive role in such effects. In principle, despite the challenges and complexity of pharmacological studies, the results of such studies indicate the potential of new Mannich base derivatives of 2-mercaptobenzimidazole as templates in further pharmacological optimization.

Keywords: Mannich base, 2-Mercaptobenzimidazole, Secondary amines, Linkers, Structure activity relationship.

INTRODUCTION

With an increase in drug resistance, it is the need of time to discover new pathways to synthesize new drugs having potent therapeutic activity but limited side effects. An increase in scientific knowledge gives an efficient manner to synthesize libraries containing hundred to thousand compounds but breakthrough discoveries relevant to disease continued to be slow and debatable (Galloway et al., 2010).

For this purpose small molecules having any sort of biological activities but not having any specific target like protein are synthesized and derivatize to find out the biological pathway in cells or organisms (Ali et al., 2025. One of other objective is to synthesize small molecules having the ability to regulate any biological pathway so that helps to identify therapeutic protein targets ((Abbasi et al., 2021, Welsch et al., 2010). Nowadays new strategy for drug discovery is the use of advantageous scaffolds having any potent bioactivity and can serve as ligands for a diverse list of receptors (Kuehnert et al., 2001).

2-Mercaptobenzimidazole is derived from benzimidazole having thiol group in the 2- position. Its synonyms are benzimidazole-2-thion, o-phenylen thiourea with a molecular formula of C7H6N2S (Husain et al., 2011). It can react easily to give derivatives having substitution at Sulphur or Nitrogen atoms (Ahamed et al., 2013). It possesses C=S and C-S-H groups, hence it can occur in the dimer (Fahmy et al., 1986) and show the property of tautomerism, thiol, and thione form (Reddy et al., 2008).

2-Mercaptobenzimidazole derivatives have been synthesized and reported to exhibit a variety of biological activities including analgesic (Anandarajagopal et al., 2010), antiallergy H1 receptor blocker (Mor et al., 2004), neutropic (Bakhareva et al., 1996), antimicrobial (Mauro et al., 2007). Besides medicinal importance, this Pharmacophore possesses non-biological activities including plant growth regulators (Rebstock et al., 1955), anti-oxidant for plastics and rubber (Norford et al., 1993), insecticidal (Saxena et al., 1982).

Mannich Reaction History

Mannich reaction is one of the basic and significant reaction, it has a large diversity of functional groups, hence it has grown in modern chemistry (Mannich and Krösche, 1912). Amino alkylation is done easily during Mannich reaction which allows the synthesis of derivatives (Luo et al., 2009). The classical Mannich reactions have limitations such as competitive aldol condensation and regioselectivity but nowadays these limitations are overcome by using optimal catalyst and reaction conditions along with utilizing new functional groups, imines and enolates (Yang et al., 2011). Mannich reaction is a condensation reaction between diverse substrates having at least one active hydrogen atom, an aldehyde component (generally R1-CHO) and an amine (primary or secondary) reagent which results to a class of compounds generally known as Mannich bases. In Mannich reaction nucleophilic substitution reaction takes place via active hydrogen atom compound allowed to react with aldehyde or amine (primary or secondary), the final product is amine compound known as Mannich base having N, S linked to the R substrate through methylene bridge (Tramontini and Angiolini, 1994).

Mannich reaction mechanism

Mannich reaction is a condensation reaction including substrate (nucleus), amine (primary or secondary) linker (aldehyde). Mannich reaction occurs in two steps.

1) The reaction between amine and linker to form methyleneimmonium salt
2) Methyleneimmonium salt attacks the substrate to form Mannich base (Tramontini and Angiolini, 1994).

Reactants Of Mannich Reaction

Mannich reaction is a condensation of a compound containing an active H atom, despite that is attached to C, N, S or other atoms. Only reaction conditions and reagents differ in each case. The functional group is a vital basic component of Pharmacophore so that aminomethylation can occur dynamically (Ried and Stahlhofen, 1957). Substrates having nucleophilic properties are preferred, -XH compounds having –X is equivalent to -C, -S or any other heteroatom, -NH substrates might be amides, amines or heterocycles. Mannich products of alcohols are mostly stable (Tramontini, 1973). Like substrates amine or drug also contains one active H atom to proceed with the reaction. Secondary amines are preferred as they give mono substituted Mannich bases whereas primary amines will give double Mannich bases which are not as suitable as the prior one. Hydroxylamine derivatives, ammonia, and hydrazine are used as well as drugs containing suitable functional groups were also used (Tramontini and Angiolini, 1990). Formalin 37% is most commonly used as a linker, it is employed to make methylene bridge between substrates and amine groups (Tramontini and Angiolini, 1990). Moreover, many other aldehydes including Benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde and so on are used as linker (Desai and Desai, 2006).

MATERIALS & METHODS

All the chemicals, which were used, are manufactured by Merck, Sigma Aldrich, Daejung and utilized in the synthesis of Mannich based derivatives of 2-Mercaptobenzimidazole.

Materials

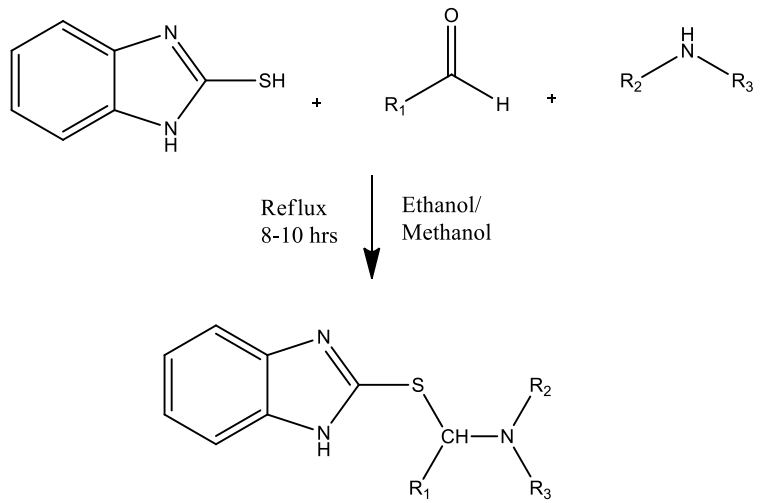
Table 1: Description of substrate, linkers, secondary amines and solvents

Substrate	Linker	Secondary Amine/Drug	Solvent/ Catalyst
2-Mercaptobezimidazole	Formalin	4-Hydroxydiphenyl amine	Methanol
	4-Chlorobenzaldehyde	Diethanolamine	Ethanol
	Benzaldehyde	Tizanidine HCl	Acetone
		Ceftazidime. $5H_2O$	Ethyl acetate
		Cefotaxime Na	Conc. HCl

Methods

Optimization and general synthesis mechanism

For the process of optimization, we use different solvents (Ethanol, Methanol), to obtain the maximum yield of the product. Different TLC systems were employed for checking reaction progress n-Hexane: Ethyl Acetate (3:1), n-Hexane: Ethyl Acetate (1:1), Chloroform: Ethanol (9:1). Among these (3:1) system and Ethanol as a solvent gives maximum yield. A mixture of equimolar 2-Mercaptobenzimidazole (0.01mol) and linkers Formalin, Benzaldehyde, 4-Chlorobenzaldehyde (0.01mol) was taken in a round bottom flask containing Methanol (30ml). Reflux this reaction mixture for approximately 1 hour along with gentle stirring. After stirring secondary amine/drug (0.01mol) was added and refluxed for 8-10 hours. TLC was employed to check the progress of the reaction, after reaction completion, the filtrate was cooled and dried, if needed the recrystallized product is recovered by using an organic solvent (Ethanol/n- Hexane) (Gupta et al., 2015).



Scheme 1: Scheme of synthesis of Mannich based derivatives of 2-Mercaptobenzimidazole

Table 2: Description of R1, R2 and R3 substitution

Compounds	R1	R2	R3
AK1	Formalin	Phenol	Benzene
AK2	4-Chlorobenzaldehyde	Phenol	Benzene
AK3	Benzaldehyde	Phenol	Benzene
AK4	Benzaldehyde	Hydoxyethyl	Hydoxyethyl
AK5	Formalin	Hydoxyethyl	Hydoxyethyl
AK6	4-Chlorobenzaldehyde	Hydoxyethyl	Hydoxyethyl
		Drugs	
AK7	4-Chlorobenzaldehyde	Tizanidine	
AK8	Formalin	Tizanidine	
AK9	Benzaldehyde	Tizanidine	
AK10	4-Chlorobenzaldehyde	Ceftazidime	
AK11	Benzaldehyde	Cefotaxime	

AK12	4-Chlorobenzaldehyde	Cefotaxime

Characterization

The newly synthesized compound did not require any further type of purification and they were recrystallized out by using different solvents (Ethanol). TLC made by Merck TLC Silica gel 60 F254 performed to verify the purity during synthesis. TLC is the most economical way to identify the ongoing synthesis, by this technique numbers of components in a mixture are determined and the extent of reaction can be determined. Different spots will give information about the formation of the product, unreacted components, and impurity. The spots were visualized by using an ultraviolet lamp having a wavelength between 254nm to 366nm. The mobile phase used consist of n-hexane, ethyl acetate (3:1). Change in melting point indicates the synthesis of the new compound, Gallen Kamp apparatus is used to determine the melting point of newly synthesized compounds. The solubility of any compound gives characteristic properties, the newly synthesized compounds show different solubility as compared to the parent molecule. FTIR and 1HNMR spectroscopy is employed to determine the structure of newly synthesized compounds.

RESULTS

Synthesis of compounds was carried out by using a scheme mentioned in section 2.2. The purity and reaction proceeding was checked by the help of TLC. TLC confirms that reaction yields a pure compound having only one spot. The melting point was determined by using Gallen Kamp apparatus. Structures of the newly synthesized compounds were verified by FTIR and 1HNMR spectroscopy. Finally, compounds were evaluated for antioxidant activity, antibacterial, antifungal, Brine shrimp lethality assay for confirmation of biological activities.

Physico-chemical Properties of Synthesized Compounds

All compounds were obtained in fine crystalline powder by recrystallization technique. Detailed physical characteristics are given in the table. Following table 3.1 shows physico-chemical properties of synthesized compounds.

Table 3. Physico-chemical properties of synthesized compounds (AK1-AK12)

Code	Description	Washing	Physical State	Melting Point	Molecular Weight	% Yield
AK1	0.01M of nucleus 2-MB+4HDPA+HCHO dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Greenish Black Powder	184°C	347g/mol	91%
AK2	0.01M of nucleus 2-MB+4HDPA+4-CBA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Green Powder	171°C	457g/mol	82%
AK3	0.01M of nucleus 2-MB+4HDPA+BEA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Green Powder	164°C	423g/mol	68.3%
AK4	0.01M of nucleus 2-MB+DEA+BEA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Brown Sticky Powder	147°C	343g/mol	72.5%
AK5	0.01M of nucleus 2-MB+DEA+HCHO dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Yellow Powder	149°C	267g/mol	92%
AK6	0.01M of nucleus 2-MB+DEA+4-CBA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane Ethanol soluble on heating	Yellow Luster Powder	143°C	377g/mol	79.4%
AK7	0.01M of nucleus 2-MB+TZN+4-CBA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane:	n-Hexane Ethanol soluble on	Yellow Powd	205°C	525g/mol	91.4%

	EA)	heating	er			
AK8	0.01M of nucleus 2-MB+TZN+HCHO dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Yellow Powder	198°C	415g/mol	89.3%
AK9	0.01M of nucleus 2-MB+TZN+BEA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Dull Yellow Powder	212°C	491g/mol	85.7%
AK10	0.01M of nucleus 2-MB+CFT+4-CBA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Orange Powder	201°C	820g/mol	89.2%
AK11	0.01M of nucleus 2-MB+CFX+BEA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Orange Powder	211°C	691g/mol	74%
AK12	0.01M of nucleus 2-MB+CFT+4-CBA dissolved in 30ml Methanol, few drops of HCl (3:1 n-Hexane: EA)	n-Hexane	Yellow Powder	207°C	725g/mol	81%

FTIR Spectral Data of Synthesized Compounds

FTIR is a tool to confirm different functional groups, expected stretches of a secondary amine, hydroxyl, imidazole, was observed at expected wave number. Values are enlisted in the table below. Following table 3.2 shows FTIR of synthesized compounds.

Table 4. FTIR Spectral Data of synthesized compounds (AK1-AK12)

Compound	(C-H) cm-1 Aromatic	(C-H) cm-1 Aliphatic	(C=C) cm-1 Aromatic	(C=N) cm-1 Imidazole	(C-S) cm-1	(N-H) cm-1	(O-H) cm-1 Aromatic	(O-H) cm-1 Aliphatic
2-MBI	3040	-	1515	1624	659	3159	-	-
AK1	3056	2916	1567	1616	675	3345	3434	-
AK2	3078	2878	1582	1618	665	3450	3391	-
AK3	3075	2943	1534	1626	683	3345	3472	-
AK4	3067	2924	1547	1610	645	3328	-	3250
AK5	3086	2897	1576	1613	634	3245	-	3267
AK6	3048	2904	1539	1623	662	3187	-	3278
AK7	3021	2934	1579	1630	651	3376	-	-
AK8	3062	2940	1545	1628	674	3469	-	-
AK9	3059	2884	1549	1620	639	3328	-	-
AK10	3027	2893	1529	1616	645	3378	-	3254
AK11	3075	2939	1519	1623	672	3421	-	3269
AK12	3091	2928	1567	1627	682	3146	-	3288

Table 5. 1HNMR spectral data of synthesized derivatives

Compound	δ (ppm) ^{1}H-NMR (DMSO-d_6, 400 MHz)
AK1	6.43-7.59 (m, 13H, Ar-H); 5.35 (s, 1H, OH); 4.94 (s, 1H, –NH); 4.70 (s, 2H, CH_2)
AK2	6.43-7.77 (m, 17H, Ar-H); 5.55 (s, 1H, OH); 5.14 (s, 1H, –NH); 4.94 (s, 1H, CH)
AK3	6.23-7.44 (m, 18H, Ar-H); 5.25 (s, 1H, OH); 5.22 (s, 1H, –NH); 4.88 (s, 1H, CH)
AK4	7.22-7.89 (m, 9H, Ar-H); 3.65 (s, 2H, OH); 5.04 (s, 1H, –NH); 4.95 (s, 1H, CH), 2.55 (s, 2H, CH_2), 3.65 (s, 2H, CH_2)
AK5	7.13-7.59 (m, 4H, Ar-H); 3.35 (s, 2H, OH); 4.94 (s, 1H, –NH); 3.95 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 3.45 (s, 2H, CH_2)

Compound	δ (ppm) ^{1}H-NMR (DMSO-d_6, 400 MHz)
AK6	7.17-7.69 (m, 9H, Ar-H); 3.55 (s, 2H, OH); 4.94 (s, 1H, –NH); 4.85 (s, 1H, CH), 2.55 (s, 2H, CH_2), 3.63 (s, 2H, CH_2)

SUPPLEMTARY FIGURES

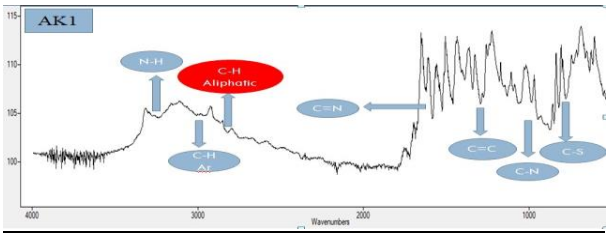


Figure S1 FTIR spectra of AK1

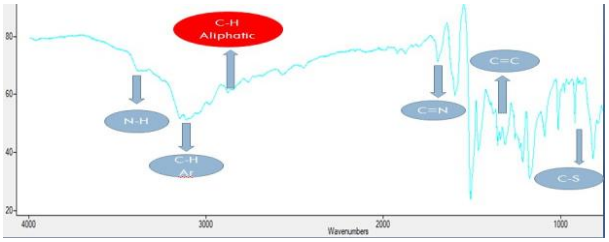


Figure S2 FTIR spectra of AK2

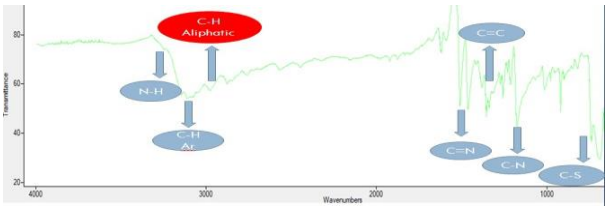


Figure S3 FTIR spectra of AK3

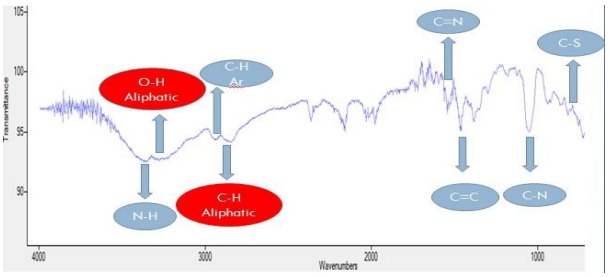


Figure S4 FTIR spectra of AK4

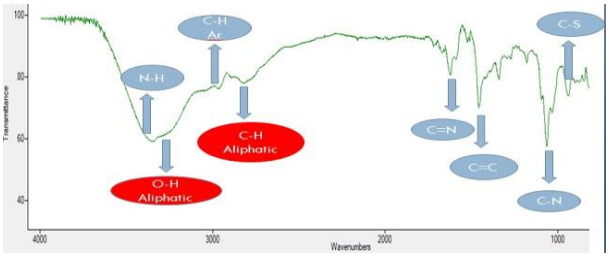


Figure S5 FTIR spectra of AK5

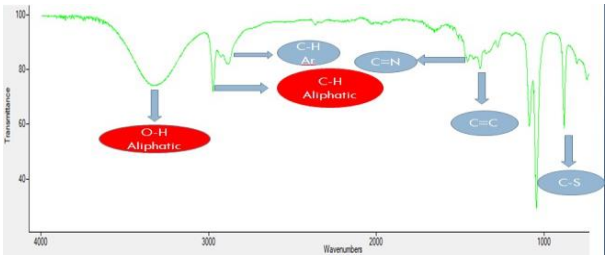


Figure S6 FTIR spectra of AK6

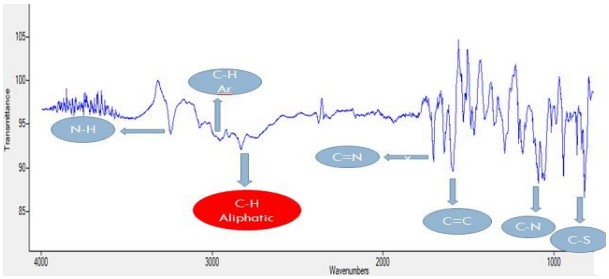


Figure S7 FTIR spectra of AK7

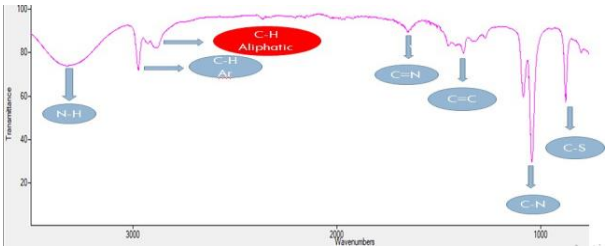


Figure S8 FTIR spectra of AK8

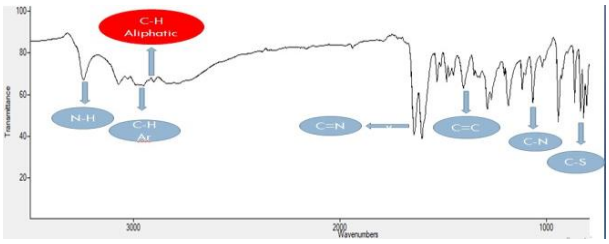


Figure S9 FTIR spectra of AK9

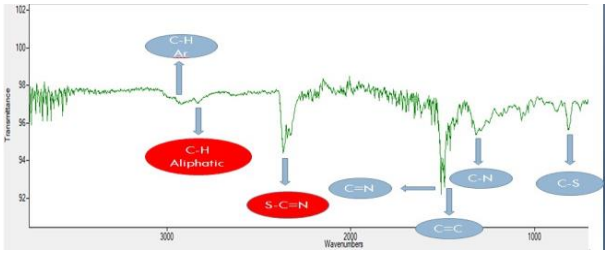


Figure S10 FTIR spectra of AK10

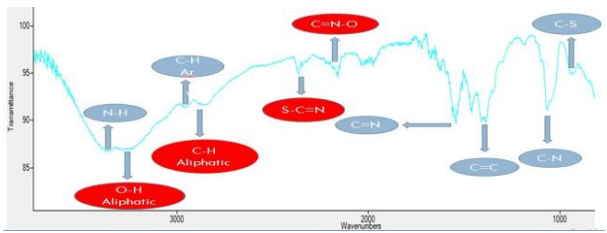


Figure S11 FTIR spectra of AK11

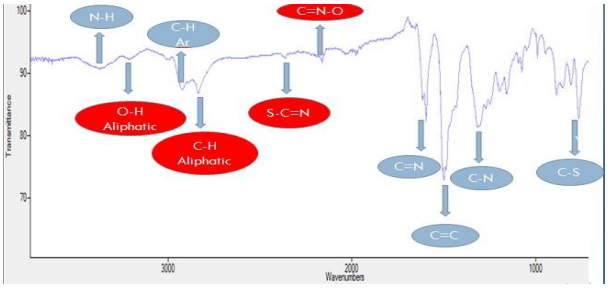


Figure S12 FTIR spectra of AK12

DISCUSSION

This study is concerned with the synthesis of structurally diverse Mannich base derivatives of a privileged heterocyclic scaffold. 2-Mercaptobenzimidazole, that is well-documented for its broad spectrum of biological activities . The Mannich reaction was selected as a strategic synthetic tool owing to its operational simplicity, functional group tolerance, and capability of introducing amino-methyl substituents that can considerably modulate physicochemical and biological properties. Twelve Mannich bases were prepared by reflux condensation of 2-Mercaptobenzimidazole with secondary amines in the presence of different linkers in mild acidic conditions (Gupta et al., 2015). The reaction takes place in two steps. TLC was employed to check the reaction progress after completion compounds were purified and recrystallized from ethanol/n-hexane. Spectroscopic analyses confirmed the successful formation of Mannich bases. The FTIR spectra of all synthesized compounds had characteristic shifts, representing newly formed C-N bonds, disappearance of thiol-associated vibrations, and the presence of secondary amine (N-H) and hydroxyl (O-H) stretching bands, confirming amino-methylation at the nucleophilic center of 2-Mercaptobenzimidazole. The 1HNMR spectra further corroborated these structure assignments due to the presence of diagnostic singlets corresponding to methylene (-CH_2-) protons bridging the benzimidazole nucleus and the amine moieties. Benzimidazole and 2-Mercaptobenzimidazole have gained considerable interest in the field of medicinal chemistry, as these both have ring structures that have biological activity (Wazir et al., 2025, Jakopin and Dolenc, 2010).

However, the nature of variation in the linker and secondary amine used could be responsible for the yield and physical characteristics differences among the synthesized compounds. Generally, formaldehyde-based Mannich reactions gave good yields probably because of increased electrophilicity and reduced steric hindrance, while aromatic aldehydes bulkier in nature and drug-based amines gave comparatively moderate yields. Worth noting are the incorporation of pharmacologically active secondary amines such as tizanidine, cefotaxime, and ceftazidime, which significantly raised the molecular weight and structural complexity that may influence the biological interaction.

Although the main focus of the present chemistry-oriented study was not comprehensive biological evaluation, preliminary screening indeed showed that aromatic or drug-linked amine moieties bearing compounds AK7–AK12 exhibited comparatively better biological responses. The presence of electron-withdrawing substituents like the 4-chloro group appeared to favor activity by increasing lipophilicity or by improving receptor binding interactions. This observation forms an initial structure activity relationship framework; both electronic effects as well as steric factors appear to play a modulating role in biological performance.

CONCLUSION

A total of twelve new Mannich base compounds derived from 2-Mercapto-benzimidazole (AK1-AK12) were synthesized via a simple and effective method. The results confirmed by FTIR and 1HNMR proved that these compounds were synthesized correctly and were obtained with good to excellent yields under mild reaction conditions. Some initial screening results indicate that modifying these compounds with amino-methylation reactions involving aromatic and drug-related compounds may lead to compounds with increased biological properties. The significance of this paper is presented due to its potential applications and contribution to research and development regarding medicinal chemistry optimization studies involving 2-mercapto-benzimidazole-derived Mannich bases.

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