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Synthesis and evaluation of antitubercular activity of some thiobenzimidazolyl derivatives

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ABSTRACT

We have synthesized some thiobenzimidazole derivatives, a series of alkyl sulphonyl benzimidazole was prepared by oxidation of substituted sulphanyl benzimidazole, also a set of benzimidazoles bearing indole-2, 3-dione substituents was synthesized. Intermediate benzimidazolyl-2-mercaptoacetic acid hydrazide was condensed with 5(un)substituted indole-2,3-dione to give different benzimidazolyl-5-(un)substituted-2-oxoindoline-3-ylidine acetohydrazide.All the compounds were analyzed by IR and ^{1}H NMR and Mass spectra. Antitubercular activity was evaluated for synthesized compounds; most of them reported good antitubercular activity against Mycobacterium Tuberculosis.

Keywords: Benzimidazole, Isatin, Mycobacterium Tuberculosis, synthesis.

INTRODUCTION

Despite a numerous attempts to develop new structural prototype in the search of more effective therapeutic agent the benzimidazoles still remain as one of the most versatile class of heterocyclic compounds. The current literature indicates that benzimidazole derivatives possess Diverse pharmacological activities, including Anthelmintic [1], antifungal [2], antiallergic, antimicrobial [3-5], antiviral [6] and antineoplastic [7] activities. These properties make benzimidazole ring as an important pharmacophore for further molecular explorations. On the other hand Isatin (1H-indol-2, 3-dione) analogues have proved to be versatile starting materials for the synthesis of heterocyclic compounds with potential biological activities [8] such as antibacterial [9], antifungal [10,11], anti-HIV[12-13] and anticonvulsant [14.]These findings prompted us to prepare some compounds obtained by incorporating these moieties in a single molecule overall we

synthesized some 2-(1*H*-benzimidazolylthio)-N(5-substituted-2-oxoindoline-3-ylidine)acetohydra - zides. The structures of all the compounds were established by IR and ^{1}H NMR spectra.

MATERIALS AND METHODS

Melting points were determined by open capillary method and are uncorrected. Commercially available reagent grade chemicals procured from Qualigen, Loba chemie, Sigma Aldrich were used All reactions were monitored by TLC, using silica gel G (Merck) TLC plates. Spots were detected by using Iodine chamber. The IR spectra of compounds were recorded on Alpha Bruker FTIR Spectrophotometer. And ^{1}HNMR spectra were obtained from Zydus research, Ahemadabad.^{1}H NMR spectra are expressed in δ value (ppm) relative to TMS as internal std.using CDCl3.. Starting material 2-mercapto benzimidazole was prepared according to reported procedure [15]

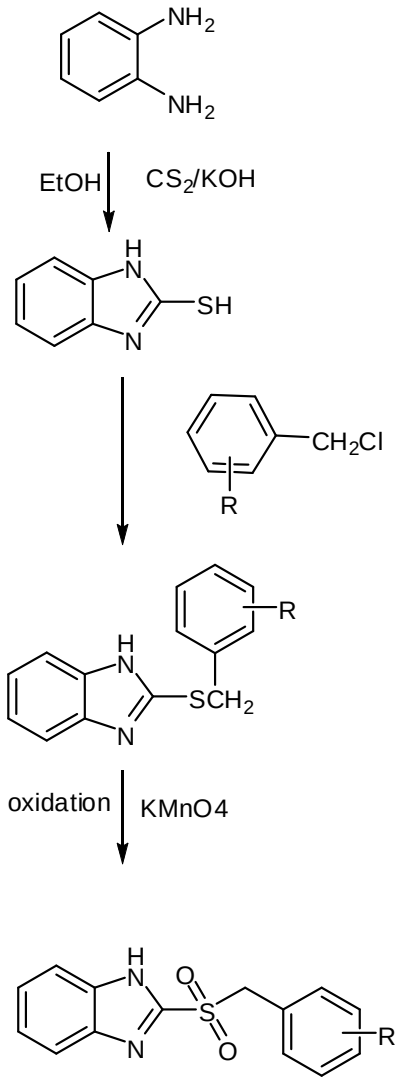

Fig.1-Synthesis of 2-alkyl sulphonyl benzimidazole derivatives:(a) 2-mercapto benzimidazole,(b) 2-alkyl sulphanyl benzimidazole derivatives ,(c)2-alkyl sulphonyl benzimidazole derivatives

Synthesis of 2-alkyl sulphonyl benzimidazole derivatives:SA1-SA6(Table 1)

Procedure

2-alkyl sulphanyl -1*H*- benzimidazole derivatives (b)

Benzimidazol-2-thiol **a** was dissolved in dry N, N-dimethylformamide (8 ml) was added to a solution of sodium (0.12 g, 5 mmol) in dry methanol (2.5 ml).After 10 min of stirring at room temperature, substituted benzyl chloride **3** (5 mmol) was added in 2–3 portions, and the resultant suspension was stirred for 5-7 hrs. The reaction mixture was then cooled and poured into an ice bath with stirring a white colored solid was precipitated and left at overnight. The solid was filtered off, washed with cold water (2×30 ml) and air-dried. The crude products were purified by preparative TLC using acetone–light petroleum (1:2,), followed by crystallization from ethanol, to afford the white needles of the pure compounds

2-alkyl sulphonyl -1*H*- benzimidazole derivatives (c)

About 5mmol 2-(benzylthio)-1-H-benzimidazole was dissolved in 20ml of glacial acetic acid by warming on a water bath, Then prepare a a 7%aqueous solution of Potassium Permanganate and added gradually in the solution at 30-40°C.As the oxidation proceeded and pink color of Potassium Permanganate discharged. Further $KMnO_4$ solution was added, till its color persisted. After allowing the reaction mixture to cool over night, sodium bi sulphite($NaHSO_3$) was added to decompose the excess of $KMnO_4$ used, the mixture become colorless.Then the mixture was poured in to ice water when the Sulphonyl derivative was precipitated. It was filtered,washed with water and crystallized from ethanol.

Scheme 2

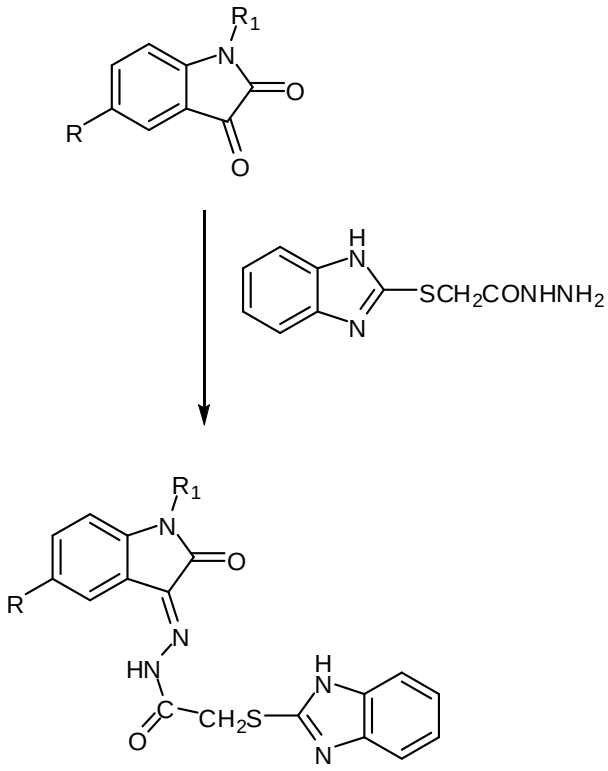

Fig.2: Synthesis of 2-(1H-benzimidazolyl thio)-N'-substituted -2-oxoindolin-3-ylidine) acetohydrazide

General procedure for synthesis of 1H-benzimidazolyl thio-5-(un)substituted –N'(1-(un)substituted-2-oxoindolin-3-ylidine)acetohydrazide: SB1-SB5

In a round bottom flask place a mixture of 5-substituted-1H-indole-2, 3-dione (3mmol) and 1H-benzimidazolylmercaptoacetic acid hydrazide (3mmol) in 30ml ethanol[16] containing about 1 ml glacial acetic acid and heated under reflux for 3 hrs.Cool the mixture and poured in ice water, filter the precipitate and washed with water and purified 2-3 times by using ethanol as a recrystalizing solvent

Table 1: Physicochemical data of synthesized compounds (SA1-SA6)

S.No.	Comd. code	Mol. Formula	R	Mol.Wt.	M.P.(°C)	% Yield	R_f Value
1	SA-1	$C_{14}H_{12}N_2S$	H	240.07	180-182	58	0.82
2	SA-2	$C_{14}H_{12}N_2O_2S$	H	272.32	238-240	84	0.65
3	SA-3	$C_{14}H_{11}N_3O_2S$	4-NO_2	285.05	190-192	85	0.58
4	SA-4	$C_{14}H_{11}N_3O_4S$	4-NO_2	317.05	228-230	88	0.76
5	SA-5	$C_{15}H_{14}N_2OS$	4-OCH_3	270.15	124-126	76	0.73
6	SA-6	$C_{15}H_{14}N_2O_3S$	4-OCH_3	302.07	221-223	80	0.82

RESULT AND DISCUSSION

Table-2: Physicochemical properties of compounds(SB1-SB5)

S.No.	Compound Code	Substitution R	Substitution R_1	Molecular Formula	Mol. Wt.	M.P. (^{0}C)	R_f
1	SB-1	H	H	$C_{15}H_{10}N_3O$	351.08	222-228	0.68
2.	SB-2	H	-CH_2OH	$C_{18}H_{15}N_5O_3S$	381.09	192-196	0.57
3	SB-3	H	-$CH_2C_6H_5$	$C_{24}H_{19}N_5O_2S$	441.13	168-171	0.78
4	SB-4	5-Br	H	$C_{17}H_{12}BrN_5O_2S$	428.99	140-144	0.66
5	SB-5	5,7-Br	H	$C_{17}H_{11}Br_2N_5O_2S$	506.90	>300	0.73

Table 3: Spectral data of compounds SA1-SA6

S. No.	Compound code	IR Spectra(cm^{-1})	^{1}H NMR/MASS Spectral data
1	SA-1	3388(NH),3188-2168.78(H-bridges)	4.51(s,2H,CH_2S),9.82(s,1H,NH)
2.	SA-2	3475(NH),3172-2352(H-bridges),1070.42(O=S=O)	El-MS: 272(M^+)
3.	SA-3	3402.20(NH),3195-2343.35(H-bridges),1517.87(NO_2)	----------
4.	SA-4	3396.41(NH),3164-2360(H-bridges),1072.35(O=S=O)	El-MS:317(M^+)
5.	SA-5	3375.20(NH),3163.04-2657.73(H-bridge),2786(OCH_3)	7.40(2H,m),4.67(2H,s,CH_2S)
6.	SA-6	3390(NH),3184-2360(H-bridge),1076(O=S=O),1116(C-O-C)	El-MS:302(M^+)

Antitubercular Activity

Antitubercular activity of synthesized compounds were evaluated by Serial dilution method and Disc Diffusion Method using *Middlebrook 7H9 medium (broth and agar based*) *and ATCC 25177* strain of mycobacterium Tuberculosis. Activity of samples was determined from the zone of inhibition surrounding the well. The sensitivity of microorganism to the sample was determined by measuring the zones of inhibition surrounding the well using a millimeter scale.

The actual diameter of zone of inhibition was measured including diameter of the well. Four replicates of each test were done for each sample.

Table-4: Spectral data of synthesized compounds(SB1-SB5)

S.No.	Comd.code	IR	NMR
1	SB-1	3195(NH), 1682, 1614(C=O)	4.14, 4.58(2s, 2H,SCH_2), 6.68-7.31(m, 7H, Aro.)
2	SB-2	3191(NH) , 1689(C=O)	5.18 or 5.07(2H,d,CH_2OH) 6.32(1H,t,CH_2OH)
3	SB-3	3217(NH), 1681(C=O)	4.99(2H, s,-$CH_2C_6H_5$)
4	SB-4	3105(NH), 1688(C=O) 1615(C=N) 669(Br)	4.14, 4.58(2s,H,SCH_2)
5	SB-5	3066(NH), 1743(C=O), 1605(C=N) 658,683(-Br)	6.68-7.31(m,7H,Ar.matic)

Table 5: Zone of Inhibition

Test Sample	25 %	50 %	75 %	100 %
SA 1	19±0.40825	22.1375±0.45712	23±0.40825	24.0125±0.3881
SA-2	16.5±0.40825	18.125±0.75	19.25±0.28868	21±0.70711
SA-3	19.25±0.5	24.375±0.47871	24.5±1.22474	25.125±0.85391
SA-4	11.625±0.47871	12±0.40825	14.125±0.75	15±0.40825
SA-5	NI	NI		
SA-6	14.875±0.25	15.375±0.25	16.875±0.25	17.3875±0.25941
SB-1	13.5±0.40825	15.25±0.6455	16.125±0.25	16.875±0.25
SB-2	NI	NI	NI	NI
SB-3	15.3875±0.25941	16.125±0.25	17.25±0.6455	17.875±0.47871
SB-4	14.37±0.40825	15.2±0.40825	16.334±0.259	17.125±0.837
SB-5	19.375±0.47871	20.875±0.62915	21.375±0.25	21.625±0.47871
Rifampin*	Complete clearance of quadrant	Complete clearance of quadrant	Complete clearance of quadrant	Complete clearance of quadrant

** In the same concentration as to that of samples used and same incubation period it was observed that there was no bacterial growth in each quadrant (complete clearance)*

CONCLUSION

A set of alkyl sulphonyl benzimidazole(SA1-SA6) was prepared by oxidation of sulphanyl benzimidazole.A series of benzimidazole derivatives (SB-1 to SB-5) using benzimidazolyl mercapto acetic acid hydrazide and substituted isatins was synthesized in moderate yield using the synthetic route as indicated in scheme 1.Structures of synthesized compounds were established using IR, ^{1}H NMR and Mass. Antitubercular activity was performed by Serial dilution method and Disc Diffusion Method using Middlebrook 7H9 medium (broth and agar based) and ATCC 25177 strain. It was anticipated that oxidation of Sulfur atom in alkyl sulphanyl benzimidazoles lead to decreased activity, however electronegative p-NO_2 group

substituted compounds found having greater activity.Compound SB-5 have shown best activity among other compounds of SB series.SB3 and SB 4 also shown some activity.

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