Synthesis and characterization of some thiazolidinone derivatives possessing benzimidazole nucleus

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ABSTRACT

Synthesis of new thiazolidinone derivatives possessing benzimidazole nucleus by condensation reaction of various substituted mercapto acids in presence of anhydrous ZnCl₂. In our present study we have also synthesized Schiff bases of benzimidazole derivatives. All synthesized compounds were characterized by IR, ¹H NMR and Mass spectroscopy.

Keywords: 4-Thiazolidinone; Benzimidazole; Schiff-base

1. INTRODUCTION

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio [1-3]. The benzimidazole ring is an important pharmacophor in modern drug discovery. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives.

The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, show easy interactions with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man [4].

There is a growing interest over the past years for the synthesis of benzimidazole-based heterocycles due to the crucial role of benzimidazole unit in the functions of biologically important molecules [5-7].

There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance.

Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. However, its

derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature [8].

Similarly 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position 4 have been subjected to extensive study in the recent years.

The 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. They have found uses as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agents [9].

The therapeutic importance of the compounds inspired us to synthesize some potential thiazolidinones containing benzimidazole as scaffold [10-14].

2. EXPERIMENTAL

All chemicals and solvents were purchased from Spectrochem Pvt Ltd., Mumbai of AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet.

¹H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO-d₆ solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

2. 1. Procedure for synthesis of 2-(1H-Benzimidazol-2-yl)-N-(4-hydrazinocarbonyl-phenyl) benzamide (1)

Step 1: An equimolar amount of phthalic anhydride and o-phenylene diamine were taken in an RBF and the reaction mass was heated directly at 140-150 °C to obtain o-Benzoylene 2-1-benzimidazole [10].

Step 2: A mixture of o-benzoylene 2-1-benzimidazole (1 mmol) and benzocaine (1 mmol) were refluxed for 4-5 hours in DMF at 150 °C. Completion of reaction was monitored by TLC. The reaction mass was poured on ice-cold water and the crude product was filtered out and dried in vacuo. Crude product was crystallized from DMSO to obtain analytical grade pure 2-o-(4'-carbethoxyphenyl amino carbonyl phenyl) benzimidazole. Yield 85%.

Step 3: In ethanolic solution of 2-o-(4'-carbethoxyphenyl amino carbonyl phenyl)-benzimidazole (1 mmol), hydrazine hydrate (10 mmol) was added and refluxed overnight. The reaction mass was cooled and the obtained product was filtered. The product was washed with chilled ethanol to collect the analytical pure grade 2-(1H-Benzimidazol-2-yl)-N-(4-hydrazinocarbonyl-phenyl) benzamide. Yield 80 %

Scheme I

2. 2. General process for synthesis of 2(Benzimidazol-2'-yl)-N-(p'-substituted benzal Hydrazino Carbonylphenyl): 2(a-j)

A mixture of **(1)** (1 mmol) and substituted benzaldehyde (1 mmol) in presence of catalytic amount of acetic acid was refluxed with stirring until the reaction got complete (reaction progress was monitored by TLC) (Scheme II).

The mixture was then cooled down and poured on crushed ice. The solid product was separated by filtration, dried and purified by crystallization.

Scheme II

2. 3. General procedure for the synthesis of 2-aryl-o-benzimidazol-2'-yl-benzamido-p'-benzamido-5-H/Methyl/ Carboxymethyl-4-Thiazolidinones

A mixture of compound **2(a-j)** (1 mmol) and substituted thioacids (1 mmol) was taken in a round bottom flask and anhydrous ZnCl_2 was added to it. The reaction mixture was refluxed in oil bath (Scheme III). The progress of the reaction was checked by TLC. The reaction mass was poured on crushed ice and the product obtained was dissolved in sodium bicarbonate and reprecipitated from con. HCl. The product was dried and recrystallized from DMSO.

Scheme III

Table 1. Physical data table for 2-(1*H*-benzo[d]imidazol-2-yl)-*N*-(4-((4-oxo-2-substituted thiazolidin-3-yl)carbamoyl)phenyl)benzamide: 3(a-j).

Sr. No.	R = Substituted Aldehyde	Molecular Formula	M.P. °C	Yield (%)
3a	Phenyl	C ₃₀ H ₂₃ N ₅ O ₃ S	197	62
3b	4-Aminophenyl	C ₃₀ H ₂₄ N ₆ O ₃ S	268	58
3c	2-Chlorophenyl	C ₃₀ H ₂₂ N ₅ O ₃ ClS	246	49
3d	4-Chlorophenyl	C ₃₀ H ₂₂ N ₅ O ₃ ClS	238	55
3e	3,4-dimethylphenyl	C ₃₂ H ₂₆ N ₅ O ₃ S	279	48
3f	3,4-dimethoxy-5-nitrophenyl	C ₃₂ H ₂₆ N ₆ O ₇ S	305	54
3g	2-Furyl	C ₂₈ H ₂₁ N ₅ O ₄ S	215	55
3h	2-Hydroxyphenyl	C ₃₀ H ₂₃ N ₅ O ₄ S	237	54
3i	4-Methoxyphenyl	C ₃₁ H ₂₅ N ₅ O ₄ S	217	60
3j	4- <i>N,N</i> -dimethylaminophenyl	C ₃₂ H ₂₈ N ₆ O ₃ S	278	64

Table 2. Physical data table for 2-(1*H*-benzo[d]imidazol-2-yl)-*N*-(4-((2-substituted-5-methyl-4-oxothiazolidin-3-yl)carbamoyl)phenyl)benzamide: 4(a-j).

Sr. No.	R = Substituted Aldehyde	Molecular Formula	M.P. °C	Yield (%)
4a	Phenyl	C ₃₁ H ₂₅ N ₅ O ₃ S	185	58
4b	4-Aminophenyl	C ₃₁ H ₂₆ N ₆ O ₃ S	197	60
4c	2-Chlorophenyl	C ₃₁ H ₂₄ N ₅ O ₃ ClS	245	59

4d	4-Chlorophenyl	C ₃₁ H ₂₄ N ₅ O ₃ ClS	203	63
4e	3,4-dimethylphenyl	C ₃₃ H ₂₉ N ₅ O ₃ S	155	53
4f	3,4-dimethoxy-5-nitrophenyl	C ₃₃ H ₂₈ N ₆ O ₇ S	167	61
4g	2-Furyl	C ₂₉ H ₂₃ N ₅ O ₄ S	289	65
4h	2-Hydroxyphenyl	C ₃₁ H ₂₅ N ₅ O ₄ S	217	60
4i	4-Methoxyphenyl	C ₃₂ H ₂₇ N ₅ O ₄ S	186	59
4j	4-N,N-dimethylaminophenyl	C ₃₃ H ₃₀ N ₆ O ₃ S	198	63

Table 3. Physical data table for 2-(1*H*-benzo[d]imidazol-2-yl)benzamido) benzamido)2-substituted-4-oxothiazolidin-5-yl)acetic acid: 5(a-j).

Sr. No.	R = Substituted Aldehyde	Molecular Formula	M.P. °C	Yield (%)
5a	Phenyl	C ₃₂ H ₂₅ N ₅ O ₅ S	191	42
5b	4-Aminophenyl	C ₃₂ H ₂₆ N ₆ O ₅ S	269	48
5c	2-Chlorophenyl	C ₃₂ H ₂₄ N ₅ O ₅ ClS	215	50
5d	4-Chlorophenyl	C ₃₂ H ₂₄ N ₅ O ₅ ClS	245	43
5e	3,4-dimethylphenyl	C ₃₄ H ₂₉ N ₅ O ₅ S	198	45
5f	3,4-dimethoxy-5-nitrophenyl	C ₃₄ H ₂₈ N ₆ O ₉ S	167	49
5g	2-Furyl	C ₃₀ H ₂₃ N ₅ O ₆ S	235	52
5h	2-Hydroxyphenyl	C ₃₂ H ₂₅ N ₅ O ₆ S	249	57
5i	4-Methoxyphenyl	C ₃₃ H ₂₇ N ₅ O ₆ S	287	43
5j	4-N,N-dimethylaminophenyl	C ₃₄ H ₃₀ N ₆ O ₅ S	173	56

3. SPECTRAL ANALYSIS OF SOME 4-THIAZOLIDINONE DERIVATIVES

Compound 3a : IR (KBr) $\nu(\text{cm}^{-1})$: 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H

def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.85 (s, 1H), 8.91 (s, 1H), 8.06 (dd, 1H), 7.82 – 7.48 (m, 9H), 7.47 – 7.39 (m, 2H), 7.33 – 7.18 (m, 5H), 6.16 (d, 1H), 5.92 (s, 1H), 3.67 (d, 1H), M⁺ (m/z) = 533.

Compound 3d : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.85 (s, 1H), 8.92 (s, 1H), 8.06 (dd, 1H), 7.83 – 7.71 (m, 4H), 7.71 – 7.39 (m, 9H), 7.24 (dd, 2H), 5.92 (s, 1H), 5.68 (d, 1H), 3.67 (d, 2H), M⁺ (m/z) = 567.

Compound 3i : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.85 (s, 1H), 8.91 (s, 1H), 8.06 (dd, 1H), 7.83 – 7.71 (m, 4H), 7.70 – 7.49 (m, 5H), 7.47 – 7.39 (m, 2H), 7.24 (dd, 2H), 6.97-6.89 (m, 2H), 5.92 (s, 1H), 5.66 (t, 1H), 3.80 (s, 3H), 3.71 – 3.57 (m, 2H), M⁺ (m/z) = 563.

Compound 4a : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.86 (s, 1H), 9.03 (s, 1H), 8.06 (dd, 1H), 7.83 – 7.39 (m, 11H), 7.33 – 7.18 (m, 5H), 6.15 (t, 1H), 5.92 (s, 1H), 3.71 – 3.61 (m, 1H), 1.58 (d, 3H), M⁺ (m/z) = 547.

Compound 4d : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.97 (s, 1H), 8.85 (s, 1H), 8.03 (dd, 1H), 7.89 – 7.71 (m, 4H), 7.71 – 7.53 (m, 3H), 7.48 – 7.39 (m, 6H), 7.24 (dd, 2H), 6.23 (s, 1H), 5.92 (s, 1H), 3.71 – 3.63 (m, 1H), 1.60 (d, 3H), M⁺ (m/z) = 581.

Compound 4i : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1720 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.85 (s, 1H), 9.09 (s, 1H), 8.06 (dd, 1H), 7.83 – 7.71 (m, 4H), 7.71 – 7.53 (m, 3H), 7.47 – 7.36 (m, 4H), 7.24 (dd, 2H), 6.95 – 6.86 (m, 2H), 6.15 (t, 1H), 5.92 (s, 1H), 3.78 (s, 3H), 3.66 (q, 1H), 1.59 (d, 3H), M⁺ (m/z) = 577.

Compound 5a : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.85 (s, 1H), 9.27 (s, 1H), 8.26 (s, 1H), 8.06 (dd, 1H), 7.82 – 7.39 (m, 11H), 7.33 – 7.18 (m, 5H), 6.20 (d, 1H), 5.92 (s, 1H), 4.22 (t, 1H), 3.03 (dd, 1H), 2.75 (dd, 1H), M⁺ (m/z) = 591.

Compound 5d : IR (KBr) ν(cm⁻¹): 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), ¹H NMR (DMSO-d₆) δ (ppm) 10.99 (s, 1H), 9.00 (s, 1H), 8.26 (s, 1H), 8.03 (dd, J = 7.5, 2.0 Hz, 1H),

7.85 – 7.53 (m, 7H), 7.47 – 7.38 (m, 4H), 7.24 (dd, 2H), 6.98 – 6.90 (m, 2H), 6.18 (t, 1H), 5.92 (s, 1H), 4.25 (t, 1H), 3.79 (s, 3H), 3.02 (dd, 1H), 2.74 (dd, 1H), M^+ (m/z) = 625.

Compound 5i : IR (KBr) $\nu(\text{cm}^{-1})$: 3290 (N-H str.), 3040 (C-H str.), 2970 (C-H str.), 2873 (C-H str.), 1620 (C=C str.), 1455 (C-H bend.), 1375 (C-H bend.), 1310 (C-N str.), 1220 (C-H def.), 1140 (C-N-C str.), 1020 (C-O-C str.), 1060 (C=O str.), 810 (C-H def. bend.), **$^1\text{H NMR}$ (DMSO- d_6) δ (ppm)** 10.99 (s, 1H), 9.00 (s, 1H), 8.26 (s, 1H), 8.03 (dd, 1H), 7.85 – 7.53 (m, 7H), 7.47 – 7.38 (m, 4H), 7.24 (dd, 2H), 6.98 – 6.90 (m, 2H), 6.18 (t, 1H), 5.92 (s, 1H), 4.25 (t, 1H), 3.79 (s, 3H), 3.02 (dd, 1H), 2.74 (dd, 1H), M^+ (m/z) = 621.

4. CONCLUSION

In present report, we synthesized new carbohydrazide derivative of benzimidazole from very cheap starting material. Synthesis of some new thiazolidinones derivatives **3(a-j)**, **4(a-j)**, **5(a-j)** were carried out by reaction with substituted arylidene derivatives (**2a-2j**). All synthesized compounds were obtained in good to moderate yield. The synthesized compounds were characterized by $^1\text{H NMR}$, Mass and IR spectroscopy and the obtained results are showing good agreement with the synthesized structures.

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