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SYNTHESIS CHARACTERIZATION AND ANTICANCER ACTIVITY OF THIAZOLIDINONE DERIVATIVES CONDENSED WITH AZO MOIETY

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ABSTRACT

Different thiazolidine derivatives were synthesized in this work. Thiazolidinemotifs are highly interesting heterocyclic five-membered moieties that are found in a variety of natural and bioactive compounds. They have nitrogen at the third position and sulfur at the first. Is a five-membered ring that contains one atom each of nitrogen and sulfur. It has also been discovered that hydrazides and their hetrocyclized derivatives play a significant part in biological processes. They are employed as vehicles in the synthesis of valuable organic combinations because the presence of sulfur improves their pharmacological characteristics. The newly synthesized compounds were analyzed using IR, 1H-NMR, and 13C-NMR spectral analysis. The presence of an azo moiety also increases data.

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INTRODUCTION

Cancer affects every region and socioeconomic level, posing a massive global health burden. Approximately one out of every eight deaths worldwide is attributable to cancer. In 2018, cancer killed 9.6 million people worldwide, more than the combined deaths from TB, HIV/AIDS, and malaria. The current method of treating cancers is chemotherapy, which involves using drugs to kill cancer cells. One of the most pressing issues facing oncologists and chemists is the advancement of targeted cancer therapies. It has been demonstrated that isatin and its derivatives are adaptable substrates that serve as a starting point for the synthesis of numerous heterocyclic compounds that hold promise as pharmacological agents[1–3]. Furthermore, because of their biological activities[16–19], including antimicrobial[20], antiviral[21] antifungal[24], and antituberculosis properties[27] , thiazolidinone derivatives have been the focus of extensive research. Many efforts have been known to be made to adopt a hybridization.

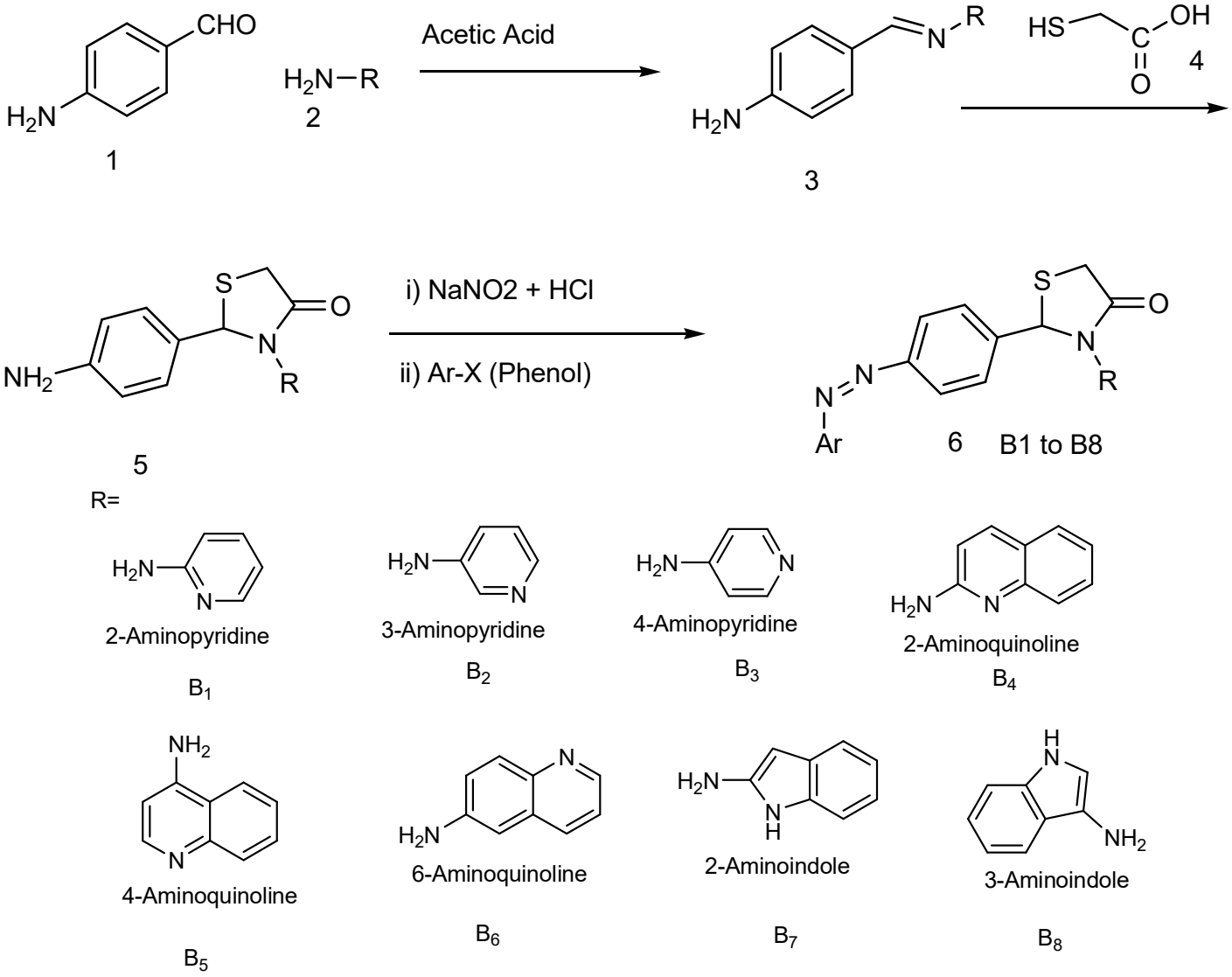
MATERIAL AND METHODS

Without any additional refinement, all solvents were operating as commercial anhydrous marks. The column chromatography was performed on a 100–120 esh silica gel. The open capillary tube is used to determine melting points. A Bruker 400 MHz spectrometer was used to record 1H NMR spectra using TMS as the internal standard in DCl3 solvent. From 80% ethanol, the crude product was recrystallizing.

Present Work: In the present work, first aromatic substituted Schiff bases were synthesized by condensing substituted amine, the synthesized Schiff base was reacting with thioglycolic acid to form Thiazolidinone, this product further diazotise to form a final product.

Step I: General Procedure for the synthesis of Schiff base: A round-bottom flask containing 5 to 10 milliliters of ethanol was used to dissolve compound 1 (0.01 mmole). A trace amount of acetic acid was added to the mixture to act as a catalyst and encourage the formation of imines after 0.01 mmole of aromatic amine (2) was added gradually while being constantly stirred. For three to five hours, the reaction mixture was heated to temperatures ranging from 40 to 600C, depending on the substrate. Using a suitable solvent system, TLC (Thin Layer Chromatography) was used to track the reaction's progress. Once finished, allow the reaction mixture to cool to room temperature. To get rid of contaminants, the solid product was filtered and then washed with cold ethanol or water. The raw material was either vacuum-dried or dried in a desiccator. To create a pure compound, recrystallize the Schiff base from ethanol or an ethanol-water mixture.

Step II: General Procedure for the synthesis ofThiazolidinone: 5–10 mL of dry ethanol should be used to dissolve 0–1 mmole of the Schiff base in a round-bottom flask. To encourage cyclization, add a



Scheme 1

few drops of $ZnCl_2$ (catalytic amount) to the reaction mixture after adding 0–1 mmol of thioglycolic acid gradually, drop by drop. For 4–6 hours, reflux the mixture. Use TLC to track the reaction's progress (e.g. A. the solvent system of n-hexane and ethyl acetate.

Cool the reaction mixture to room temperature after finishing. After filtering, the dense product was washed down with cold ethanol or water to get rid of contaminants. In a desiccator or under vacuum, the crude product was dried out. The product can be recrystallized from ethanol or an ethanol-water mixture to produce a pure compound.

Step II: General Procedure for the synthesis Diazotization: 5–10 ml of 2 M HCl was used to dissolve 0–1 mmol of the aromatic amine in a flask. Using an ice bath, cool the reaction mixture to between 0 and 5 degrees Celsius.

To stop the Diaz onium salt from breaking down, the reaction's temperature was kept continuously between 0 and 5 °C. The sodium nitrite solution was added dropwise to the cold amine/HCl solution while stirring after 0–1 mmol of sodium nitrite ($NaNO_2$) had been dissolved in 2-3 mL of cold distilled water. in order to keep the temperature below 5°C. In situ nitrous acid generation during the reaction forms the Diazonium salt by reacting with the amine. Adding a tiny amount of urea destroyed the excess nitrite. The colored product was then separated from the ethanol and recrystallized to yield compound $B_{1\text{-}8}$ after 0.1 mmole of phenol was added to this solution.

Spectral Data

1) (B_1): Redish Brown , 62%,M.P. 230 °C, FT-IR (KBr, cm−1): 1480 For C=C Ar str, 1555 for N=N str, 1690 for Carbonyl str, 2875 for C-H str, 3160 for Ar–O-H Str . 1H-NMR ($CDCl_3$, 400 MHz) δ: 8.02 (s, 1H, OH), 7.26–7.56 (m, 4H, Ar–H), 6.90 (d, 2H, Ar–H, J = 8.4 Hz), 7.20 (d, 2H, Ar–H, J = 8.4 Hz), 7.88-7.91 (m, 5H, Ar–H) ppm; 4.90(S1H) 3.88(S, 2H) ppm.13C-NMR ($CDCl_3$-d6, 100 MHz) δ: 49.2 (Aliphatic Alpha Carbon), 91.2(Benzylic Carbon), 111.5(Ar Carbon),119.3 ppm,122.8 (Ar Carbon), 125.6(ArCarbon), 135.7(Ar Carbon),142.6(Ar Carbon),149.6(Ar Carbon),166.9 (Ar-C), 190.7(Carbonyl), 118.4 (Ar Carbon), ppm;

2) (B_2): Dark brown solid, 63%, M.P. 256 °C, FT-IR (KBr, cm^{-1}): 1670 (C═O Str), 1460 for C=N Ar str, 1670 for Carbonyl str, 2824 for C-H str, 3350 for Ar–O-H Str . 1H-NMR ($CDCl_3$, 400 MHz) δ6.20–6.50 (m, 4H, Ar–H), 7.2(d, 2H, Ar–H, J = 8.4 Hz), 7.3 (d, 2H, Ar–H, J = 8.4 Hz), 7.60- 8.20 (m, 5H, Ar–H) ppm; 4.90 (s1H)ppm,

ppm; 5.60(s2H) ppm ^{13}C-NMR (DMSO-d_6, 100 MHz) δ:) δ: 58.3 (Aliphatic Alpha Carbon), 89.1 (Benzylic Carbon), 116.1 (Ar Carbon), 121.3 ppm, 128.2 (Ar Carbon), 132.2(Ar Carbon), 138.1(Ar Carbon),142.7(Ar Carbon), 151.2(Ar Carbon), 158.9 (Ar-C), 205.8 (Carbonyl), 118.5 (Ar Carbon), ppm;

(B_3): Brown Red**, 54%,**1.5 g. mp 140-145°C. FT-IR (KBr, cm−1): 1470 for C=N Ar str, 1650 for Carbonyl str, 2890 for C-H str, 3160 for Ar–O-H Str . 1H-NMR ($CDCl_3$, 400 MHz) δ7.90–8.10 (m, 4H, Ar–H), 8.50(d, 2H, Ar–H, J = 8.4 Hz), 8.8 (d, 2H, Ar–H, J = 8.4 Hz), 6.50- 6.90 (m, 5H, Ar–H) ppm; 4.31 (s1H) ppm, 5.71 (s2H) ppm 13C-NMR ($CDCl_3$-d6, 100 MHz) δ: 55.2 (Aliphatic Alpha Carbon), 81.2 (Benzylic Carbon), 111.0 (Ar Carbon), 118.30 ppm, 124.2 (Ar Carbon), 130.8 (Ar Carbon), 135.6 (Ar Carbon), 147.6 (Ar Carbon), 151.6 (Ar Carbon), 165.2 (Ar-C), 210.2 (Carbonyl),

(B_4): Dark Red, 60 %, mp 170-173°C. 1490 for N=N Ar str,1510 for C=C str, 1650 for Carbonyl str, 2880 for C-H str, 3200 for Ar–O-H Str . 1H-NMR ($CDCl_3$, 400 MHz) δ: 9.00 (s, 1H, OH), 7.55–7.57 (m, 4H, Ar–H), 7.36 (d, 2H, Ar–H, J = 8.4 Hz), 7.10 (d, 2H, Ar–H, J = 8.4 Hz), 6.66–6.75 (m, 5H, Ar–H) ppm; 4.21(S1H) 4.55 (S, 2H) ppm. 13C-NMR ($CDCl_3$-d6, 100 MHz) δ: 46.2 (Aliphatic Alpha Carbon), 92.5 (Benzylic Carbon), 115.5(Ar Carbon),120.5 ppm127 (Ar Carbon),131.6 (Ar Carbon), 140.1 (Ar Carbon),145.3 (Ar Carbon),153.2 (Ar Carbon), 158.2 (Ar-C), 115.8(Carbonyl), 118.2 (Ar Carbon), ppm;

Anticancer Evaluation of B_1 to B_8 Derivatives: Diverse biological activities, with a focus on anticancer activity. The ability of a substance to prevent the growth and survival of cancer cells by causing cell death, stopping the cell cycle, or interfering with tumor development is known as anticancer activity. We conducted in vitro anticancer activity against MCF7 (human breast cancer) using the MTT MTT (3-(4, 5-dimethyl thiazol-2yl)-2, 5-diphenyl tetrazolium bromide) assay, as outlined by Florento L et al., to assess the biological activity of the synthesized compounds. [21] with minor adjustments. Initially, 96-well microtiter plates were seeded with 1 × 105 cells/mL, supplemented with Minimum Essential Medium containing fetal bovine serum, and incubated for a full night. To obtain the test concentrations of 0.001, 0.01, 0.1, 1.0, and 10uM, all of the compounds were serially diluted with the entire medium after being dissolved in DMSO to reach a final concentration of 0.1M. After being seeded with MCF-7 breast cancer cells and treated with varying concentrations of the test compounds, the 96-well plate was incubated for 96 hours at 37°C with 5% CO2 concentration to maintain the system's pH. The cells were subsequently treated.

$$\% \text{ of Ceel Inhibition} = \frac{(OD\ Control - OD\ Treated)}{2!\ OD\ Control}\ X\ 100$$

Scheme 1

Entry	Product	Anticancer Activity (MFC7)					
		0.001	0.01	0.1	1	10	IC-50(uM)
1	B_1	0.14	1.15	9.60	15.9	21.5	25.7
2	B_2	1.2	15	9.5	17.3	22.6	20.95
3	B_3	1.6	2.1	8.4	12.5	19.5	24.87
4	B_4	1.2	3.14	15.34	29.3	34.6	14.94
5	B_5	4.25	13.4	20.3	45.12	51.6	1.2
6	B_6	1.1	3.5	8.7	11.09	17.6	29.49
7	B_7	1.35	3.3	5.9	8.9	18.2	25.75
8	B_8	1.75	3.9	6.3	12.3	13.6	32.6
ADR	Adriamycin	13.42	27.36	49.64	82.49	96.71	0.57

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RESULT AND DISCUSSION

To sum up, we have created a practical smart technique for the synthesis of derivatives of Thiazolidinone Derivatives Containing with Azo Moiety. This protocol's pleasing aspects include its ease of use, the use of catalysts and solvents that are safe for the environment, its mild reaction conditions, and its excellent yields of corresponding derivatives.

When compared to the control (adriamysin), the newly synthesized compounds showed notably better inhibition activities against human breast cancer cell (MCF-7) cell lines, according to the preliminary assays. These compounds could be developed as novel lead scaffolds for possible anticancer agents

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