CHAPTER – 5

A Microwave Assisted Synthesis of Thiazolidinones like 3-(2-Methylindoline-1-yl)-2-substituted phenylthiazolidin-4-ones using thioglycolic acid
5.1 SYNTHETIC STRATEGIES FOR 4-THIAZOLIDINONE

Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. This array of biological response profile has attracted the attention of scientists’ the world over to further investigate the potential of this organic motif. The referencing on this topic revealed that a lot of work has been done in this particular field in past.

4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position (1). Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (R and R’ in 2 or X in 3). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.

Several protocols for the synthesis of 4-thiazolidinones are available in the literature. Essentially they are three component reactions involving an amine, a carbonyl compound, and a mercapto-acid. The process can be either a one-pot three-component condensation or a two-step process.

An improved protocol has been reported wherein N,N-dicyclohexyl carbodiimide (DCC) or 2-(1H-benzotriazo-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphat (HBTU) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields. The DCC/HBTU-mediated protocol has the advantage of mild reaction conditions, a very
short reaction time, and product formation in almost quantitative yields. More importantly, yields of the 4-thiazolidinones are independent of the nature of the reactants. This modification is compatible with a solid-phase combinatorial approach to generate a library of compounds.

Cesur et al. and Vicini et al. have reported another method of synthesis of 4-thiazolidinones by the use of thiocyanate, alkylisothiocynate and ammonium thiocyanate with hydrazide/acetamide, followed by the treatment with ethyl bromoacetate and sodium acetate\textsuperscript{15-16}.

Ottana et al. also reported synthesis of 4-thiazolidinones using the starting material N-propyl-N0-phenylthiourea, obtained by the reaction of propylamine and phenylisothiocyanate in chloroform at room temperature for 4 h followed by workup under acidic conditions\textsuperscript{17}.

Fraga-Dubreuil et al. pioneered the use of task-specific ionic liquid as synthetic equivalent of ionic liquid-phase matrice for the preparation of a small library of 4-thiazolidinones\textsuperscript{18}. The starting ionic liquid-phase (ethyleneglycol) is functionalized in good yields with 4-(formylphenoxy)butyric acid by using usual esterification reaction conditions (DCC/DMAP as catalyst). The synthesis of the ionic liquid-phase bound 4-thiazolidinones was performed by a one-pot three-component condensation under microwave dielectric heating.

Recently Dandia et al. have reported a microwave-assisted three-component, regioselective one-pot cyclocondensation method for the synthesis of a series of novel spiro[indole-thiazolidinones] using an environmentally benign procedure at atmospheric pressure in an open vessel. This rapid method produces pure products in high yields within few minutes, in comparison to conventional two-step procedure\textsuperscript{19}.

Holmes et al. reported solution and polymer-supported synthesis of 4-thiazolidinones derived from amino acids\textsuperscript{20}. A three-component condensation of an amino ester or resin bound amino acid (glycine, alanine, b-alanine, phenylalanine, and valine), an aldehyde (benzaldehyde, o-tolualdehyde, m-tolualdehyde, p-tolualdehyde,
and 3-pyridine carboxaldehyde), and a α-mercapto carboxylic acid, led to the formation of 5-membered heterocycles.

Recently Maclean et al. reported an encoded 4-thiazolidinone library on solid phase \(^1\). Three sets of 35 building blocks were combined by encoded split-pool synthesis to give a library containing more than 42,000 members. Building block selection was based in part on a novel small molecule follicle stimulating hormone receptor agonist hit and in part for diversity.

\(H.Chen\ et.\ al\)\(^2\) have reported an improved microwave assisted synthesis of 2-(2,6-dihalophenyl)-3-(5-(un)substituted-4,6-dimethyl pyrimidin-2-yl)thiazolidin-4-ones in good yields promoted by DCC (Scheme-1), and the reaction process of such intramolecular cycloamidation via the key uncyclized intermediate which they eventually screened for HIV-RT inhibitory activity.

\[\text{Scheme-1: Synthesis of 5 and 6 Reagents and conditions (a) (1) MW, 140 }^\circ\text{C in sealed tube, 10 min, 7a:8:10 = 1:1:2; (2) MW, 140 }^\circ\text{C in sealed tube, 2 equiv DCC, 5 min.}\]
C. Saiz et al.\textsuperscript{23} have reported an efficient tandem procedure for the synthesis of 2-hydrazone-4-thiazolidinones under microwave conditions. Different solvents and various reaction equivalents were explored until good isolated yields of thiazolidinones were obtained (Scheme 2). Microwave heating for the synthesis of thiazolidinone 5a resulted in a significantly better yield compared to thermal conditions (75% vs 40%). Microwave irradiation also allowed for a faster conversion. For tandem reactions, the best yields were obtained when a solvent mixture of PhMe/DMF (1:1) was used. Thiazolidinone 5a was prepared in 68% yield using a stepwise sequence and in 82% yield under tandem conditions.

![Stepwise 2-hydrazone-4-thiazolidinone synthesis under conventional conditions.](image)

**Scheme 2:** Tandem and stepwise reactions for the synthesis of 2-hydrazone-4-thiazolidinone.
5.1.1 4-THIAZOLIDINONE: A BIOLOGICALLY ACTIVE SCAFFOLD

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures 24, with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry 25. There are numerous biologically active molecules with five membered rings, containing two hetero atoms. Thiazolidine is an important scaffold known to be associated with several biological activities 26.

The potency of the thiazolidinone moiety against various diseases is discussed at length in Chapter no. 1 pertaining to the General Introduction of this same thesis. However, the latest references for the same activities discussed in Chapter 1 are given herein viz. Ant-HIV 27, Anti Cancer 28-33, Follicle Stimulating Hormone (FSH) receptor agonist 34, 35, Anti Microbial 36-39 and Anti inflammatory 40.

The activities shown by 4-Thiazolidinone, other than those conversed in Chapter 1, have been discussed herein.

A  Hypnotic Activity

Several 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones 41 and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones 42 were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time. The increase in the duration of sleep ranged from 10±3 min in untreated control to 98.6±10 min in mice pretreated with substituted thiazolidinones.
B Anti Tubercular activity

The emergence of multi-drug resistant tuberculosis, coupled with the increasing overlap of AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern. Turkevich et al. reported few 2-Imino-4-thiazolidinone derivatives as possible antitubercular compounds. In other study, 5-(5-Nitrofururylidene)-3-ethylrhodanine has been found to be a promising tuberculostatic compound. Few derivatives of 2-Imino-4-thiazolidinones have also been reported as having antitubercular activity with low toxicity. Repeated therapeutic doses were found to possess antitubercular activity comparable to streptomycin or phthivazid. Kapustayak et al. has studied structure-tuberculostatic activity relationship of some 4-Thiazolidinones. Another study reported chemotherapeutic effectiveness against Myobacterium tuberculosis. A few derivatives were found to inhibit the growth of human tubercle bacilli, H37Rv strain, in a concentration of 12.5 mg/mL. Several other derivatives of thiazolidinones have also been found to inhibit the growth of Myobacterium tuberculosis H37Rv strain. In an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway, a virtual library of 2,3,5 trisubstituted-4-thiazolidinones was created.
C Anthelmintic Activity

3-Methyl-5-[(4-nitrophenyl)azo]rhodanin, nitrodan, was reported as a potent anthelmintic compound\textsuperscript{50-52} which was effective when administered in feed against Hymenolepis nana and Syphacia obvelata infections in mice, Asceridia galli infections in chickens, and Toxocera canis, Ancylostoma caninum, and Uncinaria stenocephala infections in dogs, pigs and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have been found to be effective in vitro against horse Strongyloids at concentration of 10±3-10±6 M\textsuperscript{53}. Various 2-Thiono-3-substituted-5-[(2-methyl-4-nitrophenyl)azo]-4-thiazolidinones and 2-Thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone as potent anthelmintic agents, which were not only effective alone but also showed activity with other parasiticides\textsuperscript{54,55}.

![Chemical structures](image)

D Cardiovascular Activity

Cardiovascular effects of a series of 2-Cyclopentyl/(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acids on adult cats of either sex were reported\textsuperscript{56}. All substituted 4-Thiazolidinones induced hypotension of varying degree. The duration of hypotensive activity observed with most of these compounds was less than 15 min.
Suzuki et al. examined the effects of CP-060S (3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-4-thiazolidinone) on cardiac function and myocardial oxygen consumption (MVO2) in anesthetized dogs. CP-060S (10-300 mg/kg IV) decreased heart rate, increased aortic flow and decreased mean blood pressure in a dose-dependent manner. The PR (pulse rate) interval was significantly prolonged by administration of CP-060S (300 mg/kg IV). It increased coronary blood flow in a dose-dependent manner (10-300 mg/kg IV). Left ventricular end-diastolic pressure and maximal first derivative of left ventricular pressure were not significantly affected. CP-060S (10-300 mg/kg IV) increased coronary sinus blood flow and decreased arteriovenous oxygen difference and MVO2 in a dose-dependent manner. Its effect on cardiac function and MVO2 are qualitatively similar to those of diltiazem, a typical Ca-channel blocker.

### E Antihistaminic activity (H1-antagonist)

Thiazolidinones are known to show their action on histamine receptors. The geometrical similarity between 2-Aryl-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-ones and different histamine (H1) antagonists such as bamipine, clemastine, cyproheptadine, triprolidine, promethazine, chlorpheniramine, and carboxamine prompted Diurno et al. to evaluate these compounds for antihistaminic activity. Singh et al. have investigated the antihistaminic (H1-antagonist) activity of 2,3-disubstituted thiazolidin-4-ones and concluded that the hydrophobic substitution at the 4-position of the phenyl ring and cumulative negative
polar effects of all the substituents in the phenyl group are advantageous for antihistaminic activity \(^{61,62}\).

In another study, Diurno et al. synthesized, characterized and evaluated a new series of 2-(Substituted-phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-ones for their capacity to inhibit the contraction induced by histamine on guinea pig ileum \(^{63}\). 2-(3-Carbamoyl-phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-one and derivatives of series as free bases were converted into the corresponding hydrochlorides for the pharmacological assays. The H1-antihistaminic activity of the synthesized compounds was evaluated in vitro by measuring their ability to inhibit the histamine-induced contractions of isolated guinea pig ileum \(^{64}\). Results show that whenever the phenyl moiety of the 4-thiazolidinones interacts with a complementary area of the H1-receptor, the \(\pi\) interaction was enhanced by hydrophobic substituents increasing the HOMO energy and is affected by the size of the 4-alkyl substituent. These studies have highlighted the importance of overall hydrophobicity of the compounds in deciding the antihistaminic activity \(^{65,66}\).
V. Ravichandran et al. have predicted the Anti-HIV activity for Thiazolidin-4-ones using 3D-QSAR approach. The basic structure for their studies is given below.

The observations arrived based on the 3D-QSAR calculations are as under.

- The electron withdrawing groups such as F, Cl, Br, CN etc., on 3’, 2”, 6” will increase the Anti-HIV activity.
- The electron withdrawing group at position 4’ has detrimental effect on Anti HIV activity.
- If 2’, 4’, 2”, 3”, 6” have bulky groups then they will impart negative impact on the activity.
- Smaller electronegative groups at 2”, 6” will increase the activity.
- Hydrophobic groups at position 3’, 2”, 6” augment the Anti-HIV activity.
- Hydrophobic groups at position, 4’, 3”, and 4” are not favorable for biological activity.
- Hydrogen bond acceptors on position no. 3’, 2”, 6” will increase the activity.
- Hydrogen bond donors at 4’ is a favorable condition whereas the same at position no 2” and 6” will have a detrimental effect on the activity.
5.2 AIM OF CURRENT WORK

Thiazolidinones have been extensively explored in the past decades for various therapeutic activities using a Fragment Based Drug Discovery (FBDD) approach. Moreover, the indole moiety, a privileged structure has its own advantages when it comes to biological activity. The Mannich reactions carried out with the indole moiety in our lab has shown promising anti-cancer results\(^a\). Also the literature revealed that the thiazolidine-4-one have shown promising results in Anti HIV activity.

In the current work we intended to synthesize various 4-Thiazolidinones appended with 2-methyl indoline as a core fragment and also to study their biological activity.

\(^a\) Joshipura, D, N; Shah, A, K. Ph.D. Thesis-2009, Department of Chemistry, Saurashtra University, Rajkot
5.3 REACTION SCHEME

\[
\begin{align*}
\text{N-benzylidene-2-methylindolin-1-amine} & \quad \text{+ 2-mercaptoacetic acid} \\
\rightarrow & \quad \text{Thiazolidi-4-ones}
\end{align*}
\]

Reagents & Conditions: \( \text{H}_2\text{SO}_4 \), MWI-180 watts, Air Condenser, 3-5 Mins.

R and R’=Differently substituted aldehydes and pyrazolealdehydes.

A Rapid Microwave assisted synthesis of Thiazolidine-4-one like 3-(2-methylindolin-1-yl)-2-substituted phenylthiazolidin-4-one

5.3.1 PHYSICAL DATA TABLE

<table>
<thead>
<tr>
<th>Code</th>
<th>R / R’</th>
<th>M. F.</th>
<th>M. W.</th>
<th>M. P. ⁰C</th>
<th>Time (min)</th>
<th>Yield %</th>
<th>Rf</th>
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<tbody>
<tr>
<td>TZD-2-1-01</td>
<td>R = H</td>
<td>C₁₈H₁₈N₂O₂S</td>
<td>310.41</td>
<td>178-180</td>
<td>5.20</td>
<td>52</td>
<td>0.54</td>
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<tr>
<td>TZD-2-1-02</td>
<td>R = 3-Cl</td>
<td>C₁₈H₁₇ClN₂O₂S</td>
<td>344.86</td>
<td>190-192</td>
<td>4.50</td>
<td>64</td>
<td>0.50</td>
</tr>
<tr>
<td>TZD-2-1-03</td>
<td>R = 3,4-ΟCH₃</td>
<td>C₂₀H₂₂N₂O₃S</td>
<td>370.47</td>
<td>206-208</td>
<td>6.30</td>
<td>55</td>
<td>0.52</td>
</tr>
<tr>
<td>TZD-2-1-06</td>
<td>R = 3-NO₂</td>
<td>C₁₈H₁₇N₂O₂S</td>
<td>355.41</td>
<td>174-176</td>
<td>4.30</td>
<td>75</td>
<td>0.55</td>
</tr>
<tr>
<td>TZD-2-1-07</td>
<td>R = 4-Cl</td>
<td>C₁₈H₁₇ClN₂O₂S</td>
<td>344.86</td>
<td>208-210</td>
<td>5.00</td>
<td>70</td>
<td>0.54</td>
</tr>
<tr>
<td>TZD-2-1-10</td>
<td>R = 4-NO₂</td>
<td>C₁₈H₁₇N₂O₃S</td>
<td>355.41</td>
<td>212-214</td>
<td>5.30</td>
<td>64</td>
<td>0.58</td>
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<td>TZD-1-1-01</td>
<td>R’ = H</td>
<td>C₂₇H₂₄N₄O₂S</td>
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<td>218-220</td>
<td>6.00</td>
<td>66</td>
<td>0.48</td>
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<td>6.30</td>
<td>55</td>
<td>0.45</td>
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<tr>
<td>TZD-1-1-03</td>
<td>R’ = 4-NO₂</td>
<td>C₂₇H₂₃N₅O₃S</td>
<td>497.57</td>
<td>214-216</td>
<td>6.10</td>
<td>70</td>
<td>0.50</td>
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<tr>
<td>TZD-1-1-09</td>
<td>R’ = 4-Br</td>
<td>C₂₇H₂₃BrN₄O₂S</td>
<td>531.47</td>
<td>242-244</td>
<td>6.40</td>
<td>60</td>
<td>0.52</td>
</tr>
</tbody>
</table>

TLC solvent system for Rf: Toluene:Ethyl acetate - 7:3.

Microwave Irradiation: 180 Watts.
5.4 PLAUSIBLE REACTION MECHANISM

5.4.1 Formation Of 4-Thiazolidinone from N-Benzylidene-2-methylindolin-1-amine

The reaction proceeds by the attack of mercaptoacetic acid upon the C=N group, with the HS-CH$_2$-COOH adding to the carbon atom followed by capture of the proton by nitrogen and subsequent cyclization. During the reaction an uncyclized intermediate is formed in few cases. In many instances 4-Thiazolidinones can conveniently be prepared by refluxing the mixture of thioglycolic acid and the Schiff base in benzene, dry ether or ethanol.

The nucleophilic attack of the mercaptoacetic acid anion will take place on the carbon of azomethine which has got a positive character; while it is evident that the nitrogen has the negative character. Simultaneous removal of water that forms in the reaction helps in condensation and determination of the reaction time.
5.5 EXPERIMENTAL

5.5.1 MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. All the reactions were carried out in Samsung MW83Y Microwave Oven which was locally modified for carrying out chemical reactions. IR spectra were recorded in Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. $^1$H NMR was determined in DMSO-$d_6$ solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

5.5.2 GENERAL PROCEDURE: 3-(2-Methylindolin-1-yl)-2-substituted phenyl thiazolidin-4-ones

A neat fusion reaction has been carried out in the presence of strong acid such as sulfuric acid to prepare the thiazolidine-4-one. 0.005 moles of N-substituted benzylidene-2-methylindoline-1-amine was taken in an Erlenmeyer flask. Slurry was prepared using 5 to 10 times i.e. 0.05 moles of Thioglycolic Acid which served as the solvent for the reaction as well hence we call it a neat fusion. Very few drops of sulfuric acid were added in the reaction mixture to catalyze the reaction. The reaction mixture was then subjected to microwave irradiation for a specific time (see Physical data Table) at low power (180 W) with an air condenser attached to the reaction assembly. The progress of the reaction was monitored by TLC examination at an interval of every 10 seconds. On completion of reaction, it was cooled at room temperature and poured onto ice water which afforded the crude product. Sodium bicarbonate was added to maintain the pH at 6-7. The organic mass was extracted using ethyl acetate thrice. The combined organic extracts were then washed thrice with demineralized water to remove traces of acids from the reaction. After separation, sodium sulphate was put in the combined organic extracts to remove any traces of water and then vacuum distilled. The product thus obtained was filtered, washed with cold water, dried, and recrystallized using DMF.
5.6 ANALYTICAL DATA

5.6.1 3-(2-Methylindolin-1-yl)-2-phenylthiazolidin-4-one (TZD-2-1-01)

Yield: 52%; M.P.- 178-180 °C; IR (cm⁻¹): 1615 (Ring stretching for Indoline), 1414 (Ring
stretching modes for thiazolidinone ring), 875-660
(C-H out of plane bending for Thiazolidinone ring,
several bands observed), 2972-2935 (C-H
asymmetric stretching for R-CH₃), 2855 (C-H
symmetric stretching for R-CH₃), 1447 (C-H
asymmetric bending for R-CH₃), 1382 (C-H symmetric bending for R-CH₃), 3080-
3000 (C-H stretching frequency for aromatic region), 1590 (C-C skeletal stretching of
phenyl nucleus), 1238 (C-H in plane bending for phenyl ring), 710 (C-C out of plane
bending for mono substituted benzene ring), 2925 (C-H stretching frequency for
ketone), 1750 (C=O stretching frequency for ketone in 5 membered saturated ring),
1080-1025 (C-N stretching frequency for tertiary amine); MS: m/z: 310.11; Anal.
Calcd. for C₁₈H₁₈N₂O₃S: C, 69.65; H, 5.84; N, 9.02; O, 5.15, S, 10.33; Found: C,
69.61; H, 5.80; N, 9.00; O, 5.12; S, 10.28.

5.6.2 2-(3-Chlorophenyl)-3-(2-methylindolin-1-yl)thiazolidin-4-one
(TZD-2-1-02)

Yield: 64%; M.P.- 190-192 °C; IR (cm⁻¹): 1600 (Ring
stretching for Indoline), 1393 (Ring stretching modes
for thiazolidinone ring), 860-640 (C-H out of plane
bending for Thiazolidinone ring, several bands
observed), 2945-2915 (C-H asymmetric stretching for
R-CH₃), 2838 (C-H symmetric stretching for R-CH₃),
1430 (C-H asymmetric bending for R-CH₃), 1359 (C-H
symmetric bending for R-CH₃), 3095-3005 (C-H stretching frequency for aromatic
region), 1575 (C-C skeletal stretching of phenyl nucleus), 1216 (C-H in plane bending
for phenyl ring), 705 (C-H out of plane bending for 1,3-Substituted benzene ring),
2905 (C-H stretching frequency for ketone), 1730 (C=O stretching frequency for
ketone in 5 membered saturated ring), 1066-1007 (C-N stretching frequency for
tertiary amine), 757 (C-Cl stretching frequency for mono chlorinated aromatic
compounds); MS: m/z: 344.08; Anal. Calcd. for C₁₈H₁₇ClN₂O₂S: C, 62.69; H, 4.97; Cl, 10.28; N, 8.12; O, 4.64; S, 9.30; Found: C, 62.63; H, 4.94; Cl, 10.25; N, 8.10; O, 4.61; S, 9.23

5.6.3  2-(3,4-Dimethoxyphenyl)-3-(2-methylindolin-1-yl)thiazolidin-4-one (TZD-2-1-03)

Yield: 55 %; M.P.- 206-208 °C; IR (cm⁻¹): 1611 (Ring stretching for Indoline), 1409 (Ring stretching modes for thiazolidinone ring), 859-637 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2958-2915 (C-H asymmetric stretching for R-CH₃), 2861 (C-H symmetric stretching for R-CH₃), 1444 (C-H asymmetric bending for R-CH₃), 1388 (C-H symmetric bending for R-CH₃), 3069-3019 (C-H stretching frequency for aromatic region), 1597 (C-C skeletal stretching of phenyl nucleus), 1233 (C-H in plane bending for phenyl ring), 887 (C-H out of plane bending for 1,2,4-trisubstituted benzene ring), 2925 (C-H stretching frequency for ketone), 1744 (C=O stretching frequency for ketone in 5 membered saturated ring), 1089-1030 (C-N stretching frequency for tertiary amine), 3110 (C-H stretching for aryl-alkyl ether); MS: m/z: 370.14; Anal. Calcd. for C₂₀H₂₂N₂O₃S: C, 64.84; H, 5.99; N, 7.56; O, 12.96; S, 8.66; Found: C, 64.80; H, 5.94; N, 7.51; O, 12.93; S, 8.62.

5.6.4  3-(2-Methylindolin-1-yl)-2-(3-nitrophenyl)thiazolidin-4-one (TZD-2-1-06):

Yield: 75 %; M.P.- 174-176 °C; IR (cm⁻¹): 1617 (Ring stretching for Indoline), 1409 (Ring stretching modes for thiazolidinone ring), 866-680 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2968-2931 (C-H asymmetric stretching for R-CH₃), 2852 (C-H symmetric stretching for R-CH₃), 1438 (C-H asymmetric bending for R-CH₃), 1373 (C-H symmetric bending for R-CH₃), 3094-3015 (C-H stretching frequency for aromatic region), 1579 (C-C skeletal stretching of phenyl nucleus), 1223 (C-H in plane bending for phenyl ring), 717 (C-C out of plane bending for 1,3-Disubstituted benzene ring), 2921 (C-H stretching frequency for ketone), 1746 (C=O stretching frequency for ketone in 5 membered saturated ring).
ketone in 5 membered saturated ring), 1083-1021 (C-N stretching frequency for tertiary amine), 1539-1527 (NO₂ asymmetric stretching frequency for aromatic Nitro group), 1308 (NO₂ symmetric stretching for aromatic NO₂ group); MS: \textit{m/z}: 355.10; Anal. Calcd. for C_{18}H_{17}N_{3}O_{3}S: C, 60.83; H, 4.82; N, 11.82; O, 13.50; S, 9.02; Found: C, 60.79; H, 4.78; N, 11.79; O, 13.45; S, 9.00.

5.6.5 2-(4-Chlorophenyl)-3-(2-methylindolin-1-yl)thiazolidin-4-one (TZD-2-1-07)

![TZD-2-1-07](image)

Yield: 70%; M.P.- 208-210 ºC; IR (cm⁻¹): 1603 (Ring stretching for Indoline), 1417 (Ring stretching modes for thiazolidinone ring), 873-657 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2975-2915 (C-H asymmetric stretching for R-CH₃), 2826 (C-H symmetric stretching for R-CH₃), 1430 (C-H asymmetric bending for R-CH₃), 1378 (C-H symmetric bending for R-CH₃), 3083-3017 (C-H stretching frequency for aromatic region), 1563 (C-C skeletal stretching of phenyl nucleus), 1229 (C-H in plane bending for phenyl ring), 826 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2917 (C-H stretching frequency for ketone), 1732 (C=O stretching frequency for ketone in 5 membered saturated ring), 1064-1006 (C-N stretching frequency for tertiary amine), 723 (C-Cl stretching for monochlorinated aromatic compounds); MS: \textit{m/z}: 344.08; Anal. Calcd. for C_{18}H_{17}ClN_{2}O_{3}S: C, 62.69; H, 4.97; Cl, 10.28; N, 8.12; O, 4.64; S, 9.30; Found: C, 62.66; H, 4.95; Cl, 10.25; N, 8.09; O, 4.61; S, 9.26.

5.6.6 3-(2-Methylindolin-1-yl)-2-(4-nitrophenyl)thiazolidin-4-one (TZD-2-1-10)

Yield: 64 %; M.P.- 212-214 ºC; IR (cm⁻¹): 1606 (Ring stretching for Indoline), 1402 (Ring stretching modes for thiazolidinone ring), 871-650 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2960-2922 (C-H asymmetric stretching for R-CH₃), 2850 (C-H symmetric stretching for R-CH₃), 1433 (C-H asymmetric bending for R-CH₃), 1375 (C-H symmetric bending for R-CH₃), 3088-3005 (C-H stretching frequency for aromatic region), 1583 (C-C skeletal stretching of phenyl nucleus), 1224 (C-H in plane bending for phenyl ring), 831 (C-H ...
out of plane bending for 1,4-Disubstituted benzene ring), 2914 (C-H stretching frequency for ketone), 1739 (C=O stretching frequency for ketone in 5 membered saturated ring), 1074-1016 (C-N stretching frequency for tertiary amine), 1531-1525 (NO₂ asymmetric stretching frequency for aromatic Nitro group), 1303 (NO₂ symmetric stretching frequency for aromatic NO₂ group); ¹H NMR (DMSO-d₆) δ ppm: 1.27-1.28 (d, 3H, H₁), 4.47-4.52 (m, 1H, H₂), 2.69-2.74 (d, 1H, H₃), 3.39-3.46 (q, 1H, H₃), 7.05-7.07 (d, 1H, H₄, J=8 Hz), 7.13-7.16 (m, 2H, H₅ & H₇), 6.79-6.83 (m, 1H, H₆), 7.37 (s, 1H, H₈), 7.64-7.66 (d, 2H, H₉ & H₁₂, J value= 8 Hz), 8.09-8.11 (d, 2H, H₁₀ & H₁₁, J value= 8 Hz), 5.37 (s, 2H, H₁₃); MS: m/z: 355.10; Anal. Calcd. for C₁₈H₁₇N₃O₃S: C, 60.83; H, 4.82; N, 11.82; O, 13.50; S, 9.02 Found: C, 60.78; H, 4.77; N, 11.78; O, 13.46; S, 9.00.

5.6.7 3-(2-Methylindolin-1-yl)-2-(1,3-diphenyl-1H-pyrazol-4-yl)thiazolidin-4-one-(TZD-1-1-01)

Yield: 66 %; M.P.- 218-220 °C; IR (cm⁻¹): 1612 (Ring stretching for Indoline), 1645 (Ring stretching for Pyrazole), 1537 (Ring stretching modes for thiazolidinone ring), 885 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2963 (C-H asymmetric stretching for R-CH₃), 1429 (C-H asymmetric bending for R-CH₃), 3128-3047 (C-H stretching frequency for aromatic region), 1224 (C-H in plane bending for phenyl ring), 703 (C-C out of plane bending for mono substituted benzene ring), 2918 (C-H stretching frequency for ketone), 1731 (C=O stretching frequency for ketone in 5 membered saturated ring), 1453 (CH₂ bending for –CH₂-C=O group), 1017 (C-N stretching frequency for tertiary amine); MS: m/z: 452.17; Anal. Calcd. for C₂₇H₂₄N₄O₅S: C, 71.65; H, 5.35; N, 12.38; O, 3.54; S, 7.09 Found: C, 71.62; H, 5.31; N, 12.33; O, 3.51; S, 7.06.
5.6.8 2-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-methylindolin-1-yl)thiazolidin-4-one (TZD-1-1-02):

Yield: 55 %; M.P.- 222-224 °C; IR (cm⁻¹): 1608 (Ring stretching for Indoline), 1659 (Ring stretching for Pyrazole), 1522 (Ring stretching modes for thiazolidinone ring), 894 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2964 (C-H asymmetric stretching for R-CH₃), 1434 (C-H asymmetric bending for R-CH₃), 3127-3055 (C-H stretching frequency for aromatic region), 1225 (C-H in plane bending for phenyl ring), 835 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2917 (C-H stretching frequency for ketone), 1738 (C=O stretching frequency for ketone in 5 membered saturated ring), 1453 (CH₂ bending for –CH₂-C=O group), 1013 (C-N stretching frequency for tertiary amine), 722 (C-Cl stretching for mono chlorinated aromatic compounds); MS: m/z: 486.13; Anal. Calcd. for C₂₇H₂₃ClN₄OS: C, 66.59; H, 4.76; Cl, 7.28; N, 11.50; O, 3.29; S, 6.58; Found: C, 66.56; H, 4.72; Cl, 7.23; N, 11.46; O, 3.25; S, 6.55.

5.6.9 3-(2-Methylindolin-1-yl)-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)thiazolidin-4-one (TZD-1-1-03):

Yield: 70 %; M.P.- 214-216 °C; IR (cm⁻¹): 1606 (Ring stretching for Indoline), 1654 (Ring stretching for Pyrazole), 1527 (Ring stretching modes for thiazolidinone ring), 898 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2966 (C-H asymmetric stretching for R-CH₃), 1437 (C-H asymmetric bending for R-CH₃), 3126-3053 (C-H stretching frequency for aromatic region), 1228 (C-H in plane bending for phenyl ring), 837 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2922 (C-H stretching frequency for ketone), 1737 (C=O stretching frequency for ketone in 5 membered saturated ring), 1450 (CH₂ bending for –CH₂-C=O group), 1016 (C-N stretching frequency for tertiary amine), 1332 (NO₂ symmetric stretching for aromatic NO₂ group); ¹H NMR (DMSO-d₆) δ ppm: 1.37-1.39 (d, 3H, H₁), 4.49-4.53 (m, 1H, H₂), 2.78-2.83 (d, 1H, H₃), 3.48-3.54 (q, 1H, H₃),
7.06-7.08 (d, 1H, H4, J=8 Hz), 7.14-7.22 (m, 2H, H5 & H7), 6.84-6.88 (t, 1H, H6), 7.62 (s, 1H, H8), 7.36-7.40 (t, 1H, H9), 7.50-7.55 (t, 2H, H10 & H14), 8.34-8.38 (m, 3H, H11, H12, H13), 7.82-7.85 (d, 2H, H15 & H18, J value=11.6 Hz), 8.01-8.04 (d, 2H, H16 & H17, J Value=13.6), 5.45 (s, 2H, H19); MS: m/z: 497.15; Anal. Calcd. for C27H23N5O3S: C, 65.17; H, 4.66; N, 14.08; O, 9.65; S, 6.44; Found: C, 65.13; H, 4.62; N, 14.02; O, 9.61; S, 6.40.

5.6.10 2-(3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-methylindolin-1-yl)thiazolidin-4-one (TZD-1-1-09):

Yield: 60 %; M.P.- 242-244 ºC; IR (cm⁻¹): 1612 (Ring stretching for Indoline), 1667 (Ring stretching for Pyrazole), 1537 (Ring stretching modes for thiazolidinone ring), 882 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2960 (C-H asymmetric stretching for R-CH₃), 1431 (C-H asymmetric bending for R-CH₃), 3120-3055 (C-H stretching frequency for aromatic region), 1229 (C-H in plane bending for phenyl ring), 831 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2927 (C-H stretching frequency for ketone), 1735 (C=O stretching frequency for ketone in 5 membered saturated ring), 1458 (CH₂ bending for –CH₂-C=O group), 1013 (C-N stretching frequency for tertiary amine), 537 (C-Br stretching for aromatic ring); MS: m/z: 532.08; Anal. Calcd. for C₂₇H₂₃BrN₄O₅S: C, 61.02; H, 4.36; Br, 15.03; N, 10.54; O, 3.01; S, 6.03; Found: C, 60.99; H, 4.32; Br, 15.01; N, 10.52; O, 3.00; S, 6.01.
5.7 SPECTRAL DISCUSSION

5.7.1 IR SPECTRAL STUDY

IR spectra were recorded on Shimadzu FT-IR-8400 model using KBr pellet method. Various functional groups present in molecule were identified by characteristic frequency obtained for them. The characteristic bands of ring stretching for indoline were observed at 1600-1500 cm\(^{-1}\). The ring stretching mode for thiazolidinone gave frequency in the range of 1540-1400 cm\(^{-1}\) while the C-H out of plane bending for thiazolidinone gave several characteristic bands around 900-650 cm\(^{-1}\). The pyrazole ring showed ring stretching bands around 1650-1380 cm\(^{-1}\). The C-H asymmetric stretching for methyl moiety was seen around 2972-2952 cm\(^{-1}\), similarly the C-H symmetric stretching for methyl moiety gave characteristic bands near 2885-2860 cm\(^{-1}\). The asymmetric bending frequencies of methyl were observed in the range of 1475-1450 cm\(^{-1}\) while the symmetric bending frequencies gave the characteristic bands near 1383-1377 cm\(^{-1}\). The C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\) and the in plane bending frequencies of the same were found at 1250-950 cm\(^{-1}\). The out of plane bending frequencies for aromatic region were observed around 830-700 cm\(^{-1}\). The C-H stretching frequencies for the ketone function gave characteristic bands at 2925-2850 cm\(^{-1}\), while it’s C=O stretching frequency was observed at 1750-1740 cm\(^{-1}\). The C-N stretching frequencies for tertiary amine were seen at 1350-1020 cm\(^{-1}\). The C-Halogen stretching frequencies for aromatic rings were observed around 750-500 cm\(^{-1}\). The above mentioned respective frequencies suggest the correct formation of the desired products.

5.7.2 MASS SPECTRAL STUDY

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of respective compound. The probable Mass fragmentation pattern for the representative compound of each series is discussed below.
5.7.2.1 **PLAUSIBLE MASS FRAGMENTATION PATTERN OF TZD-2-1-10**

3-(2-Methylindolin-1-yl)-2-(4-nitrophenyl) thiazolidin-4-one (TZD-2-1-10)

1. The target compound showed the characteristic molecular ion peak 356 $m/z$.
2. The bond cleavage between C$_{19}$-N$_{22}$ generated a molecular ion which corresponds to a characteristic peak at 309 $m/z$ (A).
3. A bond cleavage between C$_2$-C$_4$ and N$_1$-C$_{10}$ generated a molecular ion which corresponds to a characteristic peak at 266 $m/z$ (B).
4. Bond cleavages between N$_1$-N$_{11}$ generated a molecular ion which corresponds to a characteristic peak at 219 $m/z$ (C).
5. Bond cleavages between N$_1$-N$_{11}$ and C$_{15}$-C$_{16}$ generated a molecular ion which corresponds to a characteristic peak at 100 $m/z$ (D).
6. Bond cleavages between N$_1$-N$_{11}$ generated another molecular ion which corresponds to a characteristic peak at 132 m/z (E).

7. Bond cleavages between C$_{12}$-O$_{23}$ generated a molecular ion which corresponds to a characteristic peak at 339 m/z (F).

8. Bond cleavages between C$_{15}$-C$_{16}$ generated a molecular ion which corresponds to a characteristic peak at 233 m/z (G).

9. Bond cleavages between N$_1$-N$_{11}$ and C$_2$-C$_3$ generated a molecular ion which corresponds to a characteristic peak at 117 m/z (H).

10. Bond cleavages between C$_{13}$-S$_{14}$, S$_{14}$-C$_{15}$, generated a molecular ion which corresponds to a characteristic peak at 323 m/z (I).

11. Bond cleavages between C$_2$-C$_3$, C$_{19}$-N$_{22}$ generated a molecular ion which corresponds to a characteristic peak at 294 m/z (J).

12. Bond cleavages between C$_2$-C$_3$, C$_{12}$-O$_{23}$ and C$_{19}$-N$_{22}$ generated a molecular ion which corresponds to a characteristic peak at 278 m/z (K).

13. Bond cleavage between C$_{12}$-C$_{13}$ and C$_{13}$-C$_{14}$ generated a molecular ion which corresponds to a characteristic peak at 341 m/z (L).
5.7.2.2 PLASIBLE MASS FRAGMENTATION PATTERN OF TZD-1-1-03

3-(2-Methylindolin-1-yl)-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-thiazolidin-4-one (TZD-1-1-03)

1. The target compound shows the desired characteristic molecular ion peak of 497 m/z.

2. The bond cleavage between C2-C3 generated a molecular ion which corresponds to a characteristic peak at 482 m/z (A).

3. The bond cleavage between N11-C12 and C12-C13 generated another molecular ion which corresponds to a characteristic peak at 469 m/z (B).
4. The bond cleavage between N\textsubscript{11}-C\textsubscript{12}, S\textsubscript{14}-C\textsubscript{15} and C\textsubscript{2}-C\textsubscript{3} generated a molecular ion which corresponds to a characteristic peak at 408 \textit{m/z} (C).

5. The bond cleavages between N\textsubscript{1}-N\textsubscript{11} generated a molecular ion which corresponds to a characteristic peak at 132 \textit{m/z} (D).

6. The bond cleavages between C\textsubscript{15}-C\textsubscript{16} generated a molecular ion which corresponds to a characteristic peak at 233 \textit{m/z} (E).

7. The bond cleavages between C\textsubscript{15}-C\textsubscript{16} generated another molecular ion which corresponds to a characteristic peak at 264 \textit{m/z} (F).

8. The bond cleavages between N\textsubscript{1}-N\textsubscript{11} generated another molecular ion which corresponds to a characteristic peak at 365 \textit{m/z} (G).

9. The bond cleavages between N\textsubscript{1}-N\textsubscript{11}, C\textsubscript{15}-C\textsubscript{16}, C\textsubscript{12}-C\textsubscript{13}, & C\textsubscript{13}-S\textsubscript{14} generated a molecular ion which corresponds to a characteristic peak at 91 \textit{m/z} (H).

10. The bond cleavage between N\textsubscript{18}-C\textsubscript{27}, and C\textsubscript{20}-C\textsubscript{21} generated a molecular ion which corresponds to a characteristic peak at 298 \textit{m/z} (I).

11. Bond cleavages between C\textsubscript{20}-C\textsubscript{21} generated a molecular ion which corresponds to a characteristic peak at 118 \textit{m/z} (J).

12. Bond cleavages between C\textsubscript{13}-S\textsubscript{14}, and S\textsubscript{14}-C\textsubscript{15}, generated a molecular ion which corresponds to a characteristic peak at 465 \textit{m/z} (K).

13. Bond cleavage between C\textsubscript{24}-N\textsubscript{33} generated a molecular ion which corresponds to a characteristic peak at 451 \textit{m/z} (L).

**5.7.3 \textsuperscript{1}H-NMR SPECTRAL STUDY**

\textsuperscript{1}H-NMR spectra of the synthesized compounds were recorded on \textbf{Bruker Avance II 400} spectrometer. Sample solutions were made in DMSO solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons identified from H-NMR spectrum and their chemical shift (\(\delta\) ppm) were in the agreement of the structure of the molecule. \(J\) values were calculated to identify o, m and p coupling. In some cases, aromatic protons were obtained as multiplet. The spectral interpretation can be discussed as under.
1. The three protons of the methyl function has a single proton in its vicinity thus showing a characteristic strong doublet between 1.27-1.28 δ ppm.

2. The proton no. 2 is surrounded by several protons like the three methyl protons and two geminal protons on the other carbon. This will split its signal into a multiplet which is seen in the NMR spectrum between 4.47-4.52 δ ppm.

3. As seen in the previous chapters there are two geminal protons at 3 position. Both these geminal protons show different signals for each of them one of them shows a characteristic doublet between 2.69-2.74 δ ppm while the other proton shows a quartet between 3.39-3.46 δ ppm as expected.

4. The proton no.4 shows a characteristic doublet in the aromatic region of 7.05 -7.07 δ ppm and its J value was calculated to be 8 Hz which clearly suggests that it is ortho coupled to any other proton. On observing the structure it is quite evident that proton no. 4 is ortho to proton no.5 hence the above mentioned doublet is definitely for proton no.4.

5. The proton no. 5 and 7 are seen in the NMR spectrum as a multiplet in the aromatic region between 7.13 -7.16 δ ppm. The multiplet is seen due to the fact that first proton no. 5 is ortho coupled to two protons i.e. proton no. 4 and 6 while it is meta coupled to proton no. 7. On the other hand the proton no.7 is also ortho coupled to proton o.6 but is meta coupled to proton on.5 hence all these effects give rise to a multiplet and hence we assign it to protons 5 and 7.

6. The proton no. 6 is again surrounded and coupled to a number of protons. It is ortho coupled to protons 5 and 7 while it is meta coupled to proton no.4. Thus it shows a multiplet for its single proton in the aromatic region between 6.79 - 6.83 δ ppm.
7. The proton no. 8 is not surrounded by any other proton hence it should normally show a singlet. Moreover, on three sides it is surrounded by a Nitrogen atom, a sulphur atom as well as a phenyl nucleus which are all electron withdrawing in nature. This will deshield the proton to a large extent forcing it to give a signal in the down filed region. On observing the NMR spectrum, a singlet at 7.37 δ ppm is observed which is assigned to proton no.8 without any doubt.

8. On looking at the structure it can be assumed that the proton no. 9 and 12 are having similar kind of chemical environment which will lead to a single signal for both these protons and moreover as they are ortho coupled to other set of protons, a sharp doublet should be observed in the aromatic region. This is evidently seen in the spectrum as a sharp doublet between 7.64-7.66 δ ppm. The J value for this doublet was found out to be 8 Hz. Hence this doublet is assigned to proton nos. 9 and 12.

9. Similarly, proton nos. 10 and 11 are also chemically equivalent due to similar environment only difference being that as they are near to the electron withdrawing Nitro group their signal would shift towards a bit downfield region. As they are ortho coupled to proton nos. 9 and 12, the spectra reveals another doublet in the aromatic region between 8.09-8.11 δ ppm and the calculated J value again found to be 8 Hz. Hence without any doubt this doublet is assigned to proton nos. 10 and 11.

10. The methylene protons at position 13 are also not having any other protons in its vicinity hence their signal will not split giving us a characteristic singlet at 5.37 δ ppm. The main reason for this signal to shift downfield is that this proton is surrounded by sulphur on one side and a ketone group on the other side which again are both electron withdrawing in nature which will deshield the protons thus forcing them to go downfield as compared to any other proton in isolation.

Thus, by assigning all the peaks as per the above given justifications and by calculating the J value for the respective protons the proposed structure of TZD-2-1-10 is confirmed.
3-(2-Methylindolin-1-yl)-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) -thiazolidin-4-one (TZD-1-1-03)

1. The proton no. 1 is a methyl proton having one proton in its vicinity hence a strong doublet for these three proton is observed in the NMR spectrum between 1.37-1.39 δ ppm.

2. The proton no. 2 is a single proton surrounded by three protons on one side and two geminal protons on the other side hence it is evident that a multiplet signal should be observed for this proton between 4.49-4.53 δ ppm in the NMR spectrum.

3. As discussed above the two geminal protons will show a doublet and a quartet respectively. The characteristic doublet is seen in the NMR spectrum at 2.78 2.83 δ ppm while the characteristic quartet of the other geminal twin is observed between 3.48-3.54 δ ppm.

4. The proton no. 4 is a single proton which is ortho coupled to proton no. 5. On observing the spectra a characteristic doublet is found in the aromatic region between 7.06-7.08 δ ppm and by the means of the J value which was calculated to be 8 Hz, it can easily be assigned to proton no. 4.

5. The proton nos. 5 and 7 are seen in the NMR spectrum again as a multiplet for two protons in the aromatic region between 7.14-7.22 δ ppm which is due to the various coupling effects from their neighboring protons viz. proton no. 4 as well as proton no.6

6. The proton no. 6 is a single proton having two protons in its direct vicinity which will split its signal into a triplet. This characteristic triplet for proton no. 6 is observed between 6.84-6.88 δ ppm in the NMR spectrum.
7. The proton no. 8 does not have any other proton in its vicinity. Also, as there are two electron withdrawing groups like Nitrogen as well as Sulphur in its direct contact its proton will get highly deshielded and would be seen at much downfield region. This characteristic strong singlet is observed in the NMR spectrum at 7.62 δ ppm which is assigned to proton no. 8 without any doubts.

8. Under normal circumstances the proton no. 9 should give a singlet as there are no other protons in its direct vicinity. But, this singlet is not found in the NMR spectrum. Instead, a triplet is found at 7.36-7.40 δ ppm which accounts for a single proton. This triplet is assigned to proton no. 9 because of the fact that there is a rotation of the single bond between the two nitrogen atoms of Indoline and thiazolidinone moieties. Due to these rotations there will be field effect interactions between proton no. 9 and proton no.7 or proton no.9 and proton no.1. These combined field effects on proton no.9 will give rise to a complex triplet which should otherwise have shown a simple singlet. Hence this triplet found in the NMR spectrum accounting for a single proton is assigned to proton no.9 without any further doubts.

9. The proton nos. 10 and 14 show a characteristic triplet in the aromatic region between 7.50-7.55 δ ppm this is due to the fact that they both have two protons ortho coupled to it and one proton is meta coupled to it respectively.

10. A multiplet accounting for 3 protons is assigned to proton nos. 11, 12, and 13 as they too will not only couple with each other but will also couple with proton nos. 10 and 14. These coupling effects will give rise to a multiplet. This multiplet is seen in the NMR spectrum between 8.34- 8.38 δ ppm which is assigned to proton nos. 11, 12, and 13.

11. Again on observing the structure, proton no 15 and 18 are chemically equivalent as their chemical environments are similar. Hence they will show a doublet for 2 protons which is seen in the NMR spectrum between 7.82-7.85 δ ppm and the J values were calculated to be 11.6 Hz. This high J value suggests that they are ortho coupled to another set of protons.
12. Similarly, proton nos. 16 and 17 are also chemically equivalent and will show a doublet the only difference is that as they are near to the electron withdrawing Nitro group their protons would be deshielded giving a doublet signal in a bit downfield region as compared the signals from proton no. 15 and 18. This doublet is seen in the NMR spectrum between 8.01 to 8.04 δ ppm and its J value was calculated to be 13.6 Hz which is in accordance with the structure as they are ortho coupled to protons nos. 15 and 18. Hence this doublet between 8.01 to 8.04 δ ppm is assigned to proton nos. 16 and 17.

13. The proton no. 19 is the methylene proton of the thiazolidinone motif which is surrounded by a ketone group on one side and a sulphur group on the other side. Thus, its signals should be a singlet which must be found at a downfield region which is exactly the case a sharp singlet at 5.45 δ ppm is observed in the NMR spectrum which is assigned to proton no.19.

Thus, by observing and assigning the peaks in the NMR spectrum and by the calculation of the J values for each of the above proton it can clearly be suggested that the proposed structure for compound no. TZD-1-1-03 has been confirmed.
5.8 SPECTRAL REPRESENTATIONS OF THE COMPOUNDS

5.8.1 IR SPECTRUM OF TZD-2-1-10

5.8.2 MASS SPECTRUM OF TZD-2-1-10
5.8.3 $^1$H-NMR SPECTRUM OF TZD-2-1-10

5.8.3.1 EXPANDED $^1$H-NMR SPECTRUM OF TZD-2-1-10
5.8.4 IR SPECTRUM OF TZD-1-1-03

5.8.5 MASS SPECTRUM OF TZD-1-1-03
5.8.6 $^1$H-NMR SPECTRUM OF TZD-1-1-03

5.8.6.1 EXPANDED $^1$H-NMR SPECTRUM OF TZD-1-1-03
5.9 RESULTS AND DISCUSSIONS

This chapter deals with the 3-(2-methylindolin-1-yl) thiazolidin-4-one core structure. The importance of 2-Methylindoline-1-amine as a privileged structure as well as the biological significance of thiazolidinones has been discussed at length in the chapter no. 1 of this thesis and also in this chapter which served as the rational for the synthesis of these kinds of compounds. Moreover, this chapter has quite a lot of interesting features in terms of synthesis methodology as well as biological activity study. Previously, the thiazolidinone moiety was prepared by refluxing the Schiff base with the thioglycolic acid for longer time in presence of various different solvents as well as catalysts. In the recent years, many new synthetic methodologies haven been used such as synthesis using Ionic liquids, synthesis using better catalysts such as DCC and HBTU etc. and also using Microwave irradiation.

The synthesis has been taken up using Microwave irradiation over other methods owing to their advantages such as reduction in time, higher yields as well as hassle free work up procedures on one hand and on the other hand it is a small step forward in our endeavor towards the sustainable development through implementing the newer research work using eco friendly processes.

5.10 CONCLUSION

The synthesized compounds have been screened for their Anti viral (HIV-I and HIV-II) activities which have been discussed in Chapter no.6.
## REFERENCES


