



Synthesis and Characterization of New Thiazolidin-4-One Derivatives via the Reaction of Various Imines with Mercaptoacetic Acid

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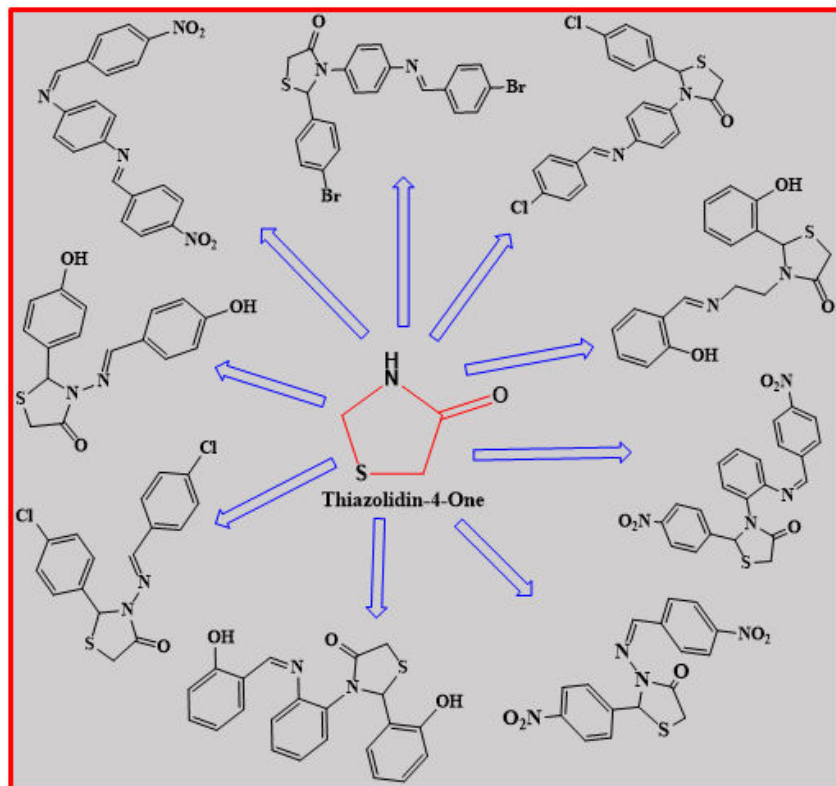
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Graphical Abstract

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ABSTRACT

New 2, 3-disubstituted-1, 3-thiazolidin-4-one derivatives were synthesized by cycloaddition reaction of mercaptoacetic acid with various imines in anhydrous benzene by reflux under dry conditions. Imines were synthesized by acid-catalysed thermal condensation of the amino group of the phenylenediamines, ethylenediamine and hydrazine with the carbonyl group of the aromatic aldehydes in absolute ethanol. The target products were identified by their melting points, FT-IR and ¹HNMR spectra.

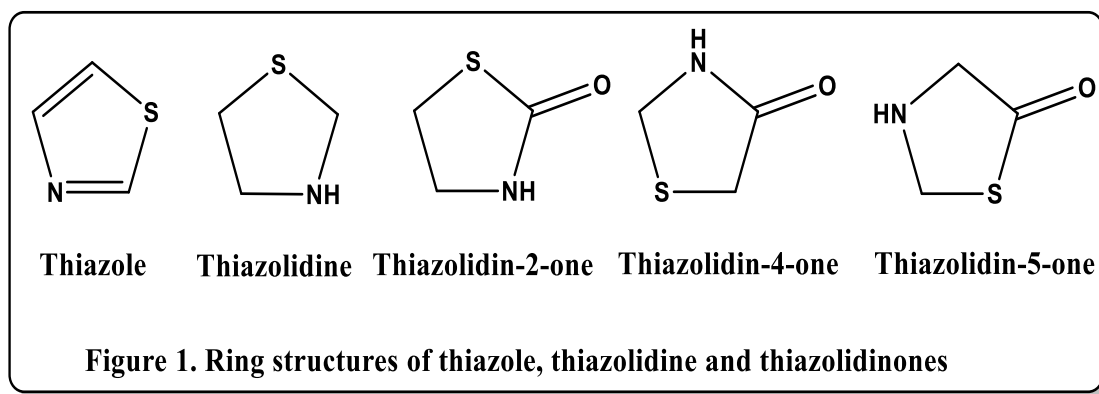
Key words: Thiazolidin-4-one, Imines, Mercaptoacetic Acid, cycloaddition reaction

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1. INTRODUCTION

Thiazolidine is a 5-membered saturated ring with sulphure and nitrogen atoms in the 1 and 3 positions respectively, and carbonyl group at position 2, 4, or 5, Figure 1. It is a sulphure analog of oxazolidine with formula (CH₂)₃(NH) S. Thiazolidines is a class of heterocyclic organic compounds associated with significant biological activities and medical importance which are considered very vital precursor for the

organic and bio-organic synthesis. Thiazolidine derivatives are the core moieties for many drugs; for example the syntheses of 2-aryl 3-alkyl and 2-hetero-3-alkyl derivatives were reported in early publications. In past decades a variety of researches were establishes to explore the chemistry of thiazolidines especially for the medical and the bio-active compounds syntheses [1-3].



The presence of sulphur enhances their pharmacological properties, and therefore, they are used as key intermediate in the synthesis of valuable biologically active organic compounds and drugs. Thiazolidinones are possessing a wide

spectrum of biological activities such as anti-cancer, anti-viral, anti-microbial, anti-inflammatory, anti-fungal, anti-oxidant, anti-convulsant, anti-bacterial, anti-tubercular, anti-Parkinsonism, anti-obesity, anti-diabetic, anti-oxidant, anti-biotic, anti-

tumors and non-narcotic analgesic activities [4-8]. Thiazolidin-4-ones are particularly synthesized by the cycloaddition reaction of imines and mercaptoacetic acid with more than 80% yield [9]. Recently 2,3-disubstituted-thiazolidin-4-one were synthesized by one-pot three-component system by cycloaddition condensation of an aldehyde and amine with thioglycolic acid in presence of convenient catalytic system, $\text{HClO}_4\text{-SiO}_2$ which is found to be suitable for different reaction systems of aldehydes (aryl/heteroaryl/alkyl/cycloalkyl) and the amines.

The relative catalytic potential of acid- SiO_2 on silica gel (230–400 mesh size) catalyst system is following the order $\text{HClO}_4\text{-SiO}_2 > \text{TfOH-SiO}_2 \gg \text{H}_2\text{SO}_4\text{-SiO}_2 > p\text{-TsOH-SiO}_2 > \text{MsOH-SiO}_2 \sim \text{HBF}_4\text{-SiO}_2 > \text{TFA-SiO}_2 \sim \text{HOAc-SiO}_2$. For example 2, 3-disubstituted-thiazolidin-4-one analogs were prepared by this reaction in 72–89% yield [10, 11]. 2,3-Disubstituted-1,3-thiazolidine-4-one derivatives were efficiently synthesized by one-pot three component system via solvent free reaction from one equivalent of each of hydrazines and aldehydes or ketones with three equivalent of mercaptoacetic acid [12].

2. EXPERIMENTAL PART

2.1- Characterization of the Compounds

The melting points were recorded on an Electro-thermal 9100 melting point apparatus LTD, UK, expressed in degree ($^{\circ}\text{C}$) and are uncorrected. Aluminum and glass plates coated with 0.25mm layer of silica gel (Fluke) were to do thin layer chromatography (T.L.C). All FT-IR spectra

Table 1: Structural formula, names, melting points, %yield and colours of the synthesized imines.

(1% KBr pellets) for imines and thiazolidinones were recorded by using Fourier Transform Infrared, Shimadzu, 8400 Spectrophotometer, Japan within the range of $4000\text{-}600\text{ cm}^{-1}$. Their proton nuclear magnetic resonance spectra ($^1\text{H-NMR}$) were recorded on a Bruker DRX 500 Vance spectrometer (500 MHz) by using DMSO-d_6 as solvent and Me_4Si (TMS $\delta=0$) as internal standard, the chemical shifts were reported in δ (ppm) units, relative to TMS signal.

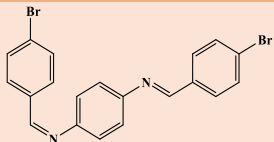
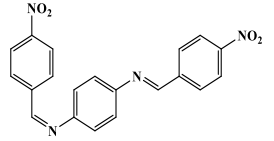
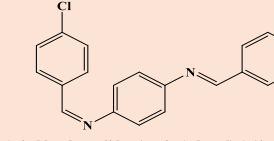
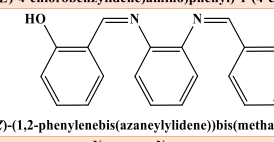
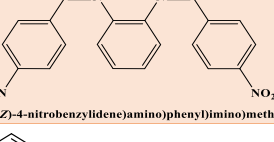
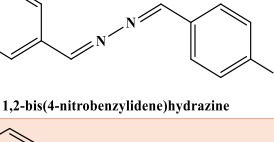
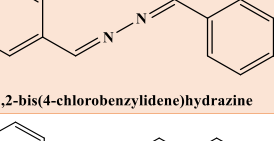
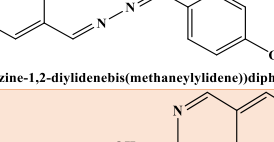
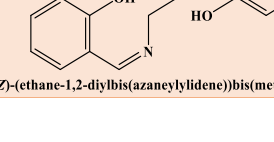
2.2- Synthesis of Schiff-Bases (1a-i)

Schiff's bases have been synthesized by thermal condensation reaction of various benzaldehydes and phenylenediamines, ethylenediamine and phenyl hydrazine in absolute ethanol in the presence of few drops of glacial acetic acid as catalyst by reflux of the reaction mixture for certain time according to literature procedure [13].

Synthesis of Schiff-bases (1a).

Amount of p-bromobenzaldehyde (0.02 mol) and phenylenediamine (0.01 mol) were dissolved in absolute ethanol (50ml) and acidified with (3-5) drops glacial acetic acid as catalyst was refluxed for 5 hours. The reaction of mixture was cooled down whereby a solid product was precipitated then was filtered off. The resulting compound was purified by recrystallization from absolute ethanol and dried under reduced pressure over anhydrous CaCl_2 . Other Schiff's bases (1b-i) were prepared by using the same procedure. The physical properties for the prepared imines are listed in table 1.



Cod.	Structural Formula	m.p.	Yield %	Colour
1a	 (Z)-N-(4-((E)-4-bromobenzylidene)amino)phenyl)-1-(4-bromophenyl)methanimine	225-227	79	White
1b	 (Z)-N-(4-((E)-4-nitrobenzylidene)amino)phenyl)-1-(4-nitrophenyl)methanimine	240-248	79	Yellow
1c	 (Z)-N-(4-((E)-4-chlorobenzylidene)amino)phenyl)-1-(4-chlorophenyl)methanimine	198-200	70	White
1d	 2,2'-(1Z,1'Z)-(1,2-phenylenebis(azanelylidene))bis(methaneylylidene)diphenol	168-170	60	Yellow
1e	 4-(Z)-((2-((Z)-4-nitrobenzylidene)amino)phenyl)imino)methylphenol	206-208	60	Brown
1f	 1,2-bis(4-nitrobenzylidene)hydrazine	273-275	80	Orange
1g	 1,2-bis(4-chlorobenzylidene)hydrazine	212-214	69	Golden
1h	 4,4'-(hydrazine-1,2-diylidenebis(methaneylylidene))diphenol	272-274	68	Yellow
1i	 2,2'-(1Z,1'Z)-(ethane-1,2-diylbis(azanelylylidene))bis(methaneylylidene)diphenol	126-128	60	Golden

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2.3- Synthesis of 2, 3-disubstituted-1, 3 thiazolidin-4-one derivatives (2a-i)

Thiazolidin-4-ones were synthesized by cycloaddition reaction of Schiff-bases (imines) and mercaptoacetic acid in dry benzene with trace amount of acid catalyst

under reflux conditions according to literature procedure [14].

Synthesis of 2, 3-disubstituted-1, 3 thiazolidin-4-one (2a)

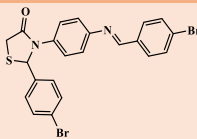
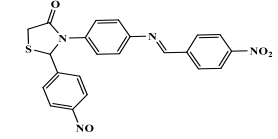
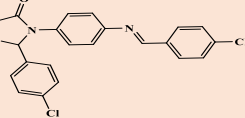
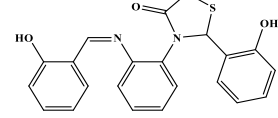
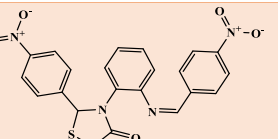
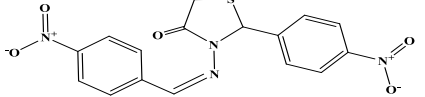
A reaction mixture of (0.01mol) of compound (1a) and (0.01mol) of



mercaptoacetic acid in dry benzene (50 ml) with trace amount of zinc chloride as catalyst and trace amount of triethylamine were contained in a well dried (100 ml) round-bottom flask equipped with condenser, magnetic stirrer, and anhydrous calcium chloride guard tube. The mixture was refluxed for 6 hours, then was cooled down in an ice bath, whereby a yellow

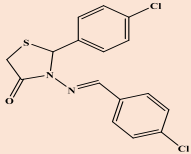
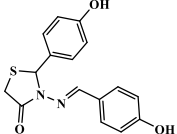
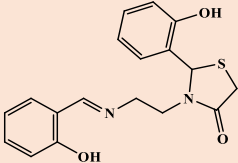
colour solid product is precipitated, the product was filtered off, recrystallized from absolute ethanol and dried under reduced pressure over anhydrous CaCl₂. All other products were prepared by using the same procedure. The percentage yields and the physical properties of the prepared 2,3-disubstituted -1,3- thiazolidin-4-one derivatives are listed in table 2.

Table 2: Structural formula, names, melting points, %yield and colour for the synthesized 2, 3-disubstituted-1, 3 thiazolidin-4-one derivatives (2a-i).

Cod.	Structural Formula	m.p.	Yield%	Colour
2a	 (E)-3-(4-((4-bromobenzylidene)amino)phenyl)-2-(4-bromophenyl)thiazolidin-4-one	230-233	65	Green
2b	 (E)-3-(4-((4-nitrobenzylidene)amino)phenyl)-2-(4-nitrosophenyl)thiazolidin-4-one	240-242	66	Yellow
2c	 (E)-3-(4-((4-chlorobenzylidene)amino)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one	223-226	62	Brown
2d	 (Z)-3-(2-(2-hydroxybenzylidene)amino)phenyl)-2-(2-hydroxyphenyl)thiazolidin-4-one	167-169	66	Orange
2e	 (Z)-3-(2-((4-nitrobenzylidene)amino)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one	217-219	65	Yellow
2f	 (E)-3-(4-(4-nitrobenzylidene)amino)-2-(4-nitrophenyl)thiazolidin-4-one	Dec.	60	Yellow

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2g	 (E)-3-((4-chlorobenzylidene)amino)-2-(4-chlorophenyl)thiazolidin-4-one	209-212	68	Yellow
2h	 (E)-3-((4-hydroxybenzylidene)amino)-2-(4-hydroxyphenyl)thiazolidin-4-one	199-201	65	Yellow
2i	 (E)-3-(2-((2-hydroxybenzylidene)amino)ethyl)-2-(2-hydroxyphenyl)thiazolidin-4-one	128-130	67	Yellow

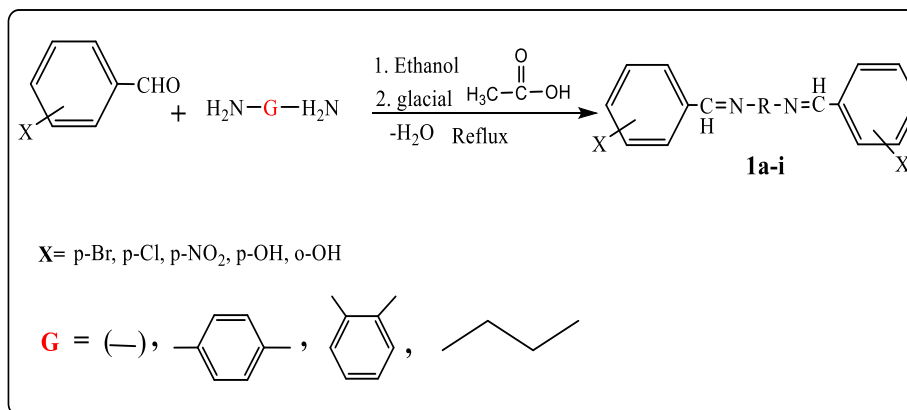
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. RESULTS AND DISCUSSION

Schiff bases (imines) were synthesized by condensation reaction in absolute ethanol at reflux condition from

commercially available substituted benzaldehyde and primary phenylenediamines, ethylenediamine and hydrazine as illustrated in scheme 1.

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Scheme1: The overall reaction for the synthesis of imines (Schiff bases).

The products were identified by their melting points and FT-IR absorption spectra, table (3), via the appearance of the absorption bands of azomethine (-C=N-) group at the range (1612-1686 cm⁻¹) of the resulting imines beside the characteristic

bands of the residual groups in the structure, and the disappearance of absorption bands of the carbonyl group in the range (1700-1735 cm⁻¹) in the FT-IR spectra, the spectral data of the synthesized



imines are in quite agreement with the literature values [15-18].

Table 3: FT-IR absorption bands in (cm^{-1}) of the synthesized imines (1a-i).

Comp. No.	$\nu\text{C-H}_{\text{arom.}}$	$\nu\text{C-H}_{\text{aliphatic}}$ Asym. Sym	$(-\text{CH}_2-)$ Sym	$\nu\text{C=N}$	$\nu\text{C=C}_{\text{ring}}$ Asym Sym	Others
1a	3080	2981	1893	1612	1582 1483	833 C-Br
1b	3005	2935	1882	1612	1602 1480	1342 C-NO ₂
1c	2987	2882	1768	1618	1602 1456	730 C-Cl
1d	3002	2980	1878	1635	1596 1485	3472 O-H
1e	3085	2965	1790	1632	1598 1482	1455 C-NO ₂
1f	3114	2916	1830	1686	1594 1516	1325 C-NO ₂
1g	3049	2997	1881	1622	1484 1484	817 C-Cl
1h	3095	2953	1860	1640	1489 1489	3460 O-H
1i	3060	2990	1885	1638	1485 1485	3458 O-H

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In this work the synthesis of novel 2, 3-disubstituted-1,3 thiazolidin-4-one derivatives (2a-i) were achieved by the cycloaddition reaction of thioglycolic acid and Schiff bases in dry benzene with trace amount of zinc chloride as catalyst and triethylamine. Formation of the products were monitored by TLC using silica gel G and were identified by their melting points, FT-IR and ¹HNMR spectra.

The FT-IR spectra of the products showed the appearance of absorption bands ($\nu\text{C-H}_{\text{arom.}}$) within the range (3050-

3077 cm^{-1}), and the appearance of absorption bands ($\nu\text{C-H}_{\text{aliph.}}$) within the range (2970 -2990 cm^{-1}). In addition to the appearance of the bands at (1670-1680 cm^{-1}) related to the stretching absorption of (C=O) bond of the beta-lactam ring and the absorption band at (1610- 1640) related to the stretching absorption of (C=N) group, the spectral in table (4) are identical to the literature values [17-19].

Table (4): FT-IR spectral absorption bands cm^{-1} for 2,3- di substituted -1,3- thiazolidin-4-one derivatives: (2a-i).

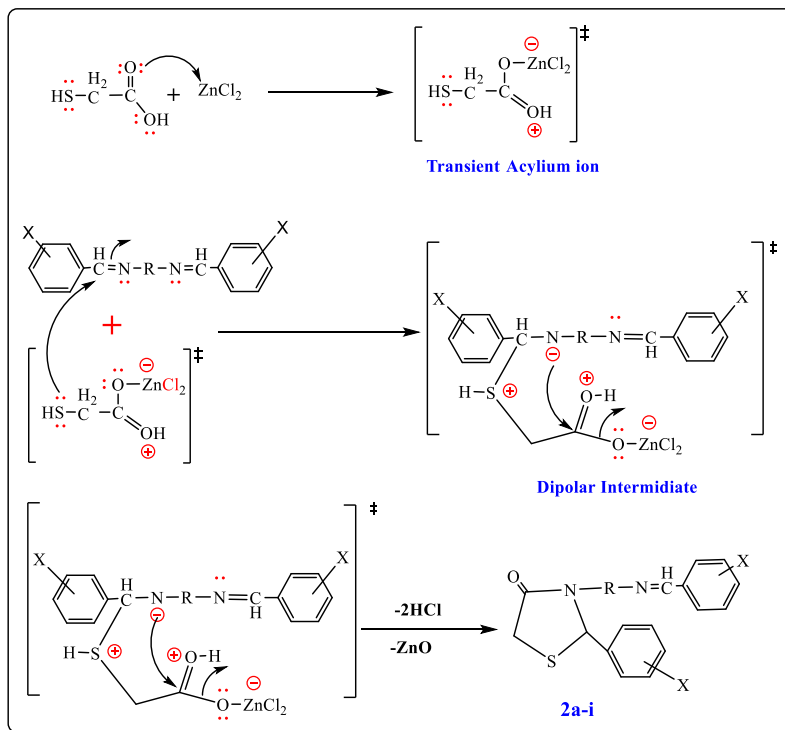


Comp. No.	νC-H _{arom.}	νCH(-CH ₂) _{aliph}		ν C=C _{aromatic}		N-C=O lactam	ν C=N	ν C-N	ν C-S	Others
		Asym.	Sym	Asym	Sym					
2a	3062	2985 2893		1583	1489	1674	1611	1270	740	1085 C-Br
2b	3077	2978 2890		1592	1493	1680	1622	1190	683	1414 C-NO ₂
2c	3073	2988 2900		1590	1488	1672	1620	1270	688	1080 C-Cl
2d	3066	2982 2899		1588	1408	1676	1638	1265	755	3385 O-H
2e	3075	2987 2893		1604	1503	1670	1624	1236	717	1432 C-NO ₂
2f	3064	2980 2897		1590	1470	1673	1634	1256	735	3447 O-H
2g	3050	2990 2891		1601	1478	1671	1628	1245	727	1430 C-NO ₂
2h	3070	2883 2898		1590	1518	1677	1630	1238	718	1082 C-Cl
2i	3062	2985 2897		1577	1455	1675	1629	1248	743	3275 O-H

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It may be plausible assumption to propose that the mechanism of the reaction of imines with mercaptoacetic acid is started by the initial attack of the nucleophilic sulphure atom on the electropositive carbon of the azomethine group to give a dipolar intermediate, scheme 2. This reaction is formally named as (3+2) cycloaddition reaction, that involve 1, 3 dipolar moieties. The dipolar intermediate is then collapses to give the five-membered heterocyclic molecule.





Scheme (2): Mechanism for the synthesis of Thiazolidine (2 a-i).

As a conclusion the roll of zinc chloride as Lewis acid catalyst can be explained by formation of an incipient dipolar intermediate which in turn enhance the electropositivity of the carbon of the carbonyl group which facilitate the nucleophilic attack of the negatively charged nitrogen of the azomethine group.

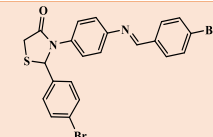
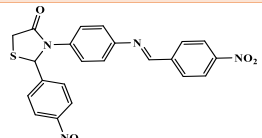
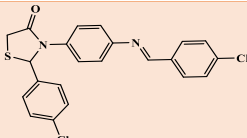
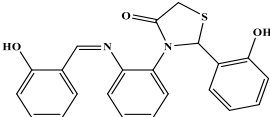
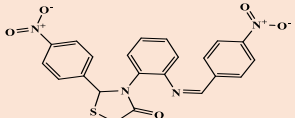
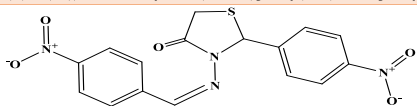
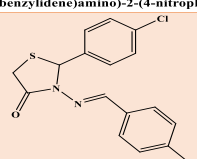
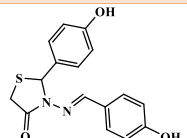
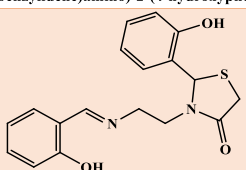
The ^1H NMR spectra of the products showed significant signals of the chemical shifts for each compound, Table (5) which are in clear agreement with the values in the scientific literature [17-21].

Representative ^1H NMR spectra, figure (2) and figure (3) are given.

The protons of the thiazolidine ring exhibited significant signals at chemical shifts for $-\text{S-CH}_2-$ protons at ($\delta = 3.56- 4.12$ ppm) and the $-\text{CH-N-}$ protons at ($\delta = 5.66- 6.30\text{ppm}$), whereas the aromatic protons of the products displayed chemical shifts signals at ($\delta = 6.59-8.30$ ppm) and the signals of the $-\text{CH=N-}$ protons are seen at ($\delta = 8.25- 8.70$).

Table (5): Molecular structure, Chemical Shift δ ppm of thiazolidin-4-one (2a-2i).

Comp. No.	Molecular structure	Chemical Shift ppm
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2a	 <p>(E)-3-((4-bromobenzylidene)amino)phenyl)-2-(4-bromophenyl)thiazolidin-4-one</p>	3.88(s, 2H, S-CH ₂), 6.20(s, 1H,-CH-N), 6.73-7.85(m,12H, Aromatic protons), 8.52(s,1H,-CH=N).
2b	 <p>(E)-3-((4-nitrobenzylidene)amino)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one</p>	3.91(s,2H,S-CH ₂) 6.30(s,1H,-CH-N) 6.73-8.10(m,12H, Aromatic protons) 8.40(s,1H, -CH=N).
2c	 <p>(E)-3-((4-chlorobenzylidene)amino)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one</p>	3.87(s,2H,S-CH ₂) 6.33(s,1H,-CH-N) 6.83-8.10(m,12H, Aromatic protons) 8.61(s,1H, -CH=N).
2d	 <p>(Z)-3-(2-(2-hydroxybenzylidene)amino)phenyl)-2-(2-hydroxyphenyl)thiazolidin-4-one</p>	3.94(s,2H,S-CH ₂) 6.37(s, 1H,-CH-N) 6.73-8.10(m,12H, Aromatic protons) 8.70 (s,1H,-CH=N) 9.55-10.90 (s,2H, -OH).
2e	 <p>(Z)-3-(2-(4-nitrobenzylidene)amino)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one</p>	3.86(s,2H,S-CH ₂) 6.10(s,1H,-CH-N) 6.59-8.23(m,12H, Aromatic protons) 8.55(s,1H, -CH=N).
2f	 <p>(E)-3-((4-nitrobenzylidene)amino)-2-(4-nitrophenyl)thiazolidin-4-one</p>	3.56(s,2H,S-CH ₂) 5.66(s,1H,-CH ₂ -N) 7.71-7.77(m, 8H, Aromatic protons) 8.34(s, 1H, CH=N).
2g	 <p>(E)-3-((4-chlorobenzylidene)amino)-2-(4-chlorophenyl)thiazolidin-4-one</p>	4.12(s,2H,S-CH ₂) 5.88(s,1H-CH-N) 7.20-7.88(m,8H, Aromatic protons) 8.25(s, 1H, CH=N).
2h	 <p>(E)-3-((4-hydroxybenzylidene)amino)-2-(4-hydroxyphenyl)thiazolidin-4-one</p>	3.90(s,2H,S-CH ₂) 5.85(s,1H,-CH-N) 6.71-7.66(m,8H,Aromatic protons) 9.16-9.60(s,2H,-OH) 8.35(s, 1H, CH=N).
2i	 <p>(E)-3-(2-(2-hydroxybenzylidene)amino)ethyl)-2-(2-hydroxyphenyl)thiazolidin-4-one</p>	3.77(s,2H,-S-CH ₂ -CH ₂), 3.80(s,2H,-CH ₂ -N), 5.90(s,1H,-CH-N), 6.82-7.66(m,8H, Aromatic protons) 9.24-9.60(s,2H,-OH) 8.45(s, 1H, CH=N).

The compound (2b) showed a binary signal at ($\delta=4.02- 4.07$ ppm, 2H, CH₂ thiazole) related to the proton of the thiazole ring, and a single signal appeared at ($\delta=6.92$ ppm, s, 1H, CH-thiazole) belongs to the proton of the methine group in the thiazole ring. The multiple signals that are located at

the range ($\delta=7.26-7.96$ ppm, m 12H, CH-Arom.) belong to the protons of the aromatic rings, and the single signal appeared at ($\delta=8.53$ ppm, s, 1H CH=N) belongs to the proton of the azomethine group, as shown in Figure (2).

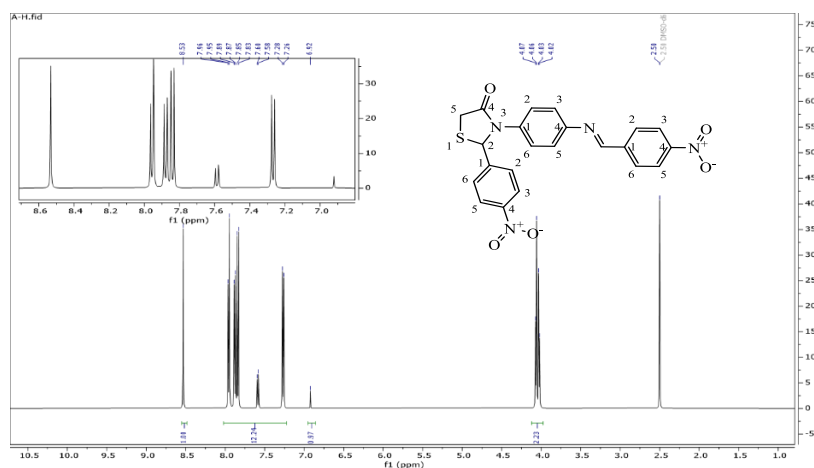


Figure (2) Extended and condensed ¹H-NMR spectrum of 2b

Compound (2i) showed a triple signal at ($\delta=3.58-3.88$ ppm, t, 4H,CH₂) belong to the aliphatic homologous group protons, and showed a single signal at ($\delta=4.01$ ppm, s,2H, CH₂ thiazole) due to the proton of the thiazole ring, and a single signal appeared at ($\delta=5.93$,ppm, s,1H, CH- thiazole) belongs to the proton of the methine group in the thiazole ring. While the multiple signals

which are located at the (6.83-7.53ppm range, m 8H , CH-Arom.) belong to the protons of the aromatic rings, and the single signal appeared at ($\delta=8.49$ ppm, s,1H,CH=N) belongs to the proton of the azomethine group, in addition to two single signs appearing at ($\delta=9.64, 11.05$ ppm, s, 2H,OH) related to the protons of the hydroxyl groups as shown in Figure (3)

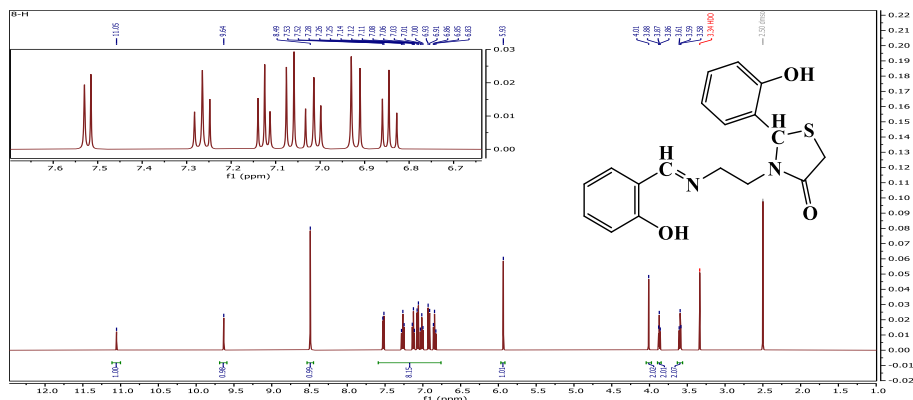


Figure (3) Extended and condensed ^1H -NMR spectrum of 2i

5. CONCLUSION

Novel 2,3-disubstituted 1,3-thiazolidin-4-one derivatives were synthesized by (2+3) cycloaddition reaction of pure imines and mercaptoacetic acid in good yield (60-80%). The synthesized derivatives consist of thiazolidine ring with aromatic substituted in position-2 and imine substituted in position -3. Their structures were elucidated by the spectral data of FT-IR, tables (3 and 4) and ^1H NMR, table (5).

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