Preliminary Green route Synthesis of Substituted Hydrazono Thiazolidin-4-Ones

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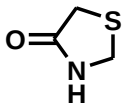
Abstract:

Thiazolidinones is a class of privileged heterocycles which act as drug-candidates with multiplicity of biological activities. In the modish series of development, Thiazolidinone has appear as a very strong scaffold as per its clinical importance. 4-Thiazolidinone has attracted the attention of researchers due to massive pharmacological activities of such as anti-viral, anti-inflammatory, anti-fungal, anti-cancer, anti-convusant and anti-diabetic. Present study deal with the synthesis of hydrazono thiazolidine-4-ones through green route synthesis using water as a green solvent system. The synthesized compounds were confirmed by TLC and spectral data analysis using ^{1}H NMR, ^{13}C NMR and mass sectra. Further DFT studies validate the claim of two regio-isomers.

Keywords: Thiazolidinone, Thiosemicarbazone, Heterocyclic, biological activities, cyclocondensation

1. INTRODUCTION

Heterocycles compounds are backbone for drug design owing to their biological resemblance and excellent biological behaviour. They are basic scaffolds in many natural and non-natural moieties. Many broader aspects of heterocyclic compounds are recognized as discipline of general significance that impinges on almost all aspect of modern chemistry. Thiazolidinone are saturated form of thiazole, that have an atom of Sulphur at position 1 and an atom of Nitrogen at position at 3 and a carbonyl group at position 2,4 or 5. 4-Thiazolidione is derivatives of thiazolidin with a carbonyl group in the 4th position.



Thiazolidin-4-one

The potency of 4-thiazolidinone nucleus is cleared from theinically used drugs. Though the antibacterial and antitubercular, antiviral and antidiabetic (PTP1B inhibitors) are the four major areas of clinical use, other potential targets are still to be explored. Most of the positions were explored to improve the antibacterial and antitubercular profile of 4-thiazolidinone but still none of the derivatives showed promising antitubercular activity. Thiazolidinones derivatives are one of the potent scaffold with multitudinous pharmacological activities such as anti-convulsant [1], anti-inflammatory, anti-HIV, anti-cancer[2], anti-diabetic[3], anti-microbial, antiviral [4] and anti-inflammatory [5] and antifungal [6]. Wide spectrum of biological activities are strongly correlated with derivatization and position of the substituents at the aryl moiety attached with thiazolidinone ring [7]. Methyl group substituted derivatives at C-5 of the thiazolidinone ring has been reported to be responsible for remarkable antiviral activity whereas 5-Non substituted 4-thiazolidinone derivative exhibited no variation in activity [8]. Anticancer activity is often related to a reactive oxygen species dependent mode of action and effect of 4-thiazolidinones [9,10]. It was noticed that the compounds with electron donating groups at C-terminal of the phenyl ring resulted in an increase in activity by inducing cell death while compounds with electron withdrawing groups (CN, F, CF3) exhibited decreased activity [2]. Thiazolidinones derivatives present promising pharmacological potential for the treatment of T. gondii infections. Molina et al (11) have designed thiazolidinone derivatives as protein targets in Toxoplasma gondii infection. These derivatives show inhibitory activity (IC50) against the Toxoplasma gondii parasite, as well as high selectivity with high therapeutic index. These compounds derived from the thiazolidinone core have a preference for protein kinases of T. gondii, being promising compounds for the development of new drugs with potential anti-toxoplasmosis activity . Thiazolidinone derivatives with phenyl, methyl, ethyl and hydrogen groups located at N-3 position and nitrobenzene groups modulate the pharmacological properties. Phenyl substituent at N-3 position based thiazolidinone derivatives display superior values of IC50 for both infected cells and intracellular parasites [12]. 2-arylhydrazone moiety substituent at para position with hydrogen displayed higher anti-proliferative effect in comparison to chlorine and the nitro group [13]. Thiazolidinones derivatives are considered as important therapeutically-active molecules due to their multiplicity in biological retaliation profile and as a part of various clinically used drugs. Pioglitazone and rosiglitazone are

thiazolidinone core ring based diabetes drugs used to control high sugar in patients with type 2 diabetes. This drug restore body's proper response to insulin and helps in lowering blood sugar. Chloroquine analogues an antimalarial drugs have 1,3-thiazolidin-4-one nucleus at terminal side chain amino group of 4-aminoquinoline.These compounds have antimalarial activity against P.falciparum and some compounds have activity against P.yoelli.

Novel derivatives of 4–thiazolidinone shows antimicrobial, anticancer evaluation and their structure activity relationship [14][15].Literature Survey reveals several substituted biological active thiazolidinones compounds were prepared and found to have antibacterial [16] and anti-fungal properties[17]. Keeping in view the diverse pharmacological profile of thiozolidinones, present study is to synthesize thiazolidinones derivatives viz: hydrazono thiazolidine-4-ones adopting a green route synthesis[18].

2.EXPERIMENTAL

2. 1 MATERIALS AND METHODS

Acetophenone, thiosemicarbazide, chloroacetic acid, anhydrous sodium acetate, conc. HCl, ethanol .All the chemicals used were obtained from Sigma were used as such without further purification.

2.2 INSTRUMENTATIONS

Melting points were determined in sulphuric acid bath and are reported uncorrected. TLC was performed by using petroleum ether-ethyl acetate (4:1) as eluent on silica gel G plates and iodine vapours as visualizing agent. ^{1}H NMR spectra were recorded in $CDCl_3$ on BRUKER AVANCE II 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm. IR spectra were recorded on Perkin Elmer (RZX) FTIR spectrometer and the results are reported in cm^{-1}. Mass spectra were recorded on Shimadzu GC-MS QP 2010 Ultra spectrometer. Thin layer chromatography (TLC) was performed on silica gel G coated plates and using iodine vapors as visualizing agent

2.3 GENERAL PROCEDURE OF SYNTHESIS

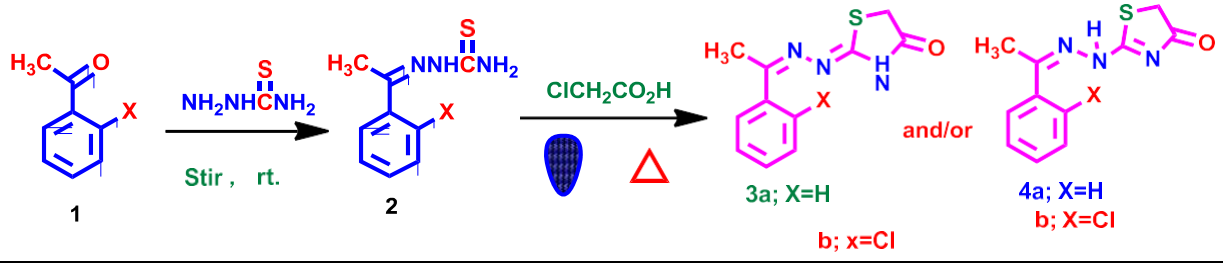
General procedure for the synthesis of 2

A mixture of acetophenone (0.01mol), concentrated HCl (0.5 ml) in ethanol (20 mL) and thiosemicarbazide (0.01mol) and was stirred at room temperature for 3 hours. The mixture was poured into cold water. The resultant off white solid was filtered, dried and crystallized

from ethanol.

General procedure for synthesis of 3

An equimolar mixture of thiosemicarbazone (0.1 mol) and chloroacetic acid (0.1 mol.) in water heated under reflux for 3-4 hours. The progress of reaction was monitored by TLC. After completion reaction mixture was then poured into ice cold water the solid obtained was filtered and recrystalize in suitable water. Complete reaction sequence is presented in Scheme 1.



Scheme 1:- Synthesis of thiazolidin-4-ones from thiosemicarbazones.

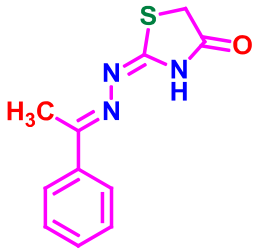
3. RESULT& DISCUSSION

The synthesis of hydrazono thiazolidin-4-one derivatives has been accomplished from thiosemicarbazone and chloroacetic acid. The classical synthesis reported can be either a one-pot three-component condensation or a two-step process. This reaction starts by formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketones), which go through attack by generated sulfur nucleophile, followed by intramolecular cyclization on elimination of water **(Scheme-1)**. The two step synthesis involves hazardous solvents and long reaction times with moderate to poor yields. In two step synthesis different desiccants such as DCC, anhydrous $ZnCl_2$, Dean- Stark apparatus, molecular sieves etc. are used for removal of water from the reaction mixture [19,20]. In the present investigations a convenient solvent free cyclocondensation using water as solvent under heating condition is used to assemble thiazolidin-4-one moiety on some one side of the carbon chain.

The condensation of **1** with thiosemicarbazide in ethanol containing a catalytic amount of concentrated HCl afforded hydrazinecarbothioamide **2**. Compound **2** was allowed to react with

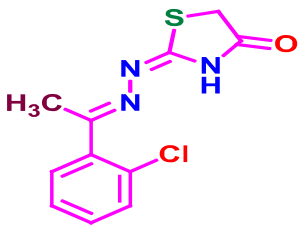
chloroacetic acid in the presence of anhydrous sodium acetate (conventional method) affording either **3** or its **regioisomer 4** in 71 % yield. The reaction proceeds via intramolecular cyclization on elimination of water. The ^{1}H NMR spectrum of **3a or 4a** exhibited a sharp singlet at δ 3.79 for the SCH_2 group in the thiazolidin-4-one unit, suggesting that cyclization had occurred. Two multiplets at δ 7.40, δ 7.86 integrating for five protons each in ^{1}H NMR spectrum of **3a or 4a** were assigned to the chloro substituted benzene ring **(Figure 1)** . ^{13}C NMR display characteristic peaks at δ173.48 which attributes to (C=O), at δ 162.78 due to (C=N), and closely lying peaks at δ 137.87, δ 130.06, δ 128.37, δ 126.8, δ 126.7 due to substituted aromatic ring system **(Figure 2)**. The mass spectrum of **3a** showed the $[M]^{+}$ peaks at m/z 232 (30%) **(Figure 3)**. Thiazolidin-4-one **3a/4a** and **3b/4b** was also obtained under solvent free conditions by heating **2** and chloroacetic acid in the presence of water for 2-3 h in 90 % yield . However, structure **3a** was finally assigned to this cyclization product in preference to the structure **4a** on the basis of DFT studies[21]. In the present investigation conventional procedure needs a much longer reaction time and yields are also not very good. Solvent free method, i.e. heating reactants with water gave better yields and the reaction completes faster.

4.4.4. (*E*)-2-((*E*)-(1-phenylethylidene) hydrazono) thiazolidin-4-one (3a)



Light yellow shining needles, yield 90 %, Mp -152-155 ^{0}C, IR (ν,cm^{-1}); 3144 (NH), 1695 (C=O), 1611 (C=N). , ^{1}H NMR (400 MHz, $CDCl_3$) δ; 2.42 (s, 3H, CH), 3.79 (s, 2H,SCH_2), 7.39-7.40 (m, 3H, Ar), 7.85-7.87 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ173.48 (C=O), 162.78 (C=N), 162.54 (C=N), 137.87, 130.06, 128.37, 126.8, 126.7 (Ar),33.13 (SCH_2), 15.06 (CH_3). MS, m/z 232 (M^{+}, 30 %). Anal. Calcd for $C_{11}H_{11}N_3OS$: C,56.63; H, 4.75; N, 18.01; S, 13.2 Found: C, 56.46; H, 4.81; N, 18.11; S, 13.77 %.

4.4.5. (*E*)-2-((*E*)-(1-(2-chlorophenyl) ethylidene) hydrazono) thiazolidin-4-one (3b)



White color shining needles, yield 85 %, Mp -139-140 ^{0}C, IR (ν,cm^{-1}); 3148 (NH), 1705 (C=O), 1610 (C=N). , ^{1}H NMR (400 MHz, $CDCl_3$) δ; 2.48 (s, 3H, CH), 3.82 (s, 2H, SCH_2), 7.43-7.46 (m, 2H, Ar), 7.87-7.89 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.58 (C=O), 165.68 (C=N), 165.44 (C=N), 135.77, 131.06, 129.37, 126.7 (Ar), 34.13 (SCH_2), 16.06 (CH_3). Anal. Calcd for $C_{11}H_{10}ClN_3OS$: C, 49.35; H, 3.76; N, 15.69; S, 11.98 Found: C, 49.46; H, 3.81; N, 15.71; S, 11.77 %.

Computational studies of compound 3a and regioisomer 3b.

The molecular geometry optimization, were performed with the Gaussian 09 W software package, Frisch, *et al.*, (2009), by using DFT methods with B3LYP (Becke three parameter Lee-Yang-Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke, *et al.*, (1988), with the gradient-correlation functional of Lee, *et al.*, (1988). The 6-31G (d) basis set was used for DFT studies on isomeric pair **3a**/**4a.** The optimized configurations of compounds **3a** and its isomer **3b** with atom numbering schemes are shown in (**Figure 4**).

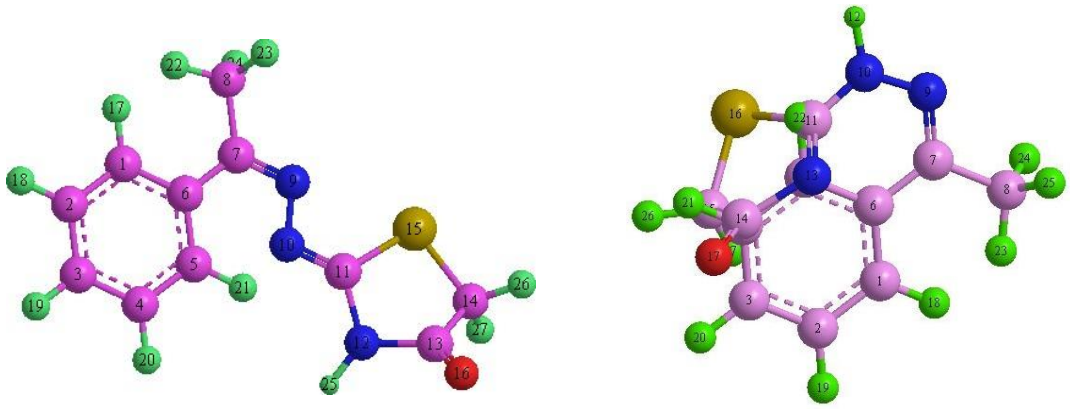


Fig 4. Optimised structures of 3a and its isomer 4a.

The total energy obtained for optimized structures **3a** is less as compared to **4a**. This shows structure **3a** is more stable than isomer **4a.**The total energy obtained for optimized structures **3a** is less as compared to **4a**. This shows structure **3a** is more stable than isomer **4a.**

Table 1: Selected calculated bond parameters of compound 3a and isomer 4a.

Compound 3a		**isomer 4a**	
Parameters	Calculated	Parameters	Calculated
Bond lengths(Å)			
C(11)-C(10)	1.52631	C(10)-C(11)	1.54831
S(12)-C(8)	1.83431	N(9)-C(10)	1.39361
C(8)-N(9)	1.37101	C(8)-N(9)	1.27021
N(9)-C(10)	1.36721	C(8)-S(12)	1.84091
C(11)-S(12)	1.8749	C(11)-S(12)	1.8693
N(7)-C(8)	1.24991	N(7)-C(8)	1.32941
N(6)-N(7)	1.45971	N(5)-N(6)	1.25831
C(10)-O(13)	1.20961	C(10)-O(13)	1.20121
C(11)-H(23)	1.07631	N(6)-N(7)	1.40421
C(11)-H(24)	1.07671	C(11)-H(23)	1.07641
Bond Angles (°)			

C(8)-S(12)-C(11)	90.2783	C(8)-S(12)-C(11)	86.8213
C(10)-C(11)-S(12)	107.7325	S(12)-C(11)-C(10)	106.9763
C(11)-C(10)-N(9)	111.1222	C(11)-C(10)-N(9)	112.8635
N(9)-C(10)-O(13)	124.6517	C(11)-C(10)O(13)	121.9697
C(10)-N(9)-C(8)	117.7043	N(9)-C(10)-O(13)	125.1632
N(9)-C(8)-S(12)	110.0539	C(10)-N(9)-C(8)	115.121
N(9)-C(8)-N(7)	128.9464	S(12)-C(8)-N(7)	118.6557
C(8)-N(7)-N(6)	113.4681	N(9)-C(8)-N(7)	123.2178
N(7)-N(6)-C(5)	112.6876	H(22)-N(7)-C(8)	118.2476
C(11)-C(10)-O(13)	124.2249	H(23)-C(11)-S(12)	109.5666

CONCLUSION:

The method of thiazolidinones has been presented. Some thiazolidinone derivatives have been prepared by using the water synthesis . The experimental set up of synthesis of substituted hydrazono thiazolidin-4-ones by using the thiosemicarbazones and chloroacetic acid on heating at ambient temperature results a good yield. The synthesis of thiazolidinone are obtained by the various experimental method good yields formed in a minimum time. These thiazolidinone derivative are good biologically active for future.

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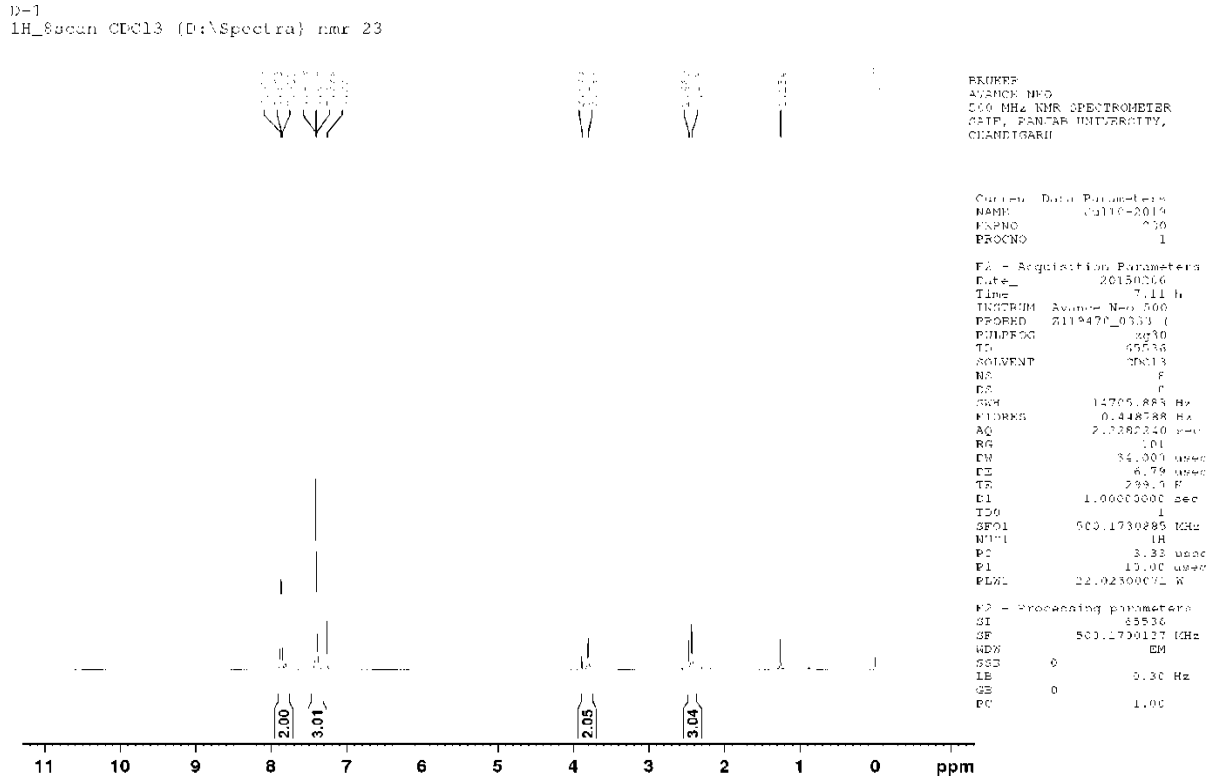

Fig. 1: ^{1}H NMR Spectrum of (E)-2-((E)-1-phenylethylidene) hydrazone) thiazolidin-4-ones. (3a)

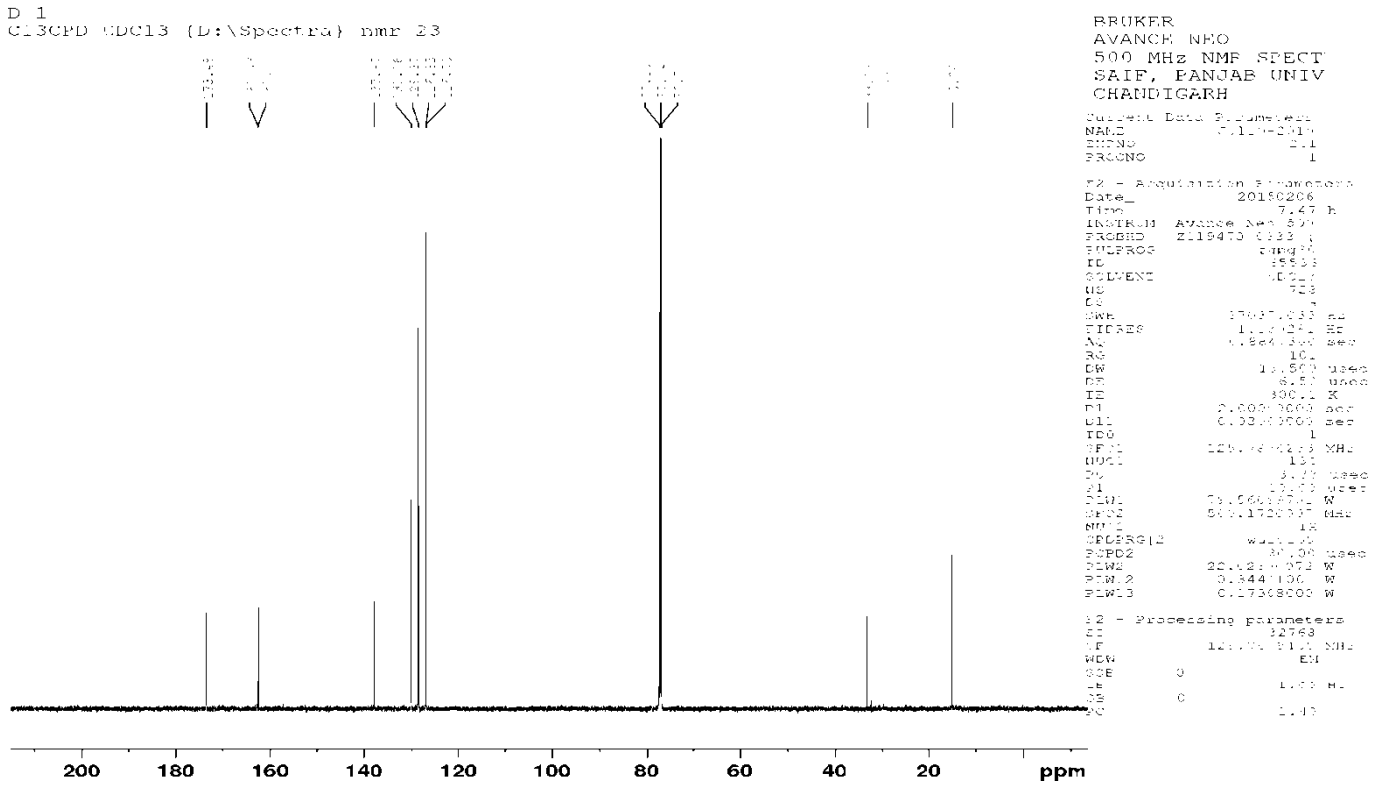

Fig. 2: ^{13}C NMR Spectrum (E)-2-((E)-(1-phenylethylidene) hydrazone) thiazolidin-4-ones (3a)

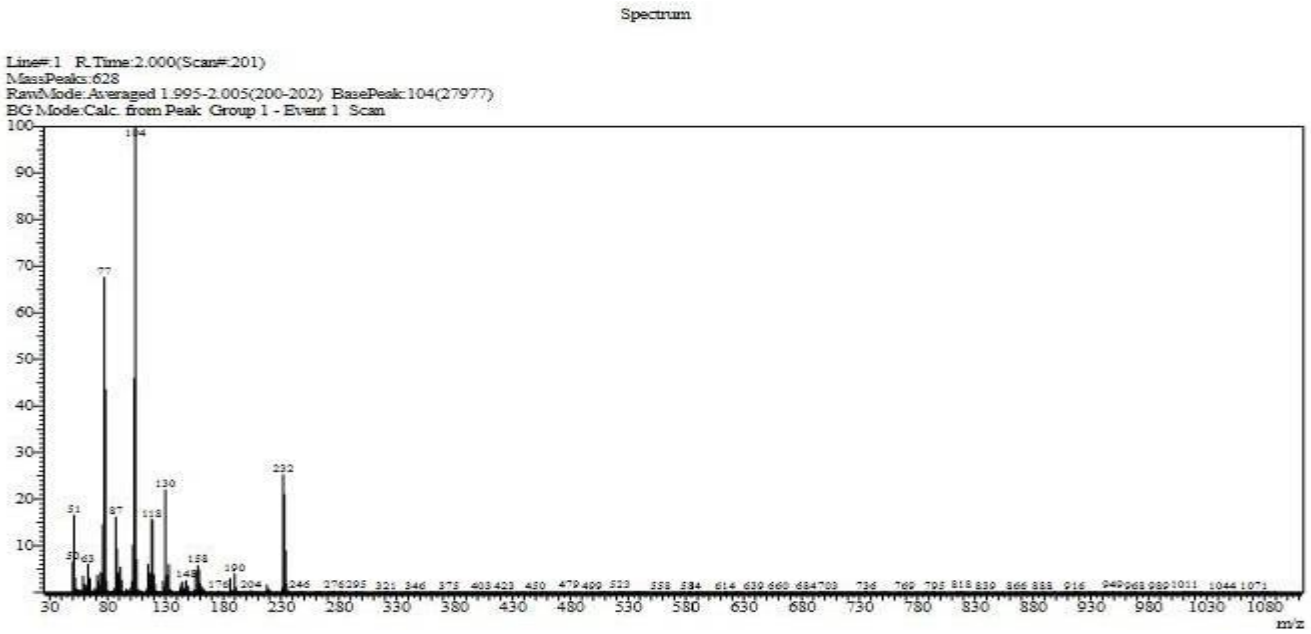

Fig. 3: Mass spectra of (E)-2-((E)-(1-phenylethylidene) hydrazone) thiazolidin-4-ones (3a)