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Synthesis of New Ibuprofen Derivatives Containing (Oxothiazolidin-3-yl) Amino Moiety with Expected Biological Activity

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs that help reduce inflammation, which often helps to relieve pain. In this research new ibuprofen oxothiazolidnone derivatives were synthesized from the reaction of Schiff base derivatives of Ibuprofen with mercapto acetic acid VI a-c, to improve the potency and to decrease the drug's potential side effects, a new series of 4-thiazolidinone derivatives of ibuprofen was synthesized **VI a-c** . The characterizations of the compounds were identified by using FTIR, 1HNMR technique and by measuring the physical properties.

Keywords: Ibuprofen, 4-thiazolidinone.

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INTRODUCTION

Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells and toxic compounds or irradiation [1]. These factors could induce acute and / or chronic inflammatory responses within the heart, pancreas, liver, kidney, lung, brain, GI tract and reproductive system, probably resulting in tissue injury or disease [2], and acts by removing injurious stimuli and initiating the healing process [3]. The inflammatory response is regulated inflammatory mediator levels by activation of signaling pathways that in resident tissue cells and inflammatory cells recruited from the blood [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the category of drugs that can minimize pain, lower fever, prohibit blood clots and, in higher doses, lower inflammation. Undesirable effects depend upon the precise drug, but largely contain a raised risk of gastrointestinal ulcers and bleeds, heart attack and kidney disease [6]. Prostaglandins are lipid substances formed when cyclooxygenase (COX) enzymes metabolize arachidonic acid released from membrane phospholipids. Prostaglandins mediate a range of normal biological functions involving gastric protection, renal homeostasis, vascular homeostasis, uterine function, embryo implantation and labor, regulation of the sleep-wake cycle, body temperature and inflammation [7].There are three isoforms of COX enzymes, COX-1, COX-2[8] and COX-3 [9] . The distribution and the roles of COX-1 and COX-2 in the body, COX-1 is constitutively found in most normal cells and tissues. It achieves the housekeeping functions of prostaglandins (PGs). Prostaglandins synthesized in the gastric mucosa via COX-1 can increase mucus and bicarbonate secretion, mucosal blood flow, and turnover, as well as inhibit acid secretion [10]. The selectivity of NSAIDs is based on an IC50 value (the concentration at which an NSAID produces 50% inhibition of COX-1 and/or COX-2). A selectivity ratio is then calculated, namely COX-2 IC50 / COX-1 IC50 or vice versa, using the IC50 values for both of the COX enzymes [11]. The higher IC50 is the most drugs necessary for inhibiting the specific enzyme. Therefore, COX-1: COX-2 ratio greater than 1 would therefore point out that drugs inhibit COX-1more than COX-2 [12]. Traditional NSAIDs work by blocking COX-1 and COX-2 enzymes. The inhibitors of COX-2 work by blocking only the COX-2 enzyme. By blocking the COX-2 enzyme, these new drugs can help block pain and inflammation and still allow the COX-1 enzyme to work. This is important because COX-1 enzymes help protect the stomach lining, which decreases the chance of having a stomach ulcer and / or bleeding [13].Cyclooxygenase-1 (COX-1) is the central enzyme within the biosynthetic pathway to prostaglandins from arachidonic acid. This protein was isolated more than 40 years ago and cloned in 1988[14] , while COX-2 is an inducible enzyme, that rapidly Expressed in several types of cells in response to growt h factors , cytokines , and pro-inflammatory molecules and

The isoform is mainly responsible for the production of prostaniods in acute and chronic inflammatory condition s [15]. Cyclooxygenase-3 (COX-3)was discovered in 2002, and been found to be selectively inhibited by paracetamol, phenacetin , antipyrine , dipyrone, and some NSAIDs in rodent studies[16] .Ibuprofen is a medication of the non-steroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever, and inflammation, and this includes painful menstrual periods, migraines, and rheumatoid arthritis. It can be used orally or parentrally. It typically begins working within an hour [17].

Thiazolidinones arebiologically active moleculescontainin g various heteroatoms nitrogen, sulfur and oxygen.The in terest of the chemist has always been drawn over the yea rs primarily because of their biological significance, Thiazolidinones are thiazolidine derivatives having an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5 [18]. The thiazolidinone ring has been integrated into a wide range of recognized biolo gically active compounds. either as a substituent group or as a substitute for another ring , researchers have been inspired to synthesize a nu mber of compounds containing this bundle like antibacterial activity [19] , antifungal activity [20] , anti-inflammatory and analgesic activity [21] , anticancer activity [22] , anticonvulsant and antidepressant activity

[23] , anti-tubercular activity [24] , antiviral activity [25] , The aim of this work is to synthesize and anti-inflammatory evaluation of 4-thiazolidinone derivatives of Ibuprofen with expected selectivity towards COX-2 enzyme.

MATERIALS AND METHODS

Chemicals used during the synthesis were supplied by hyper-chem (China). Completion of reactions and the purity of compounds were monitored by thin-layer chromatography (TLC), using silica gel GF254 (type 60) pre-coated aluminum sheets, Merck (Germany) exposed to UV-254 nm light, five solvent systems were used which include: ethyl acetate:hexane(4:6) , ethyl acetate:hexane (6:4) ,. Melting points were detected by using Stuart SMP3 melting point apparatus in open capillary tubes and are uncorrected. The infrared spectra were performed in thin film techginqe, (υ, cm^{-1}), on Shimadzu FTIR spectrophotometer, (Japan) which have been done in University of Baghdad, college of pharmacy and in Almustansiria University college of science. 1HNMR spectra were obtained on BRUKER model Ultra shield 300 MHz spectrophotometer, and BRUKER model Ultra shield 400 MHz spectrophotometer, using deuterated DMSO-d6 as solvents and TMS as an internal standard, at Al-albayt University, Amman-Jordan.

Chemical synthesis

Synthesis of Phenyl-alanine ethyl ester HCl (I) [26]***:***

Phenylalanine (2 gm, 9.3 mmol) was suspended in (50 ml) absolute ethanol and cooled to 5ºC, using an ice bath and thionyl chloride (2.3 ml, 32 mmol) was added drop-wise over a period of time of 15min with continuous stirring.The temperature of the reaction mixture has been preserved at 5ºC during the addition, and then the reaction mixture was refluxed for 3 hours. The solvent was then evaporated using a hot air stream and the residue was re-dissolved in absolute ethanol and evaporated. This process was repeated twice. Finally, the residue dissolved in a minimum amount of hot ethanol: diethyl ether was added till turbidity appears. The mixture was kept in the refrigerator to complete crystallization. The crystals of Phenylalanine ethyl ester HCl salt was filtered, collected and dried in oven at 40ºC. The percent yield and physical data are given in Table (2), FTIR: 3308 cm^{-1}; 3074 cm^{-1}(C-H stretching of aromatic H); 1717 cm^{-1} (C=O of ester) and 1579 cm^{-1} (C=C of benzene).

Synthesis of ibuprofen acid chloride (II) [27]***:***

In a 100 ml round bottom flask, ibuprofen (1 gm, 4.8 mmol) was suspended in 10 ml of dry chloroform then the mixture was placed in an ice bath and during gradual addition of thionyl chloride (2.5 ml) for 10 minutes with continuous stirring. Then reaction mixture has been refluxed for 3 hours, followed by solvent evaporation to dryness using hot air stream, and re-dissolved in 3 ml dry chloroform and evaporated, this process was repeated twice. The ibuprofen acid chloride was obtained as light-yellow oil.

Synthesis of ethyl – (2- (4- isobutyl phenyl) propanoyl)-phenylalaninante (III) [26]***:***

In a 100 ml round bottom flask, (1gm, 5.1 mmol) of phenyl-alanine ethyl ester HCl was suspended in 50ml dry DCM, the mixture was kept in 25 ºC. Triethylamine (2-3 ml) was added drop wise over a period of 15 minutes with stirring, then the precipitated triethylamine hydrochloride had been filtered, ibuprofen acid chloride (1.1gm, 5.1mmol) was dissolved in 10 ml of dry chloroform and added slowly with continuous stirring at 1 ºC.The solvent was evaporated under vacum to dryness, then the oil residue was dissolved in 30 ml of ethyl acetate and filtered. The filtrate was transferred to a separatory funnel and washed with 10 ml (1 *N* HCl), 10 ml D.W., 10 ml NaHCO3 5%, 10 ml D.W., twice for each one and finally washed with NaCl solution. The organic layer was separated and dried with anhydrous magnesium sulphate and filtered. The filtrate was evaporated to get an oily residue. The percent yield and physical data are given in Table (2), FTIR: 3204 cm-1(N-H stretching of amide); 3063 cm-1(C-H stretching of aromatic H; 1710 cm-1 (C=O of ester) and 1637 cm-1(C=O of amide).

Synthesis of N-(1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl) propanamide (IV) [28] *:*

Ibuprofen amide derivative(compound III) (0.8 gm, 3 mmol) has been dissolved in 10 ml methanol, then hydrazine hydrate 99% (1.5 ml ,30 mmol) was added , The mixing of reaction was refluxed for 9 hours at 65ºC, then left over night with continuous stirring. The solvent was evaporated under hot air stream, then cold water was added to the residue, white precipitate formed, filtered washed with cold water, dried and washed with ether. The percent yield and physical data are given in Table (2), FTIR: 3398 , 3346 cm-1(N-H stretching of amine); 3233cm-1(N-H stretching of amide); 1661 cm-1 (C=O of amide) and 1247 cm-1(C-N of amide).

N-(1-(2-benzylidenehydrazineyl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl) propanamide (V) [29]***:***

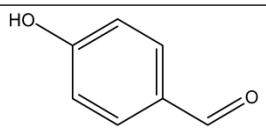
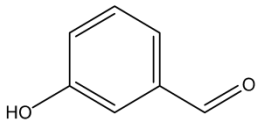
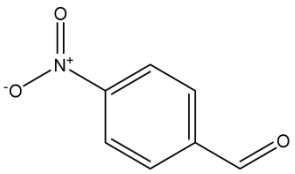
A mixture of (0.59g, 1.9 mmol) of a hydrazine derivative of ibuprofen compound(IV) and (1.9 mmol) of the corresponding aldehydes listed in Table (1) in 20 ml of absolute ethanol was stirred at room temperature for 0.5 to 1h, with addition of two to three drops of HCl as a catalyst. The end of the reaction was detected by TLC, and the hydrazones were isolated by concentration of the crude product at reduced pressure, the resulting precipitate was filtered, washed with 10 ml water and re-crystallized from ethanol. The percent yield and physical data are given in Table (2)

N-(1-(2-(2-(4-hydroxyphenyl)-2-oxoethyl-idene)hydrazineyl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl)propanamide(V-a): FTIR: 3410 cm-1(O-H stretching); 3281cm-1(N-H stretching of amide) ; 1695 cm-1 (C=O of amide) and 1649 cm-1(C=N of amide) .

N-(1-(2-(2-(3-hydroxyphenyl)-2-oxoethyl-idene)hydrazineyl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl) propanamide(V-b): FTIR: 3371 cm-1(O-H stretching); 3267cm-1(N-H stretching of amide) ; 1697 cm-1 (C=O of amide) and 1626 cm-1(C=N of amide) .

2-(4-isobutylphenyl)-N-(1-(2-(2-(4-nitrophenyl) -2-oxo ethylidene)hydrazineyl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl) propanamide(V-c): FTIR: 3269cm-1(N-H stretching of amide) ; 1654 cm-1 (C=O of amide) and 1634 cm-1(C=N of amide) , 1527 cm-1(assym) , 1386(symm)of (NO_2 stretching).

Table 1: Aromatic aldehydes name and products no.

No.	Aromatic aldehyde name	R	Product no.	Quantity of aromatic aldehyde
a.	4-hydroxybenzaldehyde		**V a**	2.32 mg
b.	3-hydroxybenzaldehyde		**V b**	2.32 mg
c.	4-nitrobenzaldehyde		**V c**	1.86 ml

Synthesis of 2-(4-isobutylphenyl)-N-(1-oxo-1-(5-oxothiazolidin-3-yl)-3-phenylpropan-2-yl) propanamide (VI a-c) [30]:

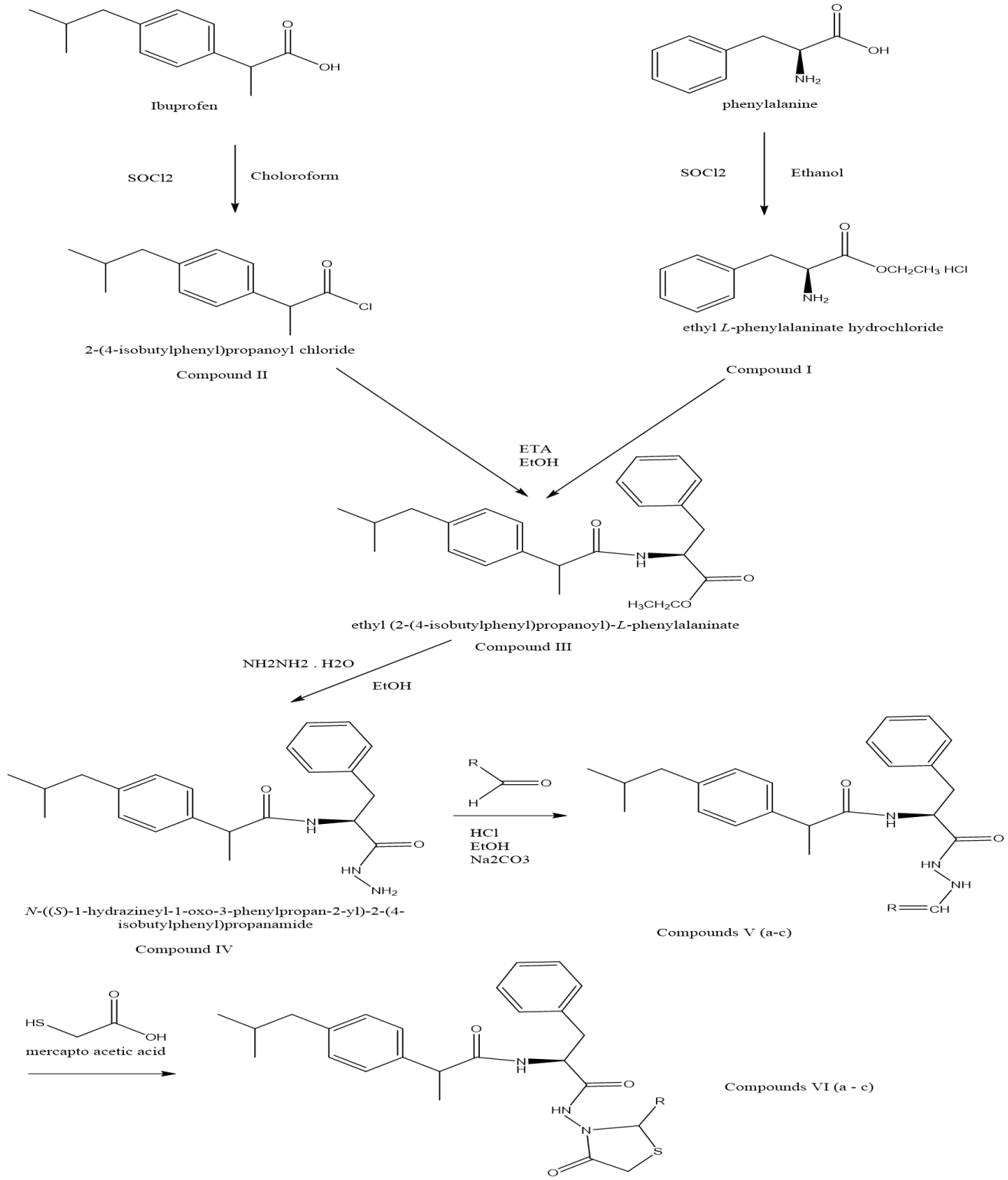
A mixture of hydrazine derivatives V a-c (1 mmol) and excess of mercaptoacetic acid (5 ml) was heated at 60 ºC until reaction complete, as shown by TLC (about 6 h). Ethyl acetate (5 ml) was added, then the reaction mixture was washed by water (1 × 10 ml), dried with MgSO4, andconcentrated to produce an oily material, the final product was triturated with petroleum ether. The percent yield and physical data are given in Table (2),

N-(1-(2-(4-hydroxybenzoyl)-5-oxothiazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutyl phenyl) propanamide (VI-a):

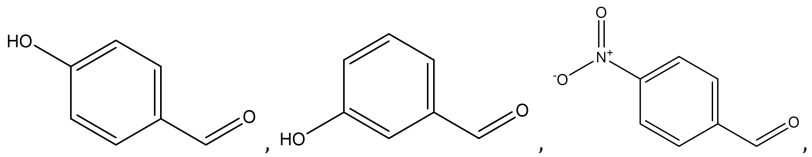
FTIR: 3308 cm-1(phenolic O-H stretching); 3181cm-1(N-H stretching of amide) ; 1717 cm-1 (C=O of amide thiazolidinone) , 1211cm-1(C-S stretching) and 1601 cm-1 (C=C of aromatic stretching). 1HNMR (300 MHz, : DMSOd6)9.62 (1H,s,OH); 3.72 (1H,d,CO-CH-N); 3.64(1H, d, N-CH -S) (thiazolidinone); 6.9-7.9 (13H, m, Ar-H) .

N-(1-(2-(3-hydroxybenzoyl)-5-oxothiazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutyl phenyl) propanamide (VI-b): FTIR: 3362 cm-1(phenolic O-H stretching); 3271cm-1(N-H stretching of amide) ; 1716 cm-1 (C=O of amide thiazolidinone) , 1213cm-1(C-S stretching)and 1605 cm-1 (C=C of aromatic stretching) . 1HNMR (300 MHz, : DMSOd6) : 9.50 (1H,s,OH); 3.57 (1H,d,CO-CH-N); 3.62(1H, d, N-CH -S) (thiazolidinone); 6.9-7.9 (13H, m, Ar-H) .

N-(1-(2-(4-nitrophenyl)-5-oxothiazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutyl phenyl) propanamide (VI-c): FTIR: 3308 cm-1(phenolic O-H stretching); 3277cm-1(N-H stretching of amide) ; 1732 cm-1 (C=O of amide thiazolidinone) and 1690 cm-1 (C=O cyclic amide stretching) , 1661 cm-1 (C=O of aliphatic amide stretching) , 1527 cm-1(assym) , 1386 cm-1 (symm)of (NO_2 stretching) , 1213cm-1(C-S stretching) . 1HNMR (300 MHz, DMSOd6) 3.78 (1H, d,CO-CH-N); 5.20(1H, d, N-CH -S) (thiazolidinone); 7.76-7.23 (13H, m, Ar-H) .



Scheme (1): Synthesis of Ibuprofen derivatives containing oxothiazolidin-3-yl) amino moiety

R= 

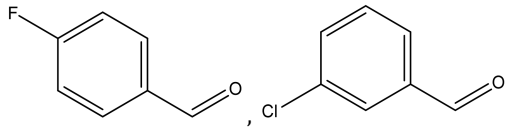


Table 2: The characterization and physical parameters of the target compounds and their intermediates

No.	Molecular formula	Molecular weight	Melting Point °C	% yield	physical appearance
I	$C_{11}H_{15}NO_2$	193.25	291	88	White powder
II	$C_{13}H_{17}ClO$	224.73	-	62	Pale-green oily
III	$C_{24}H_{31}NO_3$	381.52	-	56	Pale-yellow oily
IV	$C_{22}H_{29}N_3O_2$	367.49	129	71	White powder
V a	$C_{30}H_{33}N_3O_4$	499.61	189-191	59	Off white powder
V b	$C_{30}H_{33}N_3O_4$	499.61	182-183	44	Off white powder
V c	$C_{30}H_{32}N_4O_5$	528.61	186-187	52	White powder
VI a	$C_{31}H_{35}N_3O_4S$	545.70	-	73	Pale yellow oil
VI b	$C_{31}H_{35}N_3O_4S$	545.70	-	54	Pale yellow oil
VI c	$C_{31}H_{34}N_4O_5S$	574.70	-	32	Pale yellow oil
Ibu	$C_{13}H_{18}O_2$	206.24	75-78		White powder

DISCUSSION

All compound prepared are identified by FT-IR spectroscopy, compound I is prepared by reaction of phenylalanine and thionyl chloride in which show the C=O stretching of ester at 1717 cm^{-1} and disappear of OH carboxylic group and change in melting point to 291 °C, while in compound II which is prepared by reaction of Ibuprofen with thionyl chloride can't make FT-IR spectroscopy due to the acyl group which prepared is unstable at room temperature so kept in the solvent we use in the next step of synthesis, Compound III was prepared by reaction of ibuprofen acid chloride and Phenyl-alanine ethyl ester and show N-H stretching vibration at 3204 cm^{-1}, C=O stretching of amide at 1637 cm^{-1} and C-N stretching of amide at 1240 cm^{-1}.

In compound IV has been prepared of N-(1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-2-(4-isobutylphenyl) propanamide with hydrazine hydrate and show N-H stretching vibration of primary amine at 3398, 3346 cm^{-1} , and N-H stretching vibration of amide at 3235cm^{-1}, C=O stretching of amide at 1661cm^{-1} and C-N stretching of amide at 1247cm^{-1} and show melting point 129°C.

Compound V were prepared by mixture of hydrazine derivative of ibuprofen compound (IV) and of the corresponding aldehydes listed in Table (1), so in compound Va show O-H stretching vibration at 3410 cm^{-1} and disappear of N-H stretching vibration of primary amine and the melting point appear 189-191°C. Compound Vb show O-H stretching vibration at 3371cm^{-1} and disappear of N-H stretching vibration of primary amine and the melting point appear 182-183°C, while compound Vc show the disappearing of O-H stretching vibration and appear of N-H stretching vibration of amide and asymmetric NO_2 stretching vibration at 1527 cm^{-1} and symmetric NO_2 stretching vibration at 1386 cm^{-1} the melting point appear 186-187°C.

Compound VI were prepared by mixture of hydrazine derivatives V a-c and excess of mercaptoacetic acid, compound VI a show O-H (phenolic) stretching vibration at 3308cm^{-1} and appear of C=O stretching of thizolidine group at 1717 cm^{-1}, C=O stretching of cyclic amide group at 1697 cm^{-1}, C=O stretching of aliphatic amide group at 1649 cm^{-1} and C-S stretching vibration at 1211cm^{-1}.

Compound VI b show O-H (phenolic) stretching vibration at 3362cm^{-1} and appear of C=O stretching of thizolidine group at 1716 cm^{-1}, C=O stretching of cyclic amide group at 1686 cm-1and C-S stretching vibration at 1213cm^{-1}.

Compound VI c show N-H stretching vibration of amide at 3277cm^{-1} and appear of C=O stretching of thizolidine group at 1732 cm^{-1}, C=O stretching of cyclic amide group at 1690cm^{-1}, C=O stretching of cyclic amide group at 1661 cm^{-1}, Asymmetric stretching of NO_2 at 1524 cm^{-1}, symmetric stretching of NO_2 at 1346 cm^{-1} and C-S stretching vibration at 1213cm^{-1}.

CONCLUSION

1. The synthesis of the designed compounds has been successfully achieved.
2. Characterization and identification of newly synthesized of compounds were confirmed by determination of physical properties, FT-IR spectroscopy, 1H-NMR spectra.

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