World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 7, Issue 8, 2018 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

SYNTHESIS AND CHARACTERIZATION OF TWO NOVEL THIOFIBRATES DERIVED FROM 7-HYDROXY-4-METHYL-2H CHROMEN-2-ONE

Niranjan M.S. * and Chaluvaraju K.C

Department of Pharmaceutical Chemistry, Government College of Pharmacy, Bengaluru -560 027, INDIA.

Received on: 24-07-2018; Revised and Accepted on: 13-08-2018

ABSTRACT

Two novel thiofibrates bearing 1,3,4-oxadizole and 1,2,4-triazole are prepared from 7-hydroxy-4-methyl-2H-chromen-2-one (1). The compound (1) is obtained by treating resorcinol with ethyl acetate in the presence of concentrated sulphuric acid. It is then treated with ethylchloroacetate to get ethyl((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetate (2). This on hydrogenolysis gives 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide (3) which on further reaction with phenyl isothiocyanate in presence of sodium hydroxide gives4-methyl-7-((5-sulfanyl-4H-1,2,4-triazol-3-yl)methoxy)-2H-chromen-2-one (4). Also the compound (3) on reaction with carbon disulphide in presence of powdered 10% potassium hydroxide gives 4-methyl-7-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methoxy)-2H-chromen-2-one (5). The compounds (4) and (5) on reaction with ethyl-2-bromo isobutyrate in presence of anhydrous potassium carbonate in DMF forms ethyl 2-methyl-2-((5-{((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl}-4H-1,2,4-triazol-3-yl)sulfanyl)propanoate (6) and ethyl-2-methyl-2-((5-{((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl}-1,3,4-oxadiazol-2-yl)sulfanyl)propanoate (7) respectively. The reaction progress was monitored by TLC. The structures of the synthezised compounds were characterized by physical data-m.p, R_f and spectral investigations of IR and ^1H NMR.

***KEYWORDS**: 7-hydroxy-4-methyl coumarin, 1,3,4-oxadizole, 1,2,4-triazole, ethyl-2-bromo isobutyrate, DMF, ethyl-2-bromo-isobytatrate.*

INTRODUCTION

It is observed that about half of the death in the United States is due to hyperlipoproteinemias [1]. Usually it is associated with atherosclerosis, thrombosis, infarction, life threatening pancreatitis [2] *etc*., This situation is counter attacked by use of drugs that lower the concentrations of plasma proteins either by diminishing the production of lipoproteins or by enhancing the efficiency of their removal from plasma [3]. The use of these drugs are known to cause flatulence, abdominal pain, nausea, constipation, hemorrhoids, angioneurotic edema, eosinophilia, paresthesias [4] *etc*., These facts and the encouraging results of our previous study [5-8] influenced us to continue our work further in the synthesis of novel thiofibrates in our laboratory so that they could be a better and safer antihyperlipedemic drugs in clinical use. 7-hydroxy-4-methyl coumarin and its derivatives are known to have a wide range of therapeutic effects like anticoagulant, antipsychotic, antimicrobial, analgesic and anti-inflammatory [9-12] *etc*., keeping the biological importance and less paucity of literature on 7-hydroxy-4-methyl coumarin and need of the hour, in the present study two novel thiofibrates are synthesized as these could be a replacement to existing fibrates for hyperlipidemia.

MATERIALS AND METHODS

The chemicals required for the study are procured from – Alembic, Spectrochem, Loba chemie, Merck laboratories and are used without further purification. The melting points of the synthesized compounds were determined in an open capillary tube and are uncorrected. The progress of the reactions were monitored by thin layer chromatography using mobile phase chloroform: methanol in the ratio of 9:1 and n-hexane:ethylacetate in 4:1 ratio [13] and the spots were observed under UV at 254nm. IR spectra of the compounds were recorded using shimadzu spectrometer 8400. The ^{1}HNMR spectra of the compounds were recorded in δ ppm at 400MHz using $CDCl_3$ solvent and TMS as internal standard [14].

1. Synthesis:

1.1. Synthesis of 2-((4-methyl-2-oxo-2H-chromen-7-yl) oxy) acetohydrazide (3):

1.1.1. Step 1: Synthesis of 7-hydroxy-4-methyl-2H-chromene-2-one (1): A beaker containing 100 ml of conc. sulphuric acid was kept in ice-bath, added with solution of resorcinol (0.1mol, 1.1 g) and ethyl acetoacetate (0.1 mol, 1.3 ml) with continuous stirring for 2h maintaining the temperature below 10^{0}C. The reaction mixture was kept at room temperature for 18h and then poured into the mixture of crushed ice and distilled water, with vigorous stirring. The white precipitate formed was collected by vacuum filtration, washed with ice cold water, dissolved in 5% w/v sodium hydroxide solution and filtered. The filtrate was added with conc. sulphulric acid with vigorous stirring until the solution was acidic. The crude 7-hydroxy-4-methyl coumarin obtained was collected by filtration, washed with cold water, dried, purified and recrystallized from ethanol [15]. % Yield: 60; M.F: $C_{10}H_8O_3$; M.W:194.18; m.p. 189-190^{0}C; R_f: 0.51; IR (KBR, cm^{-1}): 2835 (CH Ar), 1674 (C=O), 1585 (C=C Ar), 3620 (-OH), 1330(-CH).

1.1.2. Step 2: Synthesis of Ethyl((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetate (2): 7-hydroxy 4-methyl coumarin (0.01mol, 1.93g) and ethyl chloroacetate (0.01mol,1.23 ml) were dissolved in dimethyl Formamide separately and added 2gms of potassium carbonate and refluxed for 24h with a reflex condenser. The reaction mixture was extracted with ethyl acetate in triplicate and the combined ethyl acetate

***Corresponding author:**

Niranjan M.S.

Department of Pharmaceutical Chemistry,

Government College of Pharmacy, Bengaluru -560 027, INDIA.

** E-Mail: niranjangcp@gmail.com*

DOI: https://doi.org/10.5281/zenodo.1345716

layer was separated, evaporated to get the compound [16]. % Yield:65; M.F: $C_{14}H_{14}O_5$; M.W:263; m.p. 98-100^{0}C; R_f: 0.45; IR (KBR, cm^{-1}): 2835 (CH Ar), 1674 (C=O), 1585 (C=C Ar), 1085 (C-O-C).

1.1.3. Step 3: Synthesis of 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide (3): The step 2 product ethyl((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetate was dissolved in triple the quantity of hydrazine hydrate and refluxed for 2h at 60-80^{o}C and then kept at room temperature. The precipitate thus formed was filtered, dried and characterized [17]. % Yield:59; M.F: $C_{12}H_{10}O_4$; M.W:263; m.p. 195-196^{0}C; R_f: 0.65; IR (KBR, cm^{-1}): 2835 (CH Ar), 1674 (C=O), 1585 (C=C Ar), 1068 (C-O-C), 1225 (C-N).

1.2. Synthesis of thiophenols:

1.2.1. Synthesis of 4-methyl-7-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methoxy)-2H-chromen-2-one (4): To 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy) acetohydrazide (2.4824g, 0.01mol) in 50 ml of ethanol was added sufficient potassium hydroxide to make it neutral and then further additional 6.35g (0.1mol) of Potassium hydroxide pellets, 5.653g, 7 ml (0.1mol) of Carbon-disulphide was added and refluxed for 3 hours in a 250 ml round bottomed flask. 3-4g of activated animal charcoal was added to the above refluxed mixture and further heated to 10 min, cooled and filtered. The filtrate obtained was then heated to 60-70^0 C on a water-bath with sufficient quantity of acetic-acid till the filtrate is acidic and 20 ml of water where these were added under constant stirring of the filtrate. During this process glistering white crystals were formed and were allowed to crystallize in a refrigerator overnight. The product thus obtained was collected by filtration, recrystallized from ethanol and dried [18]. % Yield: 52.13; M.F: $C_{13}H_{10}N_2O_4S$; M.W: 290. R_f 0.65; IR (KBR, cm^{-1}):3180(CH-Ar), 2825(CH-aliphatic), 2592(SH), 1697(C=O), 1139(C-O-C).

1.2.2. Synthesis of 4-methyl-7-((5-sulfanyl-4H-1,2,4-triazol-3-yl)methoxy)-2H-chromen-2-one (5):

1.2.4.1. Step 1: Synthesis of 2-{((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetyl}-N-phenyl hydrazine carbothiomide: 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy) acetohydrazide (2.4824g, 0.01mol) was dissolved in toluene (10ml) and 1.19 ml (0.01mol) of phenyl isothiocyanate was added drop wise to the above and resulting mixture was refluxed for 4 hours. The solid thus formed was collected and further refluxed for about 4 hours in 20 ml of 40% sodium hydroxide solution. The resulting solution was treated with charcoal and filtered. The filtrate obtained was acidified with acetic acid and the semi-solid formed was separated and are directly used in the next step without purification and characterizations. However confirmed with TLC studies.

1.2.4.2. Step2: Synthesis of 4-methyl-7-((5-sulfanyl-4H-1,2,4-triazol-3-yl)methoxy)-2H-chromen-2-one (5): To 2-{((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetyl}-*N*-phenyl hydrazine carbothiomide, 0.01 mol (3.8342 g) of (step 1 product), 0.2 mol (1.0g, 2 ml) of sodium hydroxide was added in 250 ml round bottomed flask fitted with a reflux condenser and refluxed for about 5h. The resulting solution was diluted with 100 ml of water and acidified with concentrated hydrochloric acid [19]. The solid thus precipitated was filtered, washed with water and recrystallized from ethanol.% Yield: 55; M.F: $C_{13}H_{11}N_3O_3S$; M.W: 289. R_f 0.72; IR (KBR, cm^{-1}):3100(CH-Ar), 2900(CH-aliphatic), 2500(SH), 1589(C=O).

1.3. Synthesis of thiofibrates :

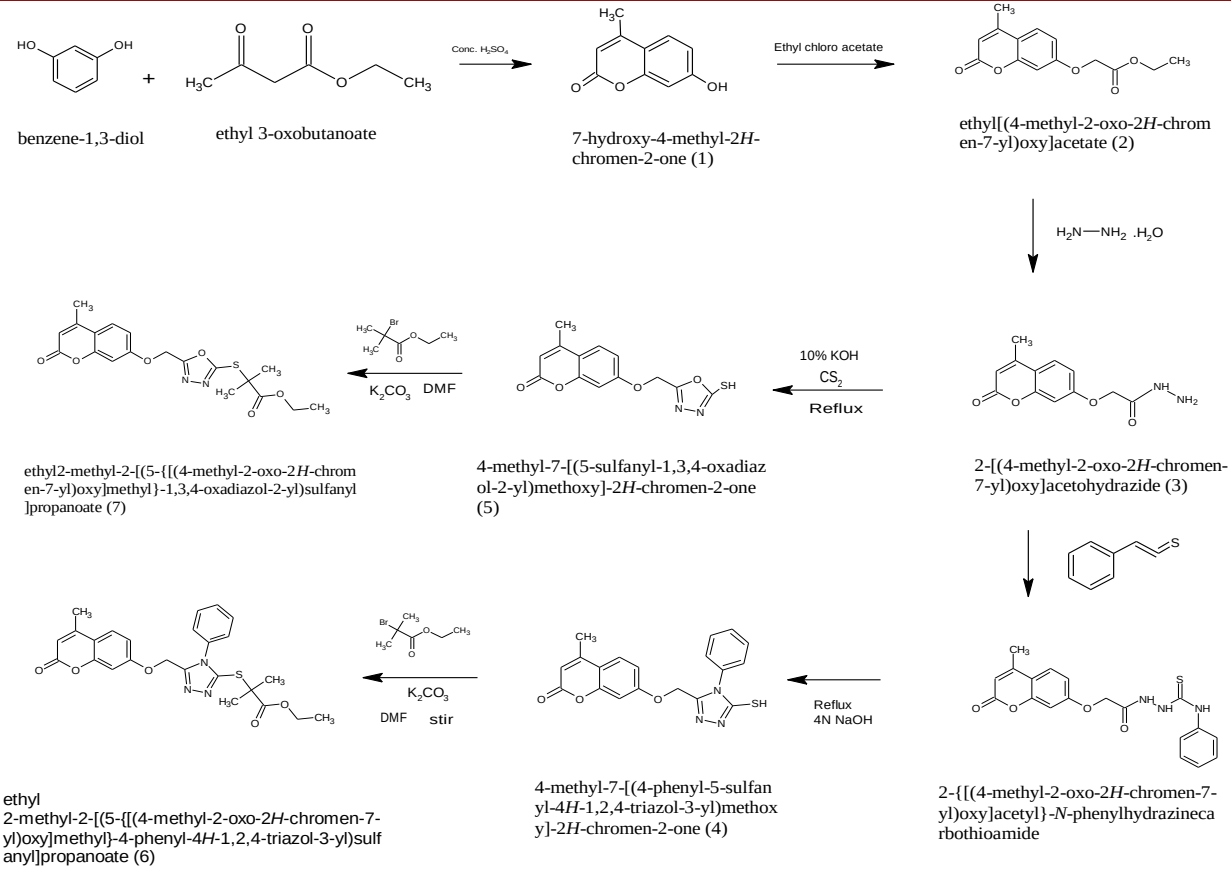
1.3.1. Synthesis of Ethyl 2-methyl-2-((5-{((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl}-4-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl) propanoate (6): 0.2893g (0.001mol) of 4-methyl-7-((5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methoxy)-2*H*-chromen-2-one dissolved in 10 ml of dimethyl formamide and 4g (0.04 mol) of anhydrous potassium carbonate were taken in a 100 ml round bottomed flask attached with dropping funnel and calcium chloride guard tube. 2.56 ml (0.01mol) of ethyl-2-bromoisobutyrate in 10 ml of dimethyl formamide was added drop-wise to the above solution with constant stirring at room temperature. The reaction mixture was then continuously stirred for about 24 hours and progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was added to 300 ml of water and stirred well; the product obtained was extracted with ethyl acetate (3 portions). From the combined extract, ethyl acetate was distilled off using rotavapour and oily yellow colored product separated was then collected **(scheme)** M F: $C_{19}H_{25}N_3O_5S$; M W: 417. R_f0.52; IR(KBR,cm^{-1}), 3130(CH-aromatic), 2960(CH-aliphatic), 1597(C=O); ^{1}HNMR($CDCl_3$, δppm); 3365(CH-aromatic), 2939(CH-aliphatic), 1650(C=O); ^{1}H NMR($CDCl_3$δppm): 6.92-7.60(m, 8H, Ar-H), 6.19(s, 1H, Ar-H), 5.31(s,2H, methylene connecting 1,2,4-triazole and 7 hydroxy- 4 methyl coumarin), 4.11(q, 2H, methylene), 2.41(s, 3H, coumarinemethyl), 1.51(s, 6H, dimethyl), 1.28(t, 3H, methyl).

1.3.2. Synthesis of Ethyl 2-methyl-2-((5-{((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl}-1,3,4-oxadiazol-2-yl)sulfanyl)propanoate (7): 0.2902g (0.001mol) of 4-methyl-7-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methoxy)-2*H*-chromen-2-one dissolved in 10 ml of dimethyl formamide and 4g (0.04 mol) of anhydrous potassium carbonate were taken in a 100 ml round bottomed flask attached with dropping funnel and calcium chloride guard tube. 2.56 ml (0.01mol) of ethyl-2-bromoisobutyrate in 10 ml of dimethyl formamide was added drop-wise to the above solution with constant stirring at room temperature. The reaction mixture was then continuously stirred for about 24 hours and progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was added to 300 ml of water and stirred well; the product was extracted with ethyl acetate (3 portions). From the combined extract, ethyl acetate was distilled off using rotavapour and oily yellow colored product separated was then collected **(scheme)** % Yield: 51; M F: $C_{19}H_{20}N_2O_6S$; M W: 404. R_f 0.61 ; IR (KBR, cm^{-1}) 3142 (CH-aromatic), 2976 (CH-aliphatic) 17525 (C=O); ^{1}H NMR ($CDCl_3$, δppm); ^{1}H NMR ($CDCl_3$δppm): 6.90-7.70 (m, 3H, Ar-H), 6.13 (s, 1H, Ar-H), 5.33 (s, 2H, methylene connecting 1,3,4-oxadiazole and 7 hydroxy-4-methyl coumarin), 4.10 (q, 2H, methylene), 2.40 (s, 3H, coumarinemethyl), 1.50 (s, 6H, dimethyl), 1.30(t, 3H, methyl).

RESULTS AND DISCUSSION

7-hydroxy-4-methyl-2H-chromen-2-one was prepared by resorcinol with ethyl acetoacetate in presence of conc. sulphuric acid through conventional method. It is then converted into its acetohydrazide by refluxing with hydrazine hydrate **(scheme)** ethyl 2-methyl-2-((5-{((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl}-1,3,4-oxadiazol-2-yl)sulfanyl)propanoate was prepared from using 4-methyl-7-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methoxy)-2*H*-chromen-2-one thiophenol in two step reaction. Similarly, ethyl 2-methyl-2-((5-{((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl}-4*H*-1,2,4-triazol-3-yl) sulfanyl) propanoate from thiophenol 4-methyl-7-((5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methoxy)-2*H*-chromen-2-one was also synthesized.

The structures of these compounds were characterized by R_f value, IR, ^{1}H NMR,. IR spectra showed peak at 2592 and 2500 indicating the presence of SH group in thiols and its presence is further confirmed by sodium fusion extract test (test for Nitrogen, Sulfur). The homogencity of the compounds were checked by TLC. R_f value were obtained from n-hexane:ethyl acetate: (1:3) as developing solvents and found to be in the range of 0.65- 0.72. Further, the absence of mercapto group at 2592 and 2500 cm^{-1}in the IR spectras of the thiofibrates indicates their formation from respective thiols. The m.p. of the thiofibrates and few of the intermideates could not be determined as they were in semisolid form. The appearance of protons in methylene group as quartet at δ 4.11-4.10 ppm, methyl group as triplet at δ 1.26-1.30ppm , dimethyl group as singlet at δ 1.50-1.51 ppm and aromatic protons as multiplets at δ 6.90-7.70 ppmin the ^{1}HNMR spectra of the compounds indicates its assigned structures.



Scheme I: Synthetic protocol of thiofifrates bearing 7-hydroxy-4-methyl-2H-chromen-2-one

CONCLUTONS

The synthesized thiofibrates 6 and 7 are in good agreement with the physical data and spectral studies. However, firther purification of the compound needs to be carried out before subjecting them for antihyperlipidemic activity in further studies.

ACKNOWELEDGEMENT

The authors would like to thank drugs controller for the state of Karnataka for providing laboratory facilities to carry out the present work. The authors also extend their gratitude to director IISc Bengaluru for providing spectral details.

REFERENCES:

1. Verma N. Int J Curr Pharm Res **2013**;9(1):6-14.
2. Idrees GA, Aly OM, Abuo-Rahma GE, Radwan MF. Euro J Med Chem **2009**;44(10):3973-3980.
3. Brown MS and Goldstein JL. Drugs used in the treatment of hyperlipoprotenimieas. Burger vol 1:874-893
4. F S Ghassan. Biomed Pharmac J **2015**;7(2):399-409.
5. Niranjan MS, Chaluvaraju KC. J Pharm Chem **2016**;10(2):3-6
6. Niranjan MS, Chaluvaraju KC. J. Pharm. Chem **2016**;10(4):13-18
7. Niranjan MS, Chaluvaraju KC. Int J Chem Tech Res **2018**;11(8);309-313.
8. Niranjan MS, Chaluvaraju KC. World J Pharm Sci **2018**;6(11):1085-1093.
9. Lei L, Xue YB, Liu Z, Peng SS, He Y, Zhang Y, Fang R, Wang JP, Luo ZW, Yao GM, Zhang JW. Scientific reports **2015**;5:13544.
10. Arora P, Das S, Arora N, Gawai AB, Baghel US. Int J Pharm Life Sci **2010**;1:113-115.
11. Singh AD, Kumar S, Saini S, Prabha H. J Health Sci **2017**;4:84-93.
12. Jayashree BS, Nigam S, Pai A, Chowdary PV. Arab J Chem **2014**;7(6):885-899.
13. Peter AS, Brian C. Chromatographic separations. Wiley India Pvt. Ltd., **2008**;53-59.
14. Kalsi PS, Spectroscopy of organic compounds. New age Intered. **2014**;6:415.
15. Sabou R, Hoelderich WF, Ramprasad D, Weinand R. J Catalysis **2005**;232;34-37
16. Karrouchi K, Doudach L, Chemlal L, Karim M, Taoufik, Cherrah Y, Radi S, Faouzi MEA, Ansar M. Int J Pharm **2014**;4(2);79-87
17. Mishra A, Rathod J, Namera D, Thakrar S, Shah A. ILCPA. **2014**;30;193-201.
18. VanAllan JA, Deacon BD. Org.synthesis John Wiley and Sons **1963**;4:p-569.
19. Mandal A, Dutta TK, Gupta RL. Ind J Chem **2015**;54B:228-39.

How to cite this article:

Niranjan M.S. and Chaluvaraju K.C. SYNTHESIS AND CHARACTERIZATION OF TWO NOVEL THIOFIBRATES DERIVED FROM 7-HYDROXY-4-METHYL-2H CHROMEN-2-ONE. J Pharm Res 2018;7(8):190-193. **DOI: https://doi.org/10.5281/zenodo.1345716**

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil