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SYNTHESIS AND SPECTRAL CHARACTERIZATION OF NOVEL FATTY ACID CHAIN SUBSTITUTED PYRAZOLINE DERIVATIVES

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ABSTRACT

A series of novel 1, 3, 5-trisubstituted pyrazolines (5a-c and 6a-c) were synthesized in good yield by the reaction of chalcones (3a, 3b) with three fatty acid hydrazides (4a-c) in presence of piperidine. The easy work-up of the products under mild conditions with rapid reaction are notable feature of the synthesis of pyrazoline derivatives. The structures of the synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

Keywords: Fatty acid hydrazides, chalcones, pyrazolines, synthesis

INTRODUCTION

The approach of pharmacophore hybrid for the exploration of novel and highly active compounds is an effective and commonly used direction in modern medicinal chemistry. Pyrazolines have been found to possess broad-spectrum of biological activities[1, 2]. Among the various existing pyrazoline derivatives, 1, 3, 5-trisubstituted pyrazoline have been recognized as one of the most promising scaffold[3]. The increasing evidence suggests that pyrazoline derivatives possess a wide range of medicinal applications such as antibacterial[4], antifungal[5], antiinflamatory[6], analgesic[7], antioxidant[8], insecticidal[9], molluscicidal[6], antidepressant[10], antitubercular[11], anti HIV[12], antimalarial[13] and anticancer[14, 15] activities. One of the most promising and notable applications of pyrazoline is the use of pyrazolines as a fluorescent brightening agent[16]. The prevalence of the pyrazoline scaffold in bioactive molecules has also sparked interest in current times. In view of enormous applications of this pyrazoline moiety and fatty acid heterocyclic derivatives as biologically active agents[17], we herein planned and described the synthesis of novel fatty acid chain substituted pyrazoline derivatives. Products (**5a-c** and **6a-c**) were obtained via formation of different effectively used chalcones (**3a**, **3b**) through Claisen-Schmidt condensation followed by cyclization through various fatty acid hydrazides (**4a-c**) in good yield. This synthetic approach typically entails the easily affordable reactions under mild conditions (< 90 ˚C) with cheaply available reagents.

EXPERIMENTAL

Chemicals and Instruments

To achieve anhydrous conditions to carry out synthesis smoothly, the flasks and other equipments were dried in the oven. When needed, solvents were dried and distilled before use. Undec-10-enoic acid (purity 98%) and (*9Z*)-octadec-9-enoic acid (purity 97%) were purchased commercially from Fluka Chemicals, Switzerland. (9*Z*, 12*R*)-12-Hydroxyoctadec-9-enoic (ricinolic) acid was isolated from *Ricinus communis* (castor) oil following Gunstone's partition procedure[18]. Furfural and *p*-chlorobenzaldehyde were purchased from HIMEDIA and s. d. fine, Mumbai, India, respectively. Thin layer chromatography (TLC) was performed on glass plates with a layer of silica gel G, Merck, Mumbai, India (0.5 mm thickness). Mixture of petroleum ether: ethyl acetate: acetic acid (75:25:1; v/v) were used as developing solvent. Silica gel, Merck, Mumbai, India (60-120 mesh) was used to carry out column chromatography. The eluent was a mixture of ethyl acetate and petroleum ether in different proportion for different compounds. IR spectra were recorded on Perkin Elmer FTIR spectrophotometer. ^{1}H NMR spectra were

recorded on a Bruker Avance II 400 spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are quoted in ppm and coupling constant (*J*) are expressed in Hz. ^{13}C NMR spectra were recorded on Bruker Avance II at 100 MHz spectrometer in $CDCl_3$ (δ = 77.00). Compounds (**3a**) and (**3b**) were prepared by using known procedure[19].

Synthesis of 1-phenyl-3-furyl-2-propen-1-ones (3a)
A mixture of acetophenone (**1**) (0.1 mol) and furfural (**2a**) (0.1 mol) was dissolved in ethanol (50 mL) and sodium hydroxide solution (10 mL, 40%) was added to make it alkaline. The reaction mixture was stirred for 5-7 hrs at room temperature and worked-up with diethyl ether (Et_2O). Compound with Et_2O was dried over anhydrous sodium sulphate and solvent was evaporated.

Synthesis of 1-phenyl-3-(*p*-chlorophenyl)-2-propen-1-one (3b)
A mixture of acetophenone (**1**) (0.1 mol) and *p*-chlorobenzaldehyde (**3a**) was dissolved in ethanol (50 mL) and sodium hydroxide (9 mL, 40%) was added just to make it alkaline. The reaction mixture was stirred continuously for 6 hrs at room temperature. The compound thus obtained was worked-up with diethyl ether and dried.

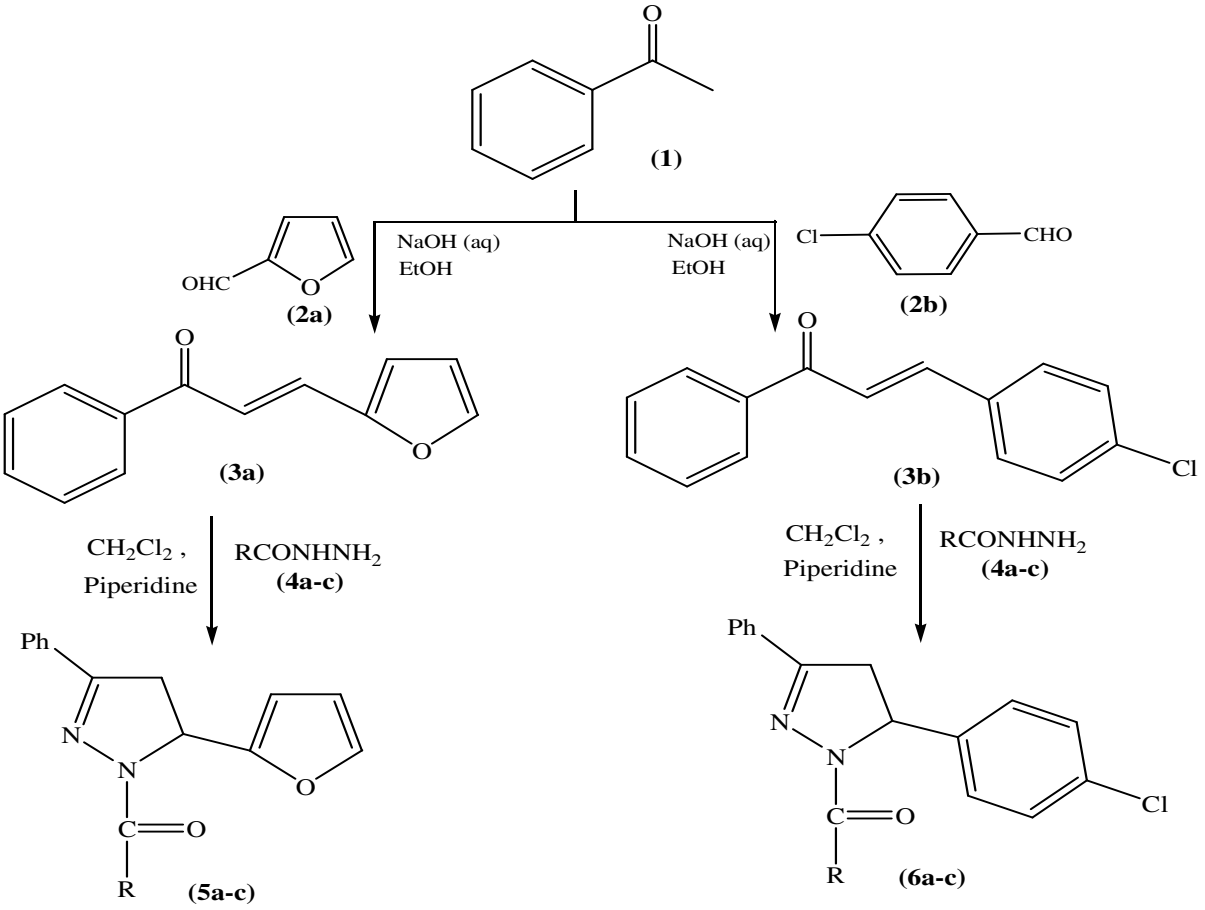
Synthesis of fatty acid hydrazides (4a-c)
The fatty acid hydrazides (**4a-c**) were prepared from the method reported[20] in literature.

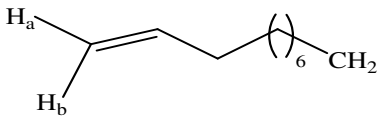
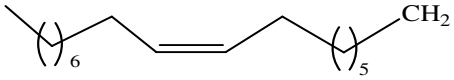
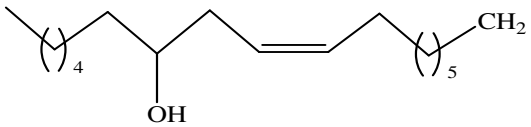
Synthesis of 1, 3, 5-trisubstituted pyrazoline derivatives
The fatty acid hydrazides (**4a-c**) (0.01 mol) and 1-phenyl-3 furyl-2-propen-1-one (**3a**) (0.01 mol) were mixed in presence of dichloromethane (50 mL) and piperidine (2 mL) and refluxed for 15-16 hrs. The reaction mixtures undergo cyclization to give substituted pyrazoline derivatives. Progress of the reaction was monitored by TLC. Once the reaction completed, the reaction mixture was cooled and worked-up with Et_2O and then dried over anhydrous sodium sulfate. The purified products (**5a-c**) were obtained by silica gel column chromatography with a mixture of petroleum ether-ethyl acetate as eluent. Similarly, reaction of (**4a-c**) was carried out with 1-phenyl-3-(*p*-chlorophenyl)-2-propen-1-one (**3b**) to produce (**6a-c**). The characterization data of compounds (**5a-c** and **6a-c**) are summarized below:

1-(Undec-10′-enoyl)-3-phenyl-5-furylpyrazoline (5a): Yellow oily compound, Yield = 67%, IR (KBr, cm^{-1}): 2932 (C-H asymm.), 2857 (C-H symm.), 1670 (C=O), 1593 (C=N).^{1}H NMR ($CDCl_3$, δ_H): 7.56 (m, 5H, Ar*H*), 6.10 - 6.75 (m, 3H, furan ring), 5.80 (tdd, 1H, $J_{H-^9CH_2}$ = 6.60 Hz, J_{H-H_a} = 10.10 Hz, J_{H-H_b} = 16.70 Hz, CH_2=C*H*), 5.48 (1H, dd, *J* = 12.0, 4.6 Hz, C*H* pyrazoline), 5.01 (dd, 1H, J_{H_a-H} = 10.10 Hz, $J_{H_a-H_b}$ = 2.80 Hz, H_aC=CH), 4.92 (dd, 1H, J_{H_b-H} = 16.70 Hz, $J_{H_b-H_a}$ = 2.80 Hz, H_bC=CH), 3.69 (dd, 1H, *J* = 17.2, 12.0 Hz, *H*-CH pyrazoline), 3.25 (dd, 1H, *J* = 17.2, 4.6 Hz, *H*-CH pyrazoline), 2.38 (t, 2H, *J* = 7.7 Hz, CH_2CO), 2.04 (m, 2H, CH_2=CH-CH_2), 1.68 (m, 2H, C$H_2$$CH_2$CO), 1.30 (10H, br.s, CH_2(CH_2)$_5$). ^{13}C NMR ($CDCl_3$, δ_C): 172.0 (C=O, C-1′), 152.5 (C=N), 140.0, 138.7 (furyl C-O), 130.8, 129.4, 128.9, 128.2 (Ph) 125.1, 124.6 (CH_2=CH, C-10′, C-11′), 116, 115 (furyl CH),53.3 (CH pyrazoline), 42.6 (CH_2 pyrazoline), 41.8 (CH_2, C-2′), 37.3 (CH_2, C-9′), 33.5,29.5,29.1,28.8, 28.5, 24.6 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-8′). MS (ESI): *m/z* = 378.441, M^+ Calculated = 378.456.

1-[Octadec-9′-enoyl]-3-phenyl-5-furyl pyrazoline (5b): Yellow oily compound, Yield = 72%, IR (KBr, cm^{-1}): 2924 (C-H asymm.), 2857 (C-H symm.), 1662 (C=O), 1598 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.45 (m, 5H, Ar*H*), 6.07-6.80 (m, 3H, furan ring), 5.37 (m, 2H, -C*H*=C*H*-), 5.40 (1H, dd, *J* = 12.0, 4.5 Hz, C*H* pyrazoline), 3.80 (dd, 1H, *J* = 17.4, 12.0 Hz, *H*-CH pyrazoline), 3.09 (dd, 1H, *J* = 17.4, 4.5 Hz, *H*-CH pyrazoline), 2.54 (t, 2H, *J* = 7.4 Hz, CH_2-CO), 2.30 (m, 4H, CH_2-CH=CH-CH_2), 1.84 (m, 2H, CH_2-CH_2-CO), 1.30 (br. s, 20H, (CH_2)$_{10}$), 0.89 (dist. t, 3H, t-CH_3).^{13} C NMR ($CDCl_3$, δ_c): 171.5 (C=O, C-1′), 159.0 (C=N), 141.0, 137.1 (furyl C-O), 130.2, 129.7, 128.6, 128.2 (Ph), 124.1, 123.4 (CH=CH, C-

9′, C-10′), 115.0, 113.8 (furyl CH), 53.2 (CH pyrazoline), 43.2 (CH_2 pyrazoline), 40.0 (CH_2, C-2′), 36.1, 35.6 (CH_2, C-8′, C-11′), 33.9, 31.9, 31.5, 30.3, 29.7, 29.5, 29.3, 29.2, 29.0, 27.2, 22.7 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-12′, C-13′, C-14′, C-15′, C-16′, C-17′), 14.2 (t-CH_3, C-18′). MS (ESI): *m/z* = 476.611, M^+ Calculated = 476.616.



Compounds	(R)
4a, 5a, 6a	
4b, 5b, 6b	
4c, 5c, 6c	

Scheme-1: Synthesis of novel series of fatty acid chain substituted pyrazoline derivatives

1-[(9′*Z*, 12′*R*)-12′-Hydroxyoctadec-9′-enoyl]-3-phenyl-5-furyl pyrazoline (5c): Yellow oily compound, Yield = 65%, IR (KBr, cm^{-1}): 3343 (OH), 2922 (C-H asymm.), 2851 (C-H symm.), 1674 (C=O), 1599 (C=N).^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.51 (m, 5H, Ar*H*), 6.15-6.85(m, 3H, furan ring), 5.48 (m, 2H, -C*H*=C*H*-), 5.45 (1H, dd, *J* = 12.3, 4.1 Hz, C*H* pyrazoline), 3.77 (1H, dd, *J* = 17.2 , 12.3 Hz, *H*-CH pyrazoline), 3.55 (m, 1H, -C*H*-OH), 3.12 (1H, dd, *J* = 17.2, 4.1 Hz, *H*-CH pyrazoline),

2.36 (t, 2H, *J* = 7.49 Hz, CH_2-CO), 2.32 (s, 1H, CH-O*H*), 1.90 (m, 4H, -CH_2-C=C-CH_2), 1.82 (m, 2H, CH_2-CH_2-CO), 1.44 (br.s, 18H, (CH_2)$_9$), 0.85 (dist.t, 3H, t-CH_3). ^{13}CNMR ($CDCl_3$, δ_c): 173.0 (C=O, C-1′), 155.4 (C=N), 141.0, 136.2 (furyl C-O), 133.4, 131.0, 129.2, 128.8 (Ph), 125.2, 124.6 (CH=CH, C-9′, C-10′), 114.2, 111.0 (furyl CH), 72.0 (CH-OH, C-12′), 53.2 (CH pyrazoline), 42.2 (CH_2 pyrazoline), 40.5 (CH_2, C-2′), 38.1 (CH_2, C-11′), 37.6 (CH_2, C-13′), 36.0 (CH_2, C-8′), 31.5, 30.3, 29.9, 29.7, 29.6, 28.7, 28.3, 27.4, 25.3 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-14′, C-15′, C-16′, C-17′), 14.2 (t-CH_3, C-18′). MS (ESI): *m/z* = 492.601, M^+ Calculated = 492.616.

1-(Undec-10′-enoyl)-3-phenyl-5-(*p*-chlorophenyl)-pyrazoline (6a): White oily compound, Yield = 68%, IR (KBr, cm^{-1}): 2925 (C-H asymm.), 2858 (C-H symm.), 1667 (C=O), 1595 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.44-7.52 (m, 9H, Ar*H*), 5.80 (tdd, 1H, $J_{H-^9CH_2}$ = 6.67 Hz, J_{H-H_a} = 10.08 Hz, J_{H-H_b} = 16.90 Hz, CH_2=C*H*), 5.33 (1H, dd, *J* = 12.1, 4.2 Hz, C*H* pyrazoline), 4.96 (dd, 1H, J_{H_a-H} = 10.0Hz, $J_{H_a-H_b}$ = 2.40 Hz, H_aC=CH), 4.91 (dd, 1H, J_{H_b-H} = 17.2 Hz, $J_{H_b-H_a}$ = 2.10 Hz, H_bC=CH), 3.82 (dd, 1H, *J* = 17.5, 12.1 Hz, *H*-CH pyrazoline), 3.27 (dd, 1H, *J* = 17.5, 4.2 Hz, *H*-CH pyrazoline), 2.28 (t, 2H, *J* = 7.40 Hz, CH_2CO), 2.02 (m, 2H, CH_2=CH-CH_2), 1.61 (m, 2H, CH_2CH_2CO), 1.32 (10H, br.s, CH_2(CH_2)$_5$). ^{13}C NMR ($CDCl_3$, δ_C): 172.4 (C=O, C-1′), 159.6 (C=N), 139.1, 131.2, 130.0, 129.4, 128.8, 128.0 (Ph, Ph-Cl), 124.2, 123.9 (CH_2=CH, C-10′, C-11′), 53.5 (CH pyrazoline), 42.3 (CH_2 pyrazoline), 40.1 (CH_2, C-2′), 36.3 (CH_2, C-9′), 33.8, 31.9, 29.4, 29.1, 28.9, 25.7 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-8′). MS (ESI): *m/z* = 422.921, M^+ Calculated = 422.937.

1-[Octadec-9′-enoyl]-3-phenyl-5-(*p*-chlorophenyl)-pyrazoline (6b): White oily compound, Yield = 69%, IR (KBr, cm^{-1}): 2920 (C-H asymm.), 2854 (C-H symm), 1657 (C=O), 1594 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.80-7.77 (m, 9H, Ar*H*), 5.29 (m, 2H, -C*H*=C*H*-), 5.38 (1H, dd, *J* = 12.2, 4.4 Hz, C*H* pyrazoline), 3.81 (1H, dd, *J* = 17.2, 12.2 Hz, *H*-CH pyrazoline), 3.25 (1H, dd, *J* = 17.2, 4.4 Hz, *H*-CH pyrazoline), 2.56 (t, 2H, *J* = 7.45 Hz, CH_2-CO), 2.02 (m, 4H, CH_2-CH=CH-CH_2), 1.70 (m, 2H, CH_2-CH_2-CO), 1.25 (br. s, 20 H, (CH_2)$_{10}$), 0.85 (dist. t, 3H, t-CH_3). ^{13}CNMR ($CDCl_3$, δ_c): 171.0 (C=O, C-1′), 156.4 (C=N), 140.0, 133.2, 130.4, 129.0, 128.3, 128.1, (Ph, Ph-Cl), 124.1, 122.9 (CH=CH, C-9′, C-10′), 52.0 (CH pyrazoline), 43.6 (CH_2 pyrazoline), 41.5 (CH_2, C-2′), 36.9, 35.8 (CH_2, C-8′, C-11′), 31.9, 30.9, 30.6, 30.2, 29.7, 29.4, 29.3, 29.1, 28.8, 27.0, 22.6 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-12′, C-13′, C-14′, C-15′, C-16′, C-17′), 14.1 (t-CH_3, C-18′). MS (ESI): *m/z* = 521.079, M^+ Calculated = 521.098.

1-[(9′*Z*, 12′*R*)-12′-Hydroxyoctadec-9′-enoyl]-3-phenyl-5-(*p*-chlorophenyl)-pyrazoline (6c): White oily compound, Yield = 71%, IR (KBr, cm^{-1}): 3352 (OH), 2923 (C-H asymm.), 2851 (C-H symm.), 1664 (C=O), 1597 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.65-7.70 (m, 9H, ArH), 5.35 (m, 2H, -C*H*=C*H*-), 5.32 (1H, dd, *J* = 12.3, 4.3 Hz, C*H* pyrazoline), 3.80 (1H, dd, *J* = 17.1, 12.3 Hz, *H*-CH pyrazoline), 3.50 (m, 1H, -C*H*-OH), 3.07 (1H, dd, *J* = 17.1, 4.3 Hz, *H*-CH pyrazoline), 2.34 (t, 2H, *J* = 7.4 Hz, CH_2CO), 2.27 (s, 1H, CH-O*H*), 1.94 (m, 4H, -CH_2-C=C-CH_2), 1.65 (m, 2H, CH_2-C-CO), 1.25 (br.s, 18H, (CH_2)$_9$), 0.80 (dist.t, 3H, t-CH_3). ^{13}CNMR ($CDCl_3$, δ_c): 171.6 (C=O, C-1′), 158.2 (C=N), 136.0, 133.6, 131.0, 129.8, 128.2, 127.9 (Ph, Ph-Cl), 123.0, 122.6 (CH_2=CH, C-10′, C-11′), 71.3(CH-OH, C-12′), 52.0 (CH pyrazoline), 43.1 (CH_2 pyrazoline), 41.4 (CH_2, C-2′), 38.2 (CH_2, C-11′), 36.8 (CH_2, C-13′), 35.7 (CH_2, C-8′), 31.2, 30.7, 29.3, 29.1, 28.8, 28.5, 27.4, 25.5, 23.1 (chain CH_2, C-3′, C-4′, C-5′, C-6′, C-7′, C-14′, C-15′, C-16′, C-17′)14.4 (t-CH_3, C-18′). MS (ESI): *m/z* = 537.085, M^+ Calculated = 537.097.

RESULTS AND DISCUSSION

The synthetic work was carried out beginning from acetophenone (**1**) which in a Claisen-Schmidt condensation with furfural (**2a**) and *p*-chlorobenzaldehyde (**2b**) afforded of 1-phenyl-3-furyl-2-propen-1-one (**3a**) and 1-phenyl-3-(*p*-chlorophenyl)-2-propen-1-one (**3b**) which undergo cyclization with various olefinic and hydroxy (internal and terminal) fatty acid hydrazides (**4a-c**) under reflux in presence of piperidine in CH_2Cl_2 to give different 1,3,5-trisubstituted pyrazolines (**5a-c** and **6a-c**). The synthetic route

for the preparation of 1, 3, 5-trisubstituted pyrazoline derivatives (**5a-c** and **6a-c**) is summarized in scheme. The synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectral data.

CONCLUSION

We have developed an effective method for the synthesis of novel 1, 3, 5-trisubstituted pyrazoline derivatives using selected fatty acids in simple, economical, convenient, easier work up with appreciable yields and to the best of our knowledge this was done for the first time using these fatty acids.

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