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Synthesis, Characterization and Study of Antioxidant Activities of Some New Pyrazoline Derivatives Containing Isatin Moiety

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ABSTRACT: A series of substituted pyrazoline derivatives 5(a-c) have been synthesized by the reaction of substituted chalcones 4(a-c) with isatinhydrazide. The starting materials, chalcones were prepared by clasien schimidt condensation of appropriate 1-hydroxy-2-acetonaphthone with substituted aldehydes in the presence of sodium hydroxide and in poly ethylene glycol (PEG-400). The structures of the synthesized compounds were confirmed by IR, 1HNMR & Mass spectral data. The synthesized compounds were screened for Antioxidant Activity by DPPH method.
Keywords: Pyrrole, Chalcones, Pyrazolines, Isatin, PEG (400), Antioxidant Activity

I. INTRODUCTION

Pyrazolines are well known and important nitrogen containing five-membered heterocyclic compounds and various methods have been worked out for their synthesis. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. They have found to possess anti-fungal[1],anti-depressant [2-7],anti-convulsant [8], anti-inflammatory [9-12], anti-bacterial [13-14], anti-cancer[15-18], anti-pyretic[19], anti-neoplastic activities [20-21], anti-viral [22], anti-amoebic [23-24], acaricidal agro chemical fungicides or insecticides [25], anti-cholinergic [26-27], antidiabetic [28], anti-HIV [29-32], anti-malarial [33], anesthetic [34], anaxiolytic [35], antiparasitic[36], anti-allergic[37], anti-microbial [38-40], anti-tuberculosis[41-44], tyrosinase inhibitor [45], blue photo luminescence and electro luminescence [46], food and chemical toxicology [47], herbicidal [48-50], hypoglycaemic [51], hypertensive [52], immunosuppressive[53], anti-tumor[54]. Moreover, many selectively chloro-substituted organic compounds show peculiar pharmacological and agrochemical properties.

Based on the above biological activities exhibited by the pyrazoline compounds, we report here, the synthesis and biological evaluation of some new pyrazoline derivatives. Chalcones (4a-c) were prepared from substituted aldehydes and ketones, in presence of alkali NaOH and poly ethylene glycol (PEG-400) as solvent medium. The later compounds (4a-c) were converted into the title compounds (5a-c) by reacting with isatinhydrazide in glacial acetic acid medium.

Isatinhydrazides are important classes of nitrogen containing heterocycles and they constitute useful intermediates in organic synthesis [55-57]. They have been reported for their applications in dyes and have also been used as building blocks for the synthesis of organic semiconductors. More interestingly studies have discovered that these compounds exhibit diverse medical functions such as antioxidant properties. [58-59].

II. MATERIALS AND METHODS

2-hydroxy-1-aceto naphthone, all aromatic aldehydes, hydrazine hydrate were purchased from Sigma Aldrich. PEG used was of Thomas baker. Ethanol and other chemicals of A.R. grade were used as received.

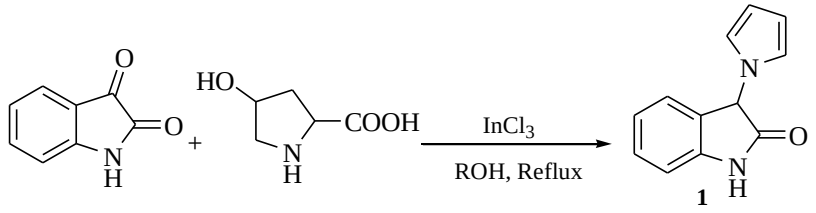
General procedure for the Synthesis 3-Pyrrol-1-yl-1,3-dihydro-indol-2-one (1): *1H*-Indole-2,3-dione (Isatin) (0.5mmol), 4-hydroxy -L-proline (0.5 mmol) and $InCl_3$ (10 mol%) were stirred in 2 ml of EtOH at 80 ℃ and the reaction progress was monitored by TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by flash chromatography (ethyl acetate: petroleum ether.

General procedure for the Synthesis of (2-Oxo-3-pyrrol-1-yl-2, 3-dihydro-indol-1-yl)-acetic acid ethyl ester (2): 3-Pyrrol-1-yl-1, 3-dihydro-indol-2-one (0.5mmol), ethylchloroacetate (0.05mmol) and potassium carbonate (0.10mmol) in dry acetone was refluxed for 20 h. The reaction mixture was poured onto crushed ice, and the solid was then filtered, washed with water and recrystallised from methanol.

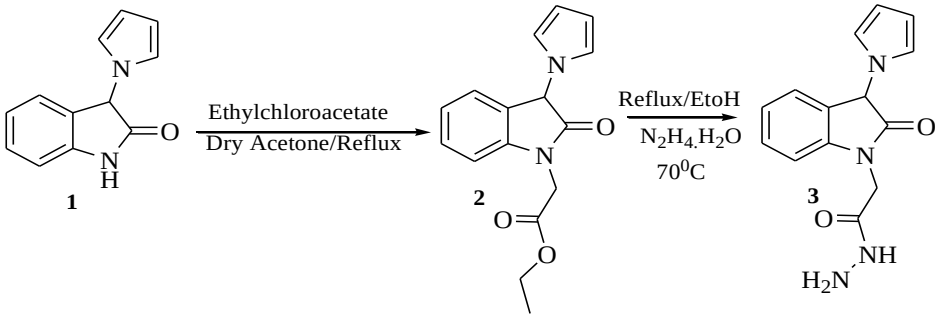
General procedure for the synthesis of (2-Oxo-3-pyrrol-1-yl-2,3-dihydro-indol-1-yl)-acetic acid hydrazide (3): (2-Oxo-3-pyrrol-1-yl-2,3-dihydro-indol-1-yl)-acetic acid ethyl ester **(**10 mmol) and $N_2H_4.H_2O$ (25 mmol) in 10 cm^3 ethanol was heated under reflux for 4h.The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol.

General procedure for the synthesis of chalcones (4a-c): A solution of 1-hydroxy-2-acetonaphthone (1mmol) in poly ethylene glycol (PEG-400) (2ml) and substituted aromatic aldehyde (1.1.mmol) was added. To this mixture aqueous sodium hydroxide (40%, 10 ml) was poured gradually while stirring a soid mass was obtained. The mixture was kept at room temperature for 1-5 hrs. Then poured into crushed ice and acidified with HCl (30%). The solid separated was filtered and recrystallized from ethanol.

General procedure for the Synthesis of Pyrazoline Derivatives (5a-c): The solution of appropriate Chalcone (0.01mol) and (2-Oxo-3-pyrrol-1-yl-2, 3-dihydro-indol-1-yl)-acetic acid hydrazide (0.02 mol) in ethanolic sodium hydroxide 20 ml was refluxed for 4 hour. The product was poured into ice water and the crude product which was separated out was filtered and crystallised from proper solvent.



Scheme 1



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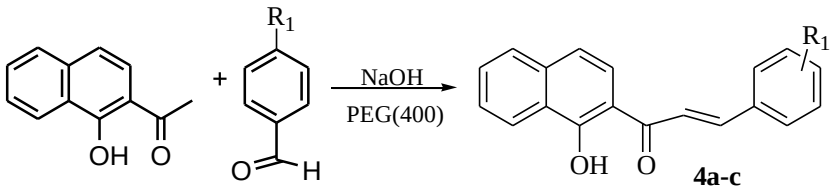
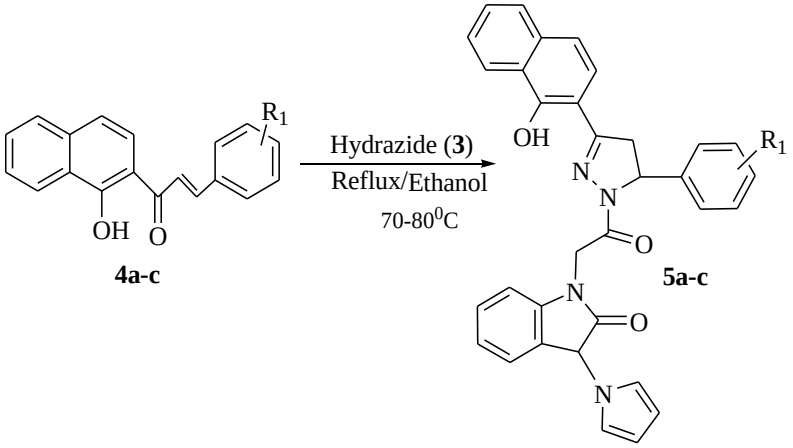


Where 4a = R_1= -Cl, 4b = R_1 = -NO_2, 4c = R_1= H

Scheme 3



Where 5a = R_1= -Cl, 5b = R_1 = -NO_2, 5c = R_1= H

Scheme 4

Physical measurements and analytical data: The entire compounds obtained were purified by column chromatography using silica-gel (100-200 mesh). Hexane/ethyl acetate was used as an eluent. ^{1}H and ^{13}C NMR were recorded on a Bruker AV-400 spectrometer operating at 400, 100 MHz respectively, using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 39.5 ppm. The coupling constants *J* are given in Hz. IR spectra were recorded on FT/IR-5300. Elemental analysis was performed on Thermo Finningan FLASH EA 1112 CHN analyzer. IR spectra (In KBr pellets) were recorded on a Shimadzu FT-IR 5300 spectrophotometer. Reactions were monitored by TLC silica coated plates obtained from Merck. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were measured in open capillary tubes and are uncorrected.

III. RESULTS AND DISCUSSION

1-(1-Hydroxy-naphthalen-2-yl)-3-phenyl-propenone (4a-c) were prepared by carrying out the reactions of 2-hydroxy-1-aceto naphthone with 4-chloro benzaldehyde, 4-nitro benzaldehyde, benzaldehyde and ethanol using aqueous sodium hydroxide and (PEG-400) as a catalyst. Synthesis of chalcone is a single step method. The synthesized chalcones were condensed with Isatin hydrazide to form pyrazoline derivatives (5a-c). All the synthesized compounds have been reported their elemental analysis for the percentage of carbon, hydrogen, oxygen and nitrogen was found to be experimentally equivalent to the calculated values.

The data obtained of the synthesized compounds –

(**1**) 3-Pyrrol-1-yl-1, 3-dihydro-indol-2-one: White amorphous powder: %; m.p. 140°C. Anal.: Calcd. for $C_{12}H_{10}N_2O$: Calcd, C,72.71;H,5.08; N,14.13;(%)Found: C,72.43; H ,5.19; N,14.22; (%)IR (KBr, nmax, cm-1): , 3194, 1717, 1618, 1466, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (s, 1H), 6.17 (t, 2H, *J* = 2.21 Hz), 6.63 (t, 2H, *J* = 2.21 Hz), 6.85-7.09 (m, 2H), 7.21-7.30 (m, 2H), 9.5 (brs, 1H) MS m/z 198 (M+).

(**2**) (2-Oxo-3-pyrrol-1-yl-2,3-dihydro-indol-1-yl)-acetic acid ethyl ester: brick red solid: yield: 95 %; m.p. 230˚C; Anal.Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67 (%); Found: C, 67.65; H, 5.69 (%) IR (KBr, nmax, cm-1):-1650 (C=O), 1585, 1560 (C=C), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.78 (m, 1H), 7.75 (m, *J* = 2.8 Hz, 6H), 7.73 (t, *J* = 3.8 Hz, 2H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.08-7.07 (m, 1H), 4.34 (q, *J* = 5.8 Hz, 2H), 1.36 (t, *J* = 5.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 162.2, 134.0, 133.2, 132.1, 127.8, 127.6, 61.1, 14.3; MS m/z 285 (M+).

(**3**) (2-Oxo-3-pyrrol-1-yl-2, 3-dihydro-indol-1-yl)-acetic acid hydrazide: white power: yield: 90 %; m.p.186^{0}C; Anal.: calcd. (%) for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73; Found (%): C, 62.25; H, 5.29; N, 20.75; IR (KBr, nmax, cm-1):- 3433, 3337(NH), 1669(C=O), 1612(C=N); MS m/z 270 (M+).

(**4a**) 3-(2-Chloro-phenyl)-1-(1-hydroxy-naphthalen-2-yl)-propenone: light creamy solid: Yield: 91 %; m.p. 130˚C; Anal.Calcd. for $C_{20}H_{16}O_3Cl$: C, 79.47; H, 6.03 (%); Found: C, 78.67; H, 5.61 IR (KBr, nmax, cm-1):-3100 (OH), 1722 (CO), 1645 (CH=CH), 855 (C-Cl); 1H NMR (400 MHz, CDCl3) d9.44 (1H, d, *J* = 9Hz, C-8c-H), 7.95 (1H, d, *J* = 16Hz, C-7-H), 7.75 (1H, d, *J* = 16 Hz, C-8-H), 7.60-7.70 (2H, m, C-4c and 5c-H), 7.55-7.65 (2H, d, C-3 and C-5), 7.39-7.56 (4H, m, C-2 and C-6, C-6c and 7c-H), 7.20 (1H, d, *J*= 9 Hz, C-3c-H). MS m/z 308 (M+).

(**4b**) 1-(1-Hydroxy-naphthalen-2-yl)-3-(4-nitro-phenyl)-propenone: brown solid: Yield: 90%; m.p. 165˚C; Anal.Calcd. for $C_{19}H_{13}NO_4$: C, 71.46; H, 4.10 (%); Found: C, 71.83; H, 4.12 (%);IR (KBr, nmax, cm-1):- 3100 (OH), 1721 (C=]O), 1640 (CH=CH), 1345 (C-N); 1H NMR (400 MHz, CDCl3) d 13.5 (1H, s, C-2c-OH), 9.47 (1H, d, *J* = 9Hz, C-8c-H), 7.98 (1H, d, *J* = 16Hz, C-7-H), 7.77 (1H, d, *J* = 16 Hz, C-8-H), 7.71 (2H, s, C-2 and 4-H), 7.62- 7.68 (2H, m, C-4c and 5c-H), 7.28-7.55 (4H, m, C-5,6 and 6c, 7c-H), 7.17 (1H, d, *J* = 9 Hz, C-3c-H); MS m/z 318 (M+).

(**4c**) 1-(1-Hydroxy-naphthalen-2-yl)-3-phenyl-propenone: light green solid: Yield: 90%; 80; m.p. 160˚C; Anal.Calcd. for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14(%); Found: C, 85.19; H, 5.16 (%); IR (KBr, nmax, cm-1):-3446 (OH),, 1614, 1743; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.78 (m, 1H), 7.51 (d, *J* = 3.8 Hz, 1H), 7.08-7.07 (m, 1H), 4.34 (q, *J* = 5.8 Hz, 2H), 1.36 (t, *J* = 5.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 162.2, 134.0, 133.2, 132.1, 127.8, 127.6, 61.1, 14.3; MS m/z 385 (M+).

(**5a**)1-[5-(4-Chloro-phenyl)-3-(1-hydroxy-naphthalen-2-yl)-4,5-dihydro-pyrazol-1-ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one: light brown solid: Yield: 80%; mp 190˚C; Anal.Calcd. for $C_{32}H_{25}ClN_4O_2$: C, 72.11; H, 4.73; N, 10.51(%); Found: C, 72.13; H, 4.75; N, 10.53 (%); IR (KBr, nmax, cm-1):- 3110 (OH), 3042 (CH), 1594 (C=N), 1722 (C=O), 855 (C-Cl); MS m/z 533 (M+).

(**5b**) 1-[3-(1-Hydroxy-naphthalen-2-yl)-5-(4-nitro-phenyl)-4,5-dihydro-pyrazol-1-ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one: yellowish red solid: Yield: 75%; mp 140˚C; Anal.Calcd. for $C_{32}H_{25}N_5O_4$: C, 70.71; H, 4.64; N, 12.88 (%); Found C, 70.73; H, 4.67; N, 14.88 (%);IR (KBr, cm-1): 3110 (OH), 3042 (CH), 1676 (C=O), 1593 (C=N), 1542 (-NO_2) MS m/z 543 (M+).

(**5c**) 1-[3-(1-Hydroxy-naphthalen-2-yl)-5-phenyl-4,5-dihydro-pyrazol-1-ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one: dark green solid: Yield: 90 %; mp 135˚C; Anal.Calcd. for $C_{32}H_{26}N_4O_2$: C, 77.09; H, 5.26; N, 11.24(%); Found C, 77.10; H, 5.28; N, 11.26 (%);IR (KBr, nmax, cm-1) 3120 (OH), 3042 (CH), 1682 (C=O), 1593 (C=N); MS m/z 497 (M+).

Screening for Antioxidant activity by DPPH Method

DPPH assay: (2, 2-diphenyl-1-picrylhydrazyl):

DPPH is a common abbreviation for an organic chemical compound 2,2-diphenyl-1-picrylhydrazyl. It is a crystalline powder composed of stable free-radical molecules. DPPH has two major applications, both in laboratory research: one is a monitor of chemical reactions involving radicals, most notably it is a common antioxidant assay.

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Principle:

The scavenging reaction between DPPH and antioxidant (H-A) can be written as:

$$\underset{\text{(Purple)}}{\text{(DPPH)}} + \text{(H-A)} \rightarrow \underset{\text{(Yellow)}}{\text{DPPH-H}} + \text{(A)}$$

Antioxidants react with DPPH., which is a stable free radical and is reduced to the DPPHH and as consequence the absorbance's decreased from the DPPH radical to the DPPH-H form. The degree of discoloration indicates the scavenging potential of the antioxidant compounds or extracts in terms of hydrogen donating ability.

Materials required:

1. Methanolic solution of DPPH (0.1 mM): 39.4 mg of DPPH was dissolved in one liter of analytical grade methanol.
2. Test sample

Antioxidant activity (using DPPH Method)

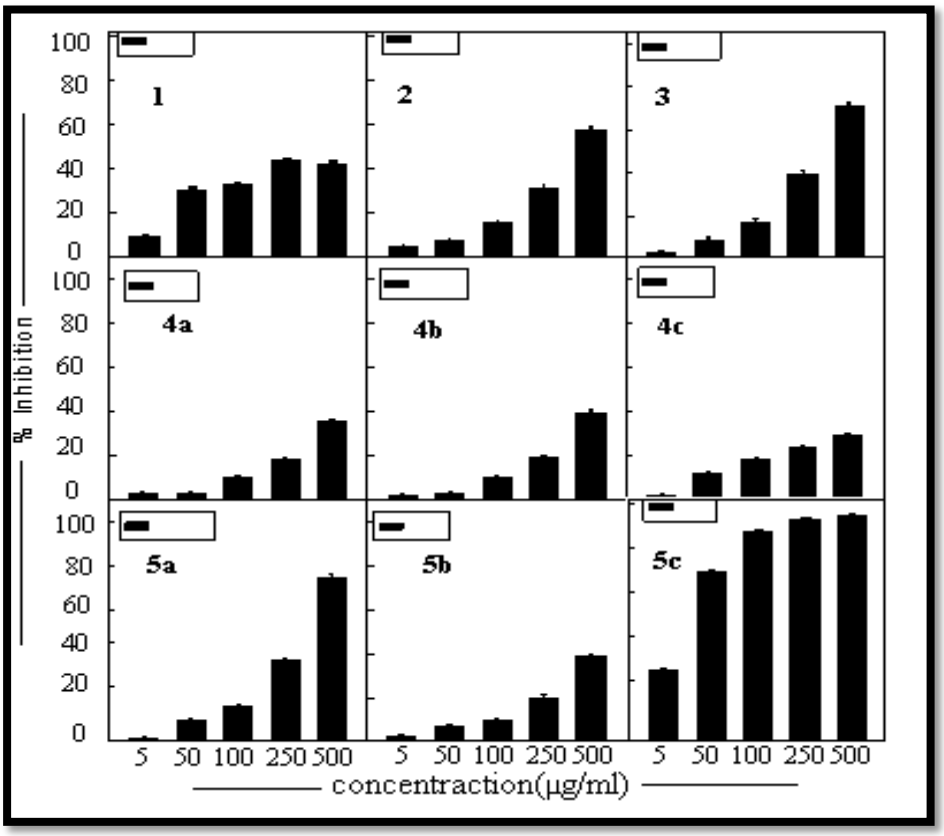
0.1mM solution of DPPH in methanol was prepared and 1.0 ml of this solution was added to 3.0 ml of extract solution in methanol at different concentration (1-16 µg/ml). Thirty minutes later, the absorbance was measured at 517 nm. A blank was prepared without adding sample. Lower the absorbance of the reaction mixture indicates higher free radical scavenging activity (expressed as % inhibition) . The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH Scavenged } \textbf{(\%)} = \textbf{X} \quad \frac{\text{Control-Test}}{\text{Control}} \quad 100$$

Control is the absorbance of the methanol in DPPH alone.

Test means the absorbance in the presence of sample.

Antioxidant activity of the different successive compounds mentioned as graphs below.



We have synthesized the above mentioned compound in the laboratory. All the compounds showed the antioxidant activity and which compound have the pyrrole ring group (5c) showed the more active molecule comparatively in all other compound as we observed.

Where 1 = 3-Pyrrol-1-yl-1, 3-dihydro-indol-2-one
2 = 2-Oxo-3-pyrrol-1-yl-2, 3-dihydro-indol-1-yl)-acetic acid ethyl ester
3 = (2-Oxo-3-pyrrol-1-yl-2, 3-dihydro-indol-1-yl)-acetic acid hydrazide
4a = 3-(2-Chloro-phenyl)-1-(1-hydroxy-naphthalen-2-yl)-propenone
4b = 1-(1-Hydroxy-naphthalen-2-yl)-3-(4-nitro-phenyl)-propenone
4c = 1-(1-Hydroxy-naphthalen-2-yl)-3-phenyl-propenone
5a = 1-[5-(4-Chloro-phenyl)-3-(1-hydroxy-naphthalen-2-yl)-4,5-dihydro-pyrazol-1- . ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one
5b = 1-[3-(1-Hydroxy-naphthalen-2-yl)-5-(4-nitro-phenyl)-4,5-dihydro-pyrazol-1-ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one
5c = 1-[3-(1-Hydroxy-naphthalen-2-yl)-5-phenyl-4,5-dihydro-pyrazol-1-ylmethyl]-3-pyrrol-1-yl-1,3-dihydro-indol-2-one

IV. APPLICATIONS

This is an environmentally benign procedure and reduces the total reaction time and good to excellent yields of chalcones, pyrrole and pyrazoline derivatives.

V. CONCLUSIONS

In summary, we have synthesized a new series of pyrazoline derivatives containing isatin moiety by the treatment of 1-(1-Hydroxy-naphthalen-2-yl)-3-phenyl-propenone or substituted chalones with substituted hydrazides respectively, in ethanol under reflux condition. The synthesis following compounds using PEG (400) as a catalyst results enhancement in the rate of reaction. The proposed method for the synthesis reduces the total reaction time and good to excellent yields, also allows easy separation of the product.

VI. ACKNOWLEDGEMENTS

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