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Research Article

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Synthesis and biological evaluation of β-amino naphthyl substituted chalcones for anti-inflammatory and antioxidant activities

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ABSTRACT

*A series of N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2-enamides were synthesized by reaction of β -acetyl amino naphthalene with substituted aromatic aldehydes in presence of absolute ethanol and 30% NaOH. The intermediate β-acetyl amino naphthalene was prepared by refluxing β-amino naphthalene with acetic anhydride and glacial acetic acid. A total of nine compounds were synthesized, purified and characterized on the basis of their spectral data. The title compounds were screened for anti-inflammatory activity by carrageenan induced rat hind paw method and antioxidant activity by using nitric oxide scavenging activity and reduction of stable free DPPH. Among the series of compounds 4-methoxy **(3)** and 4-dimethyl amino **(6)** derivatives exhibited significant anti-inflammatory activity. Among the test compounds 4-dimethyl amino **(6)** and 4-isopropyl **(7)** derivatives exhibited good antioxidant activity in both nitric oxide (NO) scavenging activity and reduction of stable free radical DPPH.*

Keywords: β-acetyl amino naphthalene, chalcones**,** anti-inflammatory activity, antioxidant activity

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INTRODUCTION

Naphthalene, an aromatic nucleus has gained prominence after the discovery of naproxen [1] and nabumetone [2] which are currently useful drugs for the treatment of various inflammatory disorders. Heterocyclic/aliphatic functionalized systematic variation at β- position of naphthalene nucleus remarkably increases the antiinflammatory activity [3-5]. Curcumin, a natural constituent of Curcuma longa has a styryl carbonyl moiety in its structure and displays anti-inflammatory activity [6]. Curcumin and dehydrozingerone were reported to be potent scavengers of oxygen free radicals and also possess good anti-inflammatory activity. Both are styryl ketones with similar substitution on the phenyl ring. In view of the potentiality of naphthalene nucleus and styryl carbonyl pharmacophores it was thought worthwhile to synthesize some new β-substituted amino naphthyl chalcones and evaluate them for their anti-inflammatory and antioxidant activities.

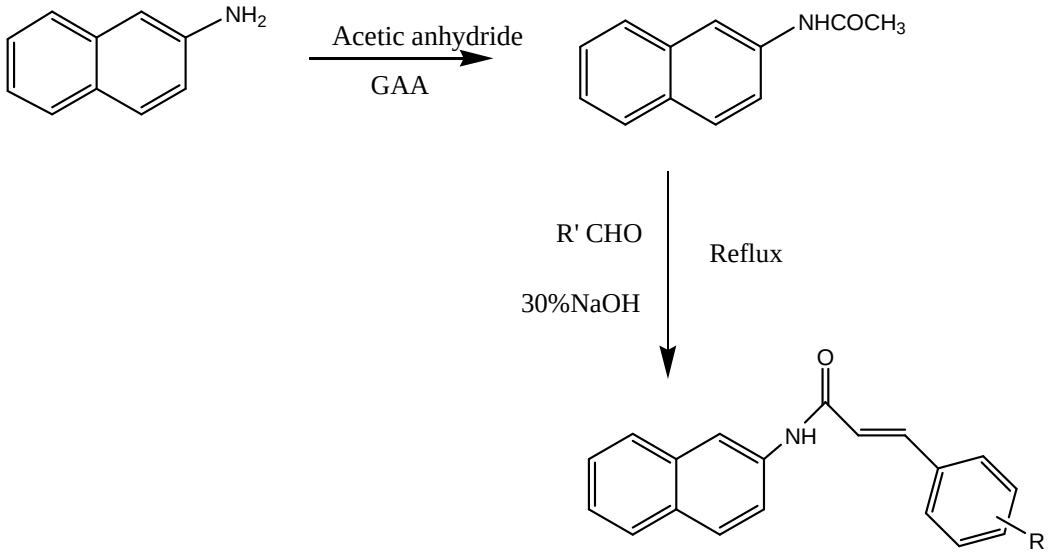
EXPERIMENTAL SECTION

β- Naphthylamine was procured from Sigma Aldrich chemicals. All other chemicals and solvents are of AR grade. All the melting points reported in this series were determined in open capillaries using Thermonik precision melting point cum boiling point apparatus model C-PMB-2 and are uncorrected. The progress of all reactions was monitored by pre-coated TLC plates (E. Merck Kieselgel 60 F_{254}) using Toluene and Ethyl acetate (9:1 v/v) and the spots were visualized by iodine vapour. The IR spectra were recorded using KBr pellets on a Perkin-Elmer 1760 Spectrophotometer (cm^{-1}). ^1H NMR spectra were recorded on GE Omega 400 MHz spectrometer or Bruker Avance 300 MHz spectrometer, using Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL-JMS-D-300 spectrometer. Animal ethical committee approval number: SPMVV/IAEC/2014a/09.

Synthesis of β-acetyl amino naphthalene:
To a solution of β-amino naphthalene (0.01mol), acetic anhydride and glacial acetic acid was added equipped with reflux condenser. The contents are mixed and refluxed for six hours. The reaction mixture was poured on to ice. The solid thus obtained was filtered and recrystallized from ethanol: water.

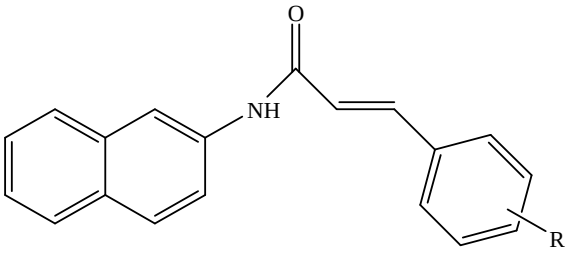
General method of synthesis of N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2-enamides (1-9):
A solution of β-acetyl amino naphthalene (0.01mol) in absolute ethanol (50 mL) was refluxed with various aromatic aldehydes in the presence of 30% NaOH for 6 hours, concentrated, cooled and poured on to ice. The solid thus obtained were recrystallized from ethanol. The various N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2-enamides **(1-9)** were prepared by similar procedure.

SCHEME-I



(1-9)
GAA-Glacial Acetic Acid

Table 1 - Physicochemical data of N-(naphthalene-2-yl)-3-(substituted phenyl)- prop-2-enamides (1-9)



Compound	R	M.P ^{0}C	Yield in %
1	H	138-140	70
2	4-CH_3	188-190	75
3	4-OCH_3	134-136	60
4	4-Cl	170-172	70
5	4-NO_2	180-182	70
6	4-$N(CH_3)_2$	152-154	70
7	4-$CH(CH_3)_2$	186-188	72
8	3,4,5- $(OCH_3)_3$	200-202	60
9	3,4- $(OCH_3)_2$	195-197	70

Recrystallization Solvent: Ethanol

N-(naphthalen-2-yl)-3-phenyl prop-2-enamide (1):
IR (KBr cm^{-1}): 3414(N-H), 1710(C=O), 1624(CH=CH), 1580(C=C of aromatic ring). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ, ppm: 6.85 (d,1H,-CO-CH=), 7.57-6.79 (m,12H, Ar-H), 7.54 (d,1H,=CH-Ar), 8.2 (s,1H,NH). **Mass Spectra** [M+]**:** 273.

3-(4-Methyl phenyl)-N-(naphthalen-2-yl)-prop-2-enamide (2):
IR (KBr cm^{-1}): 3408(N-H), 1720(C=O), 1625(CH=CH). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ, ppm: 2.40 (s,3H,Ar-CH_3), 6.84 (d,1H,-CO-CH=), 7.70-6.92 (m,11H, Ar-H), 7.55 (d,1H,=CH-Ar), 8.5 (s,1H,NH).

3-(4-Methoxyphenyl)-N-(naphthalen-2-yl)-prop-2-enamide (3):
IR (KBr cm^{-1}): 3425 (N-H) ,1716 (C=O), 1645 (CH=CH). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ, ppm: 3.75 (s,3H,Ar-OCH_3) 6.86 (d,1H,-CO-CH=), 7.60 (d,1H, =CH-Ar), 7.54-6.80 (m,11H,Ar- H), 8.5(s,1H,NH). **Mass Spectra** [M+]**:** 303.

3-(4-Chloro phenyl)-N-(naphthalen-2-yl)-prop-2-enamide (4):
IR (KBr cm^{-1}): 3410(NH), 1720 (C=O), 1630 (CH=CH). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ, ppm: 6.86 (d,1H,-CO-CH=), 7.58-6.76 (m,11H,Ar-H), 7.70 (d,1H,=CH-Ar), 8.4 (s,1H,NH).

N-(naphthalen-2-yl)-3-(4-nitrophenyl)-prop-2-enamide (5):
IR (KBr cm^{-1}): 3420 (N-H), 1740 (C=O), 1625 (CH=CH). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ, ppm: 6.79 (d,1H,-CO-CH=), 7.52-6.74 (m,11H,Ar-H), 7.59 (d,1H,=CH-Ar), 8.6 (s,1H,NH).

3-(4-(Dimethylamino)phenyl)-N-(naphthalen-2-yl)-prop-2-enamide (6):
IR (KBr cm^{-1}): 3412 (N-H), 1730 (C=O), 1610 (CH=CH). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ, ppm: 2.90 (s, 6H,-$N(CH_3)_2$), 6.85 (d,1H,-CO-CH=), 7.60-6.86 (m,11H,Ar-H), 7.60 (d,1H,=CH-Ar), 8.2 (s,1H,NH), **Mass Spectra**[M+]**:** 316.

N-(naphthalen-2-yl)-3-(4-(propan-2yl) phenyl)-prop-2-enamide (7):
IR (KBr cm^{-1}): 3415 (N-H), 1710 (C=O), 1624 (CH=CH). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ, ppm: 1.29 (d, 6H,$(CH_3)_2$ -C), 3.14 (m, 1H,CH (CH_3)), 6.84 (d,1H,-CO-CH=), 7.55-6.76 (m,11H,Ar-H), 7.52 (d,1H,=CH-Ar), 8.6 (s,1H,NH).

N-(naphthalen-2-yl)-3-(3, 4, 5-trimethoxyphenyl)-prop-2-enamide (8):
IR (KBr cm^{-1}): 3420(N-H), 1720(C=O), 1615 (CH=CH). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ, ppm: 3.73 (s,9H,$(OCH_3)_3$), 6.82 (d,1H,-CO-CH=), 7.54-6.28 (m,9H,Ar-H), 7.50 (d,1H,=CH-Ar), 8.5 (s,1H,NH).

3-(3, 4-Dimethoxyphenyl)-N-(naphthalen-2-yl)-prop-2-enamide (9):
IR (KBr cm^{-1}): 3414(N-H), 1716 (C=O), 1625 (CH=CH). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ, ppm: 3.75 (s, 6H, $(OCH_3)_2$), 6.89 (d, 1H,-CO-CH=), 7.62-6.80 (m,10H,Ar-H), 7.60 (d,1H,=CH-Ar), 8.6 (s,1H,NH).

BIOLOGICAL EVALUATION

Anti-inflammatory activity

The *in vivo* anti-inflammatory activity of all title compounds was evaluated using carrageenan induced hind paw edema test in male albino rats (150–180 g) of Wistar strain at 100 mg/kg body weight [7].

The rats were divided into groups of six animals. Control group received 0.5 % sodium carboxy methylcellulose, the standard group received standard drug phenylbutazone 100 mg/kg body weight, and the test groups received the synthesized compounds at the dose of 100 mg/kg body weight. The volume of the injected paw was measured by water displacement in a plethysmograph immediately after carrageenan injection. The paw volume was again measured after 3 h. A mark was made at the lateral maleolus, and the foot was dipped to the same distance into the arm of the plethysmograph.

Average edema volumes for test compound treated and positive control rats were compared statistically with those of the vehicle treated control animals and expressed as the present edema inhibition which was calculated using the formula.

Percent edema inhibition = 100 (1- V_t/V_c)

Where, V_c volume of the edema in the control group, and V_t volume of the edema in the treated group.

Antioxidant Activity

1. Assay of Nitric Oxide (NO) scavenging activity [8]

Sodium nitroprusside (10μM) in phosphate buffer pH 7.4; was incubated with 100 μM concentrations of drug dissolved in a suitable solvent (dioxane/methanol) and tubes were incubated at 25^{o}C for 120 minutes. 2 mL of incubation solution was removed and diluted with 2 mL of Griess reagent. The absorbance of the chromophore

formed during diazotization of nitrite with sulphanilamide and on subsequent coupling with N-naphthylethylene diamine was read at 546 nm. Control experiments without test compound were conducted in an identical manner.

2. Interaction with stable free radical DPPH [9]

Solutions of various drugs at 100 μM concentration were added to 100 μM DPPH in 95% ethanol and tubes were kept at an ambient temperature for 20 minutes and absorbance was measured at 517 nm. Ethanol was used as a blank solution and DPPH solution in ethanol served as the control.

Table 2 - Anti-inflammatory activity of N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2- enamides (1-9)

Compound	R	Edema volume ml (±SD)[a]	% of Edema Inhibition at 100mg/kg [c]
1	H	0.30 (0.01)[b]	23
2	4-CH_3	0.27 (0.02) [b]	31*
3	4-OCH_3	0.25(0.02) [b]	36*
4	4-Cl	0.28 (0.03) [b]	28
5	4-NO_2	0.29 (0.01) [b]	26
6	4-$N(CH_3)_2$	0.25 (0.017) [b]	36*
7	4-$CH(CH_3)_2$	0.26 (0.02) [b]	33*
8	3,4,5- $(OCH_3)_3$	0.28 (0.03) [b]	28
9	3,4- $(OCH_3)_2$	0.026 (0.015) [b]	33*

[a] Edema volume was measured 3 h after carrageenan injection and expressed as mean ± standard deviation.
[b] Control edema volume= 0.39 (0.02).
[c] At 100 mg/kg (p.o) percent edema inhibition was calculated by comparing edema volume with that of the respective vehicle-treated control animals
** Statistically Significant (p< 0.05, Mann–Whitney)*

Table 3 - Antioxidant activity of N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2-enamides (1-9)

Compound	R	Nitric oxide scavenging activity at 100μM	Reduction of DPPH at 100 μM
1	H	30	27
2	4-CH_3	32	29
3	4-OCH_3	42	39
4	4-Cl	28	27
5	4-NO_2	40	44
6	4-$N(CH_3)_2$	60	63
7	4-$CH(CH_3)_2$	56	57
8	3,4,5- $(OCH_3)_3$	24	25
9	3,4- $(OCH_3)_2$	42	40
	Ascorbic acid	70	72

RESULTS AND DISCUSSION

Chemistry

Synthesis of N-(naphthalene-2-yl)-3-(substituted phenyl) prop-2-enamides (1-9)

The intermediate β-acetyl amino naphthalene **(scheme-I)** was prepared by refluxing β-amino naphthalene, acetic anhydride and glacial acetic acid. The intermediate β-acetyl amino naphthalene upon nucleophilic addition with substituted benzaldehydes in absolute ethanol and 30% NaOH yielded the title compounds. A total of nine compounds were synthesized in this series. The compounds were obtained in good yield ranging from 60-80% **(Table 1)**.

Pharmacology and biochemical studies

Among the series of compounds electron donating groups at 4^{th} position such as 4-methoxy **(3)**, 4-dimethyl amino **(6)**, 4-isopropyl **(7),** 3,4-dimethoxy **(9)** and 4-methyl **(2)** derivatives exhibited significant anti-inflammatory activity [10] **(Table 2)** .Among the test compounds 4-dimethyl amino **(6)**, 3,4-dimethoxy **(9)** derivatives exhibited good antioxidant activity in both nitric oxide (NO) scavenging activity and reduction of stable free radical DPPH **(Table 3)**.

CONCLUSION

The present study leads to a convenient method for the synthesis of new compounds. Among the series of compounds, four compounds showed significant anti-inflammatory activity and two compounds showed significant antioxidant activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically potential compounds.

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