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Synthetic Studies of Novel Azaflavanone Derivatives and its Biological Activities

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ABSTRACT

Flavanones comprise a large and important group of naturally occurring secondary metabolites. As these secondary metabolites possess a wide range of activities so aim was to explore an easy route to synthesize aza analogues of flavanones and to evaluate their pharmacological activities. This newer approach has attempted that 2'-amino acetophenone can be successfully used in the synthesis of biologically active azaflavanones. Aza analogues of flavanones(2,3-dihydro-2-phenyl-4-quinolone) were synthesized via base catalysed oxidative cyclization of respective aza-chalcones. Claisen-Schmidt reaction is a simple and inexpensive method to synthesize chalcones so, the aza-chalcones were reported by Claisen-Schmidt condensation of 2´-amino acetophenone with substituted aromatic aldehydes. Various analogues of azaflavanone i.e., 1(a); 2,3-dihydro-2-phenyl quinolin-4-[1H]-one, 1(b); 2-(3-nitrophenyl)-2,3-dihydroquinolin-4[1H]-one, 1(c); 2-(2-hydroxyphenyl)-2,3-dihydroquinolin-4[1H]-one, 1(d); 2-(4-chlorophenyl)-2,3-dihydroquinolin-4[1H]-one, were synthesized with yield of 61,55, 53 and 72%, respectively. Synthesized compounds 1b-1d were evaluated for anti-inflammatory and anti-ulcer activity. Compound 1(b)-1(d) showed maximum percentage inhibition of paw edema i.e. 62.1, 63 and 65%, respectively, as compare to standard drug diclofenac sodium, at dose of 200 mg kg^{-1}. The same compounds at same dose, showed maximum percentage of inhibition of ulcers i.e., 65, 76 and 69.6%, respectively, in indomethacin induced ulcers and 60, 64 and 62.8%, respectively in ethanol induced ulcers. All the synthesized compounds were characterized on the basis of their elemental analysis, IR and ^{1}H-NMR spectroscopic data. All the tested compounds have shown moderate to good anti-inflammatory activity by carrageenan-induced rat paw edema method as well as anti-ulcer property by indomethacin induced ulcer and ethanol induced ulcer methods. Synthesized compounds exhibit potent anti-inflammatory and anti-ulcer activity so; azaflavanone derivatives can be used for drug discovery of various potent anti-inflammatory and anti-ulcer agents.

Key words: Chalcones, oxidative, azaflavanone, anti-inflammatory activity, anti-ulcer activity

INTRODUCTION

One of the intentions of medicinal chemistry research and drug discovery is to develop compounds that show desirable biological activities and easily accessible. Such compounds should be either isolated from natural resources or synthesized in the laboratory. The time and resources required to bring such biologically active compounds to the market can be minimized (Akcok and Cagir, 2010).

Flavonoids are naturally occurring polyphenolic compounds with flavone nucleus having anti-inflammatory, anti-oxidant, anti-ulcer and anti-tumor activities. It has been reported that various flavonoids have cyclooxygenase/lipoxygenase inhibitory activity (Park and Lee, 2004). They are available as flavone, flavonol, flavanone, isoflavone, chalcone and their derivatives, in nature. In flowers, the function of flavonoids is to provide colours that attract plant pollinators. Flavonoids are involved in protection of plants from UV-B radiations. They have been reported to possess many other properties, including inhibition of microbial infections in plants (Harborne and Williams, 2000). The synthesized molecules azaflavanones, whether they come under a class of flavonoids but these possess quinolones ring system so these may contain some same biological activities. It is large class of synthetic antimicrobial agents that are very effective in the treatment of infection, particularly bacterial infections (Andriole, 2000). Quinolone can be classified into four group of generations. Pipemidic acid comes under first generation; ciprofloxacin, norfloxacin and ofloxacin belong to second generation. Levofloxacin belongs to third and fluoroquinolone moxifloxacin is in fourth generation (Gonzalez *et al.*, 2005). Nalidixic acid is the predecessor of quinolone family including all four generations (Singh *et al.*, 2011).

Quinolones promote cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase that results in rapid bacterial death (Hooper, 1999). Generally, gram-negative bacterial activity is due to inhibition of DNA gyrase and gram-positive bacterial activity is due to inhibition of DNA type IV topoisomerase (Catherine and Gary, 2002). A generation of quinolone lead antimalarials has been discovered having dual mechanism of action against two respiratory enzymes. NADH: ubiquinone oxidoreductase (*Plasmodium falciparum* NDH_2) and cytochrome bc_1 inhibitor specificity for the two enzymes can be controlled by manipulating quinolone core at the 2 or 3 positions (Biagini *et al.*, 2012).

The flavonoids basically possess 15-carbon basic skeleton (C6-C3-C6) and are phenyl substituted chromones (benzopyran derivatives). These are the compounds of chroman nucleus (C6-C3). The benzo ring A and the heterocyclic ring C with a phenyl (the aromatic ring B) substitution at 2-position. Various substitutions can occur in the rings A and B (Kandaswami *et al.*, 2005). Flavonoids are found mainly in red wine, apples, blueberries, bilberries, onions, soy products and tea (Bylka *et al.*, 2004). These could participate in the photosynthetic process as the flavonoids are ubiquitous to green plant cells (Havsteen, 2002).

Various substituted chalcones act as intermediates in many heterocyclic syntheses (Prasad *et al.*, 2008). Chalcones or 1,3-diphenyl-2-propen-1-one derivatives are open chain unsaturated carbonyl system in which three carbons of having α, β-unsaturated system join two aromatic rings. Chalcones act as the precursors of flavonoids and isoflavonoids. These secondary metabolites of terrestrial plants exhibit various biological activities (Appu, 2010).

The aim of this work was to replace the oxygen atom of B ring of flavanones (Fig. 1) with the nitrogen atom to optimize a synthesis route for the preparation of aza analogues of flavanones and to explore their anti-inflammatory and anti-ulcer property. This work reports the synthesis of the title compounds, novel 2,3-dihydro-2-phenyl-4-quinolone i.e., azaflavanone derivatives.

MATERIALS AND METHODS

All the laboratory chemicals required for the study were procured from S.D. Fine Chemicals Ltd., Mumbai, India and Lab Sales Pvt. Ltd, Pune, India. Carrageenan was obtained from HiMedia Labs, Mumbai. The purity of compounds was checked by Thin Layer Chromatography (TLC) using Toluene: ethyl acetate (7:3) as the solvent system and the spots were visualized in UV

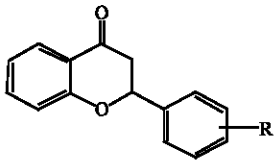

Fig. 1: General structure of flavanones

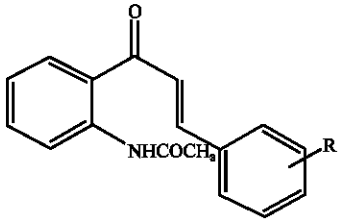

Fig. 2: General structure of aza-chalcones

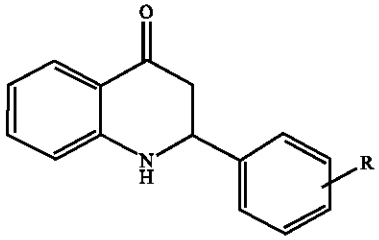

Fig. 3: General structure of synthesized azaflavanones

chamber. Melting points were determined with a Buchi 530 melting point apparatus in open capillaries. The IR spectra were recorded on Perkin Elmer BX FTIR 882 spectrometer using KBr pellet method in the range of 4000-400 cm^{-1}. NMR spectra were recorded on Bruker Avance II 400 Spectrometer. In ^{1}H-NMR, chemical shift values were reported in parts per million on the scale in dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. Elemental analysis was done from CHNS (O) elemental analyzer, PU Chandigarh.

Experimental: All the ortho amino substituted chalcones (aza-chalcones, Fig. 2) was synthesized by base catalysed Claisen-schmidt condensation using various aromatic benzaldehydes (Vatkar *et al.*, 2010). Acetylation of ortho amino acetophenone was carried out before condensation to avoid Shiff's base formation with aldehydes. The synthesized aza-chalcones was cyclised with 5% HCl under reflux to afford the desired [1]-Azaflavanones (2,3-dihydro-2-phenyl-4-quinolone, Fig. 3) Scheme 1 outlines the systematic steps involved in synthesis of these compounds (Fig. 4).

General synthesis of 2, 3-Dihydro-2-phenyl quinolin-4-[1H]-one: 2´-amino acetophenone (2 g) was reacted with acetic anhydride (5 mL) in the presence of di-methyl amino pyridine (DMAP) as a catalyst to obtain N-(2-acetylphenyl acetamide). N-(2-acetylphenyl acetamide) (0.3 g, 0.0013 M) was dissolved in methanol (15 mL) in a 100 mL conical flask. To this solution substituted aromatic aldehyde (0.0013 M) and 5% aq. NaOH solution (2 mL) were added, respectively, to yield respective aza-chalcone. Reaction mixture was kept in stirred condition. Temperature was

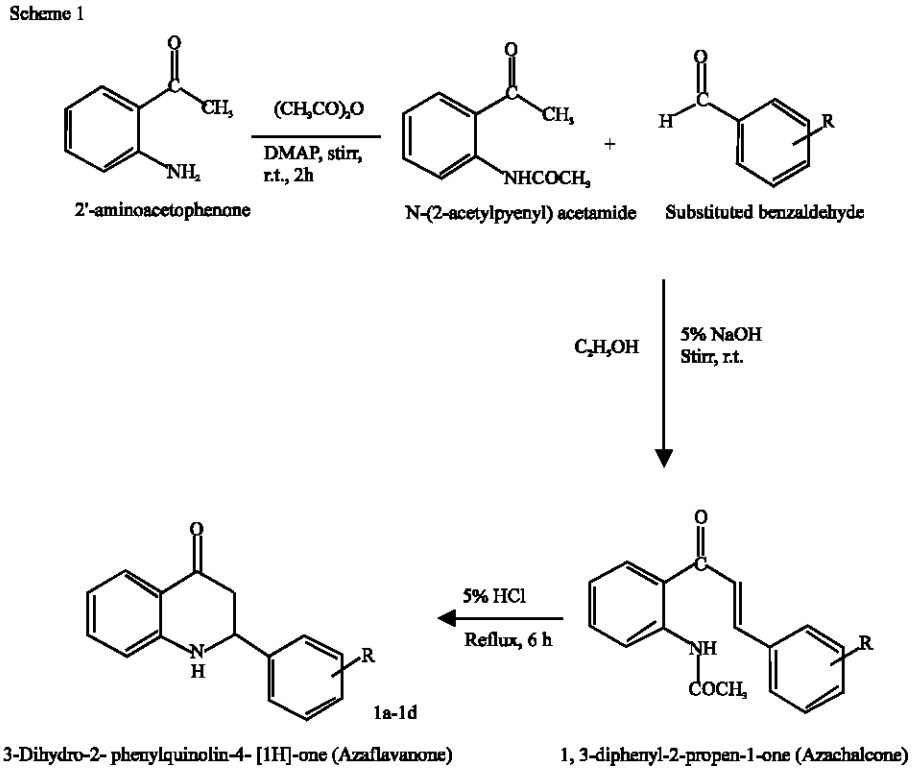

Fig. 4: Systematic steps involved in synthesis of compounds

maintained below 15°C (in any case not more than 20°C). The progress of reaction was monitored on TLC (Toluene: ethyl acetate). After the completion of the reaction (usually in 12-13 h), mixture was poured in ice cold water. The solid was separated by filtration, washed with cold ice water and crystallized from alcohol. Purity of the product was monitored on TLC (Toluene: ethyl acetate). Spots were visualized in UV chamber. Then, the prepared open chain chalcone was dissolved in methanol (15 mL), added 50 mL of dil. HCl (10: 40) and was refluxed. Then the progress of the reaction was monitored on TLC (Toluene: ethyl acetate). The crystals obtained were filtered and washed with water.

Anti-inflammatory activity

Carrageenan-induced rat paw edema: The carrageenan-induced rat paw edema assay was carried out according to Winter *et al.* (1962). Wistar rats were divided into 4 groups each consisting of 6 animals for each derivative (Gill *et al.*, 2011):

Group I: (Disease Control) Carrageenan (1%) was administered in the plantar surface of rats (p.o.)

Group II: (Standard) Suspension of diclofenac sodium (10 mg kg^{-1}) in 1% Gum acacia (p.o.)+ Carrageenan

Group III: (Test) Suspension of test compounds 1b-1d, respectively (100 mg kg^{-1}) in 1% Gum acacia (p.o.)+Carrageenan

Group IV: (Test) Suspension of test compounds 1b-1d, respectively (200 mg kg^{-1}) in 1% Gum acacia (p.o.)+Carrageenan

Edema was induced on the left hind paw of the rats by subplantar injection of 0.1 mL of a solution of 1% (w/v) carrageenan in a 0.9% NaCl (w/v). The paw volume was measured at intervals of 60, 120, 180 min by the mercury displacement method using a plethysmograph after administration of the suspension of test compounds in 1% Gum acacia orally. The average paw edema volume of all the groups were calculated and compared with that of control. The percentage inhibition of paw edema in drug treated group was compared with the carrageenan control group and calculated according to the following Eq. 1:

$$\text{Inhibition of edema (\%)} = \frac{V_c - V_t}{V_t} \times 100 \quad (1)$$

where, V_c is the inflammatory increase in paw volume of control group of animals and V_t is the inflammatory increase in paw volume of drug-treated animals.

Statistical analysis: All the results were expressed as Standard Error of Means (SEM). The data was statistically analyzed by one way Analysis of Variance (ANOVA) followed by Tukey using GraphPad Prism 5 Software. The p-value <0.05 was considered to be statistically significant.

Anti-ulcer activity

Ethanol induced ulcer model: The ulcer was induced by administering ethanol. All the animals were fasted for 36 h before administration of ethanol. The animals were divided into five groups, each consisting of six rats:

Group I: Represented the control group which received distilled water orally
Group II: Disease group receive ethanol 90% (1 mL 200 g^{-1})
Group III: Ranitidine (50 mg kg^{-1}) were administered orally as reference standard drug
Group IV: Received suspension of test compounds 1b-1d (100 mg kg^{-1} p.o.) in 1% Gum acacia, 15 min before ethanol administration
Group V: Received suspension of test compounds 1b-1d (200 mg kg^{-1}, p.o.) in 1% Gum acacia, 15 min before ethanol administration

They were kept in specially constructed cages to prevent coprophagia during and after the experiment. The animals were anaesthetized 1 h later, with anaesthetic ether and stomach was incised along the greater curvature. Stomach was rinsed under tap water and ulceration was scored (Raju *et al.*, 2009).

Indomethacin induced ulcer: Animals were divided into 5 groups and each comprising 6 rats (Ukwe *et al.*, 2010):

Group I: Administered vehicle (normal saline 0.9% w/v, p.o.) 30 min before indomethacin administration
Group II: Disease control group administered indomethacin (25 mg kg^{-1} p.o.) for induction of gastric ulcer
Group III: Administered standard (Ranitidine 50 mg kg^{-1} p.o.) 30 min before indomethacin administration
Group IV: Administered suspension of test compounds 1b-1d (100 mg kg^{-1} in 1% Gum acacia, 30 min before indomethacin administration

Group V: Administered suspension of test compounds 1b-1d (200 mg kg^{-1} in 1% Gum acacia, 30 min before indomethacin administration

Four hours after indomethacin administration, animals were killed by decapitation method. Stomachs were removed and open along the grater curvature. Macroscopic examination was carried out with a hand lens and the presence of lesions was scored (Govind *et al.*, 2010).

Determination of percentage ulcer protection: Percent age ulcer protection was found out by following Eq. 2:

$$\text{Ulcer protection (\%)} = \frac{U_c - U_t}{U_c} \times 100 \quad (2)$$

where, U_c is the mean ulcer index of disease control group and U_t is the mean ulcer index of tested group.

RESULTS

Various azaflavanones (1a-1d) were synthesized via cyclization of respective aza-chalcones, which were formed by Claisen-Schmidt reaction between 2′-amino acetophenone and various substituted benzaldehydes.

Synthesis of 2, 3-dihydro-2-phenyl quinolin-4-[1H]-one (1a): Compound 1(a) was synthesized via oxidative cyclization of its aza-chalcone. Aza-chalcone was formed via base catalysed Claisen-Schmidt reaction between N-(2-acetylphenyl) acetamide and benzaldehyde. The percentage yield obtained was 61% having molecular formula $C_{15}H_{13}ON$ and molecular weight 223 g mol^{-1}. The observed melting point was 91-94°C and the R_f of TLC (Toluene: ethyl acetate (7: 3) was 0.37 (Table 1). Structure was confirmed by IR, ^{1}H-NMR spectral and elemental analysis as:

- **IR (KBr) cm^{-1}:** 3320(N-H str), 2987 (C-H str), 1681 (C=O str), 1596 (Nitro compounds asymmetric) and 1019 (C-N str)
- **^{1}H-NMR (DMSO-d_6):** δppm-7.88 (d, 1H), 7.27-7.39 (3H, m), 7.28 (1H, t), 6.92-6.94 (2H, m), 4.82 (1H, dd), 4.54 (1H, s, D_2O exchangeable proton) and 2.72-2.94 (2H, m)

Elemental analysis (%): C-80.64, H-5.85, N-6.24, O-7.14.

Synthesis of 2-(3-nitrophenyl)-2, 3-dihydroquinolin-4[1H]-one (1b): Compound 1(b) was synthesized via oxidative cyclization of its aza-chalcone. Base catalysed Claisen-Schmidt reaction between N-(2-acetylphenyl) acetamide and 3-Nitro benzaldehyde formed aza-chalcone. The yield

Table 1: Physicochemical properties of synthesized Azaflavanones

Compounds code	R	Molecular formula	Mol. Wt. (g mol^{-1})	Yield (%)	Melting point (°C)	R_f
1a	H	$C_{15}H_{13}ON$	223	61	91-94	0.37
1b	3-NO_2	$C_{15}H_{12}O_3N$	268	55	157-160	0.23
1c	2-OH	$C_{15}H_{13}O_2N$	239	53	142-145	0.31
1d	4-Cl	$C_{15}H_{12}ONCl$	258	72	165-167	0.28

Table 2: Anti-inflammatory activity for 1b-1d compounds

Groups	Dose (mg kg^{-1}) orally	Mean paw volume (mL) 60 min	120 min	180 min	Inhibition of edema (%)
Control	1 % CMC	0.52±0.006	0.62±0.005	0.66±0.008	----
Diclofenac sodium	10	0.37±0.003[a]	0.33±0.012[a]	0.20±0.008[a]	69.60
1b	100	0.59±0.024[ab]	0.67±0.014[ab]	0.31±0.015[ab]	53.00
1b	200	0.60±0.006[ab]	0.69±0.015[ab]	0.25±0.012[ab]	62.10
1c	100	0.70±0.016[ab]	0.70±0.011[ab]	0.31±0.001[ab]	53.03
1c	200	0.66±0.006[ab]	0.70±0.017[ab]	0.24±0.014[ab]	63.00
1d	100	0.62±0.014[ab]	0.66±0.008[ab]	0.32±0.012[ab]	51.50
1d	200	0.67±0.014[ab]	0.68±0.008[ab]	0.23±0.008[ab]	65.00

Values are expressed as Means±SEM (n = 6), [a]p<0.05 vs. Control, [b]p<0.05 vs. Diclofenac sodium

Table 3: Effect of 1b-1d compounds on Indomethacin induced ulcers in rats

Group	Treatment	Dose(mg kg^{-1})	Mean±SEM ulcer index	Ulcer inhibition (%)
I	Normal		0.00±0.00	0.00
II	Disease		2.50±0.08	0.00
III	Ranitidine	50	0.433±0.03[a]	82.68
IV	1b	100	1.2±0.110[ab]	52.00
V	1b	200	0.86±0.08[ab]	65.00
VI	1c	100	0.94±0.09[ab]	64.00
VII	1c	200	0.60±0.05[ab]	76.00
VIII	1d	100	1.16±0.08[ab]	56.00
IX	1d	200	0.76±0.08[ab]	69.60

n = 6, [a]p<0.05 vs. control, [b]p<0.05 vs. ranitidine

obtained of compound 1(b) was 55% having molecular formula $C_{15}H_{12}O_3N$ and molecular weight 268 g mol^{-1}. The observed melting point was 157-160°C and the R_f of TLC (Toluene: ethyl acetate (7: 3) was 0.23 (Table 1). Structure was confirmed by IR, ^{1}H-NMR spectral and elemental analysis, which is given below:

- **IR (KBr) cm^{-1}:** 3333 (N-H str), 2926 (C-H str), 1687 (C = O str), 1596 (Nitro compounds asymmetric) and 1378 (Nitro compounds symmetric)
- **^{1}H-NMR (DMSO-d_6):** δppm-8.38 (1H, d), 8.16 (1H, m), 7.86 (1H, d), 7.72 (1H, d), 7.54 (1H, t), 7.34 (1H, m), 6.68-6.9 (2H, m), 4.89 (1H, s, D_2O exchangeable proton) and 2.71-2.86 (2H, m).

Elemental analysis (%): C-67.13, H-4.56, N-10.40, O-17.85.

Further the compound was evaluated for its anti-inflammatory activity and it showed potent anti-inflammatory activity with 62.1% inhibition of paw edema as compare to standard drug diclofenac sodium, at a dose of 200 mg kg^{-1}. Furthermore, synthesized compound 1(b) was evaluated for anti-ulcer activity. At dose of 200 mg kg^{-1} it showed 65% inhibition of ulcers in indomethacin induced ulcers and 60% inhibition in ethanol induced ulcers as compare to standard drug ranitidine (Table 2-4).

Table 4: Effect of 1b-1d compounds on ethanol induced ulcers (EIU) in rats

Group	Treatment	Dose(mg kg^{-1})	Mean ulcer index±SEM	Ulcer inhibition (%)
I	Normal		0.00±0.00	0.0
II	Disease		3.53±.080	0.0
III	Ranitidine	50	0.80 ± 0.05^{a}	77.1
IV	1b	100	$1.50\pm0.17^{a,b}$	57.1
V	1b	200	$1.40\pm0.08^{a,b}$	60.0
VI	1c	100	$1.60\pm0.08^{a,b}$	54.2
VII	1c	200	$1.20\pm0.08^{a,b}$	64.0
VIII	1d	100	$1.70\pm0.12^{a,b}$	51.4
IX	1d	200	$1.30\pm0.08^{a,b}$	62.8

Values are expressed as Means±SEM (n = 6), $^{a}p<0.05$ vs. Control, $^{b}p<0.05$ vs. Ranitidine

Synthesis of 2-(2-hydroxyphenyl)-2, 3-dihydroquinolin-4[1H]-one (1c): Compound 1(c) was synthesized via oxidative cyclization of its aza-chalcone. Aza-chalcone was formed via base catalysed Claisen-Schmidt reaction between N-(2-acetylphenyl) acetamide and 2-Hydroxy benzaldehyde. The yield obtained of compound 1(c) was 53% having molecular formula $C_{15}H_{13}O_2N$ and molecular weight 239 g mol^{-1}. The observed melting point was 142-145°C and the R_f of TLC [Toluene: ethyl acetate (7: 3)] was 0.31 (Table 1). Structure was confirmed by IR, ^{1}H-NMR spectral and elemental analysis, which is given below:

- **IR (KBr) cm^{-1}:** 3510 (N-H str), 3250 (O-H str), 2985 (C-H str), 1690 (C=O str), 1581 (Nitro compounds asymmetric) and 1019(C-N str)
- **^{1}H-NMR** (DMSO-d_6): δppm-8.56 (d, 1H), 8.10 (1H, m), 7.8 (1H, d), 7.40 (1H, d), 7.25 (1H, t), 7.04 (1H, m), 6.51-6.8 (2H, m), 4.4 (1H, s, D_2O exchangeable proton) and 2.8-3.1 (2H, m)

Elemental analysis (%): C-75.34, H-5.44, N-5.81, O-13.34. Further the compound was evaluated for its anti-inflammatory activity and it showed potent anti-inflammatory activity with 63% inhibition of paw edema as compare to standard drug diclofenac sodium, at dose of 200 mg kg^{-1}. Furthermore, synthesized compound 1(c) was evaluated for anti-ulcer activity. Dose of 200 mg kg^{-1} showed 76% inhibition of ulcers in indomethacin induced ulcers and 64% inhibition in ethanol induced ulcers. Its anti-ulcer activity was maximum among all the tested compounds (Table 2-4).

Synthesis of 2-(4-chlorophenyl)-2, 3-dihydroquinolin-4[1H]-one (1d): Compound 1(d) was synthesized via oxidative cyclization of its aza-chalcone. Aza-chalcone was formed via base catalysed Claisen-Schmidt reaction between N-(2-acetylphenyl) acetamide and 4-Chloro benzaldehyde. The yield obtained of compound 1(d) was 72% having molecular formula $C_{15}H_{12}ONCl$ and molecular weight 258 g mol^{-1}. The observed melting point was 165-167 ^{0}C and the R_f of TLC [Toluene: ethyl acetate (7: 3)] was 0.28 (Table 1). Structure was confirmed by IR, ^{1}H-NMR spectral and elemental analysis as given below:

- **IR (KBr) cm^{-1}:** 3353(N-H str), 2935 (C-H str), 1687 (C = O str), 1596 (Nitro compounds asymmetric), 1078(C-N str) and 767(C-Cl str)
- **^{1}H-NMR (DMSO-d_6):** δppm-7.83 (d, 1H), 7.31-7.41 (5H, m), 6.72-6.81 (2H, m), 4.69 (1H, dd), 4.60(1H, s, D_2O exchangeable proton), 2.79 (1H, dd), 2.70 (1H, dd)

Elemental analysis (%): C-69.89, H-4.65, Cl-13.74, N-5.41, O-6.25. Further the compound was evaluated for its anti-inflammatory activity and it showed potent anti-inflammatory with 65% inhibition of paw edema as compare to standard drug diclofenac sodium, at dose of 200 mg kg^{-1}. Furthermore, synthesized compound 1(d) was evaluated for anti-ulcer. It showed 69.6% inhibition of ulcers in indomethacin induced ulcers and 62.8% inhibition in ethanol induced ulcers (Table 2-4).

Anti-inflammatory activity: Diclofenac sodium was used as a standard drug. Positive control, Diclofenac sodium and test compounds (1b-1d) significantly inhibited the paw edema response in comparison to control group. Diclofenac sodium showed an inhibition of 69.6% after 3 h. Compound 1d at dose of 200 mg kg^{-1} showed maximum activity with an inhibition of 65% and minimum activity with an inhibition of 51.5% at dose of 100 mg kg^{-1} after 3 hours. Compounds 1(c) and 1(d) have 2-hydroxy and 4-chloro substitutions and they show significant anti-inflammatory activity at 200 mg kg^{-1} dose (Table 2).

Anti-ulcer activity: Ranitidine showed marked anti-ulcer response. All the test compounds 1b-1d also showed good anti-ulcer activity.

Indomethacin induced ulcers: Compound 1c showed maximum activity with an inhibition of 76% in indomethacin induced ulcers. Minimum anti-ulcer activity with an inhibition of 52% was shown by compound 1b. Here also, 1(c) and 1(d) showed significant anti-ulcer activity at 200 mg kg^{-1} dose but their 100 mg kg^{-1} dose showed less significant activity (Table 3).

Ethanol induced ulcers: Maximum inhibition of 64% for ethanol induced ulcers was shown by compound 1c. Compound 1d showed minimum inhibition of 51.4% in ethanol induced ulcer models (Table 4).

Two different doses of 100 and 200 mg kg^{-1} were used and among them 200 mg kg^{-1} were found to be more potent (Table 3, 4).

DISCUSSION

Azaflavanones were successfully synthesized. Their structures were confirmed from their elemental analysis and their respective spectral data such as IR and ^{1}H-NMR studies. Results showed that presence of electron-withdrawing group in aza-chalcones increased the percentage yield of azaflavanones. Synthesis of azaflavanones by this method is easy and does not require any extreme environmental conditions.

Among synthesized compounds three were evaluated for their pharmacological activities i.e. anti-inflammatory and anti-ulcer activity. The tested derivatives showed significant anti-inflammatory activity and anti-ulcer activity.

Anti-inflammatory activity: Anti-inflammatory activity was done by using carrageenan induced rat paw edema method. Flavanones have been reported to possess significant free radical scavenging activity (Ramamoorthy and Bono, 2007) so this can be responsible for the reduction of inflammation in the carrageenan-induced paw edema in rats. Compounds showed potent anti-inflammatory activity at dose of 200 mg kg^{-1} as compare to standard drug diclofenac sodium. The mechanism of anti-inflammatory activity is not clarified but may be due to inhibition of lipoxygenase or inhibition of TNFα-induced NF-κB transcriptional activation as shown by some flavanones (Clavin *et al.*, 2007). 4-Chloro derivative showed maximum anti-inflammatory activity.

Anti-ulcer activity: Azaflavanones possess anti-ulcer activity and the proposed mechanism is inhibition of formation and release of endogenous histamine in the gastric mucosa as shown by other flavanones (Mota *et al.*, 2009). 2-Hydroxy derivative showed maximum anti-ulcer activity.

It was revealed that every tested compound showed better response with increase in concentration from 100 to 200 mg kg^{-1}.

CONCLUSION

Various azaflavanones were synthesized using 2′-amino acetophenone as starting material. The entire tested compounds showed significant anti-inflammatory and anti-ulcer activity. It can be proposed that further modifications may obtain compounds of better activity with less toxic effects.

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