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INHIBITION OF ALBUMIN DENATURATION AND ANTI INFLAMMATORY ACTIVITY OF FURFURYL SUBSTITUTED PYRIMIDINOIMIDAZOLINONES

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ABSTRACT

The various substituted pyrimidinoimidazolinones have been synthesized and evaluated for their antimicrobial activity. Structure of these products have been established by IR and ^{1}H NMR data. Significant antimicrobial activity was observed for some members of the series.

Key words: Pyrimidine, Imidazole, Furan

INTRODUCTION

Pyrimidines, being an integral part of DNA and RNA imparts to diverse pharmacological properties as effective bactericide, fungicides[1-5]. Certain pyrimidine derivatives are also known to display antimalarial[6-8], antifilarial and antileishmanial activities. The biodynamic property of this ring system prompted up to design pyrimidine[9-13] derivatives stimulating pharmacophore and substituents responsible for diverse pharmacological activities[14].

Imidazolinones exhibit diverse biological properties. Hence, synthesis of new imidazolinones is of considerable interest. In the recent years, the chemistry of oxazolones has received much attention due to their use as intermediate for the synthesis of some hetereocyclic system. Imidazolinones have been reported to possess antifungal, antiinflammatory, anti viral and antihistaminic activity.

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The denaturation of proteins as one of the causes as inflammation is well documented. Production of auto-antigens in certain rheumatic diseases may be due to *in vivo* denaturation of proteins.

A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins. Mizushima and Kobayashi[15] have employed protein denaturation as *in vitro* screening model for anti-inflammatory compounds.

EXPERIMENTAL

Bovine serum albumin (Loba Chem), Diclofenac sodium (standard) and all others chemicals were of analytical grade.

Melting point was determined by open capillary tube method and is uncorrected. T.L.C was run on silica gel G plates using butanol, ethyl acetate and chloroform (1 : 2 : 1) as developing solvent for the purity of the compounds. IR spectra were recorded on Shimadzu FTIR – 89005 spectrophotometer, by using nujol mull technique.

Preparation of 6-furfuryl-5-cyano-2-mercapto-3, 4-dihydropyrimidin-4-one (I)

Mixture of ethylcyanoacetate (50 mmoles) thiourea (50 mmoles), furfuraldehyde (50 mmoles) and potassium carbonate (50 mmoles) in absolute ethanol (50 mL) was refluxed for 12 hrs and then neutralized with glacial acetic acid. The product was isolated and crystallized from aq. ethanol. The IR of product shows the presence of CN group (2200 cm^{-1}), pyrimidine carbonyl group (1680 cm^{-1}) and aromatic C=C (1600 cm^{-1}).

Preparation of 6-furfural-5-cyano-2-methyl thio-3-N-methyl-3, 4-dihydropyrimidin-4-one (II)

The above synthesized product (10 mmoles) in DMF (20 mL), potassium carbonate (20 mmoles) and methyl iodide (20 mmoles) were mixed and stirred for 3 hrs. Then reaction mixture was diluted with cold water and neutralized by glacial acetic acid. The product was crystallized from dioxan. The IR of the product shows the presence of CN group (1617 cm^{-1}), pyrimidine carboxyl, C=N-(1542 cm^{-1}), N-methyl (2820-2760 cm^{-1}) and for S-methyl (1330 cm^{-1}) groups.

Preparation of 6-furfuryl-5-cyano-2-hydrazino-3-N-methyl-3, 4-dihydropyrimidin-4-one (III)

The compound **(II)** (10 mmoles) and hydrazine hydrate (30 mmoles) in absolute ethanol was refluxed for 10 hrs. Then the reaction mixture was poured into ice, the product was crystallized by DMF. The IR spectrum shows -NH-NH_2 stretching (3425 cm^{-1}), CN group (2300 cm^{-1}), and primary amino wagging (909 to 666 cm^{-1}).

General procedure for preparation of furfuryl substituted pyrimidinoimidazolinones (IV)

The mixture of **(III)** (0.005 mol) and separately prepared azalactones of aromatic, substituted aromatic and heterocyclic aldehyde (0.005 mol) was refluxed in presence of dry pyridine for 6 hrs. Then the reactant mass was poured into the crushed ice and acidified with dilute hydrochloric acid. The product was crystallized by suitable solvent. The IR spectrum of the product shows the presence of CN group (2250 cm^{-1}), pyrimidine (1675 $cm^{-1)}$ and imidazolinone ring (1700 cm^{-1}), C=C (1600 cm^{-1}) and C=N (1400 cm^{-1}) of the aromatic ring system.

Material and methods

The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique, which was studied according to Muzushima and Kabayashi with slight modification[16, 17].

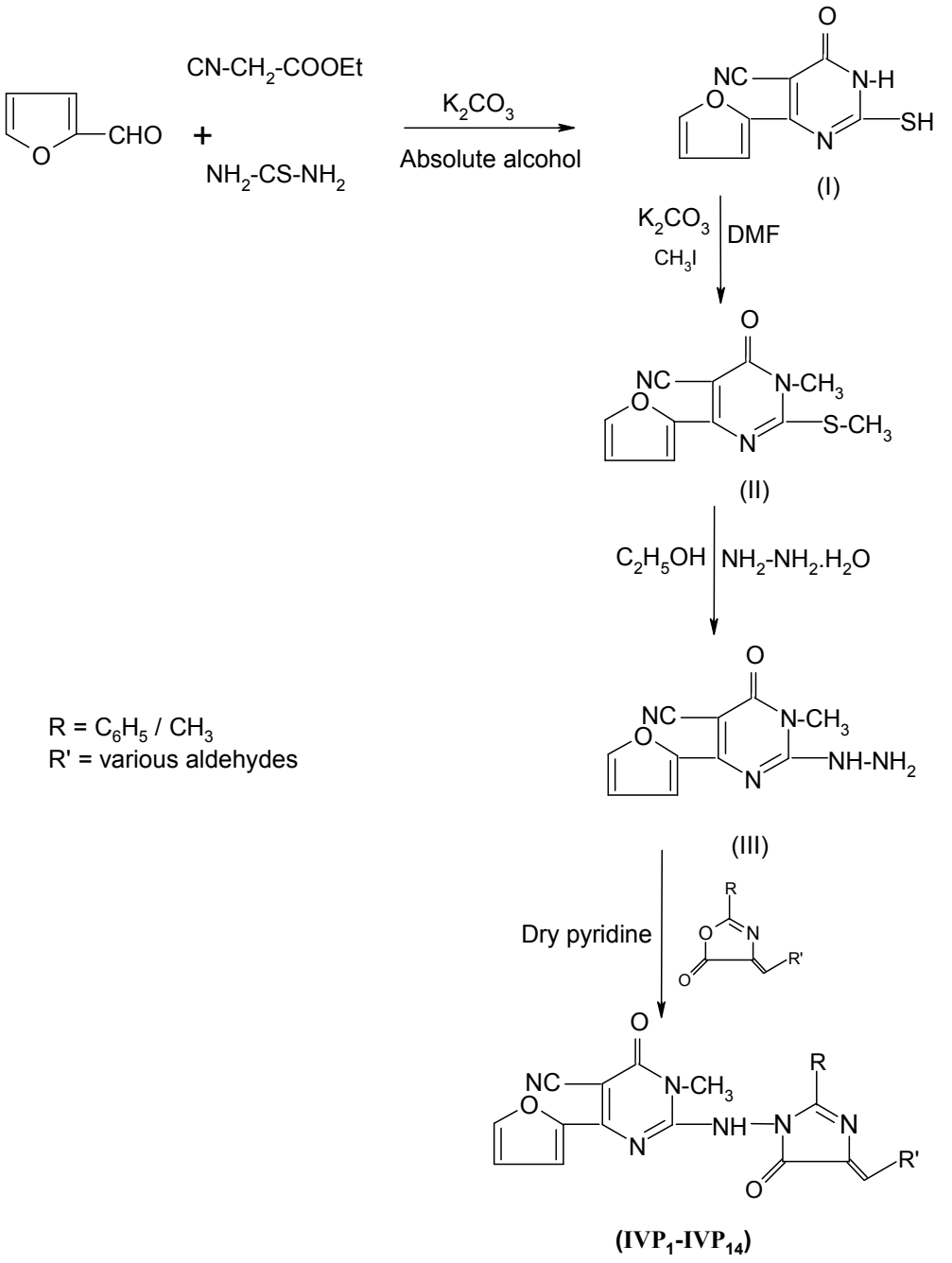
The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.5%. Test solution (1 mL) containing different concentrations of drug was mixed with 1 mL of 1 mM albumin solution in phosphate buffer and incubated at 27˚ ± 1˚ C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60˚ ± 10˚ C in water bath for 10 min. After cooling, the turbidity was measured at 660 nm (UV-Visible Spectrophotometer SL-159, Elico India Ltd.). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The diclofenac sodium was used as standard drug.

RESULTS AND DISCUSSION

Synthesised compounds of furfuryl substituted pyrimidinoimidazolinones were tested for anti-inflammatory activity by *in vitro* model method compared to standard diclofenac sodium and they showed acceptable anti-inflammatory activity.

Table 1. Analytical data

Comp. code	% Yield	M. P.	Mol. formula	M. Wt.	% Calculated		
					C	H	N
IV P_1	60	107	$C_{26}H_{18}O_3N_6$	462	67.53	3.89	18.18
IV P_2	68	147	$C_{26}H_{17}O_3N_6Cl$	495.5	62.90	3.40	16.90
IV P_3	67	152	$C_{26}H_{17}O_5N_7$	507	61.53	3.35	19.32
IV P_4	59	112	$C_{27}H_{20}O_5N_6$	508	63.77	3.90	16.53
IV P_5	70	109	$C_{27}H_{20}O_4N_6$	492	65.80	4.06	17.07
IV P_6	67	107	$C_{28}H_{23}O_3N_7$	505	66.53	4.50	19.40
IV P_7	59	179	$C_{26}H_{18}O_4N_6$	478	65.20	3.70	17.50
IV P_8	67	144	$C_{28}H_{20}O_3N_6$	488	68.85	4.09	17.20
IV P_9	74	179	$C_{24}H_{16}O_4N_6$	452	63.70	3.53	18.58
IV P_{10}	74	116	$C_{21}H_{16}O_3N_6$	400	63.00	4.00	21.00
IV P_{11}	75	162	$C_{20}H_{15}O_3N_6Cl$	421.5	56.93	3.50	19.92
IV P_{12}	70	152	$C_{21}H_{15}O_5N_7$	445	56.62	3.30	22.00
IV P_{13}	71	129	$C_{22}H_{18}O_5N_6$	446	59.10	4.00	18.80
IV P_{14}	82	134	$C_{22}H_{18}O_4N_6$	430	61.30	4.10	19.50


CN-CH2-COOEt
CHO
+
NH2-CS-NH2
K2CO3
Absolute alcohol
(I)
K2CO3
CH3I
DMF
(II)
C2H5OH
NH2-NH2.H2O
(III)
R = C6H5 / CH3
R' = various aldehydes
Dry pyridine
(IVP1-IVP14)

Scheme

Table 2. Anti-inflammatory activity

Compound code	Absorbance value (Mean ± SE)	Inhibition of denaturation (%)
Control	0.087 ± 0.001	-
IV P_1	0.105 ± 0.001	20.68
IV P_2	0.103 ± 0.001	18.39
IV P_3	0.097 ± 0.002	11.49
IV P_4	0.098 ± 0.001	12.64
IV P_5	0.099 ± 0.001	13.79
IV P_6	0.100 ± 0.002	14.94
IV P_7	0.101 ± 0.003	17.20
IV P_8	0.105 ± 0.002	20.68
IV P_9	0.110 ± 0.003	26.43
IV P_{10}	0.111 ± 0.001	27.58
IV P_{11}	0.102 ± 0.002	17.24
IV P_{12}	0.110 ± 0.001	26.43
IV P_{13}	0.105 ± 0.001	20.68
IV P_{14}	0.104 ± 0.002	19.54
Diclofenac sodium	0.363 ± 0.004	83.33

Among compounds tested, IV P_1, IV P_3, IV P_8, IV P_9, IV P_{10}, IV P_{11} and IV P_{12} showed promising anti-inflammatory activity.

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