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Synthesis & Evaluation of Pyrrole Derivative Conjugates as Effective Nsaid's:

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Abstract:- The anti- inflammatory, analgesic, & antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions & side effects. The prototype is aspirin; hence these compounds are also referred to as aspirin- like drugs; they are also frequently called as Non Steroidal anti-inflammatory drugs, or NSAID's. The pyrrole derivatives have been shown to have varying degree of analgesic, anti-inflammatory, & antipyretic activities [1, 10]. On the basis of this observation the present work was designed to synthesize some pyrrole derivative conjugates with some standard NSAID's & evaluate those conjugates for their anti-inflammatory activity. There are tremendous possibilities that such conjugates may be useful in the treatment of various inflammatory disorders, with lower incidence of GI ulceration. This may be due to the presence of pyrrole ring which acts as the basic template of COX-2 inhibition and not COX-1 which protects the GI tract.

Keywords:- *Pyrrole, Anti Inflammatory, COX, NASID'S.*

I. INTRODUCTION

Now a day's wide interest has been developed in synthesis of heterocyclic molecules which possess wide range of therapeutic applications. The anti- inflammatory, analgesic, & antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions & side effects [4]. The prototype is aspirin; hence these compounds are also referred to as aspirin- like drugs; they are also frequently called as ***Non Steroidal anti-inflammatory drugs, or NSAID's*** [2]**.** The pyrrole derivatives have been shown to have varying degree of analgesic, anti-inflammatory, & antipyretic activities [3]. On the basis of this observation the present work was designed to synthesize some pyrrole derivative conjugates with some standard NSAID's & evaluate those conjugates for their anti-inflammatory activity.

II. MATERIALS & METHODOLOGY

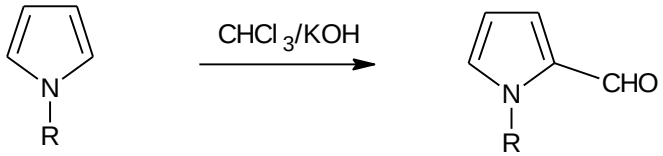
All the chemicals were of laboratory grade & were purified by the established methods. Melting points were determined in open capillary tubes & are uncorrected. Purity & homogeneity of the synthesized compounds was routinely ascertained by TLC on glass plates using silica gel G as adsorbent and solvent system benzene: methanol (1:1). Spots were visualized by iodine vapor or by irradiation with UV light (254 nm). IR spectra were recorded using KBr disc on FTIR 8010 Shimadzu model. Mass spectra of the synthesized compounds were recorded using double focusing mass spectrometer. Anti-inflammatory activity was performed on albino rats (100-150g) by paw edema method using Indomethacin as reference standard [12, 13].

EXPERMENTAL

1. Synthesis of Pyrrole-2-Carboxylic acid:

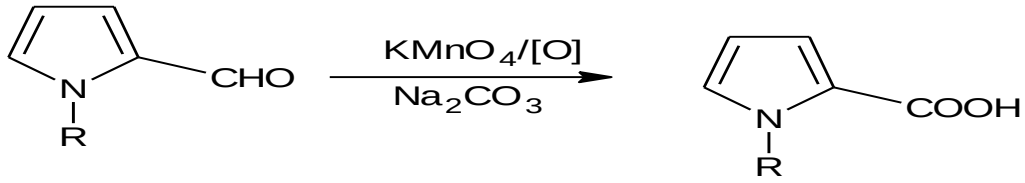
The synthesis of pyrrole-2-carboxylic acid was achieved in two steps:

a)**Synthesis of pyrrole-2-carbaldehyde:**



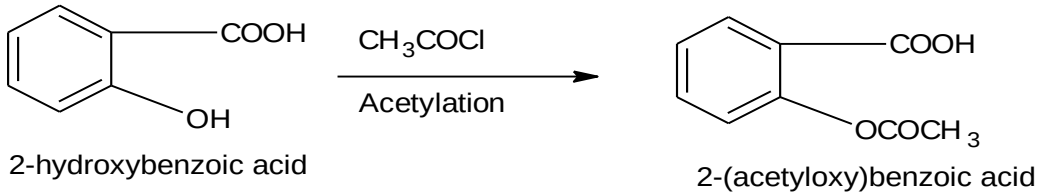
50 ml of chloroform was taken in a 250 ml conical flask and to it slight excess KOH solution (55ml) was added. The mixture was stirred on a magnetic stirrer without external warming. 25ml pyrrole was then added drop wise & mixture was allowed to stir on a magnetic stirrer for about 2.5 hrs. After the completion of stirring the mixture was extracted thrice with ether (10ml). The organic layer was separated and the ether was evaporated. Finally the residue was distilled off to get pyrrole-2-carbaldehyde [5, 6]. Yield=66%.

b)Synthesis of Pyrrole-2-carboxylic acid:



About 20ml of pyrrole-2-carbaldehyde was taken in a 250ml conical flask and to it 15ml of saturated $KMnO_4$ solution and 0.5 gm of Na_2CO_3 were added. The mixture was then warmed on a water bath for 20 minutes. Then the resulting mixture was acidified using conc. HCl, and then 25% solution of sodium sulphite was added until the precipitated manganese dioxide got re-dissolved. The mixture was then cooled to give the precipitate of pyrrole-2-carboxylic acid [6, 12]. Yield=63%.

2. Synthesis of Pyrrole derivative conjugates of NSAID's (Salicylic Acid):
Protection of the phenolic "-OH" group of salicylic acid by acetylation:

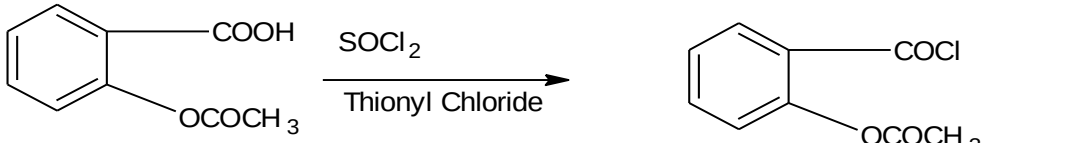


2-hydroxybenzoic acid

2-(acetyloxy)benzoic acid

10 gm of salicylic acid was dissolved in 7ml of dry pyridine in a 250ml conical flask. After that 7.5ml of acetyl chloride was added (adding 1ml each time) and the mixture was shaken continuously. The mixture was then heated on a water bath for 5 minutes and than after cooling it was poured into 300ml of cold water. The crude acetyl salicylic acid separated as a white precipitate, which was than filtered off & then recrystalized from equimolar mixture of water & acetic acid. The acetyl salicylic acid was obtained as white crystals [12]. Yield=70%.

Chlorination of acetyl salicylic acid to its acid chloride:

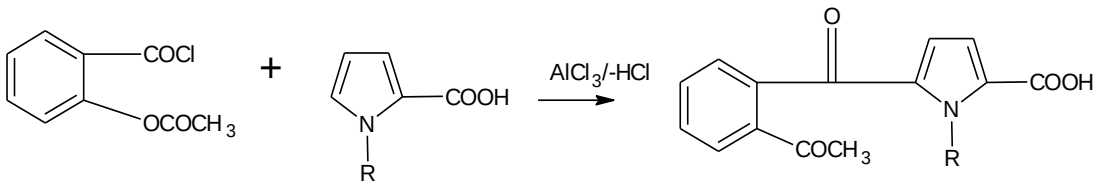


2-(acetyloxy)benzoic acid

2-(chlorocarbonyl)phenyl acetate

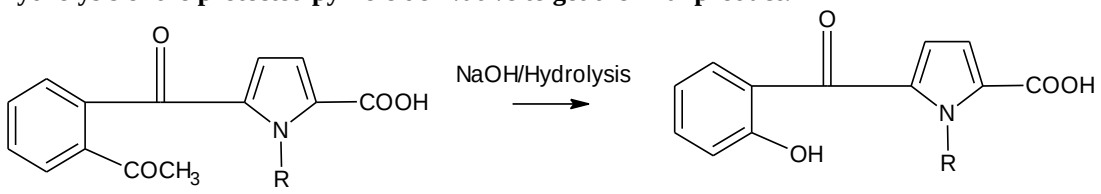
An equimolar quantity of acetyl salicylic acid was taken in a 250ml conical flask & to it about 20ml of chloroform was added. Than to it 1gm K_2CO_3 was added and the mixture was stirred at room temperature. Than to it 5ml of thionyl chloride was added drop wise and the mixture was allowed to stir for 30 min. After that the excess of thionyl chloride and chloroform was evaporated to get the acid chloride [6, 11]. Yield=59.5%.

Treatment of the acid chloride with pyrrole-2-carboxylic acid to get the protected pyrrole derivative:



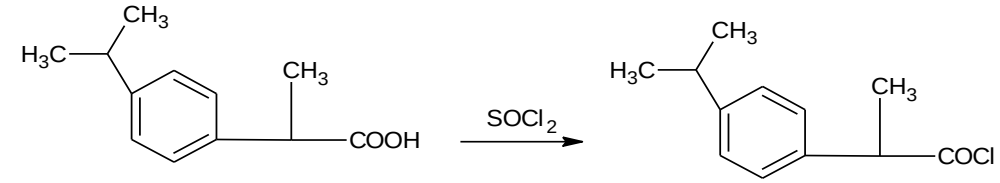
6gm of finely powdered aluminum chloride was taken in a 250ml RBF fitted with a reflux condenser. Equimolar quantities of the acid chloride and pyrrole-2-carboxylic acid were dissolved in about 20ml chloroform and this mixture was added in the RBF. The reaction mixture was then refluxed on the water bath for 30 minutes at 50^0C. Steady evolution of hydrogen chloride gas occurred. When the evolution of hydrogen chloride gas ceased the mixture was then poured into about 50ml of cold water. Immediately the yellow colored protected pyrrole derivative separated off**.** It was then washed with dilute NaOH to remove the traces of hydrogen chloride. The product was then filtered off and was recrystallized from ethanol [7]. Yield=56.2%.

Hydrolysis of the protected pyrrole derivative to get the final product:



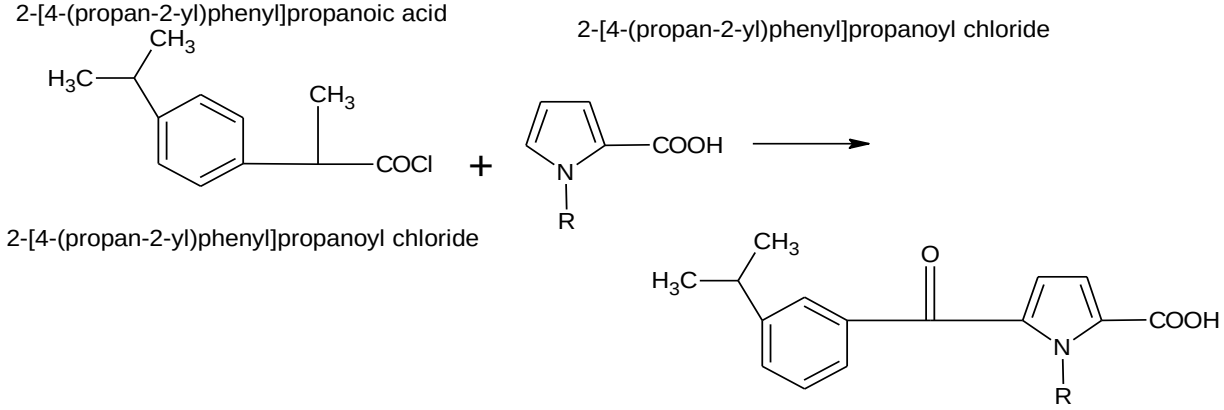
5gm of the protected pyrrole derivative was taken in a 250ml RBF and to it 25ml of 10% NaOH solution was added. The resulting mixture was refluxed on a boiling water bath for about 30 minutes until a clear solution was obtained. Then this solution was cooled thoroughly in an ice bath and 50% H_2SO_4 was added until the solution was just acidic to litmus paper. The precipitated product (I) was filtered through suction and was recrystallized from ethanol to give [5(2-hydroxy) phenyl keto pyrrole-2-carboxylic acid] (I) as the final product [7, 9]. Yield= 56%.

3. Synthesis of Pyrrole derivative conjugates of NSAID's (Ibuprofen):



2-[4-(propan-2-yl)phenyl]propanoic acid

2-[4-(propan-2-yl)phenyl]propanoyl chloride



2-[4-(propan-2-yl)phenyl]propanoyl chloride

Chlorination of Ibuprofen to its acid chloride:

An equimolar quantity of acetyl salicylic acid was taken in a 250ml conical flask & to it about 20ml of chloroform was added. Than to it 1gm K_2CO_3 was added and the mixture was stirred at room temperature. Than to it 5ml of thionyl chloride was added drop wise and the mixture was allowed to stir for 30 min. After that the excess of thionyl chloride and chloroform was evaporated to get the acid chloride [11, 12]. Yield=65%.

Synthesis of the pyrrole derivative conjugate of Ibuprofen:

6gm of finely powdered aluminum chloride was taken in a 250ml RBF fitted with a reflux condenser. Equimolar quantities of the acid chloride and pyrrole-2-carboxylic acid were dissolved in about 20ml chloroform and this mixture was added in the RBF. The reaction mixture was then refluxed on the water bath for 30 minutes at 50^0C. Steady evolution of hydrogen chloride gas occurred. When the evolution of hydrogen chloride gas ceased the mixture was then poured into about 50ml of cold water. Immediately the yellow colored protected pyrrole derivative separated off**.** It was then washed with dilute NaOH to remove the traces of hydrogen chloride. The product was then filtered off and was recrystallized from ethanol [7]. Yield=68.6%.

SPECTRAL CHARACTERIZATION [8, 13]**:**

Table 1: Melting points and I.R. spectral interpretation of compounds:

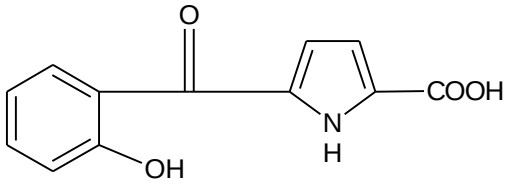
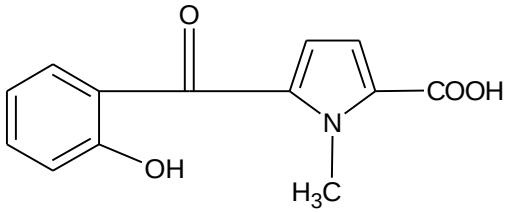
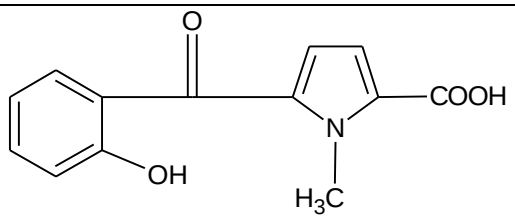
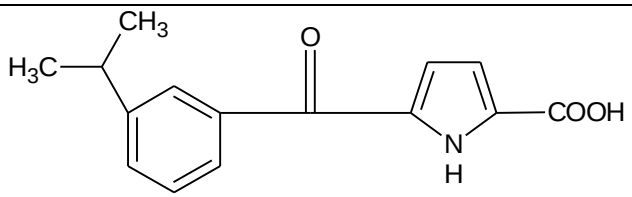
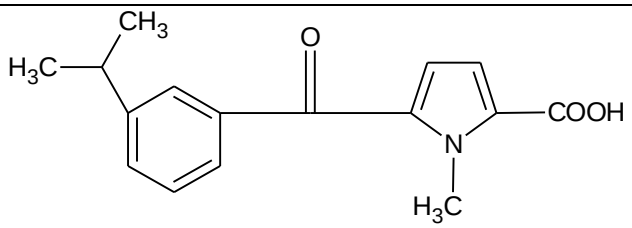
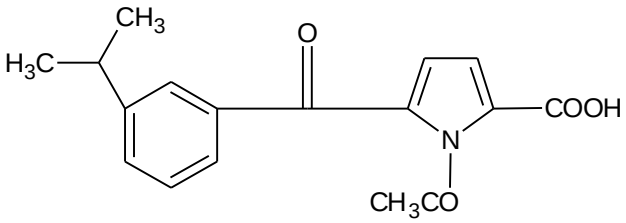
S.No	Structure of the compound	Melting point (^{0}C)	I.R. Spectra (cm^{-1})
1		150-162	N-H str. (pyrrole ring)=3267.19 C=O str. (COOH gp)=1670.24 O-H str. (COOH gp)=2977.89 C-H str. (benzene ring)=3136.04
2		175-190	C-N str. (pyrrole ring)=1296.08 C=O str. (COOH gp)=1658.67 O-H str. (COOH gp)=2854.45 C-H str. (benzene ring)=2360.71
3		210-220	C-N str. (pyrrole ring)=1087.78 C=O str. (COOH gp)=1631.09 O-H str. (COOH gp)=2358.78 C-H str. (benzene ring)=2989.4
4		234-250	N-H str. (pyrrole ring)=3266.19 C=O str. (COOH gp)=1670.24 O-H str. (COOH gp)=2977.89 C-H str. (benzene ring)=3063.36
5		240-260	C-N str. (pyrrole ring)=1278.72 C=O str. (COOH gp)=1672.17 O-H str. (COOH gp)=2318.53 C-H str. (benzene ring)=2989.46
6		272-280	C-N str (pyrrole ring)=1263.29 C=O str. (COOH gp)=1670.24 O-H str. (COOH gp)=2310.27 C-H str. (benzene ring)=2929.67

Table 2: Mass spectral interpretation of compounds [8, 13]**:**

S.No.	Compound	Molecular mass	m/z value (M^++1 peak)
1.	I	232	233
2.	III	272	273
3.	IV	298	299.1
4.	VI	340	341.2

PHARMACOLOGICAL SCREENING [14, 15]**:**

The compounds were screened at 20mg/kg subcutaneously in rats for anti-inflammatory activity using paw edema method. Synthesized compounds were administered by s.c. route and paw edema tests were performed for each compound. In paw edema test, the compounds were found to be active in a dose of 20mg/kg. The abolition or reduction in paw volume was recorded as a measure of anti-inflammatory activity.

Table-3: Anti-inflammatory action of Indomethacin, Compound-I and II in carrageenan induced rat paw edema

S.No.	No. of animals used	Average body wt. (gm)	Treatment	Dose (mg/kg)	Mean paw swelling	% edema inhibition
1	4	155	Control	-	0.3	-
2	4	167	Indomethacin	20, s.c.	0.18	40
3	4	175	Compound I	20, s.c.	0.14	53.33
4	4	182	Compound II	20, s.c.	0.17	43.33

Table-4: Anti-inflammatory action of Indomethacin, Compound-III and IV in carrageenan induced rat paw edema

S.No.	No. of animals used	Average body wt. (gm)	Treatment	Dose (mg/kg)	Mean paw swelling	% edema inhibition
1	4	155	Control	-	0.3	-
2	4	167	Indomethacin	20, s.c.	0.18	40
3	4	182	Compound III	20, s.c.	0.15	50
4	4	182	Compound IV	20, s.c.	0.12	60

Table-5: Anti-inflammatory action of Indomethacin, Compound-V and VI in carrageenan induced rat paw edema

S.No.	No. of animals used	Average body wt. (gm)	Treatment	Dose (mg/kg)	Mean paw swelling	% edema inhibition
1	4	155	Control	-	0.3	-
2	4	167	Indomethacin	20, s.c.	0.18	40
3	4	182	Compound V	20, s.c.	0.16	46.66
4	4	182	Compound VI	20, s.c.	0.10	66.66

III. CONCLUSION

From anti-inflammatory screening of the synthesized compounds it is clear that percent edema inhibition increases in case of conjugates with pyrrole or N-acetyl pyrrole residues then in compounds with N-methyl pyrrole residue when compared with that of Indomethacin as the standard. Thus there are tremendous possibilities that such conjugates may be useful in the treatment of various inflammatory disorders, with lower incidence of GI ulceration. This may be due to the presence of pyrrole ring which acts as the basic template of COX-2 inhibition and not COX-1 which protects the GI tract.

ACKNOWLEDGEMENT

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