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Synthesis, Characterization and Biological Evaluation of Some 2, 4-Dimethyl-(1-Oxo-1H-Inden-2-Ylidene)-Methyl-1H-Pyrrole-3-Carboxamides

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Keywords: 1*H*-pyrrole-carboxamides, indanone , anti-fungal activity, Cork-Borer method, anti-inflammatory, protein denaturation.

ABSTRACT

An effort was carried out to synthesise some 1-oxo-1*H*-inden-2-ylidene-1*H*-pyrrole-carboxamide derivatives by conventional method. Different primary amines were reacted with N-substituted-2,4-dimethyl-1*H* -pyrrole-3-carboxamide and indanone respectively. This method provides a simple and an effective means for the synthesis of huge number of 1*H*-inden-2-ylidene-1*H*-pyrrole-carboxamides. All the synthesised compounds were evaluated for *Invitro* antifungal and anti-inflammatory activities. From the biological studies, it was well understood that 1-oxo-1*H*-inden-2-ylidene-1*H*-pyrrole-carboxamides were showing good anti-inflammatory property. Among the ten synthesised compounds, INS-IV/AIN having di 1*H*-inden-1-yl substitutions at 3rd and 5th position on 1*H*-pyrrole-3-carboxamide showed significant anti-inflammatory activity by protein denaturation method. In addition, it also showed potent anti-fungal activity by Cork-Borer method with good zone of inhibition at all the three concentrations 3mg/ml, 5mg/ml and 7mg/ml. Further the compounds, INS-IV/IPA and INS-IV/DEA were also found to have better anti-inflammatory activity. Thus, from this study, it can be concluded that the N-(2,3dihyro-1*H*-inden-1-yl)-carboxamide substitution at the 3rd position could impart in the improvement of biological activities of the scaffold 1*H*-pyrrole.

INTRODUCTION

Drug resistance is becoming a major problem in the treatment of diseases. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Pyrrole is a five membered ring composed of four carbon atoms and one nitrogen atom with the formula C_4H_4NH. Another moiety worthwhile to be mentioned is indanone which is a polynuclear hydrocarbon derivative with molecular formula C_9H_8O. It has a six membered benzene ring fused with a five membered cyclopentanone ring. Depending on the position of carbonyl functional group it is called as either 1-indanone or 2-indanone. Pyrrole and indanone are important nitrogen-containing aromatic heterocycles found in both plant and animal kingdom because of its participation as a subunit of chlorophyll in plant cells as hemin and vitamin B12 in animal cells. It was revealed that these heterocycles were widely exposed to the therapeutic world, because of their known antibacterial and Antitubercular activities[1], antidiabetic[2], antitumor[3], anti-inflammatory[4] activities. There were also reported for other biological activities like anticonvulsant [5], Nonsteroidal Aromatase Inhibitor [6] and antimicrobial[7] activities.

Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as, the increase of vascular permeability, increase of protein denaturation and membrane alteration. Several experimental protocols of inflammation are used for evaluating the potency of drugs. Denaturation of proteins is one of the main factors for causing inflammation. The increase of protein denaturation was inhibited by using chemically active compounds which inhibits the protein denaturation process[8]. The management of inflammation related diseases is a real issue in the rural community.

Infectious diseases caused by fungi are a major threat to public health, despite the tremendous progress in human medicine. Symptoms of fungal infections differ depending on the type and severity of infection. Itching of the feet, scaling and flaking of the skin feet, red itchy area on the scalp, hair loss in the affected area, lesions or sores that are yellow- white colour appear in throat and tongue, sore, bleeding gums. Most of the yeast infections, such as vaginal thrush, oral thrush and fungal gastroenteritis are caused by fungus *Candida albicans*. Fungus can also cause infections of the lungs due to inhaled fungal spores. Their impact is particularly large in developing countries due to the relative unavailability of medicines and the emergence of widespread drug resistance. Research on new antimicrobial substances must therefore be continued and all possible strategies should be explored.

MATERIALS AND METHODS

Chemistry: Synthesis of indanone from cinnamic acid

Step 1: Synthesis of 3-phenyl propanoic acid from cinnamic acid.

Into a clean and dry 1L hydrogenator kettle, cinnamic acid 25g (0.1689moles) and methanol 250ml and Raney-Ni (wet 20g) were charged. The kettle was fixed to the hydrogenator and agitated under hydrogen pressure (40-60psig). After completion of the reaction the catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure to get 3-phenyl propanoic acid as white solid.

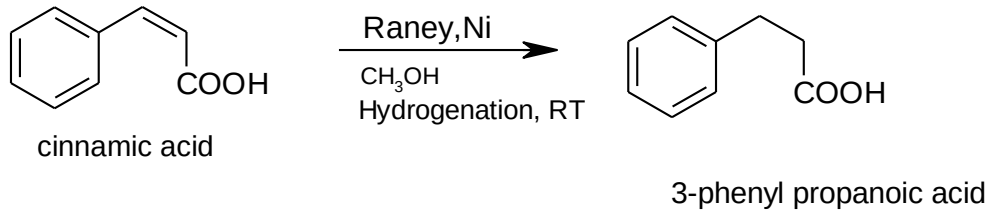


Fig.1: Synthesis of 3-phenyl propanoic acid from cinnamic acid.

Step 2: Synthesis of 3-phenyl propanoyl chloride from 3-phenyl propanoic acid

Into a clean and dry 4 necked 1L round bottom flask fitted to a mechanical stirrer, thermometer socket, reflux condenser and guard tube, 3-phenyl propanoic acid 20g(0.133moles) and 100ml of chloroform were charged. After dissolution, thionyl chloride 24.02g (0.2018moles) was added dropwise through addition funnel to the solution. After addition, the solution was heated to 60-65ºC and maintained for 4-5 h. After completion of reaction the excess solvent was removed by distillation under reduced pressure to get 3-phenyl propanoyl chloride as dark brown colour oily mass. The product was used for next step without further purification.

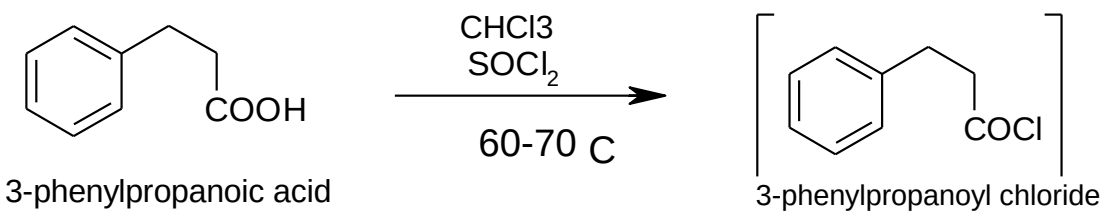


Fig.2. Synthesis of 3-phenyl propanoyl chloride from 3-phenyl propanoic acid

Step 3. Synthesis of 2,3-dihydro-*1H-inden*-1-one from 3-phenyl propanoyl chloride

Into a clean and dry four Necked, 1L round bottom flask fitted with a mechanical stirrer, thermometer socket, reflux condenser and guard tube, 3-phenyl propanoyl chloride 20g (0.119moles), 90ml of chloroform were charged. To the stirred $AlCl_3$ 18g (0.133moles) was added in 4 equal lots to the reaction mixture at room temperature. After addition of $AlCl_3$ the solution was stirred for overnight at room temperature under dry atmosphere. After completion of reaction the complex was decomposed in a beaker containing aq.HCl (chilled). The product was extracted with chloroform and distilled off the solvent completely to get 1-indanone as low melting brown solid. The solid was further purified by high vacuum distillation to get highly crystalline solid.

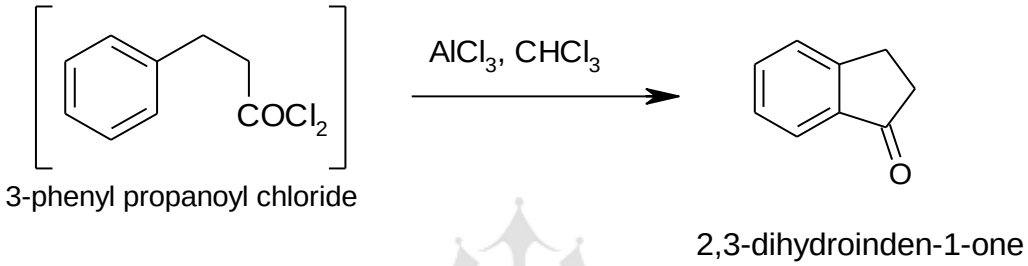


Fig.3: Synthesis of 2,3-dihydro-1H-inden-1-one from 3-phenyl propanoyl chloride

Step 4: Synthesis of 5-formyl-N-(substituted) 2,4-dimethyl-*1H-pyrrole*-3-carboxamide

Into a 250ml four necked round bottomed flask equipped with a mechanical stirrer, guard tube and T-socket added 5-formyl-2,4-dimethyl-*1H-pyrrole*-3-carboxylic acid (1.0mol), THF as solvent and allowed to mix well under stirring. HOBT (1.5mol) and DCC (1.4mol) were added slowly to the above reaction mixture while stirring. 25mins after stirring triethylamine TEA (2.0mol) was added drop wise using an addition funnel, this turns the reaction mixture into brown colour. Desired primary amine (1.38mol) was added at this stage and left the reaction mixture to stir for overnight at RT. The reaction is then transferred onto a water bath (60ºC) after 24h. The obtained mass was filtered in a sintered flask and washed with methanol, recyrstallised with boiling methanol to obtain pure product (Fig.4).

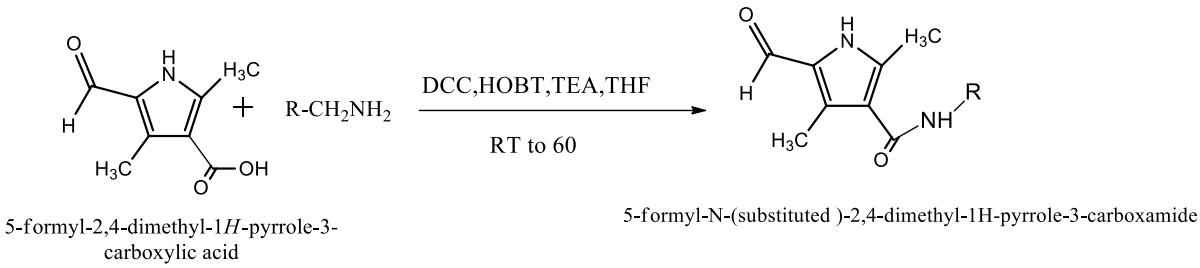


Fig.4: Synthesis of 5-formyl-N-(substituted) 2,4-dimethyl-1H-pyrrole-3-carboxamide

Step 5: Synthesis of N-(substituted)-2, 4-dimethyl-5-((E) (1-oxo-*1H-inden*-2-ylidene)-methyl)-*1H-pyrrole* carboxamides

Into a 100ml RBF equipped with a magnetic stirrer with hot plate, condenser, guard tube, N-(substituted) 2,4-dimethyl-*1H-pyrrole*-3-carboxamide (1.0mol) and indanone (0.96mol) were added and allowed to stir with addition of methanol as solvent . 2-3 drops of pyrrolidine was added drop wise this acts as base. The reaction mixture was heated to reflux for 2h. After completion of the reaction, the content was filtered in a sintered flask, the solid obtained was washed and recyrstallised from boiling methanol (Fig.4).

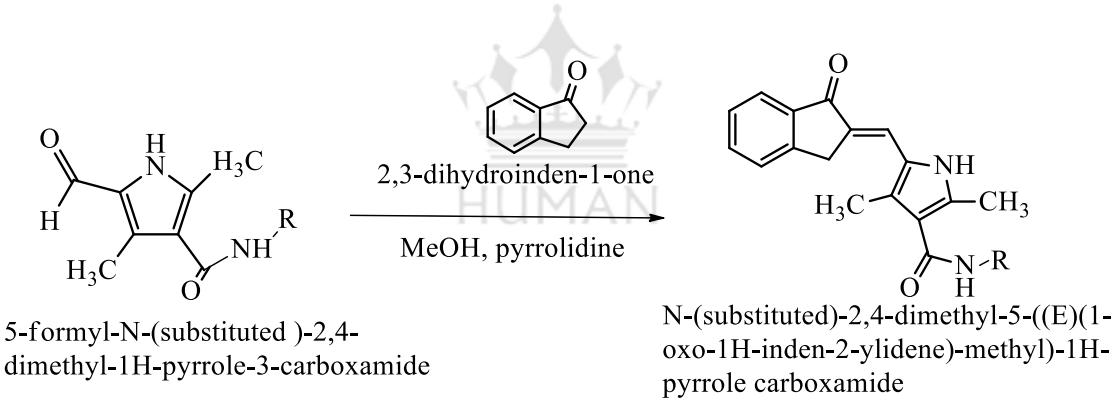


Fig.5. Synthesis of N-(substituted)-2, 4-dimethyl-5-((E) (1-oxo-1H-inden-2-ylidene)-methyl)-1H-pyrrole carboxamides

The melting point of the synthesized compounds was found out by using one-end open capillary tubes in scientific melting point apparatus. The advancement in the reaction was monitored by using pre-coated silica gel TLC plates. The purity of the compounds were checked using TLC plates which were run in solvent systems like hexane:ethylacetate (1:1) or chloroform: methanol (9:1) depending on the polarities of the compounds. The spots on the TLC were visualized under UV light. Characterization of the compounds was done by IR spectrometer. Proton and carbon-13 NMR spectra were recorded on Bruker 400Hz ultra shield. Mass spectra of the synthesised compounds were recorded on ESI-MS.

Biological evaluation

***Invitro* Anti-fungal Activity**

The anti-fungal activity of the synthesized compounds was carried out by Cork-Borer method. *Aspergillus Niger* (NCIM 1196) test strain maintained on PDA, sub cultured and served as test pathogen for the assay. Standard drug used for this evaluation was 1mg of Voricanazole in 10 ml of DMSO (0.1mg/ml). Samples were prepared at a concentration of 3mg/ml, 5mg/ml, and 7mg/ml. Agar media plates were prepared by using the following composition (gm/lt) and sterilized by using autoclave at 121°C for 15min. Bacto peptone- 9.4gm, Yeast extract – 4.7g, Beef extract – 2.4gm, Sodium chloride – 10gm, Dextrose anhydrous – 10gm, Agar -23.5gm. Inoculum was prepared by washing a slant of Aspergillus Niger with 5 ml sodium chloride.1% of inoculum was added to 25 ml melted medium at temperature 45 –50ºC and plates were prepared. Bores of diameter of 7 mm were made in to the agar plates with sterile borer and filled with 30µl drug. The plates were incubated at 28 ±1ºC temperature for 72 h. Zone of inhibition was measured and results were compared with that of standard Voricanazole [9].

Invitro Anti-inflammatory Activity

The inhibition of protein denaturation was measured as a parameter of compounds having anti-inflammatory activity. The procedure involves, the preparation of test solutions of each compound having 100 µg/ml concentration using DMSO and PBS buffer (pH: 6.4). The final test and control samples were prepared as it contains 2% of DMSO concentration. The reaction mixtures of total volume of 5ml were prepared as follows:

Test: 0.2 ml egg albumin + 2.8 ml PBS + 2.0 ml varying concentrations of drug

Control: 0.2 ml egg albumin + 0.1 ml DMSO + 4.7 ml PBS

Blank: PBS (pH: 6.4).

After preparation of sample mixtures, they were incubated at 37 ^{0} C in a BOD incubator for 15 minutes. Then they were kept in hot water bath at 70^{0}C for 5 minutes. After cooling, the absorbance was measured at 660 nm using UV visible Spectrophotometer [10]. The percentage inhibition of protein denaturation was calculated.

$$\% \text{ inhibition} = 100 \text{ X } (Vt / Vc - 1)$$

Where, Vt = absorbance of test sample,

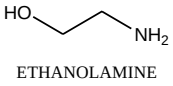
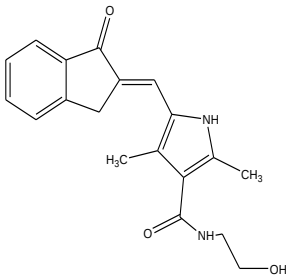
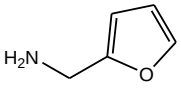
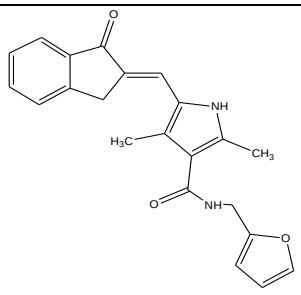
Vc = absorbance of control

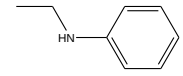
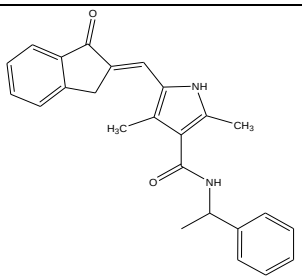
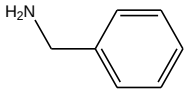
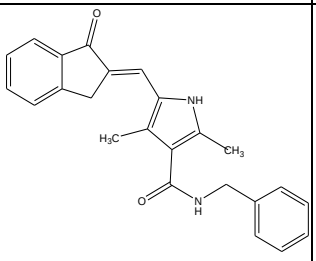
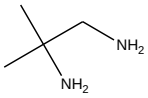
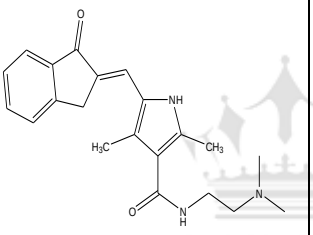
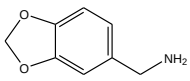
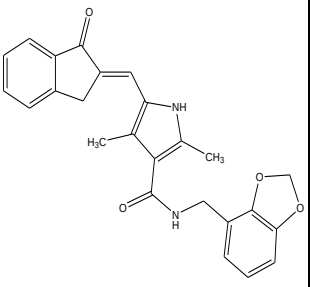
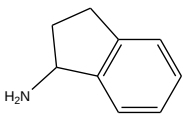
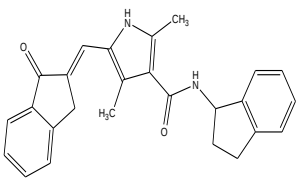
RESULTS AND DISCUSSION

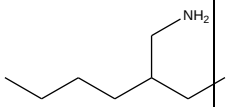
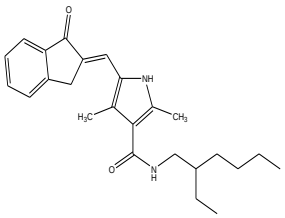
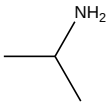
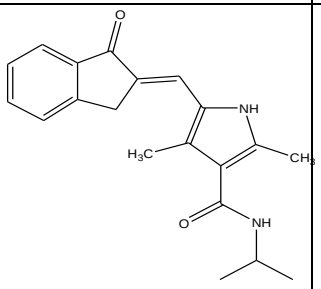
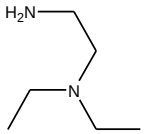
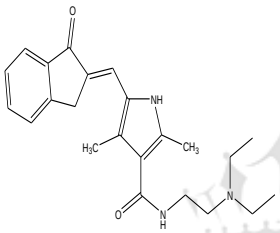
Chemistry

Indanones and pyrroles have wide spectrum of biological activities like antimicrobial, anticonvulsant, antimalarial because of these observations, it was decided to undertake the investigation to synthesise a new series of 1-oxo-*1H-inden*-2-ylidene-*1H-pyrrole*-carboxamide derivatives. In the present study, totally 10 compounds of 1-oxo-*1H-inden*-2-ylidene-*1H-pyrrole*-carboxamide derivatives were synthesised (Table 1). The addition of different primary amines followed by condensation of N-(substituted)- 2,4-dimethyl-*1H-pyrrole*-3-carboxamide with indanone in the presence of pyrrolidine and MeOH resulted in the formation of the N-(substituted)-2,4-dimethyl-(1-oxo-*1H-inden*-2-ylidene)-*1H-pyrrole*-carboxamides(Fig.5) respectively. The progress and the completion of reaction were monitored by TLC method using hexane: ethylacetate (1:1) or chloroform: methanol (9:1) mixture. The melting points of the compounds were determined using capillary tubes.

Table 1. List of compounds synthesised

S.NO	R (Amine used)	Molecular structure	IUPAC name	Molecular formula
1	 ETHANOLAMINE		INS-IV/EA: N-(2-hydroxyethyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{19}H_{20}N_2O_3$
2	 Furfurylamine		INS-IV/FA: N-(furan-2-yl)methyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-	$C_{22}H_{20}N_2O_3$

			carboxamide	
3	 (-) phenyl ethylamine		INS-IV/(-)PEA: 2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-N-(1-phenylethyl)-*1H-pyrrole*3-carboxamide	$C_{25}H_{24}N_2O_2$
4	 benzylamine		INS-IV/BA : N-(benzyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{24}H_{22}N_2O_2$
5	 dimethyl ethylene diamine		INS-IV/DMA : N-(2-(dimethylamino)ethyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{21}H_{25}N_3O_2$
6	 3,4methylenedioxy benzylamine		INS-IV/MDB : N-((benzo[d][1,3]dioxol-4-yl)methyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-1Hpyrrole-3-carboxamide	$C_{25}H_{22}N_2O_4$
7	 1-aminomonindane		INS-IV/AIN : N-(2,3dihyro-*1H-inden*-1-yl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{26}H_{24}N_2O_2$

8	 2-ethyl1-hexylamine		INS-IV/EHA : N-(2-ethylhexyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{25}H_{32}N_2O_2$
9	 isopropylamine		INS-IV/IPA : N-(isopropyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{20}H_{22}N_2O_2$
10	 N,N-diethyl ethylene diamine		INS-IV/DEA : N-(2-(diethylamino)ethyl)-2,4-dimethyl-5-((E)(1-oxo-*1H-inden*-2(3H)-ylidene)-methyl)-*1H-pyrrole*3-carboxamide	$C_{23}H_{29}N_3O_2$

The proposed structure of the synthesised compounds was confirmed by UV, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis. All the compounds showed characteristic peaks as expected. The IR spectra of all the 1-oxo-*1H-inden*-2-ylidene-*1H-pyrrole*-carboxamide derivatives were recorded on Bruker FT-IR using KBr pellets. The absorption bands in the regions 1623-1686cm^{-1} and 1539-1659cm^{-1} indicated the presence of C=O and CONH groups respectively. The absorption band due to the N-H group in the pyrrole ring appeared in between 3254-3294cm^{-1} and N-H group in the peptide bond appeared in between 1525-1540cm^{-1}. The aromatic C=C stretching showed a peak in the region 1580-1610cm^{-1}.

The ^{1}H NMR spectra were recorded on Bruker Biospin Avance -400 MHz using d-DMSO as solvent. The chemical shifts were reported in parts per million downfield from tetramethylsilane. The protons of the methyl group in INS-IV/EA showed a singlet at δ2.26-2.13 and at δ2.43-2.46 indicating that both cis and trans forms are present in the compound.

Whereas, in INS-IV/FA showed a sharp singlet at δ2.30 and δ2.45. ^{13}C NMR spectrum were also analysed to confirm the structures. The results were found satisfactory.

In addition to the above data, Mass spectra were recorded on Agilent technologies-6120 Quadrapole LCMS. The M+1 peak of the reference compounds INS-IV/EA, FA, PEA, BA, DMA, MDB, AIN, EHA, IPA, DEA were observed at δ 325.42, 361.2, 385.2, 371.2, 352.3, 415.2, 397.51, 393.3, 323.54 and 380.3.

Biological evaluation

***Invitro*-Antifungal Activity**

All the synthesised compounds with concentrations 3mg/ml, 5mg/ml, 7mg/ml were tested for their anti-fungal activity by Cork-Borer method. The potency of the test compounds was determined based on their zone of inhibition values. Among the tested compounds, INS-IV/AIN exhibited antifungal activity better than other compounds, with zone of inhibition values 0.8cm, 1.6cm, 1cm at 3mg/ml, 5mg/ml, 7mg/ml concentrations respectively as shown in Table 2. Whereas, compounds INS-IV/EA showed 0.6cm zone of inhibition at 3mg/ml and INS-IV/MDB showed zone of inhibition value 0.4cm at 5mg/ml. However, the rest of the synthesised compounds did not show any zone of inhibition at all the three concentrations.

Table 2. Zone of inhibition of test compounds for antifungal activity.

S.No	Sample ID	Concentration of the drugs(mg/ml)	Zone of inhibition (cm)
01	Standard drug (Voricanazole)	0.1	1.4
02	INS-IV/EA	3	0.6
03	INS-IV/EA	5	-
04	INS-IV/EA	7	-
05	INS-IV/FA	3	-
06	INS-IV/FA	5	-
07	INS-IV/FA	7	-
08	INS-IV/(-)PEA	3	-
09	INS-IV/(-)PEA	5	-
10	INS-IV/(-)PEA	7	-

11	INS-IV/BA	3	-
12	INS-IV/BA	5	-
13	INS-IV/BA	7	-
14	INS-IV/DMA	3	-
15	INS-IV/DMA	5	-
16	INS-IV/DMA	7	-
17	INS-IV/MDB	3	-
18	INS-IV/MDB	5	0.4
19	INS-IV/MDB	7	-
20	INS-IV/AIN	3	0.8
21	INS-IV/AIN	5	1.6
22	INS-IV/AIN	7	1
23	INS-IV/EHA	3	-
24	INS-IV/EHA	5	-
25	INS-IV/EHA	7	-
26	INS-IV/IPA	3	-
27	INS-IV/IPA	5	-
28	INS-IV/IPA	7	-
29	INS-IV/DEA	3	-
30	INS-IV/DEA	5	-
31	INS-IV/DEA	7	-

'-' : No zone of inhibition

Invitro Anti-inflammatory activity

Invitro anti-inflammatory activity of the synthesised compounds was tested by seeing the capacity of the compounds to inhibit protein denaturation in egg albumin. The results revealed that compounds INS-IV/EA and INS-IV/MDB were having good % inhibition of protein denaturation which is proportional to their anti-inflammatory activity (Table 3). The compound INS-IV/AIN showed exhibited better anti-inflammatory activity as it had % inhibition of protein denaturation at 25.24 and absorbance at 1.3543. The compounds INS-IV/IPA and INS-IV/DEA showed percentage inhibitory activity 24.94 and 21.76 respectively.

The rest of the compounds were also found to have anti-inflammatory activity but very less, when compared to the standard, Diclofenac sodium.

Table 3. Percentage inhibition of protein denaturation

Compound Code	Absorbance at 660nm	%inhibition of protein denaturation
Control	1.0813	-
SINS-IV/EA	1.2511	15.70
INS-IV/FA	1.2472	15.34
INS-IV/(-)PEA	1.2525	15.83
INS-IV/BA	1.1927	10.30
INS-IV/DMA	1.2785	18.23
INS-IV/MDB	1.2839	18.73
INS-IV/AIN	1.3543	25.24
INS-IV/EHA	1.1257	4.10
INS-IV/IPA	1.3510	24.94
INS-IV/DEA	1.3166	21.76
DICLOFENAC	0.3993	63.07

CONCLUSION

An effort was carried out to synthesise some 1-oxo-*1H-inden*-2-ylidene-*1H-pyrrole*-carboxamide derivatives by conventional method. Different primary amines were reacted with N-substituted-2,4-dimethyl-*1H-pyrrole*-3-carboxamide and indanone respectively. This method provides a simple and an effective means for the synthesis of huge number of *1H-inden*-2-ylidene-*1H-pyrrole*-carboxamides. All the synthesised compounds were evaluated for *Invitro* antifungal and anti-inflammatory activities. From the biological studies, it was well understood that 1-oxo-*1H-inden*-2-ylidene-*1H-pyrrole*-carboxamides were showing good anti-inflammatory property. Among the ten compounds synthesised, INS-IV/AIN showed significant anti-inflammatory activity. In addition, it also showed potent anti-fungal activity with good zone of inhibition at all the three concentrations. Thus, from this study, it can be concluded that the N-(2,3dihyro-*1H-inden*-1-yl)-carboxamide substitution at the 3rd position could impart in the improvement of biological activities of the scaffold *1H-pyrrole*.

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