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ORIGINAL ARTICLE

Synthesis of some novel 2-(4- substituted)-1-H-indole-3-carbaldehyde derivative as potent Anti-inflammatory agents

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ABSTRACT
We have made an attempt in the current study to synthesize eight novel indole derivatives (5a-h) and evaluate them for anti-inflammatory activity using Carrageenan-induced rat paw edema method.In the first step, we synthesized substituted acetophenone phenyl hydrozone(3a-h) by using phenyl hydrazine and substituted acetophenone in the presence of acetic acid and H_2O.The substituted acetophenone phenyl hydrozone(3a-h) was further reacted with Vilsmeier-Hack reagent ($POCl_3$–DMF) at 0-5^{0}C to afforded 2-(4- substituted)-1-H-indole-3-carbaldehyde (5a-h). The final indole derivatives (5a-h) were synthesized and recrystallized using ethanol. The structure of the final compound has been confirmed on the basis of FTIR and ^{1}H NMR. All the values of FT-IR, ^{1}H NMR, melting point, solubility and TLC were found to be prominent. The pharmacological screening by Carrageenan-induced rat paws edema method for anti-inflammatiory activity revels that synthesized compounds 5a and 5f were found to be the most potent with compare to standard drugs Diclofenac sodium.
***Keyword**: Indole,Vilsmeier-Hack reagent, Anti-inflammatory activity, Carrageenan-induced rat paw edema method.*

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INTRODUCTION

Inflammation is portion of the complex biological response of body tissues to harmful stimuli, for example pathogens, damaged cells or irritants, and is a protective response containing immune cells, blood vessels also molecular mediators. The role of inflammation is to remove the initial cause of cell injury, clear out necrotic cells and tissues damaged after the original insult and the inflammatory process formerly to initiate tissue repair. [1]The classical symbols of acute inflammation are pain, redness, swelling and loss of function. Inflammation is a generic response, and therefore it is careful as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen. Too little inflammation could lead to advanced tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a most of diseases such as hay fever, peritonitis, atherosclerosis, rheumatoid arthritis, and even cancer. [2] White blood cells then assist by releasing more cytokines. This link between adiposity and inflammation has been shown to produce 10-35% of IL-6 in a resting individual, and this production increases with increasing adiposity.Loss of white adipose tissue reduces levels of inflammation markers. The association of systemic inflammation with insulin resistance and atherosclerosis is the subject of intense research [3].thus there is a regular need for thr development of compound with a safer and less toxic anti-inflammatory drug [4]. The synthesis of various hetero annulated indole derivative in recent years.

Indole is the most beneficial heterocyclic nucleus which has gained prominence in medicinal chemistry due to its diverse biological activities such as anticonvulsant [5-9], anti-inflammatory [10] antipsychotic [11] Antifungal [12] Antibacterial [13] Antiviral [14] activities. The present work highlights the synthesis of2-(4- substituted)-1-*H*-indole-3-carbaldehyde **(5a-h)**.The newly synthesized indole derivatives were screened *in vivo* for their anti-inflammatory activity by Carrageenan-induced rat paw edema method by using diclofenac as standard drug.

MATERIAL AND METHODS

Experimental

All the chemicals used were procured from Spectrochem Pvt. Ltd., SD Fine Chemical Limited Mumbai and Central Drug House (P) Ltd., New Delhi. Melting point ranges of the newly synthesized compounds were determined by the open capillary method and are uncorrected. Thin Layer Chromatography using silica gel-G (E. Merk) plates was used to access the reaction and purity of the synthesized compounds, on the elemental analyzer. IR spectrum of compounds in KBr pellets was recorded on an FTIR- PerkinElmer Spectrum Version 10.03.06. The proton magnetic resonance spectra were recorded by means of Bruker Advance DX 300 MHz spectrometer using DMSO-d_6 as a solvent and DMSO or TMS as internal standard respectively. The results are presented in the following: chemical shift δ (ppm), multiplicity, values in Hertz (Hz), number of protons, proton's position.

General procedure for synthesis of substituted acetophenone phenyl hydrazone (3a-h)

Phenylhydrazine (0.01mol) was added in glacial acetic acid (10ml) and water (10 ml) to a solution of substituted acetophenone(0.01 mol) in glacial acetic acid (20 ml) contained in a beaker. The mixture was cooled in ice and shaken for 5 min, colourless crystals obtained and filtered, washed with glacial acetic acid and water then dried [15].

General procedure for the synthesis of 2-Substituted-Indole(4a-h)

A solution of compound (3a-h) (0.1mol)and (0.1mol) of polyphosphoric acid was heated with stirring at 100-120°C for 10 min. Add 16 ml of cold water and stir well to complete solution of the polyphosphoric acid. Filter at the pump and wash well with water.Heat the crude solid under reflex with 0.9 ml of rectified spirit,add a little decolourising charcoal and filter through a preheated Buchner funnel wash the residue with hot rectified spirit. The completion of the reaction was monitored by TLC. Cool the combined filtrates at room temperature,filter off the 2-phenylindole and wash it three times with 10 ml portions of cold alcohol.Dry in a vacuum desiccator over anhydrous calcium chloride. The final 2-phenyl indole compound was recrystallized from ethanol [16].

General procedure for the synthesis of 2-(4-Substituted-Indole-3-carboxaldehydes) (5a-h)

Phosphorous oxychloride(0.1mol) was added drop wise to N,N-dimethylformamide (DMF) (0.1mol) under cooling with an ice bath and the reaction mixture was stirred for 2 h. to prepare the Vilsmeier reagent.Then substituted-2-phenyl-1*H*-indole (0.019mol) in DMF (5 ml) was added drop wise into the Vilsmeier reagent with continuous stirring and kept at room temperature for 2 h. The reaction mixture was allowed to stand overnight and was then refluxed for 2 h under vigorous stirring. The mixture was then poured onto ice cold water and neutralized with dilute ammonia solution till the precipitation occurs. The product obtained was collected by filtration and recrystallized from ethanol to give final compound (5a-h) [17].

2-(4-aminophenyl)-1*H*-indole-3-carbaldehyde (5a)

FTIR (KBr ν, cm^{-1}): 1222.87 (C-N), 1290.38(C=C), 1411.89(C=O), 1666.55(C-N), 3091.68 (Ar C-H), 3414.51 (N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):1.25 (m, 1H, Ali-H), 6.61-6.94 (m, 4H, Ar-H), 7.26 (s, 3H, Ar-H),7.64 (m, 4H, Ar-H).

2-(2-bromophenyl)-1-*H*-indole-3-carbaldehyde(5b)

FTIR (KBr ν, cm^{-1}): 677.01(C-Br),1411.86 (Indole,CN), 1553.70(ArC=C), 1637.56(C=O),1666.5 (C-N), 3113.11 (Ar C-H), 3457.47 (N-H). ^{1}H-NMR (300 MHz, DMSO-d_6): 1.25 (m, 2H, Ali-H), 6.61-6.94 (m, 4H, Ar-H), 7.64 (m, 4H, Ar-H).

2-(3,4dimethoxyphenyl)-1-H-indole-3-carbaldehyde (5c)

FTIR (KBr ν, cm^{-1}):1090.38 (C-N), 1348.24(ArC=C), 1492.90 (C=O), 1166.50 (C-N), 3018.52 (Ar C-H), 3097.68 (N-H). ^{1}H-NMR (300 MHz, DMSO-d_6):2.15 (m, 2H, Ali-H), 2.10-3.45 (s, 6H, OCH_3), 6.61-6.94 (m, 4H, Ar-H), 7.26 (s, 3H, Ar-H).

2-(4-nitrophenyl)-1-*H*-indole-3-carbaldehyde (5d)

FTIR (KBr ν, cm^{-1}): 1011.89 (C-N), 1411.89(Ar-NO_2), 1502.55 (ArC=C),1598.99 (C=O), 1666.43 (C-N), 3011.52 (Ar. C-H), 3318.51 (N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):1.10-2.54 (m, 2H, Ali-H), 6.61-6.94 (m, 4H, Ar-H), 7.64 (m, 4H, Ar-H).

2-(3-hydroxyphenyl)-1-*H*-indole-3-carbaldehyde (5e)

FTIR (KBr ν, cm^{-1}): 1340.33(C-N), 1544.98(ArC=C), 1664.57(C=O), 1741.11(C-N), 3113.11 (Ar.C-H), 3355.01 (N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):1.25 (m, 3H, Ali-H), 6.61-6.94 (m, 4H, Ar-H), 7.64 (m, 4H, Ar-H).

2-(4-methoxyphenyl)-1*H*-indole-3-carbaldehyde (5f)

FTIR (KBr ν, cm^{-1}): 1186(C-O),1296.89 (C-N), 1605.15(Ar. C=C), 1711.64 (C=O), 1741.11 (C-N), 3018.52 (Ar. C-H), 3258.51(N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):1.25 (m, 2H, Ali-H), 2.10 (s, 3H, OCH_3), 6.61-6.94 (m, 4H, Ar-H), 7.64 (m, 4H, Ar-H).

2-p-toly-1*H*-indole-3-carbaldehyde (5g)
FTIR (KBr ν, cm^{-1}): 1296.89 (C-N), 1605.15(Ar.C=C), 1711.64(C=O), 1741.11(C-N), 3318.52 (Ar.C-H), 3411.51(N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):2.25 (m, 2H, Ali-H), 6.61-6.94 (m, 4H, Ar-H), 7.26 (s, 3H, Ar-H),7.64 (m, 4H, Ar-H).
2-(phenyl)-1*H*-indole-3-carboxaldehyde (5h)
FTIR (KBr ν, cm^{-1}): 1250.00 (C-N), 1650.15(Ar.C=C), 1780.64(C=O), 1790.11(,C-N), 3080.50 (Ar. C-H), 3310.51**(**N-H); ^{1}H-NMR (300 MHz, DMSO-d_6):10.22-9.3 (m, 2H, Ali-H), 7.8-7.61 (m, 5H, Ar-H), 7.6-7.0 (m, 4H, Ar-H).
Anti-inflammatory activity
The anti-inflammatory activity of newly synthesized Indole derivatives were carried out using carrageenan induced rat hind paw edema method. This method has been approved by the Institutional Animal Ethical Committee at Hygia Institution of Pharmaceutical Education and Research, Lucknow (Ref. No. HIPER/IAEC/21/18/04).The drug used in the study was of pharmaceutical grade. Diclofenac sodium was supplied by A.B Enterprises available in laboratory (HIPER, LUCKNOW).Male wister Albino rat weighing 100-150 g were used for anti-inflammatory activity. They were housed in standard environmental condition like-ambient temperature (25^{o}C±1^{o}C), relative humidity (55^{o}C±5%), and 12/12 hour light dark cycle. Animals had free access to standard pellet diet and water. All animals experiments were carried out in accordance with the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). The institute animal ethical committee has given the approval for conducting animal experiment.

RESULTS AND DISCUSSION
The desired indole derivatives were prepared by multistep reaction summarized in scheme. In the first step, phenyl hydrazine and substituted acetophenone in presence of acetic acid and H_2O afforded the corresponding substituted acetophenone phenyl hydrazine derivatives (3a-h).Substituted acetophenone Phenyl hydrazine derivatives were allowed to react with polyphosphoric acid to give corresponding 2-(substituted)-1*H*-indole (4a-h). 2-(substituted)-1*H*-indole were allowed to react with $POCl_3$ in DMF to gives corresponding 1,3-substituted diphenyl-1*H*-indole-4-carbaldehyde derivatives (5a-h). 1,3-substitutd diphenyl-1*H*-pyrazole-4-carbaldehyde derivatives (5a-h) showed a intense peak in the region 1676 -1600 cm^{-1} due to the C=N stretching vibration which indicate the presence of C=N in indole ring.A strong, characteristic band in the region 1230-1200 cm^{-1} due to the C-N stretching vibration. Peak appeared at 869-820 cm^{-1} due to C=S stretching. Band for aromatic C-H stretching vibrations was observed at 3261-3025 cm^{-1}. Peak for aromatic C-H are generally appeared at longer wavelength than the aliphatic C-H. It is due to the higher stretching of pi-electrons present in aromatic ring.
The anti-inflammatory activity of the other tested compounds was found to be much less effective than diclofenac used as a standard anti-inflammatory drug. According to the results obtained it seems that the presence of the amino group is potency.

Table 1: Characterization data of the synthesized compound (3a-h)

Compound	R	m.p. (°C)	Yield (%)	R_f value
3a	4-amino acetophenon	70-75	85	0.82
3b	4- bromoacetophenone	56-60	90	0.68
3c	2,4-dimethoxy acetophenone	75-80	82	0.56
3d	3- nitro acetophenone	62-65	87	0.94
3e	p-Hydroxyacetophenone	63-70	85	0.72
3f	4-methoxy acetophenone	58-65	91	0.50
3g	4- methyl acetophenone	65-72	68	0.90
3h	Acetophenone	60-65	80	0.62

Solvent system: ethyl acetate: n-Hexane (7:3)

Table 2: characterization data of the synthesized compound (4a-h)

Compound	R	m.p. (˚C)	Yield (%)	$R_f$value
4a	4-amino acetophenone	187-190	70	0.70
4b	4- bromoacetophenone	156-160	75	0.67
4c	2,dimethoxy acetophenone	175-180	72	0.72
4d	3- nitro acetophenone	162-165	80	0.52
4e	*p*-Hydroxyacetophenone	163-170	75	0.76
4f	4-methoxy acetophenone	158-165	80	0.57
4g	4- methyl acetophenone	185-190	66	0.56
4h	Acetophenone	160-165	78	0.67

Solvent system: ethyl acetate: n-Hexane (7:3)

Table 3: Characterization data of the synthesized compound (5a-h)

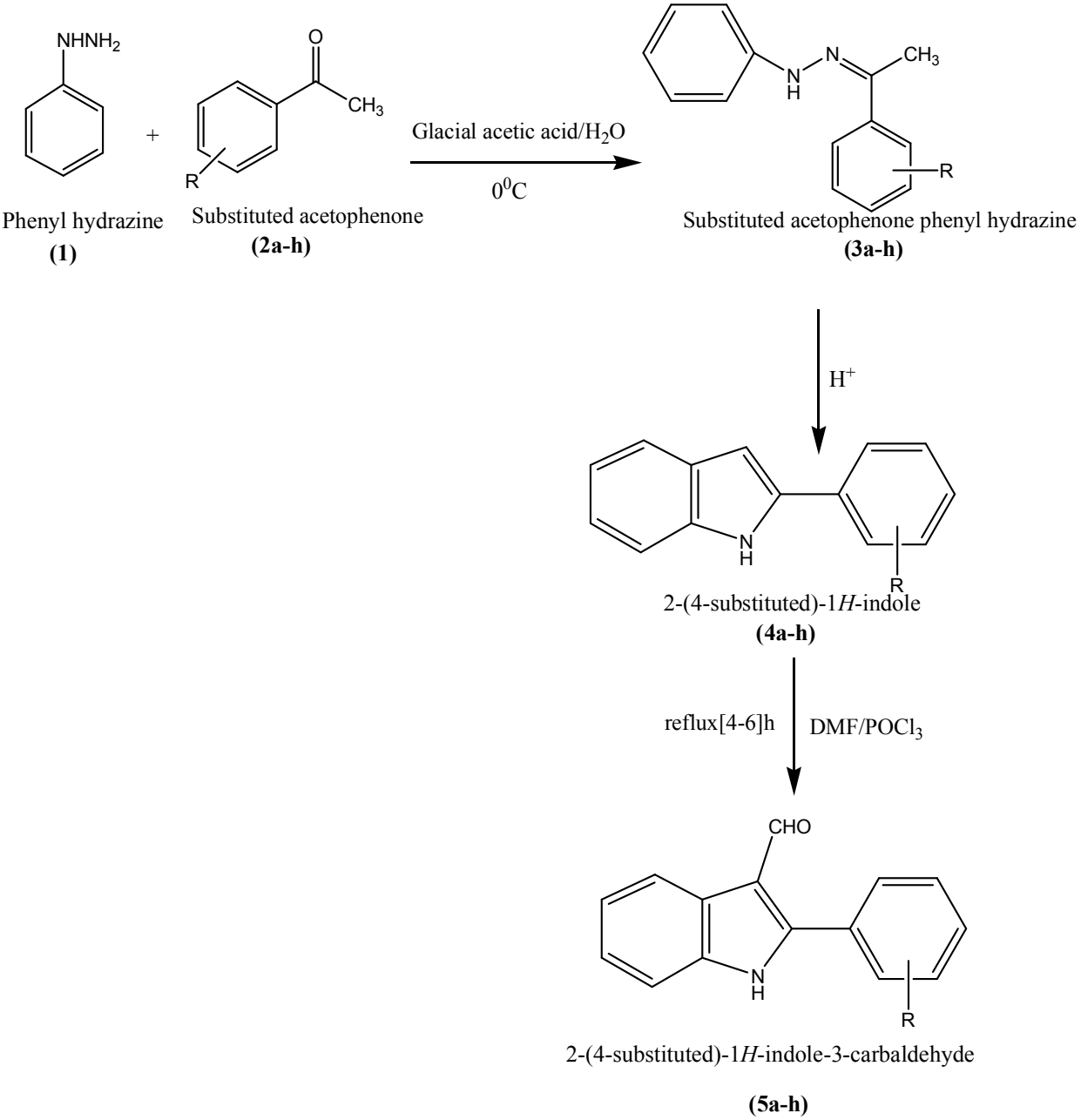
Compound	R	m.p. (˚C)	Yield (%)	$R_f$value
5a	4-amino acetophenon	240-245	65	0.67
5b	4- bromoacetophenone	256-260	67	0.44
5c	2,dimethoxy acetophenone	275-280	78	0.58
5d	3- nitro acetophenone	260-265	87	0.70
5e	*p*-Hydroxyacetophenone	245-250	58	0.64
5f	4-methoxy acetophenone	258-265	54	0.50
5g	4- methyl acetophenone	265-272	62	0.81
5h	Acetophenone	255-260	80	0.52

Solvent system: ethyl acetate: n-Hexane (7:3)

Table:4Anti-inflammatory activity of titled compounds 20 mg/kg(Dose)

Compounds	0 hr	% Inhibitation	1h	% Inhibitation	2h	%Inhibitation	4h	% Inhibitation
Control	**2.21±0.6**		**2.32±0.04**		**2.52±0.08**		**2.76±0.11**	
Standard Diclofenac	**2.14.0.26**	**3.16**	**1.94±0.19**	**16.37**	**1.86±o.10**	**27.38**	**1.88±0.26**	**31.88**
3a	2.19±o.o4	0.30	2.08±0.12	1.34	1.98±0.03	21.42	1.92±0.02	30.43
3b	2.20±0.08	0.45	2.30±0.03	0.86	2.08±0.17	17.46	2.06±0.11	25.36
3c	2.17±0.13	1.15	2.12±0.03	8.62	2.48±0.06	1.56	2.14±0.02	22.46
3d	2.16±0.03	2.26	2.04±0.09	12.06	2.02±0.09	19.8	2.10±0.09	23.91
3e	2.19±0.08	0.90	2.23±0.19	3.87	2.44±0.05	3.17	2.58±0.10	6.52
3f	2.16±0.09	2.24	2.27±0.03	2.15	2.14±0.23	15.07	1.99±0.02	27.89
3g	2.19±0.17	0.09	2.27±0.06	4.31	2.34±0.01	7.14	2.32±0.07	15.94
3h	2.20±0.06	0.45	2.21±0.12	4.31	2.24±0.08	11.11	2.44±0.03	11.59

Data are expressed as Mean ± SEM for different stages, Statistical analysis was performed using two way ANOVA followed by Dunnett'stest .***P<0.001 *vs* control (MES) ; **P<0.05 *vs* control (MES); * P,0.01 *vs*control (MES).



Phenyl hydrazine **(1)**

Substituted acetophenone **(2a-h)**

Substituted acetophenone phenyl hydrazine **(3a-h)**

2-(4-substituted)-1*H*-indole **(4a-h)**

2-(4-substituted)-1*H*-indole-3-carbaldehyde **(5a-h)**

Scheme: Synthesis of Compound (5a-h).

CONCLUSION

The structures of all new synthesize compounds have been established on the basis of their analytical and spectral data. All of the synthesized compounds were also evaluated for their anti-inflammatory activity using carrageenan-induced rat paw edemaand diclofenacsodium as the standard drug.

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