ISSN: 2456–5474 RNI No.UPBIL/2016/68367 Vol.-6* Issue-9* October (Part-1) 2021
Innovation The Research Concept

Antihistaminic Activity of 1-Aminomethyl-5-Substituted-3- {4'-(2"-Chlorobenzyl Oxy)- Benzoyl Hydrazone} Indolin-2

Paper Submission: 10/10/2021, Date of Acceptance: 19/10/2021, Date of Publication: 22/10/2021

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Abstract

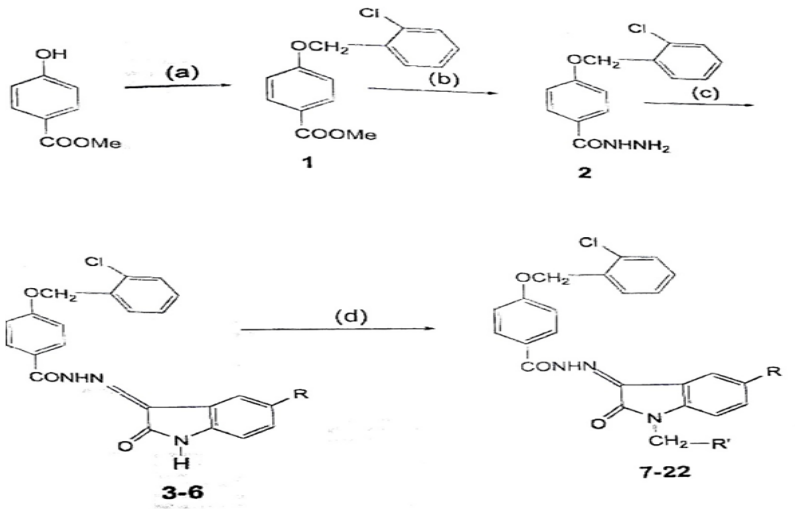
5-Substituted-3-{4'-(2"-fluorobenzoyloxy)-benzylhydrazine}-indolin-2-ones (Schiff's bases) were synthesized by the condensation of 4-(2'-chloro benzyloxy)-benzoylhydrazine and 5-substituted indole-2,3-diones. Mannich reaction in the presence of formaldehyde and heterocyclic secondary amities on 5-substituted -3-{4'-(2"-fluorobenzoyloxy) benzoyl hydrazone-indolin-2-ones, furnished 1-aminomethyl-5-substituted-3 -{4'-(2"-fluorobenzoyloxy)-benzylhydrazine }-indolin-2-ones (Mann-ich bases). The compounds were screened for their in vitro antifungal potential against human pathogenic yeasts viz; Candida albicans (CA), Cryptococcus neoformans (CN), Sporothrix schenckii (SS) and mycelial fungi viz; Trichophyton mentagrophytes (TM) and Aspergillus fumigants (AF) by Microbroth Two Fold Serial Dilution Technique and Minimum Inhibitory Concentration (MIC) in mg/mL was recorded. Ketoconazole was taken, as standard drug.

Keywords: Antihistamine, Antifungal, Antivirus, Anticonvulsant, Ileum, Recrystallised.

Introduction

Indole-2,3-diones[1] and their derivatives constitute a class of biologically active heterocyclic compounds which have been found to show antiviral[2], antimicrobial[3-5], anthelmintic[6], amoebicidal[7], antifertility[8], antileukemic[9], anticonvulsant[10], herbicidal[11], anti-HIV[12-14], CNS-depressant[15-17], cytotoxic[18-21], analgesic, antiinflammatory[22], hypotensive[23] and cysticidal[24] activities. Substituted benzyloxy group is present in many broad spectrum imidazole antifungals[25] and local anesthetics[26]. In the light of these observations, it was considered of interest to synthesize a new series of 2-chlorobenzyl oxy substitute benzonic acid hydrazide incorporated indolin-2 ones (Schiff's bases) and their Mannich Bases.

Methyl paraben was treated with 2-chlorobenzyl chloride to get methyl 4-(2'-chlorobenzyl oxy)-benzoate 1 which underwent hydrazinolysis to give 4-(2'-chloe benzyloxy)-benzoyibydrazine 2. Acid catalyzed condensation of benzoyl hydrazine 2 with 5-substituted indolc-2, 3-diones, in equimolar proportion, gave 5-substituted -3- {4' (2"-fluorobenzoyloxy) – benzoyl hydrazone} indolin-2-ones (Schiff's bases) 3-6. On being subjected to aminomethylation with heterocyclic secondary amines in the presence of formaldehyde, 3-6, gave 1-aminomethyl-5-substituted-3-4'-(2"-fluorobenzoyloxy)- benzylhydrazine}-indolin-2-ones (Mannich bases) 7-22. Indole-2,3-diones were prepared via Sandmeyer Isonitrosoacetanilide Synthesis [27].



(a) 2- Chlorobenzyl chlroide, K_2CO_3 (anhyd.), DMF
(b) $N_2H_4.H_2O$, EtOH

(c) Isatins, EtOH, AcOH R=H, Br, Cl, Me
(d) Amines, CH_2O, DMF R'=Morpholino, Piperidino, N-Methylpiperazine, Pyrrolidino

Objective of the study

The heterocyclic compounds are known to have wide spectrum pharmacological effects. It is worthwhile to study the antihistaminic activity of indulines.

Experimental Details

Methyl 4-(2'-chlorobenzyl oxy)-benzoate 1
A mixture of methyl paraben (0.045mol), 2-chlorobenzyl chloride (0.045 mol), anhydrous K_2CO_3 (7.1g) in DMF (30 mL) was refluxed for 7-8 h and pounded into ice cold water. The solid product thus obtained was filtered, washed with water, dried and recrystallized from ethanol; M.P. 76-78^{0}C, Yield 65%

4-(2'-Chlorobenzyl Oxy)-benzylhydrazine 2
Compound 1 (0.01 mol) and hydrazine hydrate (98%, 1mL) in ethanol (70 mL) were refluxed for 15-16 h. Excess of solvent was distilled off and the reaction was poured into ice cold water. The solid product thus obtained was filtered, washed with water, dried and recrystallized from ethanol; M.P.144-46^{0}C, Yield 70%.

3.(4'-(Y,,-Chlorobenzyl Oxy)-benzylhydrazine)-indolin-2-one 3
A mixture of 2 (0.01mol) and indole-2,3-dione (0.01mol) in ethanol (50 mls) containing 3-4 drops of glacial acetic acid was reflux-al for one hour and left overnight at room temperature. The solid product so obtained was filtered and washed with methanol.
Compounds 4-6 were prepared by similar method using different 5-substituted indole-2, 3-diones.

1-Morpholinomethyl-3-{4'-(2"-ehlorobenzyloxy)-benzoythydrazono}-indolin-2-one 7
3- {4 -(2"-Fluorobenzoyloxy)-benzylhydrazine -indolin-2-one 3 (0,005 mol) was suspended in minimum quantity of DMF. To this formaldehyde (37% al. solution, 0.5 mL) and morpholine (0.005 cool) were added with vigorous stiffing. The contents were warmed on a water bath for 2 min. and left overnight at room temperature. The solid product thus obtained was filtered, dried and crystallized from chloroform-pet ether (60-80°C) (1:1).

Antihistaminic Activity

The antihistaminic activity (H^1) was measured on the isolated terminal part W. ileum (5 cm long) of a guinea pig. This part of ileum was kept in a bath containing aerated Tyrode solu-tion (20 ml) at 35 °C. Spasm of the ileum was induced with $3x10^{-8}$ g/ml of histamine. The percentage inhibition was plotted at different concentration of the compound and the concentration corresponding for 50% inhibition (IC_{50}) was calculated. These values are listed in Table VI. with their standard errors.
The antihistaminic activity in vivo was tested in guinea pig by the Kongzett-Rossler preparation against histamine (2.10 mg/kg i.v.) induced bronchoconstriction. The i.v. ED_{50} value was calculated graphically by plotting percent inhibition of histamine bronchoconstriction versus dose of the compound.

Compound	R	R1	H, receptor blocking Activity
7	H	Morpholino	0.18 ± 0.3
8	Br	Morpholino	0.21 ± 0.3
9	Cl	Morpholino	0.26 ± 0.4
10	Me	Morpholino	0.24 ± 0.3
11	H	Piperidino	0.13 ± 0.2
12	Br	Piperidino	0.23 ± 0.3
13	Cl	Piperidino	0.28 ±0.24
14	Me	Piperidino	0.18 ± 0.2
15	H	N-methylpiperzino	0.21 ± 0.2
16	Br	N-methylpiperzino	0.26 ± 0.3
17	Cl	N-methylpiperzino	0.27 ± 0.2
18	Me	N-methylpiperzino	0.18 ± 0.2
19	H	Pyrolidino	0.16 ± 0.2
20	BNr	Pyrolidino	0.29 ± 0.3
21	Cl	Pyrolidino	0.30 ± 0.2
22	Me	Pyrolidino	0.16 ± 0.2

Result and Discussion

The antihistaminic activity of compound has been received in Table. Following conclusion can be drawn.

1. Moderate antihistaminic activity was shown by compounds.
2. Compounds with R=Cl & Br showed worked increased activity.
3. No quantitative structure activity relationship (QSAR) can be drawn.

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