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Synthesis and Biological Evaluation of Novel Benzochromen-1, 3-thiazolyl-4-phenylazetidin-2-one

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Abstract

A novel series of ten molecules belonging to 3-chloro-1-[4-(3-oxo-3H-benzo[f]chromen)-2-yl-1, 3-thiazolyl]-4-phenylazetidin-2-one derivatives were synthesized by a five step reactions. The synthesized molecules were characterized, tested for antimicrobial and anti-inflammatory activity. The result revealed interesting factors regarding the contribution of substitution for the activity. The presence of substitution at 2nd position on the phenyl ring is necessary for activity against *K. pneumonia* and anti-inflammatory activity.

Key words – Benzochromone, antifungal, antibacterial.

INTRODUCTION

The 1, 3-thiazole heterocycle is an interesting building block in a variety of natural as well as synthetic compounds possessing good antibacterial potential [1-3]. Fused chromenes are interesting due to their significant antibacterial [4-10] and are the important constituents of pharmacologically active compounds, as these systems have displayed a broad spectrum of biological activities such as antimicrobial [3,4], mutagenicity [5], antiviral [6], antiproliferative [7], sex pheromonal [8], antitumor [9], central nervous system (CNS) activities [10]. Several substituted 1, 3-Thiazoly-4-phenylazetidin-2-one exhibit anticonvulsant [11], antimicrobial [12], anti-inflammatory [13], analgesic [14], anthelmintic [15], antituberculosis [16, 17] activity in our confined effort to develop promising antituberculosis and antimicrobial agents. Based on the above prompted observations and in continuation of our research work on synthesis of small bio active heterocycles for biological activity [18-20] and development of novel hybridized molecules [21], in the present investigation we envisaged to hybridise three pharmacophore. In the current study a series of ten molecules belonging to 3-chloro-1-[4-(3-oxo-3h-benzo[f]chromen)-2-yl-1, 3-thiazolyl]-4-phenyl azetidin-2-one derivatives were synthesised and screened for their antimicrobial activity and anti-inflammatory activity.

MATERIALS AND METHODS

Melting points were taken in open capillary tubes and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on a Perkin Elemer FT-IR, ^{1} H NMR and ^{13}C NMR were recorded using Avance Bruker (500 MHZ, DMSO, in PPM) using TMS as an internal standard. Mass spectra's were recorded by LC-MS-2010. The Purity of compounds was monitored by Thin layer chromatography.

Synthesis of 2-Acetyl-3H-benzo[f] chromen-3 one (1) [22]

To a cooled stirred suspension of a mixture of 2-Hydroxy-1- naphthaldehyde (78g, 0.5mol) in ethylacetoacetate (65g, 0.5mol) and piperdine (10g) was added with stirring. The mixture was then maintained at 0^{O}C overnight. Yellow colored lumps which separated out were broken in cold ethanol, filtered and crystallized from hot glacial acetic acid to give needle shaped crystals. Yield 78%; m.p 190^{0} C. IR (KBr) cm^{-1}: Ar C-H 3065, C=O 1705, (lactone C=O) 1724, Ar C=C 1556, C-O-C 1228.

Synthesis of 2-(2-Bromo acetyl)-3H- benzo[f] chromen-3-one(2)

To a solution of compound 2-Acetyl-3H-benzo [f] chromen-3-one (55g, 0.25 mol) in alcohol free chloroform (200ml), bromine (39.5g, 0.25mol) in chloroform (25ml) was added with intermittent shaking and warming. The mixture was heated for fifteen minutes on a water bath cooled and filtered. The solid was washed with ether and crystallized from glacial acetic acid. Yield 78%; m.p 184^{0}C. IR (KBr) cm^{-1}Ar C-H 3044, C=O 1700, (lactone C=O) 1722, Ar C=C 1553, C-O-C 1238, C-Br 582.

Synthesis of 2-(2-Amino thiazol-4-yl)-3H-benzo [f] chromen-3-one (3)

To a suspension of compound 2-(2- Bromo acetyl)-3H-benzo [f] chromen-3-one (30.1g, 0.1mol)in sodium acetate (20ml) was treated with thiourea, (7.6g, 0.1mol) a mild exothermic reaction took place, giving a clear solution that soon deposit crystals. The deposit's were removed, washed with ethanol and boiled with water containing sodium acetate which was later recrystallized from ethanol. Yield 78%; m.p 164^{0}C. IR (KBr) cm^{-1} NH_2 3356, Ar C-H 3056, C=O 1704, Ar C=C 1558, C=N 1590, C-O-C 1244, C-S-C 780. ^{1}H NMR: 5.1 (s, 2H, NH_2), 6.9 (s, 1H, thiazole) and 7.4-8.3 (m, 7H, Ar H).

Synthesis of 2-(2-(Benzlideneamino) thiazol-4-yl)-3H-chromen-3-one (4) [23]

To a suspension of 2-(2-Aminothiazol-4-yl) -3H-benzo [f] Chromen-3-one (0.01 mol 2.81 g) in DMF and various aldehydes (0.01 mol) was added and heated under reflux for 8 hr cooled and filtered. Yield 78%; m.p 164^{0}C IR (KBr) cm^{-1}: Ar C-H 3048, C=O 1711, Ar C=C 1555, C-NO_2 1574, C=N 1596, C-O-C 1234, C-S-C 784. ^{1}H NMR: 7.0 (s, 1H, thiazole), 6.9 (s, 12H, Ar H) and 8.7 (s, 1H, CH=N).

Synthesis of 3-Chloro-1-(4-(3-Oxo-3H-benzo [f] chromen-2-yl)-4-phenylazethidin-2-one ($5S_1$) [24]

To a suspension of 2-(2-(Benzlideneamino)thaizol-4-yl)-3H-benzo [f] chromen-3-one (0.005mol) in 1,4-dioxane

(20ml), chloroacetyl chloride (0.48ml, 0.06mol) was added drop wise at room temperature with constant stirring. Then triethylamine (0.14ml, 0.001mol) was added to the reaction mixture and refluxed for 12 hr. After completion of reaction, it was poured in to water. The solid was filtered, dried and recrystallized from ethanol. IR (KBr) cm^{-1}: Ar C-H 3060, C=O 1714, Ar C=C 1562, C=N 1594, C-NO_2 1578, C-O-C 1242, C-Cl 745, C-S-C 786. ^{1}H NMR: 6-8.0 (m, 11H, Ar-H), 4.4 (s, CH, OH), 3.34 (s, 1H, CH), Mass (m/z): 475 [m^+].

Anti-inflammatory activity

The synthesized compounds were subjected to biological screening for anti-inflammatory activity using rat paw edema method by Plethysmometer. The animals were divided into groups (control, standard, test), each consisting of 4 animals. The animals were fasted for 24 h before the experiment with free access to water. Control group received only 0.1% Tween-80 suspension. Standard group administered with Diclofenac sodium intraperitoneally at a dose of 10mg/kg. The test compounds were administered at a dose of 50mg/kg. 0.1ml of 1%(v/v) carrageen solution was injected in the planter region of the left paw of each animal, 1 h after the administration of the test compounds and standard drug. The right paw was served as reference non-inflamed paw for comparison. Paw volume of both legs of animals was measured by means of a Plethysmometer. The percent inhibition of paw edema was calculated by using following formula:

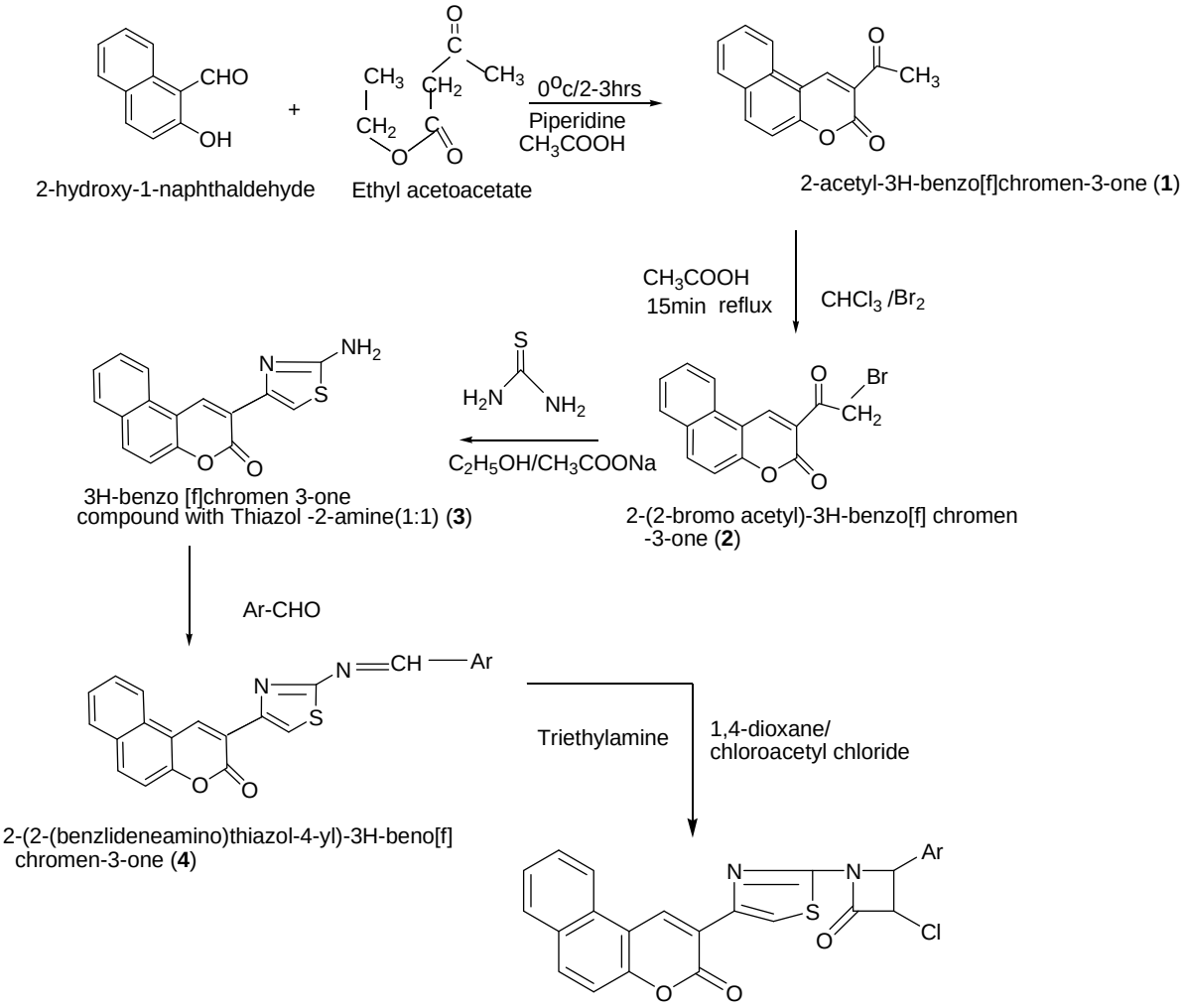
Percent edema inhibition= $(1–V_t/V_c) \times 100$

Where, $\mathbf{V_t}$ = mean increase in paw volume in rats treated with test compounds

$\mathbf{V_c}$= mean increase in paw volume in control group of rats

RESULTS AND DISCUSSION

2-Hydroxy-1-naphthaldehyde and ethylacetoacetate were reacted in presence of piperidine as a catalyst to form 2-acetyl-3H-benzo[f]chromen-3-one **(1)**. 2-(2-Bromo acetyl)-3H-benzo[f] chromen-3-one **(2)** was obtained by bromination of **(1)** in alcohol free chloroform. The intermediate **(2)** was refluxed with thiourea in ethanol and sodium acetate to yield the compound **(3).** The Compound **(3)** was reacted with various aromatic aldehyde to give 2-(2-Benzlideneamino) thiazol-4-yl)-3H-benzo[f] chromen-3-ones **(4),** which was treated with chloracetylchloride with triethlyamine in 1,4-dioxane to yield the title compounds **($5S_1$) (Scheme 1).** The synthesized target compounds were confirmed for their structural integrity.



Scheme 1

Antimicrobial activity

The antimicrobial activity of synthesized compound were determined by turbidimetric method using six organism such as *Bacillus subtitles, Staphylococcus aurevs, Escherichia coli, Klebshella pneumonia, Candida albicans* and *Aspergillus niger*. Among the ten compounds tested the entire series was found to be active against *Klebshella pneumonia* when compared to other strains. The target compounds had structure possessing OH, nitro, chlorine, methoxy and dimethyl amine over the aromatic ring. The effect of three positional isomer bearing OH at 2, 3 and 4th position were evaluated. It was found that the presence of OH at 2nd position showed better activity than the other two in case of *Klebshella pneumonia.* Similar pattern was observed when the nitro and chlorine atoms were at 2nd in the target compounds. Also structures bearing electron with drawing groups such as nitro showed better activity than the electron donating groups.

Anti-inflammatory activity

Among the ten compounds tested for anti-inflammatory activity five compounds showed more than 50% inhibition. The following compounds showed higher inhibition 5j, 5h, 5c, 5f and 5i. The most active compound 5j showed 62 % inhibition. All the five compounds have a common feature and resulted in interesting identification. The compounds bearing substitution at 4th position over the phenyl ring showed better activity than substitution at 2nd and 3rd position. However the presence of electron donating and with drawing groups at 4th position didn't show any contributing differences in their activity.

Table 1 Physical properties and anti-inflammatory activity of 3-Chloro-1- [4-(3-Oxo-3H-Benzo[f] Chromen)-2-yl-1, 3-Thiazolyl]- 4-Phenylazetidin-2-one (5a-j)

Compounds Code	Ar	% Yield	m.p^{0}C	Absorbance	% Inhibition
5a	2-OH C_6H_4CHO	64	185-186	1.330	32.2
5b	3-OH C_6H_4CHO	61	187-189	1.010	48.5
5c	4-OH C_6H_4CHO	59	195-196	0.860	56.2
5d	2-NO_2 C_6H_4CHO	60	210-211	1.260	35.8
5e	3-NO_2 C_6H_4CHO	62	193-194	1.054	46.3
5f	4-NO_2 C_6H_4CHO	65	205-206	0.861	56.1
5g	2-Cl C_6H_4CHO	66	197-199	1.210	38.3
5h	4-Cl C_6H_4CHO	64	194-195	0.810	58.7
5i	4-$N(CH_3)_2$ C_6H_2CHO	67	220-221	0.960	51.1
5j	3,4,5-$(OCH_3)_3$ C_6H_2CHO	62	190-192	0.731	62.1

Table 2 Anti-bacterial and Anti-fungal activities of newly synthesized compounds

Compounds Code	*E. coli* (µg/ml)	*B. subtilus* (µg/ml)	*S. aureus* (µg/ml)	*K. pneumonia* (µg/ml)	*A. niger* (µg/ml)	*C. albicans* (µg/ml)
5a	120	145	95	65	160	155
5b	145	105	80	105	180	145
5c	120	95	85	90	145	180
5d	155	70	120	55	160	145
5e	135	85	115	70	145	160
5f	145	105	135	65	140	155
5g	105	120	110	65	140	155
5h	95	105	105	95	155	185
5i	130	130	95	90	160	180
5j	95	70	90	105	180	145

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