SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF SOME NEW BENZOPYRONE DERIVATIVES

Shashikant R.Pattan*[1], Nachiket s Dighe[1], Jayshri S Pattan[2], Santosh R Butle[3], Santosh G Jadhav[4], Deepak S Musmade[1] and Suwarna H Kale[1]

1-Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, MS, India, 413716.

2- Department of Biotechnology, PVVP'S Art's Science and Commerce College, Loni,MS,India,413736.

3-Department of Pharmaceutical Chemistry, SRTM University, Nanded.

4-P.S.P.S.IIP, Sadavati, (Devrukh),Dist-Ratnagiri,MS,415804.

*Address for corespondance
Dr. Shashikant R.Pattan
Principal,
Pravara Rural College of Pharmacy, Pravaranagar
A/P- Loni Bk.
Tal-Rahata, Dist-Ahmednagar 413736,
India (MS).
Email:shashipattan@yahoo.com

ABSTRACT

A new series of benzopyrone derivatives were synthesized and the structure of these compounds was established on the basis of spectral data. The title compounds were evaluated for antitubercular. Some of these compounds have shown excellent antitubercular activity.

Keywords: Benzopyrone, antitubercular, CHN analysis.

INTRODUCTION

A number of natural and synthetic benzopyrone derivatives have been reported to exert anti microbial, anti tubercular and anti diabetic activity.[1] Benzopyrones having chromen (γ-benzopyrone) moiety are associated with interesting physiological activities such as anti microbial, anti tubercular, antidiaetic, antiviral, anticancer, anti-inflammatory [2] etc.In view of these observations and our interest in the synthesis of biologically active biheterocycles possessing benzopyrone nucleus we modified benzopyrone ring to explore activities associated with this nucleus & evaluated them for anti tubercular activity.

Material and Methods

ANTITUBERCULAR ACTIVITY: [3,5]

The antitubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv. Strain. Middle brook 7H9 agar medium containing different derivatives, standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of H_{37}Rv Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth.

EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were

recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on BRUKER amx-400, DMSO d_6 as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Synthesis of 6-Chloro-2-phenyl-4-benzopyron (II) [2]

To 36.6 g (0.13 mol) of 3-phenyl-4-chloro-2-acrylophenone in 325 ml methanol, 65 ml of 20 % aq. Sodium hydroxide solution was added & this mixture was cooled to 0 ^{0}. To this mixture, 65 ml of 30% hydrogen peroxide was added dropwise maintaining temp. Below 10^0. The contents were further stirred for 2 hr at temp below 10^0 and then poured on crushed ice. The mixture was then neutralized with dil. hydrochloric acid. The solid product was filtered washed with ice-cold water, dried and recystallized from rectified spirit, m.p. 72-74^0, yield 73%.

Synthesis of 6-Chloro-3-(4-chlorophenyl)-2-phenyl-4H-benzopyran-4-one (III) [4]

A solution of potassium hydroxide [5.6 g (100 mol) in 5 ml H_2O] was added to a mixture of 6-Chloro-2-phenyl-4-benzopyron (16.6 g, 100 ml) and the aromatic aldehydes (100 mmol) in ethanol (50 ml), and the reaction mixture was stirred for half an hr. The formed yellow precipitate was filtered off. Washed thoroughly with water, dried and recrystallized from ethanol, m.p. 90-92^0, yield 64%.

Synthesis of 8-Chloro-3-(chlorophenyl)-4-(Diphenyl , phenyl)-1, 2, 3, 4-tetrahydrobenzopyrano [4, 3] Pyrazole (C_1-C_2).

A suspension of **III** (2 mmol) in glacial acetic acid 10 ml was treated with phenyl hydrazine/Hydrazine hydrate 0.2 ml (0.22 mmol). The reaction mixture was refluxed for 2 hr, poured into water and solid formed was separated and recystallized from ethanol.

Synthesis of 8-Chloro-4-(4 chlorophenyl)-5-phenyl-3,4-dihydro-1H-benzopyron [4,3] pyrimidine-2 (5H)-thiones (C_3-C_4).

To a mixture of **III** (10 mmol) and thiourea /urea 1 g (13 mmol) in ethanol (50 ml), there was added a solution of potassium hydroxide 1g (18 mmol) in H2O (1 ml). The mixture was refluxed for 4 hr, poured into water and the solid formed was filtered off, dried and recrystallized from dioxan.

Synthesis of 2-Amino-8-chloro-4-(4-chlorophenyl)-5-phenyl-5H-benzopyron (4, 3)-3-carbonitrile (C_5)

A few drops of triethylamine were added to a mixture of **III** 3g (10mmol), $CH_2(CN)_2$ (10mmol) and ammonium acetate 0.62 g (80 mmol) in absolute ethanol (50 ml). The reaction mixture was refluxed for 8 hrs, allowed to cool and poured gradually while stirring in cold water. The solid formed was collected, dried and recystallized from dioxan.

Synthesis of (C_6).

A mixture of **II** (10 mmol), $CH_2(CN)_2$, 0.66 g (10mmol) and β-alanine (50 mg) in ethanol (25 ml) was refluxed for 3hrs. The reaction mixture was cooled and

poured in cold water. The solid formed was washed with water, dried and recystallized from the ethanol.

Result and Discussion

Substituted acetophenones and substituted aldehydes were reacted to get the chalcones which were treated with H_2O_2 then with other intermediate to get the various derivatives. The structures of these compounds were confirmed by IR, NMR. and CHN analysis. These compounds were subjected to anti tubercular activity by using LJ media with $H_{37}R_v$ strain. Compounds C_3, C_5 and C_6 have found to be potential anti tubercular agent when compared with standard Streptomycin C_1, C_4, C_2 have shown moderate anti tubercular activity. With suitable molecular modification these compounds may prove as potent anti tubercular drug in future.

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SCHEME

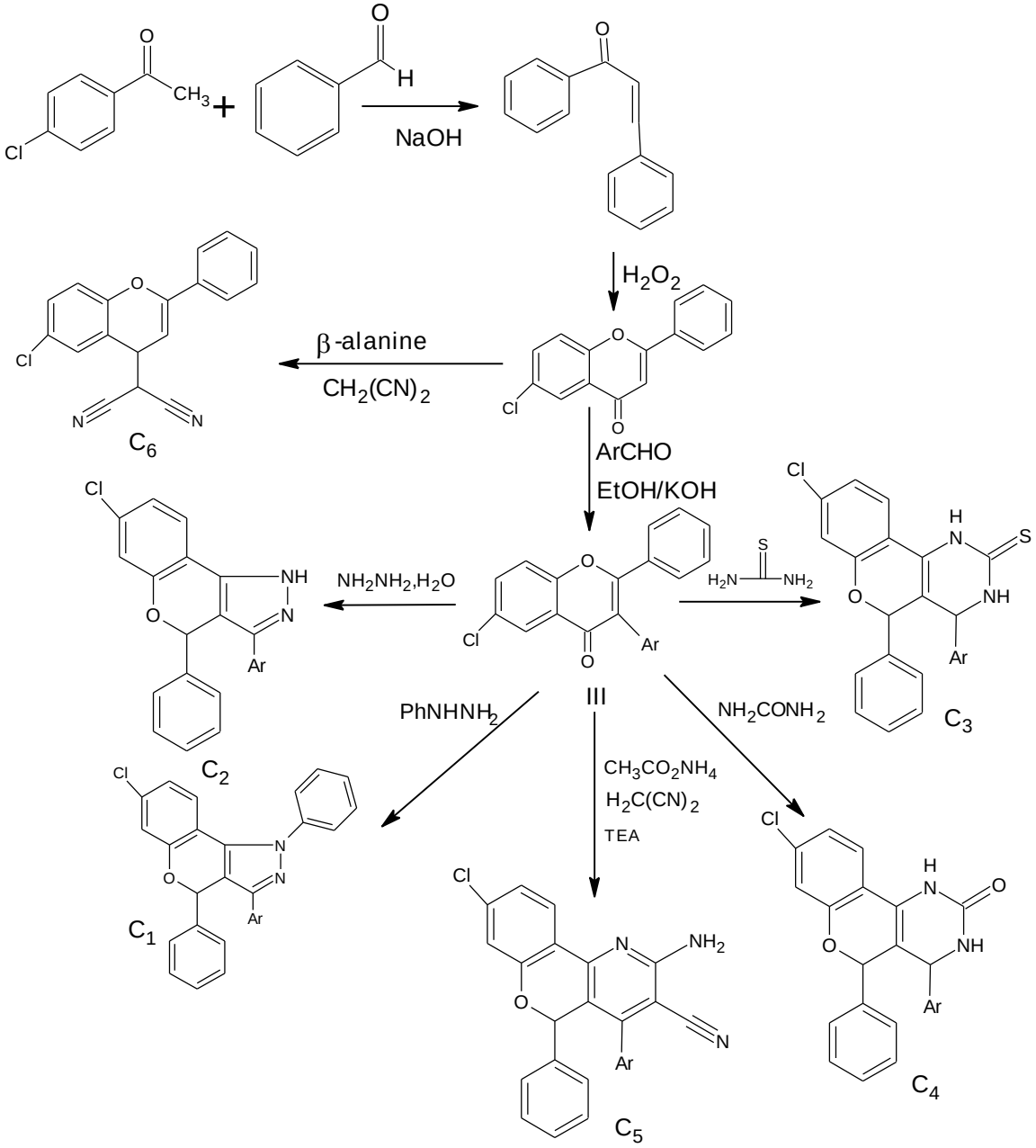
NaOH
H_2O_2
β-alanine
$CH_2(CN)_2$
ArCHO
EtOH/KOH
NH_2NH_2,H_2O
$H_2N-C(=S)-NH_2$
$PhNHNH_2$
NH_2CONH_2
$CH_3CO_2NH_4$
$H_2C(CN)_2$
TEA
III
C_1
C_2
C_3
C_4
C_5
C_6

Table no.1: Analytical data of the synthesized compounds (C_1-C_5)

Compd.	Mol. Formula	Mol. Wt.	Yield %	m.p. ° C	Elemental analyses Calcd. (Found)		
					C	H	N
C_1	$C_{22}H_{14}N_2OCl_2$	469.36	88	132	71.65	3.87	5.97
C_2	$C_{28}H_{18}N_2OCl_2$	393.26	86	104	67.19	3.59	7.12
C_3	$C_{23}H_{17}N_2OSCl_3$	475.81	56	178	58.06	3.60	5.89
C_4	$C_{23}H_{16}N_2O_2Cl_2$	423.29	64	111	65.26	3.81	6.62
C_5	$C_{25}H_{15}N_3OCl_2$	444.31	48	108	67.58	3.40	9.46
C_6	$C_{18}H_{11}N_2OCl$	306.74	32	114	70.48	3.61	9.13

The combustion analysis of compounds synthesized is within the limits of permissible errors.

Table No.2: Anti-tubercular activity of the synthesized compounds:

SL. No.	*Compounds*	25 *µcg* /mL	50 *µcg* /mL
1.	**C_1**	R	S
2.	**C_2**	R	S
3.	**C_3**	**S**	S
4.	**C_4**	R	S
5.	**C_5**	**S**	S
6.	**C_6**	S	S
STD.	**Streptomycin**	**S**	**S**

R- Resistance; **S**- Sensitive

SPECTRAL DATA

C_1:IR (KBr) cm^{-1} : 3249 (N-H str.), 3055 (C-H str.Ar),1500 (C-C str.Ar),1331 (C-Ostr.), 1255 (C-N str.), 762 (Cl).^{1} H NMR (d ppm): 6.91-7.3(17 H ,m,Ar-H),5.55(1H,s,CH),3.0(1H, s,CH), 2.5(1H,s,NH).

C_2: IR (KBr) cm^{-1} : 3276 (N-H str.), 3062 (C-H str.Ar),1517 (C-C str.Ar),1358 (C-Ostr.), 1219 (C-N str.), 764 (Cl).

C_3:^{1}H NMR (d ppm): 6.92-7.38(12 H, m, Ar-H), 5.56 (1H,s, CH), 4.51 (1H, s,CH), 9.72-12.01(2H,s,NH).

C_5:IR (KBr) cm^{-1} : 3232 (N-H str.), 3055 (C-H str.Ar),1680 (C=O str.),1515 (C-C str.Ar),1331 (C-Ostr.), 1254 (C-N str.), 761 (Cl).^{1} H NMR (d ppm): 7.0-8.12 (12 H ,m,Ar-H),6.12 (1H,s,CH), 6.79 (2H, s,CH).