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Der Pharma Chemica, 2011, 3 (6):189-196  
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X  
CODEN (USA): PCHHAX

## Synthesis, Characterization and Anti-microbial activity of 6-Bromo-4-(substituted phenyl) iminoflavone

Shubhangi G. Patil<sup>a</sup>, Prashant S. Utale<sup>b</sup>, Sumer D. Thakur<sup>c</sup>, Sachin V. Pande<sup>a</sup>

<sup>a</sup> Department of Chemistry, Laxminarayan Institute of Technology, Nagpur Maharashtra (India)

<sup>b</sup> Department of Chemistry, Shri Shivaji Science College, Nagpur Maharashtra (India)

<sup>c</sup> Department of Chemistry, Br. R.D.I.K. & N.K.D. College, Badnera Maharashtra (India)

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### ABSTRACT

Chalcone and their heterocyclic analogues are known to possess a broad spectrum of biological effects. The present study is devoted to the synthesis of 6-bromo-4-(substituted phenyl) imino flavones. The newly synthesised compounds were screened for their antimicrobial and antifungal activities. 2-hydroxy chalcone imine on refluxing in DMSO for two hrs in presence of catalytic amount of iodine in presence of conc.  $H_2SO_4$  afford a corresponding imino flavones in high yield. The structures were established on the basis of spectral data (IR, NMR) and chemical reactions.

**Keywords:** Flavones, 2-hydroxy chalcone, spectroscopy, Antimicrobial activity.

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### INTRODUCTION

Flavones are commonly found in human diet especially in fruits, vegetables, tea, red wine, and juices. Consumers and food manufacturers are interested in flavones because these compounds could exert direct or indirect beneficial effects on health [1,2]. The flavone backbone derives from a chalcone intermediate and consists of two aromatic rings interconnected by a three carbon atom heterocyclic ring. Flavanoids are a major class of oxygen containing heterocyclic natural products and are wide spread in green plants[3] The major group of plant poly phenols is represented by flavanoids and recent review has estimated their number as 6500 in the plant kingdom[4]. The major flavanoids in the plant extracts is quercetin, followed by myricetin and kaempferol. Chrysin is a flavones widely distributed in plants which was reported to have many biological Activities including, antibacterial[5], antioxidant[6], antiinflammatory[7], antiallergic[8], anticancer[9], antiestrogenic[10]. Several flavones have an interesting anti-HIV activity[11,12]. In general, the flavones are synthesized by oxidative cyclization of 2'-hydroxy chalcones[13], by the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione [14],

by Auwers methods[15] and via intermolecular Witting reaction[16]. The use of dimethyl sulphoxide (DMSO) as oxidizing agents for affecting this conversion has been reported by several workers[17-19]. However the DMSO-I<sub>2</sub> for the oxidation of 2'-hydroxy chalcones to flavones has not been used so far, though recently Iodine-DMSO-Sulphuric acid system has been applied[20] for dehydration of flavonoides and flavones derivatives are synthesized recently by using DDQ/DMSO-I<sub>2</sub>/Diphenyl disulfide by oxidative cyclization of 2-hydroxy chalcone[21-22]. Recently Chalconeimine is converted in flavoneimine by oxidative cyclisation in presence of DMSO-I<sub>2</sub>[23-26].

In this communication synthesis of flavoneimine by oxidative cyclisation of chalconeimines is performed in DMSO medium in presence of catalytic amount of Iodine and 2-3drops of conc. H<sub>2</sub>SO<sub>4</sub>.

## MATERIALS AND METHODS

### Experimental:

Melting points were determined on Vigo melting point apparatus and are uncorrected. All the compounds were routinely checked for their homogeneity by TLC on silica gel plate, IR spectra were recorded in KBr pellets on Perkin-Elmer FT-IR spectrophotometer, <sup>1</sup>H NMR spectra were recorded on BRUKER spectrometer on 300 MHz in CDCl<sub>3</sub> using TMS as an internal standard. The mass spectra were recorded on FAB mass spectrometer to confirm their structure,

Antibacterial and anti-fungal activity (anti-microbial activity) was carried out by Agar cup method. The bacterial strains are identified strains and obtained from National chemical Laboratory (NCL), Pune, India

### General procedure for Synthesis of 2-hydroxy-5-bromo-chalcone [1]:

A solution of 2-hydroxy-5-bromoacetophenone (0.01 moles) and benzaldehyde (0.01 mol) were dissolved in ethanol (10 ml), under stirring and aqueous NaOH (40%) was added drop wise. Orange colour solid was separate out. The reaction mixture was stirred at room temperature and kept overnight. The reaction mixture was acidified with HCl (50%). The separated solid was filtered and wash with 1% sodium bicarbonate solution again followed by water. Product was crystallized from ethanol and glacial acetic acid (1:1) to give yellow colour solid [1]. Yellow solid; Yield: 78%; m.p:150-155°C

### General procedure for the Synthesis of 2'-hydroxy-5'-bromo-N-(substituted phenyl)-chalconeimine (2a-i):

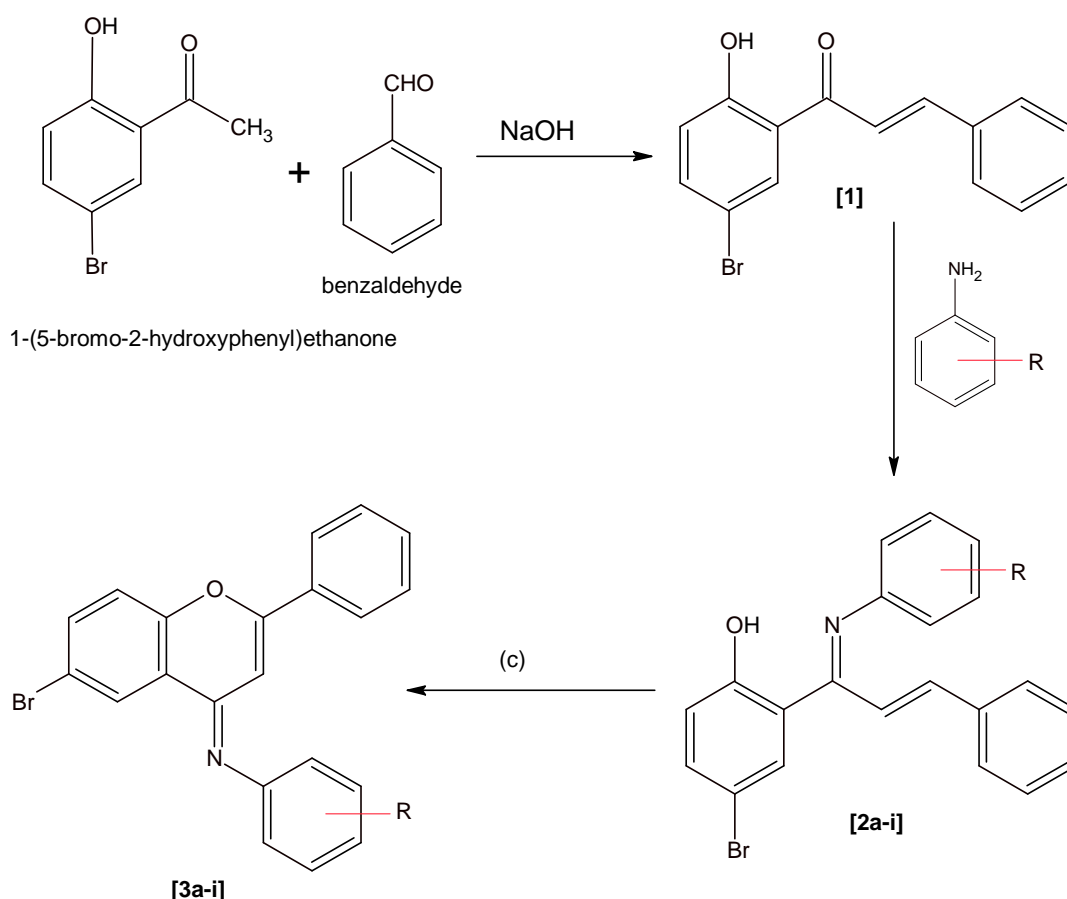
2-hydroxy-5-bromo-chalcone [1] (0.01mol) and substituted aniline (0.01 mol) was dissolved in ethanol (20 ml). To this mixture 2-3 drops of conc. H<sub>2</sub>SO<sub>4</sub> was added and it was refluxed for 3 hrs. On cooling and dilution with ice cold water, a solid mass separated out. It was recrystallized from ethanol. Dark yellow solid; Yield: 70 %; m.p:100-102 °C

### General procedure for the Synthesis of 6-Bromo-4 (substituted phenyl) iminoflavone (3a-i):

2-hydroxy-5-bromo- N-( substituted phenyl) chalcone imine [2a-i] (0.01mole) was dissolved in dimethyl sulphoxide (DMSO) (40ml) and was treated dropwise with 2-3 drops of conc. H<sub>2</sub>SO<sub>4</sub>. The mixture was refluxed for 10 min it was then cooled and little catalytic amount of

iodine was added. The reaction mixture was again heated for 3 hr on water bath, Cooled and diluted with ice cold water. The resulting solid was treated with 10% sodium thiosulphate solution to remove unreacted iodine and finally with water and crystallized from ethanol to give yellow crystalline compound [27]. Dark yellow solid; Yield: 84%; m.p: 85-90 °C

### Reaction Scheme:



### Scheme 1

- (a) *NaOH/Ethanol / RT*,  
 (b) *Ethanol /H<sub>2</sub>SO<sub>4</sub>/ Reflux*,  
 (c) *I<sub>2</sub>/ DMSO / Reflux*

### 6-Bromo-4-(phenyl) iminoflavone (3a)

Yield: 84%, Colour: dark yellow solid, m.p: 85-90 °C, Molecular formula: C<sub>21</sub>H<sub>14</sub>ONBr, Molecular weight: 375.9

### IR (KBr) $\nu$ max $\text{cm}^{-1}$ :

3084.18  $\text{cm}^{-1}$  (CH aromatic stretching), 1564.21  $\text{cm}^{-1}$  (C=C aromatic stretching), 1649.14  $\text{cm}^{-1}$  (C=N stretching), 1253.73  $\text{cm}^{-1}$  (C-O stretching), 1022.27  $\text{cm}^{-1}$  (C-Br stretching).

**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.86-8.37 (m 12H, Ar-H), 2.03 (s, 1H, C=CH)

**6-Bromo-4-(o-nitrophenyl) iminoflavone (3b):**Yield: 85%, Colour: yellow solid, m.p: 97-100°C, Molecular formula: C<sub>21</sub>H<sub>13</sub>O<sub>3</sub>N<sub>2</sub>Br, Molecular weight: 420.9**IR (KBr) ν max cm<sup>-1</sup>:**3082.25 cm<sup>-1</sup> (CH aromatic stretching), 1562.34 cm<sup>-1</sup> (C=C aromatic stretching), 1647.21 cm<sup>-1</sup> (C=N stretching), 1253.73 cm<sup>-1</sup> (C-O stretching), 1350.17 cm<sup>-1</sup> (C-NO<sub>2</sub> sym), 1527.62 cm<sup>-1</sup> (C-NO<sub>2</sub> asym), 1022.27 cm<sup>-1</sup> (C-Br stretching)**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.89-8.63 (m 12H, Ar-H), 2.177 (s, 1H, C=CH)

**6-Bromo-4-(m-nitrophenyl) iminoflavone (3c):**Yield: 84%, Colour: dark brown solid, m.p: 100-102 °C, Molecular formula: C<sub>21</sub>H<sub>13</sub>O<sub>3</sub>N<sub>2</sub>Br, Molecular weight: 420.9**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:** 6.87-8.38 (m 12H, Ar-H), 1.94 (s, 1H, C=CH)**6-Bromo-4-(p-nitrophenyl) iminoflavone (3d):**Yield: 83%, Colour: dark yellow solid, m.p 100-105°C, Molecular formula: C<sub>21</sub>H<sub>13</sub>O<sub>3</sub>N<sub>2</sub>Br, Molecular weight: 420.9**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.85-8.37 (m 12H, Ar-H), 2.71 (s, 1H, C=CH)

**Synthesis of 6-Bromo-4-(o-aminophenol) iminoflavone (3e):**Yield: 81%, Colour: light yellow solid, m.p: 155-160°C, Molecular formula: C<sub>21</sub>H<sub>14</sub>O<sub>2</sub>NBr, Molecular weight: 391.9**IR (KBr) ν max cm<sup>-1</sup>:**3263.56 cm<sup>-1</sup> (-OH aromatic stretching), 3082.25 cm<sup>-1</sup> (CH aromatic stretching), 1562.34 cm<sup>-1</sup> (C=C aromatic stretching), 1649.14 cm<sup>-1</sup> (C=N stretching), 1305.81 cm<sup>-1</sup> (C-O stretching), 1134.14 cm<sup>-1</sup> (C-Br stretching).**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.90-8.38 (m 12H, Ar-H), 2.12 (s, 1H, C=CH), 11.91 (d, 1H, Ar-OH)

**Synthesis of 6-Bromo-4-(m-aminophenol) iminoflavone (3f):**Yield: 82%, Colour: whitish solid, m.p: 77-80°C, Molecular formula: C<sub>21</sub>H<sub>14</sub>O<sub>2</sub>NBr, Molecular weight: 391.9**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.88-8.36 (m 12H, Ar-H), 2.75 (s, 1H, C=CH), 12.02 (d, 1H, Ar-OH)

**Synthesis of 6-Bromo-4-(p-aminophenol) iminoflavone (3g):**

Yield: 80%, Colour: dark brown solid, m.p: 80-85°C, Molecular formula: C<sub>21</sub>H<sub>14</sub>O<sub>2</sub>NBr, Molecular weight: 391.9

**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.91-8.38 (m 12H, Ar-H), 2.95 (s, 1H, C=CH), 11.82 (d, 1H, Ar-OH)

**Synthesis of 6-Bromo-4-(o-methylphenyl) iminoflavone (3h):**

Yield: 82% , Colour: dark brown solid, m.p: 84-86°C, Molecular formula: C<sub>22</sub>H<sub>16</sub>ONBr, Molecular weight: 389.9

**IR (KBr) ν max cm<sup>-1</sup>:**

3082.25 cm<sup>-1</sup> (CH aromatic stretching), 2922.16 cm<sup>-1</sup> ( CH Aliphatic stretching), 1562.34 cm<sup>-1</sup> (C=C aromatic stretching), 1649.14 cm<sup>-1</sup> (C=N stretching), 1253.73 cm<sup>-1</sup> (C-O stretching), 1022.27 cm<sup>-1</sup> (C-Br stretching).

**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.87-8.37 (m 12H, Ar-H), 2.67 (s, 1H, C=CH), 1.27 (d, 3-H, -CH<sub>3</sub>)

**Synthesis of 6-Bromo-4-(p-methylphenyl) iminoflavone (3i):**

Yield: 80%, Colour: dark brown solid, m.p: 102-107°C, Molecular formula: C<sub>22</sub>H<sub>16</sub>ONBr, Molecular weight: 389.9

**<sup>1</sup>H NMR: [δ CDCl<sub>3</sub>]:**

6.88-8.38 (m 12H, Ar-H), 2.49 (s, 1H, C=CH), 1.27 (d, 3-H, -CH<sub>3</sub>)

**Biological Evaluation****Anti-bacterial activity of 3a-i:**

The study has been conducted according to the method adopted by Cruickshank et al. Nutrient agar broth was melted in a water bath and cooked to 45 °C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 ml of 24 hour old culture especially and mixed well by gentle shaking before pouring on the sterilized Petri dish (25 ml each). The poured material was allowed to set (1.5 hour) and there after the “cups” was made by punching into the agar surface with a sterile cork borer and soaping out the punched part of agar. Into this “cups” 0.1 ml of test solution (prepared by dissolving 100 ml of sample in 10 ml DMF) was added by sterile micropipette. The plates were noted. The antibacterial activities of all compounds are compared against Ampicilin as a standard drug.

**Antifungal activity of 3a-i:**

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were **C. albicans** and **A. clavatus**. The antifungal activity of all the compounds was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium such a PDA medium contained potato 200 gm., dextrose 20 gm., agar 20 gm., and water 1 liter. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120 °C for 15 min and at 15 atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated

after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below.

$$\text{Percentage of inhibition} = \frac{100 (X - Y)}{X}$$

Where, X = Area of colony in control plate.

Y = Area of colony in test plate

**Table-1: Antibacterial activity of compounds 3a-i**

Compound No.	Zone of inhibition (in mm)			
	Gram +ve		Gram -ve	
	<i>S. aureus</i>	<i>S. pyrogenes</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
3a	16	18	17	19
3b	17	17	17	18
3c	16	19	16	17
3d	16	16	14	15
3e	16	17	16	21
3f	18	17	16	18
3g	18	17	18	16
3h	17	15	21	15
3i	15	19	19	17
<b>Ampicilline</b>	<b>18</b>	<b>19</b>	<b>20</b>	<b>20</b>
<b>Chloramphenicol</b>	<b>21</b>	<b>20</b>	<b>23</b>	<b>21</b>
<b>Ciprofloxacin</b>	<b>22</b>	<b>22</b>	<b>28</b>	<b>27</b>
<b>Norfloxacin</b>	<b>28</b>	<b>21</b>	<b>29</b>	<b>23</b>

**Table -2: Antifungal activity of compounds 3a-i**

Compound No.	<i>C. albicans</i>	<i>A clavatus</i>
3a	19	22
3b	21	22
3c	21	24
3d	21	17
3e	23	17
3f	23	23
3g	21	20
3h	22	23
3i	24	20
<b>Greseofulvin</b>	<b>24</b>	<b>24</b>
<b>Nystatin</b>	<b>26</b>	<b>26</b>

## RESULTS AND DISSCUTION

In the present work we have decided to carry out the synthesis of Flavoneimines on refluxing 2-hydroxy chalconeimine in DMSO-I<sub>2</sub>. This method quicker and appears to be of general applicability. The structures were established on the basis of spectral data (IR, NMR and Mass).

All newly synthesized compounds 3a-i shown significant microbial activites.

Table 1 of antibacterial activity show that the compound 3a, 3c, 3e, 3i more active in *S. pyrogenes* compare to *S. aureus* while 3f, 3g, 3h more active in *S. aureus* compare to *S. pyrogenes* and 3b and 3d having same activity in both in Gram +ve while 3a, 3b, 3c, 3d, 3e, 3f more active in *P. aeruginosa* compare to *E-coli* while 3g, 3h, 3i more active in *E-coli* compare to *P. aeruginosa* in Gram -ve . Table 2 of antifungal activity show that the compound 3a, 3b, 3c, 3h more active in *A. clavatus* compare to *C. albicans* while 3d, 3e, 3g, 3i, more active in *C. albicans* compare to *A. clavatus* and 3f has same activity in both.

### CONCLUSION

Newly synthesized iminoflavone 3a-i have been tested for their anti bacterial activity against gram positive bacteria *S. aureus* and *S. pyrogenes* while gram negative bacteria *E. coli* and *P. aeruginosa*. By punching into the agar surface with a sterile cork borer and soaping out the punched part of agar. Into this “cups” 0.1 ml of test solution, prepared by dissolving 100 ml of sample in 10 ml DMF. Ampicilline, Chloramphenicol, Ciprofloxacin Norfloxacin Greseofulvin and Nystatin were used as a reference compound. The entire compound shown good activity against gram positive and gram negative bacteria. Same compounds were tested for their anti fungal activity against *A. clavatus* and *C. albicans* using cup plate method. The compound 3a, 3d, 3e show moderate activity while 3b, 3c, 3f, and 3g, 3h, 3i show good anti fungal activity.

### Acknowledgements

The authors thanks to the Head, Department of Chemistry, Laxminarayan Institute of Technology, Nagpur for providing the necessary facilities, to carry out the research work. They are also thankful to the Microcare laboratory, Surat (Gujarat) for the biological activity.

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