Synthesis of new 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones and 8-(1*H*-benzimidazol-2-yl)-7-methoxyflavones

S. Satyanarayana Reddy, P. Sreenivas, Y. Jayaprakash Rao, and G. L. D. Krupadanam*

Department of Chemistry, Osmania University, Hyderabad-500007, A. P., India.
e-mail: davidkrupa@hotmail.com

Abstract

A simple and efficient synthesis of 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones **5a-h** and 8-(1*H*-benzimidazol-2-yl)-7-methoxyflavones **7a-d** by the reaction of 8-formyl-7-methoxyflavones **3a-h** with 2-aminothiophenol **4** or 1,2-phenylenediamine **6** under mild acidic conditions.

Keywords: 8-Formyl-7-methoxyflavones, benzothiazoles, benzimidazoles, mild acidic conditions.

Introduction

The heterocycles 2-arylbenzothiazoles and benzimidazoles have attracted considerable attention in diverse areas of chemistry. Some of their derivatives are found in a variety of naturally occurring compounds and are of significant importance in medicinal chemistry.[1-5] Benzothiazole derivatives are widely studied in bioorganic and medicinal chemistry with applications in drug discovery and development for treatment of autoimmune and inflammatory diseases, in the prevention of solid organ transplant rejection, epilepsy, amyotrophic lateral sclerosis, analgesia, tuberculosis, viral infections and cancer. Furthermore, 2-arylbenzothiazoles are currently confirmed as a novel class of potent and selective antitumor agents.[6-8] 2-Substituted benzimidazoles and their derivatives have been shown to exhibit fungicide, antitumour, immunosuppressant and anti-convulsant properties, and have recently been identified as ligands for asymmetric catalysis.[9-17] Naturally occurring flavones have a broad range of bioactivity.[18,19] Synthetic flavones flavone-8-acetic acid[20] and flavopiridol[21] are anti-cancer drugs. Similarly 8-substituted flavones demiflin and flavoxate are coronary vasodilator[22] and diuretic[23] drugs respectively.

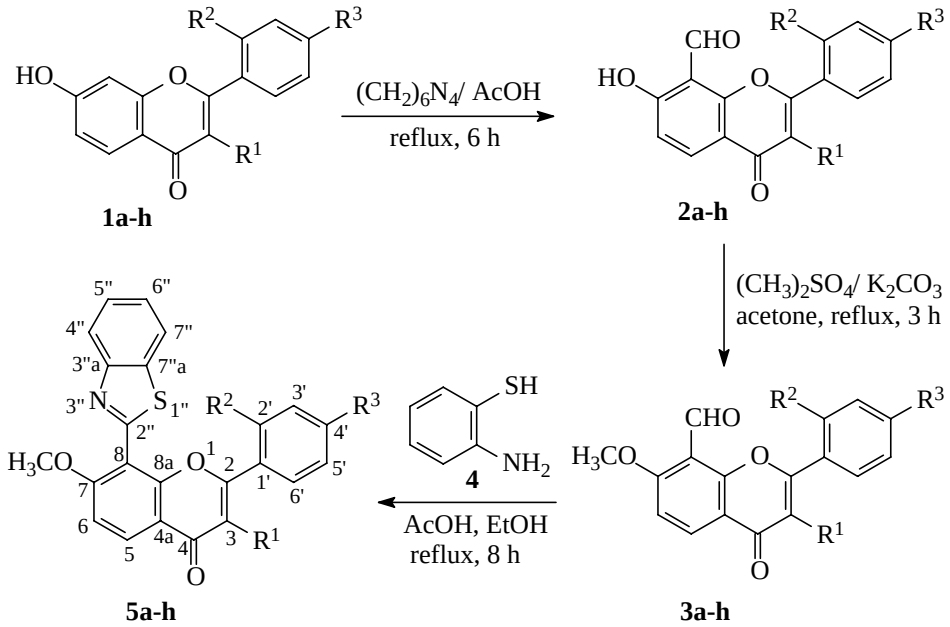
Synthetic routes that are common to the preparation of 2-arylbenzothiazoles and benzimidazoles typically involve the reaction of a carboxylic acid or its derivative with an appropriate 2-aminothiophenol **4** or 1,2-phenylenediamine **6**.[24,25] In this paper we report the

synthesis of new 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones **5a-h** and 8-(1*H*-benzimidazol-2-yl)-7-methoxyflavones **7a-d** starting from 8-formyl-7-methoxyflavones **3a-h**.

Results and discussion

7-Hydroxyflavones **1a-h** were prepared by using the modified Baker-Venkataraman transformation.[26,27] **1a-h** on Duff reaction[28,29] with hexamethylenetetramine (HMT) in AcOH gave 8-formyl-7-hydroxyflavones **2a-h**. 7-Hydroxyflavones **1a-h** and 8-formyl-7-hydroxyflavones **2a-h** are reported earlier in literature.[30-34]

8-Formyl-7-hydroxyflavones **2a-h** and dimethylsulphate in acetone/K_2CO_3 medium on heating afforded 8-formyl-7-methoxyflavones **3a-h**. Equimolar quantities of 8-formyl-7-methoxyflavones **3a-h** and 2-aminothiophenol **4** taken in ethanol containing a few drops of AcOH on refluxing gave 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones **5a-h** (Scheme-1).



1, 2, 3, 5 a) $R^1 = CH_3$, $R^2 = R^3 = H$
b) $R^1 = CH_3$, $R^2 = Cl$, $R^3 = H$
c) $R^1 = CH_3$, $R^2 = H$, $R^3 = Cl$
d) $R^1 = CH_3$, $R^2 = H$, $R^3 = OCH_3$

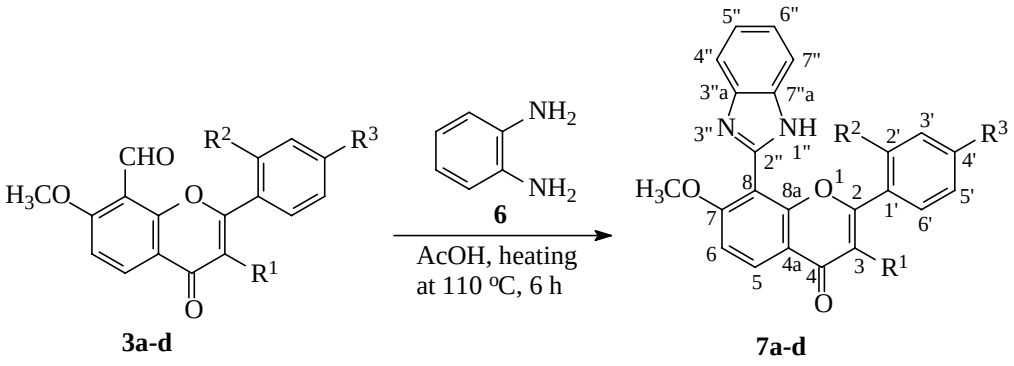
1, 2, 3, 5 e) $R^1 = R^2 = R^3 = H$
f) $R^1 = R^3 = H$, $R^2 = Cl$
g) $R^1 = R^2 = H$, $R^3 = Cl$
h) $R^1 = R^2 = H$, $R^3 = OCH_3$

Scheme-1. Synthesis of 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones **5a-h**.

8-([1,3]Benzothiazol-2-yl)-7-methoxy-3-methylflavone **5a** is characterized from its spectral data. In its IR spectrum, the C=N absorption appeared at 1594 cm^{-1} and the flavone C=O at 1628 cm^{-1} and its UV spectrum showed bands at 308 nm (log ε 4.4), 220 nm (log ε 4.7) and 204 nm

(log ε 4.5). In the ^{1}H NMR spectrum of 8-(1,3-benzothiazol-2-yl)-7-methoxy-3-methylflavone **5a** the signals due to the thiazol-2-yl ring system protons appeared as follows: H-4" appeared as a double doublet at δ 8.12 (*J* = 8.1 Hz, 1.5 Hz) while H-7" appeared at δ 7.91 as a double doublet (*J* = 7.5 Hz, 1.5 Hz), H-5" appeared as a triple doublet (ddd) at δ 7.50 (*J* = 8.3 Hz, 6.8 Hz, 1.5 Hz) and H-6" appeared as a multiplet overlapping with H-3',4',5' protons at δ 7.39. 7-OCH_3 appeared δ 4.00 as a singlet and the 3-CH_3 appeared as a singlet at δ 2.21. The other aromatic protons in flavone ring system showed the signals at expected positions, H-5 and H-6 appeared as a doublets (*J* = 9.0 Hz) at δ 8.35 and δ 7.13. The phenyl H-3',4',5' appeared at δ 7.39 as a multiplet overlapping with H-6" and H-2',6' appeared as a multiplet at δ 7.69. ^{13}C NMR spectrum of **5a** showed the signals due to the benzothiazole moiety: δ 161.5 (C-2"), 158.6 (C-3"a), 123.3 (C-4"), 125.9 (C-5"), 125.2 (C-6"), 121.3 (C-7") and 136.1 (C-7"a). The signals due to the flavone ring system are as follows: δ 154.8 (C-2), 116.9 (C-3), 178.1 (C=O at C-4), 117.0 (C-4a), 129.5 (C-5), 109.1 (C-6), 160.7 (C-7), 111.0 (C-8), 153.0 (C-8a), 133.0 (C-1'), 128.1 (C-2',6'), 129.3 (C-3',5'), 130.1 (C-4'), 56.5 (7-O<u>C</u>H_3) and 11.7 (3-<u>C</u>H_3). The ESI mass spectrum of **5a** showed quasimolecular ion $[M+H]^+$ at *m/z* 400, the $[M+Na]^+$ ion at *m/z* 422 and $[M+K]^+$ ion at *m/z* 438.

Equimolar quantities of 8-formyl-7-methoxyflavones **3a-d** and 1,2-phenylenediamine **6** taken in AcOH on heating gave 8-(1*H*-benzimidazol-2-yl)-7-methoxyflavones **7a-d** (Scheme-2).



3, 7 a) $R^1 = CH_3$, $R^2 = R^3 = H$
b) $R^1 = CH_3$, $R^2 = Cl$, $R^3 = H$
3, 7 c) $R^1 = CH_3$, $R^2 = H$, $R^3 = Cl$
d) $R^1 = CH_3$, $R^2 = H$, $R^3 = OCH_3$

Scheme-2. Synthesis of 8-(1*H*-benzimidazol-2-yl)-7-methoxyflavones **7a-d**.

In the IR spectrum of 8-(1*H*-benzimidazol-2-yl)-7-methoxy-3-methylflavone **7a**, the absorption due to the N-H was observed at 3475 cm^{-1}, the C=N at 1596 cm^{-1} and the flavone C=O at 1628 cm^{-1}. Its UV showed absorption maxima at 320 nm (log ε 4.2), 278 nm (log ε 4.6) and 224 nm (log ε 4.8). In the ^{1}H NMR spectrum of **7a**, the signals due to the benzimidazol-2-yl ring system protons H-4",7" appeared at δ 7.31-7.39 as a multiplet and the H-5",6" as a multiplet overlapping with H-3',4',5' at δ 7.10-7.28. 7-OCH_3 appeared at δ 3.79 as a singlet and the 3-CH_3

as a singlet at δ 2.01. The flavone ring protons H-5 appeared at δ 7.89 as a doublet (J = 9.0 Hz) and H-6 as a doublet at δ 6.74 (J = 9.0 Hz). Phenyl H-3',4',5' appeared at δ 7.10-7.28 as a multiplet overlapping with H-5",6" and H-2',6' appeared as a multiplet at δ 7.52-7.60. In its ^{13}C NMR spectrum, the carbon signals due to the benzimidazole moiety are as follows: δ 161.7 (C-2"), 137.6 (C-3"a, C-7"a), 114.0 (C-4", C-7") and 123.8 (C-5", C-6"). The carbon signals of the flavone ring are as follows: δ 155.3 (C-2), 116.7 (C-3), 177.6 (C=O at C-4), 117.9 (C-4a), 130.3 (C-5), 109.2 (C-6), 159.2 (C-7), 106.3 (C-8), 144.0 (C-8a), 132.2 (C-1'), 128.5 (C-2',6'), 129.1 (C-3',5'), 133.4 (C-4'), 56.6 (7-O<u>C</u>H$_3$) and 11.4 (3-<u>C</u>H$_3$). The FAB MS of **7a** showed quasimolecular ion $[M+H]^+$ peak at *m/z* 383.

Experimental Section

General. All melting points were determined on a Polmon digital melting point apparatus (Model No. MP-96) and are uncorrected. IR spectra were recorded on a Schimadzu 435 instrument using KBr and UV spectra were recorded on a Schimadzu UV-VIS 1601 spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Varian Gemini Unity Spectrometer in $CDCl_3$ using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on a VG AUTOSPEC mass spectrometer. Elemental analyses were performed on a PE-2400 elemental analyzer.

General procedure for the synthesis of 8-formyl-7-methoxyflavones 3a-h

A mixture of 8-formyl-7-hydroxyflavones **2a-h** (10 mmol) and dimethylsulphate (1.42 mL, 15 mmol) dissolved in dry acetone (100 mL) containing anhydrous potassium carbonate (3 g, 21.5 mmol) was refluxed on water bath for 4 h. Acetone was evaporated and residue treated with crushed ice**.** The crude solid which separated out, was subjected to column chromatography over silica gel (60-120 mesh) elution with petroleum ether : ethyl acetate (8 : 2) and recrystallized from benzene to afford 8-formyl-7-methoxyflavones **3a-h** in 75-80% yield.

8-Formyl-7-methoxy-3-methylflavone 3a. White needles; mp: 195 °C; IR (KBr): 1689 cm^{-1} (8-CHO), 1635 cm^{-1} (flavone C=O); UV (MeOH): 317 nm (log ε 4.5), 253 nm (log ε 4.8), 221 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 10.61 (s, 8-CHO), 8.42 (d, J = 9.0 Hz, H-5), 7.79 (m, H-2', 6'), 7.53 (m, H-3', 4', 5'), 7.08 (d, J = 9.0 Hz, H-6), 4.07 (s, 7-OCH$_3$), 2.21 (s, 3-CH$_3$); ^{13}C NMR ($CDCl_3$): δ 186.9 (8-CHO), 177.4 (C-4), 165.4 (C-7), 160.7 (C-8a), 156.2 (C-2), 133.5 (C-4'), 132.7 (C-1'), 130.4 (C-5), 129.2 (C-3', 5'), 128.4 (C-2', 6'), 117.6 (C-4a), 116.4 (C-3), 112.6 (C-8), 109.1 (C-6), 56.7 (7-O<u>C</u>H$_3$), 11.6 (3-<u>C</u>H$_3$); ESI MS: *m/z* 295 $[M+H]^+$ and 317$[M+Na]^+$; Anal. calcd. for $C_{18}H_{14}O_4$: C, 73.46, H, 4.79 Found C, 73.29, H, 4.94%.

2'-Chloro-8-formyl-7-methoxy-3-methylflavone 3b. White needles; mp: 167 °C; IR (KBr): 1697 cm^{-1} (8-CHO), 1643 cm^{-1} (flavone C=O); UV (MeOH): 309 nm (log ε 4.7), 255 nm (log ε 4.8), 219 nm (log ε 4.5); ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 10.50 (s, 8-CHO), 8.39 (d, J = 9.0 Hz, H-5), 7.45-7.61 (m, H-3', 4', 5', 6'), 7.24 (d, J = 9.0 Hz, H-6), 4.07 (s, 7-OCH$_3$), 1.90 (s, 3-CH$_3$);

^{13}C NMR ($CDCl_3$): δ 186.8 (8-CHO), 177.1 (C-4), 164.9 (C-7), 159.0 (C-8a), 157.3 (C-2), 133.4 (C-2'), 131.7 (C-1'), 131.5 (C-4'), 131.2 (C-3'), 130.9 (C-5'), 130.1 (C-5), 126.8 (C-6'), 119.9 (C-4a), 116.6 (C-3), 112.7 (C-8), 109.5 (C-6), 56.7 (7-O<u>C</u>H$_3$), 11.0 (3-<u>C</u>H$_3$); ESI MS: *m/z* 329 $[M+H]^+$, 351 $[M+Na]^+$ and 367 $[M+K]^+$; Anal. calcd. for $C_{18}H_{13}ClO_4$: C, 65.76, H, 3.99. Found C, 65.91, H, 4.10%.

4'-Chloro-8-formyl-7-methoxy-3-methylflavone 3c. White needles; mp: 174 °C; IR (KBr): 1687 cm^{-1} (8-CHO), 1643 cm^{-1} (flavone C=O); UV (MeOH): 314 nm (log ε 4.3), 261 nm (log ε 4.5), 224 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 10.60 (s, 8-CHO), 8.40 (d, *J* = 9.0 Hz, H-5), 7.81 (d, *J* = 8.7 Hz, H-2', 6'), 7.53 (d, *J* = 8.7 Hz, H-3', 5'), 7.07 (d, *J* = 9.0 Hz, H-6), 4.08 (s, 7-OCH$_3$), 2.22 (s, 3-CH$_3$); ^{13}C NMR ($CDCl_3$): δ 186.9 (8-CHO), 177.3 (C-4), 165.7 (C-7), 159.5 (C-8a), 155.8 (C-2), 136.6 (C-4'), 133.5 (C-5), 131.1 (C-1'), 130.5 (C-3', 5'), 128.7 (C-2', 6'), 117.7 (C-4a), 116.3 (C-3), 112.5 (C-8), 109.2 (C-6), 56.6 (7-O<u>C</u>H$_3$), 11.5 (3-<u>C</u>H$_3$); ESI MS: *m/z* 329 $[M+H]^+$, 351 $[M+Na]^+$ and 304; Anal. calcd. for $C_{18}H_{13}ClO_4$: C, 65.76, H, 3.99. Found C, 65.58, H, 3.87%.

8-Formyl-7,4'-dimethoxy-3-methylflavone 3d. White needles; mp: 163 °C; IR (KBr): 1690 cm^{-1} (8-CHO), 1623 cm^{-1} (flavone C=O); UV (MeOH): 311 nm (log ε 4.6), 250 nm (log ε 4.7), 217 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 10.62 (s, 8-CHO), 8.39 (d, *J* = 9.0 Hz, H-5), 7.63 (d, *J* = 8.6 Hz, H-2', 6'), 7.06 (m, H-6, 3', 5'), 4.22 (s, 7-OCH$_3$), 3.93 (s, 4'-OCH$_3$), 2.25 (s, 3-CH$_3$); ^{13}C NMR ($CDCl_3$): δ 187.2 (8-CHO), 175.8 (C-4), 166.1 (C-4'), 160.4 (C-7), 159.1 (C-8a), 156.8 (C-2), 133.9 (C-5), 129.6 (C-2', 6'), 124.0 (C-1'), 116.6 (C-4a), 114.1 (C-3), 113.3 (C-3', 5'), 111.3 (C-8), 109.1 (C-6), 56.8 (7-O<u>C</u>H$_3$), 54.6 (4'-O<u>C</u>H$_3$), 10.7 (3-<u>C</u>H$_3$); ESI MS: *m/z* 325 $[M+H]^+$, 365, 295, 259, 203, 184, 121 and 107; Anal. calcd. for $C_{19}H_{16}O_5$: C, 70.36, H, 4.97. Found C, 70.55, H, 4.76%.

8-Formyl-7-methoxyflavone 3e. White needles; mp: 211 °C; IR (KBr): 1684 cm^{-1} (8-CHO), 1643 cm^{-1} (flavone C=O); UV (MeOH): 316 nm (log ε 4.4), 245 nm (log ε 4.6), 222 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 10.52 (s, 8-CHO), 8.37 (d, *J* = 9.0 Hz, H-5), 7.61 (m, H-2', 6'), 7.52 (m, H-3', 4', 5'), 6.98 (d, *J* = 9.0 Hz, H-6), 6.55 (s, H-3), 4.14 (s, 7-OCH$_3$); ^{13}C NMR ($CDCl_3$): δ 186.0 (8-CHO), 176.7 (C-4), 167.2 (C-7), 159.8 (C-2), 157.7 (C-8a), 135.0 (C-4'), 130.4 (C-5), 128.7 (C-2', 6'), 128.6 (C-3', 5'), 128.2 (C-1'), 118.5 (C-4a), 114.8 (C-8), 108.9 (C-6), 106.3 (C-3), 56.4 (7-O<u>C</u>H$_3$); FAB MS: *m/z* 281 $[M+H]^+$, 207, 147 and 73; Anal. calcd. for $C_{17}H_{12}O_4$: C, 72.85, H, 4.32. Found C, 73.00, H, 4.17%.

2'-Chloro-8-formyl-7-methoxyflavone 3f. White needles; mp: 189 °C; IR (KBr): 1678 cm^{-1} (8-CHO), 1633 cm^{-1} (flavone C=O); UV (MeOH): 307 nm (logε 4.7), 253 nm (logε 4.3), 224 nm (logε 4.8); ^{1}H NMR ($CDCl_3$): δ 10.62 (s, 8-CHO), 8.41 (d, *J* = 9.0 Hz, H-5), 7.95 (m, H-6'), 7.49 (m, H-3', 4', 5'), 7.10 (d, *J* = 9.0 Hz, H-6), 6.86 (s, H-3), 4.08 (s, 7-OCH$_3$); ^{13}C NMR ($CDCl_3$): δ 187.1 (8-CHO), 176.0 (C-4), 167.1 (C-7), 162.4 (C-8a), 157.8 (C-2), 134.8 (C-4'), 133.3 (C-2'), 131.6 (C-3'), 131.3 (C-1'), 130.8 (C-5'), 130.1 (C-5), 126.9 (C-6'), 120.5 (C-4a), 112.3 (C-8), 109.7 (C-6), 106.4 (C-3), 56.7 (7-O<u>C</u>H$_3$); ESI MS: *m/z* 315 $[M+H]^+$, 179, 165, 121 and 107; Anal. calcd. for $C_{17}H_{11}ClO_4$: C, 64.88, H, 3.52. Found C, 64.92, H, 3.65%.

4'-Chloro-8-formyl-7-methoxyflavone 3g. White needles; mp: 194 °C; IR (KBr): 1683 cm^{-1} (8-CHO), 1642 cm^{-1} (flavone C=O); UV (MeOH): 313 nm (log ε 4.7), 258 nm (log ε 4.7), 221 nm (log ε 4.5); ^{1}H NMR ($CDCl_3$): δ 10.53 (s, 8-CHO), 8.31 (d, *J* = 9.0 Hz, H-5), 7.82 (d, *J* = 8.7 Hz, H-2',6'), 7.60 (d, *J* = 8.7 Hz, H-3',5'), 6.93 (d, *J* = 9.0 Hz, H-6), 6.64 (s, H-3), 4.12 (s, 7-OCH_3); ^{13}C NMR ($CDCl_3$): δ 186.9 (8-CHO), 177.2 (C-4), 167.2 (C-7), 158.2 (C-2), 152.1 (C-8a), 136.7 (C-4'), 135.1 (C-5), 130.9 (C-1'), 130.0 (C-3',5'), 129.0 (C-2', 6'), 118.8 (C-4a), 114.9 (C-8), 109.3 (C-6), 106.3 (C-3), 56.5 (7-O<u>C</u>H_3); ESI MS: *m/z* 315 $[M+H]^+$; Anal. calcd. for $C_{17}H_{11}ClO_4$: C, 64.88, H, 3.52. Found C, 64.61, H, 3.38%.

8-Formyl-7,4'-dimethoxyflavone 3h. White needles; mp: 168 °C; IR (KBr): 1670 cm^{-1} (8-CHO), 1616 cm^{-1} (flavone C=O); UV (MeOH): 308 nm (log ε 4.4), 256 nm (log ε 4.6), 219 nm (log ε 4.7); ^{1}H NMR ($CDCl_3$): δ 10.60 (s, 8-CHO), 8.22 (d, *J* = 9.0 Hz, H-5), 7.62 (d, *J* = 8.6 Hz, H-2', 6'), 7.16 (d, *J* = 8.6 Hz, H-3', 5'), 6.98 (d, *J* = 9.0 Hz, H-6), 6.68 (s, H-3), 4.02 (s, 7-OCH_3), 3.88 (s, 4'-OCH_3); ^{13}C NMR ($CDCl_3$): δ 191.1 (8-CHO), 171.7 (C-4), 167.5 (C-4'), 167.2 (C-7), 161.7 (C-2), 152.9 (C-8a), 127.8 (C-2', 6'), 125.0 (C-5), 123.6 (C-1'), 119.8 (C-4a), 117.1 (C-6), 114.6 (C-3', 5'), 110.3 (C-8), 106.8 (C-3), 63.7 (7-O<u>C</u>H_3), 62.8 (4'-O<u>C</u>H_3); EI MS: *m/z* 310 ($M^{+\cdot}$) (100); Anal. calcd. for $C_{18}H_{14}O_5$: C, 69.67, H, 4.55. Found C, 69.54, H, 4.87%.

General procedure for the synthesis of 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones 5a-h

To a solution of 8-formyl-7-methoxyflavones **3a-h** (10 mmol) in 20 mL of absolute ethanol, 4-5 drops of glacial acetic acid and 2-aminothiophenol **4** (1.25 g, 10 mmol) were added. The mixture was refluxed for 8 h. Ethanol was removed by distillation under reduced pressure, the residue was treated with crushed ice (100 g) and extracted three times with ethyl acetate (50 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure affording a solid. This on column chromatography with silica gel (60-120 mesh) and elution with petroleum ether: ethyl acetate (7 : 3) and recrystallization from methanol gave 8-([1,3]benzothiazol-2-yl)-7-methoxyflavones **5a-h** in 65-70% yield.

8-([1,3]Benzothiazol-2-yl)-7-methoxy-3-methylflavone 5a. Light brown colored needles; mp 176 °C; IR (KBr): 1594 cm^{-1} (C=N), 1628 cm^{-1} (flavone C=O); UV (MeOH): 308 nm (log ε 4.4), 220 nm (log ε 4.7), 204 nm (log ε 4.5); ^{1}H NMR ($CDCl_3$): δ 8.35 (d, *J* = 9.0 Hz, H-5), 8.12 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 7.91 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.69 (m, H-2',6'), 7.50 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.39 (m, H-3',4',5'; H-6''), 7.13 (d, *J* = 9.0 Hz, H-6), 4.00 (s, 7-OCH_3), 2.21 (s, 3-CH_3); ^{13}C NMR($CDCl_3$): δ 178.1 (C-4), 161.5 (C-2''), 160.7 (C-7), 158.6 (C-3''a), 154.8 (C-2), 153.0 (C-8a), 136.1 (C-7''a), 133.0 (C-1'), 130.1 (C-4'), 129.5 (C-5), 129.3 (C-3',5'), 128.1 (C-2',6'), 125.9 (C-5''), 125.2 (C-6''), 123.3 (C-4''), 121.3 (C-7''), 117.0 (C-4a), 116.9 (C-3), 111.0 (C-8), 109.1 (C-6), 56.5 (7-O<u>C</u>H_3), 11.7 (3-<u>C</u>H_3); ESI MS: *m/z* 400 $[M+H]^+$, 422 $[M+Na]^+$ and 438 $[M+K]^+$; Anal. calcd. for $C_{24}H_{17}NO_3S$: C, 72.16, H, 4.29, N, 3.51. Found C, 72.33, H, 4.10, N, 3.76%.

8-([1,3]Benzothiazol-2-yl)-2'-chloro-7-methoxy-3-methylflavone 5b. Light brown colored needles; mp 179 °C; IR (KBr): 1605 cm^{-1} (C=N), 1643 cm^{-1} (flavone C=O); UV (MeOH): 298 nm (log ε 4.2), 218 nm (log ε 4.6), 204 nm (log ε 4.8); ^{1}H NMR ($CDCl_3$): δ 8.38 (d, *J* = 9.0

Hz, H-5), 8.04 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 7.88 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.27-7.50 (m, H-3',4',5',6'; H-5'',6''), 7.15 (d, J = 9.0 Hz, H-6), 3.98 (s, 7-OCH_3), 1.91 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.5 (C-4), 161.6 (C-2''), 158.9 (C-7), 158.7 (C-3''a), 155.3 (C-2), 152.9 (C-8a), 136.3 (C-7''a), 133.2 (C-2'), 131.7 (C-1'), 131.1 (C-4'), 130.7 (C-3'), 129.8 (C-5), 129.4 (C-5'), 126.5 (C-6'), 125.7 (C-5''), 125.0 (C-6''), 123.3 (C-4''), 121.2 (C-7''), 119.2 (C-4a), 116.9 (C-3), 110.6 (C-8), 109.2 (C-6), 56.5 (7-O<u>C</u>H_3), 10.9 (3-<u>C</u>H_3); ESI MS: *m/z* 434 $[M+H]^+$ and 456 $[M+Na]^+$; Anal. calcd. for $C_{24}H_{16}ClNO_3S$: C, 66.43, H, 3.72, N, 3.23. Found C, 66.71, H, 3.50, N, 3.09%.

8-([1,3]Benzothiazol-2-yl)-4'-chloro-7-methoxy-3-methylflavone 5c. Light brown colored needles; mp 238 °C; IR (KBr): 1595 cm^{-1} (C=N), 1623 cm^{-1} (flavone C=O); UV (MeOH): 308 nm (log ε 4.4), 222 nm (log ε 4.7), 204 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 8.36 (d, J = 9.0 Hz, H-5), 8.09 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 7.92 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.68 (d, J = 8.7 Hz, H-2',6'), 7.52 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.42 (ddd, $J_{6,7}$ = 8.3 Hz, $J_{6,5}$ = 6.8 Hz, $J_{6,4}$ = 1.5 Hz, H-6''), 7.38 (d, J = 8.7 Hz, H-3',5'), 7.15 (d, J = 9.0 Hz, H-6), 4.03 (s, 7-OCH_3), 2.21 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.4 (C-4), 163.5 (C-2''), 161.3 (C-7), 156.6 (C-2), 155.9 (C-3''a), 152.8 (C-8a), 136.0 (C-7''a), 135.1 (C-4'), 131.8 (C-3',5'), 130.6 (C-2',6'), 130.1 (C-1'), 128.2 (C-5), 126.0 (C-5''), 125.4 (C-6''), 123.2 (C-4''), 121.4 (C-7''), 118.2 (C-4a), 117.5 (C-3), 111.3 (C-8), 109.3 (C-6), 56.6 (7-O<u>C</u>H_3), 11.5(3-<u>C</u>H_3); FAB MS: *m/z* 434 $[M+H]^+$; Anal. calcd. for $C_{24}H_{16}ClNO_3S$: C, 66.43, H, 3.72, N, 3.23. Found C, 66.71, H, 3.48, N, 3.45%.

8-([1,3]Benzothiazol-2-yl)-7,4'-dimethoxy-3-methylflavone 5d. White needles; mp 191 °C; IR (KBr): 1604 cm^{-1} (C=N), 1627 cm^{-1} (flavone C=O); UV (MeOH): 314 nm (log ε 4.5), 224 nm (log ε 4.7), 204 nm (log ε 4.8); ^{1}H NMR ($CDCl_3$): δ 8.33 (d, J = 9.0 Hz, H-5), 8.11 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 7.90 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.62 (d, J = 8.9 Hz, H-2',6'), 7.49 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.40 (ddd, $J_{6,7}$ = 8.3 Hz, $J_{6,5}$ = 6.8 Hz, $J_{6,4}$ = 1.5 Hz, H-6''), 7.10 (d, J = 9.0 Hz, H-6), 6.84 (d, J = 8.9 Hz, H-3',5'), 4.01 (s, 7-OCH_3), 3.80 (s, 4'-OCH_3), 2.21 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 178.0 (C-4), 161.2 (C-2''), 160.8 (C-4'), 160.6 (C-7), 158.7 (C-2), 154.6 (C-3''a), 152.9 (C-8a), 136.0 (C-7''a), 130.8 (C-3',5'), 129.4 (C-5), 127.3 (C-1'), 125.8 (C-5''), 125.1 (C-6''), 123.2 (C-4''), 121.2 (C-7''), 116.8 (C-4a), 116.0 (C-3), 113.4 (C-3',5'), 110.8 (C-8), 108.8 (C-6), 56.5 (7-O<u>C</u>H_3), 55.2 (4'-O<u>C</u>H_3), 11.8 (3-<u>C</u>H_3); ESI MS: *m/z* 430 $[M+H]^+$, 360 and 331; Anal. calcd. for $C_{25}H_{19}NO_4S$: C, 69.91, H, 4.46, N, 3.26. Found C, 70.08, H, 4.59, N, 3.42%.

8-([1,3]Benzothiazol-2-yl)-7-methoxyflavone 5e. Light brown colored needles; mp 208 °C; IR (KBr): 1588 cm^{-1} (C=N), 1627 cm^{-1} (flavone C=O); UV (MeOH): 310 nm (log ε 4.6), 232 nm (log ε 4.3), 204 nm (log ε 4.8); ^{1}H NMR ($CDCl_3$): δ 8.46 (d, J = 9.0 Hz, H-5), 8.22 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 8.00 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.89 (m, H-2',6'), 7.58 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.33-7.49 (m, H-3',4',5'; H-6''), 7.17 (d, J = 9.0 Hz, H-6), 6.79 (s, H-3), 4.07 (s, 7-OCH_3); ^{13}C NMR ($CDCl_3$): δ 177.6 (C-4), 163.6 (C-2''), 161.7 (C-2), 158.5 (C-7), 154.9 (C-3''a), 152.9 (C-8a), 136.1 (C-7''a), 131.5 (C-4'), 131.4 (C-1'), 129.2 (C-5), 128.5 (C-2',6'), 126.5 (C-3',5'), 126.1 (C-5''), 125.5 (C-6''), 123.3 (C-4''), 121.4 (C-7''),

118.3 (C-4a), 111.5 (C-8), 109.3 (C-6), 106.8 (C-3), 56.6 (7-O<u>C</u>H$_3$); FAB MS: *m/z* 386 [M+H]$^+$; Anal. calcd. for $C_{23}H_{15}NO_3S$: C, 71.67, H, 3.92, N, 3.63. Found C, 71.84, H, 3.68, N, 3.91%.

8-([1,3]Benzothiazol-2-yl)-2'-chloro-7-methoxyflavone 5f. Brown colored needles; mp 187 °C; (KBr): 1599 cm^{-1} (C=N), 1635 cm^{-1} (flavone C=O); UV (MeOH): 308 nm (log ε 4.5), 227 nm (log ε 4.8), 207 nm (log ε 4.6); ^{1}H NMR (CDCl$_3$): δ 8.31 (d, J = 9.0 Hz, H-5), 8.10 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 7.94 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.35-7.67 (m, H-3',4',5',6'; H-5'',6''), 7.19 (d, J = 9.0 Hz, H-6), 6.62 (s, H-3), 4.03 (s, 7-OCH$_3$); ^{13}C NMR (CDCl$_3$): δ 176.9 (C-4), 161.4 (C-2''), 159.0 (C-7), 158.5 (C-3''a), 155.8 (C-2), 151.6 (C-8a), 137.1 (C-7''a), 132.5 (C-2'), 131.4 (C-1'), 130.9 (C-4'), 131.0 (C-3'), 129.8 (C-5), 129.7 (C-5'), 126.8 (C-6'), 125.9 (C-5''), 124.6 (C-6''), 123.3 (C-4''), 121.5 (C-7''), 120.1 (C-4a), 111.7 (C-8), 109.4 (C-6), 106.8 (C-3), 56.2 (7-O<u>C</u>H$_3$); ESI MS: *m/z* 420 [M+H]$^+$; Anal. calcd. for $C_{23}H_{14}ClNO_3S$: C, 65.79, H, 3.36, N, 3.34. Found C, 65.92, H, 3.49, N, 3.10%.

8-([1,3]Benzothiazol-2-yl)-4'-chloro-7-methoxyflavone 5g. White needles; mp 245 °C; IR (KBr): 1595 cm^{-1} (C=N), 1646 cm^{-1} (flavone C=O); UV (MeOH): 316 nm (log ε 4.4), 228 nm (log ε 4.9), 204 nm (log ε 4.7); ^{1}H NMR (CDCl$_3$): δ 8.36 (d, J = 9.0 Hz, H-5), 8.20 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 8.01 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.89 (d, J = 8.7 Hz, H-2',6'), 7.60 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.49 (ddd, $J_{6,7}$ = 8.3 Hz, $J_{6,5}$ = 6.8 Hz, $J_{6,4}$ = 1.5 Hz, H-6''), 7.38 (d, J = 8.7 Hz, H-3',5'), 7.18 (d, J = 9.0 Hz, H-6), 6.77 (s, H-3), 4.08 (s, 7-OCH$_3$); ^{13}C NMR (CDCl$_3$): δ 177.3 (C-4), 161.6 (C-2''), 160.8 (C-2), 158.7 (C-7), 153.0 (C-3''a), 152.8 (C-8a), 137.7 (C-7''a), 130.2 (C-4'), 130.0 (C-1'), 129.2 (C-5), 129.1 (C-2',6'), 127.7 (C-3',5'), 126.2 (C-5''), 125.5 (C-6''), 123.1 (C-4''), 121.4 (C-7''), 118.5 (C-4a), 112.9 (C-8), 109.3 (C-6), 106.9 (C-3), 56.6 (7-O<u>C</u>H$_3$); ESI MS: *m/z* 420 [M+H]$^+$, 442 [M+Na]$^+$ and 327; Anal. calcd. for $C_{23}H_{14}ClNO_3S$: C, 65.79, H, 3.36, N, 3.34. Found C, 65.92, H, 3.55, N, 3.17%.

8-([1,3]Benzothiazol-2-yl)-7,4'-dimethoxyflavone 5h. White needles; mp 148 °C; IR (KBr): 1503 cm^{-1} (C=N), 1624 cm^{-1} (flavone C=O); UV (MeOH): 310 nm (log ε 4.7), 222 nm (log ε 4.5), 206 nm (log ε 4.8); ^{1}H NMR (CDCl$_3$): δ 8.35 (d, J = 9.0 Hz, H-5), 8.22 (dd, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz, H-4''), 8.01 (dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.5 Hz, H-7''), 7.85 (d, J = 8.6 Hz, H-2',6'), 7.61 (ddd, $J_{5,4}$ = 8.3 Hz, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 1.5 Hz, H-5''), 7.47 (ddd, $J_{6,7}$ = 8.3 Hz, $J_{6,5}$ = 6.8 Hz, $J_{6,4}$ = 1.5 Hz, H-6''), 7.20 (d, J = 9.0 Hz, H-6), 6.84 (d, J = 8.6 Hz, H-3',5'), 6.69 (s, H-3), 4.04 (s, 7-OCH$_3$), 3.83 (s, 4'-OCH$_3$); ^{13}C NMR (CDCl$_3$): δ 177.4 (C-4), 164.0 (C-2''), 163.5 (C-4'), 162.2 (C-2), 161.8 (C-7), 161.3 (C-3''a), 152.8 (C-8a), 136.0 (C-7''a), 130.6 (C-2',6'), 128.2 (C-5), 127.8 (C-1'), 126.0 (C-5''), 125.4 (C-6''), 123.6 (C-4''), 121.4 (C-7''), 117.5 (C-4a), 113.9 (C-3',5'), 111.3 (C-8), 109.3 (C-6), 105.3 (C-3), 56.6 (7-O<u>C</u>H$_3$), 55.4 (4'-O<u>C</u>H$_3$); ESI MS: *m/z* 416 [M+H]$^+$, 438 [M+Na]$^+$ and 382; Anal. calcd. for $C_{24}H_{17}NO_4S$: C, 69.38, H, 4.12, N, 3.37. Found C, 69.12, H, 4.39, N, 3.24%.

General procedure for the synthesis of 8-(1*H*-benzimidazol-2-yl)-7-methoxy-3-methylflavones 7a-d

To a solution of 8-formyl-3-methyl-7-methoxyflavones **3a-d** (10 mmol) in glacial acetic acid (20 mL) and 1,2-phenylenediamine **6** (1.08 g, 10 mmol) were added and stirred at room

temperature for 30 min. Then the mixture was refluxed on oil bath at 110 °C for 6 h. Acetic acid was removed by distillation under reduced pressure and the residue obtained was treated with crushed ice (100 g). The solid obtained was filtered and subjected to column chromatography with 60-120 mesh silica gel and eluted with petroleum ether : ethyl acetate (1 : 1) and on recrystallization from methanol gave 8-(1*H*-benzimidazol-2-yl)-7-methoxy-3-methylflavones (**7a-d**) in 55-65% yield.

8-(1*H*-Benzimidazol-2-yl)-7-methoxy-3-methylflavone 7a. White needles; mp 151 °C; IR (KBr): 3475 cm^{-1}(NH), 1596 cm^{-1} (C=N), 1628 cm^{-1} (flavone C=O); UV (MeOH): 320 nm (log ε 4.2), 278 nm (log ε 4.6), 224 nm (log ε 4.8); ^{1}H NMR ($CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, H-5), 7.52-7.60 (m, H-2',6'), 7.31-7.39 (m, H-4",7"), 7.10-7.28 (m, H-3',4',5'; H-5",6"), 6.74 (d, *J* = 9.0 Hz, H-6), 3.79 (s, 7-OCH_3), 2.01 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.6 (C-4), 161.7 (C-2"), 159.2 (C-7), 155.3 (C-2), 144.0 (C-8a), 137.6 (C-3"a, 7"a), 133.4 (C-4'), 132.2 (C-1'), 130.3 (C-5), 129.1 (C-3',5'), 128.5 (C-2',6'), 123.8 (C-5",6"), 117.9 (C-4a), 116.7 (C-3), 114.0 (C-4",7"), 109.2 (C-6), 106.3 (C-8), 56.6 (7-O<u>C</u>H_3), 11.4 (3-<u>C</u>H_3); FAB MS: *m/z* 383 $[M+H]^+$; Anal. calcd. for $C_{24}H_{18}N_2O_3$: C, 75.38, H, 4.74, N, 7.33. Found C, 75.52, H, 4.89, N, 7.21%.

8-(1*H*-Benzimidazol-2-yl)-2'-chloro-7-methoxy-3-methylflavone 7b. Light brown colored needles; mp 167 °C; IR (KBr): 3489 cm^{-1} (NH), 1604 cm^{-1} (C=N), 1634 cm^{-1} (flavone C=O); UV (MeOH): 304 nm (log ε 4.5), 280 nm (log ε 4.7), 246 nm (log ε 4.8); ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J* = 9.0 Hz, H-5), 7.54 (m, H-6'), 7.13-7.35 (m, H-5'; H-4",5",6",7"), 6.82-6.97 (m, H-6; H-3',4'), 3.83 (s, 7-OCH_3), 1.84 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.3 (C-4), 161.6 (C-2"), 159.1 (C-7), 154.8 (C-8a), 143.5 (C-2), 138.7 (C-3"a, 7"a), 132.6 (C-2'), 131.1 (C-4'), 130.9 (C-3'), 130.5 (C-5), 129.5 (C-5'), 128.9 (C-1'), 126.6 (C-6'), 122.3 (C-5",6"), 118.8 (C-4a), 116.3 (C-3), 115.2 (C-4", 7"), 109.0 (C-6), 107.3 (C-8), 56.3 (7-O<u>C</u>H_3), 11.0 (3-<u>C</u>H_3); ESI MS: *m/z* 417 $[M+H]^+$ and 419 $[MH+2]^+$; Anal. calcd. for $C_{24}H_{17}ClN_2O_3$: C, 69.15, H, 4.11, N, 6.72. Found C, 69.31, H, 4.27, N, 6.58%.

8-(1*H*-Benzimidazol-2-yl)-4'-chloro-7-methoxy-3-methylflavone 7c. Light brown colored needles; mp 192 °C; IR (KBr): 3476 cm^{-1} (NH), 1605 cm^{-1} (C=N), 1639 cm^{-1} (flavone C=O); UV (MeOH): 309 nm (log ε 4.6), 274 nm (log ε 4.7), 221 nm (log ε 4.9); ^{1}H NMR ($CDCl_3$): δ 8.04 (d, *J* = 9.0 Hz, H-5), 7.22-7.50 (m, H-2',6'; H-4",5",6",7"), 7.03 (d, *J* = 8.7 Hz, H-3',5'), 6.57 (d, *J* = 9.0 Hz, H-6), 3.87 (s, 7-OCH_3), 2.02 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.4 (C-4), 161.6 (C-2"), 159.3 (C-7), 155.7 (C-2), 144.5 (C-8a), 138.0 (C-3"a, 7"a), 136.2 (C-4'), 133.1 (C-5), 131.3 (C-1'), 130.8 (C-2',6'), 128.5 (C-3',5'), 122.2 (C-5",6"), 117.9 (C-4a), 116.7 (C-3), 114.3 (C-4",7"), 109.4 (C-6), 106.0 (C-8), 56.7 (7-O<u>C</u>H_3), 11.6(3-<u>C</u>H_3); ESI MS: *m/z* 417 $[M+H]^+$; Anal. calcd. for $C_{24}H_{17}ClN_2O_3$: C, 69.15, H, 4.11, N, 6.72. Found C, 69.41, H, 4.04, N, 6.85%.

8-(1*H*-Benzimidazol-2-yl)-7,4'-dimethoxy-3-methylflavone 7d. White needles; mp 183 °C; IR (KBr): 3481 cm^{-1} (NH), 1605 cm^{-1} (C=N), 1629 cm^{-1} (flavone C=O); UV (MeOH): 314 nm (log ε 4.4), 278 nm (log ε 4.6), 248 nm (log ε 4.8), 224 nm (log ε 4.7); ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 8.20 (d, *J* = 9.0 Hz, H-5), 7.53-7.71 (m, H-2',6'; H-4",7"), 7.10-7.28 (m, H-6; H-5",6"), 6.80 (d, *J* = 8.6 Hz, H-3',5'), 3.97 (s, 7-OCH_3), 2.14 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 176.6 (C-4), 160.5 (C-4'), 159.7 (C-2"), 159.5 (C-7), 153.7 (C-2), 142.8 (C-8a), 137.4 (C-3"a,7"a), 129.5

(C-2',6'), 127.7 (C-5), 123.9 (C-1'), 121.2 (C-5",6"), 115.2 (C-4a), 114.5 (C-3), 114.0 (C-4",7"), 112.4 (C-3',5'), 108.0 (C-6), 106.7 (C-8), 55.5 (7-O<u>C</u>H$_3$), 54.2 (4'-O<u>C</u>H$_3$), 10.7 (3-<u>C</u>H$_3$); ESI MS: *m/z* 413 $[M+H]^+$ and 435 $[M+Na]^+$; Anal. calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80, H, 4.89, N, 6.79. Found C, 72.67, H, 5.01, N, 6.62%.

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