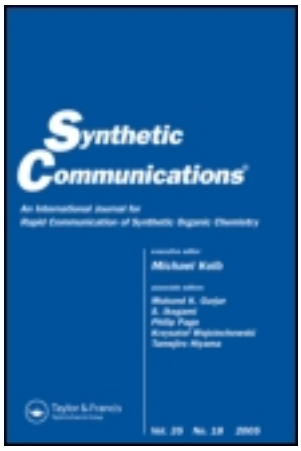

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SYNTHESIS OF α-AZIDO-2′-HYDROXYCHALCONES FROM CHALCONE DIBROMIDES WITH AZIDE ION

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Dedicated to Prof. Albert Lévai on the occasion of his 60th birthday

ABSTRACT

The reaction of the 2′-hydroxychalcone dibromides with azide ion was found to afford various products such as α-azido-2′-hydroxychalcones, flavones, aurones, isoxazoles or the parent chalcones depending on the substituent pattern of the substrate. Efficient transformation of α-azido-2′-hydroxychalcones to 3-amino-2-substituted chromones was also demonstrated.

Key Words: Azides; Chalcones dibromides; Flavones; Isoxazoles; Substituent effect

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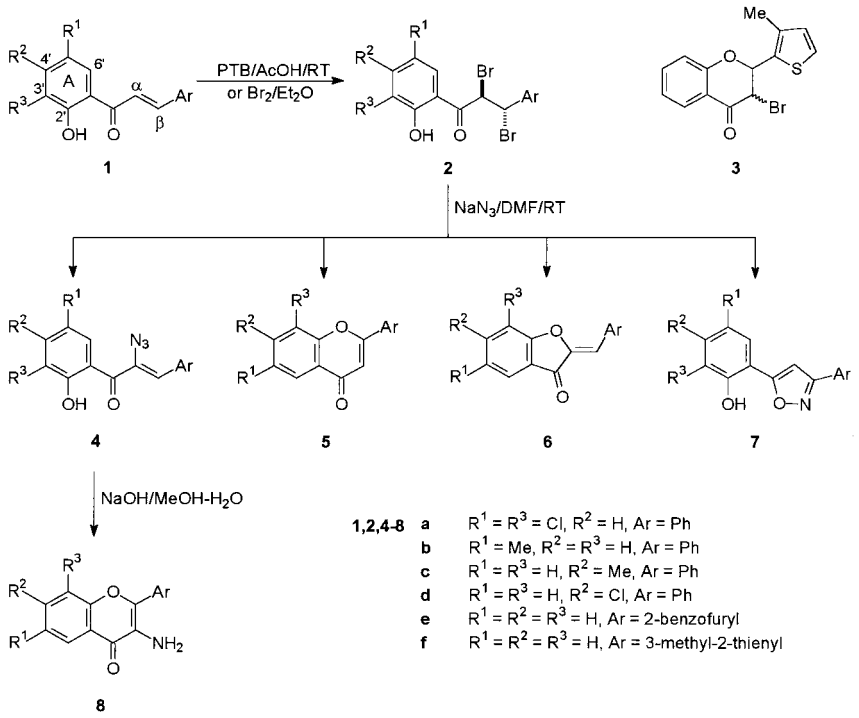
INTRODUCTION

2′-Hydroxychalcone dibromides have been studied very thoroughly due to their synthetic importance in the preparation of 2-aryl-4*H*-1-benzopyran-4-ones (flavones), 2-arylmethylenbenzo[b]furan-3(2*H*)-ones (aurones) and related derivatives.[1–3] It was also pointed out that the reaction of 2′-hydroxychalcone dibromide and its 4-substituted derivatives with azide ion resulted in the formation α-azido-2′-hydroxychalcone.[4,5] The reaction was found to depend strongly on the electronic character of the substituent in position 4. In the presence of electron-withdrawing group other reactions such as the formation of aurones, 3-(2-hydroxyphenyl)-5-(4-substituted phenyl)isoxazoles and 3(5)-(2-hydroxybenzoyl)-5(3)-(4-substituted phenyl)-1,2,3-triazoles dominated and α-azides were only minor products. The product distribution was interpreted on the basis of mechanistic considerations [5] but no studies were performed on the effect of the substituents in ring A or the change of ring B for heteroaromatic moiety. As a part of an on-going project we were interested in the synthesis of various 3-aminoflavones and -chromones and investigated the reaction of chalcone dibromides with the above-mentioned substituent pattern and azide ion. Some selected and characteristic results are presented in this contribution.

RESULTS AND DISCUSSION

Starting material dibromides **2a–e** were synthesized in good yields (60–79%) by the reaction of the corresponding 1-(2-hydroxyphenyl)-3-phenyl/hetaryl-2-propen-1-ones **1a–e** with pyridinium tribromide (PTB) in acetic acid[6] at room temperature (Scheme 1). The *erythro* relative configuration was proven by the large $^{3}J_{\alpha,\beta}$ coupling constants (11.0–11.7 Hz) observed in their ^{1}H NMR spectra. Surprisingly, no chalcone dibromide **2f** but a diastereomeric mixture of *cis* -and *trans*-3-bromo-2-(3-methyl-2-thienyl)chromanone (**3**) with a ratio of 58 : 42 was obtained from chalcone **1f** under similar conditions. The structure of **3** was supported by spectroscopic evidences and its easy transformation into chromone **5f** upon treatment by triethyl amine. The desired *erythro*-**2f** was prepared by using bromine in diethyl ether as brominating reagent.

The reaction of dibromides **2a–f** with sodium azide in DMF solution at room temperature[5] afforded various products such as *Z*-α-azidochalcones **4**, flavones **5**, aurones **6**, isoxazoles **7** and parent chalcones **1** which were separated by column chromatography. The product ratio depended strongly on the substituents R^1–R^3 and Ar (Scheme 1, Table 1). The formation of azides **4** took place with complete diastereoselectivity, the *Z*



Scheme 1.

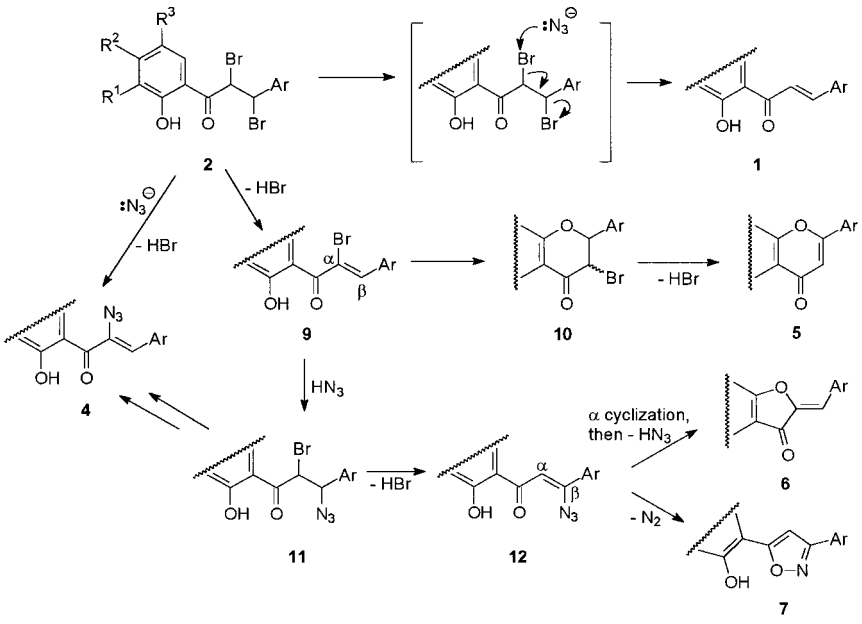
Table 1. Product Distribution in the Reaction of Dibromides **2** and NaN_3

Starting Mat'l	R^1	R^2	R^3	Ar	Yield[a] (%) **1**	**4**	**5**	**6**	**7**
2a	Cl	H	Cl	Ph	0	0	93	0	0
2b	Me	H	H	Ph	0	75	0	0	2.5
2c	H	Me	H	Ph	0	73	1.5	0	3.8
2d	H	Cl	H	Ph	0	50	27	3.8	2.3
2e	H	H	H	2-benzofuryl	2.5	5.2	0	5.0	51.2
2f	H	H	H	3-Me-2-thienyl	47	1.7	30	0	0

[a]Yields refer to pure isolated products.

relative configuration of the products was assigned on the basis of their spectral data.[7] Structure elucidation of products **7** was crucial since both isoxazoles and the isomeric oxazoles could be formed from the intermediate β-azidochalcones **12** (vide infra) depending on their stereochemistry. *Z*-β-azidovinyl ketones were reported to give isoxazoles by spontaneous loss of nitrogen whereas *E* isomers were found more stable and yielded oxazoles only at elevated temperature or under photolytic conditions [8–12] but it was unknown how structural changes in the substrate modified its reactivity. Our products were unequivocally assigned as isoxazoles on the basis of the measured ^{13}C chemical shifts of the heteroring which fitted excellently with the ranges reported by Baumstark and his coworkers for 3,5-diarylisoxazoles.[13] Consequently, the intermediates **12** should possess of *Z* stereochemistry.

Analysis of product ratio data given in the Table 1 led us to some conclusions which could be important in designing of syntheses. In the presence of electron-attracting chloro substituent(s) the formation of chromones **5** by β cyclization of intermediate **9** and the subsequent HBr elimination from 3-bromochromanone **10** is preferred (Scheme 2), the more acidic phenolate tends to add faster to the β carbon atom of



Scheme 2.

the enone system and consequently the yield of azide **4** decreases. Data collected in the Table 1 reveal that aurones **6** and isoxazoles **7** are only minor products, if any. The only exception is the reaction of the 2-benzofuryl derivative **2e**. Compounds **6** and **7** were reported[5,8] to be formed via β-azidochalcones **12** and the participation of this pathway (Scheme 2) is usually smaller than of the route leading to azides **4** unless Ar group exerts a marked stabilizing effect on the β-carbanions of E1cB steps.[5,8] The extended delocalisation in the adjacent 2-benzofuryl unit clearly provides this stabilization.

Surprisingly, azide ion-induced dehalogenation leading to the parent chalcone **1f** was the major route in the reaction of dibromide **2f** (Scheme 2). Similar dehalogenation have also been observed as a side reaction in the case of 2′-hydroxy-4-methoxychalcone dibromide[5] but it have been found to be major pathway in the reaction of some α-arylidene benzo(hetera)cyclanone dibromides [14]. The increasing stabilization of the benzylic type cation by the β-aryl or heteroaryl group supports this dehalogenation. Noteworthy that Donnelly and coworkers[15] have been published on the similarity of the effects of 2-thienyl and 4-methoxyphenyl substituents in the chalcone series. By comparing the product distribution of heteroaryl derivatives **2e** and **2f** we can also conclude that there is no general rule for the reactivity of dibromides **2** with heterocyles in their position β and the electronic character of the group plays decisive role.

In accordance with our earlier observations,[4,5] the treatment of azides **4b–f** with sodium hydroxide in methanol solution resulted in the formation of 3-amino-2-substituted-chromones **8b–f** in good-to-excellent yields (62–93%) (Scheme 1) proving that this method is the more efficient approach to these target compounds.

EXPERIMENTAL SECTION

General

Column chromatography was performed on Kieselgel 60 or Kieselgel 40.—Melting points: Boetius hot-stage, uncorrected values. – IR: Perkin Elmer 16 PC-FT-IR; KBr pellets unless otherwise stated. – NMR: Varian Gemini 200, Bruker WP 200 SY, Bruker AM 360 (200 or 360 MHz for ^{1}H; 50 or 90 MHz for ^{13}C), recorded in $CDCl_3$ solution unless otherwise stated. Chemical shifts are given in δ relative to an internal standard TMS ($\delta = 0$) or to the residual $CHCl_3$ ($\delta = 7.26$ for ^{1}H NMR and $\delta = 77.0$ for ^{13}C NMR).—MS: VG Trio-2 (EI, 70 eV). – Elemental analysis: Carlo Erba EA 1106 CHN

analyzer.—Starting chalcones **1a**[16], **1b**[17], **1c**[18], and **1d**[19] were synthesized according to literature procedures.

Synthesis of *trans*-3-Hetaryl-1-(2-hydroxyphenyl)-2-propen-1-ones 1e,f. General procedure: A mixture of 2′-hydroxyacetophenone (14.4 mL, 0.1196 mol), the appropriate aldehyde (0.1175 mol), methanol (200 mL) and 50% NaOH solution (2.8 mL) was allowed to stand at room temperature for 24 h then acidified with dil. hydrochloric acid and the precipitation was filtered off. The crude product was purified by crystallization.

***trans*-3-(2-Benzofuryl)-1-(2-hydroxyphenyl)-2-propen-1-one(1e):** Yield: 44%. M.p. 125–126°C (methanol–ethyl acetate). IR: 1641 (C=O), 1571, 1486, 1289, 1256, 1199, 947, 801, 745 cm^{-1}. ^1H NMR: 6.97 (d, 1H, 5′-H), 7.04 (dd, $J = 8.4$, 1.6 Hz, 1H, 3′-H), 7.09 (s, 1H, 3″-H), 7.27 (m, 1H, 6″-H), 7.41 (m, 1H, 5″-H), 7.52 (m, 2H, 4′, 7″-H), 7.63 (dd, $J = 8.1$, 1.7 Hz, 4″-H), 7.79, 7.80 (AB q, $J = 16$ Hz, 2H, H_α, H_β), 8.00 (dd, $J = 7.7$, 2.0 Hz, 1H, 6′-H), 12.84 (s, 1H, 2′-OH). MS: 264 ($M^{\oplus\bullet}$, 57), 247 (M–OH, 7), 236 (M–CO, 7), 221 (6), 171 (M–PhO, 11), 144 (RDA fragment, 100), 131 (benzopyrylium ion, 88), 120 (RDA fragment, 20), 115 (36), 89 (17), 77 (8), 65 (33). Anal. calcd for $C_{17}H_{12}O_3$ (264.28): C, 77.26; H, 4.58%. Found: C, 77.02; H, 4.74%.

***trans*-1-(2-Hydroxyphenyl)-3-(3-methyl-2-thienyl)-2-propen-1-one (1f):** Yield: 59%. M.p. 77–78°C (methanol). IR: 3434 (OH), 1632 (C=O), 1560, 1440, 1336, 1302, 1264, 1246, 1200, 1152, 842, 760, 728 cm^{-1}. ^1H NMR: 2.42 (s, 3H, 3″-Me), 6.94 (m, 1H, 5′-H), 6.93 (d, $J = 5.1$ Hz, 1H, 4″-H), 7.02 (dd, $J = 8.4$, 1.5 Hz, 1H, 3′-H), 7.36 (d, $J \sim 5.0$ Hz, 1H, 5″-H), 7.38 (d, $J = 15.0$ Hz, 1H, H_α), 7.49 (m, 1H, 4′-H), 7.89 (dd, $J = 8.1$, 2.0 Hz, 1H, 6′-H), 8.14 (dd, $J = 15.0$, 0.9 Hz, 1H, H_β), 12.94 (s, 1H, 2′-OH). Anal. calcd. for $C_{14}H_{12}O_2S$ (244.30): C, 68.83; H, 4.95%. Found: C, 69.03; H, 5.11%.

Synthesis of *erythro*-2′-hydroxychalcone dibromides 2. General Procedure: To a stirred suspension of *trans*-2′-hydroxychalcone **1** (5.50 mmol) in acetic acid (15 mL), pyridinium tribromide (PTB) (2.110 g, 6.597 mmol) was added in portions at room temperature in 1 h. After 24 h stirring the mixture was poured into water, the precipitate was filtered off and washed with water. The crude product was crystallized from hexane–benzene (5 : 1).

***erythro*-3′,5′-Dichloro-2′-hydroxychalcone dibromide (2a):** Yield: 60%. M.p. 151–152°C. (Lit.[16] 115–116°C). IR: 1647 (C=O), 1430, 1322, 1238, 1226, 1160, 767, 740, 702, 692 cm^{-1}. ^1H NMR (DMSO-d_6): 5.78 (d, $J = 11.7$ Hz, 1H, H_α), 6.79 (d, $J = 11.7$ Hz, 1H, H_β), 7.46 (m, 3H, 3,4,5-H), 7.80 (dd, $J = 7.8$, 1.9 Hz, 2H, 2,6-H), 8.05 (d, $J = 2.2$ Hz, 1H, 4′-H), 8.24 (d, $J = 2.2$ Hz, 1H, 6′-H), 11.70 (s, 1H, 2′-OH). Anal. calcd for $C_{15}H_{10}Br_2Cl_2O_2$ (452.95): C, 39.78; H, 2.23%. Found: C, 40.02; H, 2.08%.

***erythro*-2′-Hydroxy-5′-methylchalcone dibromide (2b):** Yield: 78%. M.p. 146–148°C. (Lit.[20] 146°C, lit.[21] 151–152°C).

erythro-2′-Hydroxy-4′-methylchalcone dibromide (2c): Yield: 72%. M.p. 158–159°C. IR: 1639 (C=O), 1338, 1302, 1255, 1236, 1213, 1136, 783, 693 cm^{-1}. ^1H NMR: 2.41 (s, 3H, 4′-Me), 5.64 (d, $J = 11.3$ Hz, 1H, H_α), 5.87 (d, $J = 11.3$ Hz, 1H, H_β), 6.83 (dd, $J = 7.5$, 1.5 Hz, 1H, 5′-H), 6.91 (br s, 1H, 3′-H), 7.38–7.57 (m, 5H, Ph), 7.74 (d, $J = 8.2$ Hz, 1H, 6′-H), 11.89 (s, 1H, 2′-OH). Anal. calcd for $C_{16}H_{14}Br_2O_2$ (398.09): C, 48.27; H, 3.54%. Found: C, 48.07; H, 3.79%.

***erythro*-4′-Chloro-2′-hydroxychalcone dibromide (2d):** Yield: 73%. M.p. 185–187°C. (Lit.[22] 180°C). IR: 1641 (C=O), 1612, 1482, 1242, 1200, 1182, 1078, 979, 903, 773, 691 cm^{-1}. ^1H NMR (DMSO-d_6): 5.78 (d, $J = 11.4$ Hz, 1H, H_α), 6.61 (d, $J = 11.4$ Hz, 1H, H_β), 7.10–7.18 (m, 2H, 3′,5′-H), 7.34–7.48 (m, 3H, 3,4,5-H), 7.70 (dd, $J = 8.2$, 2.0 Hz, 2H, 2′,6′-H), 8.10 (d, $J = 8.0$ Hz, 1H, 6′-H), 11.74 (s, 1H, 2′-OH). Anal. calcd for $C_{15}H_{11}Br_2ClO_2$ (418.51): C, 43.05; H, 2.65%. Found: C, 42.97; H, 2.77%.

***erythro*-3-(2-Benzofuryl)-2,3-dibromo-1-(2-hydroxyphenyl)-1-propanone (2e):** Yield: 79%. M.p. 173–175°C (hexane-ethyl acetate). IR: 1633 (C=O), 1613, 1540, 1450, 1299, 1280, 1249, 1196, 751 cm^{-1}. ^1H NMR: 5.88 (d, $J = 11.0$ Hz, 1H, H_α), 6.15 (d, $J = 11.0$ Hz, 1H, H_β), 6.96 (s, 1H, 3″-H), 7.00–7.13 (m, 2H, 3′,5′-H), 7.31, 7.42 (2xm, 2H, 5″,6″-H), 7.57–7.66 (m, 3H, 4′,4″,7″-H), 7.92 (dd, $J = 8.1$, 1.3 Hz, 1H, 6′-H), 11.80 (s, 1H, 2′-OH). Anal. calcd for $C_{17}H_{12}Br_2O_3$ (424.08): C, 48.15; H, 2.85%. Found: C, 47.99; H, 2.96%.

***erythro*-2,3-Dibromo-1-(2-hydroxyphenyl)-3-(3-methyl-2-thienyl)-1-propanone (2f):** To a solution of 1-(2-hydroxyphenyl)-3-(3-methyl-2-thienyl)-2-propene-1-one (**1f**) (1.8 g, 7.368 mmol) in diethyl ether (40 mL), bromine (0.6 mL, 11.646 mmol) was dropped under stirring at 0°C. The precipitate was filtered off, washed with diisopropyl ether and recrystallized from diethyl ether to give 2.193 g (74%) of pure **2f**. M.p. 119–121°C. IR: 1636 (C=O), 1574, 1486, 1448, 1304, 1248, 1200, 752, 724 cm^{-1}. ^1H NMR: 2.33 (s, 3H, 3″-Me), 5.86 (d, $J = 11.0$ Hz, 1H, H_α), 6.06 (dd, $J = 11.0$, 0.9 Hz, 1H, H_β), 6.83 (d, $J = 5.1$ Hz, 1H, 4″-H), 6.96–7.18 (m, 2H, 3′,5′-H), 7.39 (d, $J = 5.1$ Hz, 1H, 5″-H), 7.57 (m, 1H, 4′-H), 7.84 (dd, $J = 8.4$, 1.6 Hz, 1H, 6′-H), 11.78 (s, 1H, 2′-OH). MS: 244 ($M^{\oplus\bullet}$ – Br_2, 50), 243 (19), 236 (M-Br_2 – H_2O, 29), 151 (12), 124 (3-Me-2-vinylthiophene, 100), 120 (M—Br_2 – 3-Me-2-vinylthiophene, 62), 111 (35), 97 (23), 78 (31), 77 (31). Anal. calcd for $C_{14}H_{12}Br_2O_2S$ (404.11): C, 41.61; H, 2.99%. Found: C, 41.88; H, 3.12%.

Synthesis of 2-(3-Methyl-2-thienyl)chromone (5f) via 3-bromo-2-(3-methyl-2-thienyl)chromanone (3): To a stirred solution of *trans*-1-(2-hydroxyphenyl)-3-(3-methyl-2-thienyl)-2-propen-1-one (**1f**) (2.443 g, 10.000 mmol) in acetic acid (25 mL), PTB (3.520 g, 11.055 mmol) was added at room temperature. After 18 h the mixture was poured into water, extracted with chloroform (3 × 60 mL), the extract was washed with $NaHCO_3$ solution, dried (Na_2SO_4)

and concentrated under reduced pressure. Column chromatography separation (1,2-dichloroethane–hexane = 2 : 1) of the residue afforded 2.567 g (79%) oily **3** product.

3. IR (neat): 1694 (C=O), 1606, 1580, 1472, 1462, 1338, 1300, 1222 (C–O–C), 1150, 1114, 1020, 764, 718 cm^{-1}. ^1H NMR: 2.27, 2.32 (2 × s, 2 × 3H, 3′-Me), 4.54 (d, $J = 1.5$ Hz, 1H, 3-H, *cis*-**3**), 4.95 (d, $J = 9.1$ Hz, 1H, 3-H, *trans*-**3**), 5.69 (d, $J = 1.5$ Hz, 1H, 2-H, *cis*-**3**), 5.85 (d, $J = 9.1$ Hz, 1H, 2-H, *trans*-**3**), 6.87, 6.90 (2 × d, $J = 5.1$ Hz, 2 × 1H, 4′-H), 7.03–7.19 (m, 2H, 6,8-H), 7.27, 7.35 (2 × d, $J = 5.1$ Hz, 2 × 1H, 5′-H), 7.52-7.59 (m, 1H, 7-H), 7.96–8.04 (m, 1H, 5-H). Diastereomeric ratio *trans*-**3**/*cis*-**3** = 42 : 58 was determined by ^1H NMR spectroscopy.

A mixture of **3** (2.301 g, 7.119 mmol), triethyl amine (1.3 mL, 9.366 mmol) and DMF (15 mL) was stirred for 3 d, then poured into water, extracted with chloroform (3 × 40 mL), the extract was washed with water, dried ($CaCl_2$) and the solvent was removed under reduced pressure. The oily residue solidified on standing. Hexane–abs. ethanol (10 : 1) mixture was added, the crude product was filtered off and recrystallized from hexane–ethyl acetate (5 : 1) mixture to give 651 mg (38%) pure **5f** product. M.p. 77–78°C. IR 1640 (C=O), 1596, 1569, 1466, 1414, 1362, 1128, 778 cm^{-1}. ^1H NMR: 2.58 (s, 3H, 3′-Me), 6.64 (s, 1H, 3-H), 6.99 (d, $J = 5.2$ Hz, 4′-H), 7.39 (m, 1H, 6-H), 7.44 (d, $J = 5.2$ Hz, 5′-H), 7.51 (dd, $J = 8.4$ Hz, 1H, 8-H), 7.70 (m, 1H, 7-H), 8.23 (dd, $J = 8.0$, 1.9 Hz, 1H, 5-H). Anal. calcd for $C_{14}H_{10}O_2S$ (242.29): C, 69.40; H, 4.16%. Found: C, 69.57; H, 4.02%.

Treatment of 2′-hydroxychalcone dibromides 2 with sodium azide. General procedure: A mixture of the corresponding dibromide 2 (10.000 mmol), NaN_3 (2.423 g, 37.271 mmol) and DMF (45 mL) was stirred at room temperature for 3 h then poured into water and extracted with dichloromethane (4 × 40 mL). The dried ($MgSO_4$) extract was concentrated under reduced pressure and the residue was submitted to column chromatography (hexane–ethyl acetate = 4 : 1 or 1,2-dichloroethane–toluene = 3 : 1). The mixed fractions of lower R_f value were re-chromatographed (toluene–ethyl acetate = 4 : 1 and/or hexane–acetone = 6 : 1) to give pure products. Yields of isolated products are shown in the Table 1, physical and spectral characteristics of products are listed below.

***Z*-α-Azido-2′-hydroxy-5′-methylchalcone (4b):** M.p. 82–85°C (dec.). IR: 2116 (N_3), 1630 (C=O), 1586, 1482, 1448, 1340, 1292, 1238, 1192, 840, 692 cm^1. ^1H NMR: 2.30 (s, 3H, 5′-Me), 6.36 (s, 1H, H_β), 6.99 (d, $J = 8.3$ Hz, 1H, 3′-H), 7.25–7.46 (m, 4H, 3,4,5,4′-H), 7.56 (d, $J = 1.7$ Hz, 1H, 6′-H), 7.83 (dd, $J = 8.1$, 1.8 Hz, 2H, 2,6-H), 10.94 (s, 1H, 2′-OH). ^{13}C NMR: 20.4 (5′-Me), 118.1 (C_α), 118.4 (C-3′), 127.7 (C-4), 128.2 (C-1′), 128.6 (C-2,6), 129.6 (C_β), 130.4 (C-3,5), 131.8 (C-6′), 132.5,

133.0 (C-1,5′), 137.8 (C-4′), 160.8 (C-2′), 184.6 (C=O). Anal. calcd for $C_{16}H_{13}N_3O_2$ (279.29): C, 68.81; H, 4.69; N, 15.04%. Found: C, 69.02; H, 4.55; N, 14.89%.

***Z*-α-Azido-2′-hydroxy-4′-methylchalcone (4c):** M.p. 82–85°C (methanol). IR: 2118 (N_3), 1628 (C=O), 1610, 1502, 1449, 1382, 1345, 1296, 1244, 910, 772 cm^{-1}. ^1H NMR: 2.40 (s, 3H, 5′-Me), 6.32 (s, 1H, H_β), 6.76 (d, $J = 8.1$ Hz, 1H, 5′-H), 6.89 (br s, 1H, 3′-H), 7.31–7.44 (m, 3H, 3,4,5-H), 7.69 (d, $J = 8.1$ Hz, 1H, 6′-H), 7.81 (dd, $J = 7.9$, 1.7 Hz, 2H, 2,6-H), 11.28 (s, 1H, 2′-OH). Anal. calcd for $C_{16}H_{13}N_3O_2$ (279.29): C, 68.81; H, 4.69; N, 15.04. Found: C, 69.04; H, 4.65; N, 14.99.

***Z*-α-Azido-4′-chloro-2′-hydroxychalcone (4d):** M.p. 90–94°C (dec.) (methanol). IR: 2118 (N_3), 1620 (C=O), 1485, 1447, 1377, 1331, 1203, 1060, 945, 775 cm^{-1}. ^1H NMR: 6.33 (s, 1H, H_β), 6.92 (dd, $J = 8.2$, 2.1 Hz, 1H, 5′-H), 7.11 (d, $J = 2.1$ Hz, 1H, 3′-H), 7.33–7.50 (m, 3H, 3,4,5-H), 7.74 (d, $J = 8.2$ Hz, 1H, 6′-H), 7.83 (m, 2H, 2,6′-H), 11.29 (s, 1H, 2′-OH). Anal. calcd for $C_{15}H_{10}ClN_3O_2$ (299.71): C, 60.11; H, 3.36; N, 14.02%. Found: C, 59.89; H, 3.35; N, 13.72%.

***Z*-2-Azido-3-(2-benzofuryl)-1-(2-hydroxyphenyl)-2-propene-1-one (4e):** M.p. 108–109°C (methanol). IR: 2122 (N_3), 1622 (C=O), 1598, 1584, 1544, 1484, 1370, 1340, 1278, 1208, 740 cm^{-1}. ^1H NMR: 6.49 (s, 1H, H_β), 6.96 (m, 1H, 5′-H), 7.09 (dd, $J = 8.4$, 0.9 Hz, 1H, 3′-H), 7.28, 7.34 (2 × m, 2 × 1H, 5″,6″-H), 7.45 (dd, $J = 8.2$, 0.7 Hz, 1H, 7″-H), 7.55 (m, 2H, 4′,3″-H), 7.64 (dd, $J = 7.0$, 1.2 Hz, 1H, 4″-H), 7.77 (dd, $J = 8.0$, 1.6 Hz, 1H, 6′-H), 10.97 (s, 1H, 2′-OH). ^{13}C NMR: 111.2, 111.5 (C-3″,7″), 116.4 (C-3′), 118.2 (C_α), 118.8, 119.2, 122.0, 123.4, 126.2 (C_β, C-5′,4″,5″,6″), 128.7 (C-1″), 131.9 (C-6′), 133.0 (C-3a″), 136.8 (C-4′), 150.3 (C-7a″), 154.9 (C-2″), 162.7 (C-2′), 193.1 (C-1). Anal. calcd for $C_{17}H_{11}N_3O_3$ (305.29): C, 66.88; H, 3.63; N, 13.76%. Found: C, 66.98; H, 3.42; N, 13.57%.

***Z*-2-Azido-1-(2-hydroxyphenyl)-3-(3-methyl-2-thienyl)-2-propene-1-one (4f):** Orange oil. IR (neat): 3070, 2922 (OH), 2112 (N_3), 1628 (C=O), 1558, 1330, 1260, 1218, 1176, 1030, 1010, 964, 944, 772 cm^{-1}. ^1H NMR: 2.35 (s, 3H, 3″-Me), 6.79 (s, 1H, H_β), 6.80 (d, $J \sim 5.0$ Hz, 1H, 4″-H), 7.07–7.21 (m, 2H, 3′,5′-H), 7.56 (d, $J = 5.0$ Hz, 1H, 5″-H), 7.75 (m, 1H, 4′-H), 7.92 (dd, $J = 8.7$, 2.2 Hz, 1H, 6′-H), 10.97 (s, 1H, 2′-OH). Anal. calcd for $C_{14}H_{11}N_3O_2S$ (285.32): C, 58.94; H, 3.89; N, 14.73%. Found: C, 59.11; H, 3.51; N, 14.48%.

6,8-Dichloroflavone (5a): M.p. 165–167°C (ethyl methyl ketone). (Lit.[23] 154°C). IR: 3072 (C-H), 1665 (C=O), 1640 (C=C), 1562, 1461, 1440, 1350, 1302, 872, 769 cm^{-1}. ^1H NMR: 6.88 (s, 1H, 3-H), 7.53–7.60 (m, 3H, 3′,4′,5′-H), 7.75 (d, $J = 2.5$ Hz, 1H, 7-H), 7.97–8.02 (m, 2H, 2′,6′-H), 8.11 (d, $J = 2.5$ Hz, 1H, 5-H). Anal. calcd for $C_{15}H_8Cl_2O_2$ (291.13): C, 61.88; H, 2.77%. Found: C, 61.69; H, 2.58%.

7-Methylflavone (5c): M.p. 116–120°C (hexane). (Lit.[24] 123°C). ^{1}H NMR: 2.51 (s, 3H, 7-Me), 6.88 (s, 1H, 3-H), 7.27 (dd, $J = 8.0$, 1.4 Hz, 1H, 6-H), 7.38 (br s, 1H, 8-H), 7.51 (m, 3H, 3′,4′,5′-H), 7.92 (m, 2H, 2′,6′-H), 8.12 (d, $J = 8.0$ Hz, 1H, 5-H).

7-Chloroflavone (5d): M.p. 153–154°C (hexane–abs. ethanol). (Lit.[19] 156–157°C) ^{1}H NMR: 6.83 (s, 1H, 3-H), 7.38 (dd, $J = 8.6$, 1.8 Hz, 1H, 6-H), 7.51–7.56 (m, 3H, 3′,4′,5′-H), 7.59 (d, $J = 1.8$ Hz, 1H, 8-H), 7.90 (m, 2H, 2′,6′-H), 8.16 (d, $J = 8.6$ Hz, 1H, 5′-H).

6-Chloroaurone (6d): M.p. 140–142°C (benzene–hexane). (Lit.[22] 195°C). IR: 1712 (C=O), 1658 (C=C), 1605, 1429, 1126, 1057, 919, 768 cm^{-1}. ^{1}H NMR: 6.90 (s, 1H, H_α), 7.21 (dd, $J = 8.1$, 1.9 Hz, 1H, 5-H), 7.38 (d, $J = 1.9$ Hz, 7-H), 7.45 (m, 3H, 3′,4′,5′-H), 7.75 (d, $J = 8.1$ Hz, 1H, 4-H), 7.89 (dd, $J = 7.9$, 2.3 Hz, 2H, 2′,6′-H). Anal. calcd for $C_{15}H_9ClO_2$ (256.68): C, 70.19; H, 3.53%. Found: C, 70.17; H, 3.47%.

2-[(2-Benzofuryl)methylene]coumaranone (6e): M.p. 152–154°C (methanol). IR: 1697 (C=O), 1641 (C=C), 1595, 1458, 1298, 1185, 1097, 873, 738 cm^{-1}. ^{1}H NMR: 6.93 (s, 1H, H_α), 7.04–7.39 (m, 4H, 5,7,5′,6′-H), 7.43 (s, 1H, 3′-H), 7.52 (d, $J = 8.1$ Hz, 1H, 7′-H), 7.65 (m, 2H, 6,4′-H), 7.77 (d, $J = 7.6$ Hz, 1H, 4-H). ^{13}C NMR: 101.4 (C-3′), 111.5, 112.9 (C-7, C-7′, C_α), 121.7, 123.4, 123.7, 124.6, 126.3 (C-4,5,4′,5′,6′), 128.7 (C-3a,3′a), 136.9 (C-6), 146.8 (C-2), 150.1 (C-7′a), 150.6 (C-2′), 165.8 (C-7a), 183.7 (C-3). Anal. calcd for $C_{17}H_{10}O_3$ (262.26): C, 77.86; H, 3.84%. Found: C, 78.04; H, 3.89%.

5-(2-Hydroxy-5-methylphenyl)-3-phenylisoxazole (7b): M.p. 207–210°C (DMSO). (Lit.[25] 209–211°C, Lit.[26] 214–216°C). IR: 3114 br (OH), 1624 (C=N, isoxazole), 1470 (isoxazole skeleton), 1406, 1280, 1246, 800, 766 cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, 5′-Me), 7.01 (d, $J = 8.7$ Hz, 1H, 3′-H), 7.20 (dd, $J = 8.4$, 2.3 Hz, 1H, 4′-H), 7.34 (s, 1H, 4-H), 7.56–7.59 (m, 3H, 3″,4″,5″-H), 7.67 (d, $J = 2.3$ Hz, 1H, 6′-H), 7.96–7.98 (m, 2H, 2″,6″-H), 10.44 (s, 1H, 2′-OH).

5-(2-Hydroxy-4-methylphenyl)-3-phenylisoxazole (7c): M.p. 232–235°C (DMSO). (Lit.[26] 240–242°C). IR: 3126 br (OH), 2922, 1622 (C=N, isoxazole), 1574, 1472 (isoxazole skeleton), 1410, 1256, 814, 766 cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, 4′-Me), 6.84 (d, $J = 8.0$ Hz, 1H, 5′-H), 6.92 (br s, 1H, 3′-H), 7.29 (s, 1H, 4-H), 7.55 (m, 3H, 3″,4″,5″-H), 7.74 (d, $J = 8.0$ Hz, 1H, 6′-H), 7.94–7.97 (m, 2H, 2″,6″-H), 10.57 (s, 1H, 2′-OH).

5-(4-Chloro-2-hydroxyphenyl)-3-phenylisoxazole (7d): M.p. 268–271°C (DMSO). IR: 3050 br (OH), 1616 (C=N, isoxazole), 1472 (isoxazole skeleton), 1420, 1262, 850, 796, 766 cm^{-1}. ^{1}H NMR (DMSO-d_6): 7.06 (dd, $J = 8.4$, 1.9 Hz, 1H, 5′-H), 7.12 (d, $J = 1.9$ Hz, 1H, 3′-H), 7.35 (s, 1H, 4′-H), 7.52–7.56 (m, 3H, 3″,4″,5″-H), 7.85 (d, $J = 8.4$ Hz, 1H, 6′-H), 7.92–7.97 (m, 2H, 2″,6″-H), 11.22 (br s, 1H, 2′-OH). ^{13}C NMR (DMSO-d_6): 101.3 (C-

4), 108.4 (C-3′), 119.8 (C-5′), 126.9 (C-3″,5″), 128.4 (C-6′), 128.9 (C-1″), 129.3 (C-2″,6″), 130.4 (C-4″), 135.6 (C-4′), 155.9 (C-2″), 162.7 (C-3), 166.0 (C-5). Anal. calcd for $C_{15}H_{10}ClNO_2$ (271.70): C, 66.31; H, 3.71; N, 5.16%. Found: C, 66.21; H, 3.99; N, 4.98%.

3-(2-Benzofuryl)-5-(2-hydroxyphenyl)isoxazole (7e): M.p. 248–249°C (acetone-methanol). IR: 3080 br (OH), 1614 (C=N, isoxazole), 1572, 1446 (isoxazole skeleton), 1387, 1262, 807, 753 cm^{-1}. ^1H NMR (DMSO-d_6): 7.00 (m, 1H, 5′-H), 7.11 (d, $J = 8.2$ Hz, 1H, 3′-H), 7.31–7.49 (m, 4H, 4,5″,6″,7″-H), 7.73–7.79 (m, 3H, 4′-3″,4″-H), 7.87 (d, $J = 7.8$ Hz, 1H, 6′-H), 10.81 (s, 1H, 2′-OH).). ^{13}C NMR (DMSO-d_6): 101.0 (C-4), 107.9 (C-3″), 111.8 (C-7″), 113.6 (C-1′), 116.7 (C-3′), 119.7 (C-5′), 122.9, 123.9, 126.3, 127.1 (C-6′,4″,5″,6″), 127.9 (C-3″a), 132.1 (C-4′), 146.0 (C-3), 154.9, 155.2 (C-2′, C-2″,7″a), 167.1 (C-5). Anal. calcd for $C_{17}H_{11}NO_3$ (277.27): C, 73.64; H, 4.00; N, 5.05%. Found: C, 73.82; H, 3.89; N, 5.22%.

Synthesis 3-aminoflavones 8. General procedure: To the stirred solution of α-azido-2′-hydroxychalcone **4** (4.000 mmol) in methanol (20 mL) 1% sodium hydroxide solution (4 mL) was added dropwise at room temperature. The solution turned immediately red and gas evolution started. The stirring was maintained for 18 h then the precipitate was filtered off. Addition of water (5 mL) to the mother liquor resulted in the precipitation of a next crop of crystals. The combined crude products were purified by crystallization from methanol.

3-Amino-6-methylflavone (8b): Yield: 86%. M.p. 122.5–125°C. IR: 3398, 3319 (NH_2), 1633 (C=O), 1586, 1563, 1487, 1449, 1397, 1188, 764 cm^{-1}. ^1H NMR: 2.48 (s, 3H, 6-Me), 7.37–7.62 (m, 5H, 7,8,3′,4′,5′-H), 7.94 (m, 2H, 2′,6′-H), 8.06 (d, $J = 1.7$ Hz, 1H, 5-H). ^{13}C NMR: 20.7 (6-Me), 117.8 (C-8), 120.8 (C-4a), 124.9 (C-5), 127.7 (C-2′,6′), 128.2 (C-1′), 129.0 (C-3′,5′), 129.7 (C-4′), 133.1 (C-3), 134.4 (C-6), 134.4 (C-7), 144.4 (C-2), 154.0 (C-8a), 173.7 (C-4). Anal. calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57%. Found: C, 76.41; H, 5.02; N, 5.74%.

3-Amino-7-methylflavone (8c): Yield: 93%. M.p. 113–115°C. IR: 3384, 3304 (NH_2), 1638 (C=O), 1614 (C=C), 1590, 1448, 1188, 766 cm^{-1}. ^1H NMR: 2.49 (s, 3H, 7-Me), 4.02 (s, 2H, NH_2), 7.18 (dd, $J = 8.1$, 1.9 Hz, 1H, 6-H), 7.26 (d, $J = 1.9$ Hz, 1H, 8-H), 7.41–7.59 (m, 3H, 3′,4′,5′-H), 7.91 (dd, $J = 8.4$, 2.0 Hz, 2H, 2′,6′-H), 8.15 (d, $J = 8.1$ Hz, 1H, 5-H). ^{13}C NMR: 21.8 (7-Me), 117.6 (C-8), 120.2 (C-4a), 125.4, 125.7 (C-5,6), 127.5 (C-2′,6′), 128.9 (C-3′,5′), 129.5 (C-4′), 132.9 (C-3), 139.7, 144.0 (C-2,7), 155.6 (C-8a), 173.4 (C-4). Anal. calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57%. Found: C, 76.37; H, 5.39; N, 5.42%.

3-Amino-7-chloroflavone (8d): Yield: 77%. M.p. 167–168.5°C. IR: 3391, 3307 (NH_2), 1643 (C=O), 1612 (C=C), 1593, 1561, 1450, 1439, 1183, 1078 (Ar–Cl), 759 cm^{-1}. ^1H NMR: 3.95 (vbr s, 2H, NH_2), 7.33 (dd,

$J = 8.1$, 2.0 Hz, 1H, 6-H), 7.43–7.61 (m, 4H, 8,3′,4′,5′-H), 7.89 (m, 2H, 2′,6′-H), 8.20 (d, $J = 8.1$ Hz, 1H, 5-H). ^{13}C NMR: 119.8 (C-8), 121.9 (C-4a), 125.0 (C-5,6), 127.6 (C-2′,6′), 128.4 (C-1′), 129.1 (C-3′,5′), 130.0, 132.5 (C-3), 133.1 (C-7), 144.5 (C-2), 153.9 (C-8a), 172.5 (C-4). Anal. calcd for $C_{15}H_{10}ClNO_2$ (271.70): C, 66.31; H, 3.71; N, 5.16%. Found: C, 66.48; H, 3.86; N, 4.99%.

3-Amino-2-(2-benzofuryl)chromone (8e): Yield: 79%. M.p. 147–148°C. IR: 3446, 3348 (NH_2), 1644 (C=O), 1614 (C=C), 1566, 1478, 1430, 1322, 1196, 1162, 800, 742 cm^{-1}. ^{1}H NMR: 4.7 (vbr s, 2H, NH_2), 7.27–7.42 (m, 4H, 6,8,5′,7′-H), 7.48–7.57 (overlapping dd's, 2H, 4′,7′-H), 7.66 (overlapping s and ddd, 2H, 7,3′-H), 8.26 (dd, $J = 8.0$, 1.8 Hz, 1H, 5-H). ^{13}C NMR: 106.3 (C-3′), 111.5 (C-7′), 117.9 (C-8), 120.9 (C-4a), 121.6, 124.0, 124.1, 125.7, 125.9 (C-5,6,4′,5′,6′-H), 127.9, 128.6 (C-2,3′a), 133.3 (C-7), 134.7 (C-3), 150.6, 155.3, 155.4 (C-8a, 2′,7′a), 173.4 (C-4). Anal. calcd for $C_{17}H_{11}NO_3$ (277.27): C, 73.64; H, 4.00; N, 5.05%. Found: C, 73.79; H, 3.79; N, 4.99%.

3-Amino-2-(3-methyl-2-thienyl)chromone (8f): Yield: 62%. M.p. 152–155°C. IR: 3430, 3322 (NH_2), 2924, 2852, 1632 (C=O), 1608 (C=C), 1554, 1468, 1428, 1300, 1186, 754 cm^{-1}. ^{1}H NMR: 2.38 (s, 3H, 3′-Me), 2.72 (br s, 2H, NH_2), 7.02 (d, $J = 5.1$ Hz, 4′-H), 7.38 (m, 1H, 6-H), 7.46 (d, $J = 8.5$ Hz, 1H, 8-H), 7.51 (d, $J = 5.1$ Hz, 1H, 5′-H), 7.65 (m, 1H, 7-H), 8.28 (dd, $J = 8.0$, 1.4 Hz, 1H, 5-H). Anal. calcd for $C_{14}H_{11}NO_2S$ (257.30): C, 65.35; H, 4.31; N, 5.44%. Found: C, 65.11; H, 4.55; N, 5.12%.

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