European Journal of Chemistry

Journal webpage: www.eurjchem.com

# Synthesis, characterization of flavone, isoflavone, and 2,3-dihydrobenzofuran-3-carboxylate and density functional theory studies

Huma Aslam Bhatti [1,*], Nizam Uddin [1,2], Khurshid Ayub [3,4], Bibi Saima [3], Maliha Uroos [5], Jamshed Iqbal [6], Shazia Anjum [7], Mark Edward Light [8], Abdul Hameed [1] and Khalid Mohammed Khan [1]

[1] *Husein Ebrahim Jamal Research Institute of Chemistry, International Centre for Chemical and Biological Sciences, University of Karachi, Karachi, 75270, Pakistan*
[2] *Batterje Medical College for Science and Technology, Jeddah, 21442, Kingdom of Saudi Arabia*
[3] *Department of Chemistry, Commission on Science and Technology for Sustainable Development in the South, Institute of Information Technology, Abbottabad, 22060, Pakistan*
[4] *Department of Chemistry, College of Science, King Faisal University, Al Ahas, 31982, Kingdom of Saudi Arabia*
[5] *Institute of Chemistry, University of the Punjab, Lahore, Punjab, 54590, Pakistan*
[6] *Centre for Advanced Drug Research, Commission on Science and Technology for Sustainable Development in the South, Institute of Information Technology, Abbottabad, 22060, Pakistan*
[7] *Cholistan Institute of Desert Studies, The Islamia University of Bahawalpur, 63100, Pakistan*
[8] *School of Chemistry, University of Southampton Highfield Campus, SO17 1BJ, Southampton, United Kingdom*

** Corresponding author at: Husein Ebrahim Jamal Research Institute of Chemistry, International Centre for Chemical and Biological Sciences, University of Karachi, Karachi, 75270, Pakistan.*
*Tel.: +92.219.9261701-2/214. Fax: +92.213. 4819018. E-mail address: huma_aslam31@hotmail.com (H.A. Bhatti).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.6.3.305-313.1268

Received: 28 April 2015
Received in revised form: 05 June 2015
Accepted: 08 June 2015
Published online: 30 September 2015
Printed: 30 September 2015

KEYWORDS

Oxidation
Flavanone
Isoflavone
Flavonoids
Benzofurans
Phenyliodonium diacetate

ABSTRACT

We describe the oxidation of flavanones by employing phenyliodonium diacetate to form the flavone (15), isoflavone (8) and 2,3-dihydrobenzofurane (18) in this study. The oxidative method was found to be regioselective and dependent on the substitution pattern present on the two aromatic rings of the starting flavanone. The structures of products obtained were fully characterized by using IR, $^{1}H$ and $^{13}C$ NMR spectroscopy and Mass spectrometry. X-ray crystallography further confirms the structures of flavones and isoflavone. The density field theory calculations have also been performed to get more insight about the structures, electronic and spectroscopic properties of synthetic flavonoid derivatives. The geometrical parameters such as bond lengths and angels showed a good correlation with the values obtained through X-ray crystallography. Moreover, the theoretically simulated vibrational and UV-vis spectral values are in agreement with the experimental results.

**Cite this**: *Eur. J. Chem.* **2015**, *6(3)*, 305-313

## 1. Introduction

Flavonoids are attractive targets in organic synthesis due to their presence in a wide variety of natural and synthetic compounds of biological significance [1]. They have been classified as neutraceuticals and are found in broad range of plant species and other foodstuffs including green tea, grapes, parsley, wine, and chocolates [2-4]. Flavonoids exhibit a range of biological activities, which include anticancer, anti-inflammatory, antiviral, antibacterial and antioxidant properties [5-7]. Quercetin **1** [8], genistein **2** [9] and lawsonicin **3** [10] are just a few bioactive natural flavonoids having a flavone, isoflavone and benzofuran core structure respectively (Figure 1). The regioselective efficient assembly of these moieties remains a synthetic challenge for organic chemists.

The oxidative rearrangement of flavanone has enduring importance in chemical synthesis as it provides an expedient access to flavones, isoflavones, and benzofuran derivatives from the corresponding starting materials [11-13]. In our previous report regarding the synthesis of lawsonicin **3** [14], we used Tl(III) salt for the said oxidative rearrangement which is one of the classical reagent for such transformation. Although, it proved successful on simple flavanone in low yield but the attempt to rearrange 6,7-disubstituted flavanones failed to yield functionalized 2,3-dihydrobenzo[*b*]furan, the precursor to lawsonicin **3**. As a result, we explored that a new reagent to perform this oxidative rearrangement in a regioselective manner.

Hypervalent iodine compounds have been considered on priority as they have significant impact in organic synthesis


ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) 
http://dx.doi.org/10.5155/eurjchem.6.3.305-313.1268

due to their mild properties as oxidizing agents. Although, the first hypervalent iodine compound, dichloroiodo benzene, was synthesized about a century ago [15], however, the interest to use them as catalysts in organic synthesis has been developed in last two to three decades. A range of novel hypervalent iodine compounds have been synthesized and utilized in organic synthesis of desired interests [16,17]. The hypervalent iodine reagents provide an excellent opportunity to optimize the trivial reactions with improved yields and reduced environmental hazards [18]. In addition, some reagents also provide selectivity in organic synthesis [19]. The representative members in the pool of hypervalent iodine compounds are including phenyliodonium diacetate (PIDA), (hydroxy(tosyloxy)iodo)benzene (HTIB) and phenyliodine *bis*(trifluoroacetate) (PIFA) etc. which have been frequently used in organic synthesis [20]. In present study, the phenyliodonium diacetate has been selected for the requisite oxidative arrangement which was found a complete selective way to yield the desired product. The oxidative method was successfully applied to synthesize the flavone **15**, isoflavone **8**, and alkyl 2-aryl-2,3-dihydrobenzofurane **18** cores of the corresponding flavanones.

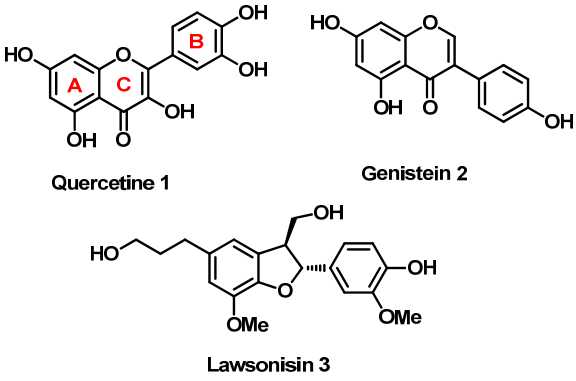



**Figure 1**. Examples of flavone, isoflavone and benzofuran core containing natural products.

## 2. Experimental

### *2.1. Reagent and instrumentation*

Vanillin (ReagentPlus®, 99%), isovanillin (≥95.0%), benzyl bromide (reagent grade, 98%), 2′-hydroxyaceto phenone (2′-HAP) (≥98%), 18-crown ether (≥ 99.0%), phenyl iodonium diacetate (98%), trimethyl orthoformate (TMOF) (99%), sodium acetate anhydrous (>99%), sodium hydroxide (reagent grade, ≥ 98%), acetyl chloride (reagent grade, 98%), *meta*-chloro perbenzoic acid (≤77%), and benzaldehyde (≥99.5%) were purchased from Sigma-Aldrich and used without purification unless described. The solvents such as acetone, $CHCl_3$, $CH_2Cl_2$ and $Et_3N$ dried over $CaH_2$. Tetrahydrofuran were dried over sodium metal and benzophenone ketyl. Thin layer chromatography was performed on silica gel 60 aluminium-coated plates having 0.063-0.200 mm as the stationary phase. Visualization was achieved by UV radiation (254 nm) or by using staining reagents such as basic potassium permanganate solution or vanillin solution for unsaturated compounds. $^1$H and $^{13}$C NMR spectra were recorded on Bruker-AV 300, 400 or 500 MHz in deuterated solvents (DMSO-$d_6$, $CDCl_3$ and MeOH-$d_4$), and tetramethylsilane ($Me_4Si$) was used as internal standard. The residual peaks for different solvents were calibrated as follow; $CDCl_3$ ($^1$H 7.26 ($H_2O$ 1.56) and $^{13}$C 77.0 ppm), DMSO ($^1$H 2.50 ($H_2O$ 3.33) and $^{13}$C 39.43 ppm) and MeOD ($^1$H 3.31 and $^{13}$C 49.0 ppm) [21]. The IR spectra were recorded on Bio-Rad FT-IR spectrometer Paragon 1000. HRMS (EI) were obtained on Bruker Apex III (FT-ICR-MS, 4.7T Magnet, MSn) for Apollo electrospray Source, HP 1100.

### *2.2. Computational methods*

Molecular geometries of flavone and isoflavone were optimized without any symmetry constraints at B3LYP/6-311G(d,p) level of density functional theory. The B3LYP method, which consists of parameter hybrid functional of Becke [22] three in conjunction with the correlation functional of Lee, Yang, and Parr [23], is a computational cost effective method for accurate prediction of geometries of a variety of organic compounds ranging from polymers [24] to natural products [25,26] The optimized geometries were evaluated as true minima by frequency analysis (no imaginary frequency). The calculated frequencies are reported as such without any scaling factor. UV-vis absorption spectra were simulated through time dependent DFT (TD-DFT) approach at B3LYP/6-311G(d,p). HOMO, LUMO and their band gap energies calculations were performed on the optimized structures of compound **8** and **15** at the same level. The band gap was calculated as the difference between the HOMO and LUMO orbital energies [27].

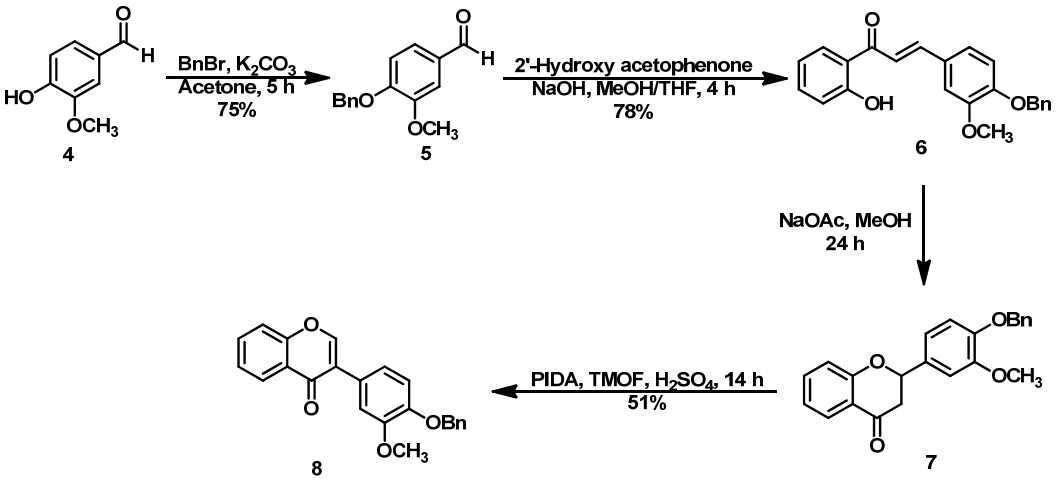
### *2.3. Synthesis*

#### *2.3.1. 4-Benzyloxy-3-methoxy-benzaldehyde (5)*

An oven dried round-bottomed flask was charged with vanillin (3.0 g, 19.0 mmol) followed by the addition of 18-crown ether (0.5 g, 9 mmol) and anhydrous $K_2CO_3$ (5.2 g, 38 mmol) in 150 mL of acetone as solvent. Now to the resulting mixture, benzyl bromide (3 mL, 19.0 mmol) was added at room temperature. The reaction mixture was heated at reflux for 5 h until TLC analysis showed no starting material, vanillin. The reaction mixture was cooled to room temperature and then solvent was evaporated on rotary evaporator. To the resulting residue distill water was added and then extracted it with ethyl acetate (50 mL × 3). All the organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to get the crude mixture which was then subsequently purified by using silica gel column chromatography with eluents (Hexane:EtOAc, *v*:*v*, 9:1) to afford the pure desired product **5** (Scheme 1). Color: White solid. Yield: 3.6 g, 75%. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.97 (s, 3H, $OCH_3$), 5.23 (s, 2H, $CH_2$), 7.01 (d, 1H, *J* = 8.0 Hz, ArH), 7.40- 7.54 (m, 7H, ArH), 9.95 (s, 1H, CHO). $^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 56.0 ($OCH_3$), 70.9 ($CH_2$), 109.5 (CH), 112.4 (CH), 126.5 (CH), 127.2 (CH), 128.2 (CH), 128.7 (CH), 130.3 (C), 136.0 (C), 150.1 (C), 153.6 (C), 190.8 (CH). MS (EI, *m/z* (%)): 265 ([M+Na], 100). HRMS (EI, *m/z*): calcd. for $C_{15}H_{14}O_3$: 242.0943, found: 242.0941.

#### *2.3.2. 3-(4-(Benzyloxy)-3-methoxyphenyl)-1-(2-hydroxy phenyl)prop-2-en-1-one (6)*

To an oven dried round bottom flask 2′-hydroyaceto phenone (0.4 mL, 4.1 mmol) was added, followed by the addition of MeOH:THF (*v*:*v*, 1:1, 10 mL), 60% NaOH (5 mL) and solution of compound **5** (0.4 mL, 4.1 mmol) in MeOH:THF (*v*:*v*, 1:1, 5 mL). The resulting mixture was stirred for 4 h and poured it in to ice cold water whose pH was adjusted to 2. Filtered the residue, dissolved in chloroform and washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated the solvents in vacuo. The product was recrystallized with EtOH to get compound **6** in pure form as crystals (Scheme 1). Color: Yellow. Yield: 1.0 g, 78%. FT-IR (Neat, ν, cm$^{-1}$): 1634, 1561, 1249. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.01 (s, 3H, $OCH_3$), 5.26 (s, 2H, $CH_2$), 6.88-7.12 (m, 3H, CH and ArH), 7.20-7.62 (m, 9H, CH and ArH), 7.82-7.80 (m, 2H, ArH), 12.9 (s, 1H, OH).




**Scheme 1**

$^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 56.1 ($OCH_3$), 70.8 ($CH_2$), 110.8 (CH), 113.3 (CH), 117.8 (CH), 118.6 (CH), 118.7 (CH), 123.3 (CH), 127.2 (CH), 128.1 (CH), 128.7 (CH), 129.5 (CH), 136.2 (CH), 145.6 (CH), 120.1 (C), 127.9 (C), 136.4 (C), 149.8 (C), 150.9 (C), 163.5 (C), 193.5 (C). MS (EI, *m/z* (%)): 361 ($[M+H]^+$, 100). HRMS (EI, *m/z*): calcd. for $C_{23}H_{20}O_4$ $[M]^+$: 360.1362, found: 360.1355.

### *2.3.3. 2-(4-Benzyloxy-3-methoxy-phenyl)-chroman-4-one (7)*

To an oven dried round bottom flask, a solution of compound **6** (0.6 g) and anhydrous NaOAc in 100 mL of MeOH was heated at reflux for 24 h. The reaction was monitored by TLC analysis. After the complete consumption of starting material, the solvent was removed in vacuo and water (30 mL) was added to the resulting residue. The aqueous phase was extracted with EtOAc (30 mL × 3). The combine organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by using flash column chromatography (15% EtOAc in hexane) to yield the compound **7** (0.4 g, 70%) as an off-white solid, with some unreacted starting material **6** (0.18 g) (Scheme 1). Yield: 0.4 g, 74%. FT-IR (Neat, ν, $cm^{-1}$): 1687, 1463, 1303. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.57 (dd, 1H, *J* = 3.7, 16.83 Hz, C*H*H), 3.06 (dd, 1H, *J* = 3.7, 16.83 Hz, C*H*H), 4.01 (s, 3H, $OCH_3$), 5.26 (s, 2H, $CH_2$), 5.61 (dd, 1H, *J* = 3.30, 13.17 Hz, CH), 6.94-7.97 (m, 12H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 44.6 ($CH_2$), 56.0 ($OCH_3$), 70.9 ($CH_2$), 79.5 (CH), 109.8 (CH), 113.7 (CH), 118.1(CH), 118.7 (CH), 120.9 (C), 121.6 (CH), 127.0 (CH), 127.2 (CH), 127.9 (CH), 128.6 (CH), 131.6(C), 136.2 (CH), 136.9 (C), 148.5 (C), 149.8 (C), 161.5 (C), 192.1 (C). MS (EI, *m/z* (%)): 383 ($[M+Na]^+$, 100). HRMS (EI, *m/z*): calcd. for $C_{23}H_{20}O_4$ $[M]^+$: 360.1362, found: 360.1371.

### *2.3.4. 3-(4-(Benzyloxy)-3-methoxyphenyl)-4H-chromen-4-one (8)*

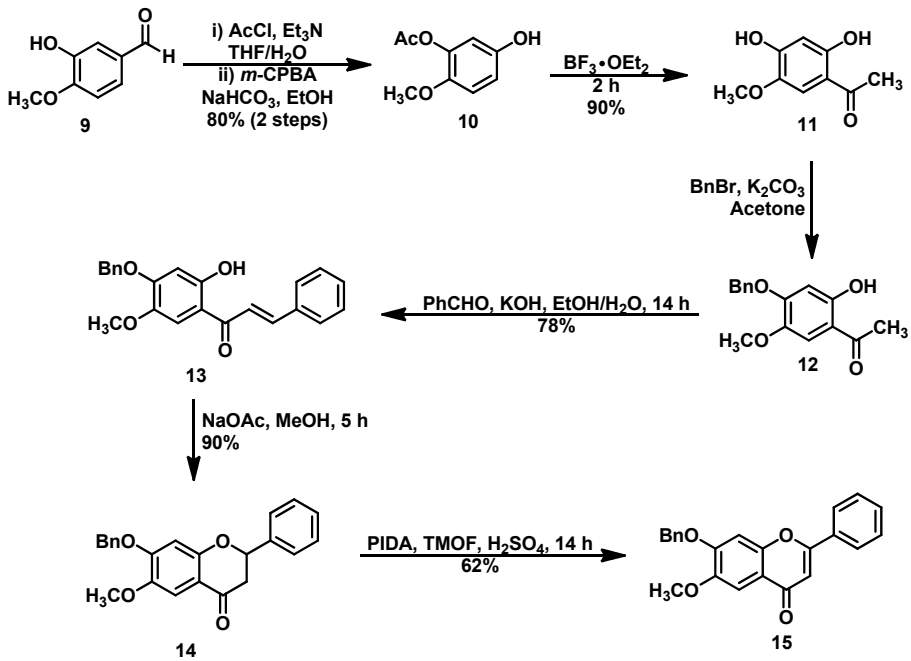
To a stirred solution of flavanone **7** (0.078 g, 0.2 mmol) in trimethyl orthoformate (TMOF) (8 mL) $H_2SO_4$ (2 drops) was added dropwise the solution of PIDA (0.09 g, 0.20 mmol) in trimethylorthoformate (3 mL) at room temperature. The resulting mixture was overnight room temperature. The solvent was removed in vacuo and then water was added to the resulting residue. The solution was stirred for further 2 h at room temperature. The mixture was then extracted with dichloromethane, washed with an aqueous solution of $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo to get oil. It was then purified by using silica gel column chromatography with eluents hexane: EtOAc (9:1, *v*:*v*) to obtain compound **8** as yellow oil (Scheme 1). Yield: 0.04 g, 51%. FT-IR (Neat, ν, $cm^{-1}$): 1689, 1463, 1303. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.01 (s, 3H, $OCH_3$), 5.26 (s, 2H, $CH_2$), 6.14-6.23 (m, 3H, ArH), 6.48 (s, 1H, CH) 6.87-6.93 (m, 3H, ArH), 7.52-7.55 (m, 6H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 56.1 ($OCH_3$), 71.0 ($CH_2$), 79.5 (CH), 113.1 (CH), 114.0 (CH), 118.0 (CH), 118.7 (CH), 120.9 (CH), 125.2 (CH), 126.3 (CH), 127.2 (CH), 127.8 (CH), 128.5 (CH), 133.5 (CH), 152.7 (CH) 131.1(C), 148.3 (C), 149.5 (C), 156.1 (C), 176.4 (C). MS (EI, *m/z* (%)): 381 ($[M+Na]^+$, 100). HRMS (EI, *m/z*): calcd. for $C_{23}H_{18}O_4$ $[M]^+$: 358.1205, found: 358.1217.

#### *2.3.4.1. Crystal structure analysis of compound 8*

Crystal structure data of compound **8** was collected on a Nonius Kappa CCD area detector (*ϕ* scans and *ω* scans to fill asymmetric unit). Cell determination: DirAx [28]. The data was collected by Hooft and Nonius sofware [29]. Data reduction and cell refinement: Denzo [30]. Absorption correction: Sheldrick, G. M. SADABS-Bruker Nonius area detector scaling and absorption correction-V2.10 Structure solution: SHELXS97 [31]. Structure refinement: SHELXL97 [32]. Graphics: Cameron-A Molecular Graphics Package [33]. Special details: All hydrogen atoms were placed in idealized positions and refined using a riding model. Crystallographic data for compound **15** has been deposited to Cambridge Crystallographic Data Center.

### *2.3.5. 3-Acetoxy-4-methoxyphenol (10)*

To the solution of 3-acetoxy-4-methoxybenzaldehyde (3.0 g, 15.4 mmol) and *m*-CPBA (5.3 g, 30 mmol) in dry DCM (60 mL) was heated under the reflux with stirring for 5 h. The reaction mixture was then cooled to room temperature. Filtration and removal of the solvent at reduced pressure afforded an oily residue, which was diluted with EtOAc and washed with 5% $NaHCO_3$ and brine. The residue was then dissolved in EtOH (50 mL), after the addition of 5% $NaHCO_3$ aq (100 mL). The solution was stirred for 17 h at room temperature. The reaction mixture was acidified to pH = 2 with 2 M HCl, salted out and extracted with EtOAc. The extract was washed with brine and 5% $NaHCO_3$ aqueous solution successively, dried over anhydrous $Na_2SO_4$ and filtered.




**Scheme 2**

After the removal of the solvent at reduced pressure, the residue was purified by column chromatography on the silica gel with DCM/ EtOAc (40:1 to 20:1) to obtain compound **10** as light yellow solid (Scheme 2). Yield: 80%. FT-IR (Neat, ν, $cm^{-1}$): 1700, 1420, 1256. $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 2.39 (s, 3H, $CH_3$), 3.88 (s, 3H, $OCH_3$), 7.10 (d, 1H, *J* = 8.0 Hz, ArH), 7.61 (d, 1H, *J* = 1.5 Hz, ArH), 7.84 (dd, 1H, *J* = 1.5, 8.0 Hz, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$, δ, ppm): 20.5 ($OCH_3$), 56.2 ($OCH_3$), 122.0 (CH), 123.4 (CH), 130.0 (CH), 140.2 (C), 156.3 (C), 168.5 (C), 189.9 (CH). MS (EI, *m/z* (%)): 205 ([M+Na]$^+$, 100). HRMS (EI, *m/z*): calcd. for $C_9H_{10}O_4$ [M]$^+$: 182.0579, found: 182.1013.

### *2.3.6. 1-(2,4-Dihydroxy-5-methoxyphenyl)ethanone (11)*

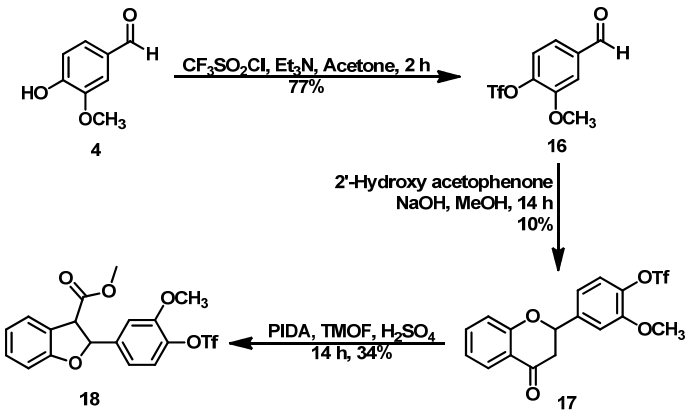
To a solution of 3-acetoxy-4-methoxyphenol **10** (1.5 g, 8.2 mmol) was added neat boron trifluoride diethyletherate $BF_3{\cdot}Et_2O$ (2 mL, 16.4 mmol). The reaction mixture was stirred at 70 °C for 2 h and then cooled to room temperature. The suspension was taken up in saturated aqueous NaOAc (25 mL) and saturated aqueous of $NaHCO_3$ was added until no further $CO_2$ was evolved. The suspension was then extracted with EtOAc:$Et_2O$ (1:1, *v*:*v*). The extract was washed with brine, dried ($Na_2SO_4$) and solvent was removed under reduced pressure to give a solid compound **11** (Scheme 2). Yield: 90%. $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 2.50 (s, 3H, $CH_3$), 3.89 (s, 3H, $OCH_3$), 6.20 (s, 1H, ArH), 6.51 (s, 1H, ArH), 7.09 (s, 1H, OH), 12.51 (s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$, δ, ppm): 20.5 ($OCH_3$), 56.5 ($OCH_3$), 109.3 (CH), 113.2 (CH), 144.1 (C), 154 (C), 159.4 (C), 202.1 (C). MS (EI, *m/z* (%)): 182 ([M]$^+$, 60.85). HRMS (EI, *m/z*): calcd. for $C_9H_{10}O_4$ [M]$^+$: 182.0579, found: 182.0981.

### *2.3.7. (E)-1-(4-(Benzyloxy)-2-hydroxy-5-methoxyphenyl)-3-phenylprop-2-en-1-one (13)*

To a solution of KOH (0.645 g, 24 equiv) in EtOH:$H_2O$ (1:1, *v*:*v*, 5 mL), was added dropwise to a mixture of benzaldehyde (5 mL) and 4-benzoyloxy-2-hydroxy-3-methoxy acetophenone (5 mL). The reaction mixture was stirred overnight at room temperature and diluted with diethyl ether (30 mL). The organic layer was separated and the aqueous layer was further extracted with ether (30 mL × 2). The combined organic layers were washed with 5% HCl, water, and brine solution, dried over $Na_2SO_4$, filtered, and concentrated in *vacuo*. The crude product was purified by using silica gel column chromatography using hexane: EtOAc (9:1, *v*:*v*)to obtain the product **13** as solid form (Scheme 2). Color: Yellow. Yield: 78%. FT-IR (Neat, ν, $cm^{-1}$): 1634, 1516, 1247. $^1H$ NMR (300 MHz, $CDCl_3$, δ, ppm): 4.02 (s, 3H, $OCH_3$), 5.21, (s, 2H, $CH_2$), 6.21 (s, 1H, ArH), 6.51 (s, 1H, ArH), 6.90 (d, 1H, *J* = 16.0 Hz, =CH), 7.31-7.78 (m, 10H, ArH), 7.90 (d, 1H, *J* = 15.3 Hz, =CH), 12.0 (s, 1H, OH). $^{13}C$ NMR (75 MHz, $CDCl_3$, δ, ppm): 56.2 ($OCH_3$), 70.7 ($CH_2$), 109.3 (CH), 110.8 (CH), 113.2 (CH), 117.8 (CH), 118.6 (CH), 118.7 (CH), 123.3 (CH), 127.2 (CH), 128.1 (CH), 128.7 (CH), 129.5 (CH), 136.2 (CH), 145.6 (CH), 120.1 (C), 127.9 (C), 136.4 (C), 144.1 (C), 154.0 (C), 159.4 (C), 163.5 (C), 193.5 (C). MS (EI, *m/z* (%)): 361 ([M+H]$^+$, 100). HRMS (EI, *m/z*): calcd for $C_{23}H_{20}O_4$ [M]$^+$: 360.1362, found: 360.1345.

### *2.3.8. 7-(Benzyloxy)-6-methoxy-2-phenylchroman-4-one (14)*

A solution of compound **13** (0.050 g, 0.138 mmole) and anhydrous sodium acetate (90.147 g, 17 mmol) in 20 mL of MeOH was heated at reflux for 5 h. After cooling, the solvent was removed in *vacuo* and $H_2O$ was added to the resulting residue. The aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic layer were dried over anhydrous $MgSO_4$, filtered and concentrated on rotary evaporator under reduced pressure. The crude product was purified using column chromatography with eluents hexane: EtOAc (9:1, *v*:*v*) as a white solid **14** (Scheme 2). Yield: 90%. FT-IR (Neat, ν, $cm^{-1}$): 1686, 1463, 1302. $^1H$ NMR (300 MHz, $CDCl_3$, δ, ppm): 2.56 (dd, 1H, *J* = 3.7, 16.83 Hz, C*H*H), 3.07 (dd 1H, *J* = 3.7, 16.83 Hz, C*H*H), 3.90 (s, 3H, $OCH_3$), 5.20 (s, 1H, CH), 5.49 (dd, 2H, *J* = 3.30, 13.17 Hz, $CH_2$), 6.51 (s, 1H, ArH), 7.31-7.69 (m, 11H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$, δ, ppm): 44.5 ($CH_2$), 56.1 ($OCH_3$), 70.9 ($CH_2$), 79.5 (CH), 120.9 (C), 121.6 (CH), 127.0 (CH), 127.2 (CH), 127.9 (CH), 128.6 (CH), 131.6 (C), 136.2 (CH), 136.9 (C), 148.5 (C), 149.8 (C), 161.5 (C), 192.1 (C).




**Scheme 3**

MS (EI, *m/z* (%)): 383 ([M+Na]$^+$, 100%). HRMS (EI, *m/z*): calcd. for $C_{23}H_{20}O_4$ [M]$^+$: 360.1362, found: 360.1378.

### *2.3.9. 6-(Benzyloxy)-7-methoxy-2-phenyl-4H-chromen-4-one (15)*

To a stirred solution of flavanone **14** (0.015 g, 0.041 mmol) in TMOF (5 mL), conc. $H_2SO_4$ (20 µL) was added. To this mixture, a solution of PIDA (0.0132 g, 0.041 mmol) in TMOF (3 mL) was added drop wise at room temperature and the reaction mixture was stirred for overnight. Subsequently, the solvent was removed and water was added to the residue. The solution was stirred for 2 h, then extracted with DCM, washed with an aqueous solution of $NaHCO_3$, and dried. Evaporation of the solvent gave an oil which was purified by column chromatography on silica gel using hexane: EtOAc (7.5:2.5, *v:v*) to obtained the compound **15** as a colorless solid (Scheme 2). Yield: 62%. FT-IR (Neat, ν, cm$^{-1}$): 1689, 1463, 1303. $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.90 (s, 3H, $OCH_3$), 5.02 (s, 2H, $CH_2$), 6.70 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.19 (s, 1H, CH), 7.31-7.57 (m, 8H, ArH), 7.87 (m, 2H, ArH). $^{13}$C NMR (100 MHz, $CDCl_3$, δ, ppm): 56.8 ($OCH_3$), 71.6 ($CH_2$), 101.9 (CH), 105.1 (CH), 107 (CH), 126.3 (CH), 127.6 (CH), 128.7 (CH), 129.2 (CH), 129.3 (CH), 131.1 (C), 131.6 (CH) 148.3 (C), 149.5 (C), 156.1 (C), 176.4 (C). MS (EI, *m/z* (%)): 381 ([M+Na]$^+$, 100). HRMS (EI, *m/z*): calcd. for $C_{23}H_{18}O_4$ [M]$^+$: 358.1205, found: 358.1233.

#### *2.3.9.1. Crystal structure analysis of compound 15*

Crystal structure data of compound **15** was collected on a Nonius Kappa CCD area detector ($\phi$ scans and $\omega$ scans to fill asymmetric unit). Cell determination: DirAx [28]. The data was collected by Hooft and Nonius sofware [29]. Data reduction and cell refinement: Denzo [30]. Absorption correction: Sheldrick, G. M. SADABS-Bruker Nonius area detector scaling and absorption correction-V2.10 Structure solution: SHELXS97 [31]. Structure refinement: SHELXL97 [32]. Graphics: Cameron-A Molecular Graphics Package [33]. Special details: All hydrogen atoms were placed in idealized positions and refined using a riding model. Crystallographic data for compound **15** has been deposited to Cambridge Crystallographic Data Center.

### *2.3.10. 4-formyl-2-methoxyphenyl trifluoromethane sulfonate (16)*

To the solution of vanillin (0.5 g, 3.2 mmole) in dried acetone (30 mL), $Et_3N$ (0.4 mL, 3.2 mmol) and $CF_3SO_2Cl$ (0.3 mL, 3.2 mmol), was added. The resulting reaction mixture was heated at reflux for 2 h. After completion of reaction, the solvent was removed under reduced pressure. The resulting residue was washed with 1M $KHSO_3$ (20 mL), and then extracted with DCM (30 mL x 3). The combined organic layer was dried over $MgSO_4$ to obtain the product **16** as pure yellow oil (Scheme 3). Yield: 0.76 g, 77%. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.97 (s, 3H, $OCH_3$), 7.39 (d, 1H, *J* = 8.0, ArH), 7.49 (dd, 1H, *J* = 1.83, 8.4, ArH), 7.53 (d, 1H, *J* =1.47, ArH), 9.95 (s, 1H, -CHO). $^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 56.5 ($OCH_3$), 111.8 (CH), 123.2 (CH), 124.0 (CH), 136.8 (C), 142.7 (C), 152.2 (C), 190.2 (CH). $^{19}$F NMR (300 MHz, $CDCl_3$, δ, ppm): -73.7 (s, $CF_3$). HRMS (EI, *m/z*): calcd. for $C_9H_7F_3O_5S$ [M]$^+$: 283.9966, found: 283.9985.

### *2.3.11. Trifluoro-methanesulfonic acid 2-methoxy-4-(4-oxo-chroman-2-yl)-phenyl ester (17)*

An aqueous solution of NaOH (60%, 50 mL) was added to the solution of 2′-hydroxyacetophenone (0.2 mL, 1.6 mmol) in MeOH (50 mL) and the resulting mixture was heated at reflux. The solution was cooled to room temperature, and then **16** (0.5 g, 1.6 mmol) was added. The reaction mixture was poured into the mixture of water and HCl with pH = 2. The mixture was further stirred overnight and then extracted with $CHCl_3$ (30 mL × 3), followed by washing with 5% aqueous $NaHCO_3$, and the combined organic layer was dried over $MgSO_4$. The reaction mixture was purified by using silica gel column chromatography using hexane:EtOAc, (9:1, *v:v*) to obtain a compound as amorphous solid **17** with a 10% yield (Scheme 3). FT-IR (Neat, ν, cm$^{-1}$): 1692, 1464, 1304, 877. $^1$H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.57 (dd, 1H, *J* = 3.7, 16.83 Hz, C*H*H), 3.06 (dd, 1H, *J* = 3.7, 16.83 Hz, CH*H*), 4.01 (s, 3H, $OCH_3$), 5.61 (dd, 1H, *J* = 3.30, 13.17 Hz, CH), 7.20-7.40 (m, 5H, ArH), 7.65 (t, 1H, *J* = 8.0 Hz, ArH), 8.06 (d, 1H, *J* = 8.0 Hz, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$, δ, ppm): 44.8 ($CH_2$), 56.3 ($OCH_3$), 78.8 (CH), 110.7 (CH), 118.0 (CH), 118.3 (CH), 120.8 (C), 122.0 (CH), 122.8 (CH), 127.1 CH), 136.4 (CH), 138.5 (C), 140.3 (C), 151.7 (C) 161.5 (C), 191.2 (C). MS (EI, *m/z* (%)): 425 ([M+Na]$^+$, 46.95). HRMS (EI, *m/z*): calcd. for $C_{17}H_{13}F_3O_6S$ [M]$^+$: 402.0385, found: 402.1008.

### *2.3.12. 2-(3-Methoxy-4-trifluoromethanesulfonyloxy-phenyl)-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester (18)*

To a stirred solution of flavanone **17** (0.1 g, 0.27 mmol) in TMOF (12.5 mL) $H_2SO_4$ (20 µL) was added a solution of PIDA (0.087 g, 0.27 mmol) in TMOF (2.7 mL) drop wise at room temperature. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and water (20 mL) was added to the residue, followed by stirring for 2 h. The

mixture was then extracted with DCM (30 mL × 3), washed with an aqueous solution of $NaHCO_3$. The combined organic layer was dried over $Na_2SO_4$, filtered and evaporated in *vacuo*. The resulting residue was purified by using silica gel column chromatography with eluents hexane: EtOAc (9:1, *v*:*v*) to obtain compound **18** as yellow oil (Scheme 3). Yield: 0.037 g, 34%. FT-IR (Neat, ν, $cm^{-1}$): 1738, 1420, 1205, 877. $^1H$ NMR (300 MHz, $CDCl_3$, δ, ppm): 3.97 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 4.12 (d, 1H, *J* = 7.6 Hz, CH), 6.05 (d, 1H, *J* = 7.6 Hz, CH), 7.05-7.51 (m, 7H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$, δ, ppm): 52.9 (CH), 55.7 ($OCH_3$), 56.2 ($OCH_3$), 84.5 (CH), 110.0 (CH), 110.3 (CH), 116.5 (C) 117.9 (CH), 120.8 (C), 121.4 (CH), 122.7 (CH), 123.2 (CH), 125.3 (CH), 129.8 (C), 138.3 (C), 142.2 (C), 151.6 (C),158.9 (C), 171.0 (C). MS (EI, *m/z* (%)): 455 ([M+Na]$^+$, 38.5). HRMS (EI, *m/z*): calcd. for $C_{18}H_{15}F_3O_7S$ [M]$^+$: 432.0491, found: 432.0407.

## 3. Results and discussion

### *3.1. Synthesis*

Flavanones were synthesized *via* a three-step procedure and reaction path, depending upon the substitution pattern on the starting material, different flavanones were prepared and oxidative rearrangement was attempted. Initially, the benzylated flavanone **7** was synthesized using vanillin **4** as the starting material. Vanillin **4** was benzylated using standard conditions to yield 4-benzyloxy-3-methoxy-benzaldehydein **5** in 75% yield. The resulted benzylated compound **5** underwent aldol condensation [34], with the 2′-hydroxyacetophenone to produce chalcone intermediate **6** which was then subjected to cyclization in the presence of sodium acetate to form flavanone **7** in an excellent yield of 95% [35,36]. The flavanone **7** was then oxidized with the PIDA and TMOF (Trimethyl orthoformate) [37-40], surprisingly the oxidative rearrangement proved highly regioselective to form isoflavone **8** as a major product in moderate yield, X-ray crystallography was used to confirm the structure of compound **8** (Scheme 1, Figure 2). The details concerning data collection and refinement are given in Table 1.

**Table 1.** Crystal data and structure refinement for compound **8**.

| | |
|---|---|
| Empirical formula | $C_{23}H_{18}O_4$ |
| Formula weight | 358.37 |
| Temperature | 120(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | $a$ = 10.4036(3) Å |
| | $b$ = 20.8256(6) Å |
| | $c$ = 8.1261(2) Å |
| | $\beta$ = 100.103(2) ° |
| Volume | 1733.31(8) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.373 Mg / m$^3$ |
| Absorption coefficient | 0.094 mm$^{-1}$ |
| *F(000)* | 752 |
| Crystal | Fragment; Colourless |
| Crystal size | 0.3 × 0.3 × 0.06 mm$^3$ |
| $\theta$ range for data collection | 3.10 - 27.48° |
| Index ranges | $-13 \le h \le 13$, $-27 \le k \le 26$, $-10 \le l \le 10$ |
| Reflections collected | 24806 |
| Independent reflections | 3973 [$R_{int}$ = 0.0571] |
| Completeness to $\theta$ = 27.48° | 99.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Absorption correction | 0.9972 and 0.9625 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3973 / 0 / 245 |
| Goodness-of-fit on $F^2$ | 0.958 |
| Final *R* indices [$F^2 > 2\sigma(F^2)$] | *R1* = 0.0477, *wR2* = 0.1220 |
| *R* indices (all data) | *R1* = 0.0865, *wR2* = 0.1462 |
| Largest diff. peak and hole | 0.219 and -0.296 e Å$^{-3}$ |

Following the successful synthesis of the flavone core, we moved towards our next target, the isoflavone core. To achieve this task, the commercially available isovanillin **9** was acetylated under basic conditions. The resultant acetylated product subsequently treated with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by hydrolysis with sodium bicarbonate in ethanol afforded the decarbonylated product **10** in excellent yield (80%) over 2 steps. The compound **10** was then treated with $BF_3{\cdot}OEt_2$ to form 2,4-dihydroxy-5-methoxyacetophenone **11** *via* Fries rearrangement [38] in an overall 70% yield. The compound **11** was benzylated to produce compound **12** followed by aldol condensation with benzaldehyde (1 equiv.) in the presence of KOH and EtOH:$H_2O$ to synthesize chalcone derivative **13** in 78% yield. The cyclization with sodium acetate resulted in the flavanone **14**. Oxidation of this particular flavanone **14** using TMOF and PIDA only resulted in flavone **15** regioselectively in 62 % yield. X-ray crystallography proved the structure of compound **15** (Scheme 2, Figure 3). The details concerning data collection and refinement are given in Table 2.

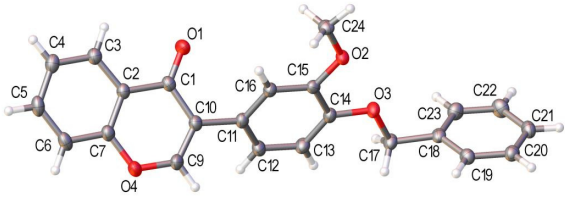



**Figure 2**. The molecular structure of compound **8**. Displacement ellipsoids are drawn at the 50% probability level.

**Table 2.** Crystal data and structure refinement for compound **15**.

| | |
|---|---|
| Empirical formula | $C_{23}H_{18}O_4$ |
| Formula weight | 358.37 |
| Temperature | 120(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Triclinic |
| Space group | *P*-1 |
| Unit cell dimensions | $a$ = 5.0051(3) Å |
| | b = 11.6649(8) Å |
| | c = 14.9236(11) Å |
| | $\alpha$ = 83.448(3) ° |
| | $\beta$ = 83.971(4) ° |
| | $\gamma$ = 87.747(4) ° |
| Volume | 860.49(10) Å$^3$ |
| Z | 2 |
| Density (calculated) | 1.383 Mg/m$^3$ |
| Absorption coefficient | 0.094 mm$^{-1}$ |
| *F(000)* | 376 |
| Crystal | Rod; Colourless |
| Crystal size | 0.34 x 0.06 x 0.03 mm$^3$ |
| $\theta$ range for data collection | 3.11 - 27.48 ° |
| Index ranges | $-6 \le h \le 6$, $-15 \le k \le 15$, $-19 \le l \le 19$ |
| Reflections collected | 13606 |
| Independent reflections | 3926 [$R_{int}$ = 0.0770] |
| Completeness to $\theta$ = 27.48° | 99.2 % |
| Absorption correction | Semi-empirical from equivalents |
| Absorption correction | 0.9972 and 0.9586 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3926 / 0 / 245 |
| Goodness-of-fit on $F^2$ | 1.041 |
| Final *R* indices [$F^2 > 2\sigma(F^2)$] | *R1* = 0.0675, *wR2* = 0.1528 |
| *R* indices (all data) | *R1* = 0.1273, *wR2* = 0.1793 |
| Largest diff. peak and hole | 0.316 and -0.274 e Å$^{-3}$ |

After successful synthesis of isoflavone **8** and flavone **15** using the oxidative method, the next target was benzofuran core. For this purpose, the protecting group on ring B of the flavanone was changed to methoxy methyl ether (MOM) but the oxidative rearrangement failed to give any desired product. Thus, a selection of different protecting group was required and triflate group was the next choice. Vanilin **4** was first protected with triflate group to form compound **16** which underwent aldol condensation in the presence of NaOH/MeOH and the subsequent cyclization of the intermediate took place under the same reaction mixture to produce flavanone **17** in low yield due to hydrolysis of starting material **16** to

**Table 3.** Comparison of experimental bond length and bond angles (Single crystal X-ray diffraction) for compound **8** with the theoretically calculated at B3LYP/6-311G(d,p).

| Bond | Bond length, Å (Exp) | Bond length, Å (Theor.) | Bond | Bond angles, ° (Exp) | Bond angles, ° (Theor.) |
|---|---|---|---|---|---|
| C1-O1 | 1.226 | 1.224 | O1-C1-C2 | 122.00 | 121.60 |
| C1-C10 | 1.465 | 1.478 | O1-C1-C10 | 123.22 | 123.97 |
| C1-C2 | 1.481 | 1.474 | C6-C7-O4 | 117.02 | 116.48 |
| O4-C7 | 1.375 | 1.367 | C9-C10-C11 | 120.49 | 119.66 |
| O4-C9 | 1.351 | 1.353 | C15-O2-Me | 116.67 | 118.03 |
| C10-C11 | 1.488 | 1.482 | O3-C17-C18 | 109.86 | 109.40 |
| C9-C10 | 1.349 | 1.354 | C1-C10-C11 | 120.65 | 121.87 |
| C15-O2 | 1.368 | 1.360 | C14-C15-O2 | 115.48 | 115.49 |
| C14-O3 | 1.376 | 1.359 | C16-C15-O2 | 124.74 | 124.71 |
| O17-C3 | 1.443 | 1.419 | C13-C14-O3 | 125.31 | 124.83 |

**Table 4.** Comparison of experimental bond length and bond angles (Single crystal X-ray diffraction) for compound **15** with the theoretically calculated at B3LYP/6-311G (d,p).

| Bond | Bond length, Å (Exp) | Bond length, Å (Theor.) | Bond | Bond angles, ° (Exp) | Bond angles, ° (Theor.) |
|---|---|---|---|---|---|
| C2-O9 | 1.234 | 1.227 | O2-C9-C8 | 123.7 | 123.43 |
| O1-C7 | 1.365 | 1.362 | C9-C10-C11 | 122.4 | 121.20 |
| O1-C15 | 1.376 | 1.372 | C10-C15-O1 | 122.4 | 122.17 |
| C7-C8 | 1.346 | 1.355 | O1-C15-C14 | 116.27 | 115.05 |
| C6-C7 | 1.472 | 1.475 | C6-C7-C8 | 127.1 | 126.03 |
| C12-O3 | 1.366 | 1.357 | C6-C7-O1 | 111.4 | 112.02 |
| C13-O4 | 1.366 | 1.351 | C10-C15-C14 | 122.5 | 121.55 |
| O4-C16 | 1.438 | 1.422 | C12-O3-C15 | 116.59 | 117.64 |
| C16-C17 | 1.500 | 1.510 | O4-C16-C17 | 109.27 | 109.42 |
| C15-O3 | 1.432 | 1.423 | C16-C17-C18 | 124.4 | 121.96 |

compound **4** in the presence of KOH. Surprisingly, the oxidation of flavanone **17** with PIDA and TMOF resulted in successful synthesis of dihydrobenzofuran **18** in moderate yield (Scheme 3) [14].

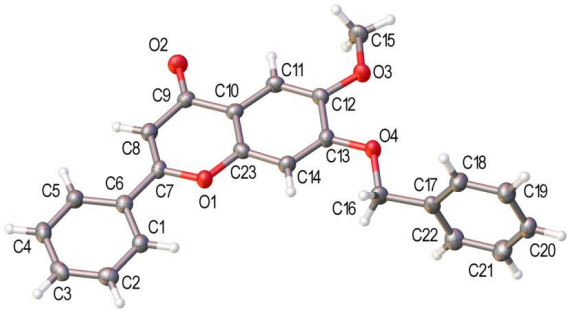



**Figure 3.** The molecular structure of compound **15**. Displacement ellipsoids are drawn at the 50% probability level.

In summary, the oxidative rearrangement proved successful on flavanones with benzyl or triflate group as protecting group on B ring, yet it remained unsuccessful on changing the protection of benzyl group with methoxy methyl ether (MOM) or having halide group substitution on A ring of flavanone. We are currently working on this methodology in further detail to overcome the limitations faced during this synthesis and to optimize conditions for the oxidative rearrangement of more substituted flavanones.

### *3.2. Geometrical studies*

DFT calculations were performed to get detailed insight into the structures of the synthesized flavonoids **8** and **15**. Geometries were optimized at B3LYP method of DFT at 6-311G(d,p) basis set. The detailed geometric analysis of compounds **8** and **15** were presented and the theoretical data for these compounds could be correlated to the experimental geometric parameters, obtained through X-ray crystal structure data of compound **8** and **15**.

Both, flavone **15** and isoflavone **8** are isomeric, however; the flavone **15** is 4.5 kcal more stable than **8**. A detailed structural analysis revealed that most of the geometric parameters are comparable in both structures. The increased stability of compound **15** was attributed to planarity of the phenyl ring relative to the chromen-4-one scaffold. The phenyl ring B had a dihedral angle of 20.7° in compound **15** compared to 38.9 ° in compound **8** (Figure 4). Non-bonding interactions of keto and alkoxy oxygen atoms were also shown in Figure 4. In compound **8**, keto oxygen atom acted a hydrogen bond donor to H-16 at a distance of 2.39 Å. In compound **15**, a similar interaction was present between O-2 and H-11 at a distance of 2.38 Å (Figure 4).

Moreover, the theoretically calculated geometric parameters were compared with the experimentally obtained through X-ray crystal analysis, and were given in Table 3 and 4. The calculated geometric parameters showed a good correlation with the experimental geometric parameters. Bond predicted lengths were generally accurate within 0.01 Å limit except a few bonds which deviating about 0.03 Å from the experimental values. Similarly differences between theoretical and experimental bond angles were less than 1 degree. These results illustrated that B3LYP/6-311G(d,p) level is quite accurate in predicting the geometrical parameters of isoflavonoid and flavonoid type natural products.

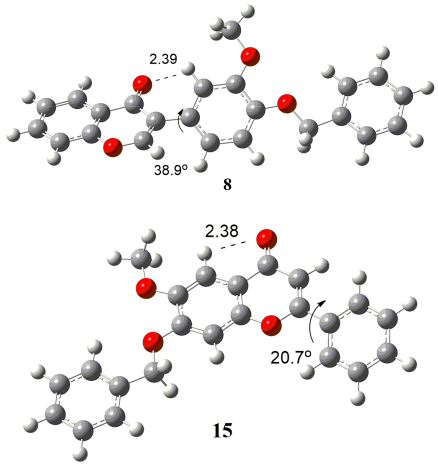



**Figure 4**. Optimized geometries of compound **8** and **15** at B3LYP/6-311G(d,p). (Bond lengths in Angstrom (Å) and bond angles in degree (°)).

### *3.3. UV-vis and IR spectra*

Compound **8** and **15** demonstrated very similar experimental vibrational spectra under neat conditions, mainly because of similar nature and number of functional groups. Band peaks for C=O functional group could be observed experimentally at 1689 $cm^{-1}$ for both compound **8** and **15**. The simulated spectra for compound **8** and **15** showed band peaks at 1711 and 1712 $cm^{-1}$, respectively. The numbers were in close agreement with the experimental values and were unscaled. Similarly, the other main band peak for both compounds was observed at 1303 $cm^{-1}$. Analysis of the theoretical vibrational spectra revealed that there were two intense peaks in this region 1300 and 1286 $cm^{-1}$. The former corresponded to aromatic C-H bending whereas the later is associated with O-C stretching. The theoretical model chosen here could accurately predict the vibrational spectra for these interesting natural products without any scaling factor.

The vibrational spectrum of compound **8** showed close similarity with compound **15**, however, the UV-vis absorption spectrum had small differences. Compound **8** showed two major peaks at 346 and 276 nm whereas in compound **15**, these peaks were observed at 341 and 273 nm. The simulated absorption spectrum of compound **8** at B3LYP/6-311G(d,p) showed two major peaks *i.e.*, at 375 and 305 nm. Although the absolute values of the simulated absorption peaks were slightly different than the experimental values however, the difference in two peaks was same theoretically and experimentally. The simulated absorption values weare about 29 nm higher than the experimental value. Similar differences in absorption peaks were well-known for DFT methods and already discussed in the literature in detail [28,29]. Furthermore, we had previously reported a closely related flavanone compounds, a difference of about 26 nm was observed between the theoretical and experimental absorption peaks [28]. The absorption at the longest wavelength for compound **8** (375 nm) corresponded to 3.3 eV energy for the excitation. We had simulated the energies of HOMO and LUMO in order to find whether this excitation was actually from HOMO to LUMO, or to some other orbitals. Simulated energies of HOMO and LUMO at B3LYP/6-311G(d,p) were -5.6 eV and -1.77 eV, which corresponded to the band gap of 3.82 ev, which was slightly higher than the excitation energy of 3.3 eV. This clearly illustrated that the transition corresponding to maximum wavelength was actually a transition from HOMO to LUMO. HOMO and LUMO for compounds **8** and **15** were shown in Figure 5 and 6, respectively. HOMO and LUMO of both compounds had maximum contribution from π bonds; however, it was interesting to note that charge densities were oriented differently. HOMO was mainly located on the chrome-4-one skeleton in compound **15** (Figure 6a) compared to its location on phenyl ring in compound **8** (Figure 5a). On the other hand, LUMO in compound **8** was oriented on the chrome-4-one scaffold (Figure 5b) whereas the LUMO was shifted to the phenyl ring (Figure 6b). An interesting characteristic feature in both compounds was the orientation of HOMO next to the benzyloxy moiety whereas the LUMO was present at the far positions. Since HOMO and LUMO are the frontier orbitals and play key role in the reactivity of any compound. It is believed from the analysis of HOMO and LUMO of compounds **8** and **15** that different rings in isoflavonoids and flavonoids would be reactive towards any chemical reaction. We believe that this study would be quite helpful in exploring the chemistry of isoflavonoids and flavonoids.

## 4. Conclusions

In conclusion, a successful oxidative method has been explored for oxidation of flavanones to flavone, isoflavone and benzofuran molecules which are highly reminiscent of the naturally occurring flavonoids, especially, quercetin **1**, genstein **2**, and lawsonicin **3**. This method is highly regioselective and sensitive to the selection of protecting group on B ring of flavanone. The efforts are underway to utilize and modify this oxidative method to approach the above mentioned natural products. DFT calculations have been performed to compare the bond lengths, bond angles to those obtained through X-ray crystallography. Moreover, the theoretically simulated vibrational and UV-Vis spectral values correspond with the experimentally observed values. Analysis of HOMO and LUMO not only revealed the band gap but also predicted the different reactive sites in flavonoid and isoflavonoid.

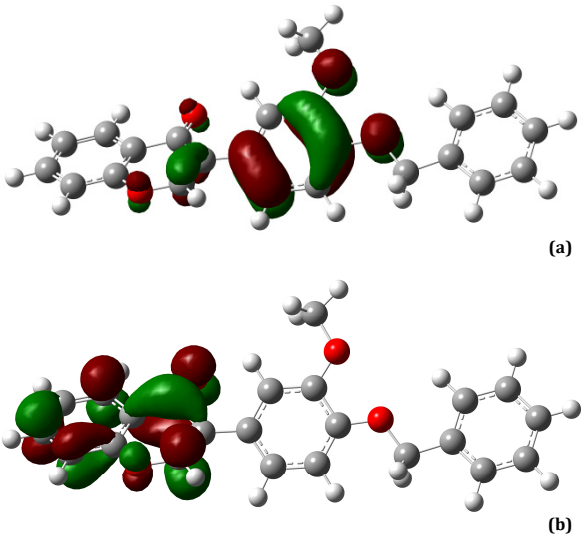



**Figure 5.** (a) HOMO and (b) LUMO of compound **8** plotted at isovalue of 0.04.

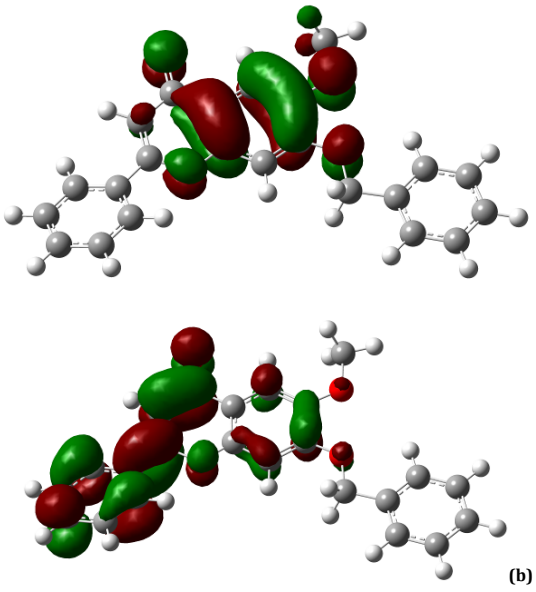



**Figure 6.** (a) HOMO and (b) LUMO of compound **15** plotted at isovalue of 0.03.

### *Supplementary information*

Supplementary information includes crystallographic data

for compound **8** and **15** can be obtained free of charge from CCDC-921451 and 921637, respectively, 12 Union Road, Cambridge CB2 1EZ, UK (fax: C44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/). $^{1}H$ and $^{13}C$ NMR spectra of compounds is available free of charge at http://www.eurjchem.com.

***Acknowledgements***

This research work was sponsored by Split Ph. D. fellowship program and Indigenous 5000 Ph.D. fellowship program of the Higher Education Commission (HEC), Pakistan and Husein Ebrahim Jamal Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, 75270, Pakistan.

## References

[1]. Ferreira, D.; Slade, D. *Nat. Prod. Rep.* **2002**, *19*, 517-541.
[2]. Corder, R.; Mullen, W.; Khan, N. Q.; Marks, S. C.; Wood, E. G.; Carrier, M. J.; Crozier, A. *Nature* **2006**, *444*, 566-566
[3]. Keen, C. L. *J. Am. Coll. Nutr.* **2001**, *20*, 436S-439S.
[4]. Ferreira, D.; Li, X. C. *Nat. Prod. Rep.* **2000**, *17*, 193-212.
[5]. Tückmantel, W.; Kozikowski, A. P.; Romanczyk, L. J. *J. Am. Chem. Soc.* **1999**, *121*, 12073-12081.
[6]. Kozikowski, A. P.; Tückmantel, W.; Böttcher, G.; Romanczyk, L. J. *J. Org. Chem.* **2003**, *68*, 1641-1658.
[7]. Anderson, J. C.; Headley, C.; Stapleton, P. D.; Taylor, P. W. *Tetrahedron* **2005**, *61*, 7703-7711.
[8]. Formica, J. V.; Regelson, W. *Food Chem. Toxicol.* **1995**, *33*, 1061-1080.
[9]. Green, N. S.; Foss, T. R.; Kelly, J. W. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 14545-14550.
[10]. Siddiqui, B. S.; Kardar, M. N.; Ali, S. T.; Khan, S. *Helv. Chim. Acta* **2003**, *86*, 2164-2169.
[11]. Prakash, O.; Pahuja, S.; Moriarty, R. M. *Synth. Commun.* **1990**, *20*, 1417-1422.
[12]. Prakash, O.; Saini, N.; Sharma, P. K. *Synlett* **1994**, *4*, 221-227.
[13]. Prakash, O.; Saini, N.; Sharma, P. K. *Heterocycles* **1994**, *38*, 409-431.
[14]. Meng, J.; Jiang, T.; Aslam Bhatti, H.; Siddiqui, B. S.; Dixon, S.; Kilburn, J. D. *Org. Biomol. Chem.* **2010**, *8*, 107-113.
[15]. Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154-160.
[16]. Banks, D. F. *Chem. Rev.* **1966**, *66*, 243-266.
[17]. Zhdankin, V. V. *Arkivoc* **2009**, *1*, 1-62.
[18]. Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404.
[19]. Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409-458.
[20]. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523-2584.
[21]. Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176-2179.
[22]. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.
[23]. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789.
[24]. Ullah, H.; Shah, A. U. H. A.; Ayub, K.; Bilal, S. *J. Phys. Chem. C* **2013**, *117*, 4069-4078.
[25]. Hashmi, M. A.; Khan, A.; Ayub, K.; Farooq, U. *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.* **2014**, *128*, 225-214.
[26]. Ullah, H.; Rauf, A.; Ullah, Z.; Fazli, S.; Anwar, M.; Shah, A. U. H. A.; Uddin, G.; Ayub, K. *Spectrochim. Acta A* **2014**, *118*, 210-214.
[27]. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr. , J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Gaussian, Inc., Wallingford, CT, USA, 2009.
[28]. Duisenberg, A. J. *J. Appl. Cryst.* **1992**, *25*, 92-96.
[29]. Hooft, R. COLLECT. Nonius BV, Delft, The Netherlands, 1998.
[30]. Otwinowski, Z.; Minor, W. Methods in Enzymology; In Macromolecular Crystallography, Part A; Jr, C. W. C. , Sweet, R. M. , Eds.; Academic Press: New York, 1997; vol. 276.
[31]. Sheldrick, G. M. *Acta Cryst. A* **1990**, *46*, 467-473.
[32]. Sheldrick, G. M. *SHELXL-97*, University of Göttingen, Germany, 1997.
[33]. Watkin, D. M.; Pearce, L.; Prout, C. K. Chemical Crystallography Laboratory; University of Oxford, 1993.
[34]. Barros, A. I. R. N. A.; Silva, A. M. S.; Alkorta, I.; Elguero, J. *Tetrahedron* **2004**, *60*, 6513-6521.
[35]. Tanaka, K.; Sugino, T. *Green Chem.* **2001**, *3*, 133-134.
[36]. Urgaonkar, S.; La Pierre, H. S.; Meir, I.; Lund, H.; RayChaudhuri, D.; Shaw, J. T. *Org. Lett.* **2005**, *7*, 5609-5612.
[37]. Juhasz, L.; Szilagyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyi, M. *Tetrahedron* **2002**, *58*, 4261-4265.
[38]. Khanna, M. S.; Singh, O. V.; Garg, C. P.; Kapoor, R. P. *Synth. Commun.* **1993**, *23*, 585-590.
[39]. Zhang, Q.; Botting, N. P. *Tetrahedron* **2004**, *60*, 12211- 12216.
[40]. Li, J. J. Name reactions: a collection of detailed mechanisms and synthetic applications, Springer Science & Business Media, 2010.