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Short communication

Synthesis and antibacterial activity of some new 2,3-dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones

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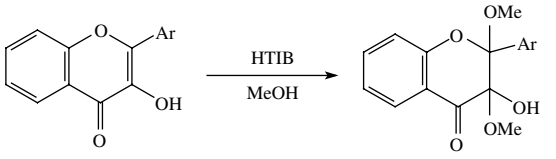
Abstract

Seven new 2,3-dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones (**5**) have been synthesized by the oxidation of 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromones (**4**) with iodobenzene diacetate in methanol. The structures of compounds **5** were established by the combined use of ^{1}H NMR, IR and mass spectra. All the seven compounds (**5**) were tested *in vitro* for their antibacterial activity against Gram-positive bacteria namely, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus pumilus* and two Gram-negative bacteria namely, *Salmonella typhi* and *Pseudomonas aeruginosa*. Three compounds, **5d**, **5f** and **5g**, have displayed antibacterial activity comparable to the commercial antibiotics, Linezolid, Cefaclor and Cefuroxime axetial.

Keywords: Hypervalent iodine; Iodobenzene diacetate; 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones; 3-Hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromones; Antibacterial activity

1. Introduction

Flavonoids are a group of natural products present in a wide variety of plants. They are found in seeds, citrus fruits, olive oil, tea and red wine and are commonly consumed with the human diet [1,2]. Flavonoids exhibit a broad range of biological activities, including antiviral, antiinflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic and antitumoral actions [3–5]. Furthermore, these compounds are used in bacteriology, pharmacology and medicine due to their bactericidal activities [6]. On the other hand, substituted pyrazoles also exhibit a broad spectrum of biological activities such as antidiabetic [7], antibacterial [8–10], antimicrobial [11–14] and herbicidal [15,16]. The use of hypervalent iodine reagents such as iodobenzene diacetate (IBD) [17–19], [hydroxy(tosyloxy)-iodo]benzene (HTIB; Koser's reagent) [20,21], etc. find interesting applications in heterocyclic compounds especially flavonoids. Among the various such applications, one noteworthy example is the oxidation of flavonols with [hydroxy(tosyloxy)iodo]benzene (HTIB) offering an efficient and convenient synthesis of 2,3-dimethoxy-3-hydroxyflavanones (Eq. (1)) [22].



(1)

A literature survey revealed that the title compounds 2,3-dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones (**5**) remain unknown. These observations, coupled with the diverse biological properties associated with pyrazole and flavanone derivatives, prompted us to study the scope of the synthetic route outlined in Eq. (1) on the oxidation of 2-pyrazolyl analogues of flavonol (**4**). There has been a particular interest in the synthesis of flavonoids with a pyrazole ring at position C-2 to find new and more potent biological activities

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[23]. We report herein synthesis of **5a–5g** by the oxidation of **4a–4g** using iodobenzene diacetate (IBD) in methanol with an expectation to find new and more potent antibacterial agents.

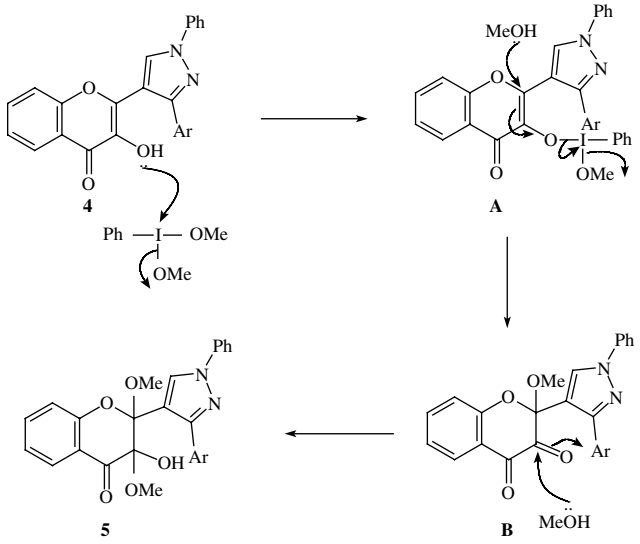
2. Results and discussion

2.1. Chemistry

The starting material 2-pyrazolyl analogues of flavonol **4** needed for the synthesis of **5** were prepared by the cyclization of pyrazolyl analogues of *o*-hydroxychalcone **3** with hydrogen peroxide (H_2O_2) in KOH–MeOH from our previous work involving Algar Flynn Oymanda (AFO) reaction [23]. The reaction of **4a** was carried out by treatment with 1.1 equiv of IBD in methanol by stirring at room temperature for 15–20 min. Usual work-up of the reaction afforded the pure crystalline product **5a** in 78% yield. Encouraged by the feasibility of our strategy for **5a**, we studied oxidation of a wide range of substituted **4b–4g** under similar conditions. This IBD mediated oxidative approach worked nicely to give the desired products **5b–5g** in all cases (Scheme 1).

The structures of all new compounds **5a–5g** were confirmed by their spectral (IR, ^{1}H NMR and mass) and elemental analytical data. The IR spectra of compounds **5a–5g** exhibited characteristic absorption band at 1690–1700 cm^{-1} and 3410–3420 cm^{-1} due to carbonyl and hydroxyl functional groups, respectively. The ^{1}H NMR spectra of all the products **5a–5g** showed two characteristic singlets due to C(2) and C(3) methoxy group protons at δ 3.00 and δ 3.15 present. The C(3)–OH proton appeared as broad singlet at δ 4.6–4.8 ppm and C(5)–H in pyrazole ring appeared as singlet at δ 8.30. Other protons appeared in the aromatic regions.

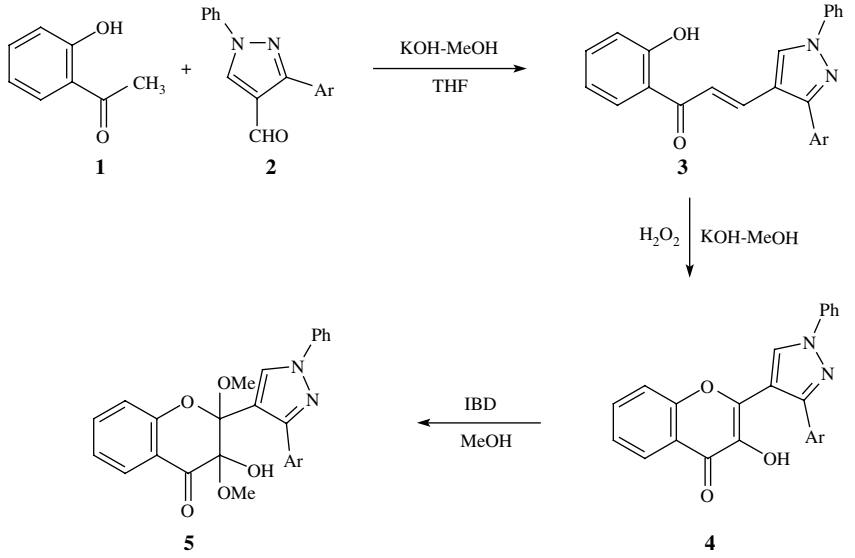
The conversion of **4** → **5** probably proceeds accordingly to Scheme 2 which is analogous to earlier reports [24].



Scheme 2.

2.2. Antibacterial activity

All the seven compounds (**5a–5g**) were tested *in vitro* for their antibacterial activity against three Gram-positive bacteria namely, *Staphylococcus aureus* (MTCC 3160), *Staphylococcus epidermidis* (MTCC 2639), and *Bacillus pumilus* (MTCC 1456), and two Gram-negative bacteria namely, *Salmonella typhi* (MTCC 733) and *Pseudomonas aeruginosa* (MTCC 3541) (Tables 1 and 2). Three of these compounds (**5d**, **5f** and **5g**) exhibited good antibacterial activity against both Gram-positive and Gram-negative bacteria. All of the seven compounds showed activity against Gram-positive bacteria namely *S. aureus* (MTCC 3160). Compound **5g** showed maximum antibacterial activity against *S. aureus* (MIC 2 μg/ml) and *S. epidermidis* (MIC 8 μg/ml). It also displayed inhibitory activity against *B.*



Ar = **a**, C_6H_5; **b**, 4-$CH_3C_6H_4$; **c**, 4-$OCH_3C_6H_4$, **d**, 4-ClC_6H_4; **e**, 4-BrC_6H_4; **f**, 4-FC_6H_4; **g**, 4-$NO_2C_6H_4$

Scheme 1.

Table 1
In vitro antibacterial activity of **5a–5g** by using agar diffusion assay technique

Compound	Diameter of zone of growth inhibition[a] (mm)				
	Sa	Se	Bp	St	Pa
5a	18.15	–	–	–	–
5b	16.10	12.64	–	–	–
5c	17.96	–	–	–	–
5d	20.35	16.69	–	–	14.67
5e	10.26	–	–	–	–
5f	22.99	12.11	10.11	18.16	22.16
5g	25.98	18.52	15.77	20.58	16.59
DMSO	8.11	7.17	7.07	7.78	7.23

– No activity.
[a] Mean of three replicates. Sa, *S. aureus* (MTCC 3160); Se, *S. epidermidis* (MTCC 2639); Bp, *B. pumilus* (MTCC 1456); St, *S. typhi* (MTCC 733); Pa, *P. aeruginosa* (MTCC 3541).

pumilus (MIC 32 μg/ml), *S. typhi* (MIC 8 μg/ml) and *P. aeruginosa* (MIC 8 μg/ml). Compound **5f** was found to be effective against *S. aureus* (MIC 4 μg/ml). It also inhibited the growth of *S. typhi* and *P. aeruginosa* at MIC 8 μg/ml. Compound **5d** inhibited the growth of *S. aureus* at 8 μg/ml, *S. epidermidis* at 16 μg/ml and *P. aeruginosa* at 32 μg/ml. The antibacterial activity of these compounds was also compared with three commercial antibiotics namely Linezolid, Cefaclor and Cefuroxime axetial. Three compounds (**5d**, **5g** and **5f**) showed comparable activity as displayed in Tables 1 and 2.

3. Conclusion

We described herein an efficient and convenient synthesis of new compounds **5a–5g**, thereby emphasizing the increasing utility of organoiodine(III) mediated methods. The results on the antibacterial activity are also encouraging as out of seven compounds tested, three compounds (**5d**, **5f** and **5g**) showed good antibacterial activity as displayed in Tables 1 and 2. A comparison of antibacterial activity of these compounds with that of three commercial antibiotics namely Linezolid, Cefaclor and Cefuroxime axetil indicated that compound **5g** show very good activity.

Table 2
MIC of **5a–5g** against test bacteria by using agar dilution assay

Compound	MIC[a] (μg/ml)				
	Sa	Se	Bp	St	Pa
5a	16	>64	>64	>64	>64
5b	32	64	>64	>64	>64
5c	16	>64	>64	>64	>64
5d	8	16	>64	>64	32
5e	64	>64	>64	>64	>64
5f	4	64	64	8	8
5g	2	8	32	8	16
Linezolid	4	<16	4	8	<16
Cefaclor	2	2	8	8	<16
Cefuroxime axetial	8	8	>16	8	>16

[a] Mean of three replicates.

4. Experimental

Melting points were determined in open capillaries with electrical melting point apparatus and are uncorrected. The IR spectra were obtained with a Buck Scientific IR M-500 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker (300 MHz) spectrometer using tetramethylsilane as an internal standard. All the new compounds gave satisfactory analytical results (within 0.4 of the theoretical values). The starting material 2-pyrazolyl analogues of flavanol were available from our previous work involving AFO reaction of pyrazolyl analogues of *o*-hydroxychalcone [23].

*4.1. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones (**5a–5g**)*

General procedure. To a suspension of **4** (1.0 mmol) in methanol (20 ml) was added iodobenzene diacetate (1.1 mmol) and the mixture was stirred at room temperature for 15–20 min. All the reactants dissolved and a colorless crystalline product separated out. The solid product was filtered and washing with cold methanol (5–10 ml) gave almost pure products **5**. The products **5** were recrystallized with methanol.

The physical, analytical and spectral data of 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromanones **5a–5g** are given below.

*4.1.1. 2,3-Dimethoxy-3-hydroxy-2-(1,3-diphenyl-4-pyrazolyl)chromanone (**5a**)*

Yield: 78%; mp 146–148 °C; IR (ν_{max}, in KBr): 3418 cm^{-1} (–OH str.), 1697 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.15 (s, 3H, OCH_3), 3.00 (s, 3H, OCH_3), 4.89 (s, 1H, OH), 8.32 (s, 1H), 7.86–7.96 (m, 5H), 7.33–7.41 (m, 7H), 7.13–7.16 (m, 1H), 6.80 (d, 1H, $J = 7.8$ Hz). Anal. Calculated for $C_{26}H_{22}N_2O_5$: C 70.59, H 4.98, N 6.33. Found: C 70.95, H 4.69, N 6.55; MS: *m/z*, M$^+$ 442.

*4.1.2. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-tolyl)-4-pyrazolyl)chromanone (**5b**)*

Yield: 75%; mp 184–186 °C; IR (ν_{max}, in KBr): 3413 cm^{-1} (–OH str.), 1697 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.41 (s, 3H, CH_3), 3.14 (s, 3H, OCH_3), 3.00 (s, 3H, OCH_3), 4.50 (s, 1H, OH), 8.32 (s, 1H), 7.21 (d, 2H, $J = 8.1$ Hz), 7.59 (d, 2H, $J = 8.1$ Hz), 7.84–7.91 (m, 5H), 7.32–7.37 (m, 3H), 6.87 (d, 1H, $J = 8.4$ Hz). Anal. Calculated for $C_{27}H_{24}N_2O_5$: C 71.05, H 5.26, N 6.14. Found: C 70.82, H 5.32, N 6.04; MS: *m/z*, M$^+$ 456.

*4.1.3. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-anisyl)-4-pyrazolyl)chromanone (**5c**)*

Yield: 72%; mp 151–153 °C; IR (ν_{max}, in KBr): 3420 cm^{-1} (–OH str.), 1699 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.78 (s, 3H, OCH_3), 3.05 (s, 3H, OCH_3), 2.90 (s, 3H, OCH_3), 4.82 (s, 1H, OH), 8.29 (s, 1H), 8.4 (d, 3H, $J = 8.7$ Hz), 7.75 (d, 2H, $J = 8.1$ Hz), 6.79 (d, 2H, $J = 8.1$ Hz), 6.85 (d, 1H, $J = 9.0$ Hz), 7.37–7.48 (m, 3H), 7.20–7.25 (m, 1H), 7.02–7.06 (m, 1H). Anal. Calculated for

$C_{27}H_{24}N_2O_6$: C 68.64, H 5.08, N 5.93. Found: C 68.70, H 4.97, N 6.02; MS: *m/z*, M^+ 472.

4.1.4. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-chlorophenyl)-4-pyrazolyl)chromanone (**5d**)

Yield: 78%; mp 159–160 °C; IR (ν_{max}, in KBr): 3406 cm^{-1} (–OH str.), 1697 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz, δ): 3.13 (s, 3H, OCH_3), 3.00 (s, 3H, OCH_3), 4.91 (s, 1H, OH), 8.30 (s, 1H), 7.92–7.96 (m, 3H), 7.84 (d, 2H, $J = 8.1$ Hz), 7.49 (d, 2H, $J = 8.1$ Hz), 7.31–7.38 (m, 4H), 7.12–7.17 (m, 1H), 6.85 (d, 1H, $J = 8.4$ Hz). Anal. Calculated for $C_{26}H_{21}N_2O_5Cl$: C 65.55, H 4.41, N 5.88. Found: C 65.37, H 4.32, N 5.98; MS: *m/z*, M^+ 476.

4.1.5. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-bromophenyl)-4-pyrazolyl)chromanone (**5e**)

Yield: 76%; mp 179–180 °C; IR (ν_{max}, in KBr): 3412 cm^{-1} (–OH str.), 1693 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz, δ): 3.04 (s, 3H, OCH_3), 2.92 (s, 3H, OCH_3), 4.82 (s, 1H, OH), 8.21 (s, 1H), 7.76–7.86 (m, 5H), 7.39–7.44 (m, 3H), 7.52 (d, 2H, $J = 8.1$ Hz), 7.27 (d, 2H, $J = 8.1$ Hz), 6.77 (d, 1H, $J = 8.4$ Hz). Anal. Calculated for $C_{26}H_{21}N_2O_5Br$: C 60.0, H 4.03, N 5.38. Found: C 60.21, H 3.98, N 5.52; MS: *m/z*, M^+ 520.

4.1.6. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-fluorophenyl)-4-pyrazolyl)chromanone (**5f**)

Yield: 80%; mp 162–164 °C; IR (ν_{max}, in KBr): 3412 cm^{-1} (–OH str.), 1693 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz, δ): 3.12 (s, 3H, OCH_3), 3.01 (s, 3H, OCH_3), 4.92 (s, 1H, OH), 8.31 (s, 1H), 7.90–7.99 (m, 3H), 7.85 (d, 2H, $J = 8.1$ Hz), 7.56 (d, 2H, $J = 8.1$ Hz), 7.34–7.42 (m, 4H), 7.10–7.17 (m, 1H), 6.81 (d, 1H, $J = 8.4$ Hz). Anal. Calculated for $C_{26}H_{21}N_2O_5F$: C 67.82, H 4.56, N 6.09. Found: C 67.68, H 4.49, N 6.18; MS: *m/z*, M^+ 460.

4.1.7. 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-(p-nitrophenyl)-4-pyrazolyl)chromanone (**5g**)

Yield: 72%; mp 189–191 °C; IR (ν_{max}, in KBr): 3412 cm^{-1} (–OH str.), 1693 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz, δ): 3.12 (s, 3H, OCH_3), 2.92 (s, 3H, OCH_3), 4.82 (s, 1H, OH), 8.32 (s, 1H), 8.33 (d, 2H, $J = 8.1$ Hz), 8.10 (d, 2H, $J = 8.1$ Hz), 7.75–7.69 (m, 6H), 7.21–7.29 (m, 2H); 6.89 (d, 1H, $J = 8.4$ Hz). Anal. Calculated for $C_{26}H_{21}N_3O_7$: C 64.07, H 4.31, N 8.62. Found: C 63.95, H 4.45, N 8.47; MS: *m/z*, M^+ 487.

5. *In vitro* biological assay

5.1. Medium

Two solid media, namely Muller–Hinton agar (MHA; beef infusion 300 g/L, casein acid hydrolysate 17.5 g/L, starch 1.5 g/L, agar–agar 17 g/L, and distilled water 1000 ml, adjusted to pH 7.4) and soyabean casein digest agar (SCDA; casein enzymatic hydrolysate 17.0 g/L, papain digest of soyabean 3.0 g/L, NaCl 5.0 g/L, dipotassium phosphate 2.5 g/L, dextrose 2.5 g/L, and distilled water 1000 ml, adjusted to pH 7.3), were used for the biological assays.

5.2. Test microorganisms

Three Gram-positive bacteria *S. aureus* (MTCC 3160), *S. epidermidis* (MTCC 2639), and *B. pumilus* (MTCC 1456), and two Gram-negative bacteria *S. typhi* (MTCC 733) and *P. aeruginosa* (MTCC 3541) were used for the biological assays.

5.3. Primary screening

Primary screening of seven compounds (**5a–5g**) was done by the agar diffusion assay technique. Twenty-four-hour-old bacterial cultures of all test microorganisms were used as inoculum, which was adjusted to 0.5 McFarland Standard, that is, 1.5×10^8 CFU/ml [25]. The stock solutions of all the test compounds (1 mg/ml) were prepared by dissolving 1 mg of the test compound in DMSO (1 ml). Linezolid, Cefaclor, Cefuroxime axetil, and DMSO were used as positive and negative controls, respectively.

Twenty milliliters of molten and cooled MHA and 500 μl of each test bacterial culture were mixed (separate flasks were used for each bacterial culture) and poured in sterilized and labeled Petri plates. The wells of 6 mm were punched in the solidified Petri plates aseptically. Fifty microliters from stock solutions of all the compounds as well as controls was added to each well of labeled Petri plates and incubated at 35 °C for 24 h. The diameter of the zone of growth inhibition around each well was measured after incubation using a Vernier Caliper.

5.4. Minimum inhibitory concentration

The minimum inhibitory concentration (MIC) is the lowest concentration of the antimicrobial agent that prevents the development of visible growth after overnight incubation [26]. MIC of compounds against Gram-positive and Gram-negative test bacteria was determined by the method of NCCLS [27]. All the test cultures were streaked on SCDA and incubated overnight at 37 °C. Turbidity of all the bacterial cultures was adjusted to 0.5 McFarland Standard by preparing bacterial suspension of 3–5-well isolated colonies of the same morphological type selected from an agar plate culture. The cultures were further diluted 10-fold to get an inoculum size of 1.2×10^7 CFU/ml. Stock solution of 4 mg/ml of each compound was prepared in DMSO and was appropriately diluted to get a final concentration of 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, and 0.12 mg/ml. Standard antibiotics (Linezolid, Manufacturer – Alembic, Batch no. 6893002; Cefaclor, Manufacturer – Galaxo, Batch no. 1305911; Cefuroxime axetial, Manufacturer – Galaxo, Batch no. HD-313) were also diluted in the same manner. Three hundred and twenty microliters of each dilution was added to 20 ml molten and cooled MHA (separate flasks were taken for each dilution). After thorough mixing, the medium was poured in sterilized Petri plates. The test bacterial cultures were spotted in a predefined pattern by ascetically

transferring 5 ml of each bacterial culture on the surface of solidified agar plates and incubated at 35 °C for 24 h.

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