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Synthesis and antifungal activity of new dihydrofurocoumarins and dihydrofuroquinolines

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Abstract: We investigated the radical addition of 4-hydroxycoumarin (**1a**) and 4-hydroxyquinoline (**1b**) with conjugated dienes (**2a**–**f**) mediated by cerium(IV) ammonium nitrate (CAN) resulting in ethenyl substituted 2,3-dihydrofurocoumarin (**3a**–**f**) and 3,5-dihydrofuroquinoline (**3g**, **3h**) compounds in moderate to good yields. All compounds were characterized by spectroscopic methods (IR, MS, and ^{1}H and ^{13}C NMR) and microanalysis. Antifungal activities of these compounds were investigated against the fungi *Candida albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, *C. tropicalis*, and *Aspergillus fumigatus*.

Key words: Dihydrofurocoumarin, dihydrofuroquinoline, cerium(IV) ammonium nitrate, radical cyclization

1. Introduction

Coumarin derivatives are preeminent amongst the heterocyclic scaffolds found in both naturally occurring products as well as in designed medicinal agents. They possess many biological activities varying from anticancer,[1] anti-HIV,[2,3] anti-Alzheimer,[4,5] antiviral,[6] antimicrobial,[7,8] antioxidant,[9] anti-inflammatory,[10] antituberculosis,[11] anti-influenza,[12] and antihyperlipidemic.[13,14] Moreover, Warfarin is a 4-hydroxycoumarin derivative that has been used as an anticoagulant drug for a long time. In addition, scopoletin[15] and esculatin[16] were found in nature and they have antiproliferative, antioxidant, and anti-inflammatory activities (Figure 1).

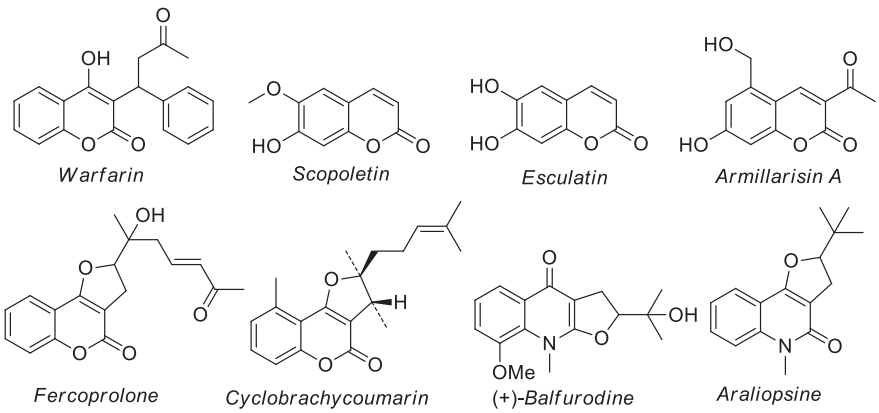

Figure 1. Naturally occurring dihydrofurans.

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Dihydrofurocoumarins such as fercoprolone,[17] mutisicoumarin,[18] cyclobrachycoumarin,[19] and isoerlengefusciol[20] have been found in nature and they have similar activities to coumarin derivatives. We have also recently reported that some 3-cyano-4,5-dihydrofurans show antifungal and antibacterial activities.[21] Lunacrine, bucharaminol, acrophylline, dicramnine, isotaifine, araliopsine, almein, and oligophylidine are quinoline alkaloids commonly found in nature. It is reported that these compounds show antiparasitic, anthelmintic, cytotoxic, antiarrhythmic, spasmolytic, sedative, antitumor, and antimalarial activities.[22−27]

Although there are some antifungal drugs clinically used in the treatment of fungal infections, there is always a need for new antifungal agents due to the low efficacy, side effects, or resistance associated with the existing drugs. Thus, the growing demand for coumarin derivatives increases the need for developing new methods in this area. Several methods for preparation of dihydrofurocoumarins have been developed in the last three decades. These include cyclization of 4-hydroxycoumarin and 4-hydroxy-2-quinoline with iodides and allene via palladium catalyses.[28] Many dihydrofurocoumarins have been synthesized by palladium catalyzed annulation of 1,3-dienes with o-iodoacetoxycoumarins.[29,30] Furthermore, synthesis of some dihydrofurocoumarins has been reported from rhodium-catalyzed reactions of α-carbonilcarbens and vinyl ethers.[31] Moreover, synthesis of these compounds obtained from the radical addition of 4-hydroxycoumarins and 4-hydroxyquinolines to various alkenes mediated by silver(I)/Celite,[32] Ce(IV) ammonium nitrate,[33,34] and $Mn(OAc)_3^{35}$ as single electron transferable metal salts has been reported.

It is well known that $Mn(OAc)_3$[36−41] and $(NH_4)_2Ce(NO_2)_6$ (CAN)[33,42,43] have been used as radical oxidants in the synthesis of dihydrofuran derivatives forming a C–C bond between active methylene compounds and alkenes. Previously, we described the formation of some dihydrofurocoumarin derivatives from the reaction of 4-hydroxycoumarin and alkenes mediated by $Mn(OAc)_3$.[35]

In the present study, we performed the reaction of 4-hydroxycoumarin and 4-hydroxyquinoline with conjugated dienes promoted by CAN leading for ethenyl substituted 2,3-dihydrofurocoumarin in moderate to good yields. We also investigated the antifungal activity of these compounds against *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata, C. tropicalis* and *Aspergillus fumigatus*.

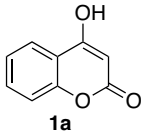
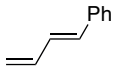
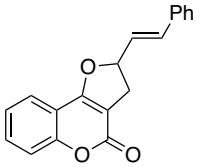
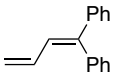
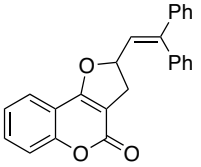
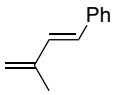
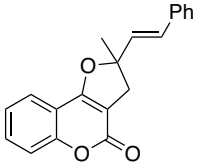
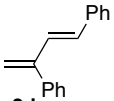
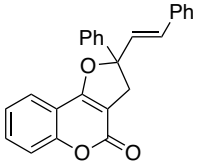
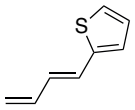
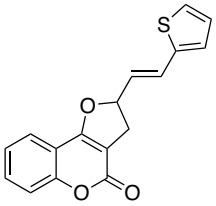
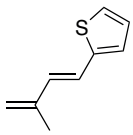
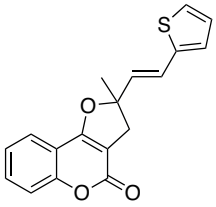
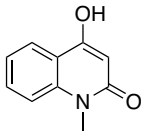
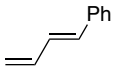
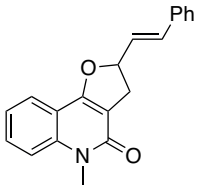
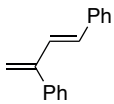
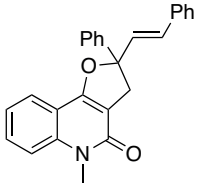
2. Results and discussion

1-Phenyl-1,3-butadiene (**2a**),[44] 3-methyl-1-phenyl-1,3-butadiene (**2c**),[45] (*E*)-2-(buta-1,3-dien-1-yl)thiophene (**2e**),[44] and 3-methyl-1-(2-thienyl)-1,3-butadiene (**2f**) were synthesized by the Wittig reaction of triphenylphosphoniummethyl bromide with suitable aldehydes and ketones. 1,3-Diphenyl-1,3-butadiene (**2d**)[46] was obtained from the Wittig reaction of benzaldehyde and triphenyl(2-phenylallyl)phosphonium bromide, which was prepared from the reaction of 2-phenylallyl bromide and triphenylphosphine.

Furthermore, 1,1-diphenyl-1,3-butadiene (**2b**) was synthesized from the water elimination of 1,1-diphenyl-but-3-en-1-ol compound obtained from the Grignard reaction of allylmagnesium bromide with benzophenone.[47]

As seen in Table 1, the reactions of 4-hydroxycoumarin **1a** with 1-phenyl-1,3-butadiene **2a** and 1,1-diphenyl-1,3-butadiene **2b** gave 2,3-dihydrofurocoumarins **3a** (65%) and **3b** (83%) in good yields, respectively. Moreover, we obtained similar results from the reaction of 3-methyl-1-phenyl-1,3-butadiene **2c** with **1a** to form dihydrofurocoumarin **3c** in 78% yield. Additionally, the treatment of **1a** with 1,3-diphenyl-1,3-butadiene **2d** formed dihydrofurans **3d** in 70% yield. Compounds **3e** (46%) and **3f** (36%) were obtained from the radical cyclization of **1a** with 1-(2-thienyl)-1,3-butadiene **2e** and 3-methyl-1-(2-thienyl)-1,3-butadiene **2f**, respectively. Similarly, 4-hydroxyquinoline **1b** with **2a** and **2d** formed 3,5-dihydrofuroquinolines **3g** (42%) and **3h** (62%) in moderate yields.

Table 1. Synthesized dihydrofurocoumarin and dihydrofuroquinoline compounds.

Entry	4-hydroxyenone	Diene	Compound	Yield (%)[a]
1	 **1a**	 **2a**		**3a**, 65
2	**1a**	 **2b**		**3b**, 83
3	**1a**	 **2c**		**3c**, 78
4	**1a**	 **2d**		**3d**, 70
5	**1a**	 **2e**		**3e**, 46
6	**1a**	 **2f**		**3f**, 36
7	 **1b**	 **2a**		**3g**, 42
8	**1b**	 **2d**		**3h**, 62

a: Yields of isolated products based on the 4-hydroxyenones.

The proposed mechanism for the radical cyclization of 4-hydroxycoumarin and 4-hydroxyquinoline with conjugated dienes mediated by CAN leading to formation of 2,3-dihydrofurocoumarin and 3,5-dihydrofuroquinoline is displayed in Figure 2. According to this mechanism, while Ce^{4+} is reduced to Ce^{3+}, a radical cation (**A**) is formed as described by Jiao.[48] Radical intermediate **B** is formed by a proton elimination of this structure. Radical intermediate **C** is obtained by an electrophilic radical addition of **B** on the diene. The radical **C** is oxidized to carbocation **D** by CAN. The intramolecular cyclization of **D** forms 2,3-dihydrofurocoumarin and 3,5-dihydrofuroquinoline **F**.

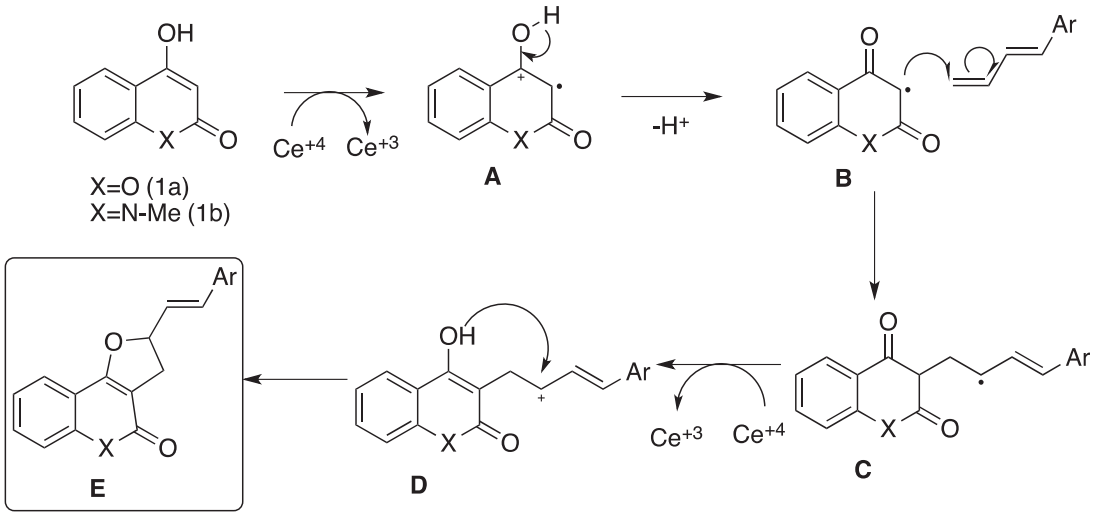


Figure 2. Mechanism for the radical cyclization of 4-hydroxyenones with conjugated dienes.

In conclusion, the radical cyclizations of 4-hydroxycoumarin and 4-hydroxyquinoline with various conjugated dienes mediated by CAN were performed in this study, leading to formation of novel dihydrofurocoumarins (**3a**–**f**) and dihydrofuroquinolines (**3g**, **3h**) in moderate to good yields. Moreover, antifungal activities of these dihydrofurocoumarin and dihydrofuroquinoline derivatives were examined against various *Candida* species and *Aspergillus fumigatus*. These compounds show medium antifungal activities since the solubility of the dihydrofurocoumarins and dihydrofuroquinolines is low in the buffer. Thus, studies on the biological activity of similar compounds that are more soluble in buffer medium and further transformation of the dihydrofuran derivatives are in progress.

3. Experimental

Melting points were determined on a Gallenkamp capillary melting point apparatus. IR spectra (KBr disc, $CHCl_3$) were obtained with a Matson 1000 FT-IR spectrophotometer in the 400–4000 cm^{-1} range with 4 cm^{-1} resolution. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 High performance Digital FT-NMR and Varian Oxford NMR300 spectrometers. The mass spectra were measured on a Waters 2695 Alliance HPLC, Waters micromass 2Q (ESI+) and Waters Xevo TQMS spectrometers. Elemental analyses were performed on a Leco 932 CHNSO instrument. Thin layer chromatography (TLC) was performed on Merck aluminum-packed silica gel plates. Purification of products was performed by column chromatography on silica gel (Merck silica gel 60, 40–60 μm) or preparative TLC on silica gel of Merck ($PF_{254-366\,nm}$). All solvents (THF, acetic acid, ethyl acetate, hexane, and chloroform) were of the highest purity and anhydrous. All reactions were

performed under an inert atmosphere. 4-Hydroxy-2*H*-chromen-2-one (**1a**) and 4-hydroxy-1-methylquinolin-2(1*H*)-one (**1c**) were purchased from Sigma Aldrich.

The antifungal activity was measured based on the recommendations of Clinical Laboratory Standard Institute (CLSI) M27 A3 documents for *Candida* species and CLSI M38 A2 document for *Aspergillus fumigatus*. The quality control strains of fungi used were as follows: *C. albicans* ATCC 90028, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *C. glabrata* ATCC 90030, *C. tropicalis* ATCC 0750, and *Aspergillus fumigatus* ATCC 204305. The compounds were dissolved in dimethyl sulphoxide (DMSO) and diluted two-fold in test medium (RPMI 1640 medium buffered with 0.165 M morpholino propanesulfonic acid [MOPS] to pH 7.0). The compound dilutions and inoculum of *Candida* species and *A. fumigatus* (10^{-4} colony forming units/mL) were placed in 96-microwell plates. First, the quality control strains were tested against antifungals such as fluconazole, caspofungin, and amphotericin B. Ten times the last concentrations of these antifungals were prepared as stock solutions. The tested concentration was prepared in RPMI 1640 medium. Fluconazole was tested between 0.016 and 256 μg/mL, while caspofungin and amphotericin B were tested between 0.002 and 16 μg/mL concentrations. The antifungal drugs, fluconazole (Pfizer), caspofungin (Merck-Sharp & Dohme), and amphotericin B (Sigma-Aldrich), were purchased from the supplying company. The last concentration ranges of all compounds in the wells were between 2.25 μL and 1000 μL. The minimum inhibitory concentration (MIC) was the minimum concentration of the compound that showed full inhibition of fungal growth in the well compared to the control well containing only fungal inoculum and culture media. MIC was determined with the naked eye by an experienced mycologist. The antifungal susceptibility test for each species was repeated three times.

3.1. Synthesis of 3-methyl-1-(2-thienyl)-1,3-butadiene (2f)

A solution of triphenylmethylphosphonium bromide (42.5 mmol) and sodium hydride (44.6 mmol) in anhydrous THF (75 mL) was stirred in an ice-salt bath for 15 min. Then the reaction mixture was heated at reflux for 2 h. After this time, the 2-acetylthiophene solution (17 mmol) in anhydrous THF was added to the reaction mixture dropwise with cooling and stirring in an ice-salt bath for half an hour. Then the reaction mixture was stirred overnight at room temperature. The THF evaporated and the mixture was extracted with *n*-hexane (monitored by TLC until product vanished). Combined organic phases were concentrated. The crude product was purified by column chromatography using *n*-hexane as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (1H, d, J = 4.4 Hz), 6.99 (2H, m), 6.71 (1H, d, J = 16.0 Hz), 6.65 (1H, d, J = 16.0 Hz), 5.08 (1H, d, J = 0.8 Hz), 5.04 (1H, d, J = 0.8 Hz), 1.94 (3H, s).

General procedure for the synthesis of dihydrofurocoumarin and dihidrofuroquinoline compounds (3a–h)

To a solution of 4-hydroxyenone (1 mmol) and diene (1.2 mmol) in THF (15 mL) under N_2 was added a mixture of CAN (2.4 mmol) and $NaHCO_3$ (2.4 mmol) at 40 °C. The reaction was monitored by TLC and completed when the orange color of CAN had disappeared (10–30 min). H_2O was added to the solution and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and concentrated and the crude product was purified by column chromatography (silica gel, 230–400 mesh) or preparative TLC (20 × 20 cm plates, 2 mm thickness, hexane/EtOAc 3:1).

2-[(*E*)-2-Phenylvinyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3a**): White solid, yield 65%, mp 96–99 °C. IR (ATR): 3026, 2974, 2924, 1759, 1701, 1654, 1494, 1446, 1384, 1325, 1176, 966, 746, 692; ^{1}H NMR (400

MHz, $CDCl_3$): δ_H 7.68 (dd, 1H, J = 8.0, 1.6 Hz), 7.56 (td, 1H, J = 8.0, 1.6 Hz), 7.43 (d, 2H, J = 7.2 Hz), 7.35 (t, 2H, J = 8.0 Hz), 7.31–7.26 (m, 3H), 6.77 (d, 1H, J = 15.6 Hz, H_{olefin}), 6.36 (dd, 1H, J = 16.0, 8.0 Hz, H_{olefin}), 5.71 (ddd, 1H, J = 10.0, 8.0, 7.6 Hz, H-2), 3.44 (dd, 1H, J = 15.2, 10.0 Hz, Ha-3), 3.06 (dd, 1H, J = 15.2, 7.6 Hz, Hb-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6 (C=O), 160.8, 155.1, 135.7, 134.3, 132.6, 128.9, 128.8, 127.1, 126.3, 124.2, 123.0, 117.1, 112.7, 102.1, 87.9, 33.3; LC-MS: m/z % 291 $[M+H]^+$, 100%. Anal. Calcd. for $C_{19}H_{14}O_3$ C, 78.61; H, 4.86. Found C, 78.53; H, 4.94.

2-(2,2-Diphenylvinyl)-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3b**): Yellow solid, yield 83%, mp 125–128 °C. IR (ATR): 3507, 2918, 1718, 1647, 1606, 1496, 1413, 1271, 1157, 1026, 894, 748, 702, 690. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (dd, 1H, J = 7.6, 1.6 Hz), 7.55 (td, 1H, J = 7.6, 1.6 Hz), 7.47–7.25 (m, 13H), 6.25 (d, 1H, J = 9.2 Hz, H_{olefin}), 5.60 (ddd, 1H, J = 10.0, 9.2, 7.6 Hz, H-2), 3.39 (dd, 1H, J = 15.2, 10.0 Hz, Ha-3), 3.10 (dd, 1H, J = 15.2, 8.0 Hz, Hb-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6 (C=O), 160.8, 155.1, 147.4, 141.0, 138.5, 130.1, 128.7, 128.6, 128.5, 128.4, 128.0, 125.4, 124.1, 123.0, 117.1, 112.8, 102.2, 85.2, 34.1. LC-MS: m/z % 367 $[M+H]^+$, 100%. Anal. Calcd. for $C_{25}H_{18}O_3$ C, 81.95; H, 4.95. Found C, 81.73; H, 5.06.

2-Methyl-2-[(*E*)-2-phenylvinyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3c**) White oil, yield 78%. IR (ATR): 3024, 1714, 1641, 1604, 1496, 1408, 1026, 962, 893, 746, 731, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (dd, 1H, J = 7.6, 1.6 Hz), 7.58 (td, 1H, J = 7.6, 1.6 Hz), 7.42–7.22 (m, 7H), 6.70 (d, 1H, J = 16.0 Hz, H_{olefin}), 6.42 (d, 1H, J = 16.0 Hz, H_{olefin}), 3.30 (d, 1H, J = 15.2 Hz, Ha-3), 3.11 (d, 1H, J = 14.8 Hz, Hb-3), 1.80 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.6 (C=O), 161.0, 155.2, 136.0, 132.5, 131.2, 129.5, 128.9, 128.5, 126.9, 124.1, 123.0, 117.2, 113.0, 101.6, 93.6, 39.5, 27.0. LC-MS: m/z % 305 $[M+H]^+$, 100%. Anal. Calcd. for $C_{20}H_{16}O_3$ C, 78.93; H, 5.30. Found C, 78.68; H, 5.52.

2-Phenyl-2-[(*E*)-2-phenylethenyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3d**): Yellow oil, yield 70%. IR (ATR): 3026, 2974, 2924, 1759, 1701, 1654, 1494, 1446, 1384, 1325, 1176, 966, 746, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.7 (dd, 1H, J = 8.0, 1.6 Hz), 7.5 (t, 1H, J = 8.0 Hz), 7.45–7.1 (m, 14H), 3.6 (d, 1H, J = 15.2 Hz, Ha-3), 3.5 (d, 1H, J = 15.2 Hz, Hb-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.1 (C=O), 159.3, 154.0, 141.3, 134.5, 131.4, 129.6, 129.5, 127.7, 127.6, 127.3, 127.2, 125.8, 125.1, 124.3, 123.0, 121.7, 111.5, 100.5, 95.0, 39.0. LC-MS: m/z % 367 $[M+H]^+$, 100%. Anal. Calcd. for $C_{25}H_{18}O_3$ C, 81.95; H, 4.95. Found C, 82.10; H, 4.73.

2-[(*E*)-2-(2-Thienyl)vinyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3e**): Yellow solid, yield 46%, mp 97–100 °C. IR (ATR): 3093, 3076, 1710, 1639, 1568, 1498, 1409, 1263, 1203, 1028, 893, 727, 655. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (dd, 1H, J = 8.0, 1.6 Hz), 7.58 (td, 1H, J = 7.6, 1.6 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.30–7.20 (m, 2H), 7.08 (d, 1H, J = 3.6 Hz), 7.0 (dd, 1H, J = 5.2, 3.6 Hz), 6.90 (d, 1H, J = 15.6 Hz, H_{olefin}), 6.20 (dd, 1H, J = 15.6, 8.0 Hz, H_{olefin}), 5.68 (ddd, 1H, J = 10.0, 8.0, 1.2 Hz, H-2), 3.48 (dd, 1H, J = 15.2, 10.0 Hz, Ha-3), 3.08 (dd, 1H, J = 15.2, 8.0 Hz, Hb-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.5 (C=O), 160.7, 155.1, 140.6, 132.6, 127.8, 127.7, 127.4, 125.9, 125.5, 124.2, 123.0, 117.1, 112.7, 102.1, 87.6. LC-MS: m/z % 297 $[M+H]^+$, 100%. Anal. Calcd. for $C_{17}H_{12}O_3S$ C, 68.90; H, 4.08. Found C, 68.78; H, 4.30.

2-Methyl-2-[(*E*)-2-(2-thienyl)vinyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**3f**): Yellow oil, yield 36%, IR (ATR): 3068, 2976, 2927, 1712, 1641, 1498, 1408, 1278, 1028, 954, 750, 727, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (dd, 1H, J = 8.0, 1.6 Hz), 7.58 (td, 1H, J = 7.6, 1.6 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.32 (td, 1H, J = 7.6, 1.2 Hz), 7.20 (d, 1H, J = 5.2 Hz), 7.02 (d, 1H, J = 3.6 Hz), 6.97 (dd, 1H, J = 5.2, 3.6 Hz), 6.82 (d, 1H, J = 16.0 Hz, H_{olefin}), 6.28 (d, 1H, J = 16.0 Hz, H_{olefin}), 3.28 (d, 1H, J = 15.2 Hz, Ha-3), 3.10 (d, 1H, J = 14.8 Hz, Hb-3), 1.78 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.5 (C=O), 160.9, 155.2,

141.0, 132.5, 130.5, 127.7, 127.2, 125.4, 124.1, 123.0, 122.9, 117.2, 112.9, 101.5, 93.3, 39.5, 27.0. LC-MS: m/z % 311 $[M+H]^+$, 100%. Anal. Calcd. for $C_{18}H_{14}O_3S$ C, 69.66; H, 4.55. Found C, 69.50; H, 4.34.

5-Methyl-2-[(*E*)-2-phenylvinyl]-3,5-dihydrofuro[3,2-*c*]quinolin-4(2*H*)-one (**3g**): Yellow solid, yield 42%, mp 125–128 °C). IR (ATR): 3057, 3022, 1656, 1631, 1598, 1506, 1354, 1246, 1153, 1101, 974, 883, 748, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (dd, 1H, J = 8.0, 1.6 Hz), 7.60 (td, 1H, J = 7.6, 1.6 Hz), 7.44–7.20 (m, 7H), 6.76 (d, 1H, J = 15.6 Hz, H_{olefin}), 6.40 (dd, 1H, J = 16.0, 7.2 Hz, H_{olefin}), 5.64 (ddd, 1H, J = 10.0, 8.0, 7.2 Hz, H_2), 3.70 (s, 3H, –CH_3), 3.50 (dd, 1H, J = 15.6, 10.4 Hz, Ha-3), 3.12 (dd, 1H, J = 15.6, 8.0 Hz, Hb-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.3 (C=O), 161.5, 140.8, 136.0, 133.2, 131.2, 128.8, 128.5, 127.5, 127.0, 123.3, 121.8, 114.7, 112.7, 108.1, 86.4, 34.5, 29.3. LC-MS: m/z % 304 $[M+H]^+$, 100%. Anal. Calcd. for $C_{20}H_{17}NO_2$ C, 79.19; H, 5.65. Found C, 79.46; H, 5.47.

5-Methyl-2-phenyl-2-[(*E*)-2-phenylvinyl]-3,5-dihydrofuro[3,2-*c*]quinolin-4(2*H*)-one (**3h**): Yellow oil yield 62%. IR (ATR): 3057, 3026, 2938, 1656, 1631, 1597, 1568, 1506, 1406, 1352, 1161, 1091, 966, 906, 748, 729, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97 (dd, 1H, J = 7.6, 1.2 Hz), 7.60 (td, 1H, J = 6.8, 1.6 Hz), 7.55 (m, 2H), 7.42–7.20 (m, 10H), 6.61 (s, 2H), 3.76 (d, 2H, J = 15.6 Hz, Ha-3), 3.65 (s, 3H, –CH_3), 3.63 (d, 2H, J = 15.6 Hz, Hb-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.4 (C=O), 161.2, 143.6, 140.9, 136.2, 131.9, 131.2, 129.9, 128.8, 128.3, 128.1, 127.0, 125.6, 123.3, 121.9, 114.8, 112.8, 107.7, 94.4, 41.6, 29.3. LC-MS: m/z % 380 $[M+H]^+$, 100%. Anal. Calcd. for $C_{26}H_{21}NO_2$ C, 82.30; H, 5.58. Found C, 82.56; H, 5.32.

4. Antifungal activity test

Antifungal activity was determined against clinically important *Candida s*pecies (*C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*) and *Aspergillus fumigatus*. The antifungal susceptibility against the tested compounds (**3a**–**h**) was determined. Table 2 shows the fluconazole, caspofungin, and amphotericin B susceptibility results as MIC values. According to these values all strains were susceptible to the tested antifungals except *C. krusei*. *C. krusei* is known as intrinsically resistant to fluconazole and so the high MIC value (32 μg/mL) was expected.

Table 2. Antifungal activity of tested dihydrofurocoumarins and dihydrofuroquinolines (**3a**–**h**).

Compounds	MIC (μg/mL)					
	C. albicans	*C. parapsilosis*	*C. krusei*	*C. glabrata*	*C. tropicalis*	*A. fumigatus*
3a	125	250	125	250	250	250
3b	125	125	125	125	250	250
3c	62.5	250	125	62.5	250	250
3d	125	250	250	62.5	250	500
3e	125	250	125	125	250	250
3f	125	250	125	125	250	250
3g	125	125	125	250	250	250
3h	250	125	125	250	250	250
Fluconazole	0.25	1	32	8	2	1
Caspofungin	0.25	4	1	4	2	0.25
Amphotericin B	0.25	0.5	0.25	0.5	0.125	1

According to Table 2, MIC values obtained with all compounds were between 62.5 and 500 μg/mL. Compounds **3c** and **3d** possess the best antifungal activity with MIC values of 62.5 μg/mL against *C. albicans*

and *C. glabrata*. The MIC value of compound **3d** was 500 μL/mL for *A. fumigatus*, which is two times higher than MIC values obtained with other compounds. Therefore, it is possible to conclude that the tested compounds (**3a**–**h**) display antifungal activity against both *Candida* species and *A. fumigatus*. However, in our study, among the species tested, *C. albicans* was found to be the most susceptible *Candida* species against the tested dihydrofurocoumarins.

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