Full Paper

Design, Synthesis and Cytotoxicity of Novel Chalcone Analogs Derived from 1-Cyclohexylpyrrolidin-2-one and 2,3-Dihydrobenzo[f]chromen-1-one

Kimberly A. Brien[1], Ravi Kumar Bandi[2], Ajaya Kumar Behera[2], Bijay Kumar Mishra[2], Poulomi Majumdar[2], Vijay Satam[1], Mia Savagian[1], Samuel Tzou[1], Megan Lee[1], Matthias Zeller[3], Andrew J. Robles[4], Susan Mooberry[4,5], Hari Pati[2], and Moses Lee[1]

[1] Division of Natural Sciences and Department of Chemistry, Hope College, Holland, MI, USA
[2] Department of Chemistry, Sambalpur University, Jyoti Vihar, Sambalpur, Orissa, India
[3] Department of Chemistry, Youngstown State University, Youngstown, OH, USA
[4] Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[5] Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Two divergent series of novel chalcone analogs, one derived from 1-cyclohexylpyrrolidin-2-one and the other derived from 1-benzo[f]chromanone, were designed, synthesized and evaluated for cytotoxicity against two murine cancer cell lines. Two 1-benzo[f]chromanone analogs, **4g** and **4j** yielded moderate toxicity against both melanoma B16 and lymphoma L1210 cell lines with IC_{50} values between the range of 5 and 6 μM. With an IC_{50} value of 3.4 μM, compound **4g** was also active against human MDA-MB-435 melanoma cells. X-ray structures of the β-hydroxy ketone product (**4a**) and the α,β-unsaturated ketone (**4h**) were collected, and confirm the *syn*-configuration between the carbonyl moiety and the β-vinylic proton in **4h**. X-ray structures of two 1-cyclohexylpyrrolidin-2-one derivatives were also obtained, and both showed an *E*-configuration for the double bond.

Keywords: Benzochromanone / Chalcones / Cytotoxicity / Tubulin / X-ray

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Introduction

One of the principal research interests of our laboratory is the study of α,β-unsaturated ketones that are analogs of chalcone [1]. The interest is due to a number of factors including ease of synthesizing chalcones from substituted benzaldehydes and acetophenones and the observation that chalcones display a wide range of biological activities including anti-inflammatory [2], anti-malarial [3], and anti-bacterial actions [4]. It is well known that chalcones are also active against cancer cells [5, 6]. As a result, a variety of chalcone analogs have been designed, synthesized and investigated for their ability to initiate cytotoxicity in multiple cancer cell lines [7].

Chalcone is a generic term given to compounds bearing the 1,3-diphenylprop-2-en-1-one template (**1**, Figure 1). There are several reports in the literature which describe structural modifications of the chalcone template such as introduction of different substituents on the phenyl moieties [8], replacement of the phenyl rings with heterocyclic and polyaromatic groups [9], introduction of a substituted enone linking the two rings [10], and cyclization of the chalcone to give conformationally restricted analogs [11].

A series of chalcone analogs derived from 1-tetralone (**2**, Fig. 1) were reported to exhibit promising cytotoxic activities against human Molt 4/C8 leukemia, CEM lymphoma, and murine L1210 lymphoma cells [12]. *In vivo* toxicity studies of these 2-benzylidene-1-tetralones (**2**) demonstrated that a

Correspondence: Moses Lee, Division of Natural Sciences and Department of Chemistry, Hope College, Holland, MI 49423, USA.
E-mail: lee@hope.edu
Fax: +1 616 395 7923

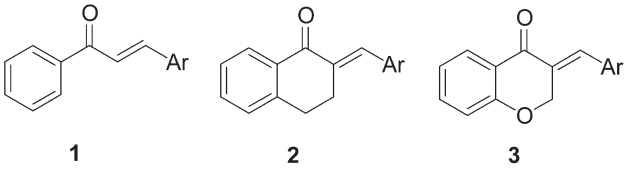


Figure 1. Chalcone and chromanone derivatives.

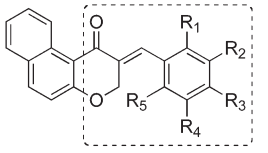
number of analogs in the series were well tolerated in mice and did not produce mortalities at doses of up to 300 mg/kg. Another series in which the 4-methylene group of the 2-benzylidene-1-tetralones was replaced by an oxygen atom to give 3-benzylidene-4-chromanones (**3**, Fig. 1) was synthesized and assessed for cytotoxic activity [13]. The study revealed that a number of 3-benzylidene-4-chromanones (**3**) displayed greater cytotoxicity and were better tolerated in mice than the related 2-benzylidene-1-tetralones (**2**).

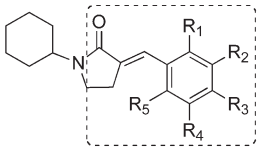
Encouraged by these results, we sought to prepare and evaluate two more classes of chalcone analogs (Fig. 2) that contain an exocyclic benzylidene functionality. It was envisaged that condensation of 1-benzo[f]chromanone with suitably substituted aromatic aldehydes would result in a novel series of prototypic molecules (**4a,b, 4d–l**, Fig. 2) that might exhibit potent cytotoxic activities against malignant cells. Hence, ten novel chalcone analogs derived from 1-benzo[f]-chromanone were designed and synthesized. In addition, fifteen related chalcone analogs (**5a–e, 5g–o**) derived from *N*-cyclohexylpyrrolidinone were also prepared by condensation reactions. All analogs were evaluated for their cytotoxic activity against murine B16 and L1210 cancer cells. Four analogs were subjected to single crystal X-ray crystallographic analysis in order to ascertain the geometry of the alkene bond as well as the overall structure and conformation of the compounds.

Results and discussion

Synthesis of novel chalcone analogs

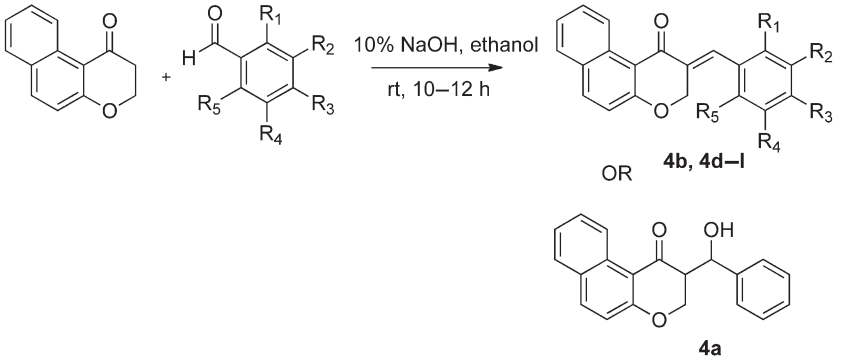
The ten novel benzochromanone-based chalcone analogs (**4b, 4d–l**) were synthesized in good yields by using a classical aldol cross-condensation reaction as outlined in Scheme 1. The suitably substituted benzaldehydes were condensed with 1-benzo[f]chromanone in ethanol at ambient temperature using 10% aqueous sodium hydroxide. In all cases except **4a**, spontaneous dehydration occurred to give the α,β-unsaturated ketones as evidenced by the ^{1}H NMR signals for the vinylic protons at >7 ppm.





	R_1	R_2	R_3	R_4	R_5
a	H	H	H	H	H
b	H	OMe	H	H	H
c	H	H	OMe	H	H
d	Cl	H	H	H	H
e	H	H	Cl	H	H
f	OMe	H	H	H	OMe
g	H	OMe	OMe	OMe	H
h	H	H	Me	H	H
i	H	H	F	H	H
j	H	Br	H	H	H
k	H	O-CH_2-O		H	H
l	Me	H	H	Br	H
m	H	H	Me_2N	H	H
n	OMe	H	H	Br	H
o	H	H	NO_2	H	H

Figure 2. General structures of chalcone analogs derived from benzochromanone (**4b, 4d–l)** and *N*-cyclohexylpyrrolidinone (**5a–e, 5g–o**).



Scheme 1. Synthesis of aldol product **4a** and the chalcone analogs **4b, 4d-l**.

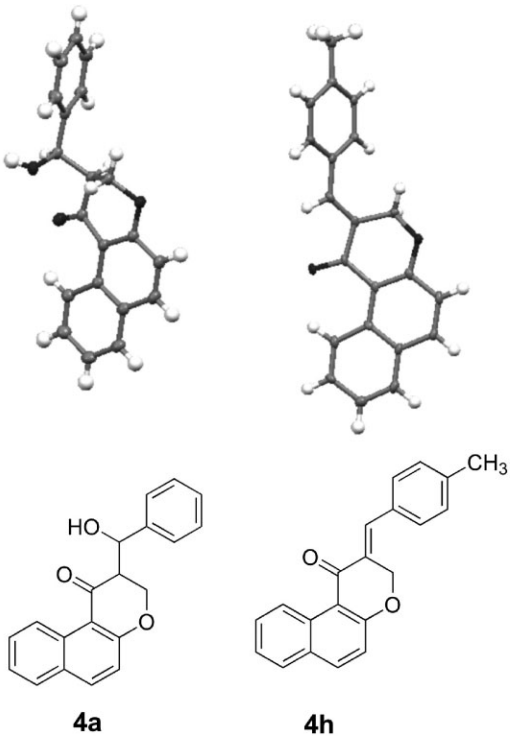
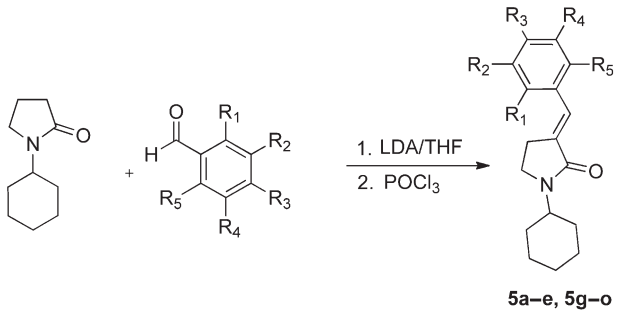


Figure 3. X-ray structures of compounds **4a** and **4h**.

The ^{1}H NMR spectrum of compound **4a** provided initial evidence for the lack of a vinylic proton, and its identity was confirmed by a phenylcarbinol proton signal at 5.72 ppm. Crystals of **4a** and **4h** were obtained from methanol and X-ray structures were determined (Fig. 3). Consistent with the ^{1}H NMR data, **4a** was isolated as the β-hydroxy ketone product. The benzochromanone structure of **4h** was unambiguously ascertained by the X-ray analysis. The core benzochromanone portion of the molecule is virtually planar with the exception of the methylene carbon atoms of the dihydropyrone moiety, which deviate from the benzochromanone plane by 0.530 and 0.643 Å in the two crystallographically independent molecules in the structure. The 4-methylbenzylidene groups are twisted by approximately 60.7 and 54.4° about the plane of the benzochromanone moiety, and the β-vinylic proton is held *syn* to the carbonyl group, thus confirming the *E*-configuration.

Compounds **5a–e, 5g–o** were synthesized by quantitative formation of the amide enolate followed by condensation with selected benzaldehydes (Scheme 2) to give the β-hydroxy amides in 80–85% yield. These intermediates were subsequently dehydrated using $POCl_3$ to give the α,β-unsaturated amides in 40–45% yield.

Compounds **5b** and **5c** were crystallized from methanol. The X-ray structures of these two compounds given in Fig. 4



Scheme 2. Synthetic pathway towards the chalcone analogs **5a–e, 5g–o**.

showed the alkene to exist in the *E*-configuration. Both structures reveal that the α-anisylidenyl-*N*-cyclohexylpyrrolidinone units are essentially planar. They are rotated against the chair-shaped cyclohexyl moiety at about an angle of 73.9° in **5b** and of 45.4 and 64.3° angles in the two crystallographically independent molecules in the structure of **5c**. The vinylic protons are *syn* to the carbonyl in both structures.

Cytotoxicity

All twenty-five compounds were initially screened against the murine L1210 (lymphoma) cell line at 10 μM concentration. Cytotoxicity was measured using the MTT assay after 72 h

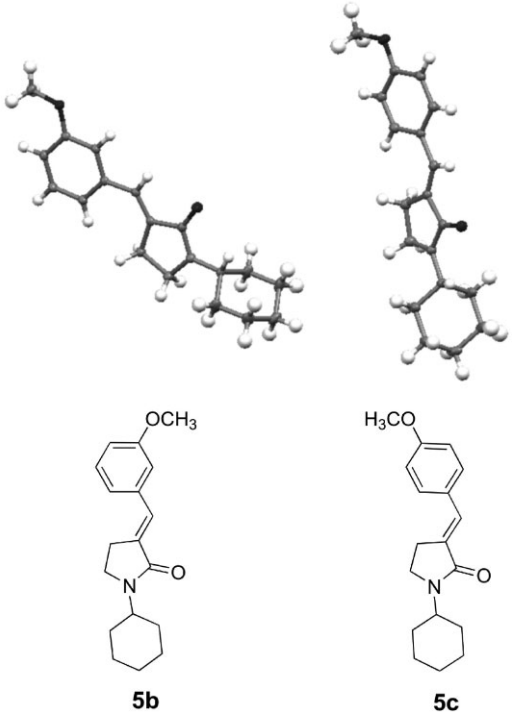


Figure 4. X-ray structures of compounds **5b** and **5c**.

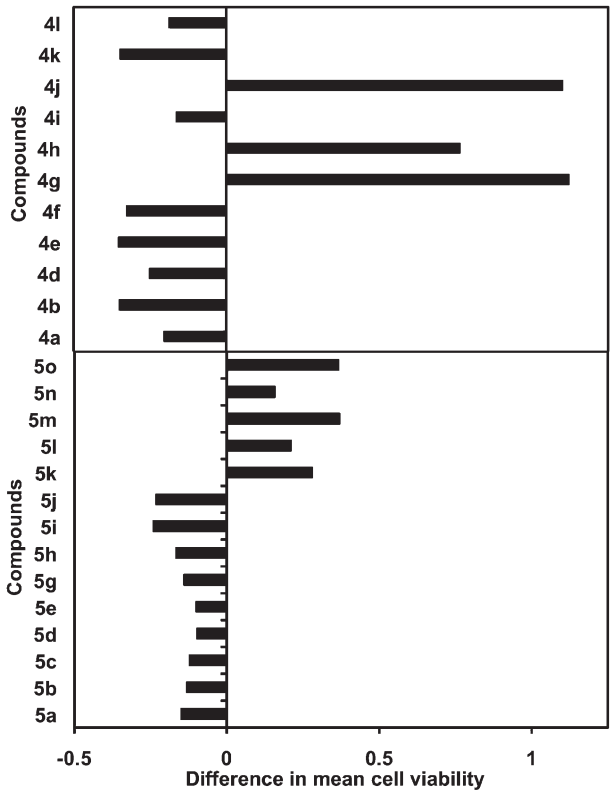


Figure 5. Average values from the initial screen of compounds **4a,b,d–l** and **5a–e, 5g–o** at 10 μM concentration for activity against murine L1210 cells. The difference in mean cell viability (x-axis) is defined as A–B, in which A = (absorbance at 570 nm for an individual compound – absorbance at 570 nm for the negative vehicle control)$^{-1}$. B = average of A for all compounds within each series. Bars to the right of the average indicate compounds that are more active than the average for each series of molecules.

incubation [1, 14]. Based on the screening data, compounds that showed greater activity than the average (i.e. bars to the right in Fig. 5) were selected for detailed studies where the IC_{50} values (concentration causing 50% cytotoxicity) were measured. Accordingly, eight compounds, **4d**, **4h**, **4j**, **5k**, **5l**, **5m**, **5n**, **5o** were selected for further testing in inhibition of the growth of murine B16 (melanoma) and L1210 cell lines using a 72 h continuous exposure MTT assay technique. The average IC_{50} (μM) for each compound was determined from duplicate experiments and the results are presented in Table 1.

Analogs in the 1-benzo[f]chromanone series were active against B16 and L1210 cancer cells, with analogs **4g** and **4j** being the most potent with IC_{50} values in the single-digit μM range. None of the *N*-cyclohexylpyrrolidinone compounds tested were active at inhibiting the growth of L1210 and B16 cell lines, even at a concentration of 100 μM.

Encouraged by the results obtained with compounds **4g** and **4h**, further tests using the SRB assay were undertaken to look at their anti-proliferative effects against human melanoma MDA-MB-435 cells. The IC_{50} values for **4g** and **4h** are 3.4 ± 0.2 and 23 ± 1 μM, respectively, which are comparable to the activities observed in murine cancer cells. It is, however, interesting to note that compound **4g** is more cytotoxic than **4h** and it contains the trimethoxyphenyl moiety. This moiety is a common structural feature present in the combretastatins, which is a class of tubulin inhibitor anticancer agents [15]. It is also worthy to indicate that compound **4j** has comparable activity to **4g** in the B16 and L1210 studies. Structurally, one common feature in these two compounds is the sizable *meta* substituent (Br or OMe group) in the benzylidene unit. This bulky substituent may affect their ability to interact with biological targets. Due to the similarity of compounds **4g** and **4h** to the combretastatins, they were tested for the ability to cause microtubule depolymerization in A-10 cells [1, 14, 16]. At 30 μM, a concentration above their cytotoxic IC_{50} values, neither compound had any effect on the microtubules suggesting that unlike the combretastatins inhibition of tubulin polymerization is not a likely biological mechanism of how these compounds inhibit cancer cell growth.

Conclusion

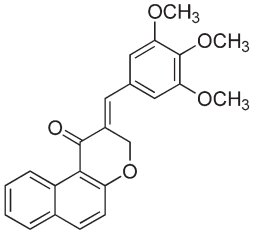
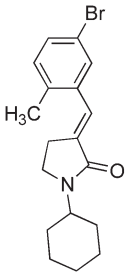
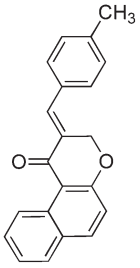
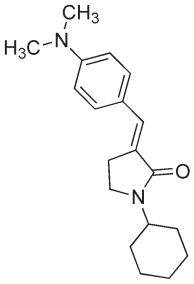
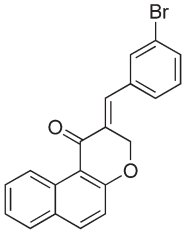
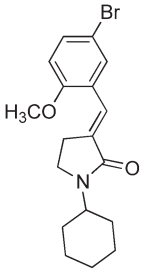
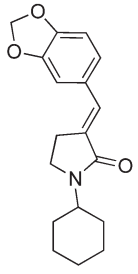
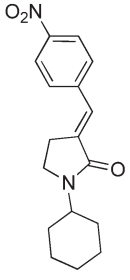
Twenty-four chalcone analogs (**4b,d–l** and **5a–e,g–o**) and one aldol product (**4a**) derived from 1-benzo[f]chromanone and *N*-cyclohexylpyrrolidinone were synthesized, characterized and tested for cytotoxicity against murine cancer cells B16 and L1210. Compounds **4g** and **4h** were also tested against the growth of human MDA-MB-435 cells. Two 1-benzo[f]chromanone derivatives (**4a** and **4h**) produced high quality crystals from which X-ray structures were determined. The results provided unequivocal evidence to support the aldol or β-hydroxy ketone structure for product **4a** and the *E*-configured, α,β-unsaturated ketone for compound **4h**. Two structures of *N*-cyclohexylpyrrolidinone derivatives also gave X-ray structures both showing an *E*-configuration about the double bond. Two compounds **4g** and **4j** yielded moderate toxicity against both B16 and L1210 cell lines with IC_{50} values between 5 and 6 μM.

Experimental

General method for preparation of 4a,b,d–l

Benzochromanone (0.3 g, 1.5 mmol, 1.0 eq.) and the appropriate arylaldehyde (1.0 eq.) were dissolved in ethanol (5 mL) at room temperature. Aqueous sodium hydroxide (10 mL, 10% solution) was added dropwise and the reaction stirred for 10–12 h while being monitored by TLC for completion. The solution was filtered

Table 1. IC_{50} values of selected compounds based on initial screening

Cmpd	Structure	B16 IC_{50} (μM)	L1210 IC_{50} (μM)	Cmpd	Structure	B16 IC_{50} (μM)	L1210 IC_{50} (μM)
4g		6.4 ± 1.3	5.0 ± 0.2	**5l**		>100	>100
4h		>100	56 ± 19	**5m**		>100	>100
4j		6.3 ± 0.8	5.6 ± 0.4	**5n**		>100	>100
5k		>100	>100	**5o**		>100	>100

and the solid product was washed with chilled ethanol (5 mL). The crude compounds were purified by silica gel (60–120 mesh) column chromatography and eluted with hexane/EtOAc (10–20%) mobile phase to obtain the pure product (yield: 35–40%).

General method for preparation of 5a–e,g–o

A freshly prepared LDA solution (1.0 eq.) was added to a solution of *N*-cyclohexylpyrrolidinone (0.5 g, 3.3 mmol) in anhydrous THF

(5 mL) at −70 to −75°C under nitrogen atmosphere. The reaction mixture was stirred at −70 to −75°C for 30 min. A solution of the appropriate arylaldehyde in dry THF (5 mL) was added at −70 to −75°C. The solution was allowed to reach 20–25°C and maintained at room temperature for 8–10 h. Completion of the reaction was monitored by TLC (hexane/EtOAc, 80:20). At that time, a saturated ammonium chloride solution was added and the solution was extracted with ethyl acetate (3 × 75 mL). The organic layers were combined, dried over sodium sulfate, and the solvents evaporated under vacuum to obtain the intermediate alcohol compound (yield: 80–85%). The residue was dissolved in $POCl_3$ (5 mL) and stirred at 20–25°C for 10–15 h. Upon completion of the reaction, the excess of $POCl_3$ was evaporated under vacuum to dryness. The residue obtained was treated with ice water and the pH adjusted to 8–10 with 2 M NaOH. The aqueous layer was extracted with ethyl acetate (3 × 75 mL). The organic layers were combined, washed with brine solution, dried over sodium sulfate and the solvent evaporated under vacuum to obtain the crude compound, which was purified by using silica gel (60–120 mesh) column chromatography using hexane/EtOAc (10–20%) as the mobile phase (yield: 40–45%).

Compounds **4a**, **4h**, **5b** and **5c** were recrystallized by dissolving the respective samples in hot methanol. The clear solutions were left at room temperature for two days. The crystals formed were filtered, washed with cold methanol and dried in vacuum. All diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 100 K using monochromatic Mo Kα radiation with the omega scan technique. Data were collected, their unit cells determined, and the data integrated and corrected for absorption and other systematic errors using the Apex2 suite of programs [17]. The structures were solved by direct methods and refined by full matrix least squares against F^2 with all reflections using SHELXTL [18]. Compound **4h** was found to be pseudomerohedrally twinned, compound **5b** to be non-merohedrally twinned (see cif files deposited with the Cambridge Crystallographic Database for details).

The analytical data for compounds selected for cytotoxicity studies and X-ray crystallography analysis are given below.

*(E)-2-Benzylidene-2,3-dihydrobenzo[f]chromen-1-one **4a***

White solid; mp: 137°C; ^{1}H NMR ($CDCl_3$): δ 9.42 (d, 1H, J = 8.8 Hz), 7.92 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 8.8 Hz), 7.65 (ddd, J = 8.8, 7.0, 1.3 Hz, 2H), 7.32–7.45 (ddd, J = 8.0, 7.0, 1.3 Hz 6H), 7.38 (m, 1H), 7.39 (m, 3H), 7.05 (d, 1H, J = 8.8 Hz), 5.72 (t, 1H, J = 4.0, 2H), 4.68 (t, 1H, J = 12.0 Hz), 4.44 (dd, 1H, J = 12.0, 5.3 Hz), 3.23 (ddd, 1H, J = (4.0, 5.3, 12.0 Hz), 2.87 (d, 1H, J = 4.0); IR (ATR): 3412, 3041, 2993, 2914, 1654, 1613, 1595, 1565, 1509, 1491, 1474, 1451, 1433, 1404, 1379, 1367, 1341, 1276, 1244, 1228, 1201, 1173, 1158, 1140, 1126, 1102, 1086, 1059, 1024, 991, 941, 896, 844, 822, 787, 767, 756, 746, 724, 700, 673, 650, 643, 577, 546, 526, 513, 486, 424, 408; MS: ESI (m/z) 305.3 $(M+H)^+$, 287.1 $(M+H-H_2O)^+$.

*(E)-2-(3,4,5-Trimethoxybenzylidene)-2,3-dihydrobenzo[f]chromen-1-one **4g***

Pale yellow solid; mp: 127.6°C; ^{1}H NMR ($CDCl_3$): δ 9.43 (d, 1H, J = 8.5 Hz), 7.94 (d, 1H, J = 8.5 Hz), 7.87 (s, 1H), 7.78 (d, 1H, J = 7.5 Hz), 7.67(t, 1H, J = 7.5 Hz), 7.46 (t, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 8.5 Hz), 6.55 (s, 2H), 6.54 (d, 2H, J = 1.8 Hz), 3.92 (s, 3H), 3.91 (s, 6H); IR (ATR): 2961, 2836, 1658, 1615, 1595, 1580, 1505, 1463, 1455, 1434, 1416, 1368, 1332, 1273, 1259, 1236, 1208, 1188, 1125, 1096, 1000, 926, 823, 792, 756, 733, 700, 665, 627, 587, 547, 500, 455; MS: ESI (m/z) 377.5 $(M+H)^+$. Accurate mass for $C_{23}H_{20}O_5$ calcd 376.1311, obsd 376.1307.

*(E)-2-(4-Methylbenzylidene)-2,3-dihydrobenzo[f]chromen-1-one **4h***

Pale yellow solid; mp: 151°C; ^{1}H NMR (DMSO-d_6): δ 9.32 (d, 1H, J = 9.0 Hz), 8.17 (d, 1H, J = 9.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.78 (s, 1H), 7.70 (t, 1H, J = 8.0 Hz), 7.51 (t, 1H, J = 8.0 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.24 (d, 1H, J = 9.0 Hz), 5.50 (s, 2H), 2.39 (s, 3H); IR (ATR): 3024, 2918, 2851, 1655, 1614, 1593, 1566, 1508, 1468, 1444, 1431, 1403, 1370, 1340, 1274, 1244, 1225, 1206, 1192, 1180, 1142, 1112, 1083, 1048, 1026, 994, 950, 916, 848, 829, 803, 790, 776, 753, 724, 709, 700, 681, 653, 638, 623, 549, 532, 514, 486, 429, 416, 405; MS: ESI (m/z) 301.5 $(M+H)^+$. Accurate mass for $C_{21}H_{16}O_2$ calcd 300.1150, obsd 300.1152.

*(E)-2-(3-Bromobenzylidene)-2,3-dihydrobenzo[f]chromen-1-one **4j***

Pale yellow solid; mp: 133°C; ^{1}H NMR ($CDCl_3$): δ 9.43 (d, 1H, J = 9.0 Hz), 7.95 (d, 1H, J = 9.0 Hz), 7.85 (s, 1H), 7.79 (d, 1H, J = 7.5 Hz), 7.68 (t, 1H, 7.5 Hz), 7.55 (d, 1H, J = 9.0 Hz), 7.49–7.47 (m, 3H), 7.34 (t, 1H, J = 7.5 Hz), 7.11 (d, 1H, J = 9.0 Hz), 5.36 (d, 2H, J = 1.8); IR (ATR): 2925, 2849, 1662, 1607, 1592, 1569, 1509, 1464, 1431, 1398, 1368, 1342, 1272, 1241, 1222, 1204, 1190, 1157, 1136, 1072, 1050, 1025, 995, 964, 929, 908, 877, 857, 825, 811, 791, 779, 746, 731, 695, 664, 638, 557, 537, 498, 437, 406; MS: ESI (m/z) 367.4 $(M+H)^+$.

*(E)-3-(3-Methoxybenzylidene)-1-cyclohexylpyrrolidin-2-one **5b***

Off white crystalline solid; mp: 147°C; ^{1}H NMR ($CDCl_3$): δ 7.33–7.23 (m, 2H), 7.07 (d, 1H, J = 8.0 Hz), 7.00 (s, 1H), 6.86 (dd, 1H, J = 8.0, 2.3 Hz), 4.10–4.14 (m, 1H), 3.83 (s, 3H), 3.47 (t, 2H, J = 6.5 Hz), 3.04 (dt, 2H, J = 6.5, 3.0 Hz), 1.83–1.69 (m, 6H), 1.50–1.41 (m, 4H); IR (ATR): 2925, 2851, 2833, 1670, 1642, 1601, 1509, 1461, 1438, 1421, 1301, 1285, 1247, 1216, 1192, 1175, 1117, 1030, 972, 949, 912, 892, 833, 810, 764, 709, 527; MS: ESI (*m/z*) 285.35 $(M+H)^+$.

*(E)-3-(4-Methoxybenzylidene)-1-cyclohexylpyrrolidin-2-one **5c***

Off white crystalline solid; mp: 137°C; ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 2H, J = 8.8 Hz), 7.29 (t, 1H, J = 2.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 4.10–4.11 (m, 1H), 3.84 (s, 3H), 3.47 (t, 2H, J = 6.5 Hz), 3.01 (td, 2H, J = 6.5, 2.8), 1.83–1.68 (m, 5H), 1.45–1.40 (m, 4H), 1.09–1.12 (m, 1H); IR (ATR): 2923, 2837, 1671, 1641, 1603, 1576, 1495, 1439, 1422, 1361, 1299, 1259, 1204, 1159, 1090, 1046, 928, 912, 888, 876, 768, 677, 631, 553, 466, 447; MS: ESI (*m/z*) 285.35 $(M+H)^+$.

*(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-cyclohexylpyrrolidin-2-one **5k***

Light brown solid; mp: 157°C; ^{1}H NMR (DMSO-d_6): δ 7.08–7.10 (m, 1H), 7.03–7.06 (m, 2H), 6.98 (d, 1H, J = 8.0 Hz), 6.04 (s, 2H), 3.84–3.92 (m, 1H), 3.39–3.47 (m, 3H), 2.95–3.02 (m, 2 H), 1.82–1.73

(m, 2H), 1.67–1.58 (m, 2H), 1.48 (qd, 1H, J = 12.0, 3.0 Hz), 1.46 (qt, 1H, J = 12.0, 3.0 Hz), 1.13 (qt, 1H, J = 12.0, 3.0 Hz); IR (ATR): 2930, 2855, 1671, 1644, 1613, 1504, 1488, 1439, 1421, 1341, 1281, 1236, 1187, 1037, 936, 922, 806, 611; MS: ESI (*m/z*) 300.4 $(M+H)^+$.

(E)-3-(5-Bromo-2-methylbenzylidene)-1-cyclohexylpyrrolidin-2-one ***5l***

Off white solid; mp: 132°C; ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1H, J = 2.5 Hz), 7.41 (t, 1H, J = 2.5 Hz), 7.30 (dd, 1H, J = 8.0, 2.5 Hz), 7.08 (d, 1H, J = 8.0 Hz), 4.16–4.10 (m, 1H), 3.45 (t, 2H, J = 6.5 Hz), 2.96 (dt, 2H, J = 6.5, 2.5 Hz), 2.34 (s, 3H), 1.85–1.66 (m, 5H), 1.50–1.38 (m, 4H), 1.16–1.11 (m, 1H); IR (ATR): 2927, 2853, 1667, 1642, 1487, 1479, 1437, 1420, 1358, 1288, 1255, 1221, 1197, 1185, 1014, 993, 908, 894, 879, 809, 772, 736, 703, 685, 562, 535, 468, 442; MS: ESI (*m/z*) 350.3 $(M+H)^+$.

(E)-3-(4-(Dimethylamino)benzylidene)-1-cyclohexylpyrrolidin-2-one ***5m***

Brown solid; mp: 217°C; ^{1}H NMR (DMSO-d_6): δ 7.38 (d, 2H, J = 8.8 Hz), 7.0 (t, 1H, J = 2.5 Hz), 6.75 (d, 2H, J = 8.8 Hz), 3.88 (tt, 1H, J = 12.0, 3.5 Hz), 3.43 (t, 2H, J = 6.4 Hz), 3.01 (s, 6H), 1.79–1.62 (m, 3H), 1.62–1.60 (m, 2H), 1.48 (qd, 2H, J = 8.8, 2.5 Hz), 1.45 (qt, 2H, J = 12.0, 3.5 Hz), 1.10 (qt, 1 H, J = 12.0, 3.5 Hz); IR (ATR): 2927, 2845, 1666, 1634, 1599, 1522, 1497, 1460, 1441, 1422, 1357, 1321, 1306, 1286, 1252, 1224, 1191, 1166, 1146, 1127, 1063, 1031, 1017, 1003, 992, 969, 948, 934, 917, 888, 816, 803, 780, 736, 710, 683, 671, 525, 479, 446; MS: ESI (*m/z*) 299.4 $(M+H)^+$.

(E)-3-(5-Bromo-2-methoxybenzylidene)-1-cyclohexylpyrrolidin-2-one ***5n***

Off white solid; mp: 194°C; ^{1}H NMR (DMSO-d_6): δ 7.56 (d, 1H, J = 2.5 Hz), 7.50 (d, 1H, J = 2.5 Hz), 7.31 (t, 1H, J = 2.5), 7.04 (d, 1H, J = 8.8 Hz), 4.14–3.87 (m, 1H), 3.83 (s, 3H), 3.42 (t, 2H, J = 6.3 Hz), 2.96 (dt, 2 H, J = 6.3, 2.5 Hz), 1.79–1.76 (m, 3H), 1.64–1.61 (m, 2H) 1.49 (qd, 2H, J = 12.0, 2.5 Hz), 1.35 (qt, 2H, J = 12.0, 2.5 Hz), 1.13 (qt, 1H, J = 12.0, 2.5 Hz); IR (ATR): 3086, 3047, 2924, 2848, 1667, 1636, 1587, 1504, 1481, 1461, 1441, 1426, 1403, 1365, 1286, 1243, 1193, 1174, 1148, 1127, 1103, 1054, 1017, 973, 952, 925, 889, 868, 826, 806, 784, 757, 745, 708, 686, 678, 622, 563, 542, 515, 489, 451, 415; MS: ESI (*m/z*) 366.3 $(M+H)^+$.

(E)-3-(4-Nitrobenzylidene)-1-cyclohexylpyrrolidin-2-one ***5o***

Brown solid; mp: 236°C; ^{1}H NMR (DMSO-d_6): δ 8.25 (d, 2H, J = 8.8 Hz), 7.81 (d, 2H, J = 8.8 Hz), 7.23 (t, 1H, J = 3.0 Hz), 3.91 (tt, 1H, J = 12.0 Hz), 3.49 (t, 2H, J = 6.3 Hz), 3.09 (ddd, 2H, J = 12.0, 6.0, 3.0 Hz), 1.78 (d, 2H, J = 12.0 Hz), 1.63 (d, 3H, J = 12.0 Hz), 1.50 (qd, 2H, J = 12.0, 3.0 Hz), 1.33 (qt, 2H, J = 6.3, 3.0 Hz) 1.14 (m, 1H); IR (ATR): 2925, 2850, 1666, 1641, 1591, 1515, 1486, 1439, 1420, 1341, 1306, 1281, 1271, 1216, 1200, 1182, 1105, 1014, 940, 863, 853, 826, 755, 723, 699, 682, 655, 512, 418; MS: ESI (*m/z*) 301.10 $(M+H)^+$.

Supporting material

X-ray structural information for products **4a**, **4g**, **5b** and **5c** are given in cif format, CCDC 835718–835721. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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