Design and Synthesis of Propeller-Shaped Dispiroisoxazolinopiperidinochromanones

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A library of novel, propeller-shaped dispirotriheterocyclic isoxazolinopiperidinochromanones is reported. Each rigid dispirotriheterocycle was prepared in five linear steps from commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate and various derivatives of 1-(2-hydroxyphenyl)ethanone, benzaldehyde oxime, and carboxylic acids. Computational chemistry was employed to analyze the three-dimensional geometries of these dispirotriheterocycles, as well as to generate chemoinformatic bioavailability data. X-ray crystallographic structure determination verified the regioselectivity of the nitrile oxide 1,3-dipolar cycloaddition reaction. The resulting library of compounds has been added to the National Institutes of Health repository (∼10 mg of each with ≥90% purity) for pilot-scale biomedical studies with bioassay data available at the National Center for Biotechnology Information PubChem database.

Introduction

Despite advances such as high throughput screening (HTS) and genome sequencing, the time required for a drug candidate to make the bench to bedside translation remains lengthy.[1] Given the repercussions of this problem, the National Institutes of Health instigated the Molecular Libraries Roadmap Initiative (MLRI) to facilitate the use of HTS and chemical libraries within the academic community to produce research tools to facilitate health-related studies in biology and physiology. The biological screening, assay protocol, and library data is publicly available for data mining via the PubChem database.[2] This program provided the impetus for us to undertake a synthetic study of the medicinally pertinent, constrained dispirotriheterocyclic isoxazolinopiperidinochromanone libraries **L1** and **L2** (see Figure 1). We speculate that these rigid dispirofused amides will afford numerous opportunities to engage biological receptors. Indeed, chromanones[3] have numerous and well-documented biological activities that, when dispiro-connected with pharmaceutically pertinent piperidine[4] and isoxazoline[5] moieties, afford a unique three-dimensional scaffold that may have interesting biological properties. Herein, we report the design and synthesis of dispiroisoxazolinopiperidinochromanone library **L2** using the tools of computational chemistry, synthesis, and X-ray crystallography. These library members and precursors are ready for allocation through the MLRI for biological study deployment.

Results and Discussion

As delineated in Scheme 1, Boc-protected spiro[chroman-2,4′-piperidin]-4-ones **1**{*1–3*} were prepared by Chandrasekhar's enamine-mediated crossed Aldol condensation method.[3c] This efficient one-pot transformation employs freshly distilled catalytic pyrrolidine to condense reagent chemset **1′** (5-substituted-2-hydroxyacetophenones) with *N*-Boc-4-piperidone; subsequent Michael addition of the phenoxy moiety to the newly generated enone delivers chromanones **1**{*1–3*} in good yields (58%, 85%, and 98%, respectively). In addition to establishment of the first spirocyclic ring fusion, this crossed Aldol condensation served to fix the first diversity point in our targeted bis-spirofused library.

With **1**{*1–3*} in hand, initial efforts were directed toward the preparation of dispiroisoxazolinopiperidinochromanone library **L1** using the retrosynthetic analyses shown in Figure 1. The key precursor for this effort was 4-methylenespiro-[chroman-2,4′-piperidine] derivative **2***, which was envisioned as arising from spiro[chroman-2,4′-piperidin]-4-one **1**{*1–3*} by methenylation. However, Wittig[6] (employing either *n*-BuLi or *t*-BuOK[7] as base), Tebbe,[8] and Peterson[9] olefinations of **1**{*1*} failed to deliver appreciable amounts of the requisite exomethylene; presumably, chromanone enolization[10] intervenes to effectively prohibit this transformation. Broggini's route to a related spiro[isoquinoline-4,5′-isoxazole] system employed the Heck reaction to construct their required exomethylene moiety from 2-iodobenzyl bromide and allylamine,[11] but similar application here would be complicated by the heterospirocyclic nature of target **2***.

In light of this turn of events, the strategic decision was made to investigate placement of the spiroisoxazolino moiety at C3 (e.g., **2**), rather than C4 (e.g., **2***), of the chroman ring because either position would allow for a dispirofused library. Indeed, this switch from olefination to α-methenylation proved tenable because treatment of spiro[chroman-2,4′-piperidin]-4-one **1**{*1–3*} with *N*,*N*,*N*′,*N*′-tetramethylmethanedi-

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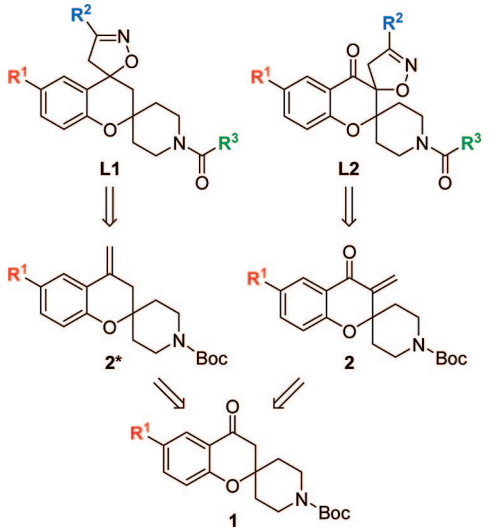
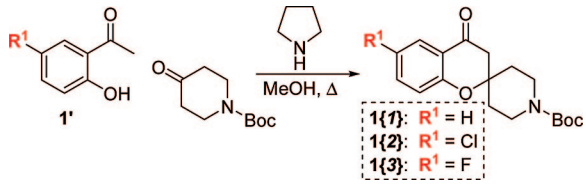
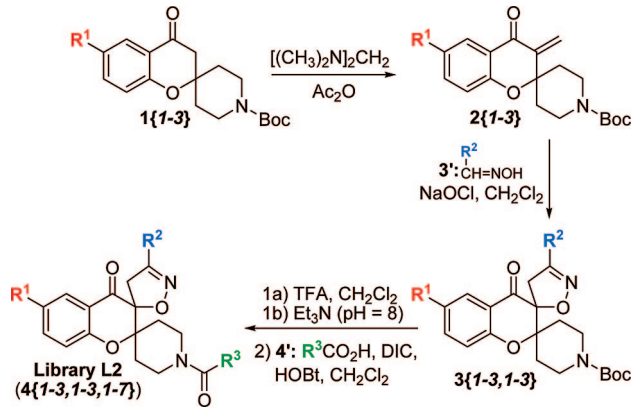


Figure 1. Retrosynthetic analysis of proposed 2,3- and 2,4-bis-spirofused libraries **L1** and **L2**, respectively.

Scheme 1. Preparation of Spiro[chroman-2,4′-piperidin]-4-ones **1**{*1–3*}



Scheme 2. Preparation of Dispiroisoxazolinopiperidinochromanone



amine and acetic anhydride in accord with Ward's method delivered the targeted 3-methylenespiro[chroman-2,4′-piperidin]-4-one **2**{*1–3*} in good yield (Scheme 2; **1**{*1–3*} → **2**{*1–3*}; 58%, 85%, and 74%, respectively).[12]

The impending question was whether sterically encumbered dipolarophile **2**, with carbonyl and ^{t}butyl-like substituents at C1 of its C,C-double bond, would participate in a nitrile oxide cycloaddition reaction. The literature is rather quiescent on this point with related examples generally limited to nitrile oxide−quinone[13] and nitrile oxide−1,4,16-pregnatriene-3,20-dione[14] cycloadditions. To the best of our knowledge, dipolar cylcoadditions to comparably crowded cyclic exomethylenones have not been previously reported. In the event (Scheme 2), biphasic treatment of exomethylenones **2**{*1–3*} with reagent chemset **3′** (aryl oximes, where diversity input R^2 in $R^2CH{=}NHOH$ = Ph, 3-pyridyl, and

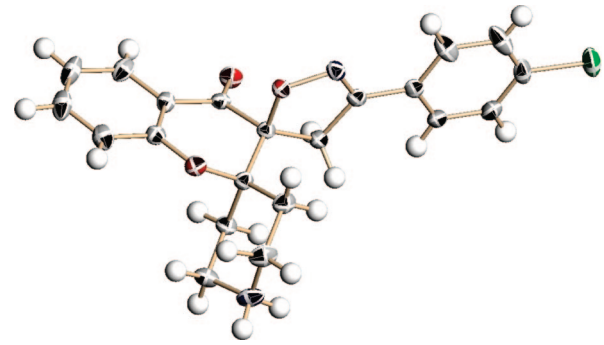


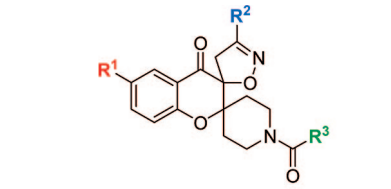
Figure 2. X-ray crystal structure of 3′-(4-chlorophenyl)-4-oxodispiro[4,5-dihydroisoxazol-5′,3-chroman-2,4″-piperidin]-1″-ium (TFA salt) showing the 5,5-disubstituted isoxazoline (trifluoroacetate anion not shown).

4-ClPh) and bleach (Huisgen method)[15] afford all nine of the targeted Boc-protected dispiroisoxazolinopiperidinochromanones **3**{*1–3*,*1–3*} in yields ranging from 55 to 94%. The regioselectivity of **2** → **3** (4,4- versus 5,5-disubstituted isoxazoline), a potential issue in 1,3-dipolar cycloaddition reactions involving α,β-unsaturated dipolarophiles,[16] was established by X-ray crystallographic analysis of 3′-(4-chlorophenyl)-4-oxodispiro[4,5-dihydroisoxazol-5′,3-chroman-2,4″-piperidin]-1″-ium (TFA salt). The results, depicted in Figure 2, establish that this particular system, which was chosen over carbamate and amide options to avoid rotamer complications, was 5,5-disubstituted. By spectroscopic analogy, all nine of these 1,3-dipolar cycloadditions enjoyed complete regioselectivity, giving only the 5,5-disubstituted isoxazoline.

The final stage in the construction of library **L2** involved TFA-mediated Boc-deprotection of cycloadducts **3**{*1–3*,*1–3*} and subsequent *N*-acylation with reagent chemset **4′** of seven carboxylic acids; Table 1 shows the chemset diversity inputs for this dispiroisoxazolinopiperidinochromanone library **L2**. It proved most expedient to perform this deprotection−acylation procedure in one pot: TFA deprotection in DCM, concentration, addition of fresh DCM, followed by basification to pH 8 (triethylamine), and finally an acid + EDC + DMAP *N*-acylation. The yield of *N*-acylated dispiroisoxazolinopiperidinochromanones **4**{*1–3*,*1–3*,*1–7*} ranged from 33 to 97% after purification by reverse phase HPLC. The low-end yields were a consequence of low solubility of the chloro-substituted chromanone (R^1 = Cl).

The energy-minimized (see Computational Methods) three-dimensional geometries in Figure 3 show that the diversity groups around the triheterocyclic scaffolds present in **L1** and **L2** are arrayed at approximately equal angles from one another. As a function of 2,3- and 2,4-dispiro connectivities (**L2** and **L1**, respectively), these molecules adopt "propeller-like" shapes where the isoxazolino, piperidyl, and chromanone moieties each constitute a blade of the propeller. A molecular shape space diversity analysis, which categorizes low energy conformers on the basis of their overall shape as various ratios of rod-, disk-, or spherelike character (Figure 4), reveals that 2,3-dispiro library **L2** is more flat and that the propeller blades are more equally distributed (overall more disklike) than that for the 2,4-dispiro library **L1**, which

Table 1. Diversity Inputs for Library **L2**



4{1-3,1-3,1-7}

R^1	R^2	R^3	
H	Ph		
{1}	{1}	{1}	{5}
Cl	3-pyr		
{2}	{2}	{2}	{6}
F	4-ClC$_6$H$_4$		
{3}	{3}	{3}	{7}
			{4}

has an overall more rodlike profile on the shape space diversity analysis plot.

To aid in library design, we use Lipinski's rule of five criterion (less than 5 H-bond donors, less than 10 H-bond acceptors, a log *P* of less than 5, and a molecular weight of less than 500) as a general guide for bioavailability because compounds with poor bioavailability face more of a challenge

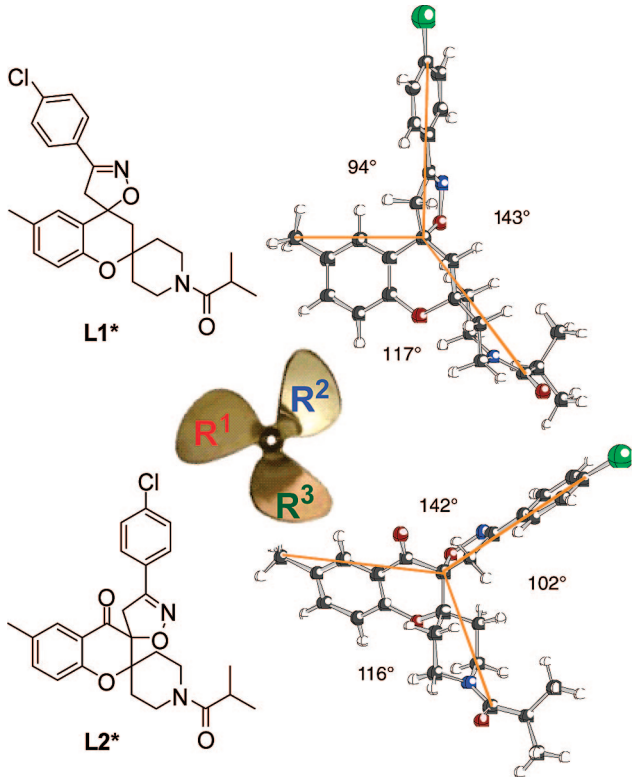


Figure 3. Energy-minimized structures (selected conformations) including angles between the diversity groups in a propeller-shaped molecule (**L2***) and its virtual library analog (**L1***).

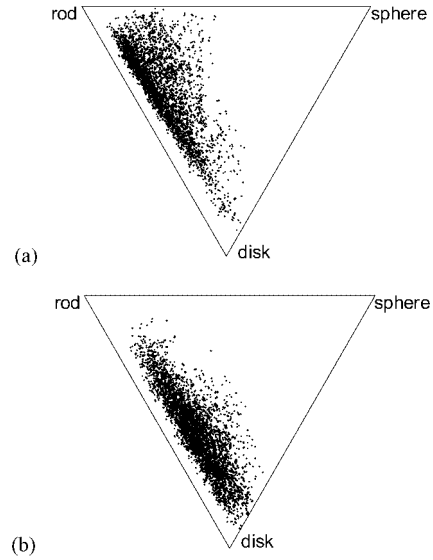


Figure 4. Molecular shape space diversity analysis for (a) 2,4-dispiro library **L1** and (b) 2,3-dispiro library **L2**. Visual inspection reveals 2,4-dispiro library **L1** is on average more rodlike than the 2,3-dispiro library **L2**, which has more density near the bottom of the plot (disklike).

in becoming successful clinical candidates.[17] We examined 2,3-dispiro library **L2** using standard chemical informatics library screening calculations on the number of Lipinski violations,[16] solubility, and number of rotatable/rigid bonds (see Supporting Information for details). For library **L2**, there are a total of 52 Lipinski violations (over half of these are for a molecular weight greater than 500), with 18 compounds having two violations and 16 compounds having only one violation. The average *X* log *P* value for these compounds is 4.83 with a minimum value of 2.82 and a maximum of 6.82. With only three or four rotatable bonds per compound and the number of rigid bonds in the range of 31−42, the library is overall very rigid.

In summary, we have demonstrated a synthetic route to the 75-membered (including precursors) dispirotriheterocyclic library **L2** containing medicinally relevant piperidine, isoxazoline, and chromanone moieties; X-ray crystallography was employed to unambiguously determine the 5,5-disubstitued isoxazolino assignment. We also further examined library **L2** computationally to understand the geometries and predict physical properties for these compounds. Library **L2** has been transferred to the NIH for pilot-scale biomedical studies with assay data being available via the PubChem database.

Experimental Section

Computational Methods. The energy-minimized structures reported herein (images generated with Ball & Stick, version 4.0a12)[18] were optimized in the gas phase using the Gaussian 03 suite of programs[19] and the Becke three-parameter hybrid functional, combined with the Lee–Yang–Parr correlation functional,[20] and the 3–21G(d) basis set. The reported structures were confirmed to be minima using vibrational frequency analysis. Coordinates for multiple low-energy conformations required for the molecular shape space diversity analysis were generated with OMEGA 2.1.0[21] using the default settings. The principal moments of inertia and

plots were generated with an unpublished PERL script written to model the method described by Sauer and Schwarz.[22] Other molecular properties were calculated using FILTER 2.0.1.[21]

General Procedure for Chromanone Synthesis: *tert*-Butyl 6-fluoro-4-oxospiro[chroman-2,4′-piperidine]-1′-carboxylate (1{*3*}). 1-(5-Fluoro-2-hydroxyphenyl)ethanone (5.00 g, 32.4 mmol) and Boc-4-piperidone (6.46 g, 32.4 mmol) were dissolved in anhydrous methanol (15 mL). Pyrrolidine (0.213 mL, 2.59 mmol) was added via pipet, and the reaction mixture was allowed to reflux at 80 °C overnight under N_2. The mixture was then concentrated, and water and EtOAc were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by flash chromatography (EtOAc/hexane, 3:7) to yield **1**{*3*}(6.284 g, 58% yield) as an off white solid. The analytical data are in accord with literature values.[23]

General Procedure for Enone Synthesis: *tert*-Butyl 6-fluoro-3-methylene-4-oxospiro[chroman-2,4′-piperidine]-1′-carboxylate (2{*3*}). A mixture of **1**{*3*} (0.100 g, 0.299 mmol) and *N,N,N,N*-tetramethyl diaminomethane (0.9 mL, 6.60 mmol) under N_2 was stirred at room temperature, while acetic anhydride (0.9 mL, 9.52 mmol) was added dropwise over 15 min. A slight temperature rise occurred, and the solution was allowed to stir overnight. Upon completion as judged by TLC (EtOAc/hexane, 3:7), the reaction mixture was extracted with ether and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude solid was purified by flash chromatography (EtOAc/hexane 3:7) to yield **2**{*3*}(0.0604 g, 59% yield) as an off-white solid. A small portion of the product was purified for analytical purposes: mp (dec) >167 °C; IR (neat) 2975, 2931, 1688, 1620, 1485, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.1, 3.3 Hz, 1H), 7.25–7.17 (m, 1H), 6.95 (dd, J = 9.0, 4.2 Hz, 1H), 6.36 (s, 1H), 5.57 (s, 1H), 3.99 (m, 2H), 3.16 (t, J = 12 Hz, 2H) 2.12–2.02 (m, 2H), 1.75 (dt, J = 12.9, 5.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 159.3, 156.1, 155.1 (d), 145.8, 124.1 (d), 122.4, 121.8, 120.3, 113.0 (d), 80.1, 79.6, 39.2, 33.9, 28.6; HRMS (ESI) calcd for $C_{19}H_{26}FN_2O_4$ 365.1871; found 365.1879 $(M + NH_4)^+$.

General Procedure for Isoxazoline Synthesis: *tert*-Butyl 6-fluoro-3′-phenyl-4-oxodispiro[4′,5′-dihydroisoxazol-5′,3-chroman-2,4″-piperidine]-1”-carboxylate (3{*3,1*}). Compound **2**{*3*} (1.00 g, 2.88 mmol) and benzaldehyde oxime (0.549 g, 4.53 mmol) were dissolved in DCM (30 mL) under N_2, and sodium hypochlorite (17.1 mL, 12.1 mmol) was added dropwise. The reaction mixture was allowed to stir overnight. Upon completion by TLC (EtOAc/hexane 3:7), the mixture was concentrated, and water and DCM were added. The layers were allowed to separate, and the aqueous layer was extracted with DCM (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by flash chromatography (EtOAc/hexane 3:7) to yield **3**{*3,1*} (1.22 g, 91%) as a white solid. A small portion of the product was purified for analytical purposes: mp (dec) >91 °C; IR (neat) 2968, 2930, 1688, 1620, 1481, 1164 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.68 (dd, J = 6.6, 1.5 Hz, 2H), 7.61–7.56 (m, 1H), 7.45–7.38 (m, 3H), 7.35–7.27 (m, 1H), 7.11–7.02 (m, 1H), 4.18–3.92 (m, 3H), 3.55–3.15 (m, 2H), 3.09 (t, J = 7.8 Hz, 1H), 2.21–2.00 (m, 2H), 1.87–1.82 (m, 1H), 1.56 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz $CDCl_3$) δ 186.0, 159.3, 156.1 (d), 154.8, 154.4, 131.0, 129.1, 128.5, 127.1, 125.0 (d), 120.3, 119.5, 113.1, 89.2, 81.6, 80.2, 38.7, 36.8, 28.6, 28.2, 27.6; HRMS (ESI) calcd for $C_{26}H_{27}FN_2O_5Na$ 489.1796; found: 489.1803 $(M + Na)^+$.

General Procedure for Amide Synthesis: 6-Fluoro-3′-(4-chlorophenyl)-1″-(2-methylpropanoyl)dispiro[4′,5′-dihydroisoxazol-5′,3-chroman-2,4″-piperidine]-4-one (4{*3,3,2*}). To a stirred solution of **3**{*3,3*} (0.100 g, 0.200 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction mixture was allowed to stir at room temperature for 2 h, after which it was concentrated by rotary evaporation. The residue was dissolved in DCM (5 mL), and triethylamine was added until the solution reached a pH of 8. A solution of isobutyric acid (0.0241 mL, 0.259 mmol) in DCM (2 mL) and DMF (2 mL) was added to the reaction mixture and allowed to stir in an ice bath for 20 min. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC, 0.0497 g, 0.259 mmol) and catalytic (4-(dimethylamino)pyridine) (DMAP) were dissolved in DCM (2 mL) and added to the reaction mixture. The solution was allowed to warm to room temperature overnight. The reaction mixture was concentrated by rotary evaporation, and EtOAc was added. The organic layers were washed with 1 M HCl, followed by saturated aqueous $NaHCO_3$ and brine. The combined organic layer was dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification by preparative HPLC yielded **4**{*3,3,2*} (0.075 g, 77%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.57 (m, 3H), 7.40 (d, J = 8.7 Hz, 2H) 7.36–7.30 (m, 1H), 7.07 (dd, J = 9.0, 4.2 Hz, 1H), 4.62–4.57 (m, 1H), 3.94 (m, 2H), 3.64–3.26 (m, 2H), 3.06–2.83 (m, 2H), 2.33–2.29 (m, 1H), 1.91 (apparent d, J = 13.2 Hz, 1H), 1.74 (apparent d, J = 12.6 Hz, 1H), 1.59 (apparent dt, J = 14.1, 4.5 Hz, 1H), 1.13 (dd, J = 6.9, 3.0 Hz, 6H); ESI-MS m/z 471, 473 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 214 nm.

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Supporting Information Available. Detailed synthetic experimental procedures, coordinates and energies for com-

puted structures, detailed table of computed chemical properties, X-ray crystallography data, and spectroscopic data. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Martin, E. J.; Critchlow, R. E. *J. Comb. Chem.* **1999**, *1*, 32–45.

(2) See Pilot-Scale Libraries for High-Throughput Screening; RFA Number: RFA-RM-05–014; http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05–014.html.

(3) (a) Kurth, M. J.; Brown, E. G.; Hendra, E.; Hope, H. *J. Org. Chem.* **1985**, *50*, 1115. (b) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. R.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125–7128. (c) Chandrasekhar, S.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2005**, *46*, 6991–6993. (d) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 12596–12597.

(4) (a) Tully, D. C.; Liu, H.; Chatterjee, A. K.; Alper, P. B.; Williams, J. A.; Roberts, M. J.; Mutnick, D.; Woodmansee, D. H.; Hollenbeck, T.; Gordon, P.; Chang, J.; Tuntland, T.; Tumanut, C.; Li, J.; Harris, J. L.; Karanewsky, D. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5107–5111. (b) Li, J.; Zhang, J.; Chen, J.; Luo, X.; Zhu, W.; Shen, J.; Liu, H.; Shen, X.; Jiang, H. *J. Comb. Chem.* **2006**, *8*, 326–337. (c) Simoni, D.; Roberti, M.; Paolo, I. F.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Alessandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. *J. Med. Chem.* **2001**, *44*, 2308–2318.

(5) (a) Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S. B.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1943–1945. (b) Wittenberger, S. J. *J. Org. Chem.* **1996**, *61*, 356–358. (c) Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanwelkar, R. R.; Vaidya, R. B.; Ajaikumar, K. B. *Eur. J. Med. Chem.* **2005**, *40*, 1143–1148.

(6) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

(7) Ainge, D.; Ennis, D.; Gidlund, M.; Stefinovic, M.; Vaz, L.-M. *Org. Process Res. Dev.* **2003**, *7*, 198–201.

(8) Tebbe, F. N.; Harlow, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.

(9) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784.

(10) (a) Roy, O.; Loiseau, F.; Riahi, A.; Hènin, F.; Muzart, J. *Tetrahedron* **2003**, *59*, 9641–9648. (b) In each of the olefination attempts, unreacted chromanone was recovered.

(11) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Masciocchi, N.; Sottocornola, S. *Org. Lett.* **2006**, *8*, 4521–4524.

(12) Ward, F. E.; Garling, D. L.; Buckler, R. T.; Lawler, D. M.; Cummings, D. P. *J. Med. Chem.* **1981**, *24*, 1073–1077.

(13) Mukawa, T.; Muraoka, J.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 739–743.

(14) Lee, H. J.; You, Z.; Ko, D.-H.; Yoon, K. J. *Drugs Exp. Clin. Res.* **1998**, *24*, 57–66.

(15) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637.

(16) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315.

(17) (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26. (b) Lipinski, C. A. *Drug Discovery Today: Technol.* **2004**, *1*, 337–341. (c) Suggiwama, Y. *Drug Discovery Today* **2005**, *10*, 1577–1581. (d) Keller, T. H.; Pichota, A.; Yin, Z. *Curr. Opin. Chem. Biol.* **2006**, *10*, 357–361.

(18) Müller, N.; Falk, A. *Ball & Stick*, version 4.0a12; Molecular Graphics Software for MacOS; Johannes Kepler University: Linz, Austria, 2000.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A. ; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.04: Gaussian, Inc.: Pittsburgh, PA, 2003.

(20) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.

(21) OpenEye Scientific Software, Santa Fe, NM.

(22) Sauer, W. H. B.; Schwarz, M. K. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987–1003.

(23) Chen Y.; O'Connor, S. J.; Gunn, D.; Newcom, J.; Chen, J.; Yi, L.; Zhang, H.-j.; Hunyadi, L. M.; Natero, R. P. Preparation of substituted 3,5-dihydro-4*H*-imidazol-4-ones for the treatment of obesity. PCT Int. Appl. WO 2004/058727 A1, 2004.

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