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(71) Applicant(s)
Myokardia, Inc.

(72) Inventor(s)
Oslob, Johan;Anderson, Robert;Aubele, Danielle;Evanchik, Marc;Fox, Jonathan Charles;Kane, Brian;Lu, Puping;McDowell, Robert;Rodriguez, Hector;Song, Yonghong;Sran, Arvinder

(74) Agent / Attorney
Watermark Intellectual Property Pty Ltd, L 1 109 Burwood Rd, Hawthorn, VIC, 3122, AU

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(71) Applicant: **MYOKARDIA, INC.** [US/US]; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US).

(72) Inventors: **OSLOB, Johan**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **ANDERSON, Robert**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **AUBELE, Danielle**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **EVANCHIK, Marc**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **FOX, Jonathan Charles**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **KANE, Brian**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **LU, Puping**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **MCDOWELL, Robert**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **RODRIGUEZ, Hector**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **SONG, Yonghong**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US). **SRAN, Arvinder**; 400 East Jamie Ct., Suite 102, South San Francisco, California 94080 (US).

(74) Agents: **KEZER, William B.** et al.; Kilpatrick Townsend and Stockton LLP, Two Embarcadero Center, Eighth Floor, San Francisco, California 94111 (US).

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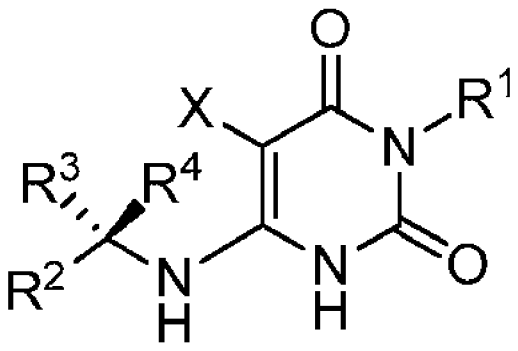

[I]

(57) Abstract: Provided are novel pyrimidine dione compounds and pharmaceutically acceptable salts thereof, that are useful for the treatment of hypertrophic cardiomyopathy (HCM) and conditions associated with left ventricular hypertrophy or diastolic dysfunction. The synthesis and characterization of the compounds and pharmaceutically acceptable salts thereof, are described, as well as methods for treating HCM and other forms of heart disease.

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PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is an application claiming benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/838,088 filed June 21, 2013, and U.S. Provisional Application No. 61/939,655 filed February 13, 2014, and U.S. Provisional Application No. 61/981,366 filed April 18, 2014, each of which is herein incorporated by reference in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0003] Genetic (heritable) hypertrophic cardiomyopathy (HCM) comprises a group of highly penetrant, monogenic, autosomal dominant myocardial diseases. HCM is caused by one or more of over 1,000 known point mutations in any one of the structural protein genes contributing to the functional unit of myocardium, the sarcomere. About 1 in 500 individuals in the general population are found to have left ventricular hypertrophy unexplained by other known causes (e.g., hypertension or valvular disease), and many of these can be shown to have HCM, once other heritable (e.g., lysosomal storage diseases), metabolic, or infiltrative causes have been excluded.

[0004] Sarcomere gene mutations that cause HCM are highly penetrant, but there is wide variability in clinical severity and clinical course. Some genotypes are associated with a more malignant course, but there is considerable variability between and even within families carrying the same mutation. Sex differences have also been noted, with male patients generally more severely affected than female patients. While many patients with HCM report

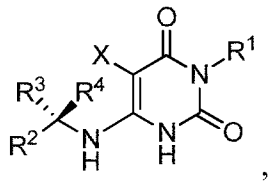
minimal or no symptoms for extended periods of time, HCM is a progressive disease with a significant cumulative burden of morbidity. Symptoms of effort intolerance predominate, and can be exacerbated by exercise and other maneuvers that increase heart rate and/or decrease preload. As with many other disorders, symptoms tend to worsen with age. By far the most prevalent clinical burden for patients with HCM is exertional dyspnea, which limits their activities of daily living and can be debilitating.

[0005] Patients with HCM are often symptomatic in the absence of documented hemodynamic abnormalities like left ventricular outflow tract obstruction (with or without mitral regurgitation). Patients' symptoms of exertional dyspnea can rapidly worsen with the onset of atrial fibrillation, a common complication of HCM that can precipitate acute pulmonary edema that increases the risk of systemic arterial thromboembolic disease, including stroke. Other adverse events associated with HCM include intolerance of hypovolemia or hypervolemia, and syncope. Concomitant coronary artery disease may confer a higher risk of acute coronary syndromes than in patients without HCM. Sudden cardiac death (SCD) in patients with HCM is both uncommon and difficult to predict but is a leading cause of non-traumatic death in young adults. For survivors of SCD, ICD placement is standard practice, and in other HCM patients risk profiling, while imprecise, is used to identify those for whom ICD placement for primary prevention is deemed prudent.

[0006] Medical therapy for HCM is limited to the treatment of symptoms and does not address the fundamental, underlying cause of disease – disruptions in normal sarcomere function. Currently available therapies are variably effective in alleviating symptoms but typically show decreased efficacy with increasing disease duration. Patients are thus empirically managed with beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide. None of these agents carry labeled indications for treating HCM, and essentially no rigorous clinical trial evidence is available to guide their use. Compounding this unfortunate situation is the fact that no new medical therapies for HCM have been identified for many years. For patients with hemodynamically significant outflow tract obstruction (resting gradient >30mmHg), in appropriately selected patients surgical myectomy or alcohol septal ablation is usually required to alleviate the hemodynamic obstruction. Provided are new therapeutic agents and methods that remedy the long-felt need for improved treatment of HCM and related cardiac disorders.

BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, provided is a compound having the formula:



,

or a pharmaceutically acceptable salt thereof. In some embodiments, the above formula, R^1 is a member selected from C_3-C_4 alkyl, C_3-C_5 cycloalkyl, phenyl, and 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a; R^2 is a member selected from phenyl, phenyl-C_1-C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C_1-C_4 alkyl, wherein each R^2 is optionally substituted with from 1-5 R^b; R^3 is a member selected from C_1-C_4 alkyl, C_3-C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-3 R^c; R^4 is H; X is a member selected from H and halo, and in some embodiments X is selected from H and F. Each R^a ,when present, is independently selected from halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenyl, phenyl-C_1-C_4 alkyl, phenyl-C_1-C_4 alkoxy, phenoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, and $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from H, C_1-C_4 alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring. Similarly, each R^b, when present, is independently selected from halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenoxy, phenyl-C_1-C_4 alkoxy, methylenedioxy, difluoromethylenedioxy, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from H and C_1-C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and each R^c, when present, is independently selected from halo, hydroxyl and C_1-C_2 alkoxy;

wherein

each cycloalkyl is a saturated or partially unsaturated ring system;

each heterocycloalkyl is a saturated ring system comprising from 1 to 4 heteroatoms selected from N, O, and S;

each heteroaryl is an aromatic ring system comprising from 1 to 4 heteroatoms selected from N, O, and S; and

each alkoxy group is optionally substituted with one or more moieties selected from halo, hydroxyl, amino, alkylamino, nitro, and cyano.

[0008] In another aspect, provided is a pharmaceutical composition containing a compound or or pharmaceutically acceptable salt described herein and a pharmaceutically acceptable excipient.

[0009] In another aspect, provided is a method of treating hypertrophic cardiomyopathy (HCM) or a cardiac disorder having one or more pathophysiological features associated with

CONTINUES ON PAGE 4

HCM. The method includes administering to a subject in need thereof an effective amount of a compound or pharmaceutically acceptable salt described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1** shows a schematic route for the synthesis of the compounds or pharmaceutically acceptable salts described herein (Figure 1A) and a route for the preparation of chiral amines (Figure 1B).

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0011] A series of pyrimidine dione compounds and pharmaceutically acceptable salts thereof has been found to reduce excess contractility in hypercontractile states and/or promote cardiac relaxation in hearts with diastolic dysfunction by stabilizing the conformation of beta cardiac myosin post-ATP hydrolysis but prior to strongly binding the actin filament and releasing phosphate, thus reducing the proportion of myosin molecules that are available to participate in the "powerstroke" portion of the muscle contraction cycle. As such, the compounds can improve cardiac elasticity, reduce dynamic and/or static left ventricular outflow obstruction, improve diastolic left ventricular relaxation, reduce left ventricular diastolic (filling) pressures, reduce functional mitral regurgitation, and/or reduce left atrial and pulmonary capillary wedge pressures in patients with HCM helping overcome the debilitating exertional dyspnea and/or symptoms referable to left ventricular outflow obstruction (presyncope or syncope) that often accompanies the disease. The compounds can also be used to treat other cardiac disorders.

II. Definitions

[0012] As used herein, the term "alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. For example, C_{1-6} alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Unless stated otherwise, alkyl groups are unsubstituted. A "substituted alkyl"

group can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0013] As used herein, the term "cycloalkyl" refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C_{3-6}, C_{4-6}, C_{5-6}, C_{3-8}, C_{4-8}, C_{5-8}, and C_{6-8}. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. Unless otherwise stated, cycloalkyl groups are unsubstituted. A "substituted cycloalkyl" group can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0014] As used herein, the term "heterocycloalkyl" refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms selected from N, O and S. Additional heteroatoms including, but not limited to, B, Al, Si and P can also be present in a heterocycloalkyl group. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and $-S(O)_2-$. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, or 4 to 7 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. Examples of heterocycloalkyl groups include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. Heterocycloalkyl groups are unsubstituted, but can be described, in some embodiments as substituted. "Substituted heterocycloalkyl" groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0015] As used herein, the term "heteroaryl" refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms including, but not limited to, B, Al, Si and P can also be present in a heteroaryl group. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -$S(O)_2$-. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 5 to 8, 6 to 8, 5 to 9, 5 to 10, 5 to 11, or 5 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. Examples of heteroaryl groups include, but are not limited to, pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Heteroaryl groups are unsubstituted, but can be described, in some embodiments as substituted. "Substituted heteroaryl" groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0016] As used herein, the term "alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: *i.e.*, alkyl-O-. As for the alkyl portion, alkoxy groups can have any suitable number of carbon atoms, such as C_{1-6} or C_{1-4}. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc. Alkoxy groups are unsubstituted, but can be described, in some embodiments as substituted. "Substituted alkoxy" groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0017] As used herein, the terms "halo" and "halogen" refer to fluorine, chlorine, bromine and iodine.

[0018] As used herein, the term "pharmaceutically acceptable" refers to a substance that is compatible with a compound or salt as described herein, as well as with any other ingredients with which the compound is formulated. Furthermore, a pharmaceutically acceptable substance is not deleterious to the recipient of the substance.

[0019] As used herein, the term "salt" refers to an acid or base salt of a compound described herein. Pharmaceutically acceptable salts can be derived, for example, from mineral acids (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like), organic acids (acetic acid, propionic acid, glutamic acid, citric acid and the like), and quaternary ammonium ions. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference. The neutral form of a compound may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner.

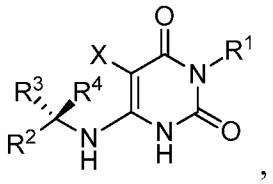
[0020] As used herein, the term "pharmaceutical composition" refers to a product comprising a compound or pharmaceutically acceptable salt described herein, an excipient as defined herein, and other optional ingredients in specified amounts, as well as any product which results directly or indirectly from combination of the specified ingredients in the specified amounts.

[0021] As used herein, the term "excipient" refers to a substance that aids the administration of an active agent to a subject. Pharmaceutical excipients include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. One of skill in the art will recognize that other excipients can be useful.

[0022] As used herein, the terms "treat," "treating" and "treatment" refer to any indicia of success in the treatment or amelioration of a pathology, injury, condition, or symptom related to hypertrophic cardiomyopathy, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms; making the pathology, injury, condition, or symptom more tolerable to the patient; decreasing the frequency or duration of the pathology, injury, condition, or symptom; or, in some situations, preventing the onset of the pathology, injury, condition, or symptom. Treatment or amelioration can be based on any objective or subjective parameter; including, *e.g.*, the result of a physical examination.

III. Compounds and Pharmaceutically Acceptable Salts Thereof

[0023] In one aspect, provided is a compound having the formula:



or a pharmaceutically acceptable salt thereof.

[0024] In the above formula, R^1 is a member selected from C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkyl, 4- to 7-membered heterocycloalkyl, phenyl, phenyl-C_1-C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C_1-C_4 alkyl, wherein each R^1 is optionally substituted with from 1-3 R^a; R^2 is a member selected from phenyl, phenyl-C_1-C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C_1-C_4 alkyl, wherein each R^2 is optionally substituted with from 1-5 R^b; R^3 is a member selected from C_1-C_4 alkyl, C_3-C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-3 R^c; R^4 is H; X is a member selected from H and halo, and in selected embodiments is selected from H and F. Each R^a ,when present, is independently selected from halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenyl, phenyl-C_1-C_4 alkyl, phenyl-C_1-C_4 alkoxy, phenoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, and $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from H, C_1-C_4 alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring. Similarly, each R^b, when present, is independently selected from halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenoxy, phenyl-C_1-C_4 alkoxy, methylenedioxy, difluoromethylenedioxy, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from H and C_1-C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and each R^c, when present, is independently selected from halo, hydroxyl and C_1-C_2 alkoxy.

[0025] In some embodiments, R^1 is selected from C_1-C_8 alkyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a. R^2 is phenyl, which is optionally substituted with from 1-5 R^b. R^3 is selected from C_1-C_4 alkyl, C_3-C_4 cycloalkyl, or 4- to 7-membered heterocycloalkyl, wherein each R^3 is optionally substituted with from 1-2 R^c. R^4 is H, and X is H or F. In some embodiments, each R^a, when present, is independently halo, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, or $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently H or C_1-C_4 alkyl. Alternatively, R^{a1} and R^{a2}, when attached to a

nitrogen atom, are optionally combined to form a 4- to 6- membered ring. Each R^b, when present, is independently halo, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, -COR^{b1}, -CO_2R^{b1}, -SO_2R^{b1}, -$SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, or 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently H or C_1-C_4 alkyl. Alternatively, R^{b1} and R^{b2}, when attached to a nitrogen atom, are optionally combined to form a 4- to 6- membered ring. Each R^c, when present, is independently halo or C_1-C_2 alkoxy.

[0026] In some embodiments, X is H.

[0027] In some embodiments, R^1 is C_3-C_4 alkyl, C_3-C_5 cycloalkyl, or 4- to 6-membered heterocycloalkyl, wherein each R^1 is optionally substituted with from 1-2 R^a.

[0028] In some embodiments, R^1 is phenyl or 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a.

[0029] In some embodiments, R^1 is C_3-C_4 alkyl, C_3-C_5 cycloalkyl, or 4- to 6-membered heterocycloalkyl.

[0030] In some embodiments, R^1 is 4- to 6-membered heterocycloalkyl, optionally substituted
with from 1-2 R^a selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -COR^{a1}, -CO_2R^{a1}, -SO_2R^{a1}, -$SO_2NR^{a1}R^{a2}$, and -$CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently H or C_1-C_4 alkyl.

[0031] In some embodiments, R^1 is cyclobutyl, isopropyl, isobutyl, 1-methoxypropan-2-yl, cyclopentyl, cyclohexyl, 4-tetrahydropyranyl, 1-(methylsulfonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 4,4-difluorocyclohexyl, phenyl, 2-pyridyl, 3-pyridyl, 3-isoxazolyl, 5-isoxazolyl, or 1-methyl-3-pyrazolyl.

[0032] In some embodiments, R^2 is optionally substituted with from 1-2 R^b.

[0033] In some embodiments, R^2 is phenyl, 3-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, 3-(3-oxazolidin-2-onyl)phenyl, 3-(2-methyl-1-imidazyl)phenyl, 3-(1-pyrazolyl)phenyl, or 3-(1,2,4-triazol-1-yl)phenyl.

[0034] In some embodiments, R^3 is C_1-C_4 alkyl, C_1-C_4 alkoxyalkyl, or C_3-C_4 cycloalkyl.

[0035] In some embodiments, R^3 is methyl, ethyl, propyl, cyclopropyl, cyclobutyl or 2-methoxymethyl.

[0036] In some embodiments, R^3 is methyl.

[0037] The compounds or pharmaceutically acceptable salts described herein can have any combination of the R^1, R^2, R^3, R^4, R^a, R^{a1}, R^{a2}, R^b, R^{b1}, R^{b2}, R^c, and X groups recited above. Selected embodiments recited for R^2, for example, can be combined with any of the selected embodiments recited for R^1 which, in turn, can be combined with any of the selected embodiments recited for R^3.

[0038] In some embodiments, for example, R^1 is C_3-C_8 alkyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, or $-SO_2R^{a1}$; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl. In still other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl, R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl.

[0039] In other embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl. In yet other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_1-C_4 alkyl; and R^2 is phenyl. In still other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl.

[0040] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo. In still other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo. In yet other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo.

[0041] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo. In other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 1-2 C_1-C_4 alkoxy or halo.

[0042] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl, R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo.

[0043] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo.

[0044] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C_1-C_4 alkyl, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, or $NR^{b1}R^{b2}$. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C_1-C_4 alkyl, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $CONR^{b1}R^{b2}$, or $NR^{b1}R^{b2}$. In other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_3-C_4 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C_1-C_4 alkyl, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $CONR^{b1}R^{b2}$, or $NR^{b1}R^{b2}$.

[0045] In some embodiments, R^1 is C_3-C_8 alkyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with CN, C_1-C_4 alkyl, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $CONR^{b1}R^{b2}$, or $NR^{b1}R^{b2}$. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C_1-C_4 alkyl, $-CO_2R^{a1}$, or $-SO_2R^{a1}$; R^3 is C_1-C_4 alkyl; and

R^2 is phenyl substituted with CN, C_1-C_4 alkyl, -COR^{b1}, -CO_2R^{b1}, -SO_2R^{b1}, $CONR^{b1}R^{b2}$, or $NR^{b1}R^{b2}$. In other embodiments, R^1 is C_3-C_8 cycloalkyl or phenyl; R^3 is C_1-C_4 alkyl; and R^2 is phenyl substituted with CN, C_1-C_4 alkyl, -COR^{b1}, -CO_2R^{b1}, -SO_2R^{b1}, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, or -$CONR^{a1}R^{a2}$.

[0046] In some embodiments, R^1 is isopropyl; R^2 is optionally substituted with 1-2 R^b; and R^3 is methyl.

[0047] In some embodiments, R^1 is 4- to 6-membered heterocycloalkyl, optionally substituted
with from 1-2 R^a selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -COR^{a1}, -CO_2R^{a1}, -SO_2R^{a1}, -$SO_2NR^{a1}R^{a2}$, and -$CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} can independently be H or C_1-C_4 alkyl; R^2 is optionally substituted with 1-2 R^b; and R^3 is methyl.

[0048] In some embodiments, R^1 is phenyl or 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a; R^2 is optionally substituted with from 1-2 R^b; and R^3 is methyl.

[0049] X can be H in any of the embodiments set forth above. In other embodiments, X can be F in any of the embodiments set forth above. Still further, compounds provided herein with an identified stereochemistry (indicated as R or S, or with dashed or wedge bond designations) will be understood by one of skill in the art to be substantially free of other isomers (e.g., at least 80%, 90%, 95% up to 100% free of the other isomer).

[0050] In some embodiments, the compound is selected from:
(S)-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-5-fluoro-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-5-bromo-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3,5-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclopropyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclopropyl(3-methoxyphenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclobutyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-methoxyphenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione;

6-(((S)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

methyl (S)-4-(2,6-dioxo-4-((1-phenylethyl)amino)-3,6-dihydropyrimidin-1(2H)-yl)piperidine-1-carboxylate;

3-((R)-sec-butyl)-6-(((S)-1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-phenylethyl)amino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(isoxazol-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(2-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-5-methyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(2-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(4-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-5-fluoro-3-isopropyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-5-fluoro-6-((1-(3-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-5-fluoro-3-isopropyl-6-((1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(2,5-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-bromophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-3-ethyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-cyclopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-phenylethyl)amino)-3-(pyridin-2-yl)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(1-methyl-1H-pyrazol-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(isoxazol-5-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(3-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(3-(2-oxooxazolidin-3-yl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-cyclohexyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-phenyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-ethyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-methyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;

(S)-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(m-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(R)-3-isopropyl-6-((2,2,2-trifluoro-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

3-((R)-1-(benzyloxy)propan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

3-((R)-1-hydroxypropan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-2-(1-((1-isopropyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)ethyl)benzonitrile

(S)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(2,6-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(4-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(R)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(o-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-3-(1-methylcyclopropyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-(1H-imidazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

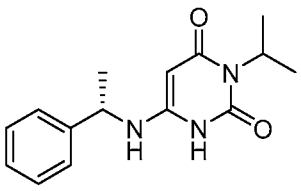
(S)-6-((1-phenylethyl)amino)-3-(pyridazin-4-yl)pyrimidine-2,4(1H,3H)-dione;

(S)-4-((1-phenylethyl)amino)-2H-[1,5'-bipyrimidine]-2,6(3H)-dione;
(S)-6-((1-phenylethyl)amino)-3-(pyrazin-2-yl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((1-(pyridin-3-yl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(1-methyl-1H-pyrazol-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((1-phenylbutyl)amino)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-phenylethyl)amino)-3-((R)-tetrahydro-2H-pyran-3-yl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-cyclopentyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((2-methyl-1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(4,4-difluorocyclohexyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(pentan-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(1-benzoylpiperidin-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((4-phenylbutan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
methyl (S)-2-(2,6-dioxo-4-((1-phenylethyl)amino)-3,6-dihydropyrimidin-1(2H)-yl)acetate
(S)-3-isopropyl-6-((1-phenylpropan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
3-((S)-1-(benzyloxy)propan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
3-((S)-1-hydroxypropan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(R)-6-((2-hydroxy-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-phenylethyl)amino)-3-((R)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-phenylethyl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-phenylethyl)amino)-3-(4,4,4-trifluorobutan-2-yl)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-phenylethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(tert-butyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(2-methoxyethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-phenylpropyl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-dione;
3-((R)-1-cyclopropylethyl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
3-((S)-1-cyclopropylethyl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclobutyl(phenyl)methyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-phenylpropyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclopropyl(phenyl)methyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclobutyl(phenyl)methyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(1,3-dihydroxypropan-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-(4-fluorophenyl)propan-2-yl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
6-((1-(2-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-phenylethyl)amino)-3-(1-(trifluoromethyl)cyclopropyl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(3,5-difluorophenyl)-6-((1-(4-fluorophenyl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(2-chlorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((1-(4-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclopropyl(phenyl)methyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
(S)-3-ethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-(3-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-(cyclopropylmethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-5-chloro-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;
(S)-3-propyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-cyclobutyl-6-((1-(4-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(2-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3,4-difluorophenyl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;

3-((S)-sec-butyl)-6-(((S)-1-(4-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(4-fluorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione; and
(S)-3-(6-fluoropyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione, or a pharmaceutically acceptable salt of any of the above.

[0051] In some embodiments, the compound is selected from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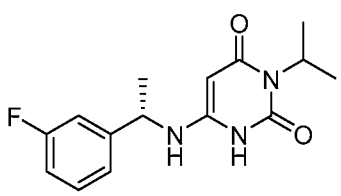
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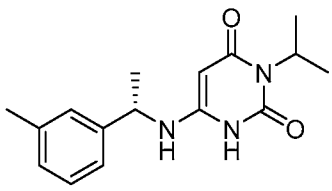
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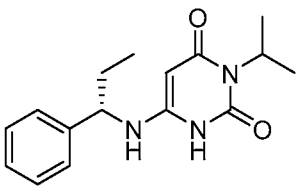
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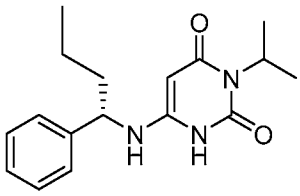
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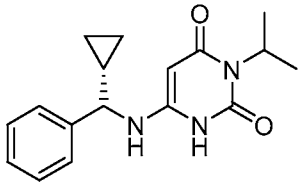
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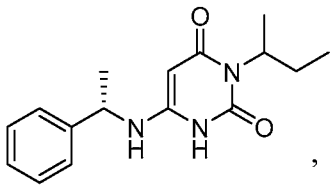
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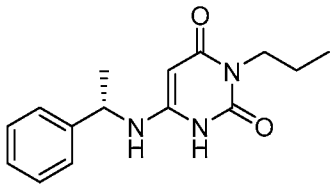
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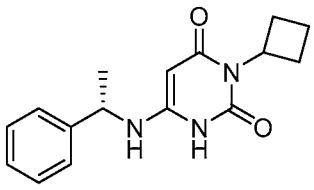
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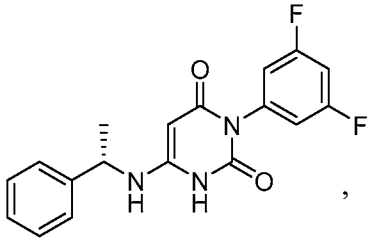
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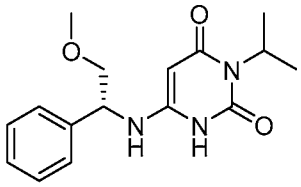


or a pharmaceutically acceptable salt thereof.

[0052] The compounds or pharmaceutically acceptable salts described herein (**I**) can be prepared via any suitable method. Compounds can be prepared, for example, by the route outlined in Figure 1. As shown in Figure 1A, a pyrimidine trione **v** can be synthesized via condensation of a urea **iii** with a malonate **iv**. The urea **iii** can be prepared via reaction of an amine **i** with an appropriate cyanate **ii**. The pyrimidine trione **v** is derivatized with a suitable leaving group (Lg) to provide intermediate **vi**. The leaving group can be, but is not limited to, a halogen such as a chloride or iodide. A halogenated intermediate **vi** can be prepared

from pyrimidine triones by methods such as those described by Brown (*The Chemistry of Heterocyclic Compounds, The Pyrimidines*, John Wiley & Sons, 2009). Intermediates **vi** can be converted to compounds of formula I via reaction with amines **vii**. Certain chiral amines can be prepared from a ketone or aldehyde **ix** as shown in Figure 1B; a sulfinyl imine **xii** derived from the ketone or aldehyde can be reacted with a Gringard reagent **xiii** to provide a chiral amine **vii**. One of skill in the art will appreciate that the compounds described herein can be prepared via other methods, such as those described by LaRock (*Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley, 1999).

IV. Compositions

[0053] Also provided is a pharmaceutical composition containing a compound or pharmaceutically acceptable salt described herein and a pharmaceutically acceptable excipient. The compositions may be useful for treating hypertrophic cardiomyopathy in humans and other subjects.

[0054] The pharmaceutical compositions for the administration of the compounds or pharmaceutically acceptable salts described herein may conveniently be presented in unit dosage form and may be prepared by any of the methods known in the art of pharmacy and drug delivery. All methods include the step of bringing the active ingredient into association with a carrier containing one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active agent is generally included in an amount sufficient to produce the desired effect upon myocardial contractility (i.e. to decrease the often supranormal systolic contractility in HCM) and to improve left ventricular relaxation in diastole. Such improved relaxation can alleviate symptoms in hypertrophic cardiomyopathy and other etiologies of diastolic dysfunction. It can also ameliorate the effects of diastolic dysfunction causing impairment of coronary blood flow, improving the latter as an adjunctive agent in angina pectoris and ischemic heart disease. It can also confer benefits on salutary left ventricular remodeling in HCM and other causes of left ventricular hypertrophy due to chronic volume or pressure overload from, *e.g.*, valvular heart disease or systemic hypertension.

[0055] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions,

dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs, solutions, buccal patch, oral gel, chewing gum, chewable tablets, effervescent powder and effervescent tablets. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, antioxidants and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated, enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release.

[0056] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[0057] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene

oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0058] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0059] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0060] The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0061] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[0062] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0063] The compounds or pharmaceutically acceptable salts described herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols. Additionally, the compounds or pharmaceutically acceptable salts can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds or pharmaceutically acceptable salts can be accomplished by means of iontophoretic patches and the like. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds or pharmaceutically acceptable salts described herein are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

[0064] The compounds or pharmaceutically acceptable salts described herein may also be coupled to a carrier that is a suitable polymer for targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds or pharmaceutically acceptable salts described herein may be coupled to a carrier that is a biodegradable polymer useful in achieving controlled release of a drug, such as polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

V. Methods of treating cardiac disorders

[0065] The mutations that lead to HCM cause significant perturbations in myosin mechanics. These mutations exert their effects via distinct mechanisms depending on their locations in the myosin gene. The well-studied HCM mutations, R403Q and R453C, are located in different sections of the motor domain and cause distinct mechanistic perturbations that lead to the common outcome of increased force production. Without wishing to be bound by any particular theory, it is believed that the compounds or pharmaceutically acceptable salts described herein can bind directly to the mutant sarcomeric proteins and correct for their aberrant function, either in *cis* (by affecting the same specific function) or in *trans* (by altering a complementary function). As such, they can provide therapeutic benefit for HCM patients by counteracting the hypercontractile and/or impaired relaxation associated with this disease. .

[0066] Also provided is a method of treating hypertrophic cardiomyopathy (HCM) or a cardiac disorder having one or more pathophysiological features associated with HCM. The method includes administering to a subject in need thereof an effective amount of a compound or pharmaceutically acceptable salt described herein.

[0067] The compounds of the invention or their pharmaceutically acceptable salts can alter the natural history of HCM and other diseases rather than merely palliating symptoms. The mechanisms conferring clinical benefit to HCM patients can extend to patients with other forms of heart disease sharing similar pathophysiology, with or without demonstrable genetic influence. For example, an effective treatment for HCM, by improving ventricular relaxation during diastole, can also be effective in a broader population characterized by diastolic dysfunction. The compounds of the invention or their pharmaceutically acceptable salts can specifically target the root causes of the conditions or act upon other downstream pathways. Accordingly, the compounds of the invention or their pharmaceutically acceptable salts can also confer benefit to patients suffering from diastolic heart failure with preserved ejection fraction, ischemic heart disease, angina pectoris, or restrictive cardiomyopathy. Compounds of the invention or their pharmaceutically acceptable salts can also promote salutary ventricular remodeling of left ventricular hypertrophy due to volume or pressure overload; *e.g.,* chronic mitral regurgitation, chronic aortic stenosis, or chronic systemic hypertension; in conjunction with therapies aimed at correcting or alleviating the primary cause of volume or pressure overload (valve repair/replacement, effective

antihypertensive therapy). By reducing left ventricular filling pressures the compounds could reduce the risk of pulmonary edema and respiratory failure. Reducing or eliminating functional mitral regurgitation and/or lowering left atrial pressures may reduce the risk of paroxysmal or permanent atrial fibrillation, and with it reduce the attendant risk of arterial thromboembolic complications including but not limited to cerebral arterial embolic stroke. Reducing or eliminating either dynamic and/or static left ventricular outflow obstruction may reduce the likelihood of requiring septal reduction therapy, either surgical or percutaneous, with their attendant risks of short and long term complications. The compounds or their pharmaceutically acceptable salts may reduce the severity of the chronic ischemic state associated with HCM and thereby reduce the risk of Sudden Cardiac Death (SCD) or its equivalent in patients with implantable cardioverter-defibrillators (frequent and/or repeated ICD discharges) and/or the need for potentially toxic antiarrhythmic medications. The compounds or their pharmaceutically acceptable salts could be valuable in reducing or eliminating the need for concomitant medications with their attendant potential toxicities, drug-drug interactions, and/or side effects. The compounds or their pharmaceutically acceptable salts may reduce interstitial myocardial fibrosis and/or slow the progression, arrest, or reverse left ventricular hypertrophy.

[0068] Depending on the disease to be treated and the subject's condition, the compounds or pharmaceutically acceptable salts described herein may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by implantation (e.g., as when the compound or pharmaceutically acceptable salt is coupled to a stent device), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[0069] In the treatment or prevention of conditions which require improved ventricular relaxation during diastole, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. In some embodiments, the dosage level will be about 0.01 to about 25 mg/kg per day; in some embodiments, about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per

day. In some embodiments, for oral administration, the compositions are provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds or pharmaceutically acceptable salts may be administered on a regimen of 1 to 4 times per day, in some embodiments, once or twice per day.

[0070] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound or pharmaceutically acceptable salt employed, the metabolic stability and length of action of that compound or pharmaceutically acceptable salt, the age, body weight, hereditary characteristics, general health, sex and diet of the subject, as well as the mode and time of administration, rate of excretion, drug combination, and the severity of the particular condition for the subject undergoing therapy.

[0071] Compounds and compositions provided herein may be used in combination with other drugs that are used in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds and compositions provided herein are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound or composition provided herein. When a compound or composition provided herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound or composition provided herein is preferred. Accordingly, the pharmaceutical compositions provided herein include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound or composition provided herein. Suitable additional active agents include, for example: therapies that retard the progression of heart failure by down-regulating neurohormonal stimulation of the heart and attempt to prevent cardiac remodeling (*e.g.*, ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, aldosterone receptor antagonists, or neural endopeptidase inhibitors); therapies that improve cardiac function by stimulating cardiac contractility (*e.g.*, positive inotropic agents, such as the β-adrenergic agonist dobutamine or the phosphodiesterase inhibitor milrinone); and therapies that reduce cardiac preload (*e.g.*, diuretics, such as furosemide) or afterload (vasodilators of any class, including but not limited to calcium channel blockers, phosphodiesterase inhibitors, endothelin receptor antagonists, renin inhibitors, or smooth

muscle myosin modulators). The weight ratio of the compound provided herein to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

VI. Examples

Abbreviations:

aq: aqueous

BBr_3: boron tribromide

CH_2Cl_2: dichloromethane

CH_3CN: acetonitrile

CH_3OH: methanol

DIAD: diisopropyl azodicarboxylate

DIEA: diisopropyl ethylamine

DMF: dimethyl formamide

DMSO: dimethyl sulfoxide

equiv.: equivalents

Et_3N: triethylamine

Et_2O: diethyl ether

EtOH: ethanol

$FeSO_4$: ferrous sulfate

h: hour(s)

HCl: hydrogen chloride

H_2O: water

K_2CO_3: potassium carbonate

$KHSO_4$: potassium bisulfate

KNCO: potassium isocyanate

LiBr: lithium bromide

$MgSO_4$: magnesium sulfate

mL: milliliter

MW: microwave (reaction done in microwave reactor)

NaCl: sodium chloride

NaH: sodium hydride

$NaHCO_3$: sodium bicarbonate

NaOEt: sodium ethoxide

NaOH: sodium hydroxide

NaOMe: sodium methoxide

Na_2SO_4: sodium sulfate

NH_4Cl: ammonium chloride

NMP: n-methyl pyrrolidinone

pH: -log $[H^+]$

$POCl_3$: phosphoryl trichloride

PPTS: pyridinium p-toluenesulfonate

RP-HPLC: reversed phase high pressure liquid chromatography

RT: room temperature

SEMCl: 2-(trimethylsilyl)ethoxymethyl chloride

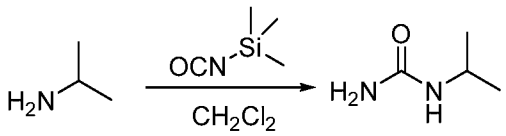
TEBAC: triethylbenzylammonium chloride

TFA: trifluoroacetic acid

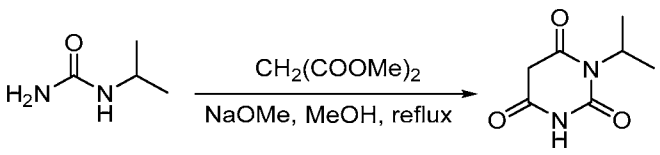
THF: tetrahydrofuran

TLC: thin layer chromatography

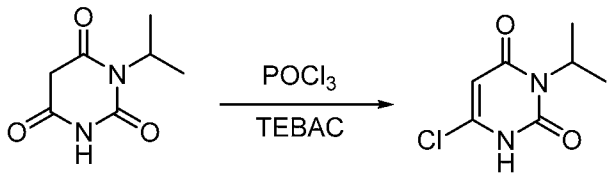
Example 1. Preparation of (*S*)-3-Isopropyl-6-((1-phenylethyl) amino) pyrimidine-2, 4(1H,3H)-dione.



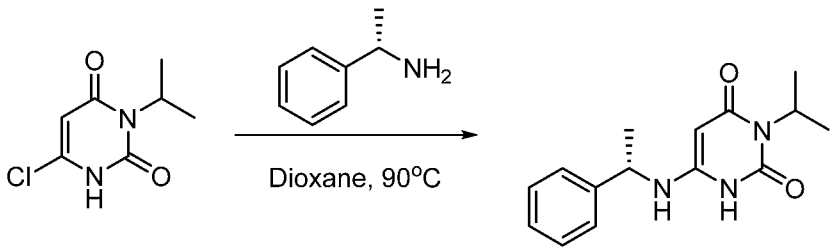
[0072] Compound 1.1. Isopropylurea. To a stirred solution of isopropylamine (15.3 g, 0.258 mol, 1.0 equiv) in CH_2Cl_2 (200 mL) under argon at 0 °C was added dropwise trimethylsilyl isocyanate (30 g, 0.26 mol, 1.0 equiv). The resulting mixture was allowed to reach ambient temperature and stirred overnight. After cooling to 0 °C, CH_3OH (100 mL) was added dropwise. The resulting solution was stirred for 2 hours (h) at room temperature and then concentrated under reduced pressure. The crude residue was recrystallized from CH_3OH:Et_2O (1:20) to yield 15.4 g (58%) the title compound as a white solid. LC/MS: m/z (ES+) 103 $(M+H)^+$.



[0073] Compound 1.2. 1-Isopropyl barbituric acid. To a stirred solution of **1.1** (14.4 g, 0.14 mol, 1.00 equiv) in CH_3OH (500 mL) were added dimethyl malonate (19.55 g, 0.148 mol, 1.05 equiv) and sodium methoxide (18.9 g, 0.35 mol, 2.50 equiv). The resulting mixture was stirred overnight at 65 °C. After cooling to ambient temperature and then to 0 °C, the pH was carefully adjusted to 3 using aqueous concentrated HCl. The resulting mixture was concentrated under reduced pressure. The residue was taken up in EtOH (200 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (20:1) as eluent to yield 16.8 g (50%) of the title compound as a white solid. . LC/MS: m/z (ES+) 171 $(M+H)^+$.[1] ^{1}H-NMR (300 MHz, d_6-DMSO): δ 11.19 (s, 1H), 4.83 (m, 1H), 3.58 (s, 2H), 1.32 (d, J = 6.0 Hz, 6H).



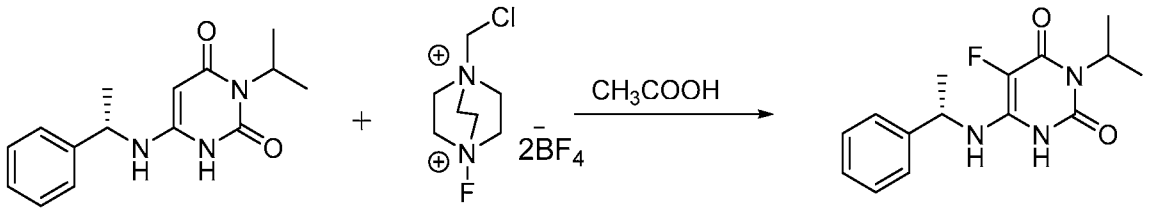
[0074] Compound 1.3. 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a 100-mL round-bottom flask containing compound **1.2** (11.4 g, 66.99 mmol, 1.00 equiv) under argon were added triethylbenzylammonium chloride (21.3 g, 93.51 mmol, 1.40 equiv) and $POCl_3$ (30 mL). The resulting mixture was stirred overnight at 50 °C. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) followed by slow addition of H_2O (100 mL). The phases were separated and the organic layer was washed with H_2O (100 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using EtOAc/petroleum ether (1:1) as eluent to yield 5.12 g (40%) of the title compound as a light yellow solid. ^{1}H-NMR (300 MHz, d_6-DMSO): δ 12.22 (s, 1H), 5.88 (s, 1H), 4.95 (m, 1H), 1.34 (d, J = 6.0 Hz, 6H).



[0075] Compound 1. (*S*)-3-Isopropyl-6-((1-phenylethyl) amino) pyrimidine-2, 4(1H,3H)-dione. To a solution of 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione (**1.3**,

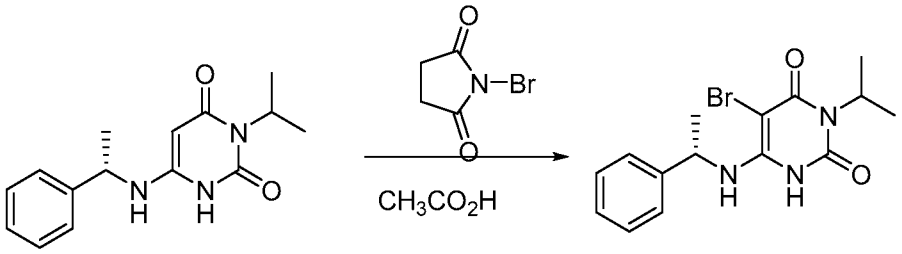
1.0 g, 5.31 mmol) in 1,4-dioxane (20 mL) was added (*S*)-α-methylbenzylamine (Sigma-Aldrich, 1.43 g, 11.7 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 24 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residual was taken up in EtOAc (70 mL) and washed with aqueous 1N HCl (2 x 50 mL) and brine (40 mL). The organic layer was dried with anhydrous Na_2SO_4 and then concentrated under reduced pressure to half the original volume to yield a precipitate. Hexane (20 mL) was added and the mixture was stirred at room temperature. The resulting solid was collected by filtration, washed with hexane (20 mL), and dried to yield 1.0 g (69%) of the title compound as a white solid. LC/MS: m/z (ES+) 274 $(M+H)^+$. ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.77 (s, 1H), 7.32 (m, 4H), 7.24 (m, 1H), 6.50 (d, *J* = 6.8 Hz, 1H), 4.87 (m, 1H), 4.52 (m, 1H), 4.31 (d, *J*=6.8 Hz, 1H), 1.37 (m, 3H), 1.24 (m, 6H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.39-7.20 (m, 5H), 5.01 (m, 1H), 4.48 (m, 1H), 1.49 (d, J = 6.7 Hz, 3H), 1.36 (m, 6H).

Example 2. Preparation of (*S*)-5-Fluoro-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione **(2)**.



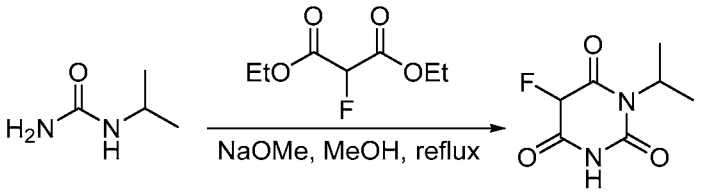
[0076] To a solution of **1** (80 mg, 0.293 mmol) in acetic acid (2.0 mL) was added selectfluor (104 mg, 0.293 mmol, 1.0 equiv.). The mixture was stirred at room temperature for 2 h. It was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0-50% EtOAc in hexanes to give 6 mg (7%) of the title compound as a white solid. LC/MS: m/z (ES+) 292 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.36-7.24 (m, 5H), 5.04-4.97 (m, 1H), 4.94-4.88 (m, 1H), 1.54 (d, J = 8.0 Hz, 3H), 1.39 (m, 6H).

Example 3. Preparation of (*S*)-5-Bromo-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione **(3)**.

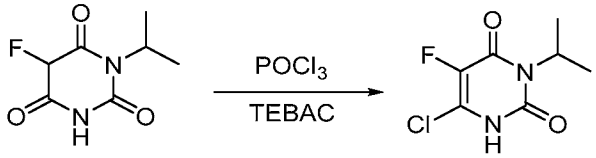


[0077] To a solution of **1** (55 mg, 0.201 mmol) in acetic acid (1.0 mL) was added N-bromosuccinamide (35 mg, 0.196 mmol). The mixture was stirred at room temperature for 1 hour. It was then concentrated under reduced pressure. The residue was purified by a silica gel column, eluted with 0-40% EtOAc in hexanes to give 52 mg (74%) of the title compound as a white solid. LC/MS: m/z (ES+) 352, 354 (M+H, bromine pattern)$^{+}$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.96 (br s, 1H), 7.43-7.28 (m, 5H), 5.28 (d, J = 7.4 Hz, 1H), 5.14 (m, 1H), 4.87 (m, 1H), 1.62 (d, J = 6.7 Hz, 3H), 1.45-1.39 (m, 6H).

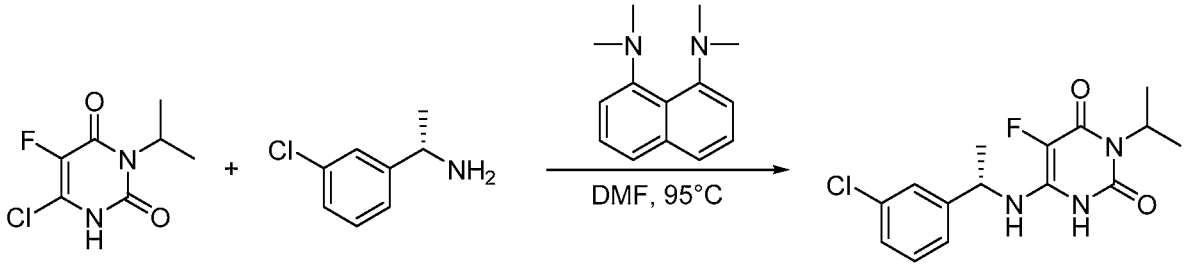
Example 4. Preparation of (*S*)-6-((1-(3-Chlorophenyl)ethyl)amino)-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0078] **Compound 4.1. 5-Fluoro-1-isopropylpyrimidine-2,4,6(1H,3H,5H)-trione).** To a 100 mL round bottom flask containing a solution of **1.1** (1.31 g, 0.013 mol, 1.00 equiv) in CH_3OH (15 mL) were added diethyl fluoromalonate (2.41 g, 0.014 mol, 1.05 equiv) and sodium methoxide (1.74 g, 0.032 mol, 2.50 equiv). The reaction flask was equipped with a reflux condenser and was stirred for 4 h in an oil bath heated at 85 °C. The reaction was cooled to 0 °C and was quenched with careful addition of concentrated HCl, adjusting to pH=2 with the addition of excess concentrated HCl. The reaction mixture was concentrated under reduced pressure and the resulting residue was dried for 18 h under high vacuum to provide 2.65 g of the title compound (98%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 5.53 (d, J = 24.0 Hz, 1H), 4.91 (m, 2H), 1.46 (m, 6H).

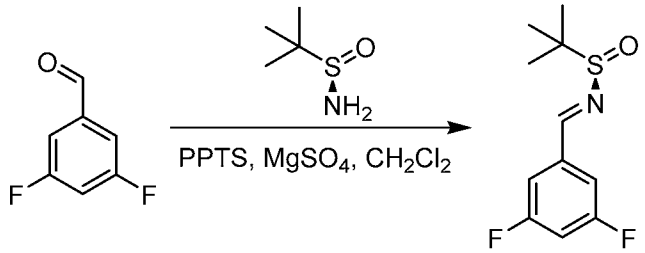


[0079] Compound 4.2. 6-Chloro-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a 100-mL round-bottom flask equiped with a reflux condensor containing **4.1** (2.65 g, 0.014 mmol, 1.00 equiv) were added triethylbenzylammonium chloride (4.50 g, 0.019 mmol, 1.40 equiv) and $POCl_3$ (25 mL). The reaction mixture was stirred for 4 h at 50 °C and then was cooled to room temperature. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (50 mL). Water (50 mL) was added slowly and the layers were separated. The organic layer was washed a second time with H_2O (100 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 2.67 g (93%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 5.19-5.05 (m, 2H), 1.48 (d, J=7.04 Hz, 6H).

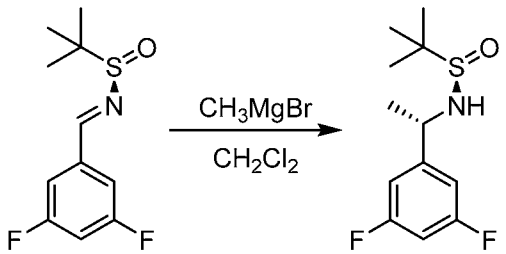


[0080] Compound 4. (*S*)-6-((1-(3-Chlorophenyl)ethyl)amino)-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a solution of **4.2** (150 mg, 0.70 mmol, 1 equiv) in DMF (2 mL) contained in a heavy wall pressure vessel were added (*S*)-3-chloro-α-methylbenzylamine (150 mg, 0.70 mmol, 1.0 equiv) and proton sponge (190 mg, 0.90 mol, 1.25 equiv). The pressure vessel was sealed and the reaction mixture was heated to 95 °C for 3 h behind a blast shield. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC utilizing a Shimadzu, Prominence LC-20AP system equipped with a Phenomenex Gemini-NX C18 column (eluting with 10-90% CH_3CN/H_2O in 30 min., 20 mL/min (both containing 0.1% TFA)). The fractions containing pure compound were combined and lyophilized to provide 30 mg (13%) of the title compound as a white solid. LC/MS: m/z (ES+) 326 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 9.47 (br s, 1H), 7.35-7.27 (m, 3H), 7.22-7.16 (m, 1H), 5.12 (m, 1H), 4.89 (m, 1H), 4.69 (d, J = 5.9 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.43 (m, 6H).

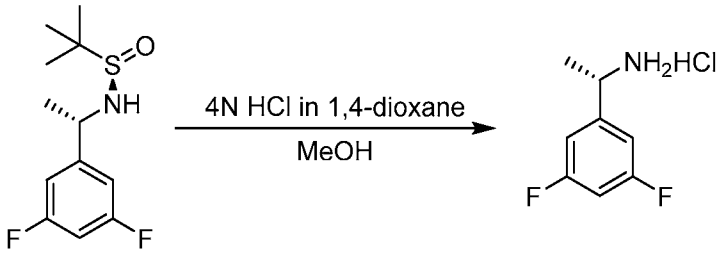
Example 5. Preparation of (*S*)-6-((1-(3,5-Difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



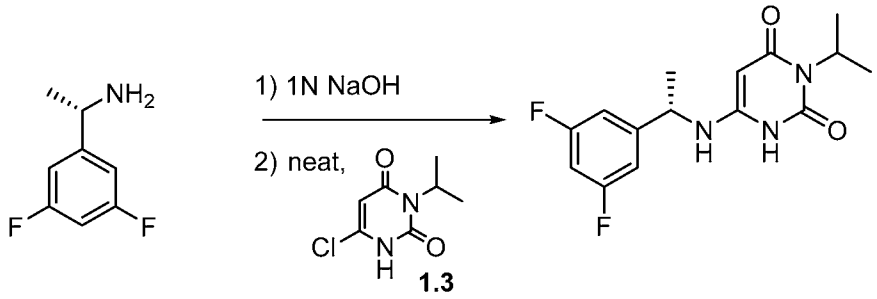
[0081] Compound 5.1. ((*R*,E)-N-(3,5-difluorobenzylidene)-2-methylpropane-2-sulfinamide. To a solution of 3,5-difluorobenzaldehyde (1.00 g, 7.04 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) were added pyridinium p-toluenesulfonate (0.089 g, 0.35 mmol, 0.05 equiv), (*R*)-(+)-2-methylpropane-2-sulfinamide (0.852 g, 7.03 mmol, 1.00 equiv), and $MgSO_4$ (4.2 g, 35.00 mmol, 5.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to provide 500 mg (29%) of the title compound as a yellow oil.



[0082] Compound 5.2. (*R*)-N-((*S*)-1-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide. Methylmagnesium bromide (5.17 mL, 3M, 2.00 equiv) was added dropwise to a solution of **5.1** (1.9 g, 7.75 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) under argon at -48 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was carefully quenched with a saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide 1.3 g (64%) of the title compound as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 6.92-6.81 (m, 2H), 6.75-6.65 (m, 1H), 4.65-4.55, (m, 1H), 3.46-3.42 (m, 1H), 1.53-1.44 (m, 3H), 1.26-1.22 (m, 9H).

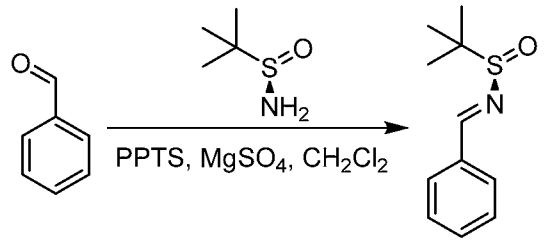


[0083] Compound 5.3. (*S*)-1-(3,5-Difluorophenyl)ethan-1-amine hydrochloride. To a solution of **5.2** (1.3 g, 4.97 mmol, 1.00 equiv) in CH_3OH (10 mL) was added 4N HCl in 1,4-dioxane (2.67 mL, 2.00 equiv). The reaction mixture was stirred for 0.5 h at room temperature and then was concentrated under reduced pressure. The resulting residue was dissolved in CH_3OH (3 mL) and Et_2O (300 mL) was added. The resulting precipitate was isolated by filtration to provide 0.80 g (83%) of the title compound. ^1H NMR (300 MHz, D_2O): δ ppm 6.98-6.83 (m, 3H), 4.45-4.38 (m, 1H), 1.51-1.48 (d, J = 6.9 Hz, 3H).

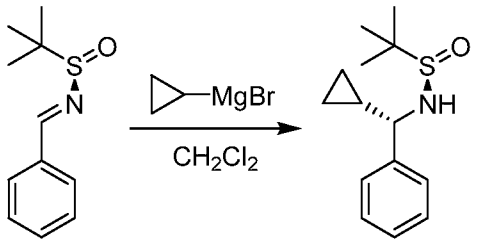


[0084] Compound 5. (*S*)-6-((1-(3,5-Difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. Compound **5.3** (50 mg, 0.32 mmol, 1.00 equiv) was dissolved in 1N NaOH (10mL), and the resulting mixture was stirred at 25 °C. After 1 h, the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue and compound **1.3** (35.6 mg, 0.19 mmol, 0.60 equiv) were combined. The mixture was stirred at 100 °C for 18 h, then was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC to provide 28 mg (29%) of the title compound as an off white solid. LC/MS: m/z (ES+) 310 $(M+H)^+$. ^1H-NMR (300 MHz, DMSO-d_6): δ ppm 9.83 (s, 1H), 7.06-7.12 (m, 3H), 6.54 (d, J = 6.6 Hz, 1H), 4.91-4.82 (m, 1H), 4.54-4.46 (m, 1H), 4.30 (m, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.9 Hz, 6H).

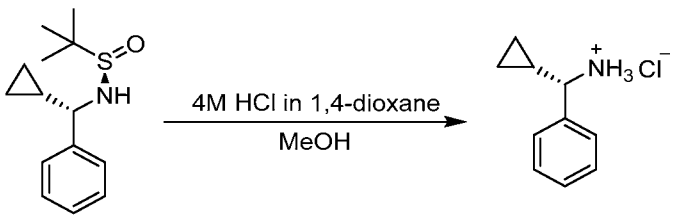
Example 6. Preparation of (*S*)-6-((Cyclopropyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0085] Compound 6.1. (*R*,E)-N-benzylidene-2-methylpropane-2-sulfinamide. The title compound was prepared in the same manner as **5.1** except benzaldehyde (5.0 g, 47.12 mmol, 1.00 equiv) was used in place of 3,5-difluorobenzaldehyde to provide 2.8 g (28%) of the title compound. ^{1}H NMR (300 MHz, d_6-DMSO): δ ppm 8.62 (s, 1H), 7.89-7.87 (m, 2H), 7.55-7.49 (m, 3H), 1.31 (s, 9H).

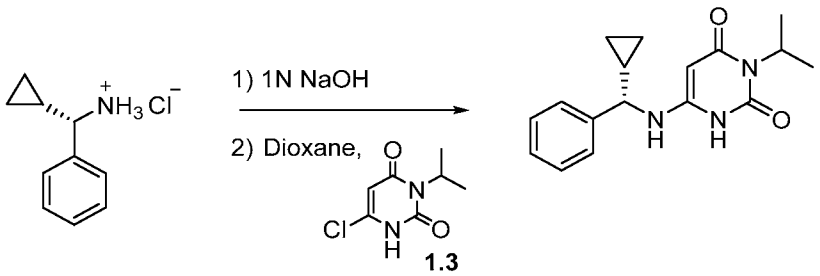


[0086] Compound 6.2. (*S*)-N-((*S*)-Cyclopropyl(phenyl)methyl)-2-methylpropane-2-sulfinamide. The title compound was prepared using a protocol similar to that used for the preparation of **5.2** except **6.1** (1.0 g, 4.78 mmol, 1.00 equiv) and cyclopropylmagnesium bromide (9.6 mL, 1M, 2.00 equiv) were used in place of **5.1** and methylmagnesium bromide to provide 0.5 g (35%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 7.36-7.23 (m, 5H), 3.67-3.51 (m, 2H), 1.31 (m, 10H), 0.85-0.15 (m, 4H).



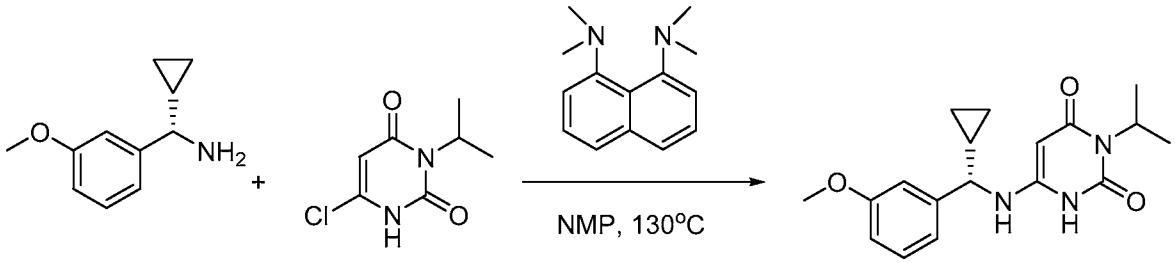
[0087] Compound 6.3. (*S*)-Cyclopropyl(phenyl)methanamine hydrochloride. The title compound was prepared using a protocol similar to that used for the preparation of **5.3** except **6.2** (500 mg, 1.69 mmol, 1.00 equiv) was used in place of **5.2** to provide 220 mg (88%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, d_6-DMSO): δ ppm 7.37-7.31 (m, 5H),

3.53 (d, J = 10.0 Hz, 1H), 1.37-1.25 (m, 1H), 0.75-0.55 (m, 1H), 0.53-0.31 (m, 2H), 0.25-0.15 (m, 1H).



[0088] Compound 6. (*S*)-6-((Cyclopropyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. The title compound was prepared using a procedure similar to that used for the preparation of **5** except **6.3** (200 mg, 1.36 mmol, 1.00 equiv) was used instead of **5.3** and 1,4-dioxane was utilized as a solvent. After concentration under reduced pressure, purificaiton utilizing a chiral HPLC (Phenomenex Lux 5μ Cellulose-4, 2.12*25, 5 μm column) with an isocratic mixture of EtOH: Hexane (1: 4) as eluent provided 22 mg (5%) of the title compound as a white solid. LC/MS: m/z (ES+) 300 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 9.82 (s, 1H), 7.39-7.25 (m, 5H), 7.25-7.32 (m, 1H), 6.72 (m, 1H), 4.90 (m, 1H), 4.22 (s, 1H), 3.78 (m, 1H), 1.27 (m, 6H), 1.57 (m, 1H), 0.60 (m, 1H), 0.56-0.32 (m, 2H).

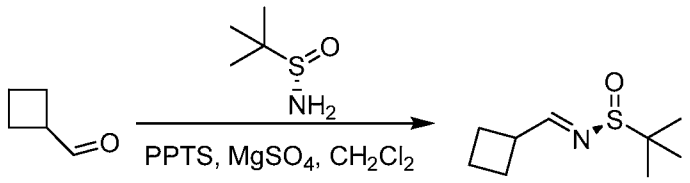
Example 7. Preparation of (*S*)-6-((cyclopropyl(3-methoxyphenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



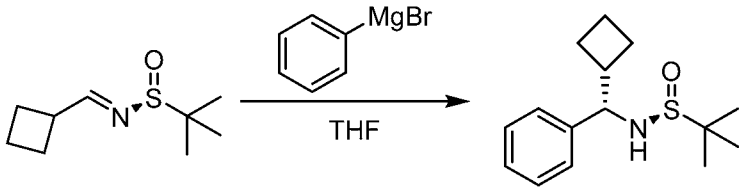
[0089] A solution of 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione (**1.3**, 50 mg, 0.265 mmol), (*S*)-cyclopropyl-(3-methoxyphenyl)methylamine (Sigma-Aldrich, 104 mg, 0.587 mmol), and proton sponge (85 mg, 0.397 mmol) in NMP (0.5 mL) was stirred at 130 °C for 2 h. After cooling to room temperature, the mixture was purified by preparative RP-HPLC (Shimadzu, Prominence LC-20AP system equipped with a Phenomenex Gemini-NX C18 column), eluting with 20-90% CH_3CN in H_2O (both containing 0.1% TFA). The fractions containing pure compound were combined and lyophilized to give 10 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES+) 330 $(M+H)^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ

ppm 7.26 (t, J = 7.8 Hz, H), 6.92-6.79 (m, 3H), 5.00 (m, 1H), 3.79 (s, 3H), 3.74 (d, J = 8.6 Hz, 1H), 1.36 (d, J = 7.0 Hz, 6H), 1.23-1.13 (m, 1H), 0.68-0.60 (m, 1H), 0.58-0.50 (m, 1H), 0.50-0.42 (m, 1H), 0.41-0.34 (m, 1H).

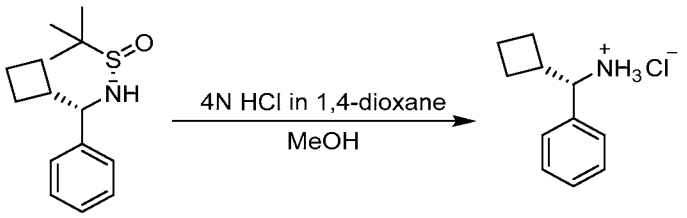
Example 8. Preparation of (*S*)-6-((Cyclobutyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



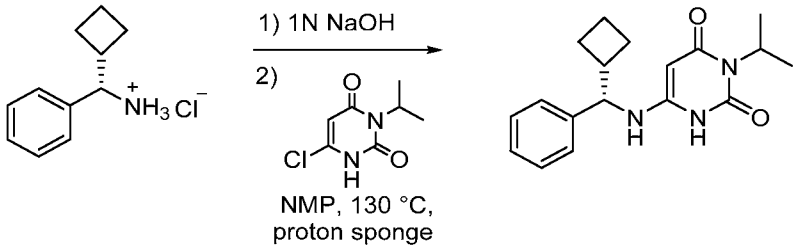
[0090] Compound 8.1. (*S*,E)-N-(cyclobutylmethylene)-2-methylpropane-2-sulfinamide. To a solution of cyclobutanecarbaldehyde (1.0 g, 11.89 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) were added pyridinium p-toluenesulfonate (0.143 g, 0.57 mmol, 0.05 equiv), (*S*)-(-)-2-methylpropane-2-sulfinamide (1.22 g, 10.07 mmol, 0.85 equiv), and magnesium sulfate (7.14 g, 59.32 mmol, 5.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 30% EtOAc in petroleum ether) to provide 2.0 g (90%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (d, J = 10.8 Hz, 1H), 3.36-3.32 (m, 1H), 2.25-2.16 (m, 4H), 2.03-1.90 (m, 2H), 1.15 (s, 9H).



[0091] Compound 8.2. (*S*)-N-((*S*)-cyclobutyl(phenyl)methyl)-2-methylpropane-2-sulfinamide. Phenylmagnesium bromide (3M in Et_2O, 15.3 mL, 2.00 equiv) was added dropwise to a solution of **8.1** (4.3 g, 22.96 mmol, 1.00 equiv) in THF (40 mL). The reaction mixture was heated for 3 h at 65 °C. It was then cooled to room temperature and carefully quenched with a saturated aqueous NH_4Cl solution (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide 5.8 g (95%) of the title compound as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5H), 4.23 (d, J = 9.6 Hz, 1H), 2.73-2.68 (m, 1H), 1.95-1.60 (m, 6H), 1.14 (s, 9H).

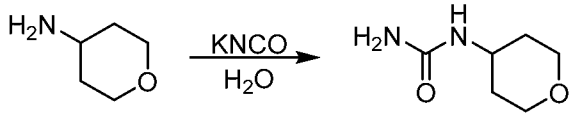


[0092] Compound 8.3. (*S*)-Cyclobutyl(phenyl)methanamine hydrochloride. The title compound was prepared using a procedure similar to that used for the preparation of **5.3** except **8.2** (5.8 g, 0.022 mol, 1.00 equiv) was used in place of **5.2** to provide 3.20 g (91%)of the title compound as a white solid. ^{1}H NMR (300 MHz, D_2O): δ ppm 7.36-7.28 (m, 5H), 4.18 (m, 1H), 2.87-2.73 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.69 (m, 5H).



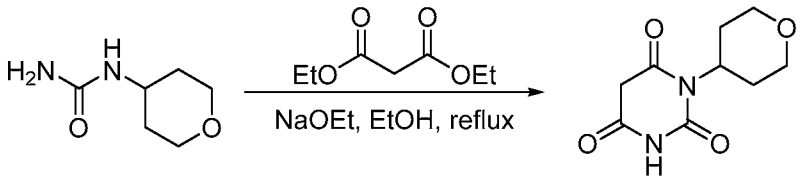
[0093] Compound 8. (*S*)-6-((Cyclobutyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. Compound **8.3** (0.200 g, 1.24 mmol, 1.00 equiv) was dissolved in 1N NaOH (10 mL), and was stirred for 1 h at 25 °C. The reaction mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was dissolved in NMP and combined with **1.3** and proton sponge and heated as described for the preparation of **7**. The title compound (35 mg, 9%) was isolated as a white solid. LC/MS: m/z (ES+) 314 $(M+H)^+$. ^{1}H NMR (300 MHz, CD_3OD): δ ppm 7.38-7.26 (m, 5H), 5.08-4.97 (m, 1H), 4.25 (d, J = 6.9 Hz, 1H), 2.68-2.58 (m, 1H), 2.19-2.13 (m, 1H), 1.98-1.83 (m, 5H), 1.36 (d, J = 6.9 Hz, 6H).

Example 9. Preparation of (*S*)-6-((1-phenylethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione.

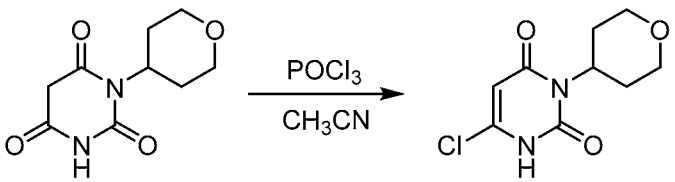


[0094] Compound 9.1. 1-(tetrahydro-2H-pyran-4-yl)urea. A mixture of tetrahydro-2H-pyran-4-amine (5.0 g, 49.4 mmol, 1.0 equiv.) and potassium isocyanate (4.0 g, 49.5 mmol, 1.0 equiv.) was refluxed in H_2O (50mL) overnight. The reaction was cooled to room temperature and excess NaCl was added to help saturate the aqueous layer. The precipitate

was isolated by filtration to provide the desired product (1.28g, 8.88 mmol). The aqueous layer was washed with EtOAc (3x 15 mL) and then was concentrated and azeotroped with toluene (3 x 100 mL). The resulting solid was suspended in 1:4 CH_3OH:EtOAc (100 mL) and filtered a total of four times. The combined organics were concentrated under reduced pressure and combined with the isolated precipitate to provide 5.01 g (70%) of the title compound. LC/MS: m/z (ES+) 145 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.14 (d, J = 7.5 Hz, 1H), 5.47 (s, 2H), 3.85 (dt, J = 11.6, 3.6 Hz, 2H), 3.65-3.52 (m, 1H), 3.38 (td, J = 11.4, 2.2 Hz, 2H), 1.80-1.72 (m, 2H), 1.42-1.27 (m, 2H).

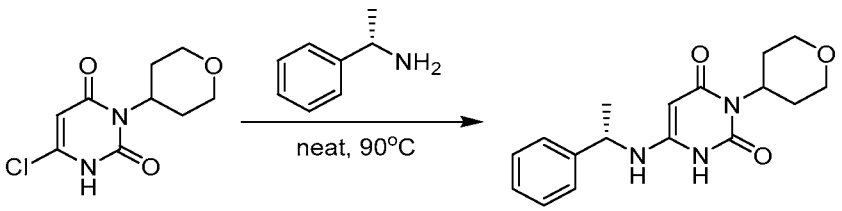


[0095] Compound 9.2. 1-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione. Compound **9.1** (2.8 g, 19.4 mmol) was dissolved in EtOH (30 mL), and diethyl malonate (2.45 mL, 21.4 mmol, 1.1 equiv.), and NaOEt (7.55 mL, 23.3 mmol, 1.2 equiv.) were added. The reaction was stirred at 85 °C overnight, and then was cooled to room temperature. The reaction mixture was diluted with H_2O (5 mL), and excess $KHSO_4$ was added to saturate the aqueous layer. The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 0-25% CH_3OH in CH_2Cl_2) to provide1.57 g of a mixture containing the title compound which was used without further purification. LC/MS: m/z (ES-) 211 $(M-H)^-$.



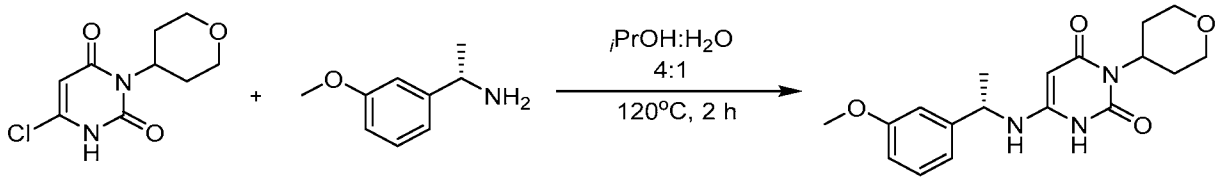
[0096] Compound 9.3. 6-chloro-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione. To a solution of **9.2** (1.57 g, 7.4 mmol, 1 equiv.) in CH_3CN (15 mL) was added $POCl_3$ (0.551 mL, 5.9 mmol, 0.8 equiv.). The reaction mixture was stirred at 80 °C overnight. An additional aliquot of $POCl_3$ (0.4 equiv.) was added and the reaction mixture was stirred at 80 °C for 3h. Additional aliquots of $POCl_3$ (0.4 equiv.) were added after 3 h

and 5 h of stirring at 80 °C. The reaction mixture was then stirred at 90 °C for 1h. The reaction was cooled to room temperature, concentrated, swirled with Et_2O (15 mL) and decanted. The resulting residue was rinsed with Et_2O (15 mL) and decanted until the Et_2O decanted clear. The resulting residue was carefully suspended in CH_3OH (10 mL), and filtered. The filtrate was concentrated to obtain a mixture of starting material and the title compound (~85% pure, 1.6 g). LC/MS: m/z (ES-) 229 $(M-H)^-$.



[0097] Compound 9. (*S*)-6-((1-phenylethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **9.3** (0.15 g, 0.65 mmol, 1 equiv.) and (*S*)-(-)-α-methylbenzylamine (470 mg, 3.88 mmol, 6.0 equiv.) was stirred overnight at 90 °C. The reaction mixture was cooled to room temperature and the resulting residue was purified by preparative RP-HPLC (0-40% CH_3CN in H_2O in 30 min.), followed by a second purification on a preparatory TLC plate (2000 um) (7% CH_3OH in CH_2Cl_2) to provide 23 mg (11%) of the title compound. LC/MS: m/z (ES+) 316 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 10.23 (s, 1H), 7.40-7.32 (m, 4H), 7.31-7.17 (m, 1H), 6.93 (s, 1H), 4.84-4.71 (m, 1H), 4.56-4.43 (m, 1H), 4.35 (s, 1H), 3.93-3.78 (m, 2H), 3.28 (t, J = 12.1 Hz, 2H), 2.63-2.39 (m, 2H), 1.40 (d, J = 6.7 Hz, 3H), 1.35-1.16 (m, 2H).

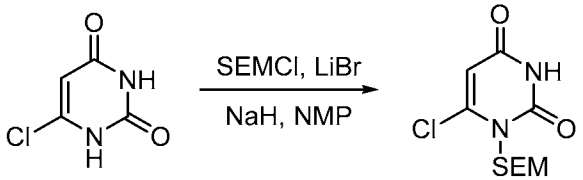
Example 10. Preparation of (*S*)-6-((1-(3-methoxyphenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione **(10).**



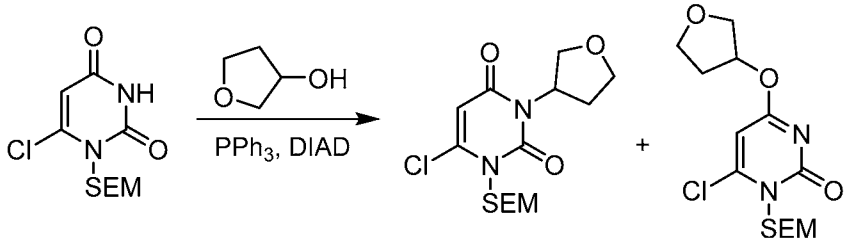
[0098] To a solution of **9.3** (0.58 g, 0.25 mmol) in a mixture of 2-propanol and H_2O (4:1, 1 mL) was added (*S*)-1-(3-methoxyphenyl)-ethylamine (0.113 g, 0.75 mmol, 3.0 equiv.). The reaction mixture was heated to 120 °C for 2 h. After cooling, the reaction mixture was concentrated under reduced pressure, dissolved in CH_3OH and filtered. The filtrate was purified by preparative RP-HPLC (20-100% CH_3CN in H_2O in 40 min. at 25 mL/min.) to

provide 18 mg (21%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 346 $(M+H)^+$. ^1H NMR (400 MHz, acetone-d_6) δ 8.90 (s, 1H), 7.15 (dd, J = 8.3, 8.1 Hz, 1H), 6.88 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.15 (s, 1H), 4.74 (m, 1H), 4.48 (m, 1H), 4.35 (s, 1H), 3.82 (m, 2H), 3.68 (s, 3H), 3.2 (m, 2H), 2.55 (m, 2H) 1.44 (d, J = 6.6 Hz, 3H) , 1.15 (m, 2H).

Example 11. Preparation of 6-(((*S*)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione.

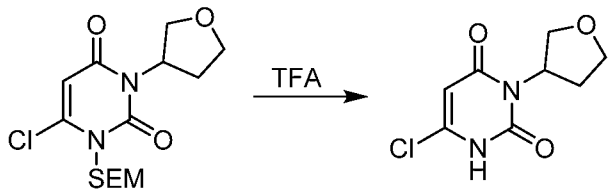


[0099] Compound 11.1. 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)pyrimidine-2,4(1H,3H)-dione. To a mixture of 6-chloro-uracil (3.0 g, 20.47 mmol, 1 equiv.) and LiBr (1.78 g, 20.5 mmol, 1.0 equiv.) in NMP (70 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.82 g, 20.5 mmol, 1.0 equiv.). The reaction mixture was stirred at 0 °C for 10 min, and 2-(trimethylsilyl)ethoxymethyl chloride (3.75g, 22.5 mmol, 1.1 equiv.) was slowly added via an addition funnel. The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (150 mL). The mixture was washed with a saturated aqueous NH_4Cl solution (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide 3.2 g (57%) of the title compound as a white solid. LC/MS: m/z (ES+) 299 $(M+Na)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 9.00-8.80 (br-s, 1H), 5.95 (s, 1H), 5.45 (s, 2H)), 3.63 (t, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 2H), 0.01 (s, 9H).

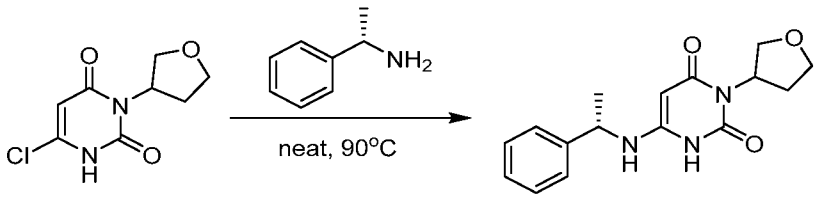


[0100] Compound 11.2. 6-chloro-3-(tetrahydrofuran-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrimidine-2,4(1H,3H)-dione. To a solution of **11.1** (277 mg, 1.0 mmol, 1 equiv.), 3-hydroxytetrahydrofuran (106 mg, 1.2 mmol, 1.2 equiv.), and triphenylphosphine (320 mg, 1.2 mmol, 1.2 equiv.) in THF (7.5 mL) at 0 °C, was added

diisopropyl azodicarboxylate (0.240 g, 1.2 mmol, 1.2 equiv.) dropwise. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by preparative RP-HPLC (20-100% CH_3CN in H_2O with 0.1% formic acid buffer in 40 min. at 25 mL/min.) to provide 102 mg (29%) of the title compound. LC/MS: m/z (ES+) 347 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 5.58 (m, 1H), 5.41(s, 2H), 4.20 (m, 1H), 4.00-3.85 (m, 3H), 3.65 (t, J = 7.0 Hz, 2H), 2.35-2.20 (m, 1H), 2.20-2.08 (m, 1H), 0.95 (t, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.7, 150.7, 145.6, 102.0, 74.8, 68.7, 67.9, 67.5, 51.9, 28.7, 18.0, 0.0.

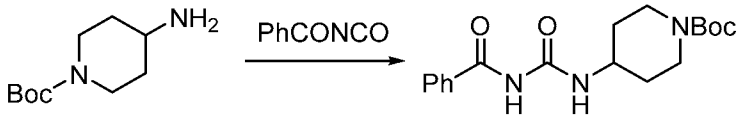


[0101] Compound 11.3. 6-chloro-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione. Compound **11.2** (0.50 g, 1.4 mmol, 1.0 equiv.) was dissolved in trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 30 minutes and then was concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC (10% CH_3CN in H_2O in 40 min. at 25 mL/min.) to provide 300 mg (96%) of the title compound as a white solid. LC/MS: m/z (ES+) 217 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 5.90 (s, 1H), 5.35 (m, 1H), 4.00 (m, 1H), 3.85-3.68 (m, 3H), 2.20 (m, 1H), 2.01 (m, 1H).

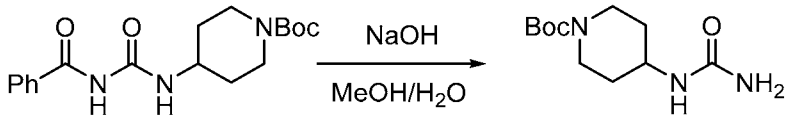


[0102] Compound 11. 6-(((*S*)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione. The title compound was prepared using a procedure similar to that used for the preparation of **9** except **11.3** (22 mg, 0.10 mmol, 1.00 equiv) was used in place of **9.3** to provide 15 mg (50%) of the title compound as a white solid. LC/MS: m/z (ES+) 302 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 10.50 (1H), 7.50-7.20 (m, 5H), 5.90 (m, 1H), 5.60 (m, 1H), 4.78 (m, 1H), 4.45 (s, 1H), 4.20 (m, 1H), 4.05-3.90 (m, 2H), 3.90-3.80 (m, 1H), 2.45-2.10 (m, 2H), 1.55 (d, J = 6.7 Hz, 3H).

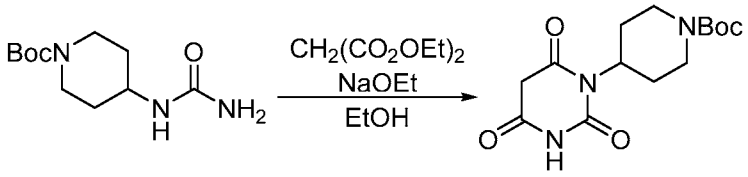
Example 12. Preparation of (*S*)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-(1-phenylethylamino)pyrimidine-2,4(1H,3H)-dione.



[0103] Compound 12.1. tert-Butyl 4-(3-benzoylureido)piperidine-1-carboxylate. To a solution of benzoylisocyanate (4.8 g, 32.6 mmol) in CH_2Cl_2 (180 mL) at 0 °C was added 4-amino-1-N-boc-piperidine (6.0 g, 30 mmol). The reaction mixture was stirred at room temperature for 4 h and concentrated. The residue was treated with Et_2O (100 mL). The precipitate was filtered and washed with Et_2O to yield 5.70 g (55%) of the title compound as a white solid. LC/MS: m/z (ES+) 337 $(M+H)^+$.

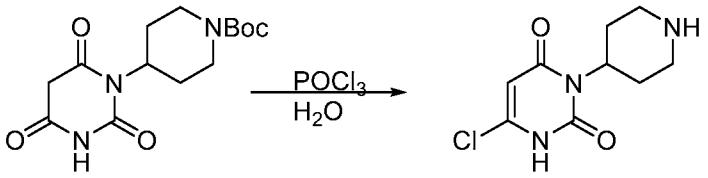


[0104] Compound 12.2. tert-Butyl 4-ureidopiperidine-1-carboxylate. To a mixture of **12.1** (5.60 g, 16.1 mmol) in CH_3OH (70 mL) and H_2O (70 mL) was added sodium hydroxide (11.6 g, 290 mmol) portionwise. The reaction mixture was stirred at room temperature overnight and then refluxed for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure to remove CH_3OH. The precipitate was filtered, washed with H_2O, and dried to yield 3.2 g (82%) of the title compound as a white solid. LC/MS: m/z (ES+) 266 $(M+Na)^+$.

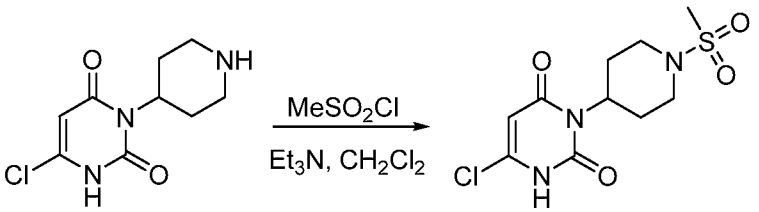


[0105] Compound 12.3. tert-Butyl 4-(2,4,6-trioxo-tetrahydropyrimidin-1(2H)-yl)piperidine-1-carboxylate. To a mixture of **12.2** (3.63 g, 14.9 mmol), diethylmalonate (2.6 mL, 16.5 mmol, 1.1 equiv.) and anhydrous ethanol (60 mL) was added NaOEt (21% in EtOH, 6.6 mL, 17.7 mmol, 1.2 equiv.). The mixture was refluxed for 14 h and concentrated. The residue was taken up in H_2O (15 mL) and washed with EtOAc (2 x 30 mL). The aqueous layer was separated and adjusted to pH=5 with concentrated. HCl. The precipitate was

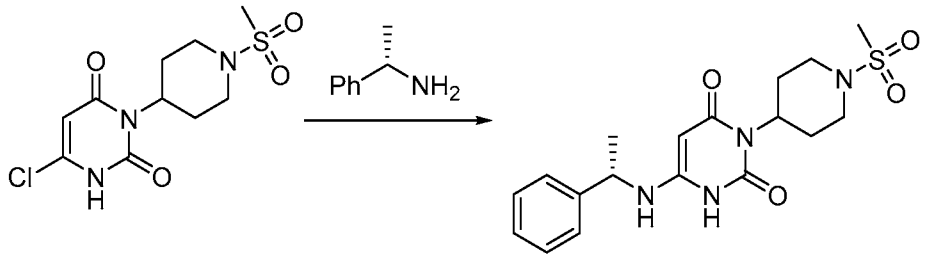
filtered, washed with H_2O and dried to give 3.70 g (80%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 334 $(M+Na)^+$.



[0106] Compound 12.4. 6-chloro-3-(piperidin-4-yl)pyrimidine-2,4(1H,3H)-dione. To a mixture of **12.3** (2.55 g, 8.19 mmol) and $POCl_3$ (10 mL, 100.65 mmol) was added H_2O (0.41 mL, 22.78 mmol) dropwise. The mixture was stirred at 120 °C for 30 min and then concentrated. The residue was carefully taken up in ice water (20 g). To the mixture was added K_2CO_3 (~8.0 g) portionwise until the pH was ~7. The precipitate was filtered, washed with H_2O (20 mL) and EtOAc (50 mL). The resulting material was dried to yield 1.45 g (77%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 230 $(M+H)^+$.

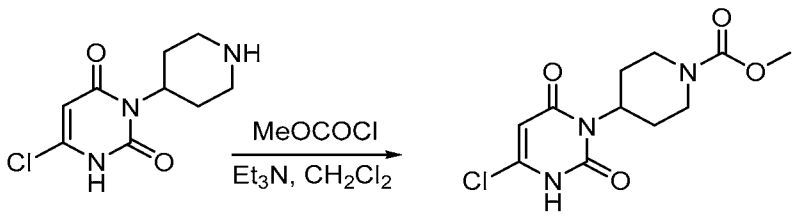


[0107] Compound 12.5. 6-chloro-3-(1-(methylsulfonyl)piperidin-4-yl)pyrimidine-2,4(1H,3H)-dione. To a mixture of **12.4** (380 mg, 1.65 mmol, 1.0 equiv.) and CH_2Cl_2 (8 mL) was added Et_3N (0.70 mL, 4.95 mmol, 3 equiv.) and methanesulfonyl chloride (0.23 mL, 2.5 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 2 h and then quenched with H_2O (3 mL) to yield precipitate. The precipitate was filtered and washed with CH_2Cl_2 (3 x 3 mL). The filtrate was concentrated to ~ 1.5 mL. Filtration of a second precipitate was followed by washing with H_2O (2 x 1 mL) and CH_2Cl_2 (3 x 2 mL). The precipitates were combined to afford 320 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 308 $(M+H)^+$.

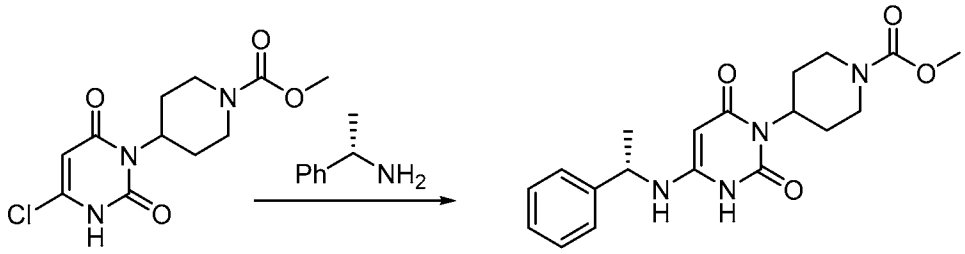


[0108] Compound 12. (*S*)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-(1-phenylethylamino)pyrimidine-2,4(1H,3H)-dione. A mixture of **12.5** (20 mg, 0.065 mmol) and (*S*)-α-methylbenzylamine (180 mg, 1.5 mmol, 23 equiv.) was stirred at 125 °C for 1 h. The mixture was concentrated under reduced pressure, dissolved in CH_3OH and filtered. The filtrate was purified using preparative RP-HPLC eluting with linear gradient 20% to 100% CH_3CN in H_2O (0.1% formic acid buffer) over 40 min to give 16 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 393 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.40 (br s, 1H), 7.35-7.25 (m, 4H), 7.15 (m, 1H), 6.55 (s, 1H), 4.58 (m, 1H), 4.42 (m, 1H), 4.30 (s, 1H), 3.52 (m, 2H), 2.79 (s, 3H), 2.70 -2.62 (m, 2H), 2.50-2.48 (m, 2H), 1.48-1.38 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H).

Example 13. Preparation of (*S*)-methyl 4-(2,6-dioxo-4-(1-phenylethylamino)-2,3-dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate.

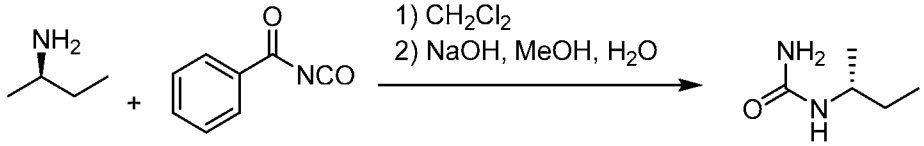


[0109] Compound 13.1. Methyl 4-(4-chloro-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate. To a mixture of **12.4** (115 mg, 0.5 mmol, 1.0 equiv.) and CH_2Cl_2 (2 mL) was added Et_3N (0.14 mL, 1.5 mmol, 3.0 equiv.), followed by methyl chloroformate (95 mg, 1.0 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (8 mL), washed with a saturated aqueous $NaHCO_3$ solution (1 mL), H_2O (1 mL), brine (1 mL), dried with anhydrous Na_2SO_4 and concentrated to yield 105 mg (73%) of an off-white solid. LC/MS: m/z (ES+) 288 $(M+H)^+$.

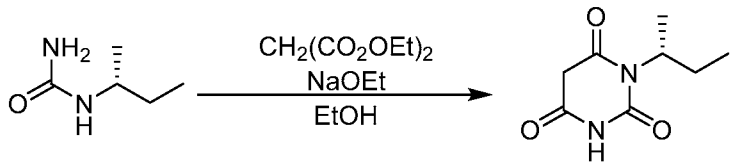


[0110] Compound 13. (*S*)-methyl 4-(2,6-dioxo-4-(1-phenylethylamino)-2,3-dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate. A mixture of **13.1** (58 mg, 0.20 mmol) and (*S*)-α-methylbenzylamine (240 mg, 1.5 mmol) was stirred at 120 °C for 0.5 h. The title compound was prepared using a procedure similar to that used for the preparation of **9** to provide 40 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 373 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.85 (s, 1H), 7.29-7.15 (m, 5H), 5.75 (br s, 1), 4.80 (m, 1H), 4.60 (s, 1H), 4.35 (m, 1H), 4.20 - 4.00 (m, 2H), 3.58 (s, 3H), 2.80 - 2.70 (m, 2H), 2.46 (m, 2H), 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H).

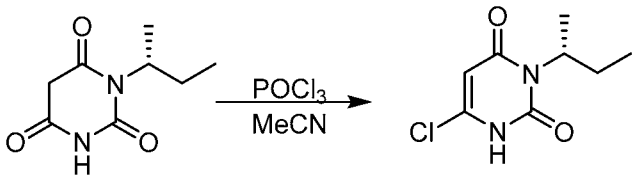
Example 14. Preparation of 3-(*R*)-sec-butyl-6-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidine-2,4(1H,3H)-dione.



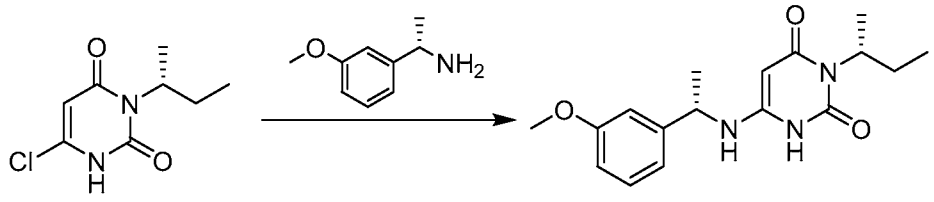
[0111] Compound 14.1. (*R*)-1-sec-butylurea. Benzoyl isocyanate (5.36 g, 36.5 mmol, 1.05 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C in an ice bath. (*R*)-butan-2-amine (2.54 g, 34.7 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was carefully added while stirring. The mixture was allowed to stir for 3 h at room temperature. After the reaction was deemed complete, the mixture was concentrated. The residue was suspended in Et_2O (20 mL) and filtered. The solid was taken up in a 1:1 mixture of CH_3OH and H_2O (200 mL) followed by the addition of NaOH (6.9 g, 174 mmol, 5 equiv.). The reaction was stirred overnight at room temperature. The CH_3OH was evaporated from the solution and the resulting precipitate (1.66g, 39%) was collected. LC/MS: m/z (ES+) 117 $(M+H)^+$.



[0112] Compound 14.2. (*R*)-1-sec-butylpyrimidine-2,4,6(1H,3H,5H)-trione. Compound **14.1** (1.66 g, 14.3 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL) , and diethyl malonate (1.8 mL, 15.7 mmol, 1.1 equiv.), and NaOEt (5.6 mL, 17.1 mmol, 1.2 equiv.) were added. The reaction was stirred at 80 °C for 2 h and then cooled to room temperature. Water (20 mL) was added and then EtOH was removed by evaporation. $KHSO_4$ (excess) was added to saturate the aqueous layer which was then extracted with EtOAc. The combined organics were dried with anhydrous $MgSO_4$ and concentrated to yield 1.6 g (61%) of the title compound as a crude residue which was used without further purification. LC/MS: m/z (ES-) 183 $(M-H)^-$.



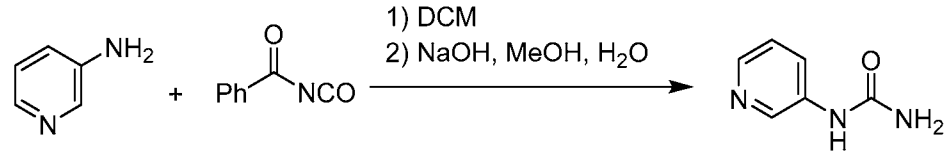
[0113] Compound 14.3. (*R*)-3-sec-butyl-6-chloropyrimidine-2,4(1H,3H)-dione. A mixture of **14.2** (1.6 g, 8.7 mmol, 1 equiv.) and $POCl_3$ (648 μL, 7.0 mmol, 0.8equiv.) in CH_3CN (10 mL) was stirred at 90 °C for 2 h. Additional $POCl_3$ (0.8 equiv.) was added and stirred at 90 °C for 3 h. The reaction was cooled to room temperature, carefully quenched with CH_3OH (10 mL), stirred for 30 minutes and purified with normal phase HPLC 0-25% CH_3OH/CH_2Cl_2 followed by a CH_3OH flush. The product and starting material co-eluted. The mixture was concentrated, the residue was taken up in CH_3CN (10 mL) and $POCl_3$ (648 uL) was added. The reaction was stirred at 90 °C for 3 h and then cooled to room temperature. The reaction was carefully quenched with CH_3OH (10 mL) and stirred for 30 minutes. The reaction mixture was purified by normal phase HPLC with previous condition, concentrated and dried under vacuum to yield 450 mg (32%) of the title compound as an off-white solid. LC/MS: m/z (ES-) 201 $(M-H)^-$.



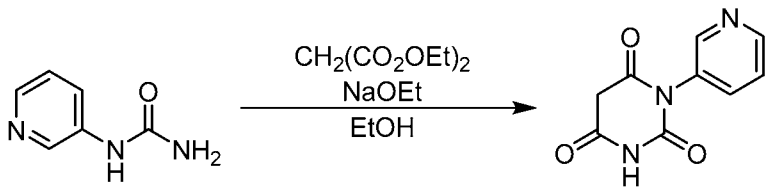
[0114] Compound 14. 3-(R)-sec-butyl-6-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidine-2,4(1H,3H)-dione. A mixture **14.3** (150 mg, 0.74

mmol, 1.0 equiv.) in neat (*S*)-1-(3-methoxyphenyl)ethanamine (400 uL) was stirred overnight at 90 °C. The reaction was purified using preparative RP-HPLC on an Agilent system with a gradient of 0-40% CH_3CN in H_2O over 45 min to yield 13 mg (6%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 318 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.79 (s, 1H), 7.28 (t, J = 8.1 Hz, 1H), 6.94-6.88 (m, 2H), 6.84 (dd, J = 8.2, 1.7 Hz, 1H), 6.51 (d, J = 6.4 Hz, 1H), 4.72-4.59 (m, 1H), 4.47 (m, 1H), 4.35 (s, 1H), 3.76 (s, 3H), 1.98-1.84 (m, 1H), 1.61 (m, 1H), 1.39 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 0.70 (t, J = 7.4 Hz, 3H).

Example 15. Preparation of (*S*)-6-(1-phenylethylamino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione.

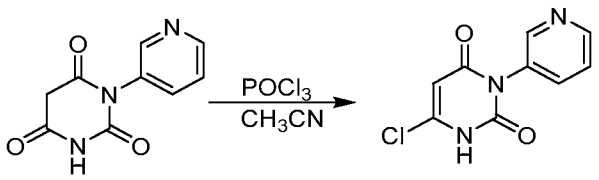


[0115] Compound 15.1. 1-(pyridin-3-yl)urea. Benzoyl isocyanate (3.28 g, 22.3 mmol, 1.05 equiv.) was taken up in CH_2Cl_2 (30 mL) and cooled to -10 °C. Pyridin-3-amine (2 g, 21.2 mmol, 1 equiv.) was added in portions while stirring. The mixture was allowed to stir for 3 h at room temperature. After the reaction was deemed complete, it was concentrated and then taken up in a 1:1 mixture of CH_3OH and H_2O (100 mL) followed by the addition of NaOH (4.25 g, 106.3 mmol, 5 equiv.). The reaction was allowed to stir overnight at room temperature, concentrated to dryness, and then azeotroped three times with toluene. A mixture of 10% CH_3OH in EtOAc (100mL) was added to the solid and stirred for 10 minutes followed by filtration. The solid was suspended and filtered two additional times. The combined filtrates were filtered once more to remove any solids that passed through the filter and concentrated. The residue was triturated with EtOAc (5 mL) and dried under vacuum to yield 3.5 g of crude material (off-white solid) that was utilized without further purification. LC/MS: m/z (ES+) 138 $(M+H)^+$.

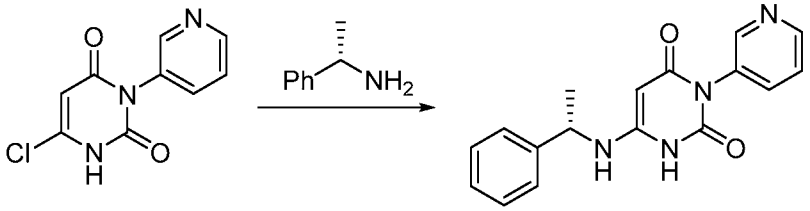


[0116] Compound 15.2. 1-(pyridin-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione. Compound **15.1** (3.0 g, 21.8 mmol, 1.0 equiv.) was taken up in EtOH (20 mL), followed by

the addition of diethyl malonate (2.75 mL, 24.1 mmol, 1.1 equiv.), and NaOEt (8.5 mL, 26.3 mmol, 1.2 equiv.). The reaction was stirred at 85°C overnight and then cooled to room temperature. Water (100 mL) was added slowly followed by careful addition of sodium bicarbonate (8 g). The resulting mixture was washed three times with EtOAc. The aqueous layer was concentrated to 50 mL and CH_3OH (150 mL) was added. The precipitate was removed by filtration and the filtrate was concentrated. The resulting residue was purified flash chromatography (silica gel, 0-25% CH_3OH/CH_2Cl_2) to yield 1.70 g (38%) of the title compound as a light yellowish solid. LC/MS: m/z (ES+) 206 $(M+H)^+$.



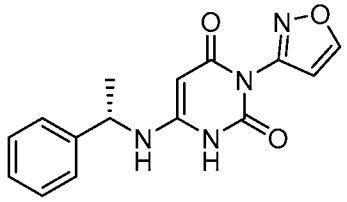
[0117] Compound 15.3. 6-chloro-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **15.2** (700 mg, 3.41 mmol, 1.0 equiv.) and $POCl_3$ (255 µL, 2.7 mmol, 0.8 equiv.) in CH_3CN (10 mL) was stirred at 90 °C for 2 h. Additional $POCl_3$ (0.8 equiv) was added and stirring was continued at 90 °C for 2 h. Additional $POCl_3$ (1.6 equiv.) was added followed by the careful addition of H_2O (150 ul 2.5 equiv.) The reaction was stirred overnight at 90 °C. After cooling to room temperature, the mixture was filtered and the solid was carefully washed with CH_3OH (1 mL). Ethyl acetate (20 mL) was added to the filtrate and the resulting precipitate was collected by filtration and dried under vacuum to yield 230 mg (30%) of the title compound as a light yellowish solid. LC/MS: m/z (ES+) 224 $(M+H)^+$.



[0118] Compound 15. (*S*)-6-(1-phenylethylamino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **15.3** (100 mg, 0.45 mmol, 1 equiv.) in neat (*S*)-(-)-α-methylbenzylamine (500 uL) was stirred overnight at 100 °C. After cooling, the reaction was purified using preparative RP-HPLC on an Agilent system with a gradient of 0-40% CH_3CN in H_2O over 45 min., followed by a second purification on a preparatory TLC plate (2000 um) with 7% CH_3OH /CH_2Cl_2 to yield 39.5 mg (28%) of the title compound. LC/MS: m/z

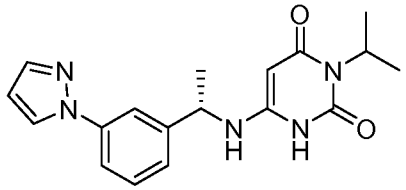
(ES+) 309 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 11.15 (s, 1H), 8.49 (dd, J = 4.8, 1.4 Hz, 1H), 8.34 (d, J = 2.4 Hz, 1H), 7.65-7.58 (m, 1H), 7.44 (dd, J = 8.1, 4.8 Hz, 1H), 7.37 (m, 5H), 7.26 (m, 1H), 4.61-4.53 (m, 1H), 4.48 (s, 1H), 1.39 (d, *J* = 6.8 Hz, 3H).

Example 16. Preparation of (*S*)-3-(Isoxazol-3-yl)-6-(1-phenylethylamino)pyrimidine-2,4(1H,3H)-dione (**16**).



[0119] The title compound was prepared using procedures similar to those used for the preparation of compound **15** except isoxazol-3-amine was used in place of pyridin-3-amine. LC/MS: m/z (ES+) 299 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.96 (s, 1H), 7.38 (d, J = 3.9 Hz, 4H), 7.28 (dd, J = 8.4, 4.3 Hz, 2H), 7.10 (s, 1H), 6.63 (s, 1H), 4.74-4.52 (m, 1H), 4.48 (s, 1H), 1.44 (d, J = 6.6 Hz, 3H).

Example 17. Preparation of (*S*)-6-((1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione (**17**).

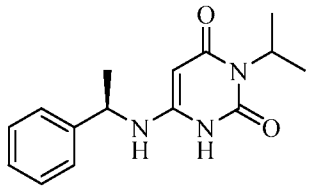
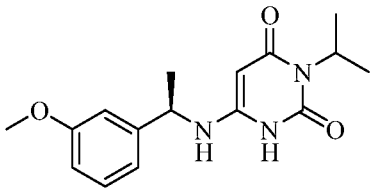
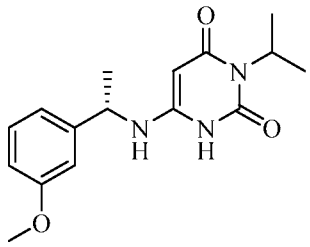
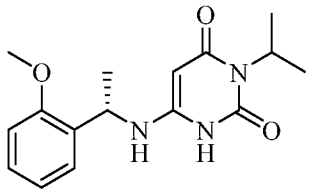
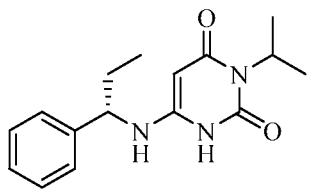


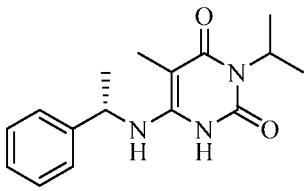
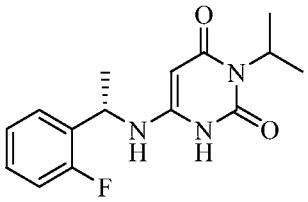
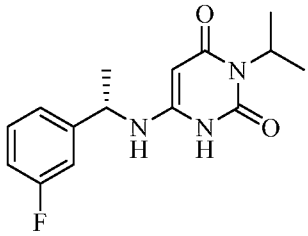
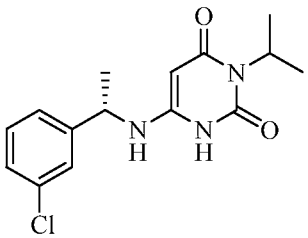
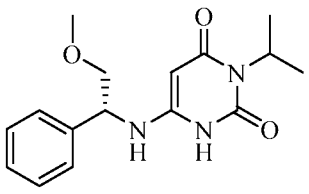
[0120] The title compound was prepared by Ullman coupling (P.E. Fanta. "The Ullmann Synthesis of Biaryls". *Synthesis,* 1974, 9–21) of **35** with 1H-pyrazole in the presence of copper iodide, cesium carbonate, and trans-N,N′-dimethylcyclohexane-1,2-diamine. LC/MS: m/z (ES+) 340 $(M+H)^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 8.26 (s, 1H), 7.70 (m, 2H), 7.66 (m, 1H), 7.51 (m, 1H), 7.34 (m, 1H), 6.55 (s, 1H), 5.05 (m, 1H), 4.62 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.37 (m, 6H).

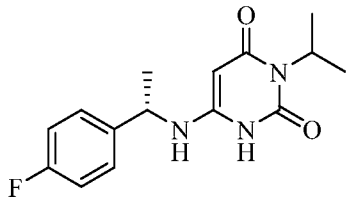
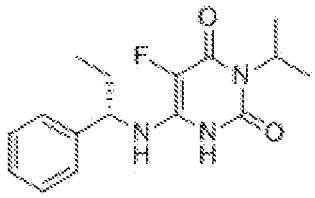
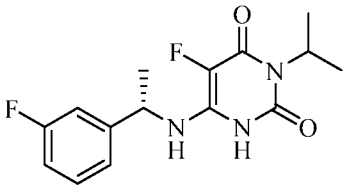
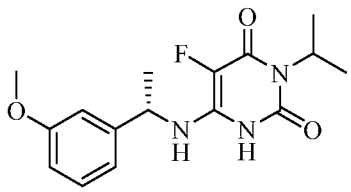
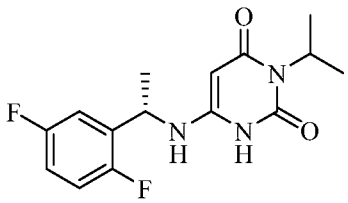
Example 18. Preparation of Additional Pyrimidine Dione Compounds.

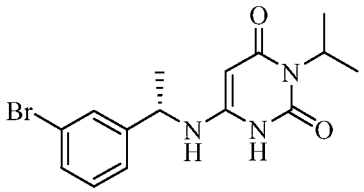
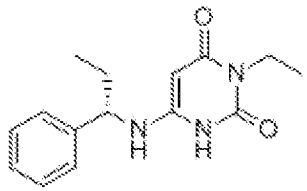
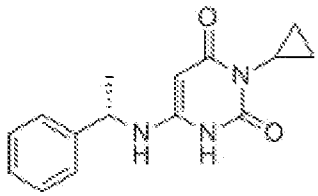
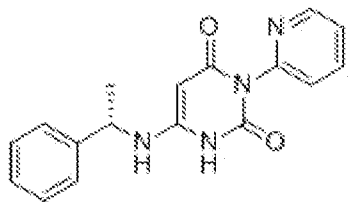
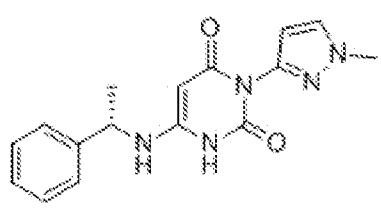
[0121] The compounds in Table 1 were prepared according to the examples as described above.

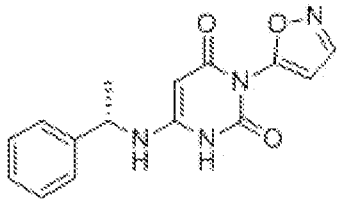
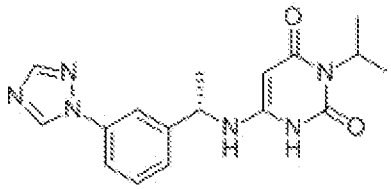
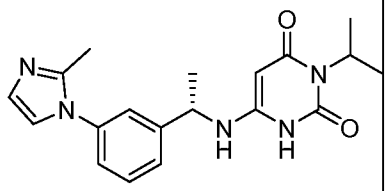
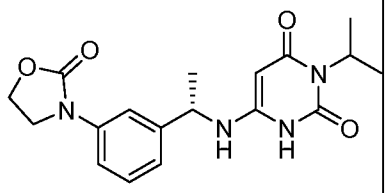
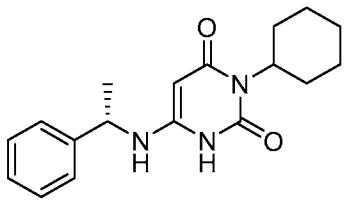
Table 1. Compounds and Analytical Data

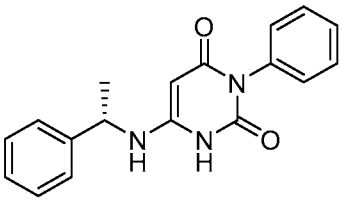
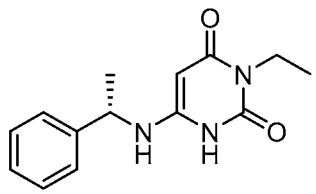
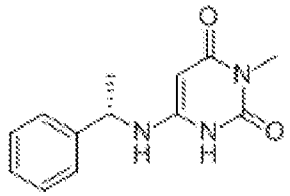
Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**19R** ---- 1	274 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.42 - 7.22 (m, 5H), 5.06 - 4.94 (m, 1H), 4.49 (m, 1H), 1.49 (d, J = 7.0 Hz, 3H), 1.36 (m, 6H).
	**20R** ---- 1	304 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.39 (br s, 1H), 7.29 - 7.23 (m, 1H), 6.88 - 6.79 (m, 3H), 5.31 (br s, 1H), 5.09 (m, 1H), 4.78 (br s, 1H), 4.48 - 4.34 (m, 1H), 3.80 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H), 1.44 - 1.38 (m, 6H).
	**21** ---- 1	304 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.26 (t, J = 7.9 Hz, 1H), 6.92 - 6.85 (m, 2H), 6.85 - 6.80 (m, 1H), 5.01 (m, 1H), 4.45 (d, J = 7.0 Hz, 1H), 3.79 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 6H).
	**22** ---- 1	304 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.29 - 7.17 (m, 1 H), 7.00 (d, J=7.4 Hz, 1 H), 6.93 (m, 1 H), 5.05 - 4.97 (m, 1 H), 4.83 (s, 1 H), 4.80 - 4.74 (m, 1 H), 3.89 (s, 3 H), 1.45 (d, J=6.7 Hz, 3 H), 1.38 - 1.34 (m, 6 H).
	**24** ---- 1	288 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.76 (br s, 1H), 7.41 - 7.13 (m, 5H), 6.50 (d, J = 7.0 Hz, 1H), 4.88 (m, 1H), 4.31 (d, J = 2.4 Hz, 1H), 4.24 (m, 1H), 1.83 - 1.58 (m, 2H), 1.35 - 1.10 (m, 6H), 0.83 (m, 3H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**25** ---- 1	288 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 7.46 - 7.29 (m, 4H), 7.27 - 7.21 (m, 1H), 6.27 (d, J = 9.0 Hz, 1H), 6.08 (br s, 1H), 5.13 (m, 1H), 4.98 (m, 1H), 1.78 (s, 3H), 1.46 (m, 3H), 1.29 (m, 6H).
	**26** ---- 1	292 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.45 (br s, 1H), 7.30 - 7.23 (m, 2H), 7.16 - 7.01 (m, 2H), 5.13 (dt, *J* = 13.8, 7.0 Hz, 1H), 4.99 (br s, 1H), 4.74 - 4.63 (m, 2H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.43 (m, 6H).
	**27** ---- 1	292 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.28 (br s, 1H), 7.36 - 7.28 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.02 - 6.93 (m, 2H), 5.17 - 5.04 (m, 1H), 4.95 – 4.82 (m, 1H), 4.75 -4.70 (m, 1H), 4.50 - 4.40 (m, 1H), 1.53 (d, J = 7.0 Hz, 3H), 1.46 - 1.37 (m, 6H).
	**28** ---- 1	308 $(M+H)^+$ ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.39 - 7.31 (m, 2H), 7.29 - 7.23 (m, 2H), 5.01 (m, 1H), 4.50 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 6H).
	**29** ---- 1	304 $(M+H)^+$ ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.38-7.26 (m, 5H), 5.04-4.97 (m, 1H), 4.56 (dd, J = 7.4, 3.9Hz, 1H), 3.67-3.63 (m, 1H), 3.56-3.51 (m, 1H), 3.37 (s, 3H), 1.36 (m, 6H).

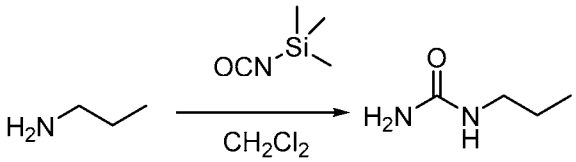
Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**30** ---- 1	292 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.34 (m, 2H), 7.08 (m, 2H), 5.07 - 4.95 (m, 1H), 4.50 (q, *J* = 6.8 Hz, 1H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.37 (m, 6H).
	**31** ---- 4 & 5	306 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.70 (br s, 1H), 7.39 - 7.22 (m, 5H), 5.19 - 5.07 (m, 1H), 4.85 (br s, 1H), 4.73 - 4.61 (m, 1H), 1.88 (dq, J = 14.3, 7.0 Hz, 2H), 1.45 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H).
	**32** ---- 4 & 5	310 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.89 (br s, 1 H), 7.40 - 7.29 (m, 1 H), 7.13 - 6.95 (m, 3 H), 5.12 (m, 1 H), 5.02 - 4.87 (m, 1 H), 4.82 - 4.69 (m, 1 H), 1.59 (d, J = 6.7 Hz, 3 H), 1.42 (m, 6 H),
	**33** ---- 4 & 5	322 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.50 (br s, 1H), 7.30 (dd, J = 9.00, 7.83 Hz, 1H), 6.93-6.90 (m, 3H), 5.19 - 5.04 (m, 1H), 4.88 (m, 1H), 4.75 (m, 1H), 3.79 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.43 (d, J = 7.0 Hz, 6H).
	**34** ---- 6	310 $(M+H)^+$ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.74 (s, 1H), 7.32 - 7.24 (m, 2H), 7.21 - 7.13 (m, 1H), 6.60 (s, 1H), 4.95 - 4.86 (m, 1H), 4.69 - 4.62 (m, 1H), 4.32 (s, 1H), 1.49 - 1.42 (d, J = 6.6 Hz, 3H), 1.28 - 1.26 (d, J = 6.9 Hz, 6H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**35** ---- 6	352 $(M+H)^+$ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.85 (s, 1H), 7.59 (s, 1H), 7.48 (m, 1H), 7.38 - 7.32 (m, 2H), 6.59 (d, J = 5.4 Hz, 1H), 4.95 - 4.88 (m, 1H), 4.57 - 4.50 (m, 1H), 4.36 (s, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H).
	**36** ---- 1 & 5	274 $(M+H)^+$ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.96 (br s, 1H), 7.39-7.24 (m, 5H), 6.58 (d, J = 6.6 Hz, 1H), 4.38 (s, 1H), 4.28 (q, J = 6.9 Hz, 1H), 3.65 (q, J = 6.6 Hz, 2H), 1.78-1.66 (m, 2H), 0.99 (t, J = 6.9 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H).
	**37** ---- 1 & 5	272 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.83 (s, 1H), 7.37 (m, 4H), 7.26 (m, 1H), 6.52 (m, 1H), 4.50 (m, 1H), 4.33 (s, 1H), 2.37 (m, 1H), 1.41 (d, J = 6.8 Hz, 3H), 0.85 (m, 2H), 0.60 (m, 2H).
	**38** ---- 15	309 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.92 (s, 1H), 8.57 – 8.42 (m, 1H), 7.85 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.46 – 7.31 (m, 5H), 7.32 – 7.19 (m, 2H), 7.13 (m, 1H), 4.67 – 4.52 (m, 1H), 4.41 (s, 1H), 1.39 (d, J = 6.8 Hz, 3H).
	**39** ---- 15	312 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 7.65 (d, J = 2.2 Hz, 1H), 7.41 – 7.35 (m, 5H), 7.32 – 7.24 (m, 1H), 6.77 (d, J = 5.9 Hz, 1H), 6.04 (d, J = 2.1 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.42 (s, 1H), 3.79 (s, 3H), 1.44 (d, J = 6.7 Hz, 3H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**40** ---- 15	299 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 11.07 (s, 1H), 8.93 (s, 1H), 7.43 – 7.31 (m, 4H), 7.31 – 7.04 (m, 2H), 6.59 (s, 1H), 4.62 (m, 1H), 4.43 (s, 1H), 1.40 (d, J = 6.7 Hz, 3H).
	**41** ---- 17	341 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.42 (s, 1H), 8.67 (s, 1H), 8.13 (s, 1H), 7.71 (s, 1H), 7.61 (m, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 5.41 (m, 1H), 5.13 (m, 1H), 4.68 (m, 1H), 4.55 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H), 1.44 (m, 6H).
	**42** ---- 17	354 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.85 (s, 1H), 7.52 (m, 1H), 7.39 (m, 2H), 7.34 (m, 2H), 6.94 (m, 1H), 6.60 (m, 1H), 4.90 (m, 1H), 4.62 (m, 1H), 4.38 (s, 1H), 2.26 (s, 3H), 1.44 (d, J = 9.2 Hz, 3H), 1.28 (d, J = 9.2 Hz, 6H).
	**43** ---- 17	359 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.84 (s, 1H), 7.62 (s, 1H), 7.42 (m, 2H), 7.12 (d, J = 7.2 Hz, 1H), 6.61 (bs, 1H), 4.91 (m, 1H), 4.69 – 4.43 (m, 3H), 4.34 (s, 1H), 4.09 (m, 2H), 1.42 (d, J = 6.8Hz, 3H), 1.28 (m, 6H).
	**44** ---- 15	314 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.28 - 7.13 (m, 5H), 4.52 (m, 1H), 4.39 (m, 2H), 2.22 (m, 2H), 1.69 (m, 2H), 1.54 (m, 1H), 1.44-1.40 (m, 2H), 1.40 (d, J = 6.7 Hz, 3H), 1.30 - 1.20 (m, 2H), 1.20 - 1.08 (m, 1H).

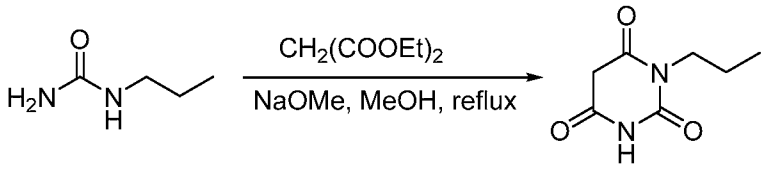
Structure	Compound No. ---- Ref. Example	Observed Mass and/or ^{1}H NMR
	**45** ---- 15	308 $(M+H)^+$ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.84 (s, 1H), 7.43 - 7.17 (m, 6H), 7.12 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 6.8 Hz, 2H), 5.55 (br s, 1H), 4.68 (s, 1H), 4.25 (m, 1H), 1.18 (d, J = 6.7 Hz, 3H).
	**46** ---- 15	260 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.37 - 7.30 (m, 4H), 7.10 - 7.06 (m, 1H), 4.55 (s, 1H), 4.51 (q, J = 6.7 Hz, 1H), 3.81 (q, J= 7.0 Hz, 2H), 1.50 (d, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H).
	**47** ---- 15	246 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.02 (s, 1H), 7.38 - 7.30 (m, 4H), 7.26 - 7.22 (m, 1H), 6.56 (s, 1H), 4.52 (q, J = 6.7 Hz, 1H), 4.39 (s, 1H), 2.97 (s, 3H) 1.40 (d, J = 6.7 Hz, 3H).

Example 48. Preparation of (*S*)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione.

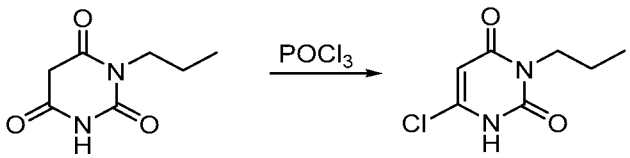


[0122] Compound 48.1. 1-propylurea. To a stirred solution of n-propylamine (2.15 g, 36.5 mmol, 1.00 equiv) in CH_2Cl_2 (35 mL) at 0 °C was added dropwise trimethylsilyl isocyanate (4.94 g (85% purity), 36.5 mmol, 1.00 equiv). The reaction mixture was stirred at room temperature for 72 h and was then cooled to 0 °C. The chilled mixture was quenched

by the dropwise addition of CH_3OH (10 mL) and was concentrated under reduced pressure. The resulting solid was suspended in Et_2O (30 mL) and was filtered. The solid was further washed with Et_2O (30 mL) and dried to afford 2.0 g (38%) of the title compound as a white solid.

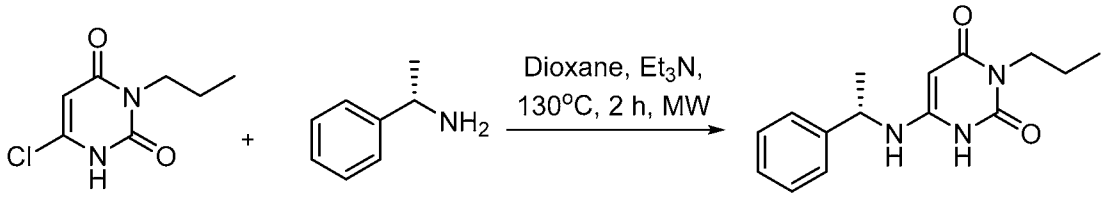


[0123] Compound 48.2. 1-propylpyrimidine-2,4,6(1H,3H,5H)-trione. To **48.1** (600 mg, 5.88 mmol, 1.00 equiv) in CH_3OH (1 mL) was added diethyl malonate (960 mg, 6.0 mmol, 1.02 equiv.) and sodium methoxide (1 mL, 25% $NaOCH_3$ in CH_3OH by weight). The reaction mixture was heated in the microwave reactor at 130 °C for 1 h. The mixture was cooled and the mixture was carefully adjusted to pH=3 with concentrated HCl. The volatiles were removed and H_2O was added (10 mL). Solid precipitated and was filtered. It was futher washed with additional H_2O (10 mL) and dried to afford 560 mg (56%) of title compopund as a white solid.



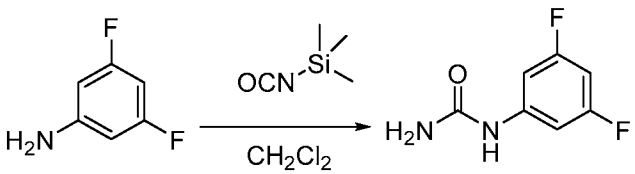
[0124] Compound 48.3. 6-chloro-3-propylpyrimidine-2,4(1H,3H)-dione. Compound **48.2** (560 mg, 3.30 mmol) and $POCl_3$ (2 mL) were added to a heavy wall pressure vessel which was subsequently sealed. The resulting solution was heated to 70 °C and stirred for 50 minutes behind a blast shield. The reaction mixture was cooled and concentrated under reduced pressure. To the resulting residue was added CH_2Cl_2 (30 mL) which was then removed under reduced pressure. The addition and evaporation of CH_2Cl_2 (30 mL) was conducted one additional time and then the resulting residue was diluted with CH_2Cl_2 (50 mL). To the organic layer was carefully added a saturated aqueous $NaHCO_3$ solution (50 mL). The layers were separated and the organics were further washed with H_2O (30 mL) and brine (30 mL). The organic layer was concentrated and purified by flash column

chromatography (silica gel, utilizing 10% EtOAc in CH_2Cl_2) to afford 160 mg (26%) of the title compound as a white solid.



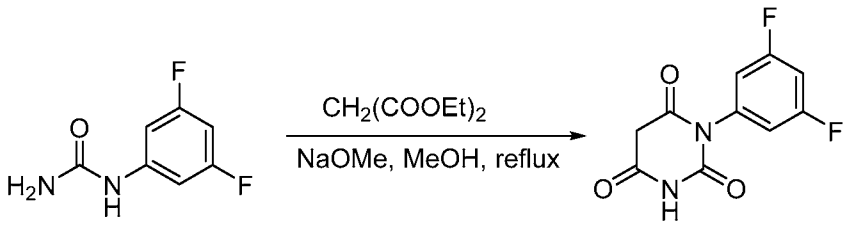
[0125] Compound 48. (*S*)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione. To **48.3** (160 mg, 0.85 mmol, 1.0 equiv.) in 1,4-dioxane (1.5 mL) was added Et_3N (200 µL) and (*S*)-α-methylbenzylamine (235 mg, 1.94 mmol, 2.3 equiv.). The mixture was heated in a microwave reactor at 130 °C for 2 h. The mixture was cooled and concentrated. The resulting residue was treated with an 8:3 mixture of H_2O:CH_3CN which resulted in precipitation. The solid was filtered and successively washed with H_2O (10 mL) and EtOAc (10 mL). The solid was dried to give 67 mg (29%) of the title compound as a white solid. LC/MS: m/z (ES+) 274 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.92 (br s, 1H), 7.36-7.22 (m, 5H), 6.54 (d, J = 7.0 Hz, 1H), 4.50 (quin, J = 6.7 Hz, 1H), 4.35 (s, 1H), 3.54 (dd, J = 8.0, 6.9 Hz, 2H), 1.42-1.36 (m, 5H), 0.76 (t, J = 7.6 Hz, 3H).

Example 49. Preparation of *(S)*-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.

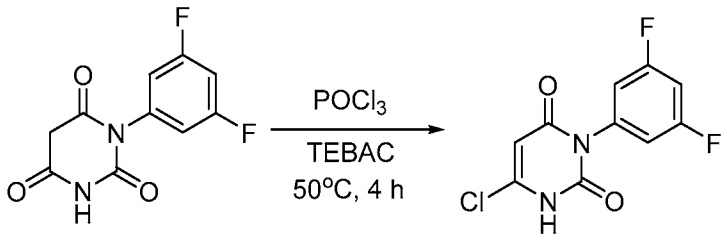


[0126] Compound 49.1. 1-(3,5-difluorophenyl)urea. To a stirred solution of 3,5-difluoroaniline (4.0 g, 31 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) under argon at room temperature was added dropwise trimethylsilyl isocyanate (3.56 g, 30.90 mmol, 1.00 equiv). The reaction mixture was stirred overnight and quenched by the dropwise addition of CH_3OH (50 mL). The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, eluting with $CHCl_3$/CH_3OH (10:1 to

7:1)) to yield 2.0 g (38%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.96 (s, 1H), 7.16-7.10 (m, 2H), 6.72-6.66 (m, 1H), 6.07 (br s, 2H).

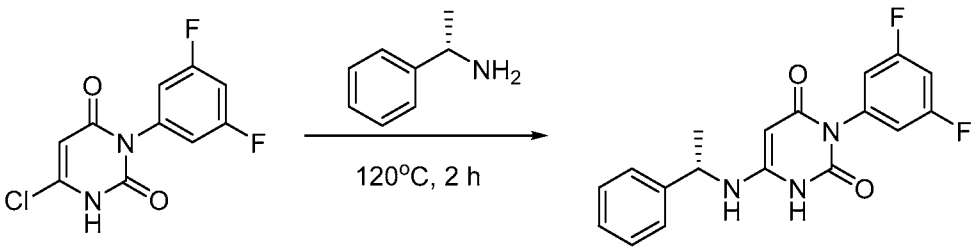


[0127] Compound 49.2. 1-(3,5-difluorophenyl)pyrimidine-2,4,6(1H,3H,5H)-trione. To a stirred solution of **49.1** (1.6 g, 0.0093 mol, 1.1 equiv) in CH_3OH (20 mL) were added diethyl malonate (1.4 g, 0.0087 mol, 1.0 equiv) and sodium methoxide (1.25 g, 0.0231 mol, 2.7 equiv). The resulting mixture was stirred overnight at 65 °C. After cooling to ambient temperature, the pH was carefully adjusted to 5 using aqueous 1N HCl. The resulting solution was extracted with EtOAc (3 x 50 mL). The organic layers were combined and concentrated under reduced pressure. The residue was washed with CH_3OH (50 mL) and the resulting solid was isolated by filtration to give 700 mg (31%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 11.66 (s, 1H), 7.43-7.35 (m, 1H), 7.11-7.08 (m, 2H), 3.77 (s, 2H).



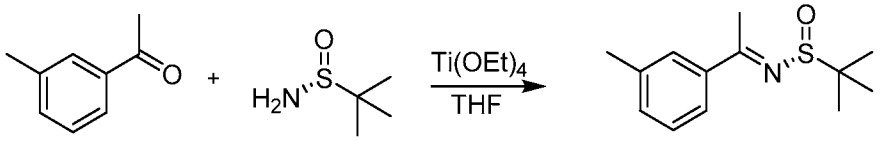
[0128] Compound 49.3. 6-chloro-3-(3,5-difluorophenyl)pyrimidine-2,4(1H,3H)-dione. To a 25-mL round-bottom flask under argon containing **49.2** (740 mg, 3.08 mmol, 1.00 equiv) were added triethylbenzylammonium chloride (840 mg, 1.20 equiv) and $POCl_3$ (3 mL). The resulting solution was stirred for 4 h at 50 °C. The reaction cooled and quenched by the careful addition of water/ice (20 mL). The pH of the solution was adjusted to 5 with 2N sodium hydroxide. The resulting solution was extracted with EtOAc (2 x 10 mL) and the organic layers were combined. The organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This resulted in 500

mg (crude) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 12.60 (br, 1H), 7.38-7.32 (m, 1H), 7.21-7.16 (m, 2H), 6.05 (s, 1H).



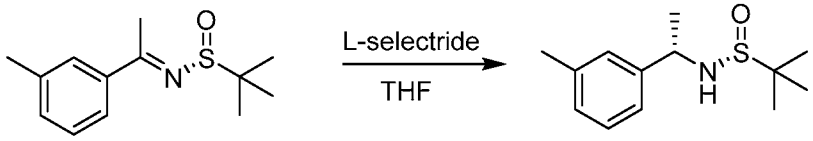
[0129] Compound 49. (*S*)-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To **49.3** (200 mg, 0.77 mmol) was added (*S*)-α-methylbenzylamine (1.5 mL). The resulting solution was stirred for 2 h at 120 °C. The reaction mixture was diluted with DMF (3 mL) and the crude product (100 mg) was purified by preparative RP-HPLC with the following conditions: XBridge Prep C18 OBD Column, 5um, 19*150mm; mobile phase, H_2O with 0.05%TFA and CH_3CN (40.0% CH_3CN to 90.0% in 10 min). This resulted in 21.6 mg (8%) of the title compound as a white solid. LC/MS: m/z (ES+) 344 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.25 (br s, 1H), 7.38-7.35 (m, 4H), 7.28-7.21 (m, 2H), 7.03-6.98 (m, 2H), 6.76 (d, J = 6.9 Hz, 1H), 4.59 (quin, J = 6.7 Hz, 1H), 4.50 (d, J = 2.0 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H).

Example 50. Preparation of (*S*)-3-isopropyl-6-((1-(m-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.

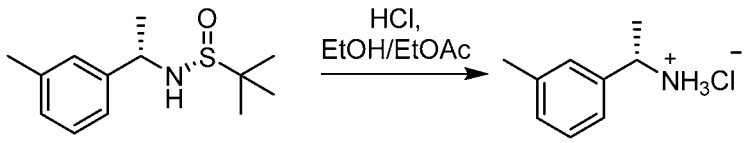


[0130] Compound 50.1. (*R*,E)-2-methyl-N-(1-(m-tolyl)ethylidene)propane-2-sulfinamide. To a stirred solution of 1-(3-methylphenyl)ethanone (1.61 g, 12.0 mmol, 1.00 equiv.) and (*R*)-(+)-2-methyl-2-propanesulfinamide (1.94 g, 14 mmol, 1.33 equiv.) in THF (50 mL) was added $Ti(OEt)_4$ (3.19 g, 14 mmol, 1.17 equiv.) dropwise. The reaction mixture was stirred for 16 h at 60 °C, cooled to room temperature, and quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The layers were separated and the aqueous layer was

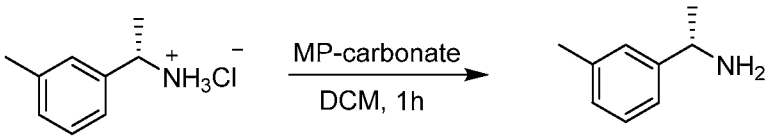
further extracted with EtOAc (2 x 100 mL). The combined organics were concentrated and the resulting residue was purified by flash chromatography (silica gel, eluting with 0-5% CH_3OH in CH_2Cl_2) to afford 1.51 g (53%) of the title compound as a white solid. LC/MS: m/z (ES+) 238 $(M+H)^+$.



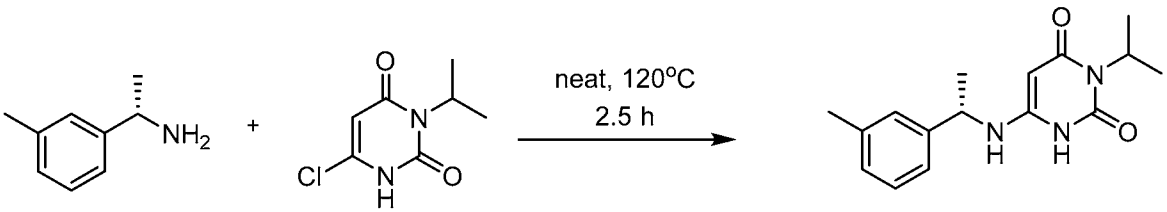
[0131] Compound 50.2. (*R*)-2-methyl-N-((*S*)-1-(m-tolyl)ethyl)propane-2-sulfinamide. To a solution of **50.1** (1.51 g, 6.37 mmol) in THF (30 mL) at -78 °C under an N_2 atmosphere was added L-selectride (dropwise, 10 mL, 1.0 M in THF, 10 mmol). The reaction mixture was warmed to 0 °C, stirred for 1 h, and carefully quenched with a saturated aqueous NH_4Cl solution (30 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 50mL). The combined organics were concentrated and the resulting residue was purified by flash chromatography (silica gel, eluted with 0-5% CH_3OH in CH_2Cl_2) to afford 0.85 g (56%) of the title compound. LC/MS: m/z (ES+) 240 $(M+H)^+$.



[0132] Compound 50.3. (*S*)-1-(m-tolyl)ethan-1-amine hydrochloride. To absolute EtOH (10 mL) was added AcCl (1.5 mL, dropwise). The mixture was stirred for 10 minutes and then was added to **50.2** (0.85 g, 3.56 mmol) in EtOH (3 mL). The reaction mixture was stirred for 2 h at ambient temperature and was concentrated. The resulting solid was suspended in Et_2O and filtered. The solid was washed with additional Et_2O and dried to give 402 mg (66%) of the title compound as white solid. LC/MS: m/z (ES+) 136 $(M+H)^+$.



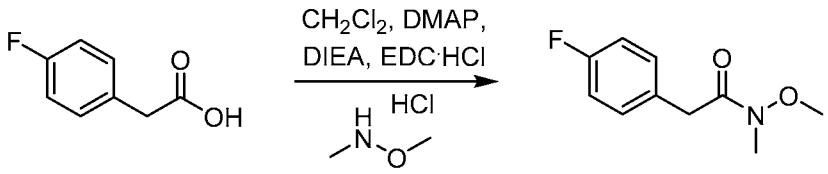
[0133] Compound 50.4. (*S*)-1-(m-tolyl)ethan-1-amine. To a stirred solution of **50.3** (205 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was added MP-carbonate (1.0g, 3.18 mmol/g). The reaction mixture was stirred at room temperature for 1 h and was then filtered. The solid beads were washed with an additional 10 mL CH_2Cl_2 and the combined filtrates were concentrated to give the title compound which was pushed forward without any purification.



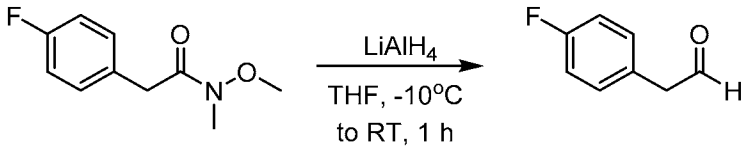
1.3

[0134] Compound 50. (*S*)-3-isopropyl-6-((1-(m-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione. To **50.4** (presumed ~1.2 mmol from prevous reaction, 2.0 equiv.) in a 0.5 to 2.0 mL microwave tube was added compound **1.3** (110 mg, 0.59 mmol, 1.0 equiv.). The microwave tube was sealed and heated at 120 °C behind a blast shield for 2.5 h. Upon cooling (to ~60 °C), NMP (2.5 mL) was added to the reaction mixture. The mixture was sonicated and heated (to ~60 °C) until the solid completely dissolved. The resulting solution was cooled to 40 °C and a 3:1 mixture of H_2O/CH_3CN (5 mL) was added. A solid precipitated and was collected through filtration. The light beige solid was subsequently washed with H_2O and dried to give 97 mg (57%) of the title compound as a white solid. LC/MS: m/z (ES+) 288 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.73 (br s, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.12-7.04 (m, 3H), 6.45 (d, J = 8.0 Hz, 1H), 4.90-4.86 (m, 1H), 4.42 (q, J = 6.7 Hz, 1H), 4.31 (d, J = 2.4 Hz, 1H), 2.29 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).

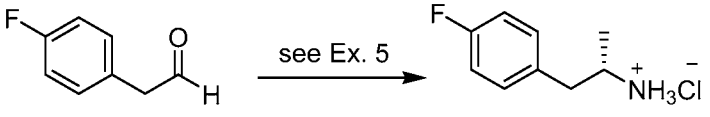
Example 51. Preparation of (*S*)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



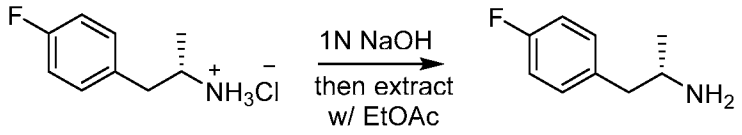
[0135] Compound 51.1. 2-(4-fluorophenyl)-N-methoxy-N-methylacetamide. To a stirred solution of 2-(4-fluorophenyl)acetic acid (15 g, 97.32 mmol, 1.00 equiv) in CH_2Cl_2 (300mL) was added methoxy(methyl)amine hydrochloride (11.1 g, 113.79 mmol, 1.20 equiv), 4-dimethylaminopyridine (12 g, 98.22 mmol, 1.00 equiv), 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (28.2 g, 147.10 mmol, 1.50 equiv), and DIEA (37.5 g, 290.14 mmol, 3.00 equiv). The resulting solution was stirred at room temperature for 16 h and then diluted with EtOAc (150 mL). The organics were washed with aqueous 1N HCl (2 x 150 mL) and brine (2 x 150 mL). It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, eluting with EtOAc/petroleum ether (1:3)). This resulted in 18 g (88%) of the title compound as yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.29-7.25 (m, 2H), 7.03-6.99 (m, 2H), 3.75 (s, 2H), 3.65 (s, 3H), 3.21 (s, 3H).



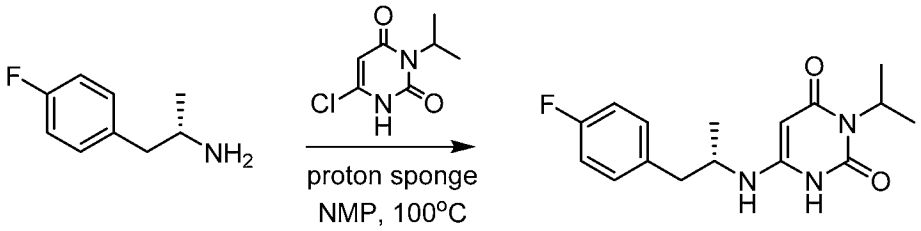
[0136] Compound 51.2. 2-(4-fluorophenyl)acetaldehyde. To a stirred solution of **51.1** (3 g, 15.21 mmol, 1.00 equiv) in THF (60 mL) under argon at -10 °C was added $LiAlH_4$ (1.15 g, 30.30 mmol, 2.00 equiv) in several batches (*CAREFUL... EXOTHERMIC REACTION*). The resulting solution was stirred for 1 h at room temperature before being cooled to -10 °C. The reaction was then quenched by the careful addition of a saturated aqueous NH_4Cl solution (50 mL). The resulting solid was filtered and the filtrate was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.5 g (crude) of the title compound as a yellow oil.



[0137] Compound 51.3. (*S*)-1-(4-fluorophenyl)propan-2-amine hydrochloride. The title compound was synthesized according to methods described for the preparation of **5.3**, utilizing **51.2** in place of 3,5-difluorobenzaldehyde. LC/MS: m/z (ES+) 154 $(M+H)^+$.

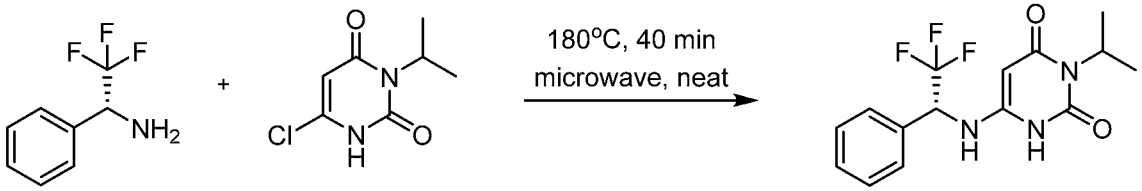


[0138] Compound 51.4. (*S*)-1-(4-fluorophenyl)propan-2-amine. To an aqueous solution of 1N NaOH (5 mL) was added **51.3** (300 mg, 1.59 mmol). The resulting mixture was stirred for one hour at 25 °C. The resulting solution was extracted with EtOAc (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 160 mg (65%) of the title compound. LC/MS: m/z (ES+) 154 $(M+H)^+$.



[0139] Compound 51. (*S*)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a stirred solution of **51.4** (160 mg, 1.04 mmol, 2.00 equiv) in NMP (0.5 mL) was added **1.3** (99 mg, 0.52 mmol, 1.00 equiv) and proton sponge (168 mg, 0.78 mmol, 1.50 equiv). The resulting solution was stirred for 5 h at 100 °C in an oil bath. The reaction mixture was concentrated under reduced pressure. The residue (100 mg) was purified by preparative RP-HPLC to afford 30 mg (19%) of the title compound as gray solid. LC/MS: m/z (ES+) 306 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.81 (br s, 1H), 7.27 (dd, J = 8.8, 5.6 Hz, 2H), 7.17-7.12 (m, 2H), 5.89 (d, J = 7.6 Hz, 1H), 5.00-4.92 (m, 1H), 4.58 (s, 1H), 3.69-3.65 (m, 1H), 2.74 (d, J = 6.4 Hz, 2H), 1.31 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 6.4 Hz, 3H).

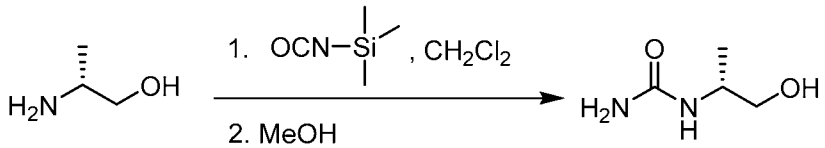
Example 52. Preparation of (*R*)-3-isopropyl-6-((2,2,2-trifluoro-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione **(52).**



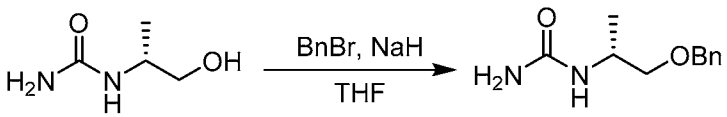
1.3

[0140] To a 0.2-0.5 mL microwave vial was added **1.3** (85 mg, 0.45 mmol) and (R)-2,2,2-trifluoro-1-phenylethan-1-amine (200 uL, excess). The reaction mixture sealed and heated at 180 °C in a microwave reactor for 40 minutes. The reaction mixture was cooled to ambient temperature and then NMP (1 mL) was added to completely dissolve the solid. Next, a 2:1 H_2O/CH_3CN mixture (6 mL) was added which resulted in precipitation. The solid was isloated by filtration, washed with H_2O and dried to give 50 mg (34%) of the title compound as a white solid. LC/MS: m/z (ES+) 328 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.79 (br s, 1H), 7.50-7.40 (m, 5H), 5.66-5.56 (m, 2H), 4.92-4.87 (m, 2H), 1.28-1.25 (m, 6H).

Example 53. Preparation of 3-((R)-1-(benzyloxy)propan-2-yl)-6-(((*S*)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.

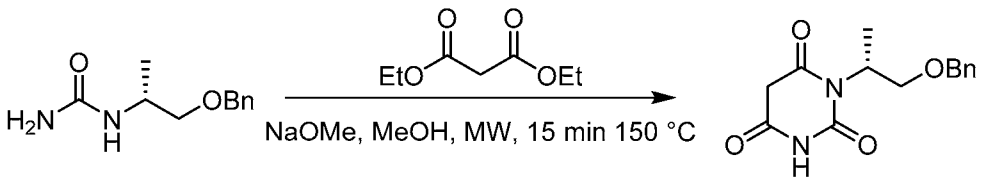


[0141] **Compound 53.1. (*R*)-1-(1-hydroxypropan-2-yl)urea.** To a stirred solution of (*R*)-(-)-2-amino-1-propanol (0.65 g, 8.68 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) under N_2 at 0°C was added dropwise trimethylsilyl isocyanate (1.00 g, 8.68 mmol, 1.0 equiv.). The reaction mixture was stirred overnight while slowly warming to room temperature. After cooling to 0 °C, CH_3OH (10 mL) was added dropwise. The resulting solution was stirred for 2 h at room temperature and was then concentrated under reduced pressure to provide the title compound (1.02 g, 99%) as a white solid.

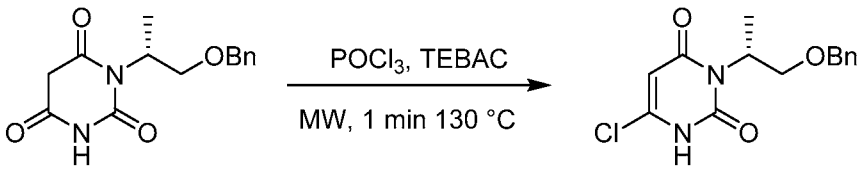


[0142] **Compound 53.2. (*R*)-1-(1-(benzyloxy)propan-2-yl)urea.** To a suspension of sodium hydride (0.52 g, 13.2 mmol, 1.5 equiv.) in THF (10 mL) at 0 °C was added **53.1** (1.02

g, 8.67 mmol, 1 equiv.). The reaction mixture was stirred for 20 minutes at 0 °C under N_2 before benzyl bromide (1.03 mL, 8.67 mmol, 1 equiv.) was added. The reaction mixture was stirred overnight while slowly warming to room temperature. The reaction mixture was quenched with H_2O (3 mL) and was extracted into EtOAc (15 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (10% CH_3OH in CH_2Cl_2) to provide 510 mg (28%) of the title compound. LC/MS: m/z (ES+) 209 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.42 - 7.27 (m, 5H), 4.79 (d, J = 6.7 Hz, 1H), 4.52 (d, J = 2.7 Hz, 2H), 3.91 (s, 1H), 3.51 (dd, J = 9.4, 3.9 Hz, 1H), 3.40 (dd, J = 9.2, 5.3 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H).

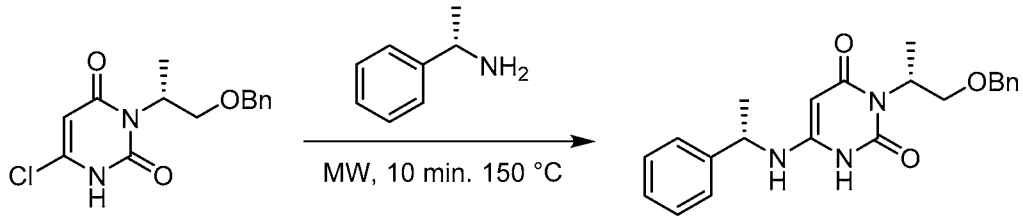


[0143] Compound 53.3. (*R*)-1-(1-(benzyloxy)propan-2-yl)pyrimidine-2,4,6(1H,3H,5H)-trione. To a microwave vial containing **53.2** (0.51 g, 2.42 mmol, 1 equiv.) in CH_3OH (10 mL) was added diethyl malonate (2.55 g, 2.55 mmol, 1.05 equiv.) followed by sodium methoxide (25% wt. soln. in CH_3OH, 1.31 g, 6.06 mmol, 2.5 equiv.). The vial was capped and the reaction mixture was heated in a microwave reactor for 15 minutes at 150 °C. After cooling to room temperature, the reaction mixture was quenched with H_2O (2 mL) and the pH was adjusted to 3 with concentrated HCl. The reaction mixture was transferred to a round bottom flask and was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% CH_3OH in CH_2Cl_2) to provide 0.62g (92%) of the title compound as a white solid. LC/MS: m/z (ES+) 277 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.99 (s, 1H), 7.38-7.22 (m, 5H), 5.16-5.11 (m, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.02 (t, J = 9.8 Hz, 1H), 3.56 (q, J = 1.57 Hz, 2H), 1.37 (d, J = 7.00 Hz, 3H).



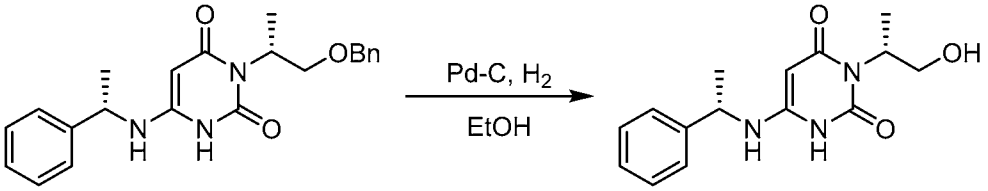
[0144] Compound 53.4. (*R*)-3-(1-(benzyloxy)propan-2-yl)-6-chloropyrimidine-2,4(1H,3H)-dione. To a microwave vial containing **53.3** (0.25 g, 0.91 mmol, 1 equiv.) was

added triethylbenzylammonium chloride (0.28 g, 1.26 mmol, 1.4 equiv.) and $POCl_3$ (1mL). The vial was capped and the reaction mixture was heated in a microwave reactor for 1 minute at 130 °C. The reaction mixture was transferred to a round bottom flask and was concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and water (2 mL) was carefully added. The mixture was stirred for 10 minutes. The layers were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) to provide 150 mg (55%) of the title compound. LC/MS: m/z (ES+) 295 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.27 (s, 1H), 7.36-7.20 (m, 5H), 5.32- 5.21 (m, 2H), 4.57 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.10 (dd, J = 10.0, 9.2 Hz, 1H), 1.40 (d, J = 7.0 Hz, 3H).



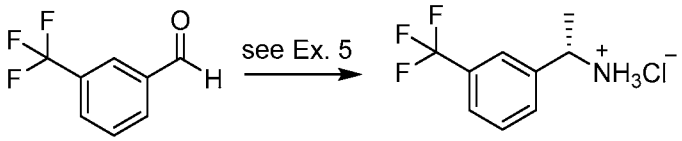
[0145] Compound 53. 3-((*R*)-1-(benzyloxy)propan-2-yl)-6-(((*S*)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To a microwave vial containing (*S*)-α-methylbenzylamine (1.5 mL) was added **53.4** (0.12 g, 0.42 mmol). The vial was capped and the reaction mixture was heated in a microwave reactor for 10 minutes at 150 °C. After cooling, the reaction mixture was filtered through a plug of silica gel (10% CH_3OH in CH_2Cl) and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and was washed with 10% HCl (5 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated to provide 150 mg (94%) of the title compound. LC/MS: m/z (ES+) 380 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.96 (br s 1H), 7.35-7.24 (m, 10H), 4.70 (br s, 1H), 4.53-4.41 (m, 4H), 4.03-3.99 (m, 1H), 3.65-3.61 (m, 1H), 1.49 (d, J = 6.7 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H).

Example 54. Preparation of 3-((*R*)-1-hydroxypropan-2-yl)-6-(((*S*)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione **(54)**.

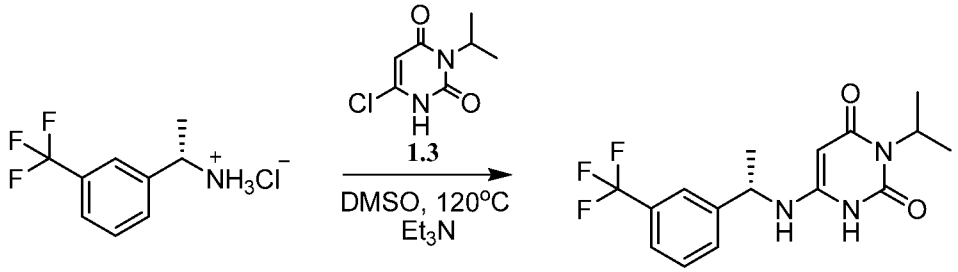


[0146] To a solution of **53** (0.10 g, 0.26 mmol, 1 equiv.) in EtOH (2 mL) was added palladium on carbon (10 wt. % loading (dry basis), matrix activated carbon, wet support, Degussa type, 0.025 g). The reaction flask was purged with nitrogen and was then fitted with a $H_{2(g)}$ balloon. The reaction mixture was evacuated and then filled with $H_{2(g)}$. This pump/purge process was repeated three times and the reaction mixture was stirred for 4 h at room temperature. After purging with nitrogen, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was suspended in CH_3CN (2 mL) and the precipitate was isolated by filtration. The precipitate was dissolved in CH_2Cl_2: CH_3OH (1:1, 2 mL) and was filtered through a .2μM PTFE 25mm filter and was concentrated under reduced pressure to provide 27 mg (35%) of the title compound. LC/MS: m/z (ES+) 290 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.67 (s, 1H), 7.35-7.24 (m, 5H), 5.64 (d, J = 5.5 Hz, 1H), 5.08-5.04 (m, 1H), 4.66 (s, 1H), 4.42-4.35 (m, 1H), 4.24 (s, 1H), 4.04-3.91 (m, 1H), 3.78-3.68 (m, 1H), 1.50 (d, J = 6.70 Hz, 3H), 1.35 (d, J = 7.00 Hz, 3H).

Example 55. Preparation of (*S*)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino) pyrimidine-2,4(1H,3H)-dione.

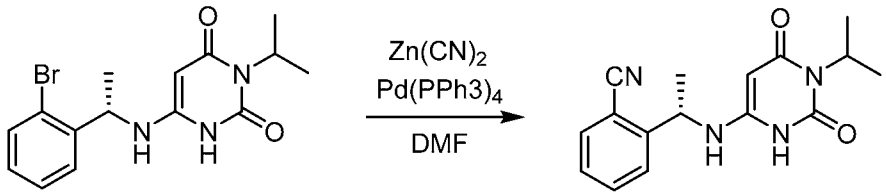


[0147] **Compound 55.1. (*S*)-1-(3-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride.** The title compound was synthesized according to methods described for the preparation of **5.3**, utilizing 3-(trifluoromethyl)benzaldehyde in place of 3,5-difluorobenzaldehyde.



[0148] Compound 55. (*S*)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino) pyrimidine-2,4(1H,3H)-dione. To a stirred solution of **55.1** (59.8 mg, 0.27 mmol, 1.00 equiv) in DMSO (1.5 mL) under an inert argon atmosphere was added Et_3N (0.2 mL) and **1.3** (50 mg, 0.27 mmol, 1.00 equiv). The resulting solution was stirred for 6 h at 120 °C in an oil bath. After cooling, the mixture was concentrated under reduced pressure and the resulting residue (75 mg) was purified by preparative RP-HPLC to give 6.5 mg (7%) of the title compound as a white solid. LC/MS: m/z (ES+) 342 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 7.78 (s, 1H), 7.74-7.60 (m, 3H), 7.20 (br, 1H), 6.02 (br, 1H), 4.96 (dt, J = 10.1, 5.1 Hz, 1H), 4.67-4.64 (m, 1H), 4.36 (s, 1H), 1.44 (d, J= 6.8 Hz, 3H), 1.31-1.28 (m, 6H).

Example 56. Preparation of *(S)*-3-isopropyl-6-((1-(2-cyanophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione **(56)**.

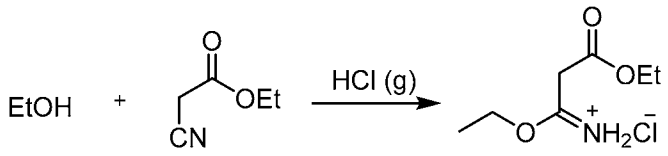


56.1

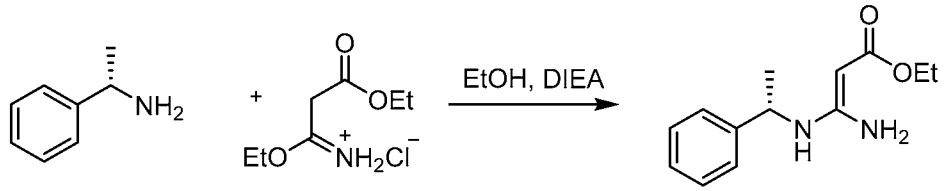
[0149] Intermediate **56.**1 was prepared using procedures similar to those for the preparation of compound **35,** utilizing **1.3** and (*S*)-1-(2-bromophenyl)ethan-1-amine hydrochloride (synthesized from the corresponding 2-bromobenzaldehyde using methods described for example 6.3). To a stirred solution of **56.1** (40 mg, 0.11 mmol, 1.00 equiv,) in DMF (2 mL) was added $Zn(CN)_2$ (20 mg, 0.17 mmol, 1.50 equiv) and tetrakis(triphenylphosphine) palladium (131 mg, 0.11 mmol, 0.20 equiv). *CAUTION: CYANIDE CONTAINING REACTION.* The resulting solution was stirred under an argon atmosphere at 100 °C in an oil bath for 2 h. Upon cooling, the reaction was quenched with a saturated aqueous $FeSO_4$ solution (5 mL). The resulting mixture was diluted with EtOAc (20 mL) and washed with a saturated aqueous $FeSO_4$ solution (2 x 20 mL). The organic layer was dried with anhydrous

Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product (5 mg) was purified by chiral preparative HPLC with the following conditions: Column, Phenomenex Lux-2 5u Cellulose-2, 30*150mm; mobile phase, Hexanes and EtOH (hold 50.0% EtOH in 35 min); resulting in 2.1 mg (6%) of the title compound. LC/MS: m/z (ES+) 299 $(M+H)^+$. ^{1}H-NMR (300 MHz, CD_3CN): δ ppm 8.59 (br s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.61-7.56 (m, 1H), 7.48-7.45 (m, 2H), 5.09-4.94 (m, 3H), 1.46 (d, J = 6.6 Hz, 3H), 1.34-1.26 (m, 6H).

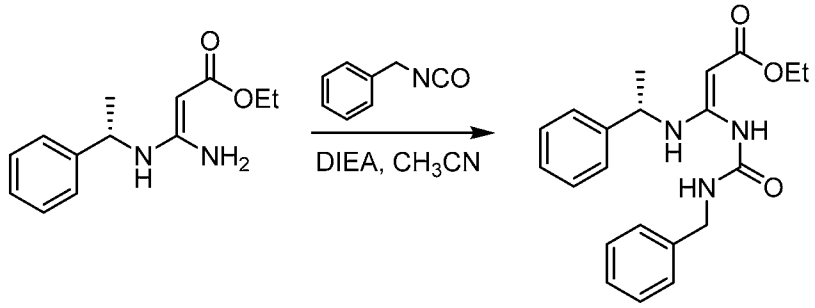
Example 57. Preparation of (*S*)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



[0150] Compound 57.1. 3-ethoxy-3-oxo-1-(1-ethoxy)propan-1-iminium chloride. To a stirred solution of ethyl cyanoacetate (5.0 g, 44 mmol) in anhydrous Et_2O (5 mL) was added absolute EtOH (3 mL). The reaction mixture was cooled to 0 °C and HCl gas was bubbled in for 10 minutes. The reaction mixture was warmed to room temperature and was stirred for 16 h. The white precipitate that formed was filtered and washed with Et_2O (40 mL) and dried to give (6.99 g) the title compound as a white solid. LC/MS: m/z (ES+) 160 $(M+H)^+$.

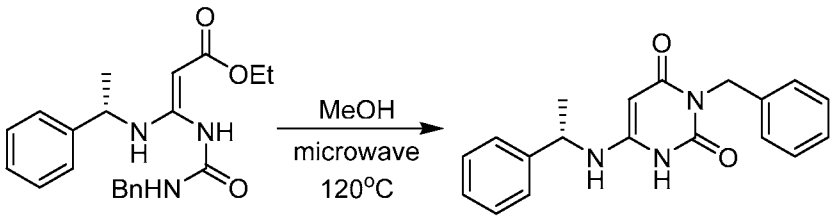


[0151] Compound 57.2. Ethyl (*S*,E/Z)-3-amino-3-((1-phenylethyl)amino)acrylate. To a stirred solution of **57.1** (585 mg, 3.0 mmol) in EtOH (15 mL) was added DIEA (0.8 mL), and (*S*)-α-methylbenzylamine (290 mg, 2.4 mmol). The reaction was stirred for 16 h and was concentrated. The crude was purified by flash column chromatography (silica gel, eluting with CH_3OH in CH_2Cl_2 (0 to 10%)) to yield 0.57 g (98%) of the title compound as a clear oil. NMR analysis revealed that the product was a mixture of E/Z isomers. LC/MS: m/z (ES+) 235 $(M+H)^+$.



[0152] Compound 57.3. Ethyl (*S*,Z)-3-(3-benzylureido)-3-((1-phenylethyl)amino)acrylate.

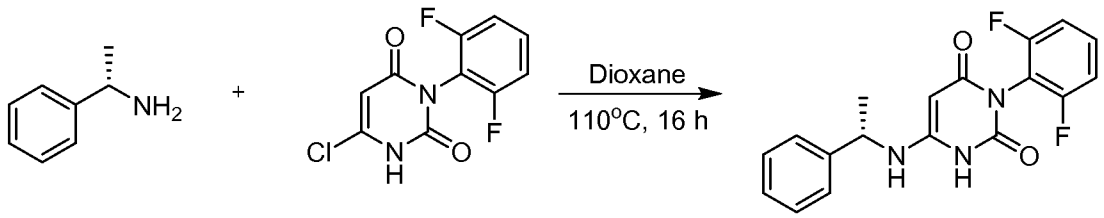
Two reactions were set up in parallel and later combined since both resulted in formation of product (by HPLC). In the first reaction, benzyl isocyanate (150 uL, 1.2 mmol) was added to a stirred solution of **57.2** (143 mg, 0.61 mmol) in CH_3CN (1 mL). After 10 min., DIEA (300 uL) was added. The reaction was stirred for an additional 10 min and was quenched with H_2O (12 mL). Solid precipitated and was removed by filtration. In the second reaction, benzyl isocyanate (150 uL, 1.2 mmol) was added to a stirred solution of **57.2** (143 mg, 0.61 mmol) and DIEA (300 uL) in CH_3CN (1 mL). After 10 min, the reaction mixture was quenched with H_2O (10 mL). The resulting mixture was diluted with EtOAc (40 mL) and the layers were separated. To the organic layer was added the filtrate from first reaction. The layers were separated and the organics were concentrated to give the title compound which was utilized without further purification.



[0153] Compound 57. (*S*)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. Two reactions were conducted and later combined since both resulted in formation of product (by HPLC). The first reaction utilized 1/3 of crude **57.3** in CH_3OH (1 mL). It was heated in a microwave reactor at 120 °C for 10 min. The remaining 2/3 of crude **57.3** in CH_3OH (2 mL) was heated in a microwave reactor at 120 °C for 20 min. After cooling to ambient temperature, the reactions were combined and the CH_3OH was removed under reduced pressure. A 50/50 mixture of CH_3CN/H_2O with 0.1% TFA (5 mL) was added to the

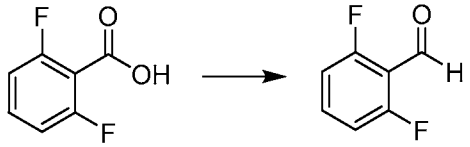
resulting resiude. Solid precipitated and was filtered. The resulting brown solid was washed with EtOAc to give 7 mg of the title compound as a white solid. LC/MS: m/z (ES+) 322 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.05 (br s, 1H), 7.35-7.31 (m, 4H), 7.26-7.16 (m, 6H), 6.61 (d, J = 7.0 Hz, 1H), 4.79 (s, 2H), 4.52 (quin, J = 6.8 Hz, 1H), 4.42 (d, J = 2.3 Hz, 1H), 1.39 (d, J = 6.7 Hz, 3H).

Example 58. Preparation of (*S*)-3-(2,6-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione **(58)**.

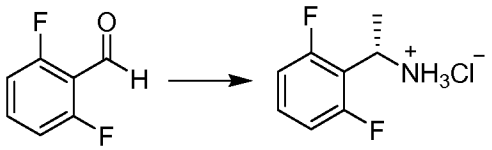


[0154] The title compound was synthesized according to a slightly modified procedure as described in Example 50. Here, 1,4-dioxane was utilized as a solvent and the reaction was heated at 110 °C for 16 h. The resulting mixture was cooled and concentrated under reduced pressure. The crude was purified by preparative RP-HPLC to give 19 mg of the title compound as a white solid. LC/MS: m/z (ES+) 344 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.44 (br s, 1H), 7.52-7.42 (m, 2H), 7.39-7.36 (m, 3H), 7.34-7.16 (m, 3H), 6.91 (br s, 1H), 4.65-4.56 (m, 1H), 4.52 (s, 1H), 1.43 (d, J = 6.7 Hz, 3H).

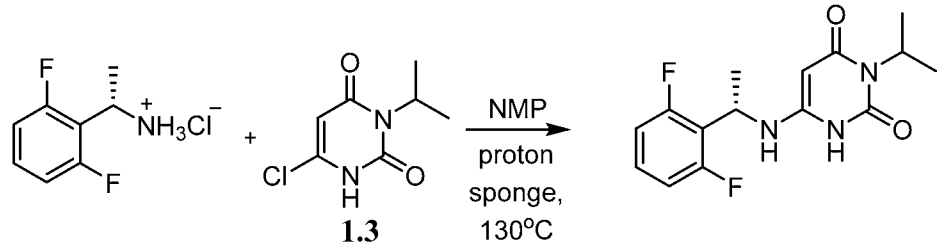
Example 59. Preparation of (*S*)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0155] **Compound 59.1. 2,6-difluorobenzaldehyde**. The title compound was synthesized according to methods described for the preparation of **51.2**. Here, commercially available 2,6-difluorobenzoic acid was utilized instead of 2-(4-fluorophenyl)acetic acid.

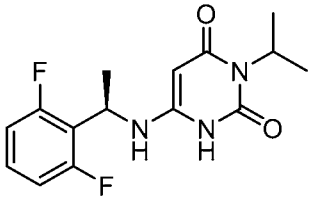


[0156] Compound 59.2. (*S*)-1-(2,6-difluorophenyl)ethan-1-amine hydrochloride. The title compound was synthesized according to methods described for the preparation of **5.3**. Here, **59.1** was utilized instead of 3,5-difluorobenzaldehyde.



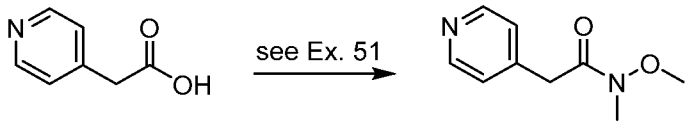
[0157] Compound 59. (*S*)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. Reaction of **59.1** with **1.3** was conducted in a similar manner as the procedure described in Example 51. Here though, the reaction mixture was heated at 130 °C for 5 h. Analysis of the reaction mixture via chiral HPLC revealed non-trivial amounts of the enantiomer. Separation of the enantiomers was performed utilizing preparative chiral HPLC with an isocratic mixture of EtOH: Hexane (1:4) as eluent from a Phenomenex Lux-2 5µ Cellulose-2, 30*150mm column (40 min run). LC/MS: m/z (ES+) 310 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.80 (br s, 1H), 7.45-7.41 (m, 1H), 7.18-7.14 (m, 2H), 6.52 (d, J = 8.0 Hz, 1H), 4.94-4.88 (m, 1H), 4.79 (quint, J = 7.6 Hz, 1H), 4.41 (s, 1H), 1.56 (d, J = 6.8 Hz, 3H), 1.30-1.26 (m, 6H).

Example 60. Preparation of (*R*)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione **(60R)**.

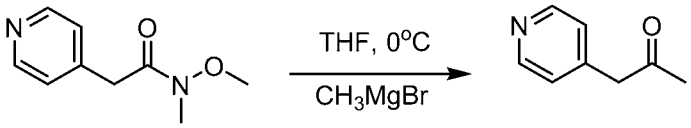


[0158] The title compound was generated as a by-product of the chemistry conducted in Example 59. It was isolated via preparative chiral HPLC with an isocratic mixture of EtOH: Hexane (1: 4) as eluent from a Phenomenex Lux-2 5µ Cellulose-2, 30*150mm column (40 min run). LC/MS: m/z (ES+) 310 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.98-9.61 (br, 1H), 7.45-7.41 (m, 1H), 7.18-7.14 (m, 2H), 6.52 (d, J = 8.0 Hz, 1H), 4.94-4.88 (m, 1H), 4.79 (quint, J = 7.6 Hz, 1H), 4.41 (s, 1H), 1.56 (d, J = 6.8 Hz, 3H), 1.30-1.26 (m, 6H).

Example 61. Preparation of (*S*)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione.



[0159] Compound 61.1. N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide. The title compound was synthesized according to methods described for the preparation of **51.1**. Here, commercially available 4-pyridineacetic acid was utilized instead of 2-(4-fluorophenyl)acetic acid.

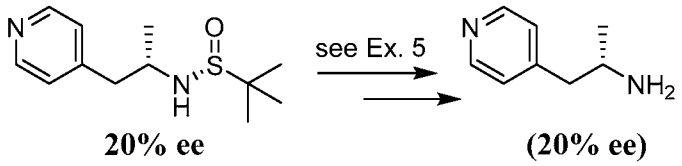


[0160] Compound 61.2. 1-(pyridin-4-yl)propan-2-one. To a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of argon, was added THF (70 mL) and N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide (7.0 g, 0.039 mol, 1.0 equiv). The mixture was cooled to 0 °C and CH_3MgBr (3M in THF, 65 mL, 5.0 equiv) was added dropwise. The resulting solution was warmed to ambient temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated NH_4Cl (aq, 100 mL). The resulting solution was extracted with EtOAc (3x200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH (20:1)) to yield 2.7 g (51%) of the title compound as yellow oil. ^{1}H-NMR (400 MHz,$CDCl_3$): δ ppm 8.58 (m, 2H), 7.17 (d, J = 0.4 Hz, 2H), 3.75 (s, 2H), 2.24 (s, 3H).

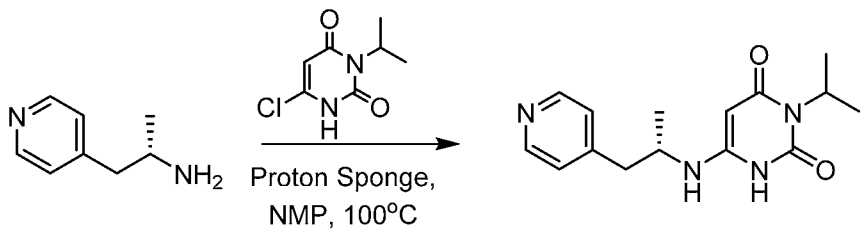
20% ee

[0161] Compound 61.3. (*R*)-2-methyl-N-((*S*)-1-(pyridin-4-yl)propan-2-yl)propane-2-sulfinamide. The title compound was prepared according to procedures described in Example 50 utilizing **61.2** in place of 1-(3-methylphenyl)ethanone. Here, the reduction

utilizing L-selectride resulted in isolation of the title compound **(61.3)** (20% enantiomeric excess).

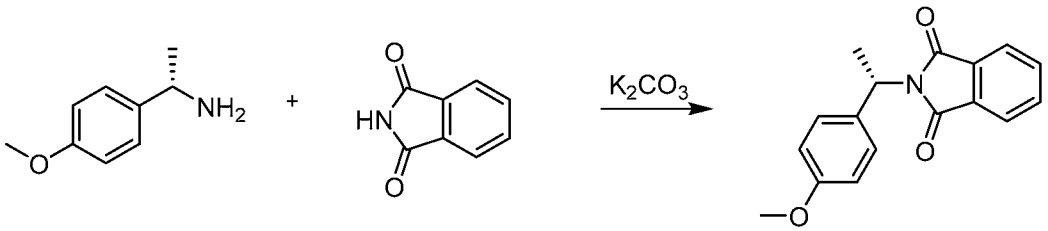


[0162] Compound 61.4. (*S*)-1-(pyridin-4-yl)propan-2-amine. The title compound was prepared utilizing a two-step procedure as described in Example 5. First, sulfonamide **61.3** was converted to the hydrochloride salt by treatment with HCl in 1,4-dioxane (see protocol for Compound **5.3**). Subsequent free-basing of the hydrochloride salt (see protocol for Compound **5**) resulted in the title compound (~20% ee).

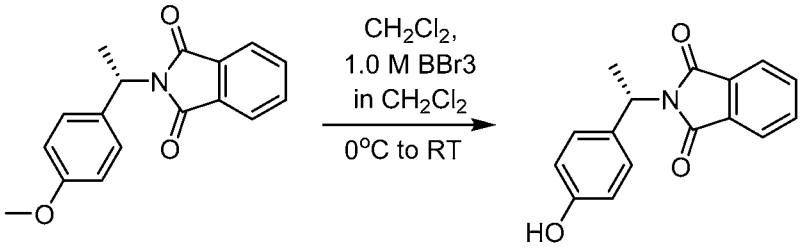


[0163] Compound 61. (*S*)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione. The title compound was prepared according to the protocol described for **51**. Here, the reaction mixture was stirred for at 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue (100 mg) was purified by Prep-HPLC to give 13.1 mg of the title compound as a mixture of enantiomers. The enantiomers were (13.1 mg) separated by chiral preparative HPLC with a Chiralpak IC, 2*25cm, 5um column, utilizing a isocratic mixture of EtOH: Hexane (1: 3) as eluent (20 min run). This resulted in 8.2 mg (8%) of the title compund as a light yellow solid. LC/MS: m/z (ES+) 289 $(M+H)^+$. ^{1}H-NMR (300 MHz,CD_3OD): δ ppm 8.41 (d, J = 5.7 Hz, 2H), 7.29 (d, J = 6.0 Hz, 2H), 5.06-4.96 (m, 1H), 4.68 (s, 1H), 3.82-3.75 (m, 1H), 2.87-2.83 (m, 2H), 1.36 (d, J = 7.2 Hz, 6H), 1.12 (d, J = 7.2 Hz, 3H).

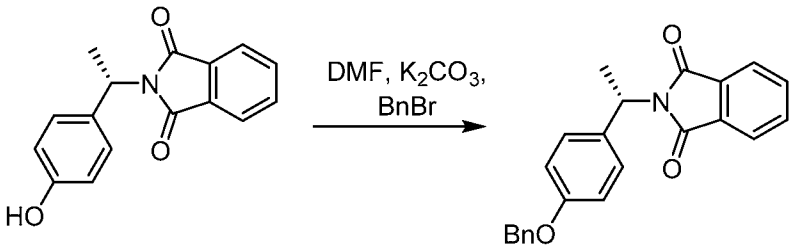
Example 62. Preparation of *(S)*-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



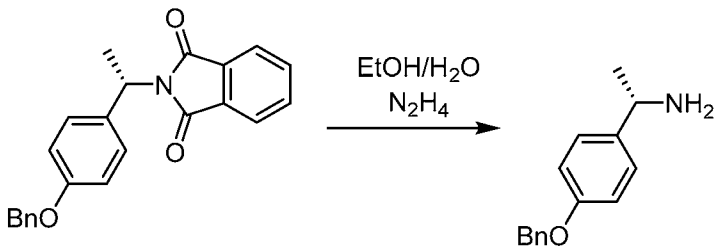
[0164] Compound 62.1. (*S*)-2-(1-(4-(methoxy)phenyl)ethyl)isoindoline-1,3-dione. To phtalimide (1.3 g, 0.0088 mol) in a 2-5 mL microwave vial was added (*S*)-1-(4-methoxyphenyl)ethan-1-amine (2.20 mL, 0.015 mol) and K_2CO_3 (1.2 g, 0.0087 mol). The reaction mixture capped and heated at 160 °C for 2 minutes. The resulting crude solid was suspended in n-BuOH and was filtered. The filtrate was put aside. The solid was washed with H_2O and the filtrate was discarded. The solid was washed with CH_2Cl_2 and the resulting filtrate was partitioned with H_2O. The organics (n-BuOH and CH_2Cl_2 layer) were combined and concentrated. The crude residue was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield 1.6 g (64%) of the title compound. LC/MS: m/z (ES+) 282 $(M+H)^+$.



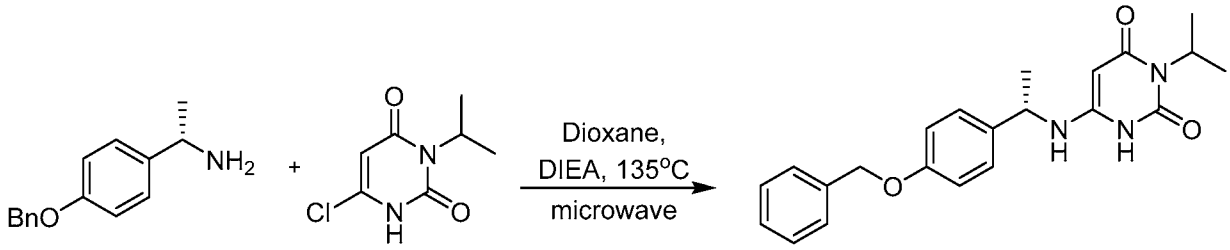
[0165] Compound 62.2. (*S*)-2-(1-(4-hydroxyphenyl)ethyl)isoindoline-1,3-dione. To a stirred solution of **62.1** (640 mg, 2.28 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2,3 mL, dropwise). The reaction was allowed to warm to room temperature over 30 minutes. Significant starting material remained so the reaction was chilled back to 0 °C. Additional BBr_3 (2 mL, 1.0 M in CH_2Cl_2) was added and the reaction was allowed to warm to room temperature over 30 minutes. The reaction mixture was poured over 5% $NaHCO_3$ (aq) in ice. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were washed with brine, dried with anhydrous Na_2SO_4 and concentrated to give 500 mg (82%) of the title compound as a white solid. LC/MS: m/z (ES+) 268 $(M+H)^+$.



[0166] Compound 62.3. (*S*)-2-(1-(4-(benzyloxy)phenyl)ethyl)isoindoline-1,3-dione. To a stirred solution of **62.2** (500 mg, 1.87 mmol) in DMF (10 mL) was added K_2CO_3 (560 mg, 4.05 mmol, 2.17 equiv.) and benzyl bromide (0.30 mL, 420 mg, 2.45 mmol, 1.3 equiv.). The reaction was stirred at 120 °C for 5 h. The reaction was cooled and filtered. Water was added (20 mL) and EtOAc (60 mL) was utilized to extract product. The organic layer was washed successively with H_2O, 10% Na_2CO_3 (aq), H_2O, and brine (2x). The organics were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with CH_2Cl_2) to yield 480 mg (72%) of the title compound. LC/MS: m/z (ES+) 358 $(M+H)^+$.

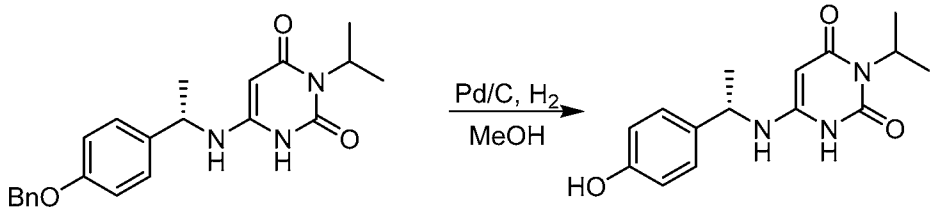


[0167] Compound 62.4. (*S*)-1-(4-(benzyloxy)phenyl)ethan-1-amine. To a stirred solution of **62.3** (480 mg, 1.34 mmol) in a 70/30 EtOH/H_2O mixture (20 mL) was added $N_2H_4 \cdot H_2O$ (1.5 mL). The reaction was stirred for 16 h and concentrated. The resulting material was partitioned between EtOAc and 5% Na_2CO_3 (aq). The layers were separated and the EtOAc layer was washed with brine and concentrated to give 280 mg (92%) of the title compound which was used without further purification. LC/MS: m/z (ES+) 228 $(M+H)^+$.



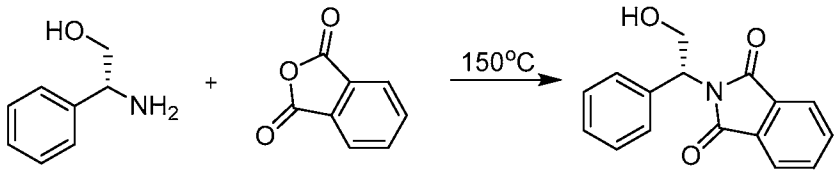
[0168] Compound 62. (*S*)-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a 0.5-2.0 mL microwave vial was added 1,4-dioxane (1 mL), **62.4** (280 mg, 1.23 mmol), **1.3** (250 mg, 1.33 mmol) and DIEA (400 uL). The reaction mixture was capped, heated at 135 °C in a microwave reactor for 1.5 h, allowed to cool, and then concentrated. The crude reaction mixture was treated with 50/50 CH_3CN/H_2O (0.1% TFA) which led to precipitation. The solid was isloated by filtration and dried to give 45 mg (10%) of a white solid. LC/MS: m/z (ES+) 380 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.73 (br, 1H), 7.43-7.29 (m, 5H), 7.23 (d, J = 14.5 Hz, 2H), 6.97 (d, J = 14.5 Hz, 2H), 6.42 (d, J = 7.0 Hz, 1H), 5.06 (s, 2H), 4.93-4.85 (m, 1H), 4.42 (quin, J = 6.8 Hz, 1H), 4.32 (d, J = 1.6 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H), (m, 1H) 1.27-1.23 (m, 6H).

Example 63. Preparation of (*S*)-6-((1-(4-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione **(63)**.

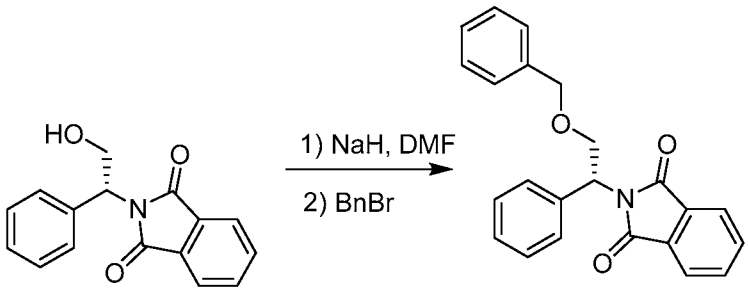


[0169] To a stirred solution of **62** (43 mg, 0.11 mmol) in CH_3OH (20 mL) was added palldium on carbon (50 mg, 10 wt. % loading (dry basis), matrix activated carbon, wet support, Degussa type). The vessel was purged with nitrogen followed by hydrogen. The reaction mixture was stirred under a H_2 atmosphere for 2 h. After purging the system with nitrogen, the mixture was filtered through celite and concentrated. The resulting solid was dissolved in 8 mL CH_3CN and then 20 mL H_2O (0.1% TFA) was added. The solution was frozen and lyophilized to give 29 mg (90%) of the title compound as a white solid. LC/MS: m/z (ES+) 290 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.70 (br, 1H), 9.32 (s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.37-4.33 (m, 2H), 1.33 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).

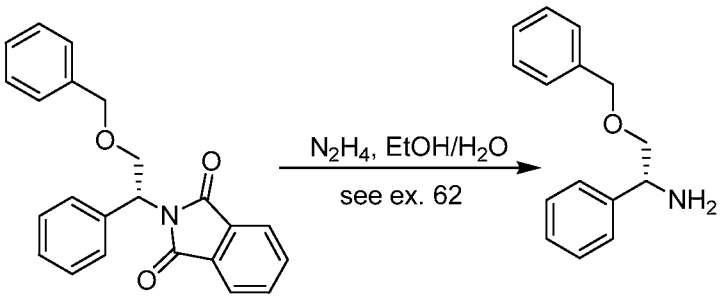
Example 64. Preparation of (*R*)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



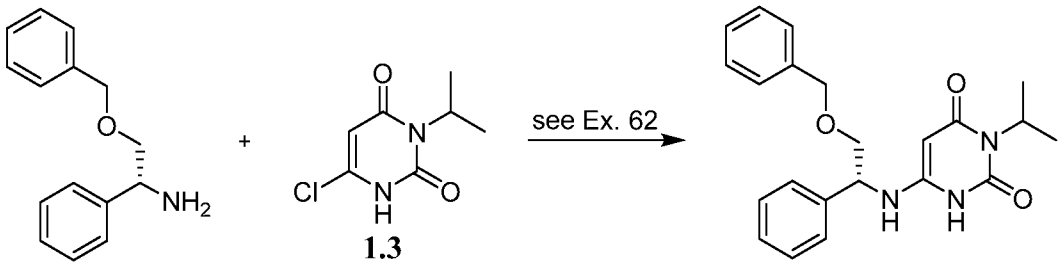
[0170] Compound 64.1. (*R*)-2-(2-hydroxy-1-phenylethyl)isoindoline-1,3-dione. To a 2.0-5.0 mL microwave vial was added (*R*)-2-amino-2-phenylethan-1-ol (1.53 g, 0.0112 mol) and phthalic anhydride (1.65 g, 0.0112 mol). The reaction mixture was capped and heated to 150 °C for 2 minutes in a microwave reactor. The mixture was cooled and diluted with CH_3CN (2 mL), recapped and heated in the microwave reactor a second time at 140 °C for 20 minutes. The volatiles were removed under reduced pressure and the resulting solid was suspended in EtOAc (50 mL). The organic layer was washed with 5% $NaHCO_3$ (aq), H_2O, and brine, dried with anhydrous $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with CH_3OH in CH_2Cl_2 (0 to 5%) to yield 2.81 g (94%) of the title compound. LC/MS: m/z (ES+) 268 $(M+H)^+$.



[0171] Compound 64.2. (*R*)-2-(2-(benzyloxy)-1-phenylethyl)isoindoline-1,3-dione. The title compound was made in a similar manner as the procedure described for **62.3**. However, in this case NaH (60% dispersion in mineral oil, 1.2 equiv.) was used in place of K_2CO_3. Specifically, NaH was added at 0 °C and stirred at room temperature for 45 minutes. The reaction was cooled back to 0 °C and then benzyl bromide (1.2 equiv.) was added. A work-up procedure as described for **62.3** followed by flash chromatography (silca gel, eluting with CH_2Cl_2) yielded the title compound in 59% yield. LC/MS: m/z (ES+) 358 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.84-7.79 (m, 2H), 7.72-7.67 (m, 2H), 7.52-7.48 (m, 2H), 7.37-7.20 (m, 8H), 5.62 (dd, J = 10.2, 5.9 Hz, 1H), 4.63 (t, J = 10.2 Hz, 1 H), 4.58 (s, 2H), 4.06-4.01 (m, 1H).

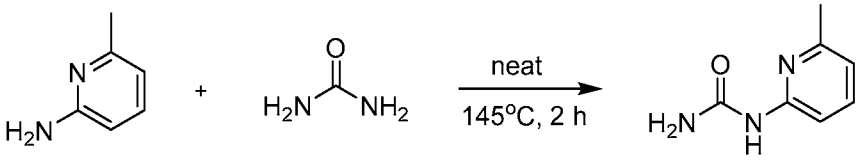


[0172] Compound 64.3. (*R*)-2-(benzyloxy)-1-phenylethan-1-amine. The title compound was prepared in a similar manner as the procedure described for **62.4**. LC/MS: m/z (ES+) 228 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.40-7.24 (m, 10H), 4.56 (d, J = 2.0 Hz, 2H), 4.25 (dd, J = 8.8, 3.7 Hz, 1 H), 3.65-3.60 (m, 1H), 3.49-3.44 (m, 1H).

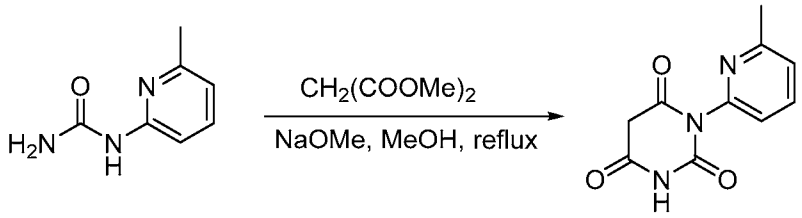


[0173] Compound 64. (*R*)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione. The title compound was prepared in a similar manner as the procedure described for **62**. Here though, the reaction was heated at 140 °C for 1 h. After cooling, the crude reaction mixture was treated with 50/50 CH_3CN/H_2O (0.1% TFA) which led to precipitation. LC/MS: m/z (ES+) 380 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.01 (br, 1H), 7.36-7.26 (m, 10H), 6.62 (d, J = 6.7 Hz, 1H), 4.93-4.83 (m, 1H), 4.67-4.62 (m, 1H), 4.50 (dd, J = 12.0, 2.0 Hz, 2H), 4.30 (s, 1H), 3.68-3.64 (m, 1H), 3.60-3.55 (m, 1H) 1.27-1.23 (m, 6H).

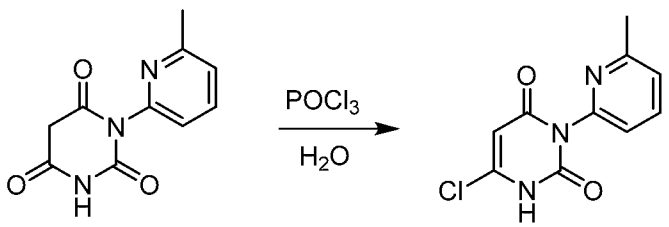
Example 65. Preparation of (*S*)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



[0174] Compound 65.1. 1-(6-methylpyridin-2-yl)urea. To a 25-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added urea (1.48 g, 24.64 mmol, 1.00 equiv) and 6-methylpyridin-2-amine (3 g, 27.74 mmol, 1.00 equiv). The resulting mixture was stirred for 2 h at 145 °C. After cooling, the crude product (4 g) was purified using CombiFlash: Column, C18 silica gel; utilizing a mobile phase of CH_3CN: H_2O = 0:100 to CH_3CN: H_2O = 50:50 over 40 min. This resulted in the isolation of 1.2 g (32%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.07 (s, 1H), 7.56-7.52 (m, 1H), 7.18-7.14 (m, 1H), 6.80-6.75 (m, 1H), 2.36 (s, 3H).

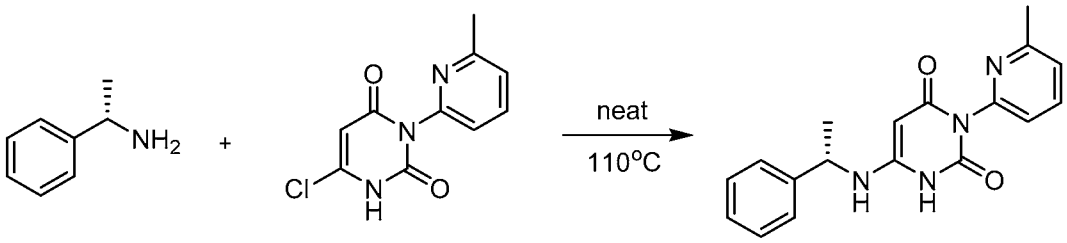


[0175] Compound 65.2. 1-(6-methylpyridin-2-yl)pyrimidine-2,4,6(1H,3H,5H)-trione. The title compound was prepared in a similar manner as the procedure described for **1.2**. Here though, after stirring overnight at 65 °C, the reaction mixture was concentrated under reduced pressure and the crude product was precipitated from CH_3OH:Et_2O (1:50). The solid was collected by filtration and dissolved in CH_3OH (50 mL). The pH value of the solution was adjusted to 7 with cation ion-exchange resin (Dowex 50WX8-100, 5 g). The solids were filtered and the filtrate was concentrated under reduced pressure resulting in 0.5 g (29%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.27 (br s, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.18 (s, 2H), 2.44 (s, 3H).



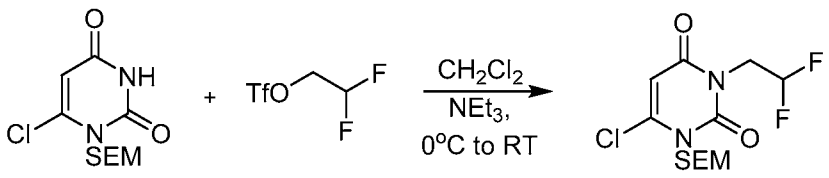
[0176] Compound 65.3. 6-chloro-3-(6-methylpyridin-2-yl)pyrimidine-2,4(1H,3H)-dione. To a stirred solution of 65.2 (500 mg, 2.28 mmol, 1.00 equiv) in $POCl_3$ (5 mL) at 0 °C was added a drop (~20 μL) of H_2O. The resulting solution was warmed to room temperature,

stirred for 30 min., heated to 70 °C and stirred for 2 h. After cooling, the resulting mixture was concentrated under reduced pressure. The resulting residue was carefully dissolved in 10 mL of ice water. The pH was adjusted to 7 with anion ion-exchange resin (activated 201×4(711) strong base styrene anion exchange resin, 20 g) and the solids were filtered. The filtrate was concentrated under reduced pressure resulting in 0.2 g (37%) of the title compound as a yellow solid.



[0177] Compound 65. (*S*)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To a 10-mL round-bottom flask purged and maintained with an inert atmosphere of argon was added *(S)*-α-methylbenzylamine (0.5mL) and **65.3** (200 mg, 0.84 mmol, 1.00 equiv). The resulting solution was stirred for 3 h at 110 °C. After cooling, the resulting mixture was concentrated under vacuum. The residue (100 mg) was purified by pareparative RP-HPLC with the following conditions:Column, XBridge Prep C18 OBD Column, 5um, 19*150mm,; mobile phase, H_2O with 0.05% $NH_4(HCO_3)$ and CH_3CN (15% CH_3CN to 80% in 8 min); This resulted in 28.8 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES+) 323 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 7.76 (t, J = 7.6 Hz, 1H), 7.39- 7.22 (m, 7H), 7.05 (d, J = 7.6 Hz, 1H), 6.82 (br, 1H), 4.63-4.59 (m, 1H), 4.46 (s, 1H), 2.43 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H).

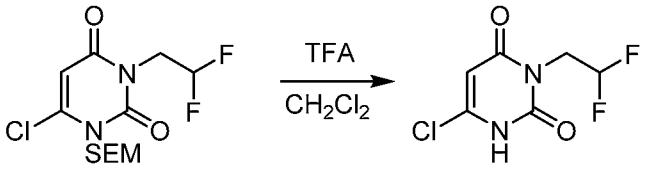
Example 66. Preparation of (*S*)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



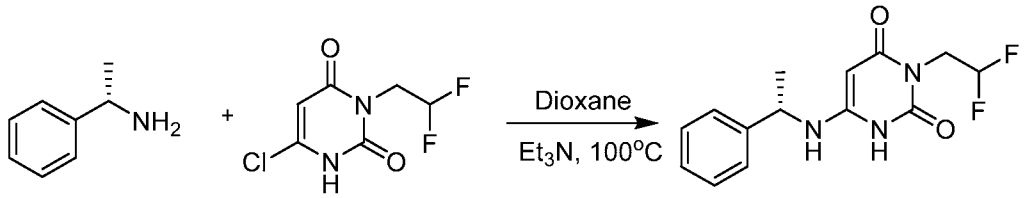
11.1

[0178] Compound 66.1. 6-chloro-3-(2,2-difluoroethyl)-1-((2-(trimethylsilyl)ethoxy)methyl) pyrimidine-2,4(1H,3H)-dione. To a stirred solution of **11.1**

(130 mg, 0.47 mmol) and Et_3N (0.2 mL) in CH_2Cl_2 (2 mL) at 0 °C was added 2,2-difluoroethyl trifluoromethanesulfonate (0.10 mL). The reaction was warmed to room temperature and stirred for 30 minutes. The mixture was concentrated to give the title compound in a crude mixture.

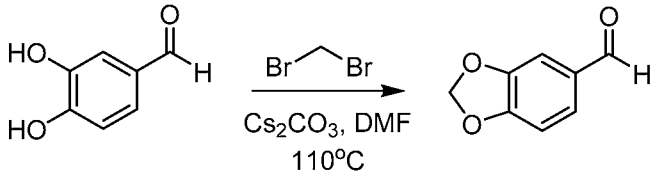


[0179] Compound 66.2. 6-chloro-3-(2,2-difluoroethyl)pyrimidine-2,4(1H,3H)-dione. Crude **65.1** was dissolved in CH_2Cl_2/TFA (1:1, 4 mL) and stirred for 3 h and concentrated. The resulting material was treated with 5% $NaHCO_3$ (aq) until the pH was 7. Ethyl acetate was added to the mixture and the layers were separated. The aqueous layer was concentrated. The resulting solid was suspended in CH_3CN (15 mL) and was remove by filtration. The filtrate was concentrated to give 52 mg of the title compound.

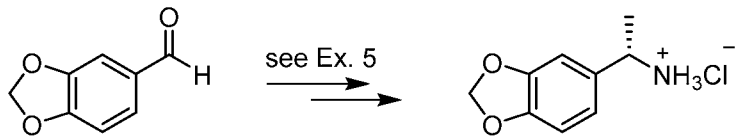


[0180] Compound 66. (*S*)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To **66.2** (52 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) was added Et_3N (100 uL) and (*S*)-α-methylbenzylamine (188 mg, 1.55 mmol). The reaction mixture was heated in a microwave reactor at 100 °C for 32 minutes, cooled to room temperature, and then concentrated. The resulting residue was dissolved in a 2:3 CH_3CN/H_2O (10 mL) with 2 drops of TFA (~40 uL). The mixture was purified by preparative RP-HPLC to provide 8 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES+) 296 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d6): δ ppm 10.20 (br s, 1H), 7.37-7.32 (m, 4H), 7.26-7.23 (m, 1H), 6.71 (d, J = 7.0 Hz, 1H), 6.07 (tt, J = 56.0, 4.5 Hz, 1H), 4.54 (quin, J = 6.8 Hz, 1H), 4.43 (d, J = 2.3 Hz, 1H), 4.02 (td, J = 14.3, 4.7 Hz, 2H), 1.40 (d, J= 6.7 Hz, 3H).

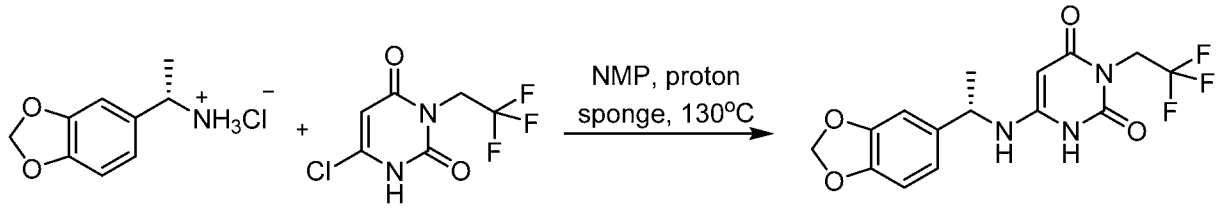
Example 67. Preparation of (*S*)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione.



[0181] Compound 67.1. 2H-1,3-benzodioxole-5-carbaldehyde. To a stirred solution of 3,4-dihydroxybenzaldehyde (10 g, 72.40 mmol, 1.00 equiv) in DMF (150 mL) was added cesium carbonate (35.4 g, 108.31 mmol, 1.50 equiv) and dibromomethane (18.7 g, 107.57 mmol, 1.50 equiv). The resulting solution was stirred for 2 h at 110 °C. The solution was cooled to room temperature and the solid was removed by filtration. The filtrate was diluted with H_2O (300 mL). The resulting solution was extracted with EtOAc (2 x 300 mL). The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluted with with EtOAc/petroleum ether (1:9) to afford 8 g (74%) of the title compound as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm 9.81 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.34 (s, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.08 (s, 2H).



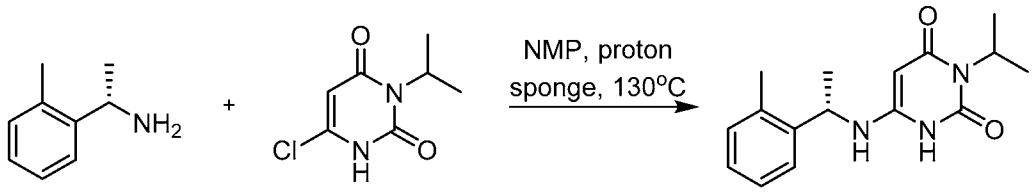
[0182] Compound 67.2. (*S*)-1-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine hydrochloride. The title compound was synthesized according to methods described for the preparation of **5.3**. Here, **67.1** was utilized instead of 3,5-difluorobenzaldehyde. LC/MS: m/z (ES+) 166 $(M+H)^+$.



[0183] Compound 67. (*S*)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione. The title compound was synthesized according to methods described in Example 59. Here, **67.2** was utilized instead of (*S*)-1-(2,6-difluorophenyl)ethan-1-amine hydrochloride and 6-chloro-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione was utilized (synthesized according to methods described in Example 1)

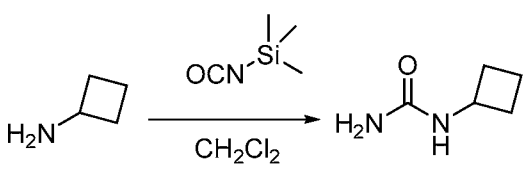
instead of **1.3**. LC/MS: m/z (ES+) 358 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.27 (br s, 1H), 6.94 (d, J= 1.2 Hz, 1H), 6.89-6.82 (m, 3H), 6.72 (d, J = 6.9 Hz, 1H), 5.99 (s, 2H), 4.48-4.40 (m, 4H), 1.38 (d, J = 6.9 Hz, 3H).

Example 68. Preparation of (*S*)-3-isopropyl-6-((1-(o-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione **(68)**.

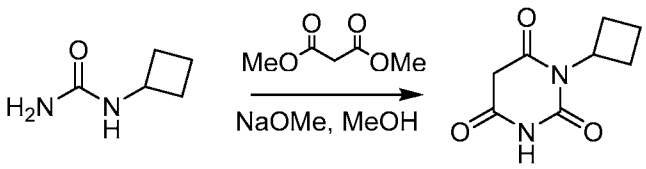


[0184] To a stirred solution of (1*S*)-1-(2-methylphenyl)ethan-1-amine (310 mg, 2.29 mmol, 1.50 equiv) in NMP (1 mL) was added proton sponge (491.4 mg, 2.30 mmol, 1.50 equiv) and **1.3** (288 mg, 1.53 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at 130 °C in an oil bath, cooled to room temperature, and then diluted with DMSO (2 mL). The solids were filtered and the filtrate was purified by Flash-Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: H_2O /0.05% TFA, Mobile Phase B: CH_3CN; Flow rate: 20 mL/min; Gradient: 30%B to 70% B in 10 min. This afforded 50 mg of crude product which was subsequently separated by chiral preparative HPLC with the following conditions: Column, Chiralpak IC, 2*25cm, 5um; mobile phase, hexanes and ethanol (9:1, 15 min). This resulted in 35.6 mg (8%) of the title compound as a white solid. LC/MS: m/z (ES+) 288 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.76 (br s, 1H), 7.28 (d, J = 7.2 Hz, 1H) 7.24-7.14 (m, 3H), 6.48 (d, J = 6.3 Hz, 1H), 4.95-4.86 (m, 1H), 4.60 (quin, J = 6.9 Hz, 1H), 4.19 (s, 1H), 2.34 (s, 3H), 1.37 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.9 Hz, 6H).

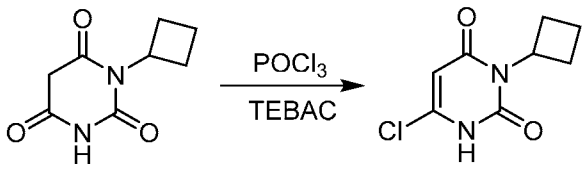
Example 69. Preparation of (*S*)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



[0185] Compound 69.1. 1-cyclobutylurea. To a stirred solution of cyclobutanamine (40 g, 562.42 mmol, 1.00 equiv) in CH_2Cl_2 (400 mL) at 0 °C was added trimethylsilyl isocyanate (64.70 g, 561.60 mmol, 1.00 equiv.) portionwise. The resulting solution was stirred overnight at room temperature and was quenched by the addition of CH_3OH (80 mL). The resulting mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. The residue was washed with Et_2O (2 x 100 mL) and filtered, which afforded 53 g (83%) of the title compound as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 6.17 (d, J = 9.0Hz, 1H), 5.33 (s, 2H), 3.99-3.91 (m, 1H), 2.16-2.07 (m, 2H), 1.81-1.68 (m, 2H), 1.61-1.45 (m, 2H).

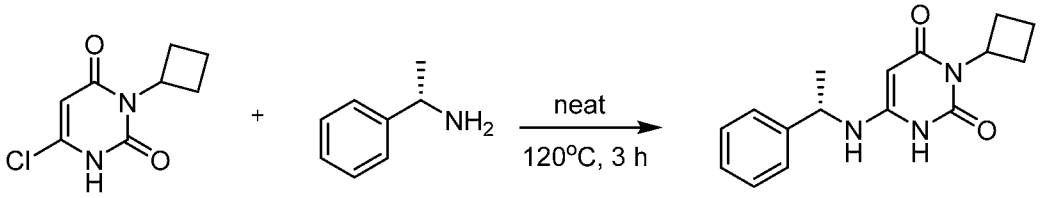


[0186] Compound 69.2. 1-cyclobutylpyrimidine-2,4,6(1H,3H,5H)-trione. To a stirred solution of sodium methoxide (62.43g, 1.156 mol, 2.40 equiv) in CH_3OH (500 mL) was added dimethyl malonate (76.42 g, 0.578 mol, 1.20 equiv) and **69.1** (55 g, 0.48 mol, 1.00 equiv). The resulting solution was heated to 65 °C and stirred overnight. The reaction was cooled and quenched by the addition of H_2O (100 mL). The pH of the solution was adjusted to 1 with concentrated HCl. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_2Cl_2/CH_3OH (20:1) as eluent to afford 60 g (68%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 11.20 (s, 1H), 4.95-4.86 (m, 1H), 3.56 (s, 2H), 2.72-2.62 (m, 2H), 2.16-2.09 (m, 2H), 1.78-1.60 (m, 2H).



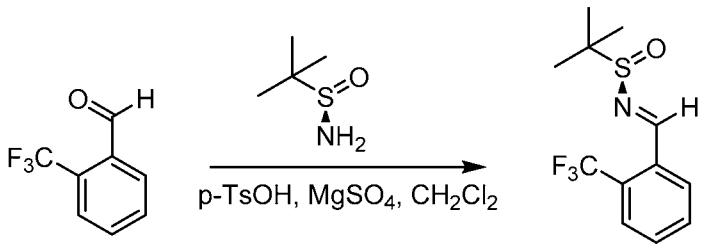
[0187] Compound 69.3. 6-chloro-3-cyclobutylpyrimidine-2,4(1H,3H)-dione. To **69.2** (80 g, 0.44 mol, 1.00 equiv) and triethylbenzylammonium chloride (140.2 g, 0.615 mol, 1.40 equiv) was added (300 mL). The reaction was stirred for 1 h at 65 °C and was then concentrated under reduced pressure. The reaction was quenched by the careful addition of 1 L of water/ice and then the pH value of the solution was adjusted to 1 with 2N NaOH (aq). The solid was filtered, washed with CH_3OH (300 mL) and Et_2O (2 x 300 mL), and dried.

This resulted in 78 g (89%) of the title compound as a light yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 12.23 (s, 1H), 5.82 (s, 1H), 5.13-5.01 (m, 1H), 2.87-2.73 (m, 2H), 2.13-2.03 (m, 2H), 1.80-1.56 (m, 2H).



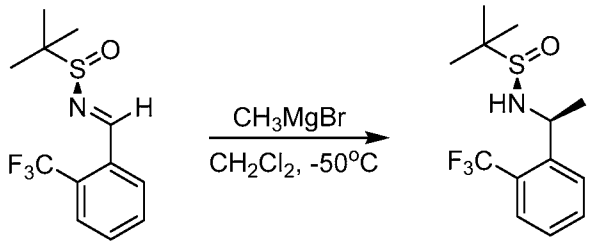
[0188] Compound 69. (*S*)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To a 500-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added **69.3** (78 g, 388.79 mmol, 1.00 equiv) and (*S*)-α-methylbenzylamine (150 mL, 2.00 equiv). The reaction mixture was stirred for 3 h at 120 °C. The reaction mixture was cooled to room temperature, diluted with CH_3OH (1 L) and further cooled to 0 °C. The resulting solid was filtered, washed with Et_2O (2 x 300 mL), and dried under vacuum to afford 57.25 g (52%) of the title compound as a white solid. LC/MS: m/z (ES+) 286 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.94 (br s, 1H), 7.40-7.32 (m, 4H), 7.30-7.26 (m, 1H), 6.40 (br s, 1H), 5.19-5.10 (m, 1H), 4.56-4.49 (m, 1H), 4.35 (s, 1H), 2.91-2.81 (m, 2H), 2.02-1.95 (m, 2H), 1.76-1.58 (m, 2H), 1.42 (d, J = 6.8Hz, 3H).

Example 70. Preparation of *(S)*-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino) pyrimidine-2,4(1H,3H)-dione.

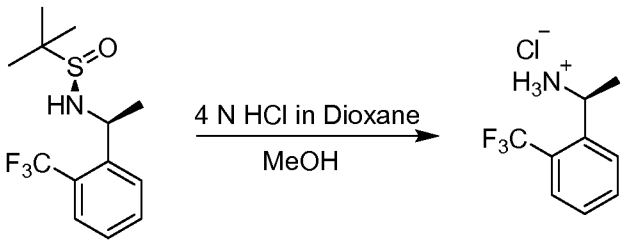


[0189] Compound 70.1. (*R,E*)-2-methyl-N-(2-(trifluoromethyl)benzylidene)propane-2-sulfinamide. To a 100-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added CH_2Cl_2 (50 mL), 2-(trifluoromethyl)benzaldehyde (2.01 g, 11.54 mmol, 1.00 equiv), (*R*)-(+)-2-methylpropane-2-sulfinamide (1.68 g, 13.86 mmol, 1.20 equiv), pyridinium p-toluenesulfonate (0.145 g, 0.05 equiv) and magnesium sulfate (6.93 g, 5.00 equiv). The resulting solution was stirred for 48 h at 40 °C. The mixture was cooled to room temperature and the solid was filtered. The filtrate was concentrated under reduced

pressure and the resulting residue was purified by flash column chromatography (silica gel, eluting with EtOAc/petroleum ether (1:20)). This resulted in 0.96 g (30%) the title compound as a light yellow solid. LC/MS: m/z (ES+) 278 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 8.82-8.80 (m, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.95-7.80 (m, 3H), 1.22 (s, 9H).

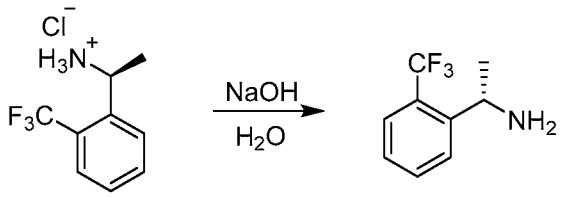


[0190] Compound 70.2. (R)-2-methyl-N-((1S)-1-(2-(trifluoromethyl)phenyl)-ethyl)propane-2-sulfinamide. To a stirred solution of **70.1** (578 mg, 2.08 mmol, 1.00 equiv) in THF (20 mL) at -50 °C was added 3 M methylmagnesium bromide in Et_2O (1.4 mL, 4.20 mmol, 2.0 equiv) dropwise. The resulting solution was stirred at -50 °C for 2.5 h and at room temperature for an additional 10 h. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL) and then concentrated under reduced pressure. The resulting residue was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. This resulted in 700 mg (60% de) of the title compound as a yellow solid. LC/MS: m/z (ES+) 294 $(M+H)^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 7.77-7.74 (m, 1H), 7.67-7.60 (m, 2H), 7.43-7.38 (m, 1H), 5.53 (d, J = 4.5Hz, 1H), 4.70-4.60 (m, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.02 (s, 9H).

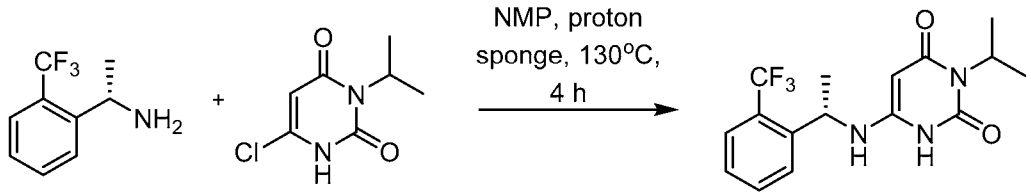


[0191] Compound 70.3. (*S*)-1-(2-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride. To a stirred solution of **70.2** (700 mg, 2.39 mmol, 1.00 equiv) in CH_3OH (4 mL) was added 4N HCl in 1,4-dioxane (2 mL) dropwise. The resulting solution was stirred for 1 h at room temperature and then concentrated under reduced pressure. Solid was

precipitated by the addition of Et_2O (5 mL). The solid was filtered and dried affording the title compound as a white solid (0.32 g, 60%).

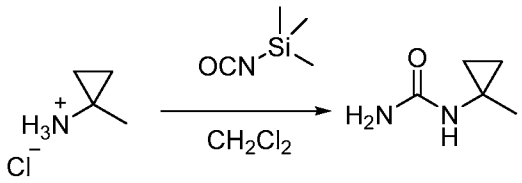


[0192] Compound 70.4. (*S*)-1-(2-(trifluoromethyl)phenyl)ethan-1-amine. To a 50-mL round-bottom flask was added **70.3** (320 mg, 1.43 mmol, 1.00 equiv) and sodium hydroxide (80 mg, 2.00 mmol, 1.40 equiv) in H_2O (20 mL). The resulting solution was stirred for 1 h at room temperature and was then extracted with EtOAc (20 mL). The organic layer was combined and concentrated under reduced pressure. This afforded 190 mg (70%) of the title compound as light yellow oil.

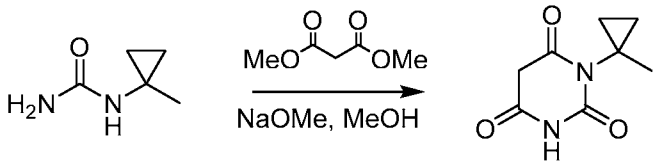


[0193] Compound 70. (*S*)-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino) pyrimidine-2,4(1H,3H)-dione. To a 10-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added NMP (2 mL), **70.4** (160 mg, 0.85 mmol, 1.00 equiv), **1.3** (160 mg, 0.85 mmol, 1.00 equiv), and proton sponge (273 mg, 1.28 mmol, 1.5 equiv.). The resulting solution was stirred for 4 h at 130 °C. The crude product (200 mg) was purified by chiral preparative HPLC with the following conditions: Column, Phenomenex Lux-2 5u Cellulose-2, 30*150mm; mobile phase, Hex-HPLC and ethanol-HPLC (hold 20% ethanol-HPLC in 14 min); Detector, uv 254/220nm. 160 mg crude product was obtained. The obtained material (60 mg) was further purified using chiral preparative HPLC with following conditions: Column: Phenomenex Lux-2 5μ Cellulose-2 30*150mm; Mobile Phase and Gradient: Hex: EtOH = 80:20; Retention Time (Peak 2) (min):11.106. This resulted in 30 mg of the title compound as a white solid. LC/MS: m/z (ES+) 342 $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.84 (br, 1H), 7.78-7.68 (m, 3H), 7.56-7.52 (m, 1H), 6.75 (br s, 1H), 4.93-4.86 (m, 1H), 4.68-4.63 (m, 1H), 4.13 (s, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 7.2 Hz, 6H).

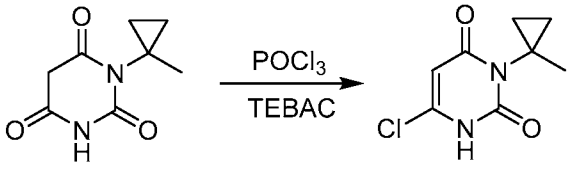
Example 71. Preparation of (*S*)-3-(1-methylcyclopropyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



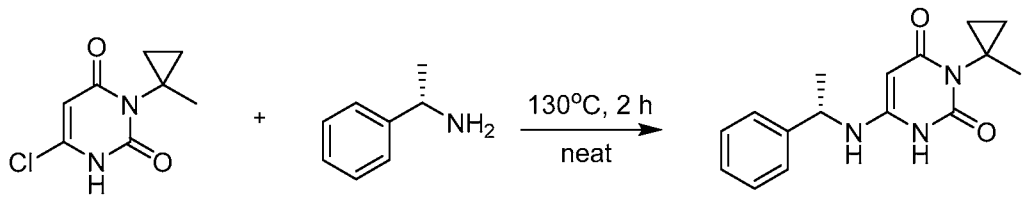
[0194] Compound 71.1. 1-(1-methylcyclopropyl)urea. To a stirred solution of 1-methylcyclopropan-1-amine hydrochloride salt (429 mg, 3.99 mmol, 1.00 equiv) and triethylamine (268 mg, 2.65 mmol, 1.00 equiv) in CH_2Cl_2 (6 mL) was added trimethylsilyl isocyanate (366 mg, 3.18 mmol, 1.20 equiv). The resulting mixture was stirred at room temperature overnight and was quenched by the dropwise addition of CH_3OH (2 mL) at 0 °C. The resulting solution warmed to room temperature and stirred for an additional 1 h. The resulting mixture was concentrated under reduced pressure. The crude product was precipitated from CH_3OH:Et_2O (1:40) affording 300 mg (66%) of the title compound as a white solid.



[0195] Compound 71.2. 1-(1-methylcyclopropyl)pyrimidine-2,4,6(1H,3H,5H)-trione. To a stirred solution of **71.1** (320 mg, 2.80 mmol, 1.0 equiv) in CH_3OH (2 mL) was added sodium methoxide (390 mg, 7.2 mmol, 2.5 equiv) and dimethyl malonate (380 mg, 2.88 mmol, 1.0 equiv). The resulting solution was stirred overnight at 65 °C. After cooling, the reaction was quenched by the addition of H_2O (100 mL). The pH of the solution was adjusted to 2 with concentrated HCl and the resulting mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography with EtOAc/petroleum ether (1:3) as eluent. This afforded 100 mg (20%) of the title compound as a white solid. ^{1}H-NMR (300 MHz, CDCl3): δ ppm 8.04 (br, 1H), 3.61 (s, 2H), 1.41 (s, 3H), 1.00-, 0.86 (m, 4H).



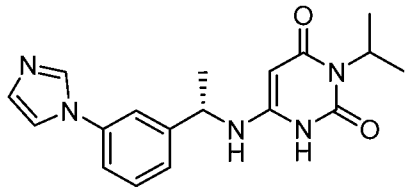
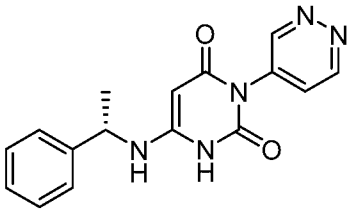
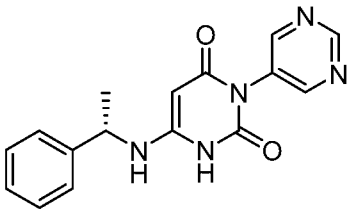
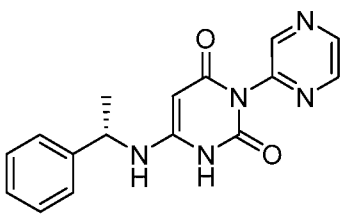
[0196] Compound 71.3. 6-chloro-3-(1-methylcyclopropyl)pyrimidine-2,4(1H,3H)-dione. To **71.2** (100 mg, 0.55 mmol, 1.00 equiv) and triethylbenzylammonium chloride (180 mg, 0.79 mmol, 1.00 equiv) was added $POCl_3$ (2 mL). The resulting solution was stirred for 3 h at 50 °C and then concentrated under reduced pressure. The residue was carefully quenched by the addition of 10 mL of water/ice and was extracted with EtOAc (2 x 30 mL). The organic layers were combined and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography with CH_2Cl_2/CH_3OH (10:1) as eluent to afford 40 mg (36%) of the title compound as a yellow solid.

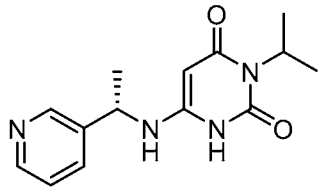
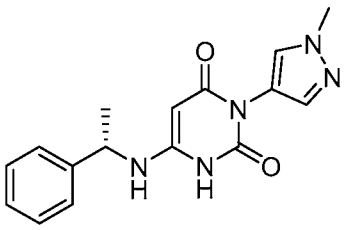
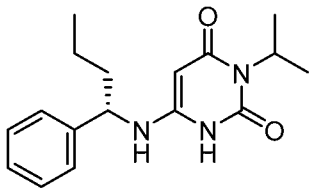
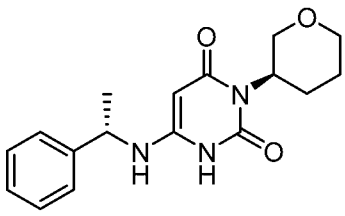


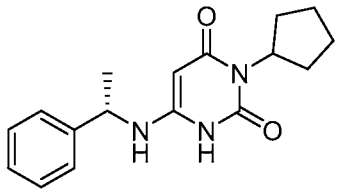
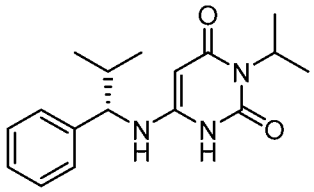
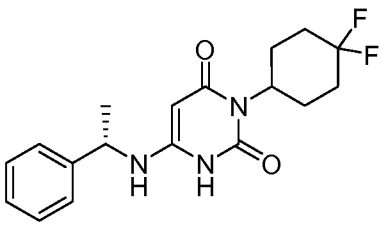
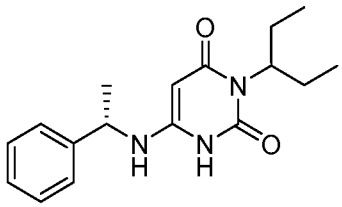
[0197] Compound 71. (*S*)-3-(1-methylcyclopropyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To **71.3** (40 mg, 0.20 mmol, 1.00 equiv) was added (*S*)-α-methylbenzylamine (0.5 mL). The reaction mixture was stirred for 2 h at 130 °C and then was concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: H_2O /0.05% TFA, Mobile Phase B: CH_3CN; Flow rate: 20 mL/min; Gradient: 30% B to 70% B in 10 min. This afforded 15.1 mg (27%) of the title compound as a white solid. LC/MS: m/z (ES+) 286 $(M+H)^+$. ^{1}H-NMR (300 MHz, CD_3CN): δ ppm 8.41 (br, 1H), 7.42-7.29 (m, 5H), 5.79 (br, 1H), 4.48-4.44 (m, 1H), 4.30 (s, 1H), 1.47 (d, J = 6.9 Hz, 3H), 1.27 (s, 3H), 0.87-0.77 (m, 4H).

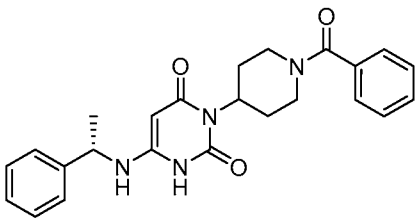
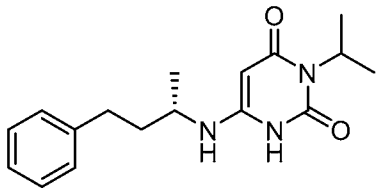
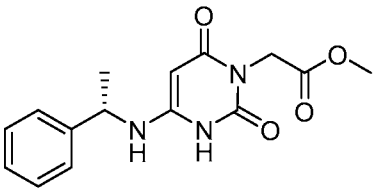
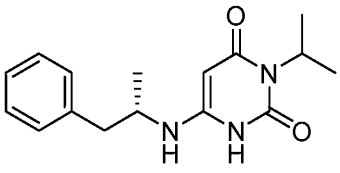
Example 72. Preparation of Additional Pyrimidine Dione Compounds.

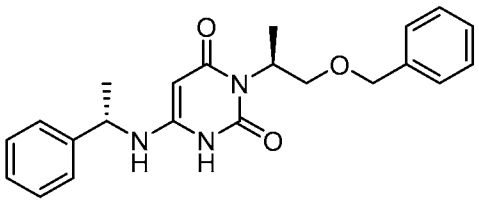
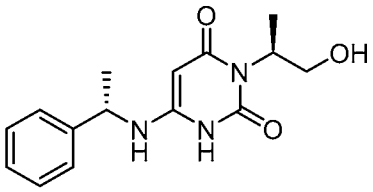
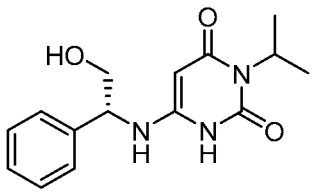
[0198] The compounds in Table 1B were prepared according to the examples as described above (exemplary methods provided as 'Reference. Ex. No.')

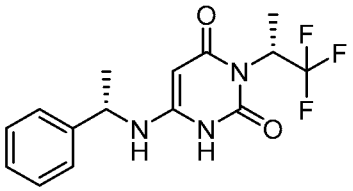
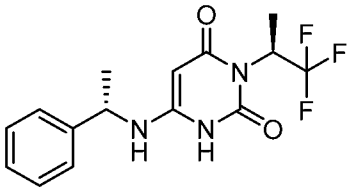
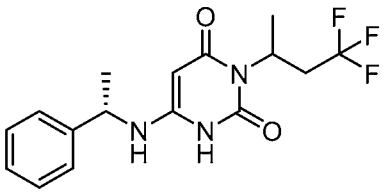
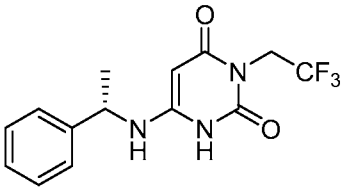
Structure	Compound No. ----- Reference Ex. No.	Observed Mass and/or ^{1}H NMR
	**72** ---- 17	340 $(M+H)^+$ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.89 (br s, 1H), 9.54 (br s, 1H), 8.22 (br s, 1H) 7.82 (br s, 1H), 7.75 (s, 1H) 7.66-7.54 (m, 2H), 7.48 (d, J = 7.5 Hz, 1H), 6.60-6.58 (m, 1H), 4.90-4.83 (m, 1H), 4.55-4.48 (m, 1H), 4.30 (s, 1H), 1.42 (d, J = 6.9 Hz, 3H), 1.27-1.21 (m, 6H).
	**73** ---- 15	310 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.20 (m, 1H), 9.04 (br s, 1H), 7.57 (m, 1H), 7.38-7.32 (m , 4H), 7.26-7.21 (m, 1H), 6.76 (m, 1H), 4.69-4.62 (m, 1H), 4.46 (s, 1H), 1.40 (d, J = 6.8 Hz, 3H).
	**74** ---- 15	310 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.56 (m, 1H), 8.49 (m, 1H), 8.37 (m, 1H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 6.68 (m, 1H), 4.71-4.65 (m, 1H), 4.34 (s, 1H), 1.37 (d, J = 6.8 Hz, 3H).
	**75** ---- 15	310 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.60 (m, 1H), 8.57 (m, 1H), 8.49 (br s, 1H), 7.39-7.32 (m, 4H), 7.26-7.22 (m, 1H), 6.68 (m, 1H), 4.69-4.64 (m, 1H), 4.41 (s, 1H), 1.39 (d, J = 6.8 Hz, 3H).

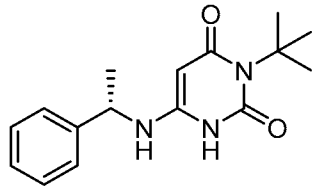
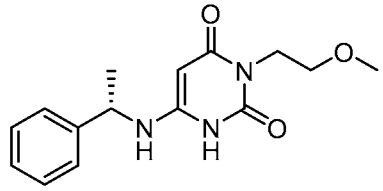
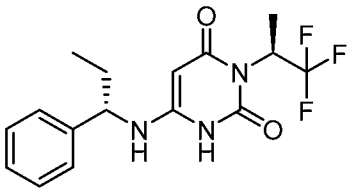
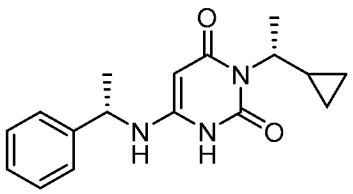
	**76** ---- 5 and 58	275 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.70 (br, 1H), 8.60 (d, J = 2.0 Hz, 1H) 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.6, 4.8 Hz, 1H), 6.67 (br s, 1H), 4.94-4.88 (m, 1H), 4.62-4.58 (m, 1H), 4.38 (s, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.30-1.28 (m, 6H).
	**77** ---- 15	312 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.69 (br s, 1H), 7.65 (s, 1H), 7.40-7.20 (m, 7H), 4.52 (quin, J = 6.8 Hz, 1H), 4.40 (s, 1H), 3.30 (br s, 3H), 1.39 (d, J = 7.0 Hz, 3H).
	**78** ---- 1	302 (M+H)+ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.58 (br s, 1H), 7.36-7.23 (m, 5H), 5.16 (m, 2H), 4.69 (s, 1H), 4.26 (m, 1H), 1.82-1.71 (m, 2H), 1.44-1.38 (m, 6H), 1.36-1.25 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H).
	**79** ---- 11	316 (M+H)+ ^{1}H-NMR (400 MHz, CD_3CN): δ ppm 7.30-7.20 (m, 4H), 7.16-7.11(m, 1H), 6.32 (m, 1H), 4.69-4.62 (m, 1H), 4.43 (quin, J = 6.7 Hz, 1H), 4.29 (s, 1H), 4.00 (t, J = 10.5 Hz, 1H), 3.67-3.59 (m, 1H), 3.44-3.40 (m, 1H), 3.14-3.08 (m, 1H), 2.48-2.38 (m, 1H), 1.56-1.45 (m, 3H), 1.38(d, J = 6.8 Hz, 3H).

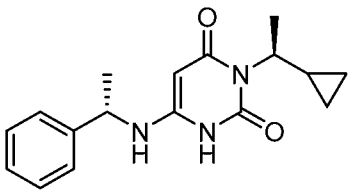
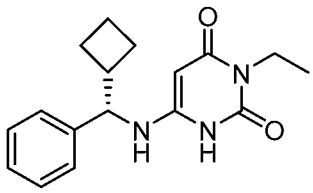
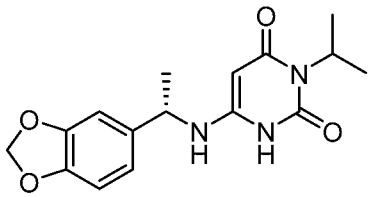
	**80** ---- 1	300 (M+H)+ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.82 (br s, 1H), 7.41-7.19 (m, 5H), 6.50 (d, J = 6.7 Hz, 1H), 5.05-5.01 (m, 1H), 4.50-4.46 (m, 1H), 4.34 (s, 1H), 2.01-1.84 (m, 2H), 1.83-1.64 (m, 2H), 1.63-1.51 (m, 2H), 1.49-1.34 (m, 5H).
	**81** ---- 5	302 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.39-7.35 (m, 2H), 7.30-7.28 (m, 3H), 5.06-5.00 (m, 1H), 4.53 (s, 1H), 4.12 (d, J = 7.2 Hz, 1H), 2.10-2.01 (m, 1H), 1.40-1.37 (m, 6H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H).
	**82** ---- 7	350 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD): δ ppm 7.43-7.33 (m, 4H), 7.30-7.26 (m, 1H), 4.82-4.75 (m, 1H), 4.54-4.49 (m, 2H), 2.74-2.65 (m, 2H), 2.15-2.05 (m, 2H), 1.93-1.79 (m, 2H),1.61-1.57 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).
	**83** ---- 1	302 $(M+H)^+$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.73 (br s, 1H), 7.40 - 7.22 (m, 5H), 6.50 (d, J = 5.1 Hz, 1H), 4.57-4.44 (m, 2H), 4.34 (br s, 1H), 1.90 (ddd, J = 13.3, 9.8, 7.4 Hz, 2H), 1.61- 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H), 0.74-0.60 (m, 6H).

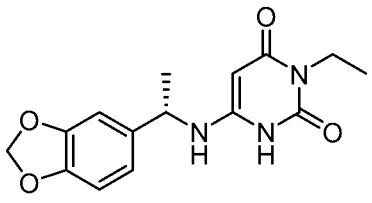
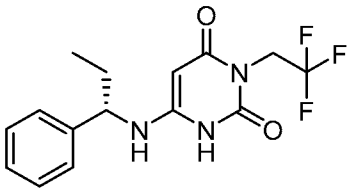
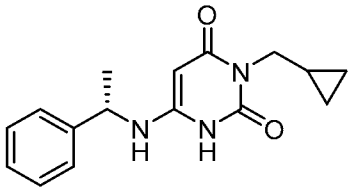
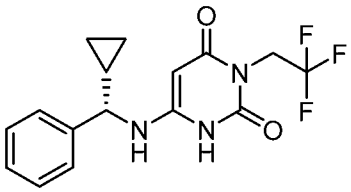
	**84** ---- 12	419 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.88 (br s, 1H), 7.45-7.41 (m, 3H), 7.37-7.29 (m, 6H), 7.27-7.22 (m, 1H), 6.54 (d, J = 6.7 Hz, 1H), 4.84-4.79 (m, 1H), 4.52-4.47 (m, 1H), 4.36 (d, J = 2.4 Hz, 1H), 3.57 (m, 2H), 3.05 (m, 2H), 2.38 (m, 2H), 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H).
	**85** ---- 1	302 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.73 (br s, 1H), 7.31-7.22 (m, 2H), 7.21-7.12 (m, 3H), 5.93 (d, J = 8.2 Hz, 1H), 5.00-4.87 (m, 1H) 4.44 (s, 1H), 4.30 (s, 1H), 3.37-3.31 (m, 1H), 2.65-2.53 (m, 2H), 1.70 (dtd, J = 9.0, 6.9, 6.9, 2.0 Hz, 1H), 1.29 (d, J = 7.0 Hz, 6H), 1.11 (d, J = 6.3 Hz, 3H).
	**86** ---- 11	304 $(M+H)^+$ ^{1}H-NMR (400 MHz, CD_3OD + $CDCl_3$): 7.22-7.15 (m, 2H), 7.13-7.07 (m, 3H), 6.28 (d, J = 6.1 Hz, 1H), 4.44 (s, 1H), 4.38 (s, 2H), 4.30-4.23 (m, 1H), 3.55 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H).
	**90** ---- 1	288 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.77 (br s, 1H), 7.32-7.26 (m, 2H), 7.23-7.12 (m, 3H), 5.85 (d, J = 7.9 Hz, 1H), 4.97-4.87 (m, 1H), 4.55 (s, 1H), 3.77-3.65 (m, 1H), 2.76-2.68 (m, 2H), 1.27 (d, J = 7.0 Hz, 6H), 1.05 (d, J = 6.7 Hz, 3H).

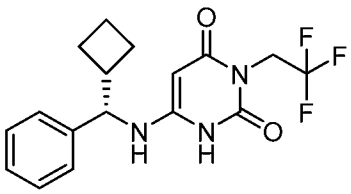
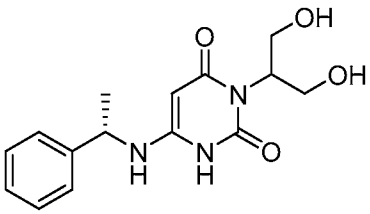
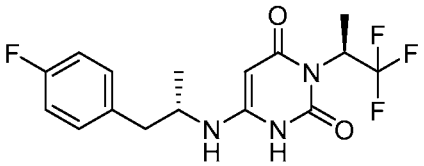
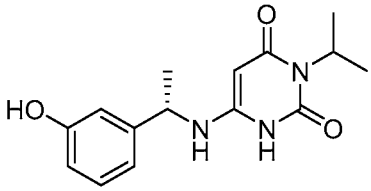
	**91** ---- 53	380 (M+H)+ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.77 (br s, 1H), 7.33-7.23 (m, 10H), 5.23 (br s, 1H), 4.67 (br s, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.44-4.37 (m, 1H), 4.09 (t, J = 9.2 Hz, 1H), 3.63 (dd, J = 9.8, 5.9 Hz, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.35 (d, J = 7.0 Hz, 3H).
	**92** ---- 54	290 (M+H)+ ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 9.68 (s, 1H), 7.41 - 7.22 (m, 5H), 5.62 (s, 1H), 5.08 (td, J = 7.3, 2.9 Hz, 1H), 4.67 (s, 1H), 4.48 - 4.35 (m, 1H), 3.98 (dd, J = 11.9, 7.6 Hz, 1H), 3.75 (dd, J = 11.7, 3.1 Hz, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 7.0 Hz, 3H).
	**93** ---- 1	290 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.01 (d, J = 2.0 Hz, 1H), 7.37-7.23 (m, 5H), 6.61 (d, J = 6.3 Hz, 1H), 5.19 (t, J = 5.1 Hz, 1H), 4.93-4.83 (m, 1H), 4.40- 4.33 (m, 1H), 4.24 (d, J = 2.4 Hz, 1H), 3.66 (dt, J = 11.1, 4.7 Hz, 1H), 3.52- 3.44 (m, 1H), 1.25 (dd, J= 6.9, 2.2 Hz, 6H).

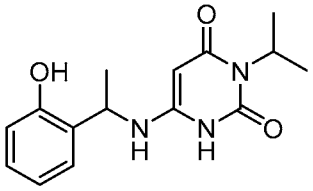
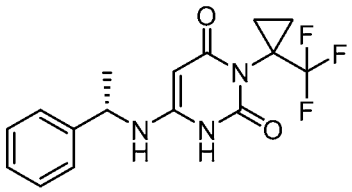
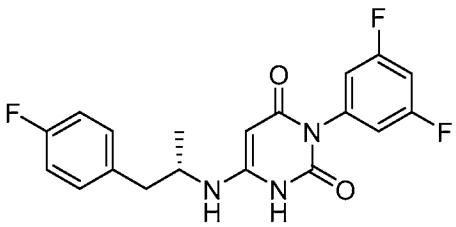
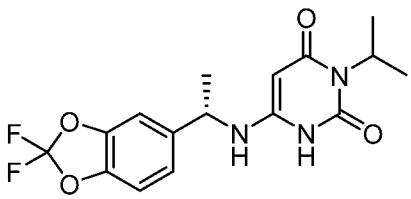
	**94** ---- 1 and 50	328 (M+H)+ ^{1}H NMR (400 MHz, DMSO-d_6 @ 75 °C): δ ppm 9.91 (br s, 1H), 7.44-7.23 (m, 5H), 6.58 (br s, 1H), 5.52 (br s, 1H), 4.59-4.51 (m, 1H), 4.46 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H).
	**95** ---- 1 and 50	328 (M+H)+ ^{1}H NMR (400 MHz, DMSO-d_6 @ 75 °C): δ ppm 9.91 (br s, 1H), 7.44-7.23 (m, 5H), 6.58 (br s, 1H), 5.52 (br s, 1H), 4.59-4.51 (m, 1H), 4.46 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H).
	**99** ---- 1	342 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6 @ 50 °C): δ ppm 9.79 (br s, 1H), 7.46-7.23 (m, 5H), 6.51 (d, J = 6.7 Hz, 1H), 5.13 (br s, 1H), 4.50 (quin, J = 6.9 Hz, 1 H), 4.37 (s, 1H), 3.15-3.01 (m, 1H), 2.60- 2.50 (m, 1H), 1.40 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H).
	**100** ---- 1 and 50	314 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.32 (br s, 1H), 7.40-7.34 (m, 4H), 7.29-7.25 (m, 1H), 6.81 (d, J = 6.6 Hz, 1H), 4.60-4.54 (m, 1H), 4.49-4.40 (m, 3H), 1.42 (d, J = 6.6 Hz, 3H).

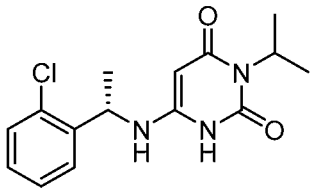
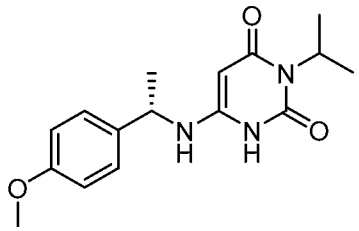
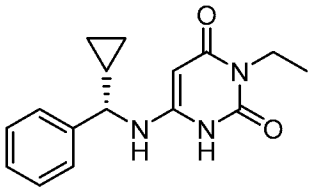
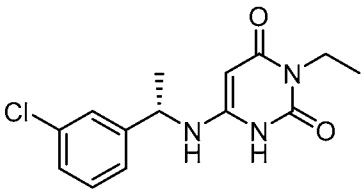
	**101** ---- 1 and 50	288 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.50 (br s, 1H), 7.56-7.44 (m, 4H), 7.38-7.24 (m, 1H), 6.41 (d, J = 6.4 Hz, 1H), 4.45 (q, J = 6.8 Hz, 1H), 4.25 (s, 1H), 1.54 (s, 9H), 1.38 (d, J= 6.8 Hz, 3H).
	**102** ---- 57	290 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.31 (br s, 1H), 7.35-7.23 (m, 5H), 5.72 (d, J = 4.7 Hz, 1H), 4.67 (s, 1H), 4.40 (quin, J = 6.6 Hz, 1H), 4.05 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.27 (s, 3H), 1.46 (dd, J= 6.7, 1.6 Hz, 3H).
	**103** ---- 1 and 59	342 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-$d_{6,@}$ 75 °C): δ ppm 9.91 (br s, 1H), 7.37-7.24 (m, 5H), 6.59 (br s, 1H), 5.51 (br s, 1H), 4.45 (br s, 1H), 4.31 (q, J = 6.9 Hz, 1H), 1.83-1.67 (m, 2H), 1.52 (d, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H).
	**104** ---- 1 and 58	300 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.80 (br s, 1H), 7.37-7.31 (m, 4H), 7.27-7.22 (m, 1H), 6.52 (br, 1H), 4.48 (q, J = 6.7 Hz, 1H), 4.32 (br s, 1H), 3.93 (br, 1H), 1.62 (br, 1H), 1.38 (d, J= 6.7 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H), 0.48-0.41 (m, 1H), 0.27-0.21 (m, 1H), 0.14 (dq, J = 9.4, 4.8 Hz, 1H), 0.02 (m, 1H).

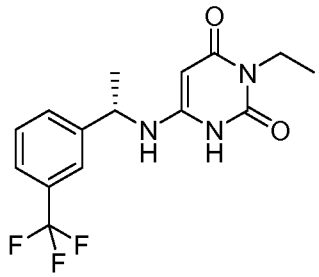
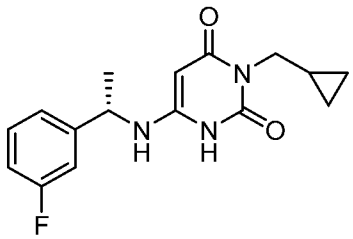
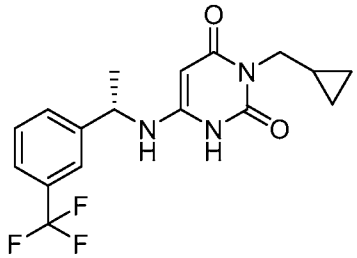
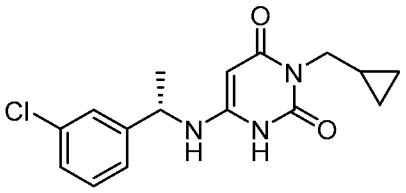
	**105** ---- 1 and 58	300 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.81 (br s, 1H), 7.37-7.30 (m, 4H), 7.26-7.22 (m, 1H), 6.53 (d, J = 5.9 Hz, 1H), 4.48 (q, J = 6.8 Hz, 1H), 4.32 (d, J = 1.6 Hz, 1H), 3.85 (m, 1H), 1.61 (m, 1H), 1.38 (d, J= 7.0 Hz, 3H), 1.32 (d, J = 6.7 Hz, 3H), 0.49-0.42 (m, 1H), 0.28-0.22 (m, 1H), 0.17-0.12 (m, 1H), 0.01- (-)0.05, (m, 1H).
	**106** ---- 8	300 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.96 (br s, 1H), 7.36-7.24 (m, 5H), 6.48 (d, J = 6.3 Hz, 1H), 4.40 (s, 1H), 4.36-4.27 (m, 1H), 3.63 (q, J = 6.6 Hz, 2H), 2.67-2.50 (partially obscured m, 1H) 2.02-1.95 (m, 1H), 1.90-1.78 (m, 4H), 1.66-1.57 (m, 1H), 0.98 (t, J = 6.6 Hz, 3H).
	**107** ---- 67 and 59	318 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.76 (br s, 1H), 6.92 (d, J= 1.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.80 (dd, J = 6.0, 1.8 Hz, 1H), 6.44 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 4.93-4.88 (m, 1H), 4.41-4.35 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H) 1.28 (d, J= 1.2 Hz, 3H) 1.26 (d, J = 1.2 Hz, 3H).

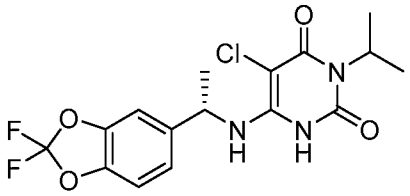
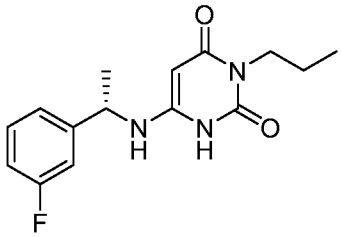
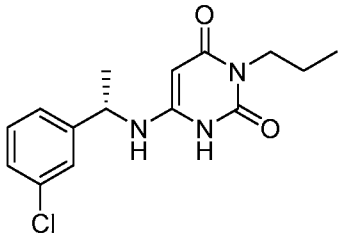
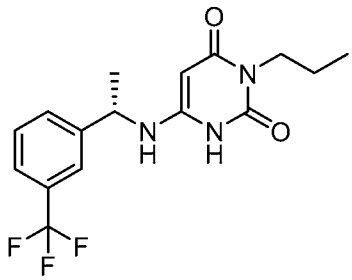
	**108** ---- 67 and 59	304 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.93 (br s, 1H), 6.92 (d, J= 1.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.82-6.79 (m, 1H), 6.48 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 4.45-4.39 (m, 2H), 3.65 (q, J = 6.6 Hz, 2H), 1.36 (d, J = 6.9 Hz, 3H) 0.99 (t, J= 6.9 Hz, 3H).
	**109** ---- 1, 5 and 7	328 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.28 (br s, 1H), 7.39-7.24 (m, 5H), 6.81 (d, J = 6.6 Hz, 1H), 4.47-4.33 (m, 4H), 1.80-1.67 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H).
	**110** ---- 1 and 50	286 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.01 (br s, 1H), 7.39-7.33 (m, 4H), 7.30-7.23 (m, 1H), 6.60 (d, J = 6.0 Hz, 1H), 4.52 (q, J = 6.6 Hz, 1H), 4.38 (s, 1H), 3.49 (d, J = 6.9 Hz, 2H), 1.40 (d, J = 6.9 Hz, 3H) 1.08-1.00 (m, 1H), 0.37-0.33 (m, 2H), 0.28-0.23 (m, 2H).
	**111** ---- 7 and 59	340 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.29 (br s, 1H), 7.37-7.33 (m, 4H), 7.30-7.25 (m, 1H), 6.98 (d, J = 5.6 Hz, 1H), 4.42 (q, J = 9.2 Hz, 2H), 4.35 (d, J= 1.6 Hz, 1H), 3.89-3.85 (m, 1H), 1.24-1.15 (m, 1H) 0.61-0.56 (m, 1H), 0.50-0.33 (m, 3H).

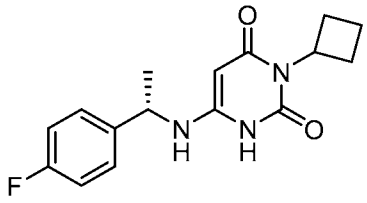
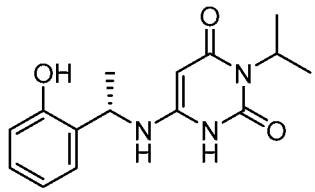
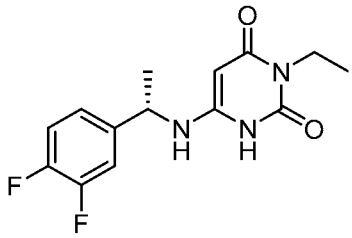
	**112** ---- 8 and 59	354 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.27 (br s, 1H), 7.45-7.25 (m, 5H), 6.73 (br s, 1H), 4.46-4.35 (m, 4H), 2.67-2.50 (partially obscured m, 1H), 2.04-2.01 (m, 1H), 1.90-1.79 (m, 4H), 1.68-1.62 (m, 1H).
	**113** ---- 15	306 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6 @ 90 °C): δ ppm 9.86 (br s, 1H), 7.39-7.31 (m, 4H), 7.29-7.25 (m, 1H), 6.48 (d, J = 6.7 Hz, 1H), 5.00-4.91 (m, 1H), 4.78 (m, 1H), 4.56-4.50 (m, 1H), 4.45-4.38 (m, 2H), 3.76-3.70 (m, 2H), 1.42 (d, J = 7.4 Hz, 3H).
	**114** ---- 1 and 51	360 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6 @ 90 °C): δ ppm 9.86 (br s, 1H), 7.25 (dd, 8.4, 5.7 Hz, 2H), 7.10-7.04 (m, 2H), 5.94 (br s, 1H), 5.52 (br s, 1H), 4.62 (br s, 1H), 3.79-3.71 (m, 1H), 2.76 (d, J= 6.7 Hz, 2H), 1.55 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H).
	**115** ---- 62	290 (M+H)+

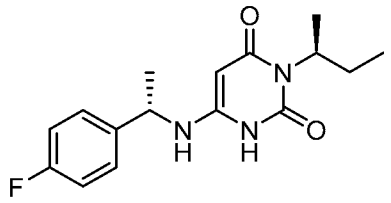
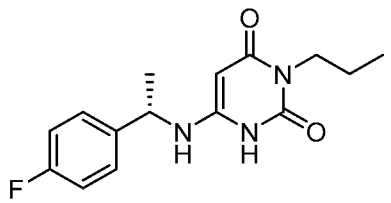
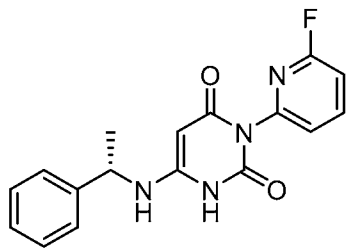
	**116** ---- 62	290 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.83 (br s, 1H), 9.68 (br s, 1H), 7.14 (dd, J = 7.4, 1.6 Hz, 1H), 7.05 (td, J = 7.6, 1.6 Hz, 1H), 6.82-6.74 (m, 2H), 6.40 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.60 (quin, J = 6.9 Hz, 1H), 4.30 (d, J = 2.4 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H), 1.27-1.22 (m, 6H).
	**117** ---- 1 and 59	340 (M+H)+ ^{1}H-NMR (300 MHz, $CDCl_3$: δ ppm 10.40 (br s, 1H), 7.44-7.26 (m, 5H), 6.13 (br s, 1H), 4.80 (br s, 1H), 4.45 (m, 1H), 1.76-1.52 (m, 5H), 1.35-1.27 (m, 2H).
	**118** ---- 1 and 51	376 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.27 (br s, 1H), 7.29-7.22 (m, 3H), 7.15-7.10 (m, 2H), 7.01 (dd, J = 8.2, 2.3 Hz, 2H), 6.12 (br s, 1H), 4.72 (d, J = 2.0 Hz, 1H), 3.79-3.71 (m, 1H), 2.76 (d, J= 6.7 Hz, 2H), 1.09 (d, J = 6.7 Hz, 3H).
	**119** ---- 5 and 59	354 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.84 (br s, 1H), 7.43 (d, J= 1.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 8.4, 1.2 Hz, 1H), 6.54 (d, J = 6.8 Hz, 1H), 4.90 (q, J = 6.8 Hz, 1H), 4.55-4.52 (m, 1H), 4.34 (d, J = 2.0 Hz, 1H), 1.39 (d, J = 6.8 Hz, 3H) 1.31-1.26 (m, 6H).

	**120** ---- 5 and 59	308 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 9.87 (m, 1H), 7.48-7.28 (m, 4H), 6.66 (d, J = 6.6 Hz, 1H), 4.93-4.84 (m, 1H), 4.70 (quin, J = 6.6 Hz, 1H), 4.08 (s, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.28-1.24 (m, 6H).
	**121** ---- 5	304 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.68 (m, 1H), 7.25-7.21 (m, 2H), 6.91-6.87 (m, 2H), 6.43 (m, 1H), 4.92-4.85 (m, 1H), 4.41 (quin, J = 6.7 Hz, 1H), 4.32 (s, 1H), 3.71 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).
	**122** ---- 7 and 59	286 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 7.38-7.33 (m, 4H), 7.28-7.25 (m, 1H), 6.80 (br s, 1H), 4.24 (s, 1H), 3.82-3.78 (m, 1H), 3.63 (q, J = 6.8 Hz, 2H), 1.17-1.13 (m, 1H), 0.97 (t, J = 6.8 Hz, 3H), 0.59-0.54 (m, 1H), 0.47-0.32 (m, 3H).
	**123** ---- 1 and 59	294 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.00 (br s, 1H), 7.44 (s, 1H), 7.42-7.30 (m, 3H), 6.61 (d, J = 6.6 Hz, 1H), 4.57-4.53 (m, 1H), 4.38 (d, J = 1.8 Hz, 1H), 3.65 (q, J = 6.9 Hz, 2H), 1.39 (d, J = 6.9 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).

	**124** ---- 1 and 59	328 (M+H) ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 7.75 (s, 1H), 7.72-7.59 (m, 3H), 6.99 (br s, 1H), 4.68-4.62 (m, 1H), 4.38 (s, 1H), 3.65 (q, J = 6.6 Hz, 2H), 1.42 (d, J = 6.6 Hz, 3H), 1.01 (t, J = 4.5 Hz, 3H).
	**125** ---- 1 and 59	304 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.01 (br s, 1H), 7.42 (dd, J = 7.8, 6.0 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 7.12-7.06 (m, 1H), 6.62 (d, J = 7.2 Hz, 1H), 4.56 (quin, J = 6.9 Hz, 1H), 4.39 (s, 1H), 3.49 (d, J = 6.9 Hz, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.07-0.99 (m, 1H), 0.37-0.34 (m, 2H), 0.30-0.22 (m, 2H).
	**126** ---- 1 and 59	354 (M+H)+ ^{1}H-NMR (300 MHz, CD_3OD): δ ppm 7.73-7.50 (m, 4H), 4.63 (q, J = 6.9 Hz, 1H), 3.62 (d, J = 7.2 Hz, 2H), 1.50 (d, J = 6.9 Hz, 3H) 1.17-1.10 (m, 1H), 0.45-0.39 (m, 2H), 0.32-0.26 (m, 2H).
	**127** ---- 1 and 59	320 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.01 (br s, 1H), 7.45 (s, 1H), 7.42-7.30 (m, 3H), 6.64 (d, J = 6.9 Hz, 1H), 4.58-4.53 (m, 1H), 4.39 (s, 1H), 3.50 (d, J = 7.2 Hz, 2H), 1.40 (d, J = 6.6 Hz, 3H) 1.07-1.03 (m, 1H), 0.37-0.31 (m, 2H), 0.25-0.22 (m, 2H).

	**128** ---- 3	388(M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.50 (br s, 1H), 7.52- 7.22 (m, 3H), 4.87-4.72 (m, 1H), 4.52-4.41 (m, 1H), 1.60-1.48 (m, 3H), 1.41-1.27 (m, 6H).
	**129** ---- 1 and 59	292 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.00 (br s, 1H), 7.40 (dt, J = 7.8 Hz, 0.6 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.09-7.06 (m, 1H), 6.60 (d, J = 6.9 Hz, 1H), 4.46 (q, J = 6.6 Hz, 1H), 4.38 (s, 1H), 3.60-3.55 (m, 2H), 1.47-1.39 (m, 5H), 0.79 (t, J = 7.5 Hz, 3H).
	**130** ---- 1 and 59	308 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.01 (br s, 1H), 7.44 (t, J = 0.9 Hz, 1H), 7.41-7.38 (m, 1H), 7.34-7.31 (m, 2H), 6.62 (d, J = 5.1 Hz, 1H), 4.55 (q, J = 6.7 Hz, 1H), 4.38 (s, 1H), 3.54 (dd, J = 6.0, 5.7 Hz, 2H), 1.47-1.39 (m, 5H), 0.84 (t, J = 7.5 Hz, 3H).
	**131** ---- 1 and 59	342 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.05 (br s, 1H), 7.74 (s, 1H), 7.68-7.56 (m, 3H), 6.69 (d, J = 6.4 Hz, 1H), 4.70-4.63 (m, 1H), 4.40 (s, 1H), 3.59-3.54 (m, 2H), 1.49-1.40 (m, 5H), 0.86 (t, J = 6.0 Hz, 3H).

	**132** ---- 1	304 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.85 (br s, 1H), 7.37-7.33 (m, 2H), 7.18-7.13 (m, 2H), 6.52 (d, J = 7.4 Hz, 1H), 5.14-5.05 (m, 1H), 4.50 (quin, J = 6.8 Hz, 1H), 4.31 (s, 1H), 2.84-2.78 (m, 2H), 1.97-1.91 (m, 2H), 1.70-1.54 (m, 2H), 1.36 (t, J = 6.7 Hz, 3H).
	**133** ---- 1	290 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.83 (br s, 1H), 9.68 (br s, 1H), 7.14 (dd, J = 7.4, 1.6 Hz, 1H), 7.07-7.03 (m, 1H), 6.81-6.74 (m, 2H), 6.42 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.60 (quin, J = 6.8 Hz, 1H), 4.31 (d, J = 2.3 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.27-1.22 (m, 6H).
	**134** ---- 1	296 (M+H)+ ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 10.03 (br s, 1H), 7.48-7.39 (m, 2H), 7.23-7.20 (m, 1H), 6.60 (d, J = 5.1 Hz, 1H) 4.58-4.53 (m, 1H), 4.38 (s, 1H), 3.66 (q, J = 5.1 Hz, 2H), 1.39 (d, J = 5.1 Hz, 3H), 0.99 (t, J = 5.1 Hz, 3H).

	**135** ---- 1	306 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.95 (br s, 1H), 7.36 (dd, J = 9.0, 5.5 Hz, 2H), 7.18-7.14 (m, 2H), 6.54 (d, J = 7.0 Hz, 1H) 4.66 (br s, 1H), 4.54-4.49 (m, 1H), 4.34 (s, 1H), 1.97-1.86 (m, 1H), 1.65-1.55 (m, 1H), 1.38 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 0.70 (t, J = 6.8 Hz, 3H).
	**136** ---- 1	292 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 9.95 (br s, 1H), 7.36 (dd, J = 9.0, 5.5 Hz, 2H), 7.18-7.14 (m, 2H), 6.54 (d, J = 7.0 Hz, 1H) 4.56-4.49 (m, 1H), 4.35 (d, J = 2.3 Hz, 1H), 3.57-3.53 (m, 2H), 1.44-1.36 (m, 5H), 0.77 (t, J = 7.4 Hz, 3H).
	**137** ---- 65	327 (M+H)+ ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 10.36 (br s, 1H), 8.09 (q, J = 8.0 Hz, 1H), 7.39- 7.35 (m, 4H), 7.30-7.22 (m, 3H), 6.87 (m, 1H), 4.61 (quin, J = 6.8 Hz, 1H), 4.49 (s, 1H), 1.44 (d, J = 6.8 Hz, 3H).

Example 73. Myosin inhibition assay

[0199] Small molecule agents were assessed for their ability to inhibit the enzymatic activity of bovine cardiac myosin using a biochemical assay that couples the release of ADP (adenosine diphosphate) from cardiac myosin to an enzymatic coupling system consisting of pyruvate kinase and lactate dehydrogenase (PK/LDH) and monitoring the absorbance decrease of NADH (at 340 nm) as a function of time. PK converts ADP to ATP (adenosine triphosphate) by converting PEP (phosphoenolpyruvate) to pyruvate. Pyruvate is then converted to lactate by LDH by converting NADH (nicotinamide adenine dinucleotide) to

NAD (oxidized nicotinamide adenine dinucleotide). The source of cardiac myosin was from bovine heart in the form of skinned myofibrils. Prior to testing small molecule agents, the bovine myofibrils were assessed for their calcium responsiveness and the calcium concentration that achieves either a 50% (pCa_{50}) or 75% (pCa_{75}) activation of the myofibril system was chosen as the final condition for assessing the inhibitory activity of the small molecule agents. All enzymatic activity was measured in a buffered solution containing 12 mM PIPES (piperazine-N,N′-bis(2-ethanesulfonic acid), 2 mM magnesium chloride at pH 6.8 (PM12 buffer). Final assay conditions were 1 mg/mL of bovine cardiac myofibrils, 0.4 mM PK/LDH, 50 uM ATP, 0.1 mg/mL BSA (bovine serum albumin), 10 ppm antifoam, 1 mM DTT, 0.5 mM NADH, 1.5 mM PEP at the desired free calcium concentration required to achieve either 50% or 75% activation of the myofibrils.

[0200] A dilution series of compound was created in DMSO such that the final desired concentration of compound would be achieved in a volume of 100 μL with a fixed DMSO concentration of 2% (v/v). Typically 2 μL of the dilution series were added to 96 well plate to achieve an 8 or 12 point dose response. Following the addition of 50 μL of a solution containing bovine cardiac myofibrils, PK/LDH and a solution of calcium (that achieved the desired activation), the enzymatic reaction was started with the addition of 50 μL of a solution containing ATP, PEP and NADH. The reaction progress was followed in a Molecular Devices M5e plate reader at ambient temperature using clear half area plates. The plate reader was configured to read absorbance at 340 nm in kinetics mode for 15 minutes. Data were recorded as the slope of the absorbance response to time. The slopes of the absorbance response as a function of time were normalized to slopes on the plate containing DMSO. This normalized rate was then plotted as a function of small molecule concentration and the data was fitted to a four-parameter fit using GraphPad Prism. The midpoint of this plot is the IC50 and is the concentration at which fifty percent of the total response is inhibited. Any agent that failed to achieve a fifty percent inhibition at the highest concentration tested was reported as an IC50 greater than the highest concentration tested (ie. IC50> 25 uM).

Table 2. Myosin Inhibition Activity of Selected Compounds[a]

Compound No.	Biochemical Activity (pCa_{75})	Biochemical Activity (pCa_{50})

1	+++	+++
2	++	
3	+++	
4	+++	
5	+++	
6	+++	
7	+++	
8	+++	
9	+++	
10	+++	
11	++	
12	+++	
13	+++	
14	+++	
15	+++	
16	++	
17	+++	
21	+++	
22	++	
24	+++	
25	+	
26	+++	
27	+++	+++
28	+++	
29	+++	
30	+++	
31	+++	
32	+++	
33	+++	
34	+++	
35	+++	+++
36		++
37	++	
38	+++	+++
39	+++	
40	+++	
41	+++	
42	+++	
43	+++	
44	+++	
45	+++	+++
46	++	
47	++	
48	++	++

49	+++	+++
50	+++	
51	++	
52	+++	
53	++	
54	++	++
55	+++	
56	+	
57		++
58	+++	
59	+++	
61	++	
62		+++
63		+++
64		++
65		++
66		++
67		+++
68		+++
69	++	+++
70	++	
71		+++
72	++	
73	++	
74	++	
75	++	
76	++	
77	++	
78	+++	
79	++	
80	+++	
81	++	
82	+++	+++
83	+++	
84	+++	
85	+++	
86	++	
90	++	
91	++	
92	++	++
93	+++	++
94	+++	
95	+++	+++
99	+++	

100	++	
101		++
102		++
103		+++
104		+++
105		+++
106		+++
107		+++
108		+++
109		++
110		++
111		++
112		+++
113		++
114		+++
115		
116		+++
117		+++
118		+++
119		+++
120		+++
121		+++
122		++
123		+++
124		+++
125		+++
126		++
127		+++
128		++
129		++
130		+++
131		+++
132		+++
133		+++
134		+++
135		+++
136		+++
137		+++

[a] +++ corresponds to IC50 values below 1 uM. ++ corresponds to IC50 values from 1 to 15 uM. + corresponds to IC50 values above 15 uM.

[0201] Selectivity against rabbit skeletal myofibrils was assessed as described above with the exception that the source of myosin was that of fast skeletal myosin from rabbit in the form of myofibrils. Dose responses against rabbit skeletal myofibrils were also determined as described above.

Example 74. Stereochemical preference for activity

[0202] Matched pairs of stereoisomers were tested for their ability to inhibit myosin activity as described above. The results are summarized in Table 3. In all cases, the (R) stereoisomer is significantly less active than the (S) stereoisomer.

Table 3. Relative activities of (S) and (R) stereoisomers[a]

(S) Stereoisomer			(R) Stereoisomer		
Cmpd No.	IC50 (pCa_{75})	IC50 (PCa_{50})	Cmpd No	IC50 (pCa_{75})	IC50 (pCa_{50})
1	0.67 μM	0.56 μM	19R	23.93 μM	51.87 μM
21	0.39 μM		20R	19.64 μM	
59	0.45 μM		60R	>39.2 μM	

[a]assay conducted using 0.5 μM myosin, therefore IC50 values below 1.0 μM are approximate.

Example 75. Cardiomyocyte contractility assay

[0203] Contractility of adult rat ventricular myocytes is determined by edge detection with an IonOptix contractility system. Aliquots of myocytes in Tyrode buffer (137 mM NaCl, 3.7 mM KCL, 0.5 mM $MgCl_2$, 1.5 mM $CaCl_2$, 4 mM HEPES, 11 mM glucose) are placed in a perfusion chamber (Series 20 RC-27NE; Warner Instruments), allowed to adhere to the coverslip, and then perfused with 37°C Tyrode buffer. Myocytes are filed stimulated at 1Hz and 10V. Only myocytes with clear striations, quiescent prior to pacing, with a cell length of 120-180 microns, a basal fractional shortening equal to 3-8% of the cell length, and a contraction velocity greater than 100 microns per second are used for contractility experiments. To determine the response to compounds, myocytes are first perfused for 60 seconds with Tyrodes buffer followed by 5 minutes of compound and a 140 second washout with Tyrodes buffer. Data is continuously recorded using IonOptix software. Contractility data is analyzed using Ionwizard software (IonOptix). For each cell, 10-20 contractility transients were averaged and compared under basal (no compound) and compound-treated

conditions. Compound activity is measured by effects on fractional shortening (FS), where fractional shortening is the ratio of the peak length of the cell at contraction divided by the basal cell length normalized to 100% for an untreated cell.

Table 4. Inhibition of Cardiomyocyte Contraction by Selected Compounds[a]

ID	Activity at 0.3 uM	Activity at 1.0 uM
1	++	+++
2	++	+++
12	n.d.	++
19	n.d.	+
27	++	n.d.
67	n.d.	+++

[a] + represents fractional shorting inhibition values less than 33%. ++ represents fractional shorting inhibition values from 33% to 66%. +++ represents fractional shortening inhibition values greater than 66%.

Example 76. Acute pharmacodynamic effect in rat.

[0204] Representative compounds were tested for their ability to modulate cardiac contractility in rat as a measure of *in vivo* target engagement. Fractional shortening, a measure of contractility, was determined by noting the change in the diameter of the left ventricle at the end of systole/contraction (LVESd) relative to diastole/relaxation (LVEDd) and expressing this change as the ratio FS = (LVEDd – LVESd)/LVEDd. Fed male Sprague-Dawley rats were lightly anesthetized with isofluorane and baseline fractional shortening was measured in the parasternal position using transthoracic echocardiography (TTE). Following this measurement, animals were recovered and received a single dose of compound (4 mg/kg) by oral gavage. At three hours post-dose, second and third echocardiograms were collected under light anesthesia to determine drug effects on contractility. Effects are represented in Table 5 as a percent reduction of baseline fractional shortening.

Table 5. Inhibition of Contractility in Rat by Selected Compounds[a]

ID	% Reduction in Fractional Shortening 3h post-dose
1	+++

45	+
48	+++
49	+++
69	+
70	++
71	+++

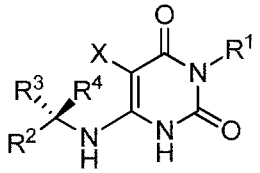
[a]+ represents a relative change in fractional shortening less than 15%. ++ represents a relative change in fractional shortening between 15-30%. +++ presents a relative change in fractional shortening greater than 30%.

[0205] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

[0206] Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

CLAIMS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R^1 is a member selected from the group consisting of C_3-C_4 alkyl, C_3-C_5 cycloalkyl, phenyl, and 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a;

R^2 is a member selected from the group consisting of phenyl, phenyl-C_1-C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C_1-C_4 alkyl, wherein each R^2 is optionally substituted with from 1-5 R^b;

R^3 is a member selected from the group consisting of C_1-C_4 alkyl, C_3-C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-3 R^c;

R^4 is H;

X is a member selected from the group consisting of H and F;

each R^a is independently selected from the group consisting of halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenyl, phenyl-C_1-C_4 alkyl, phenyl-C_1-C_4 alkoxy, phenoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, and $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from the group consisting of H, C_1-C_4 alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring;

each R^b is independently selected from the group consisting of halo, CN, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenoxy, phenyl-C_1-C_4 alkoxy, methylenedioxy, difluoromethylenedioxy, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from the group consisting of H and C_1-C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and

each R^c is independently selected from the group consisting of halo, hydroxyl and C_1-C_2 alkoxy,

wherein

each cycloalkyl is a saturated or partially unsaturated ring system;

each heterocycloalkyl is a saturated ring system comprising from 1 to 4 heteroatoms selected from N, O, and S;

each heteroaryl is an aromatic ring system comprising from 1 to 4 heteroatoms selected from N, O, and S; and

each alkoxy group is optionally substituted with one or more moieties selected from halo, hydroxyl, amino, alkylamino, nitro, and cyano.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein,

R^1 is a member selected from the group consisting of C_3-C_4 alkyl, C_3-C_5 cycloalkyl, phenyl, and 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a;

R^2 is phenyl, which is optionally substituted with from 1-5 R^b;

R^3 is a member selected from the group consisting of C_1-C_4 alkyl, C_3-C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-2 R^c;

R^4 is H;

X is a member selected from the group consisting of H and F;

each R^a is independently selected from the group consisting of halo, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, and $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from the group consisting of H and C_1-C_4 alkyl or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring;

each R^b is independently selected from the group consisting of halo, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from the group consisting of H and C_1-C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and

each R^c is independently selected from the group consisting of halo and C_1-C_2 alkoxy.

3. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is H.

4. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein each R^1 is optionally substituted with from 1-2 R^a.

5. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R1 is selected from the group consisting of phenyl and 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a.

6. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of C3-C4 alkyl, C3-C5 cycloalkyl, and 4- to 6-membered heterocycloalkyl.

7. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R1 is selected from the group consisting of cyclobutyl, isopropyl, isobutyl, 1-methoxypropan-2-yl, cyclopentyl, 1-phenyl, 2-pyridyl, 3-pyridyl, 3-isoxazolyl, 5-isoxazolyl, and 1-methyl-3-pyrazolyl.

8. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted with from 1-2 R^b.

9. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of phenyl, 3-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, 3-(3-oxazolidin-2-onyl)phenyl, 3-(2-methyl-1-imidazyl)phenyl, 3-(1-pyrazolyl)phenyl, and 3-(1,2,4-triazol-1-yl)phenyl.

10. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxyalkyl, and C_3-C_4 cycloalkyl.

11. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of methyl, ethyl, propyl, cyclopropyl, cyclobutyl and 2-methoxymethyl.

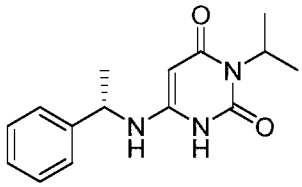
12. A compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

13. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl; R^2 is optionally substituted with 1-2 R^b; and R^3 is methyl.

14. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of phenyl and 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a; R^2 is optionally substituted with from 1-2 R^b; and R^3 is methyl.

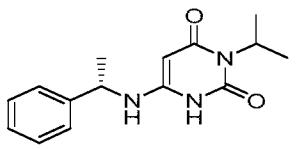
15. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

16. A pharmaceutical composition of claim 15, wherein said compound has the formula



or a pharmaceutically acceptable salt thereof.

17. A compound of claim 1, selected from the group consisting of: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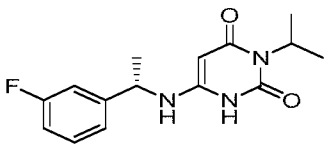
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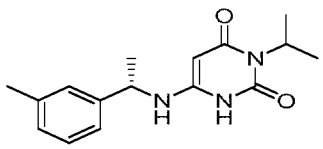
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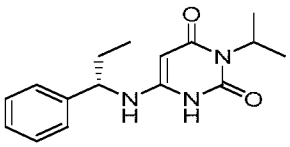
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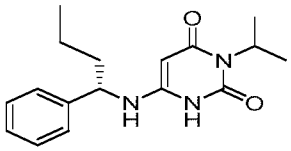
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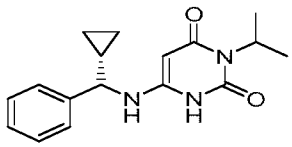
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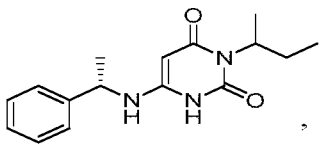
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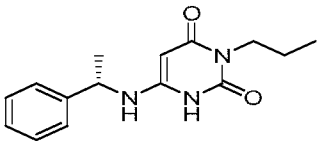
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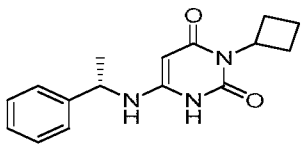
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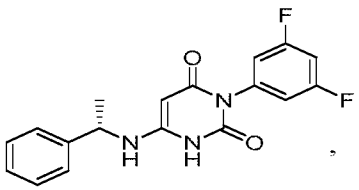
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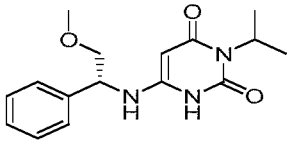
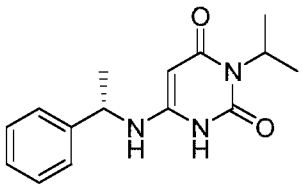


or a pharmaceutically acceptable salt thereof.

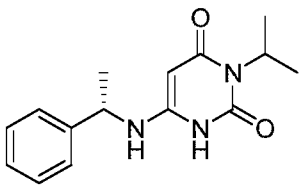
18. A compound of claim 1, having a formula of



or a pharmaceutically acceptable salt thereof.

19. A method of treating hypertrophic cardiomyopathy (HCM), comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-14, or 17-18 or a pharmaceutically acceptable salt thereof.

20. A method in accordance with claim 19, wherein said compound has the formula

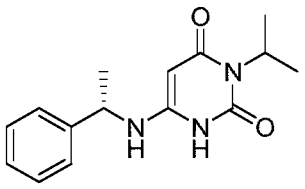


or a pharmaceutically acceptable salt thereof.

21. A method in accordance with claim 22, wherein said treatment reduces left ventricular outflow obstruction in the subject.

22. A method of treating a disease or disorder selected from the group consisting of diastolic heart failure with preserved ejection fraction, ischemic heart disease, angina pectoris, and restrictive cardiomyopathy, comprising administering to a subject in need thereof an effective amount of a compound of any of claims 1-14, or 17 or a pharmaceutically acceptable salt thereof.

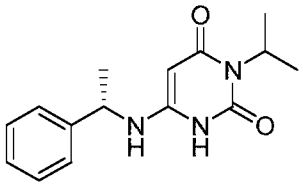
23. A method in accordance with claim 22, wherein said compound has the formula



or a pharmaceutically acceptable salt thereof.

24. A method of treating a disease or disorder characterized by left ventricular hypertrophy due to volume or pressure overload, said disease or disorder selected from the group consisting of chronic mitral regurgitation, chronic aortic stenosis, and chronic systemic hypertension; in conjunction with therapies aimed at correcting or alleviating the primary cause of volume or pressure overload, including valve repair/replacement or effective antihypertensive therapy, comprising administering to a subject in need thereof an effective amount of a compound of any of claims 1-14, or 17 or a pharmaceutically acceptable salt thereof.

25. A method in accordance with claim 21, wherein said compound has the formula



or a pharmaceutically acceptable salt thereof.

26. A method of treating hypertrophic cardiomyopathy (HCM), comprising administering to a subject in need thereof an effective amount of a compound of any of any one of claims 1-14, or 17-18 or a pharmaceutically acceptable salt thereof combined with therapies that retard the progression of heart failure by down-regulating neurohormonal stimulation of the heart and attempt to prevent cardiac remodeling, said therapies selected from the group consisting of ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, aldosterone receptor antagonists, and neural endopeptidase inhibitors.

27. A method of treating hypertrophic cardiomyopathy (HCM), comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-14, or 17-18 or a pharmaceutically acceptable salt thereof, combined with therapies that improve cardiac function by stimulating cardiac contractility, said therapy being one or more positive inotropic agents.

28. The method of claim 27, where in the positive inotropic agent is the β-adrenergic agonist dobutamine or the phosphodiesterase inhibitor milrinone.

29. A method of treating hypertrophic cardiomyopathy (HCM), comprising administering to a subject in need thereof an effective amount of a compound of

any one of claims 1-14, or 17-18 or a pharmaceutically acceptable salt thereof, combined with therapies that reduce cardiac preload or afterload, wherein

the therapies that reduce cardiac preload are diuretics, and

the therapies that reduce cardiac afterload are vasodilators.

30. A method of claim 29, wherein the diuretic is furosemide.

31. A method of claim 29, wherein the vasodilators are selected from the group consisting of calcium channel blockers, phosphodiesterase inhibitors, endothelin receptor antagonists, renin inhibitors, and smooth muscle myosin modulators.

MYOKARDIA, INC.

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P41327AU00

Figure 1