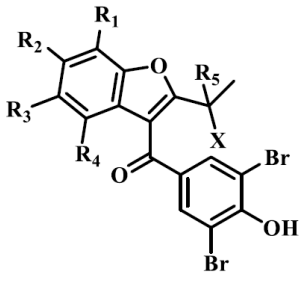
Summary

[0011a] In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof, of Formula 1:



Formula I

wherein:

either (i):

$-R_1$, $-R_2$, $-R_3$, and $-R_4$ are each independently –H or deuterium;

–X is –F or –OH; and

$-R_5$ is –H, –F, or deuterium;

or (ii):

–X is –OH or –F;

R_3 is –F, –Cl, –Br or –I; and

$-R_1$, $-R_2$, $-R_4$, and $-R_5$ are each independently –H or deuterium;

wherein at least one of $-R_1$, $-R_2$, $-R_3$, $-R_4$ and $-R_5$ is –deuterium.

[0011b] In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

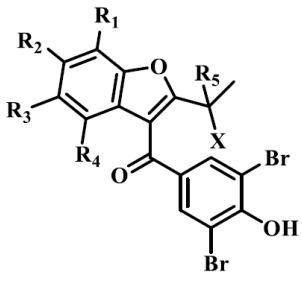
[0011c] In another aspect, the present disclosure provides the compound as described herein, or the pharmaceutical composition as described herein, for use in therapy.

[0011d] In yet another aspect, the present disclosure provides a use of the compound as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment of a condition associated with hyperuricemia, gout, hypertension, hypothyroidism, renal insufficiency, obesity, or diabetes.

[0012] Recent developments in hepatic clearance of benzbromarone has shown that significant portion of benzbromarone's biotransformation is mediated through CYP2C9, and benzbromarone itself is a potent CYP2C9 inhibitor. This complex interplay limited the identification of cause of liver toxicity both *in vitro* and *in vivo*, although the involvement of CYP2C9 is generally believed to be a cause of liver toxicity (particularly in poor CYP2C9 metabolizers).

[0013] Applicant has developed a series of compounds that show improved stability and reduction in the dependence on the CYP2C9 biotransformation pathway relative to benzbromazone, but that retain the activity of benzbromarone against URAT1 transporter.

[0014] The inventive subject matter provides compounds, compositions, and methods in which a novel compound represented by Formula 1, is capable of lowering serum acid (sUA) for the treatment of gout.



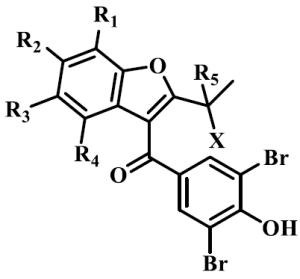
Formula I

[0015] Applicant has found that compounds of Formula 1 wherein –X is –OH, –OR, –OC(O)R, $–NH_3+$, $–NO_2$, $–SO_2R$, –CN, $–SO_3H$, –CHO, –COOH, –COCl, $–CONH_2$, –F, –Cl, –Br or –I, where –R is a –H, $–C_1$-C_{10} alkyl, or a $–C_1$-C_{10} substituted alkyl; where $–R_1$, $–R_2$, $–R_3$, $–R_4$ and $–R_5$ are each independently selected from–H, –deuterium, –F, –Cl, –Br, –I, –CN, $–C_1–C_6–$alkyl, $C_6–C_{14}–$aryl, substituted $–C_6–C_{14}–$aryl, $C_1–C_{14}–$alkoxy, –hydroxyl, –carboxyl, $–C_1–C_6–$alkylsulfonyl, –trifluoromethyl, $–C_1–C_6–$alkanoyloxy, $–C_1–C_6–$alkylthio, $–C_1–C_6–$ alkylsulfonyl, $–C_2–C_6–$alkoxycarbonyl, $–C_2–C_6–$alkanoylamino, $–O–R_6$, $–S_2R_6$, $–SO_2–$ R_6, $–NHSO_2R_6$, and $–NHCO_2R_6$, where $–R_6$ is phenyl or naphthyl, and optionally substituted with one to three groups selected from $–C_1–C_6–$alkyl, $–C_6–C_{10}–$aryl, $–C_1–C_6–$alkoxy and halogen, and $–C_4–C_{20}–$hydroxyheteroaryl, and where the heteroatoms in $–C_4–C_{20}–$hydroxyheteroaryl are selected from

CLAIMS

What is claimed is:

1. A compound, or a pharmaceutically acceptable salt thereof, of Formula 1:



Formula I

wherein:

either (i):

$-R_1$, $-R_2$, $-R_3$, and $-R_4$ are each independently –H or deuterium;

–X is –F or –OH; and

$-R_5$ is –H, –F, or deuterium;

or (ii):

–X is –OH or –F;

R_3 is –F, –Cl, –Br or –I; and

$-R_1$, $-R_2$, $-R_4$, and $-R_5$ are each independently –H or deuterium;

wherein at least one of $-R_1$, $-R_2$, $-R_3$, $-R_4$ and $-R_5$ is –deuterium.

2. The compound of claim 1, wherein:

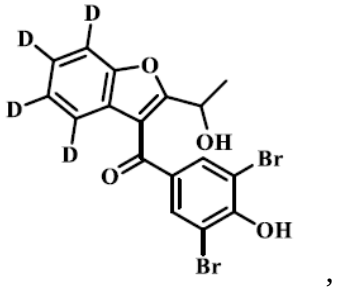
$-R_1$, $-R_2$, $-R_3$, and $-R_4$ are each independently –H or deuterium;

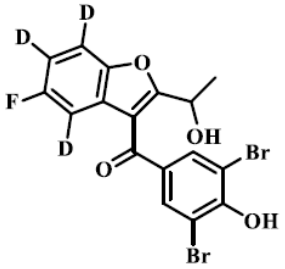
–X is –F or –OH; and

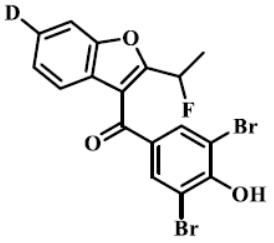
$-R_5$ is –H, –F, or deuterium;

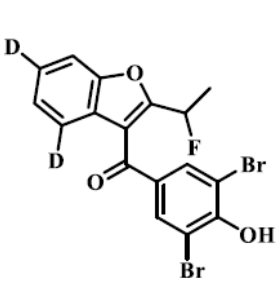
wherein at least one of $-R_1$, $-R_2$, $-R_3$, $-R_4$ and $-R_5$ is –deuterium.

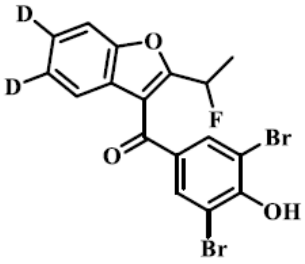
3. The compound of claim 1 selected from:

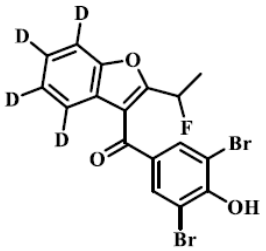


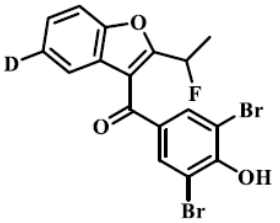
,


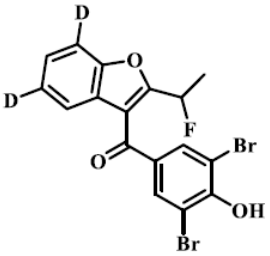
,


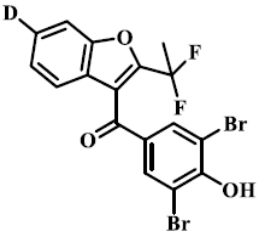
,


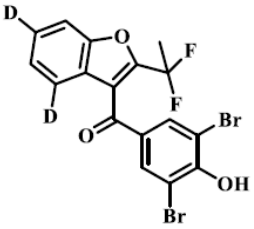
,


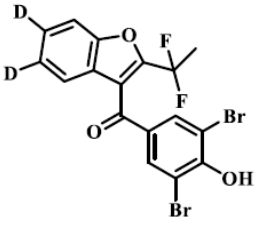
,


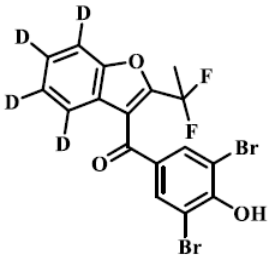
,


,


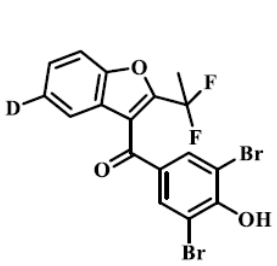
,


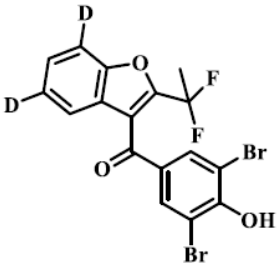
,


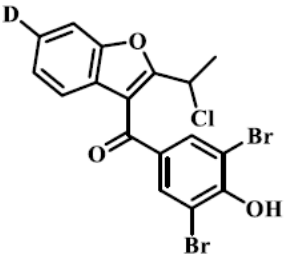
,


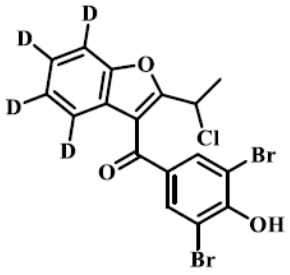
,


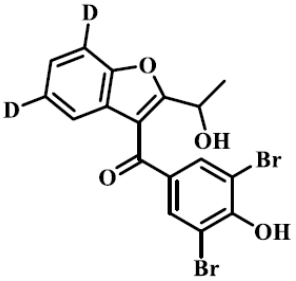
,

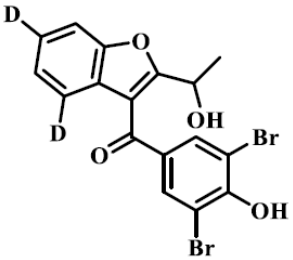


,


,


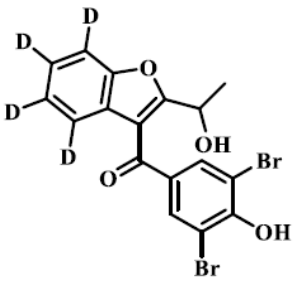
,


,


, and


.

4. The compound of claim 1 wherein the compound is:



.

5. A pharmaceutical composition comprising the compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

6. The pharmaceutical composition of claim 5, further comprising a xanthine oxidase inhibitor.

7. The compound of any one of claims 1-4, or the pharmaceutical composition of claim 5, for use in therapy.

8. Use of the compound of any one of claims 1-4, or the pharmaceutical composition of claim 5, in the manufacture of a medicament for the treatment of a condition

associated with hyperuricemia, gout, hypertension, hypothyroidism, renal insufficiency, obesity, or diabetes.