

**(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. AU 2005292345 B9

(54) Title
Novel benzimidazole derivatives useful as selective androgen receptor modulators (SARMS)

(51) International Patent Classification(s)
**C07D 235/16 (2006.01) C07D 235/12 (2006.01)
A61K 31/4184 (2006.01) C07D 401/06 (2006.01)
A61K 31/42 (2006.01) C07D 403/10 (2006.01)
A61K 31/433 (2006.01) C07D 405/06 (2006.01)
A61K 31/4439 (2006.01) C07D 409/14 (2006.01)
A61P 5/26 (2006.01) C07D 413/06 (2006.01)
A61P 5/28 (2006.01) C07D 417/10 (2006.01)
C07D 235/10 (2006.01)**

(21) Application No: **2005292345** (22) Date of Filing: **2005.09.26**

(87) WIPO No: **WO06/039243**

(30) Priority Data

(31) Number **60/614,751** (32) Date **2004.09.30** (33) Country **US**

(43) Publication Date: **2006.04.13**
(44) Accepted Journal Date: **2011.12.01**
(48) Corrigenda Journal Date: **2011.12.15**

(71) Applicant(s)
Janssen Pharmaceutica N.V.

(72) Inventor(s)
Ng, Raymond;Guan, Jihua;Lanter, James C.;Sui, Zhihua;Alford, Vernon C. Jr.

(74) Agent / Attorney
Shelston IP, Level 21 60 Margaret Street, Sydney, NSW, 2000

(56) Related Art
**EP 0 625 511 A1
US 3,897,432 A**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 April 2006 (13.04.2006)

PCT

(10) International Publication Number
WO 2006/039243 A1

(51) International Patent Classification:

C07D 235/16 (2006.01) *C07D 403/10* (2006.01)
C07D 235/12 (2006.01) *A61K 31/4184* (2006.01)
C07D 235/10 (2006.01) *A61K 31/4439* (2006.01)
C07D 401/06 (2006.01) *A61K 31/42* (2006.01)
C07D 409/14 (2006.01) *A61K 31/433* (2006.01)
C07D 405/06 (2006.01) *A61P 5/26* (2006.01)
C07D 413/06 (2006.01) *A61P 5/28* (2006.01)
C07D 417/10 (2006.01)

Research and Development, LLC, 1000 US Route 202 South, Raritan, New Jersey 08869 (US). **ALFORD, Vernon C. Jr.** [US/US]; Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 US Route 202 South, Raritan, New Jersey 08869 (US).

(74) Agents: **JOHNSON, Philip S.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

(21) International Application Number:

PCT/US2005/034462

(22) International Filing Date:

26 September 2005 (26.09.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/614,751 30 September 2004 (30.09.2004) US

(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NG, Raymond** [US/US]; Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 US Route 202 South, Raritan, New Jersey 08869 (US). **SUI, Zhihua** [US/US]; Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 US Route 202 South, Raritan, New Jersey 08869 (US). **GUAN, Jihua** [US/US]; Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 US Route 202 South, Raritan, New Jersey 08869 (US). **LANTER, James C.** [US/US]; Johnson & Johnson

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL BENZIMIDAZOLE DERIVATIVES USEFUL AS SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)

A1 (57) Abstract: The present invention is directed to novel benzimidazole derivatives, pharmaceutical compositions containing them and their use in the treatment of disorders and conditions modulated by the androgen receptor.

WO 2006/039243

NOVEL BENZIMIDAZOLE DERIVATIVES USEFUL AS SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)

FIELD OF THE INVENTION

The present invention is directed to novel benzimidazole derivatives, 5 pharmaceutical compositions containing them and their use in the treatment of disorders and conditions modulated by the androgen receptor. More particularly, the compounds of the present invention are useful in the treatment of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, as a male contraceptive, and / or as a male performance enhancer.

10

BACKGROUND OF THE INVENTION

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

15 Androgens are the anabolic steroid hormones of animals, controlling muscle and skeletal mass, the maturation of the reproductive system, the development of secondary sexual characteristics and the maintenance of fertility in the male. In women, testosterone is converted to estrogen in most target tissues, but androgens themselves may play a role in normal female physiology, for example, in the brain. The chief androgen found in serum is testosterone, and this is the effective compound in tissues 20 such as the testes and pituitary. In prostate and skin, testosterone is converted to dihydrotestosterone (DHT) by the action of 5 α -reductase. DHT is a more potent androgen than testosterone because it binds more strongly to the androgen receptor.

25 Like all steroid hormones, androgens bind to a specific receptor inside the cells of target tissues, in this case the androgen receptor. This is a member of the nuclear receptor transcription factor family. Binding of androgen to the receptor activates it and causes it to bind to DNA binding sites adjacent to target genes. From there it interacts with coactivator proteins and basic transcription factors to regulate the expression of the gene. Thus, via its receptor, androgens cause changes in gene expression in cells. These

changes ultimately have consequences on the metabolic output, differentiation or proliferation of the cell that are visible in the physiology of the target tissue.

- Although modulators of androgen receptor function have been employed
- 5 clinically for some time, both the steroid (Basaria, S., Wahlstrom, J.T., Dobs, A.S., *J. Clin Endocrinol Metab* (2001), 86, pp5108-5117; Shahidi, N.T., *Clin Therapeutics*, (2001), 23, pp1355-1390), and non-steroidal (Newling, D.W., *Br. J. Urol.*, 1996, 77 (6), pp 776-784) compounds have significant liabilities related to their pharmacological parameters, including gynecomastia, breast
- 10 tenderness and hepatotoxicity. In addition, drug-drug interactions have been observed in patients receiving anticoagulation therapy using coumarins. Finally, patients with aniline sensitivities could be compromised by the metabolites of non-steroidal antiandrogens.
- 15 Non-steroidal agonists and antagonists of the androgen receptor are useful in the treatment of a variety of disorders and diseases. More particularly, agonists of the androgen receptor could be employed in the treatment of prostate cancer, benign prostatic hyperplasia, hirsutism in women, alopecia, anorexia nervosa, breast cancer and acne. Antagonists of the
- 20 androgen receptor could be employed in male contraception, male performance enhancement, as well as in the treatment of cancer, AIDS, cachexia, and other disorders.

- Nonetheless, there exists a need for small molecule, non-steroidal
- 25 agonist and / or antagonists of the androgen receptor. We now describe a novel series of benzimidazole derivatives as androgen receptor modulators.

SUMMARY OF THE INVENTION

According to a first aspect, the present invention provides a compound selected from

- 1-(5,6-dichloro-1H-benzimidazol-2-yl)-2,2,2-trifluoro-ethanol;
5 3-(5,6-dichloro-1H-benzimidazol-2-yl)-3-hydroxy-butyronitrile;
or a pharmaceutically acceptable salt thereof.

According to a second aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the first aspect.

10 According to a third aspect, the present invention provides a method of treating a disorder mediated by an androgen receptor, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the first aspect or a pharmaceutical composition of the second aspect.

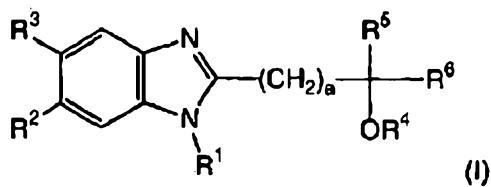
15 According to a fourth aspect, the present invention provides a method of treating a condition selected from the group consisting of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, male contraception, and male performance, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the first aspect or a pharmaceutical composition of the second aspect.

20 According to a forth aspect, the present invention provides a use of a compound of the first aspect in the manufacture of a medicament for treating a disorder mediated by an androgen receptor.

25 According to a sixth aspect, the present invention provides a use of a compound of the first aspect in the manufacture of a medicament for treating a condition selected from the group consisting of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, male contraception, and male performance.

30 Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

In general, the present invention is directed to compounds of formula (I)



wherein

5 R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl-OH, $-C_{1-4}$ alkyl-CN, $-C_{1-4}$ alkyl-NO₂, $-C_{1-4}$ alkyl-N($R^A R^B$), $-C_{1-4}$ alkyl-CO₂H, $-(C_{1-4}$ alkyl)-X-R⁷, $-CH_2$ -aryl and $-CH_2$ -heteroaryl; wherein the aryl or heteroaryl group (on the $-CH_2$ -aryl and $-CH_2$ -heteroaryl group) is optionally substituted with one or more substituents independently selected from halogen, C_{1-4} alkyl, halogen substituted C_{1-4} alkyl, C_{1-4} alkoxy, halogen substituted C_{1-4} alkoxy, $-C_{1-4}$ alkyl-CN, $-C_{1-4}$ alkyl-OH, cyano, nitro, 10 amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, $-S-C_{1-4}$ alkyl, $-S$ -(halogen substituted C_{1-4} alkyl), $-SO-C_{1-4}$ alkyl, $-SO_2-C_{1-4}$ alkyl, $-O$ -aralkyl, $-C(O)O-C_{1-4}$ alkyl, $-CO_2H$, $-C(O)H$, heteroaryl or heterocycloalkyl;

15 wherein R^A and R^B are independently selected from hydrogen or C_{1-4} alkyl; alternatively, R^A and R^B are taken together with the nitrogen atom to which they are bound to form a five to seven membered aromatic, partially unsaturated or saturated ring structure, optionally containing one to two additional heteroatoms selected from O, S or N; and wherein the ring structure is optionally substituted with C_{1-4} alkyl; 20 wherein X is selected from the group consisting of $-S$ -, $-SO$ -, SO_2 -, $-O$ - SO_2 -, $-O$ -, $-C(OH)$ -, $-C(=N(OH))$ -, $-C(O)$ -, $-C(O)-O$ -, $-NR^C$ -, $-NR^C-C(O)$ -, $-C(O)-NR^C$ -, $-NR^C$ - SO_2 - and $-SO_2-NR^C$ -, wherein R^C is selected from hydrogen or C_{1-4} alkyl;

25 wherein R^7 is selected from the group consisting of C_{1-4} alkyl, halogen substituted C_{1-4} alkyl, C_{2-4} alkenyl, aryl, aralkyl, biphenyl, cycloalkyl, cycloalkyl-(C_{1-4} alkyl)-, heteroaryl, heteroaryl-(C_{1-4} alkyl)-, heterocycloalkyl and heterocycloalkyl-(C_{1-4} alkyl)-; wherein the cycloalkyl, aryl, heteroaryl or heterocycloalkyl group, whether alone or as part of a substituent group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, halogen substituted C_{1-4} alkyl, C_1 .

$\text{C}_{1-4}\text{alkoxy}$, halogen substituted $\text{C}_{1-4}\text{alkoxy}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, di($\text{C}_{1-4}\text{alkyl}$)amino, $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-4}\text{alkyl})$, $-\text{SO}_2\text{N}(\text{R}^{\text{D}})_2$, aryl, heteroaryl or heterocycloalkyl; wherein each R^{D} is independently selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

5 provided that when X is O or NR^{C} , then R^6 is other than $\text{C}_{2-4}\text{alkenyl}$;

R^2 is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, di($\text{C}_{1-4}\text{alkyl}$)amino, $-\text{O-C}_{1-4}\text{alkyl}$, $-\text{S-C}_{1-4}\text{alkyl}$, $-\text{SO-C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{C}_{1-4}\text{alkyl}$ and $-\text{NR}^{\text{E}}\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$; wherein R^{E} is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

10 R^3 is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, di($\text{C}_{1-4}\text{alkyl}$)amino, $-\text{O-C}_{1-4}\text{alkyl}$, $-\text{S-C}_{1-4}\text{alkyl}$, $-\text{SO-C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{C}_{1-4}\text{alkyl}$ and $-\text{NR}^{\text{F}}\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$; wherein R^{F} is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

15 provided that at least one of R^2 or R^3 is other than hydrogen;

a is an integer from 0 to 1;

R^4 is selected from the group consisting of hydrogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$ and $-\text{C}(\text{O})\text{R}^8$;

20 wherein R^8 is selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, cycloalkyl, cycloalkyl-($\text{C}_{1-4}\text{alkyl}$)-, aryl, aralkyl, heteroaryl, heteroaryl-($\text{C}_{1-4}\text{alkyl}$)-, heterocycloalkyl and heterocycloalkyl-($\text{C}_{1-4}\text{alkyl}$)-; wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl group, whether alone or as part of a substituent group is optionally substituted with one or more substituents

25 independently selected from halogen, hydroxy, carboxy, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, halogen substituted $\text{C}_{1-4}\text{alkoxy}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$ or di($\text{C}_{1-4}\text{alkyl}$)amino;

R^5 is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$ and halogen substituted $\text{C}_{1-4}\text{alkyl}$;

30

R^6 is selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkyl-OH}$, $-\text{C}_{1-4}\text{alkyl-CN}$, $-\text{C}_{1-4}\text{alkyl-NO}_2$, $-\text{C}_{1-4}\text{alkyl-N}(\text{R}^{\text{G}}\text{R}^{\text{H}})$, $\text{C}_{1-4}\text{alkyl-CO}_2\text{H}$, $-(\text{C}_{1-4}\text{alkyl})\text{-Y-R}^9$, $-\text{CH}_2\text{-aryl}$ and $-\text{CH}_2\text{-heteroaryl}$; wherein the aryl

- or heteroaryl (on the $-\text{CH}_2\text{-aryl}$ or $-\text{CH}_2\text{-heteroaryl}$ group) is optionally substituted with one or more substituents independently selected from halogen, hydroxy, $\text{C}_{1\text{-}4}\text{alkyl}$, halogen substituted $\text{C}_{1\text{-}4}\text{alkyl}$, $\text{C}_{1\text{-}4}\text{alkoxy}$, halogen substituted $\text{C}_{1\text{-}4}\text{alkoxy}$, cyano, nitro, amino, $\text{C}_{1\text{-}4}\text{alkylamino}$, $\text{di}(\text{C}_{1\text{-}4}\text{alkyl})\text{amino}$, -
- 5 $\text{S}(\text{O})_{0\text{-}2}\text{-C}_{1\text{-}4}\text{alkyl}$ or $-\text{SO}_2\text{-N}(\text{R}^{\text{J}})_2$; wherein each R^{J} is independently selected from hydrogen or $\text{C}_{1\text{-}4}\text{alkyl}$;
- wherein R^{G} and R^{H} are independently selected from hydrogen or $\text{C}_{1\text{-}4}\text{alkyl}$; alternatively, R^{G} and R^{H} are taken together with the nitrogen atom to which they are bound to form a five to seven membered aromatic, partially
- 10 unsaturated or saturated ring structure, optionally containing one to two additional heteroatoms selected from O, S or N; and wherein the ring structure is optionally substituted with $\text{C}_{1\text{-}4}\text{alkyl}$;
- wherein Y is selected from the group consisting of $-\text{S}-$, $-\text{SO}-$, SO_2- , $-\text{O-SO}_2-$, $-\text{O}-$, $-\text{C}(\text{OH})-$, $-\text{C}(\text{=N}(\text{OH}))-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{-O}-$, $-\text{NR}^{\text{K}}-$, $-\text{NR}^{\text{K}}\text{-C}(\text{O})-$, $-\text{C}(\text{O})\text{-NR}^{\text{K}}-$, $-\text{NR}^{\text{K}}\text{-SO}_2-$ and $-\text{SO}_2\text{-NR}^{\text{K}}-$; wherein R^{K} is selected from hydrogen or $\text{C}_{1\text{-}4}\text{alkyl}$;
- 15 wherein R^9 is selected from the group consisting of $\text{C}_{1\text{-}4}\text{alkyl}$, halogen substituted $\text{C}_{1\text{-}4}\text{alkyl}$, $\text{C}_{2\text{-}4}\text{alkenyl}$, aryl, aralkyl, biphenyl, cycloalkyl, cycloalkyl-($\text{C}_{1\text{-}4}\text{alkyl})-$, heteroaryl, heteroaryl-($\text{C}_{1\text{-}4}\text{alkyl})-$, heterocycloalkyl and
- 20 heterocycloalkyl-($\text{C}_{1\text{-}4}\text{alkyl})-$; wherein the cycloalkyl, aryl, heteroaryl or heterocycloalkyl group, whether alone or as part of a substituent group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, $\text{C}_{1\text{-}4}\text{alkyl}$, halogen substituted $\text{C}_{1\text{-}4}\text{alkyl}$, $\text{C}_{1\text{-}4}\text{alkoxy}$, halogen substituted $\text{C}_{1\text{-}4}\text{alkoxy}$, cyano, nitro, amino, $\text{C}_{1\text{-}4}\text{alkylamino}$, $\text{di}(\text{C}_{1\text{-}4}\text{alkyl})\text{amino}$, $-\text{S}(\text{O})_{0\text{-}2}(\text{C}_{1\text{-}4}\text{alkyl})$, $-\text{SO}_2\text{-N}(\text{R}^{\text{L}})_2$ or $-\text{NR}^{\text{M}}\text{-C}(\text{O})\text{-C}_{1\text{-}4}\text{alkyl}$;
- 25 wherein each R^{L} is independently selected from hydrogen or $\text{C}_{1\text{-}4}\text{alkyl}$; and wherein R^{M} is selected from hydrogen or $\text{C}_{1\text{-}4}\text{alkyl}$;
- provided that when Y is O or NR^{K} , then R^9 is other than $\text{C}_{2\text{-}4}\text{alkenyl}$;
- 30 provided that when R^4 is hydrogen and R^5 is hydrogen, then R^6 is other than $\text{C}_{1\text{-}4}\text{alkyl}$;
- provided further that when R^1 is hydrogen; a is 0; R^4 is hydrogen and R^5 is $\text{C}_{1\text{-}4}\text{alkyl}$; then R^6 is other than $\text{C}_{1\text{-}4}\text{alkyl}$;

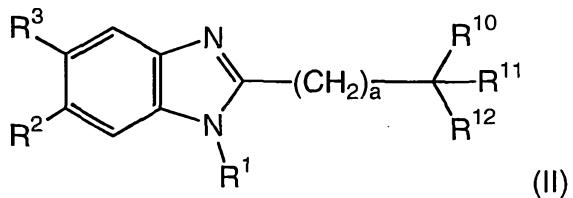
provided further that when R^1 is hydrogen; a is 0; R^2 is $-O-C_{1-4}\text{alkyl}$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; then R^6 is other than $-CH_2\text{-phenyl}$, wherein the phenyl is substituted with $-O-C_{1-4}\text{alkyl}$;

- 5 provided further that when R^1 is hydrogen, a is 0, R^4 is hydrogen and R^5 is hydrogen; then R^6 is other than $-CH_2\text{-}(benzimidazolyl)$, wherein the benzimidazolyl is substituted with one to two substituents selected from halogen, $C_{1-4}\text{alkyl}$ or $-O-C_{1-4}\text{alkyl}$;

or a pharmaceutically acceptable salt thereof.

10

The present invention is further directed to compounds of formula (II)



wherein

- R^1 is selected from the group consisting of hydrogen, $C_{1-4}\text{alkyl}$, $-C_{1-4}\text{alkyl-OH}$, $-C_{1-4}\text{alkyl-CN}$, $-C_{1-4}\text{alkyl-NO}_2$, $-C_{1-4}\text{alkyl-N}(R^A R^B)$, $-C_{1-4}\text{alkyl-CO}_2\text{H}$, $-(C_{1-4}\text{alkyl})\text{-X-R}^7$, $-CH_2\text{-aryl}$ and $-CH_2\text{-heteroaryl}$; wherein the aryl or heteroaryl group (on the $-CH_2\text{-aryl}$ and $-CH_2\text{-heteroaryl}$ group) is optionally substituted with one or more substituents independently selected from halogen, $C_{1-4}\text{alkyl}$, halogen substituted $C_{1-4}\text{alkyl}$, $C_{1-4}\text{alkoxy}$, halogen substituted $C_{1-4}\text{alkoxy}$, $-C_{1-4}\text{alkyl-CN}$, $-C_{1-4}\text{alkyl-OH}$, cyano, nitro, amino, $C_{1-4}\text{alkylamino}$, $\text{di}(C_{1-4}\text{alkyl})\text{amino}$, $-S-C_{1-4}\text{alkyl}$, $-S\text{-}(halogen substituted C}_{1-4}\text{alkyl)$, $-SO-C_{1-4}\text{alkyl}$, $-SO_2-C_{1-4}\text{alkyl}$, $-O\text{-aralkyl}$, $-C(O)O-C_{1-4}\text{alkyl}$, $-CO_2\text{H}$, $-C(O)\text{H}$, heteroaryl or heterocycloalkyl; wherein R^A and R^B are independently selected from hydrogen or $C_{1-4}\text{alkyl}$; alternatively, R^A and R^B are taken together with the nitrogen atom to which they are bound to form a five to seven membered aromatic, partially unsaturated or saturated ring structure, optionally containing one to two additional heteroatoms selected from O, S or N; and wherein the ring structure is optionally substituted with $C_{1-4}\text{alkyl}$; wherein X is selected from the group consisting of $-S\text{-}$, $-SO\text{-}$, $SO_2\text{-}$, $-O\text{-}$, $SO_2\text{-}$, $-O\text{-}$, $-C(OH)\text{-}$, $-C(=N(OH))\text{-}$, $-C(O)\text{-}$, $-C(O)\text{-}O\text{-}$, $-NR^C\text{-}$, $-NR^C\text{-}C(O)\text{-}$, $-C(O)\text{-}$

NR^C -, $-\text{NR}^C\text{-SO}_2$ - and $-\text{SO}_2\text{-NR}^C$ -, wherein R^C is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

5 wherein R^7 is selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, aryl, aralkyl, biphenyl, cycloalkyl, cycloalkyl-
 $(\text{C}_{1-4}\text{alkyl})$ -, heteroaryl, heteroaryl- $(\text{C}_{1-4}\text{alkyl})$ -, heterocycloalkyl and
 $\text{heterocycloalkyl-}(\text{C}_{1-4}\text{alkyl})$ -, wherein the cycloalkyl, aryl, heteroaryl or
 heterocycloalkyl group, whether alone or as part of a substituent group is
 $\text{optionally substituted with one or more substituents independently selected}$
 $\text{from halogen, hydroxy, carboxy, } \text{C}_{1-4}\text{alkyl, halogen substituted } \text{C}_{1-4}\text{alkyl, } \text{C}_{1-4}\text{alkoxy, halogen substituted } \text{C}_{1-4}\text{alkoxy, cyano, nitro, amino, } \text{C}_{1-4}\text{alkylamino, di}(\text{C}_{1-4}\text{alkyl})\text{amino, } -\text{S}(\text{O})_{0-2}(\text{C}_{1-4}\text{alkyl}), -\text{SO}_2\text{-N}(\text{R}^D)_2$, aryl, heteroaryl or
 heterocycloalkyl ; wherein each R^D is independently selected from hydrogen or
 $\text{C}_{1-4}\text{alkyl}$;

10 provided that when X is O or NR^C , then R^6 is other than $\text{C}_{2-4}\text{alkenyl}$;

15

R^2 is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, $\text{di}(\text{C}_{1-4}\text{alkyl})\text{amino}$, $-\text{O-} \text{C}_{1-4}\text{alkyl}$, $-\text{S-} \text{C}_{1-4}\text{alkyl}$, $-\text{SO-} \text{C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{-} \text{C}_{1-4}\text{alkyl}$ and $-\text{NR}^E\text{-C}(\text{O})\text{-} \text{C}_{1-4}\text{alkyl}$; wherein R^E is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

20

R^3 is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, $\text{di}(\text{C}_{1-4}\text{alkyl})\text{amino}$, $-\text{O-} \text{C}_{1-4}\text{alkyl}$, $-\text{S-} \text{C}_{1-4}\text{alkyl}$, $-\text{SO-} \text{C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{-} \text{C}_{1-4}\text{alkyl}$ and $-\text{NR}^F\text{-C}(\text{O})\text{-} \text{C}_{1-4}\text{alkyl}$; wherein R^F is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

 provided that at least one of R^2 or R^3 is other than hydrogen;

25

a is an integer from 0 to 1;

R^{10} is selected from the group consisting of hydrogen, halogen, $\text{C}_{1-4}\text{alkyl}$, halogen substituted $\text{C}_{1-4}\text{alkyl}$ and $-\text{O-C}(\text{O})\text{-R}^8$;

30

 wherein R^8 is selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, cycloalkyl,

 cycloalkyl- $(\text{C}_{1-4}\text{alkyl})$ -, aryl, aralkyl, heteroaryl, heteroaryl- $(\text{C}_{1-4}\text{alkyl})$ -, heterocycloalkyl and heterocycloalkyl- $(\text{C}_{1-4}\text{alkyl})$ -, wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl group, whether alone or as part of a substituent group is optionally substituted with one or more substituents

independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, C₁₋₄alkoxy, halogen substituted C₁₋₄alkoxy, cyano, nitro, amino, C₁₋₄alkylamino or di(C₁₋₄alkyl)amino;

5 R¹¹ is selected from the group consisting of hydrogen and halogen; alternatively, R¹⁰ and R¹¹ are taken together with the carbon atom to which they are bound to form -C(O)-, C=N(OH) or -C=N(O-C₁₋₄alkyl);

R¹² is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -C₁₋₄alkyl-OH, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-NO₂, -C₁₋₄alkyl-10 N(R^GR^H), C₁₋₄alkyl-CO₂H, -(C₁₋₄alkyl)-Y-R⁹, -CH₂-aryl and -CH₂-heteroaryl; wherein the aryl or heteroaryl (on the -CH₂-aryl or -CH₂-heteroaryl group) is optionally substituted with one or more substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, C₁₋₄alkoxy, halogen substituted C₄alkoxy, cyano, nitro, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, -S(O)₀₋₂-C₁₋₄alkyl or -SO₂-N(R^J)₂; wherein each R^J is independently selected from hydrogen or C₁₋₄alkyl;

wherein R^G and R^H are independently selected from hydrogen or C₁₋₄alkyl; alternatively, R^G and R^H are taken together with the nitrogen atom to which they are bound to form a five to seven membered aromatic, partially 20 unsaturated or saturated ring structure, optionally containing one to two additional heteroatoms selected from O, S or N; and wherein the ring structure is optionally substituted with C₁₋₄alkyl;

wherein Y is selected from the group consisting of -S-, -SO-, SO₂-, -O-SO₂-, -O-, -C(OH)-, -C(=N(OH))-, -C(O)-, -C(O)-O-, -NR^K-, -NR^K-C(O)-, -C(O)-NR^K-, -NR^K-SO₂- and -SO₂-NR^K-, wherein R^K is selected from hydrogen or C₁₋₄alkyl;

wherein R⁹ is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, C₂₋₄alkenyl, aryl, aralkyl, biphenyl, cycloalkyl, cycloalkyl-(C₁₋₄alkyl)-, heteroaryl, heteroaryl-(C₁₋₄alkyl)-, heterocycloalkyl and 30 heterocycloalkyl-(C₁₋₄alkyl)-; wherein the cycloalkyl, aryl, heteroaryl or heterocycloalkyl group, whether alone or as part of a substituent group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, C₁₋

$\text{C}_{1-4}\text{alkoxy}$, halogen substituted $\text{C}_{1-4}\text{alkoxy}$, cyano, nitro, amino, $\text{C}_{1-4}\text{alkylamino}$, di($\text{C}_{1-4}\text{alkyl}$)amino, $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-4}\text{alkyl})$, $-\text{SO}_2\text{N}(\text{R}^{\text{L}})_2$ or $-\text{NR}^{\text{M}}\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$; wherein each R^{L} is independently selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$; and wherein R^{M} is selected from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

5 provided that when Y is O or NR^{K} , then R^9 is other than $\text{C}_{2-4}\text{alkenyl}$;

provided that when R^1 is $-\text{CH}_2\text{-phenyl}$ wherein the phenyl is substituted with $-\text{C}(\text{O})\text{O-C}_{1-4}\text{alkyl}$ or $-\text{CO}_2\text{H}$; R^2 is methyl; R^3 is methyl; a is 0; R^{10} is hydrogen; and R^{11} is hydrogen; then R^{12} is other than $-\text{CH}_2\text{-phenyl}$;

10 provided further that when R^1 is $-\text{CH}_2\text{-phenyl}$ wherein the phenyl is substituted with $-\text{C}(\text{O})\text{O-C}_{1-4}\text{alkyl}$ or $-\text{CO}_2\text{H}$; R^2 and R^3 are selected to be (H and fluoro), (fluoro and H), (methyl, methyl) or (H and trifluoromethyl); a is an integer from 0 to 1; R^{10} is hydrogen; and R^{11} is hydrogen; then R^{12} is other than $\text{C}_{1-4}\text{alkyl}$;

15 provided further that when R^1 is hydrogen or $\text{C}_{1-4}\text{alkyl}$; a is 0; R^{10} and R^{11} are taken together with the carbon atom to which they are bound to form $-\text{C}(\text{O})-$, one of R^2 or R^3 is hydrogen and the other of R^2 or R^3 is selected from halogen, $\text{C}_{1-4}\text{alkyl}$, $-\text{O-C}_{1-4}\text{alkyl}$ or nitro, then R^{12} is other than $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyl}$ substituted with one halogen or benzyl;

20 provided further that when R^1 is $-\text{CH}_2\text{-phenyl}$; a is 0; R^{10} and R^{11} are taken together with the carbon atom to which they are bound to form $-\text{C}(\text{O})-$, of R^2 is hydrogen; and R^3 is nitro, then R^{12} is other than $\text{C}_{1-4}\text{alkyl}$;

25 provided further that when R^1 is hydrogen; a is 0; R^2 is $-\text{O-C}_{1-4}\text{alkyl}$, R^3 is $-\text{O-C}_{1-4}\text{alkyl}$; and R^{10} and R^{11} are taken together with the carbon atom to which they are bound to form $-\text{C}(\text{O})-$; then R^{12} is other than benzyl;

provided further that when R^1 is $-\text{C}_{1-4}\text{alkyl-N}(\text{C}_{1-4}\text{alkyl})_2$; a is 0; R^2 is $-\text{O-C}_{1-4}\text{alkyl}$; R^3 is $-\text{O-C}_{1-4}\text{alkyl}$; and R^{10} and R^{11} are taken together with the carbon atom to which they are bound to form $-\text{C}(\text{O})-$, then R^{12} is other than benzyl,

30 wherein the benzyl is substituted with a halogen;
or a pharmaceutically acceptable salt thereof.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described herein. An illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described herein and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described herein and a pharmaceutically acceptable carrier.

Exemplifying the invention are methods of treating disorders and conditions modulated by the androgen receptor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described herein.

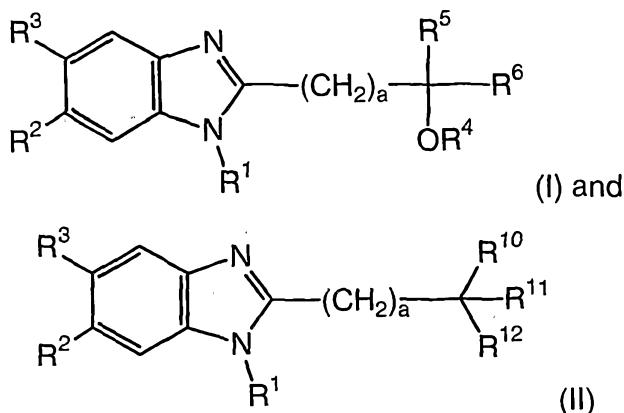
An example of the invention is a method for treating an androgen receptor modulated disorder selected from the group consisting of prostate carcinoma, benign prostatic hyperplasia, hirsutism, or for male contraception, in a subject in need thereof comprising administering to the subject an effective amount of any of the compounds or pharmaceutical compositions described herein.

20

Another example of the invention is the use of any of the compounds described herein in the preparation of a medicament for treating: (a) prostate carcinoma, (b) benign prostatic hyperplasia, (c) hirsutism, (d) alopecia, (e) anorexia nervosa, (f) breast cancer, (g) acne, (h) AIDS, (i) cachexia, for (j) male contraception, or for (k) male performance enhancement, in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula (I) and compounds of formula (II)



wherein R^1 , R^2 , R^3 , a , R^4 , R^5 , R^6 , R^{10} , R^{11} and R^{12} are as herein defined, useful as selective androgen receptor modulators for the treatment of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, as a male contraceptive, and / or as a male performance enhancer. One skilled in the art will recognize that some compounds of formula (I) may be metabolites of the corresponding compounds of formula (II).

10

One skilled in the art will recognize that some of the variables (e.g. R^1 , R^2 , R^3 , a , etc.) appear in compounds of formula (I) and compounds of formula (II). One skilled in the art will further recognize that wherein a particular substituent is selected for a given variable for a compound of formula (I), said selection is not intended to limit the scope of said variable for compounds of formula (II). Similarly, the selection of a particular substituent for a given variable for a compound of formula (II), is not intended to limit the scope of said variable for compounds of formula (I).

20 In an embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl-OH, $-C_{1-4}$ alkyl-CN, $-C_{1-4}$ alkyl-X- R^7 , $-CH_2$ -phenyl and $-CH_2$ -heteroaryl; wherein the phenyl or heteroaryl (on the $-CH_2$ -phenyl or $-CH_2$ -heteroaryl group) is optionally substituted with one or more substituents independently selected from halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, halogen substituted C_{1-4} alkyl, $-O$ -(halogen substituted C_{1-4} alkyl), $-C_{1-4}$ alkyl-CN, nitro, cyano, $-S$ -(halogen substituted C_{1-4} alkyl), $-SO_2-C_{1-4}$ alkyl, $-O-CH_2$ -phenyl, $-C(O)O-C_{1-4}$ alkyl, $-C(O)H$, heteroaryl or heterocycloalkyl.

In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-OH, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-X-R⁷, -CH₂-phenyl and -CH₂-heteroaryl; wherein the phenyl or heteroaryl (on the -CH₂-phenyl or -CH₂-heteroaryl group) is optionally substituted with one or 5 more substituents independently selected from halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-(halogen substituted C₁₋₄alkyl), -C₁₋₄alkyl-CN, nitro, cyano, -S-(halogen substituted C₁₋₄alkyl), -SO₂-C₁₋₄alkyl, -O-CH₂-phenyl, -C(O)O-C₁₋₄alkyl, -C(O)H, heteroaryl or heterocycloalkyl.

In another embodiment of the present invention, R¹ is selected from the 10 group consisting of hydrogen, -C₁₋₄alkyl, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-S(O)₀₋₂-C₁₋₄alkyl.

In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, C₁₋₂alkyl, -C₁₋₂alkyl-OH, -C₁₋₂alkyl-CN, -C₁₋₂alkyl-O-C₁₋₂alkyl and -C₁₋₂alkyl-S(O)₀₋₂-C₁₋₂alkyl.

15 In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, -CH₂-heteroaryl and -C₁₋₂alkyl-X-R⁷.

In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, -CH₂-heteroaryl and -CH₂-C(O)-heteroaryl.

20 In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, cyano-methyl, methoxy-methyl and methyl-thio-methyl.

25 In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen, methyl, 2-hydroxyethyl-, 2-hydroxy-n-butyl-, cyano-methyl-, methoxy-methyl-, methyl-thio-methyl-, methyl-sulfonyl-methyl-, 4-chlorophenyl-sulfonyl-methyl-, ethoxy-carbonyl-methyl-, ethyl-carbonyl-methyl-, phenyl-carbonyl-methyl-, 4-fluorophenyl-carbonyl-methyl-, 4-bromophenyl-carbonyl-methyl-, 4-chlorophenyl-carbonyl-methyl-, 3-nitrophenyl-carbonyl-methyl-, 4-nitrophenyl-carbonyl-methyl-, 2-methoxyphenyl-carbonyl-methyl-, 3-methoxyphenyl-carbonyl-methyl-, 2,4-dimethoxyphenyl-carbonyl-methyl-, 2-benzofuryl-carbonyl-methyl-, 2-thienyl-carbonyl-methyl-, 2-pyridyl-carbonyl-methyl-, 3-pyridyl-carbonyl-methyl-, 2-(5-(2-pyridyl)-thienyl)-carbonyl-methyl-, 5-(2,3-dihydrobenzo[1,4]dioxinyl)-carbonyl-methyl-, 3-phenyl-5-methyl-isoxazol-4-yl-carbonyl-methyl-, 4-fluorophenoxy-ethyl-, 4-chlorophenoxy-ethyl-,

- 3-fluorophenoxy-ethyl-, 4-cyanophenoxy-ethyl-, 4-benzaldehyde, benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 3-methylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 3-trifluoromethoxybenzyl, 4-trifluoromethoxybenzyl, 2,3,4,5,6-pentafluorobenzyl, 2-cyanomethylbenzyl, 3-cyanomethylbenzyl, 2-methoxy-5-nitro-benzyl, 4-cyanobenzyl, 2-nitrobenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 4-trifluoromethyl-thio-benzyl, 4-methylsulfonyl-benzyl, 4-benzyloxybenzyl, 4-ethoxycarbonyl-benzyl, 4-pyrazolyl-benzyl, 4-[1,2,3]-thiadiazol-4-ylbenzyl, 4-pyrrolyl-benzyl, 3-(5-methyl-isoxazolyl)-methyl-, 2-pyridyl-methyl-, 3-pyridyl-methyl-, 4-pyridyl-methyl- and trans-butan-2-one oxime.

In another embodiment of the present invention, R¹ is selected from the group consisting of hydrogen and methoxy-methyl-.

In another embodiment of the present invention, R¹ is hydrogen.

15

In an embodiment of the present invention, X is selected from the group consisting of -O-, S-, -SO-, -SO₂-, -C(O)-, -C(O)O- and -C(=N(OH))-.

In another embodiment of the present invention, X is selected from the group consisting of -O-, -S-, -SO₂- and -C(O)-.

20

In another embodiment of the present invention, X is selected from the group consisting of -O-, -S- and -SO₂-.

25

In an embodiment of the present invention, R⁷ is selected from the group consisting of C₁₋₄alkyl, phenyl, -CH₂-phenyl, heteroaryl and heterocycloalkyl; wherein the phenyl or heteroaryl, whether alone or as part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, cyano, nitro, -C₁₋₄alkyl, -O-C₁₋₄alkyl, phenyl or heteroaryl.

30

In another embodiment of the present invention, R⁷ is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, phenyl, benzyl and heteroaryl; wherein the phenyl or heteroaryl is optionally substituted with one to two substituents independently selected from halogen, C₁₋₂alkyl, -O-C₁₋₂alkyl, halogen substituted C₁₋₂alkyl, nitro or cyano.

In an embodiment of the present invention, R² is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, cyano and nitro.

5 In another embodiment of the present invention, R² is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl and nitro.

In another embodiment of the present invention, R² is selected from the group consisting of halogen, -C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, cyano and nitro.

10 In another embodiment of the present invention, R² is selected from the group consisting of halogen, C₁₋₄alkyl and halogen substituted C₁₋₄alkyl.

In another embodiment of the present invention, R² is halogen.

15 In another embodiment of the present invention, R² is selected from the group consisting of hydrogen, chloro, fluoro, methyl, trifluoromethyl, methoxy and nitro.

In another embodiment of the present invention, R² is selected from the group consisting of chloro and trifluoromethyl.

20 In another embodiment of the present invention, R² is selected from the group consisting of fluoro, chloro and methyl.

In an embodiment of the present invention, R³ is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, cyano and nitro.

25 In another embodiment of the present invention, R³ is selected from the group consisting of halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, cyano and nitro.

In another embodiment of the present invention, R³ is selected from the group consisting of halogen, -C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, cyano and nitro.

30 In another embodiment of the present invention, R³ is selected from the group consisting of halogen and cyano.

In another embodiment of the present invention, R³ is halogen.

In another embodiment of the present invention, R³ is selected from the group consisting of chloro, fluoro, methyl, methoxy, cyano and nitro.

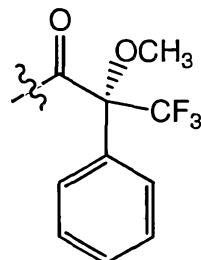
In another embodiment of the present invention, R³ is selected from the group consisting of chloro and cyano.

5 In another embodiment of the present invention, R³ is chloro.

In an embodiment of the present invention R² is halogen and R³ is halogen. In another embodiment of the present invention R² is chloro and R³ is chloro.

10

In an embodiment of the present invention, R⁴ is selected from the group

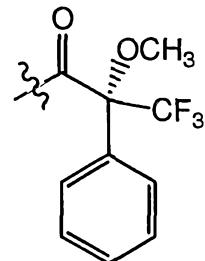


consisting of hydrogen, C₁₋₄alkyl and

In another embodiment of the present invention, R⁴ is selected from the group consisting of hydrogen, C₁₋₄alkyl and halogen substituted C₁₋₄alkyl.

15 In another embodiment of the present invention, R⁴ is selected from the group consisting of hydrogen and C₁₋₄alkyl.

In another embodiment of the present invention, R⁴ is selected from the



group consisting of hydrogen, methyl, ethyl and

20 In an embodiment of the present invention, R⁵ is selected from the group consisting of hydrogen, halogen and C₁₋₄alkyl.

In another embodiment of the present invention, R⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl and halogen substituted C₁₋₄alkyl.

In another embodiment of the present invention, R⁵ is selected from the group consisting of hydrogen and C₁₋₄alkyl.

In another embodiment of the present invention, R⁵ is selected from the group consisting of hydrogen and methyl.

5

- In an embodiment of the present invention, R⁶ is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-OH, -C₁₋₄alkyl-Y-R⁹ and -CH₂-phenyl; wherein the phenyl is optionally substituted with one to two substituent independently selected from halogen, 10 C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, -O-(halogen substituted C₁₋₄alkyl), nitro or cyano.

- In another embodiment of the present invention, R⁶ is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-OH, -C₁₋₄alkyl-Y-R⁹ and -CH₂-phenyl; wherein the phenyl is optionally 15 substituted with a halogen.

- In another embodiment of the present invention, R⁶ is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-OH and -C₁₋₄alkyl-Y-R⁹.

- In another embodiment of the present invention, R⁶ is selected from the 20 group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl and -C₁₋₄alkyl-CN.

- In another embodiment of the present invention, R⁶ is selected from the group consisting of methyl, chloro-methyl-, trifluoromethyl, cyano-methyl-, hydroxy-methyl, 3-fluoro-benzyl-, methoxy-methyl-, ethoxy-methyl-, methyl-thio-methyl-, ethyl-thio-methyl-, n-propyl-thio-methyl-, isopropyl-thio-methyl-, 25 trifluoroethyl-thio-methyl-, benzyl-thio-methyl-, 4-fluorophenyl-thio-methyl-, 4-methoxybenzyl-thio-methyl-, 4-chlorobenzyl-thio-methyl-, 4-fluorobenzyl-thio-methyl-, methyl-sulfonyl-methyl-, ethyl-sulfonyl-methyl-, n-propyl-sulfonyl-methyl-, isopropyl-sulfonyl-methyl-, trifluoroethyl-sulfonyl-methyl-, 4-fluorophenyl-sulfonyl-methyl-, 4-methylphenyl-sulfonyl-methyl-, 4-methylphenyl-30 sulfonyloxy-methyl-, benzyl-sulfonyl-methyl-, 4-fluorobenzyl-sulfonyl-methyl-, 4-methoxybenzyl-sulfonyl-methyl- and 4-methylcarbonylaminophenyl-sulfonyl-methyl-.

In an embodiment of the present invention, Y is selected from -O-, -S-, -SO-, -SO₂- and -O-SO₂-.

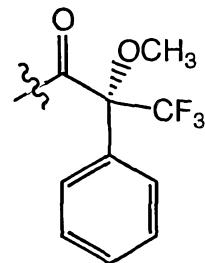
In another embodiment of the present invention, Y is selected from -O-, -S- and -SO₂-.

5

In another embodiment of the present invention, R⁹ is selected from C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, phenyl and -CH₂-phenyl; wherein the phenyl, whether alone or as part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl or -NR^M-C(O)-C₁₋₄alkyl; wherein R^M is selected from hydrogen or C₁₋₂alkyl.

In another embodiment of the present invention, R⁹ is selected from C₁₋₄alkyl, halogen substituted C₁₋₄alkyl and -CH₂-phenyl; wherein the phenyl is optionally substituted with one or more substituents independently selected from halogen, C₁₋₄alkyl or -O-C₁₋₄alkyl.

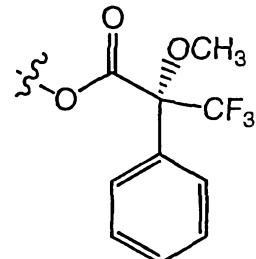
In an embodiment of the present invention, R¹⁰ is selected from the



group consisting of hydrogen, halogen, C₁₋₄alkyl and

In another embodiment of the present invention, R¹⁰ is selected from the group consisting of hydrogen, C₁₋₄alkyl and halogen substituted C₁₋₄alkyl.

In another embodiment of the present invention, R¹⁰ is selected from the



group consisting of hydrogen, fluoro, methyl and

In another embodiment of the present invention, R¹⁰ is hydrogen.

In an embodiment of the present invention, R¹¹ is selected from the group consisting of hydrogen, halogen and C₁₋₄alkyl.

In another embodiment of the present invention, R¹¹ is selected from the group consisting of hydrogen and halogen.

5 In another embodiment of the present invention, R¹¹ is selected from the group consisting of hydrogen and fluoro.

In another embodiment of the present invention, R¹¹ is hydrogen.

In an embodiment of the present invention, R¹⁰ and R¹¹ are taken
10 together with the carbon atom to which they are bound to form –C(O)- or –C(=N(OH))-.

In another embodiment of the present invention, R¹⁰ and R¹¹ are taken together with the carbon atom to which they are bound to form –C(O)-.

15 In an embodiment of the present invention, R¹² is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -C₁₋₄alkyl-CN, -C₁₋₄alkyl-OH, -C₁₋₄alkyl-Y-R⁹ and –CH₂-phenyl; wherein the phenyl is optionally substituted with one to two substituent independently selected from halogen, C₁₋₄alkyl, halogen substituted C₁₋₄alkyl, -O-C₁₋₄alkyl, -O-(halogen substituted C₁₋₄alkyl), nitro or cyano.

In another embodiment of the present invention, R¹² is selected from the group consisting of C₁₋₄alkyl, halogen substituted C₁₋₄alkyl and -C₁₋₄alkyl-CN.

In another embodiment of the present invention, R¹² is selected from the group consisting of C₁₋₄alkyl and halogen substituted C₁₋₄alkyl.

25 In another embodiment of the present invention, R¹² is selected from the group consisting of methyl, n-propyl, trifluoromethyl and 2,2,2-trifluoroethyl.

In another embodiment of the present invention, R¹² is trifluoromethyl.

In an embodiment of the present invention R² and R³ are each other
30 than hydrogen.

In an embodiment of the present invention R¹ is other than –CH₂-phenyl.

In an embodiment of the present invention, when R⁴ is hydrogen and R⁵ is hydrogen or C₁₋₄alkyl; then R⁶ is other than C₁₋₄alkyl. In another embodiment of the present invention, R⁵ and R⁶ are not each C₁₋₄alkyl. In another embodiment of the present invention, R¹⁰ and R¹¹ are not each C₁₋₄alkyl.

5

In an embodiment of the present invention, R⁶ is other than -CH₂-phenyl. In another embodiment of the present invention, R⁶ is other than -CH₂-benzimidazolyl.

10 In an embodiment of the present invention, R¹² is other than -CH₂-phenyl. In another embodiment of the present invention, R¹² is other than -CH₂-benzimidazolyl. In yet another embodiment of the present invention, R¹² is other than C₁₋₄alkyl.

15 In an embodiment of the present invention, wherein R¹⁰ and R¹¹ are taken together with the carbon atom to which they are bound to form -C(O)-, then R¹² is other than C₁₋₄alkyl.

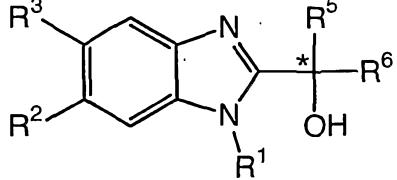
20 In an embodiment of the present invention are compounds of formula (I) selected from the group consisting of the compounds listed in Tables 1-3 below. In another embodiment of the present invention are compounds of formula (II) selected from the group consisting of the compounds listed in Tables 4-6 below.

25 Additional embodiments of the present invention, include those wherein the substituents selected for one or more of the variables defined herein (i.e. R¹, R², R³, a, R⁴, R⁵, R⁶, X, Y, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², etc.) are independently selected to be any individual substituent or any subset of substituents selected from the complete list as defined herein.

30 Representative compounds of the present invention are as listed in Tables 1-6, below. Tables 1-3 list representative compounds of formula (I). Tables 4-6 list representative compounds of formula (II). Unless otherwise noted, wherein a stereogenic center is present in the compound (as indicated

by the “*” symbol), the compound was prepared as a mixture of stereo-configurations.

Table 1: Representative Compounds of Formula (I)

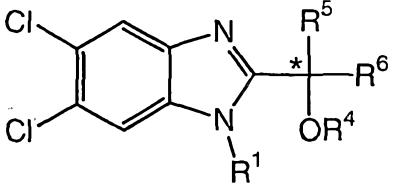
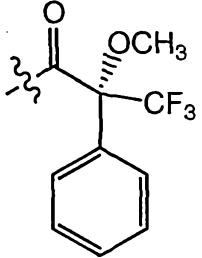
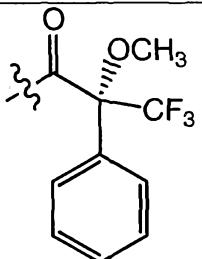
					
ID No.	R ¹	R ²	R ³	R ⁵	R ⁶
1	H	chloro	chloro	methyl	4-fluoro-phenyl-sulfonyl-methyl
2	H	chloro	chloro	methyl	4-methyl-phenyl-sulfonyl-methyl
3	H	chloro	chloro	methyl	3-fluoro-benzyl
4	H	chloro	chloro	methyl	hydroxy-methyl
5	H	chloro	chloro	methyl	methyl-sulfonyl-methyl
6	H	chloro	chloro	methyl	4-methyl-phenyl-sulfonyloxy-methyl
7	H	chloro	chloro	methyl	cyano-methyl
8	methyl	chloro	chloro	methyl	cyano-methyl
9	methyl	chloro	chloro	methyl	trifluoro-methyl
10	methyl	chloro	chloro	methyl	ethoxy-methyl
11	ethyl	chloro	chloro	methyl	chloro-methyl
12	methyl	chloro	chloro	methyl	methyl-thio-methyl
13	ethyl	chloro	chloro	methyl	trifluoro-methyl
14	n-propyl	chloro	chloro	methyl	trifluoro-methyl
15	n-butyl	chloro	chloro	methyl	trifluoro-methyl
16	ethyl	chloro	chloro	methyl	cyano-methyl
17	ethyl	chloro	chloro	methyl	methoxy-methyl
18	methyl	chloro	chloro	methyl	chloro-methyl
20	H	chloro	chloro	methyl	trifluoro-methyl

21	methyl	chloro	chloro	methyl	n-propyl-thio-methyl
22	methyl	chloro	chloro	methyl	4-fluoro-phenyl-thio-methyl
23	methyl	chloro	chloro	methyl	benzyl-thio-methyl
24	methyl	chloro	chloro	methyl	isopropyl-thio-methyl
25	methyl	chloro	chloro	methyl	ethyl-thio-methyl
29	methoxy-methyl	chloro	chloro	methyl	trifluoro-methyl
30	methoxy-methyl	chloro	chloro	methyl	cyano-methyl
31	ethyl	chloro	chloro	methyl	ethyl-thio-methyl
36	ethyl	chloro	chloro	methyl	4-methoxy-benzyl-thio-methyl
38	ethyl	chloro	chloro	methyl	4-chloro-benzyl-thio-methyl
39	ethyl	chloro	chloro	methyl	4-fluoro-benzyl-thio-methyl
40	methoxy-methyl	chloro	chloro	methyl	methyl
42	methyl	chloro	chloro	methyl	n-propyl-sulfonyl-methyl
44	ethyl	chloro	chloro	methyl	trifluoro-ethyl-thio-methyl
45	methyl	chloro	chloro	methyl	benzyl-sulfonyl-methyl
46	ethyl	chloro	chloro	methyl	4-fluoro-benzyl-sulfonyl-methyl
47	ethyl	chloro	chloro	methyl	4-methoxy-benzyl-sulfonyl-methyl
48	ethyl	chloro	chloro	methyl	ethyl-sulfonyl-methyl
49	ethyl	chloro	chloro	methyl	trifluoro-ethyl-sulfonyl-methyl

51	methyl-thio-methyl	chloro	chloro	methyl	methyl
53	cyano-methyl	chloro	chloro	methyl	methyl
54	methyl	chloro	chloro	methyl	isopropyl-sulfonyl-methyl
55	methyl	chloro	chloro	methyl	ethyl-sulfonyl-methyl
56	methyl	chloro	chloro	methyl	4-(methyl-carbonyl-amino)-phenyl-thio-methyl
64	methoxy-ethyl	chloro	chloro	methyl	methyl
66	cyano-methyl	chloro	chloro	methyl	trifluoro-methyl
59	H	chloro	chloro	H	trifluoro-methyl
82 ^a	H	chloro	chloro	H	trifluoro-methyl
83 ^a	H	chloro	chloro	H	trifluoro-methyl
111	H	methyl	methyl	H	trifluoro-methyl
112	H	chloro	fluoro	H	trifluoro-methyl
113	H	fluoro	fluoro	H	trifluoro-methyl
128	H	methyl	chloro	H	trifluoro-methyl
135	H	trifluoro-methyl	cyano	H	trifluoro-methyl
155	H	nitro	nitro	H	trifluoro-methyl
156	H	H	chloro	H	trifluoro-methyl
157	H	methoxy	methoxy	H	trifluoro-methyl

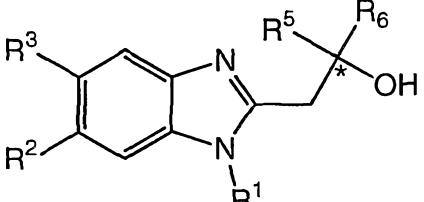
^a Racemic compound #59 was reacted to yield a mixture of diastereomers – the compounds #78 and #107, which were then separated. The isolated compounds #78 and #102 were then reacted to yield compounds #82 and #83, which were determined to have (-) and (+) optical rotation as noted.

Table 2: Representative Compounds of Formula (I)

				
ID No.	R ¹	R ⁴	R ⁵	R ⁶
28	methyl	methyl	methyl	cyano-methyl
34	methyl	methyl	methyl	trifluoro-methyl
35	H	methyl	methyl	trifluoro-methyl
61	methyl	methyl	H	trifluoro-methyl
62	ethyl	ethyl	H	trifluoro-methyl
67	H	t-butyl-dimethyl-silyl-	H	trifluoro-methyl
78 ^b	H		H	trifluoro-methyl
107 ^b	H		H	trifluoro-methyl

^b Racemic compound #59 was reacted to yield a mixture of diastereomers – the compounds #78 and #107, which were then separated.

Table 3: Representative Compounds of Formula (I)

					
ID No.	R ¹	R ²	R ³	R ⁵	R ⁶
27	H	chloro	chloro	methyl	trifluoromethyl

33	methyl	chloro	chloro	methyl	trifluoromethyl
37	ethyl	chloro	chloro	methyl	trifluoromethyl

Table 4: Representative Compounds of Formula (II)

ID No.	R ¹	R ²	R ³	W	R ⁶
26	methoxy-methyl	chloro	chloro	O	methyl
114	H	chloro	chloro	O	trifluoromethyl
141	H	chloro	chloro	N(OH)	trifluoromethyl
159	H	fluoro	chloro	O	trifluoromethyl
160	H	methyl	chloro	O	trifluoromethyl

Table 5: Representative Compounds of Formula (II)

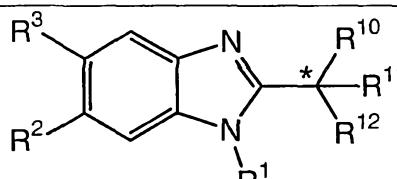
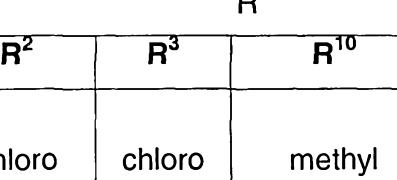
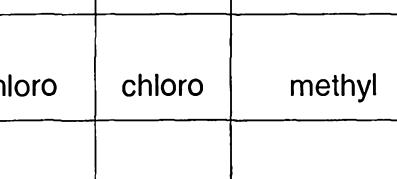
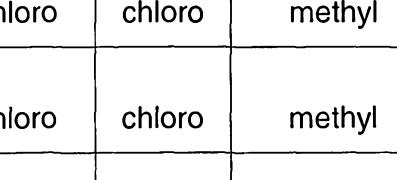
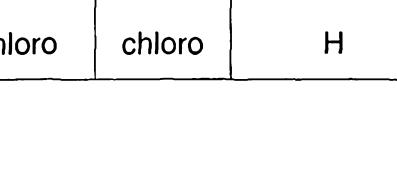
ID No.	R ¹	R ²	R ³
57	methoxy-methyl	chloro	chloro
58	methylthio-methyl	chloro	chloro
41	H	chloro	chloro
68	H	trifluoro-methyl	chloro
69	H	trifluoro-methyl	cyano
71	methyl	chloro	chloro
72	4-chloro-phenoxy-methyl	chloro	chloro
73	methyl-sulfonyl-methyl	chloro	chloro
74	phenyl-carbonyl-methyl	chloro	chloro
75	4-fluoro-phenyl-carbonyl-methyl	chloro	chloro

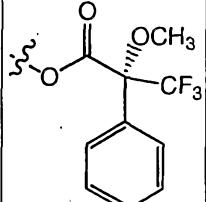
76	4-nitro-phenyl-carbonyl-methyl	chloro	chloro
77	2,4-dimethoxy-phenyl-carbonyl-methyl	chloro	chloro
79	4-bromo-phenyl-carbonyl-methyl	chloro	chloro
80	ethyl-carbonyl-methyl	chloro	chloro
81	ethoxy-carbonyl-methyl	chloro	chloro
84	2-benzofuryl-carbonyl-methyl	chloro	chloro
85	4-chloro-phenyl-carbonyl-methyl	chloro	chloro
86	3-methoxy-phenyl-carbonyl-methyl	chloro	chloro
87	3-pyridyl-carbonyl-methyl	chloro	chloro
88	2-(5-(2-pyridyl)-thienyl)-carbonyl-methyl	chloro	chloro
89	4-fluoro-benzyl	chloro	chloro
90	2-methoxy-phenyl-carbonyl-methyl	chloro	chloro
91	2-thienyl-carbonyl-methyl	chloro	chloro
92	2-pyridyl-carbonyl-methyl	chloro	chloro
93	3-trifluoro-methyl-benzyl	chloro	chloro
94	2,3,4,5,6-pentafluoro-benzyl	chloro	chloro
95	3-methyl-benzyl	chloro	chloro
96	3-nitro-phenyl-carbonyl-methyl	chloro	chloro
97	benzyl	chloro	chloro
98	2-hydroxy-ethyl	chloro	chloro
99	3-pyridyl-methyl	chloro	chloro
100	4-trifluoro-methyl-benzyl	chloro	chloro

101	4-trifluoro-methoxy-benzyl	chloro	chloro
102	2-pyridyl-methyl	chloro	chloro
	5-(2,3-dihydro- benzo[1,4]dioxinyl)-		
104	carbonyl-methyl-	chloro	chloro
105	4-nitro-benzyl	chloro	chloro
108	4-pyridyl-methyl	chloro	chloro
109	3-cyano-methyl-benzyl	chloro	chloro
110	2-cyano-methyl-benzyl	chloro	chloro
115	4-fluoro-phenoxy-ethyl	chloro	chloro
116	4-cyano-benzyl	chloro	chloro
117	2-fluoro-benzyl	chloro	chloro
119	3-fluoro-benzyl	chloro	chloro
120	3-chloro-benzyl	chloro	chloro
121	4-chloro-benzyl	chloro	chloro
123	3-fluoro-phenoxy-ethyl	chloro	chloro
124	4-chloro-phenoxy-ethyl	chloro	chloro
125	2-chloro-benzyl	chloro	chloro
	3-phenyl-5-methyl- isoxazol-4-yl-carbonyl-		
126	methyl-	chloro	chloro
129	3-methoxy-benzyl	chloro	chloro
130	2-methoxy-5-nitro-benzyl	chloro	chloro
131	4-pyrazolyl-benzyl	chloro	chloro
	4-[1,2,3]-thiadiazol-4-yl-		
132	benzyl-	chloro	chloro
	3-(5-methyl)-isoxazolyl-		
133	methyl	chloro	chloro
134	3-trifluoro-methoxy-benzyl	chloro	chloro
136	4-cyano-phenoxy-ethyl	chloro	chloro
137	2-nitro-benzyl	chloro	chloro
138	4-pyrrolyl-benzyl	chloro	chloro

139	3-nitro-benzyl	chloro	chloro
140	4-trifluoromethyl-thio-benzyl	chloro	chloro
142	4-methyl-sulfonyl-benzyl	chloro	chloro
144	trans-butan-2-one oxime	chloro	chloro
145	trans-butan-2-one oxime	chloro	chloro
146	4-benzyloxy-benzyl	chloro	chloro
147	4-methoxy-benzyl	chloro	chloro
148	2-hydroxy-n-butyl	chloro	chloro
149	4-bromo-benzyl	chloro	chloro
150	4-ethoxy-carbonyl-benzyl	chloro	chloro
151	2-bromo-benzyl	chloro	chloro
153	4-benzaldehyde	chloro	chloro

Table 6: Representative Compounds of Formula (II)

ID No.	R ¹	R ²	R ³	R ¹⁰	R ¹¹	R ¹²	Chemical Structure
							Chemical Structure
50	cyano-methyl	chloro	chloro	methyl	H	methyl	
60	methoxy-ethyl	chloro	chloro	methyl	H	methyl	
63	methoxy-methyl	chloro	chloro	methyl	H	methyl	
65	methoxy-methyl	chloro	chloro	methyl	H	n-propyl	
70	H	chloro	chloro	H	H	2,2,2-trifluoro-ethyl	

106	H	chloro	chloro		H	trifluoro-methyl
152	H	chloro	chloro	fluoro	H	trifluoro-methyl
154	H	chloro	chloro	fluoro	fluoro	trifluoro-methyl

As used herein, unless otherwise noted, “halogen” shall mean chlorine, bromine, fluorine and iodine.

5 As used herein, the term “alkyl” whether used alone or as part of a substituent group, shall include straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and the like. Similarly, “C₁₋₄alkyl” shall denote an alkyl chain as defined above comprising one to four carbon atoms.

10 As used herein, unless otherwise noted, the term “halogen substituted C₁₋₄alkyl” shall mean any of the above defined alkyl chains substituted with one or more, preferably one to three halogens. Preferably the halogen(s) are selected from chloro or fluoro. Suitable examples include, but are not limited to
15 chloromethyl, dichloromethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and the like.

As used herein, unless otherwise noted, the terms “alkoxy” and “-O-alkyl” shall denote an oxygen ether radical of the above described straight or branched
20 chain alkyl groups. For example, methoxy, ethoxy, n-propoxy, sec-butoxy, t-butoxy, n-hexyloxy and the like. Similarly, “C₁₋₄alkoxy” or “-O-C₁₋₄alkyl” shall denote an oxygen ether radical as defined above comprising one to four carbon atoms.

As used herein, unless otherwise noted, “**aryl**” shall refer to unsubstituted carbocyclic aromatic groups such as phenyl, naphthyl, and the like.

- As used herein, unless otherwise noted, “**aralkyl**” shall mean any lower alkyl group substituted with an aryl group such as phenyl, naphthyl and the like. For example, benzyl, phenylethyl-, phenyl-n-propyl-, naphthylmethyl-, and the like. One skilled in the art will recognize that the terms “**benzyl**” and “**-CH₂-phenyl**” are used interchangeably throughout the specification.
- As used herein, unless otherwise noted, the term “**cycloalkyl**” shall mean any stable 3-8 membered monocyclic, saturated ring system, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.
- As used herein, unless otherwise noted, “**heteroaryl**” shall denote any five or six membered monocyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine or ten membered bicyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heteroaryl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure.
- Examples of suitable heteroaryl groups include, but are not limited to, pyrrolyl, furyl, thienyl, oxazolyl, imidazolyl, purazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furazanyl, indolizinyl, indolyl, isoindolinyl, indazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, isothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, and the like.

As used herein, the term "**heterocycloalkyl**" shall denote any five to seven membered monocyclic, saturated or partially unsaturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected 5 from the group consisting of O, N and S; or a nine to ten membered saturated, partially unsaturated or partially aromatic bicyclic ring system containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at 10 any heteroatom or carbon atom of the ring such that the result is a stable structure.

Examples of suitable heterocycloalkyl groups include, but are not limited to, pyrrolinyl, pyrrolidinyl, dioxalanyl, imidazolinyl, imidazolidinyl, pyrazolinyl, 15 pyrazolidinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, indolanyl, chromenyl, 3,4-methylenedioxyphenyl, 2,3-dihydrobenzofuryl, and the like.

As used herein, the notation “**” shall denote the presence of a 20 stereogenic center.

When a particular group is "**substituted**" (e.g., Phe, aryl, heteroalkyl, heteroaryl), that group may have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most 25 preferably from one to two substituents, independently selected from the list of substituents.

With reference to substituents, the term "**independently**" means that when more than one of such substituents is possible, such substituents may be the same or different from each other.

30 To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "**about**". It is understood that whether the term "about" is used explicitly or not, every

quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

5

As used herein, unless otherwise noted, the term "**aprotic solvent**" shall mean any solvent that does not yield a proton. Suitable examples include, but are not limited to DMF, dioxane, THF, acetonitrile, pyridine, dichloroethane, dichloromethane, MTBE, toluene, and the like.

10

As used herein, unless otherwise noted, the term "**leaving group**" shall mean a charged or uncharged atom or group which departs during a substitution or displacement reaction. Suitable examples include, but are not limited to, Br, Cl, I, mesylate, tosylate, and the like.

15

As used herein, unless otherwise noted, the term "**nitrogen protecting group**" shall mean a group which may be attached to a nitrogen atom to protect said nitrogen atom from participating in a reaction and which may be readily removed following the reaction. Suitable nitrogen protecting groups

20

include, but are not limited to carbamates – groups of the formula $-\text{C}(\text{O})\text{O}-\text{R}$ wherein R is for example methyl, ethyl, t-butyl, benzyl, phenylethyl, $\text{CH}_2=\text{CH}-\text{CH}_2-$, and the like; amides – groups of the formula $-\text{C}(\text{O})-\text{R}'$ wherein R' is for example methyl, phenyl, trifluoromethyl, and the like; N-sulfonyl derivatives - groups of the formula $-\text{SO}_2-\text{R}''$ wherein R'' is for example tolyl, phenyl,

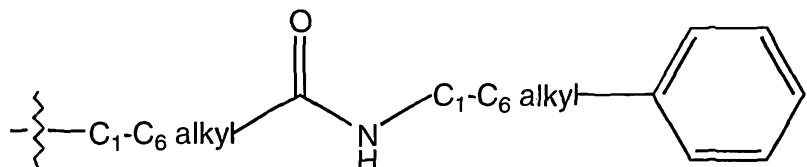
25

trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl-, 2,3,6-trimethyl-4-methoxybenzene, and the like. Other suitable nitrogen protecting groups may be found in texts such as T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

30

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a

"phenylC₁-C₆alkylaminocarbonylC₁-C₆alkyl" substituent refers to a group of the formula



5 One skilled in the art will further recognize that some substituent groups may begin or terminate with a "-", as in for example, "ethyl-carbonyl-methyl-". The presence of the "-" is intended, for the sake of clarity, to indicate the point of attachment between the substituent group and the rest of the molecule.

10 Abbreviations used in the specification, particularly the Schemes and Examples, are as follows:

DCM	=	Dichloromethane
DMAC	=	N,N-Dimethylacetamide
DME	=	1,2-Dimethoxyethane
DMF	=	N,N-Dimethylformamide
DMSO	=	Dimethylsulfoxide
EtOAc	=	Ethyl acetate
mCPBA	=	<i>m</i> -Chloro-peroxybenzoic acid
MeOH	=	Methanol
NMP	=	N-methyl-2-pyrrolidinone
Oxone®	=	Potassium monopersulfate triple salt
TEMPO	=	2,2,6,6,-Tetramethyl-1-piperidinyloxy, free radical
THF	=	Tetrahydrofuran

15 The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or

medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

5 As used herein, the term "**composition**" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

10 Where the compounds according to this invention have at least one **chiral center**, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

15 Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

20

One skilled in the art will recognize that wherein a reaction step of the present invention may be carried out in a variety of solvents or solvent systems, said reaction step may also be carried out in a mixture of the suitable solvents or solvent systems.

25

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers

30 may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-D-tartaric acid

and/or (+)-di-p-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds 5 may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by 10 means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

15

The present invention includes within its scope **prodrugs** of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present 20 invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are 25 described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "**pharmaceutically acceptable salts**." Other salts may, however, be 30 useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a

- pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following:
- 10 acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide,
- 15 isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate,
- 20 triethylsulfide and valerate.

Representative acids and bases which may be used in the preparation of pharmaceutically acceptable salts include the following:

- acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids,
- 25 adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid,
- 30 fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, α -oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (\pm)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (\pm)-DL-mandelic

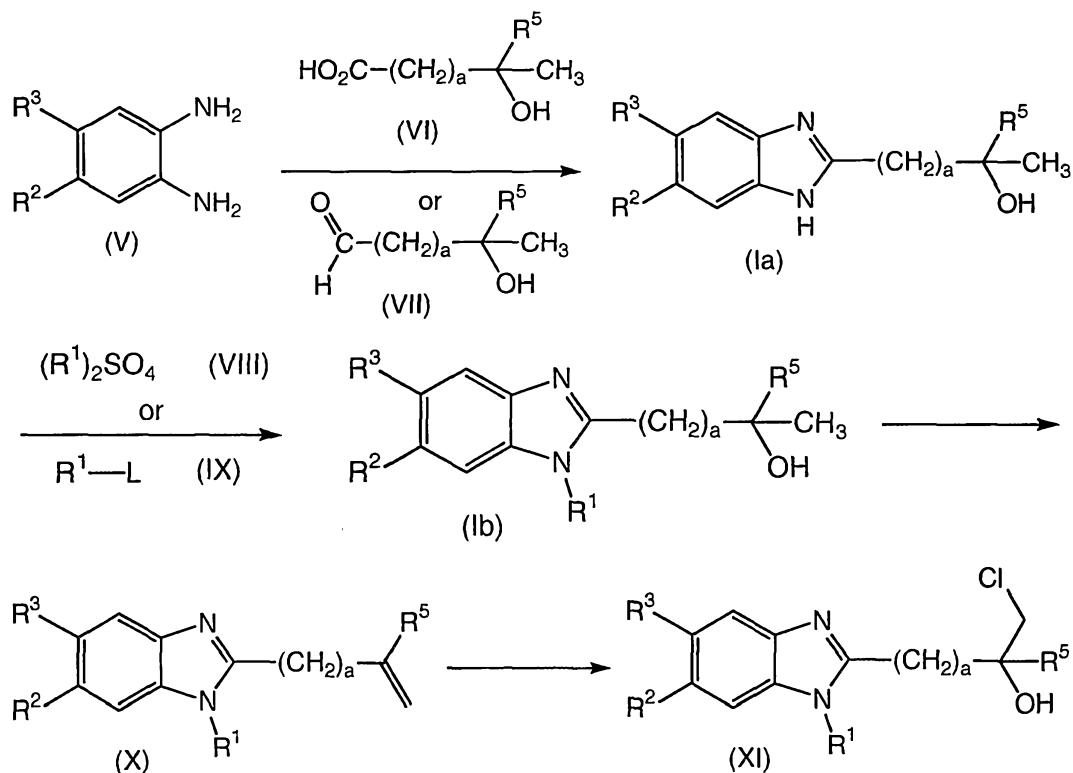
acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitric acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and

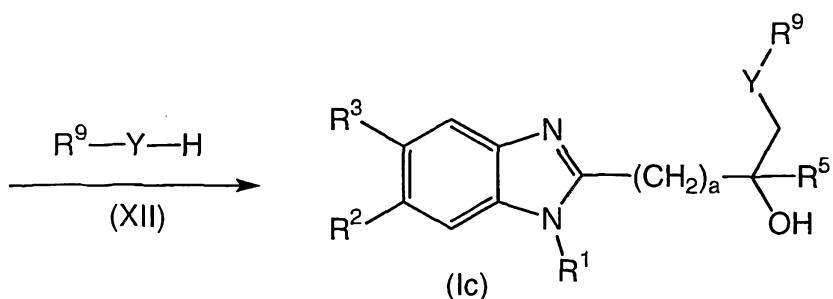
5 bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine,

10 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

Compounds of formula (I) wherein R⁴ is hydrogen may be prepared

15 according to the process outlined in Scheme 1.





Scheme 1

Accordingly, a suitably substituted compound of formula (V), a known compound or compound prepared by known methods, is reacted with a suitably 5 substituted compound of formula (VI), a known compound or compound prepared by known methods, in the presence of an acid such as HCl, H₂SO₄, acetic acid, and the like, in water, to yield the corresponding compound of formula (Ia).

Alternatively, a suitably substituted compound of formula (V), a known 10 compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (VII), a known compound or compound prepared by known methods, in the presence of sodium bisulfite, in water, to yield the corresponding compound of formula (Ia).

Alternatively, the compound of formula (V), a known compound or 15 compound prepared by known methods, is reacted with a suitably substituted compound of formula (VII), a known compound or compound prepared by known methods, in the presence of Oxone® or silica supported thionyl chloride, according to known methods, to yield the corresponding compound of formula (Ia).

20 Alternatively still, the compound of formula (V) is reacted with a suitably substituted carboxylic acid derivative, such as a suitably substituted acid chloride or anhydride, a known compound or compound prepared by known methods, according to known methods, followed by treatment with an organic acid such as toluenesulfonic acid or with a Lewis acid such as Al(CH₃)₃, (CH₃CH₂)₂AlCl, and the like, according to known methods, to yield the 25 corresponding compound of formula (Ia).

(See also for example, Mayer, J.P., Lweis, G.S., McGee, C., Bankaitis-Davis, D., Tetrahedron Letters, 1998, 39(37) pp 6655-6658; Ben Alloum, A.,

Bougrin, k., Soufiaoui, M., Tetrahedron letters, 2003, 44(31) pp 5935-5937;
Beaulieu, P.L., Hache, B., Von Moos, E., Synthesis, 2003 (11), pp 1683-1692;
and / or Matsushita, H., Lee, S-H., Joung, M., Clapham, B., Janda, K.D.,
Tetrahedron Letters, 2004 45(2), pp 313-316)

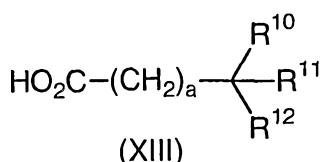
- 5 The compound of formula (Ia) is optionally reacted with a suitably substituted compound of formula (VIII), a known compound or compound prepared by known methods, or a suitably substituted compound of formula (IX), wherein L is a leaving group, a known compound or compound prepared by known methods, in the presence of a base such as NaOH, KOH, NaH,
10 K_2CO_3 , and the like, in a polar, aprotic organic solvent such as acetonitrile, THF, DMF, and the like, to yield the corresponding compound of formula (Ib).

The compound of formula (Ib) is optionally reacted with a dehydrating reagent such as Burgess' salt, and the like, in the presence of an organic solvent such as THF, DMF, DCM, acetonitrile, toluene, and the like, to yield the corresponding compound of formula (X).

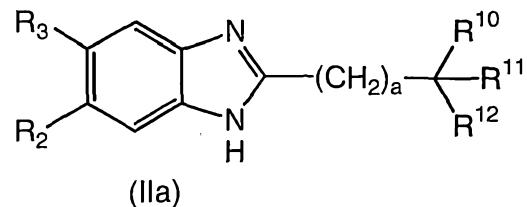
The compound of formula (X), wherein a is 0, may be further, optionally reacted with 1,3,5-trichloroisocyanic acid, in a mixture of organic solvent which is miscible with water and water such as acetone:water, THF:water, acetonitrile:water, DMF:water, dioxane:water, and the like, to yield the corresponding compound of formula (XI).

The compound of formula (XI) is reacted with a suitably substituted compound of formula (XII), a known compound or compound prepared by known methods, in the presence of a base such as sodium methoxide, sodium t-butoxide, sodium hydride, and the like, in an organic solvent such as DMF, 25 THF, dioxane, methanol, and the like, to yield the corresponding compound of formula (Ic).

One skilled in the art will recognize that compounds of formula (II) may be similarly prepared according to the process outlined in Scheme 1 above, by selecting and substituting, a suitably substituted compound of formula (XIII)



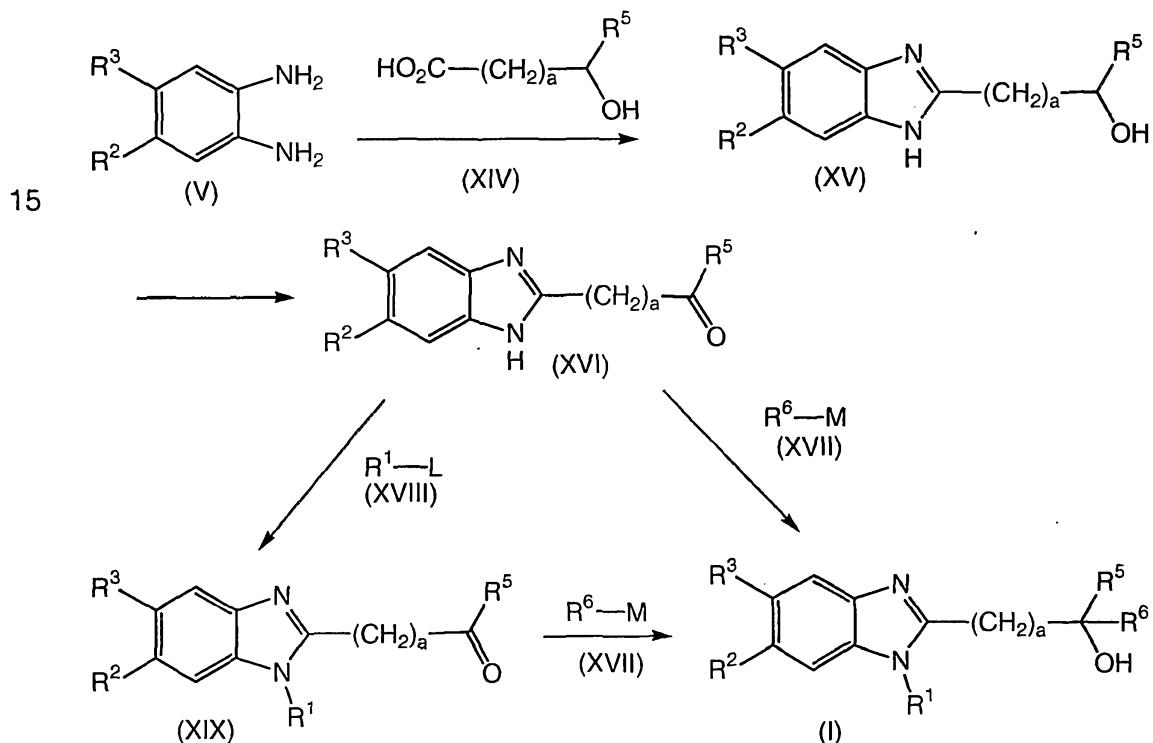
a known compound or compound prepared by known methods, for the compound of formula (VI), to yield the corresponding compound of formula (IIa)



One skilled in the art will further recognize that the compound of formula 5 (IIa) may then be further, optionally substituted with a suitably selected R¹ group, as outlined in Scheme 1 above.

One skilled in the art will recognize further that compounds of formula (I) wherein R⁴ is other than hydrogen may be prepared by reacting the 10 corresponding compound of formula (I) wherein R⁴ is hydrogen with a suitably substituted alkylating or acylating reagent, according to known methods.

Compounds of formula (I) may alternatively, be prepared according to the process outlined in Scheme 2.



Scheme 2

Accordingly, a suitably substituted compound of formula (V), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XIV), a known compound or compound prepared by known methods, in the presence of an acid such as HCl, H₂SO₄, 5 acetic acid, and the like, in water, to yield the corresponding compound of formula (XV).

The compound of formula (XV) is reacted with a suitably selected oxidizing agent such as Na₂Cr₂O₇, and the like, in the presence of an acid such as sulfuric acid, and the like, in an aqueous solvent, to yield the corresponding 10 compound of formula (XVI).

Alternatively, the compound of formula (XV) wherein R⁵ is hydrogen is reacted with a suitably selected oxidizing agent such as MnO₂ in a solvent such as dichloromethane, dichloroethane, benzene, toluene and the like at a temperature range from room temperature to 110 °, preferably at room 15 temperature; Dess-Martin Periodinane in a solvent such as dichloromethane, dichloroethane and the like at a temperature range from 0°C to room temperature, preferably at room temperature; or a mixture of (a) TEMPO, (b) bleach and (c) KBr or NaBr, in an organic solvent such as THF, DME, dioxane, and the like, at a reduced temperature in the range of about -40°C to about 20 room temperature, preferably at a reduced temperature in the range of about -10 to about 0°C; to yield the corresponding compound of formula (XVI).

The compound of formula (XVI) is reacted with a suitably substituted compound of formula (XVII), wherein M is MgBr or Li, a known compound or compound prepared by known methods, according to known methods, to yield 25 the corresponding compound of formula (I) wherein R¹ is hydrogen.

Alternatively, the compound of formula (XVI) is reacted with a suitably substituted compound of formula (XVIII), wherein L is a suitable leaving group such as Br, I, and the like, a known compound or compound prepared by known methods, in the presence of a base such as NaH, K₂CO₃, Na₂CO₃, and 30 the like, in an organic solvent such as DMF, DMAc, DMSO, NMP, and the like, to yield the corresponding compound of formula (XIX).

The compound of formula (XIX) is reacted with a suitably substituted compound of formula (XVII), wherein M is MgBr or Li, a known compound or

compound prepared by known methods, according to known methods, to yield the corresponding compound of formula (I) wherein R¹ is other than hydrogen.

One skilled in the art will recognize that compound of formula (II) may be 5 similarly prepared according to the process outlined in Scheme 2 above, by selecting and substituting, suitably substituted starting materials and reagents.

One skilled in the art will further recognize that compounds of formula (II) wherein R¹⁰ and R¹¹ are taken together with the carbon atom to which they are 10 bound to form a group selected from –C=N(OH) or –C=N(O-C₁₋₄alkyl) may be prepared from the corresponding compound of formula (II) wherein R¹⁰ and R¹¹ are taken together with the carbon atom to which they are bound to form –C(O), according to known methods.

15 The present invention further comprises pharmaceutical compositions containing one or more compounds of formula (I) and/or (II) with a pharmaceutically acceptable carrier. Pharmaceutical compositions containing one or more of the compounds of the invention described herein as the active ingredient can be prepared by intimately mixing the compound or compounds 20 with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring 25 agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be enteric-coated so as to modulate 30 major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

To prepare the pharmaceutical compositions of this invention, one or more compounds of the present invention as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 50-100 mg and may be given at a dosage of from about 0.5-5.0 mg/kg/day, preferably from about 1.0-3.0 mg/kg/day. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal

5 administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the

10 principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present

15 invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is

20 then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an

25 outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials

30 including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or 5 peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

10 The method of treating disorders or conditions modulated by the androgen receptor described in the present invention may also be carried out using a pharmaceutical composition comprising any of the compounds as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 0.01 mg and 500 mg, preferably about 50 to 100 mg, of 15 the compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules 20 (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixers, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

25 Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of 30 ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and 5 coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without 10 limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and 15 solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large 20 unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of 25 monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted 30 with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans,

polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing 5 compositions and according to dosage regimens established in the art whenever treatment of disorders or conditions modulated by the androgen receptor is required.

The daily dosage of the products may be varied over a wide range from 10 0.01 to 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage 15 to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 0.5 to about 5.0 mg/kg of body weight per day, most preferably, from about 1.0 to about 3.0 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

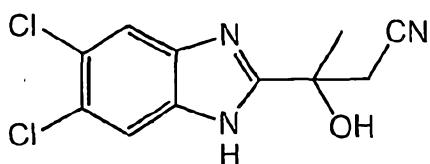
20

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the 25 particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way 30 the invention set forth in the claims which follow thereafter.

Example 1

3-(5,6-dichloro-1 H-benzimidazol-2-yl)-3-hydroxy-butyronitrile

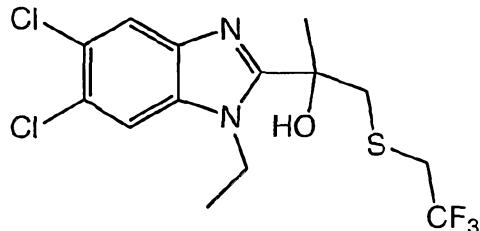


CH₃CN was added to a solution of n-butyl lithium in THF (8 ml) at -78°C and the mixture was stirred at -78°C for 45 minutes. To this solution was added 1-(5,6-dichloro-1H-benzimidazol-2-yl)-ethanone in THF (6 ml) and the 5 resulting mixture was stirred at -78°C for an addition ½ hour. After stirring at 0°C for 6 hrs, water was added, the resulting solution was extracted with EtOAc, the organic layer was washed with brine and then dried over anhydrous Na₂SO₄. Solvent was distilled off under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 10% to 50%) yielded the title 10 product as an off-white solid.

MS m/z (M+H) 270

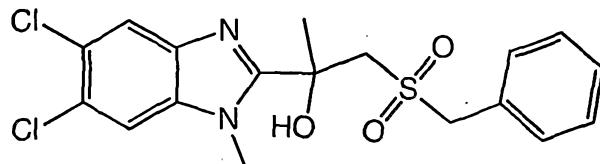
Example 2

2-(5,6-Dichloro-1-ethyl-1H-benzimidazol-2-yl)-1-(2,2,2-trifluoro-ethylsulfanyl)-15 propan-2-ol



To 1-chloro-2-(5,6-dichloro-1-ethyl-1H-benzimidazol-2-yl)-propan-2-ol (249 mg) in methanol (5 mL) at room temperature was added a solution of 2,2,2-trifluoroethanethiol (109 mg) and sodium methoxide (0.222 mls of 25 wt% 20 in MeOH). The resulting mixture was then stirred at room temperature overnight. The reaction mixture was concentrated. The crude product was purified by flash chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a brown solid.

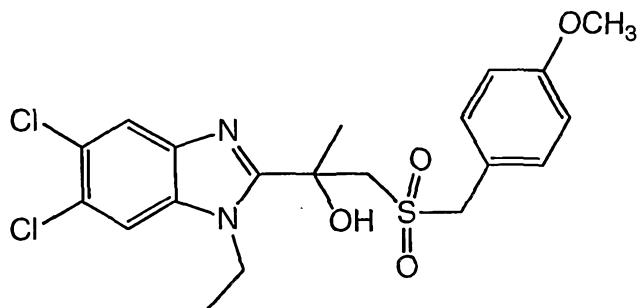
¹H NMR (400 MHz, d₆-DMSO): δ 7.96 (s, 1H), 7.88 (s, 1H), 6.12 (s, 1H), 25 4.53-4.61 (m, 2H), 3.48-3.54 (m, 2H), 3.31 (ABq, 2H, J_{AB} = 13.3 Hz, Δv_B = 71 Hz), 1.69 (s, 3H), 1.35 (t, 3H, J = 7.0 Hz).

Example 32-(5,6-Dichloro-1-methyl-1H-benzoimidazol-2-yl)-1-phenylmethanesulfonyl-propan-2-ol

5

To a solution of 2-(5,6-dichloro-1-methyl-1H-benzoimidazol-2-yl)-1-phenylmethanesulfonyl-propan-2-ol (76.5 mg) in CH_2Cl_2 (2 mL) at room temperature was added mCPBA (69 mg). The resulting mixture was stirred at room temperature overnight. The reaction was then quenched with saturated NaHCO_3 (aq) and extracted with EtOAC. The crude product was purified by flash chromatography (10% - 70% EtOAc/hexanes) to yield the title compound as a white foam.

10 ^1H NMR (300 MHz, CDCl_3): δ 7.82 (s, 1H), 7.59-7.62 (m, 2H), 7.50 (s, 1H), 7.42-7.44 (m, 3H), 5.09 (s, 1H), 4.56 (ABq, 2H, $J_{AB} = 13.7$ Hz, $\Delta\nu_{AB} = 137$ Hz), 4.02 (s, 3H), 3.86 (ABq, 2H, $J_{AB} = 15.1$ Hz, $\Delta\nu_{AB} = 354$ Hz), 1.68 (s, 3H).

Example 42-(5,6-Dichloro-1-ethyl-1H-benzoimidazol-2-yl)-1-(4-methoxy-phenylmethanesulfonyl)-propan-2-ol

20

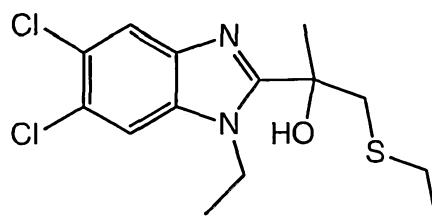
To a solution of 2-(5,6-dichloro-1-ethyl-1H-benzoimidazol-2-yl)-1-(4-methoxy-phenylmethanesulfonyl)-propan-2-ol (97.6 mg) in CH_2Cl_2 (2 mL) at room temperature was added mCPBA (93 mg). The resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated NaHCO_3 (aq) and extracted with EtOAc. The crude product was

purified by flash chromatography (20% - 60% EtOAc/hexanes) to yield the title compound as an off-white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.81 (s, 1H), 7.51 (s, 1H), 7.24 (ABq, 2H, J_{AB} = 8.6 Hz, Δv_{AB} = 173 Hz), 5.19 (s, 1H), 4.44 (ABq, 2H, J_{AB} = 13.9 Hz, Δv_{AB} = 149 Hz), 4.41-4.69 (m, 2H), 3.85 (ABq, 2H, J_{AB} = 15 Hz, Δv_{AB} = 367 Hz), 3.83 (s, 3H), 1.68 (s, 3H), 1.48 (t, 3H, J = 7.1 Hz).

Example 5

2-(5,6-Dichloro-1-ethyl-1H-benzoimidazol-2-yl)-1-ethylsulfanyl-propan-2-ol



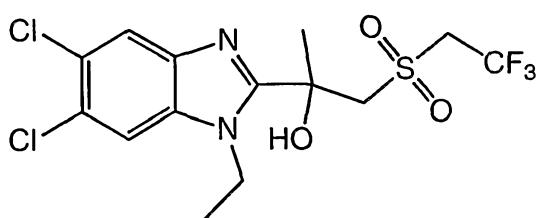
10

To 1-chloro-2-(5,6-dichloro-1-ethyl-1H-benzoimidazol-2-yl)-propan-2-ol (161 mg) in methanol (5 mL) at room temperature was added a solution of ethanethiol (37 mg) and sodium methoxide (0.144 mls of 25 wt% in MeOH). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH₄Cl (aq), extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by flash chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as an off-white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.80 (s, 1H), 7.45 (s, 1H), 4.43-4.64 (m, 2H), 3.77 (s, 1H), 3.35 (ABq, 2H, J_{AB} = 13.6 Hz, Δv_{AB} = 246 Hz), 2.48-2.60 (m, 2H), 1.71 (s, 3H), 1.47 (t, 3H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.4 Hz)

Example 6

2-(5,6-Dichloro-1-ethyl-1H-benzoimidazol-2-yl)-1-(2,2,2-trifluoroethanesulfonyl)-propan-2-ol



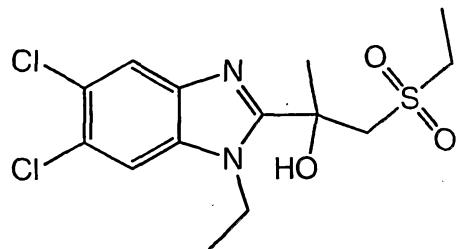
25

To 2-(5,6-dichloro-1-ethyl-1*H*-benzoimidazol-2-yl)-1-(2,2,2-trifluoroethylsulfanyl)-propan-2-ol (101 mg) in CH₂Cl₂ (2 mL) at room temperature was added *m*CPBA (106 mg). The resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. NaHCO₃ (aq), 5 extracted with EtOAc, dried over Na₂SO₄, filtered off dessicant, and concentrated. The residue was chromatographed with 10% - 60% EtOAc/hexanes as the eluant to yield the title compound as a white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.74 (s, 1H), 7.50 (s, 1H), 4.87-5.01 (m, 1H), 4.83 (s, 1H), 4.41-4.66 (m, 2H), 4.16 (ABq, 2H, J_{AB} = 15.4 Hz, Δv_{AB} = 334 Hz), 3.78-3.93 (m, 1H), 1.71 (s, 3H), 1.48 (t, 3H, J = 7.2 Hz).

Example 7

2-(5,6-Dichloro-1-ethyl-1*H*-benzoimidazol-2-yl)-1-ethanesulfonyl-propan-2-ol



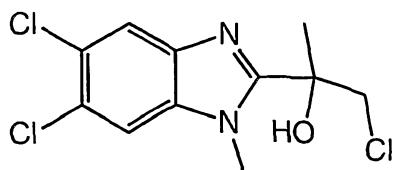
15 To 2-(5,6-dichloro-1-ethyl-1*H*-benzoimidazol-2-yl)-1-ethanesulfonyl-propan-2-ol (134.8 mg) in CH₂Cl₂ (2 mL) at room temperature was added *m*CPBA (164 mg). The resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated NaHCO₃ (aq), extracted with EtOAc, dried over Na₂SO₄, filtered off dessicant, and concentrated. The 20 residue was chromatographed with 10% - 60% EtOAc/hexanes as the eluant to yield the title compound as a white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.74 (s, 1H), 7.49 (s, 1H), 5.25 (s, 1H), 4.40-4.72 (m, 2H), 3.96 (ABq, 2H, J_{AB} = 14.8 Hz, Δv_{AB} = 289 Hz), 3.00-3.26 (m, 2H), 1.74 (s, 3H), 1.47 (t, 3H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.8 Hz).

25

Example 8

1-Chloro-2-(5,6-dichloro-1-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol

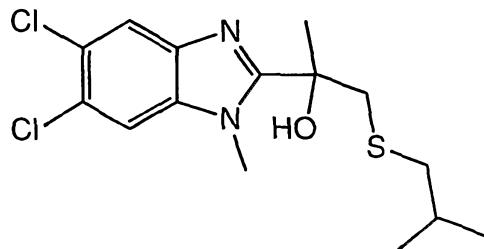


To 5,6-dichloro-1-methyl-2-isopropenyl-1*H*-benzimidazole (2.5 g) in acetone (30 mL) and water (6 mL) at room temperature was added trichloroisocyanuric acid (845 mg). The resulting mixture was stirred at room 5 temperature for 18 h. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. After removal of the dessicant by filtration, concentration yielded an orange crude oil. The crude product was purified by flash chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a yellow solid.

10 ¹H NMR (400 MHz, d₆-DMSO): δ 7.97 (s, 1H), 7.90 (s, 1H), 6.22 (s, 1H), 4.04 (m, 2H), 4.01 (s, 3H), 1.68 (s, 3H)

Example 9

2-(5,6-Dichloro-1-methyl-1*H*-benzoimidazol-2-yl)-1-isobutylsulfanyl-propan-2-ol

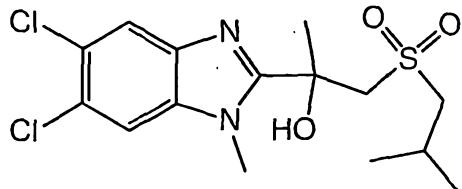


15

To 1-chloro-2-(5,6-dichloro-1-methyl-1*H*-benzoimidazol-2-yl)-propan-2-ol (408 mg) in methanol (10 mL) at room temperature was added a solution of 2-methyl-1-propanethiol (150 mg) and sodium methoxide (0.381 mls of 25 wt% in MeOH). The resulting mixture was stirred at room temperature overnight. The 20 reaction mixture was then concentrated. The crude product was purified by flash chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a light orange solid.

25 ¹H NMR (300 MHz, CDCl₃): δ 7.80 (s, 1H), 7.43 (s, 1H), 4.00 (s, 3H), 3.75 (s, 1H), 3.33 (ABq, 2H, J_{AB} = 13.6 Hz, Δν_{AB} = 248 Hz), 2.36-2.51 (m, 2H), 1.73-1.83 (m, 1H), 1.70 (s, 3H), 0.95 (d, 6H, J = 6.8 Hz)

MS (M+1) = 347.1; (M +Na) = 369.1.

Example 102-(5,6-Dichloro-1-methyl-1H-benzoimidazol-2-yl)-1-(2-methyl-propane-1-sulfonyl)-propan-2-ol

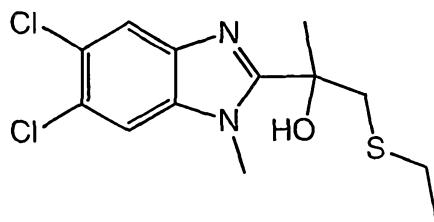
5

To 2-(5,6-dichloro-1-methyl-1H-benzoimidazol-2-yl)-1-isobutylsulfonylpropan-2-ol (97 mg) in CH_2Cl_2 (2 mL) at room temperature was added *m*CPBA (113 mg) and subsequently stirred overnight. The reaction mixture was quenched with NaHCO_3 (aq), extracted with EtOAc , and dried over Na_2SO_4 .

- 10 The crude product was purified by flash chromatography (10% - 70% $\text{EtOAc}/\text{hexanes}$) to yield the title compound as an off-white solid.

^1H NMR (300 MHz, CDCl_3): δ 7.73 (s, 1H), 7.48 (s, 1H), 5.17 (s, 1H), 4.02 (s, 3H), 3.96 (ABq, 2H, $J_{\text{AB}} = 14.9$ Hz, $\Delta\nu_{\text{AB}} = 260$ Hz), 2.37 (nonet, 1H, $J = 6.7$ Hz), 1.73 (s, 3H), 1.12 (d, 3H, $J = 6.7$ Hz), 1.07 (d, 3H, $J = 6.7$ Hz).

15

Example 112-(5,6-Dichloro-1-methyl-1H-benzoimidazol-2-yl)-1-ethylsulfanyl-propan-2-ol

To 1-chloro-2-(5,6-dichloro-1-methyl-1H-benzoimidazol-2-yl)-propan-2-ol

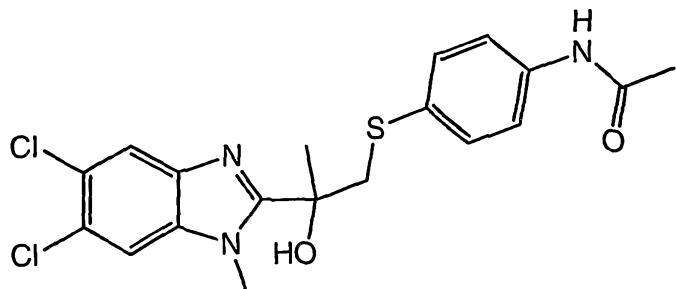
- 20 (141 mg) in MeOH (4 mL) at room temperature was added a solution of ethanethiol (34 mg) and sodium methoxide (0.132 mls of 25 wt% in MeOH). The resulting mixture was stirred at room temperature overnight. The reaction mixture was then concentrated. The crude product was purified by flash chromatography (10% - 40% $\text{EtOAc}/\text{hexanes}$) to yield the title compound as a yellow crystalline solid.

¹H NMR (300 MHz, CDCl₃): δ 7.80 (s, 1H), 7.43 (s, 1H), 4.00 (s, 3H), 3.74 (s, 1H), 3.34 (ABq, 2H, J_{AB} = 13.7 Hz, Δv_{AB} = 246 Hz), 2.48-2.62 (m, 2H), 1.71 (s, 3H), 1.25 (t, 3H, J = 7.4 Hz)
 MS (M+1) = 319.0.

5

Example 12

N-{4-[2-(5,6-Dichloro-1-methyl-1H-benzoimidazol-2-yl)-2-hydroxy-propylsulfanyl]-phenyl}-acetamide



10 To 1-chloro-2-(5,6-dichloro-1-methyl-1H-benzoimidazol-2-yl)-propan-2-ol (60 mg) in MeOH (2 mL) at room temperature was added a solution of 4-acetamidothiophenol (40 mg) and sodium methoxide (0.047 mls of 25 wt% in MeOH). The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated. The crude product was purified by flash chromatography (25% - 100% EtOAc/hexanes) to yield the title compound as a white foam solid.

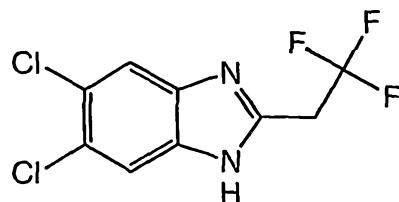
15

¹H NMR (300 MHz, CDCl₃): δ 7.72 (s, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 7.20 (s, 4H), 3.85 (s, 3H), 3.83 (s, 1H), 3.62 (ABq, 2H, J_{AB} = 14 Hz, Δv_{AB} = 179 Hz), 2.16 (s, 3H), 1.76 (s, 3H)

20 MS (M+1) = 424.0; (M +Na) = 446.0

Example 13

5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

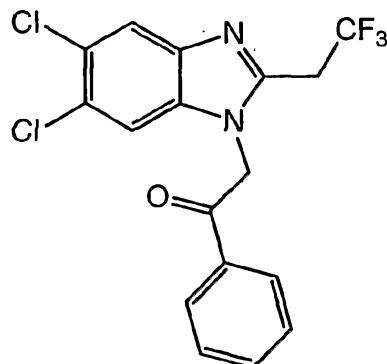


To 4,5-dichloro-1,2-phenylenediamine (25 g) was added 3,3,3-trifluoropropionic acid (25 mls) and 4N HCl (90 mL). The resulting mixture was heated to 100°C overnight. The reaction mixture was quenched with water, basicified with concentrated NH₄OH, extracted with EtOAc, and dried over 5 Na₂SO₄. The crude product was filtered through a plug of silica gel, eluting with 30% EtOAc/hexanes, and collecting the red band. The fractions were concentrated to yield a mixture of the desired title compound and 4,5-dichloro-1,2-phenylenediamine. The crude material was dissolved in small amount of CH₂Cl₂ and triturated with hexanes to yield the title compound as a tan solid.

10 ¹H NMR (300 MHz, d₆-DMSO): δ 12.92 (br s, 1H), 7.88 (s, 2H), 4.06 (ABq, 2H, J_{AB} = 11 Hz, Δv_{AB} = 19 Hz).

Example 14

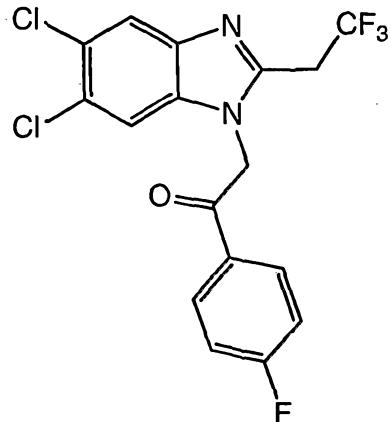
2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-phenyl-ethanone



15

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (301 mg) in DMF (5 mL) was added sodium hydride (67 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green solution was added 2-bromo-acetophenone (273 mg) and the resulting mixture 20 was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as an off-white solid.

25 ¹H NMR (300 MHz, CDCl₃): δ 8.04 – 8.07 (m, 2H), 7.92 (s, 1H), 7.73 – 7.78 (m, 1H), 7.59 – 7.64 (m, 2H), 7.29 (s, 1H), 5.59 (s, 2H), 3.72 (ABq, 2H, J_{AB} = 9.9 Hz, Δv_{AB} = 17.2 Hz).

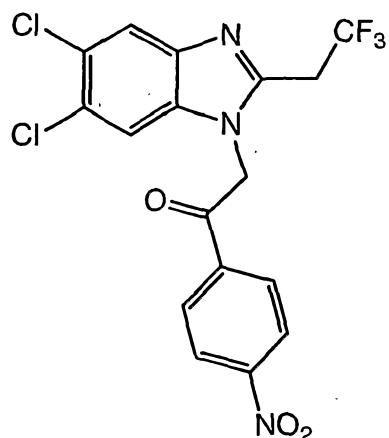
Example 152-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(4-fluoro-phenyl)-ethanone

5

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (318 mg) in DMF (5 mL) was added sodium hydride (71 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green solution was added 2-bromo-4'fluoroacetophenone (317 mg) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a peach colored solid.

10 ¹H NMR (300 MHz, CDCl₃): δ 8.07 – 8.12 (m, 2H), 7.92 (s, 1H), 7.25 – 15 7.32 (m, 3H), 5.56 (s, 2H), 3.72 (ABq, 2H, J_{AB} = 9.9 Hz, Δν_{AB} = 17.2 Hz).

Example 162-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(4-nitro-phenyl)-ethanone

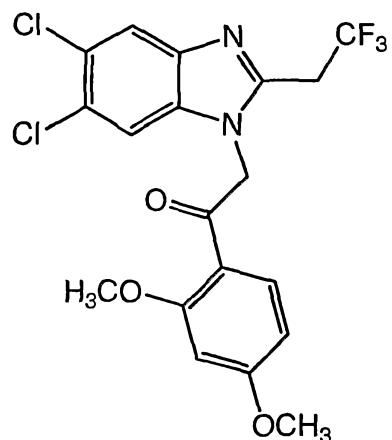


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (304 mg) in DMF (5 mL) was added sodium hydride (68 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green 5 solution was added 2-bromo-4' nitroacetophenone (348 mg) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as an orange colored solid.

10

Example 17

2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(2,4-dimethoxy-phenyl)-ethanone



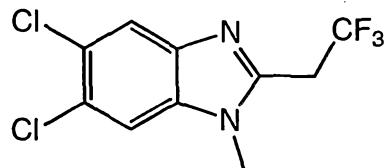
15 To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (317 mg) in DMF (5 mL) was added sodium hydride (71 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green solution was added 2-bromo-2',4'-dimethoxyacetophenone (382 mg) and the

resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a white solid.

5 ¹H NMR (300 MHz, d₆-DMSO): δ 7.97 (s, 1H), 7.96 (s, 1H), 7.78 (d, 1H, J = 7.0 Hz), 6.67-6.70 (m, 1H), 5.75 (s, 2H), 4.13 (ABq, 2H, J_{AB} = 11 Hz, Δv_{AB} = 19 Hz), 4.03 (s, 3H), 3.89 (s, 3H).

Example 18

10 5,6-Dichloro-1-methyl-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole

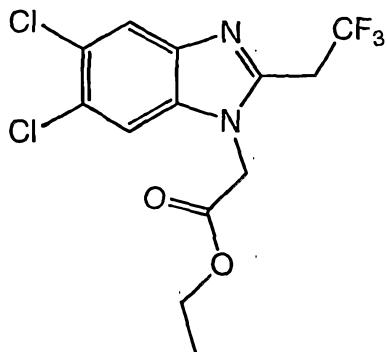


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole (1 g) in DMF (20 mL) was added sodium hydride (230 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green 15 solution was added iodomethane (815 mg) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 25% EtOAc/hexanes) to yield the title compound as an orange solid.

20 ¹H NMR (300 MHz, CDCl₃): δ 7.85 (s, 1H), 7.46 (s, 1H), 3.80 (ABq, 2H, J_{AB} = 9.9 Hz, Δv_{AB} = 14 Hz), 3.79 (s, 3H).

Example 19

[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-acetic acid ethyl ester

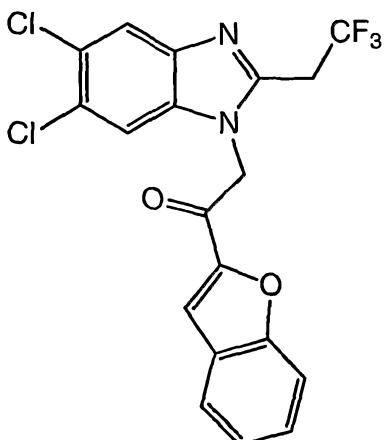


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (1 g) in DMF (5 mL) was added sodium hydride (85 mg of 60% in oil dispersion). The resulting mixture was stirred at room temperature for 5 min. To the dark green 5 solution was added ethyl bromoacetate (363 mg) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 30% EtOAc/hexanes) to yield the title compound as a yellow solid.

10 ¹H NMR (300 MHz, CDCl₃): δ 7.89 (s, 1H), 7.40 (s, 1H), 4.86 (s, 2H), 4.26 (q, 2H, *J* = 7.1 Hz), 3.79 (ABq, 2H, *J*_{AB} = 9.9 Hz, $\Delta\nu_{AB}$ = 17.1 Hz), 1.29 (t, 3H, *J* = 7.1 Hz).

Example 20

15 1-Benzofuran-2-yl-2-[5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-ethanone



To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (460.5 mg) in DMF (5 mL) was added sodium hydride (103 mg of 60% in oil dispersion). The

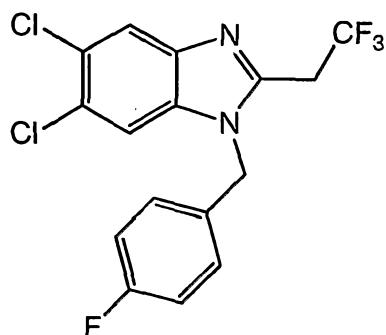
resulting mixture was stirred at room temperature for 5 min. To the dark green solution was added 1-(1-benzofuran-2-yl)-2-bromoethan-1-one (633 mg) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over 5 Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a yellow solid.

^1H NMR (300 MHz, d_6 -DMSO): δ 8.10 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.95 (d, 1H, J = 7.8 Hz), 7.81 (d, 1H, J = 8.1 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.44 (t, 1H, J = 7.4 Hz), 6.05 (s, 2H), 4.23 (ABq, 2H, J_{AB} = 10.6 Hz, $\Delta\nu_{\text{AB}}$ = 18.6 Hz).

10

Example 21

5,6-Dichloro-1-(4-fluoro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



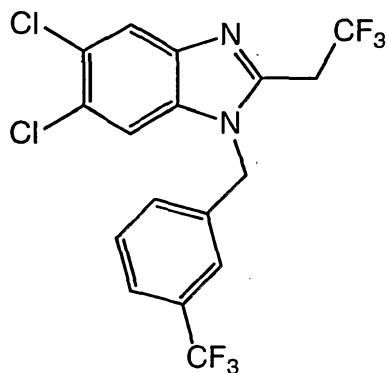
To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole (301 mg) in 15 DMF (5 mL) was added potassium carbonate powder (298 mg) and 4-fluorobenzyl bromide (841 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title 20 compound as a peach colored solid.

MS (M-1) = 375.0.

Example 22

5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1-(3-trifluoromethyl-benzyl)-1H-benzoimidazole

25

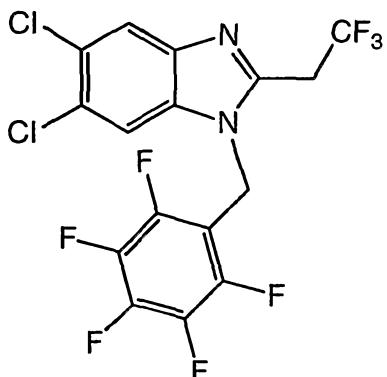


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (355 mg) in DMF (5 mL) was added potassium carbonate powder (548 mg) and 3-trifluoromethylbenzyl bromide (947 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as an orange solid.

¹H NMR (300 MHz, CDCl₃): δ 7.94 (s, 1H), 7.62 (d, 1H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 7.8 Hz), 7.36 (s, 1H), 7.30 (s, 1H), 7.05 (d, 1H, *J* = 8.1 Hz), 5.45 (s, 2H), 3.73 (ABq, 2H, *J_{AB}* = 9.7 Hz, $\Delta\nu_{AB}$ = 17 Hz).

Example 23

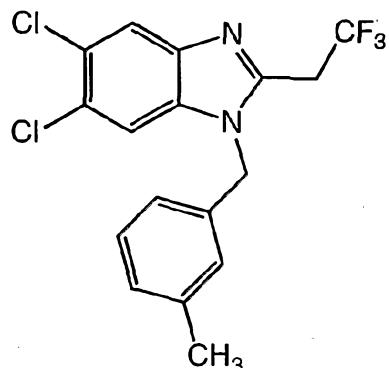
5,6-Dichloro-1-pentafluorophenylmethyl-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole



To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (354 mg) in DMF (5 mL) was added potassium carbonate powder (545 mg) and 2,3,4,5,6-pentafluoromethylbenzyl bromide (1.028 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water,

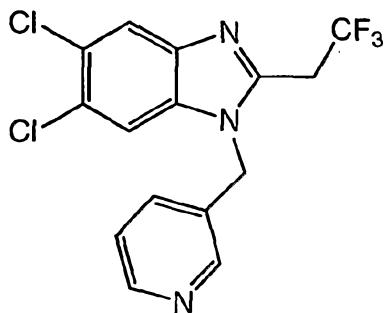
extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a tan solid.

5

Example 245,6-Dichloro-1-(3-methyl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (360 mg) in DMF (5 mL) was added potassium carbonate powder (555 mg) and 3-methylbenzyl bromide (774 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as an off-white solid.

15

Example 255,6-Dichloro-1-pyridin-3-ylmethyl-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole

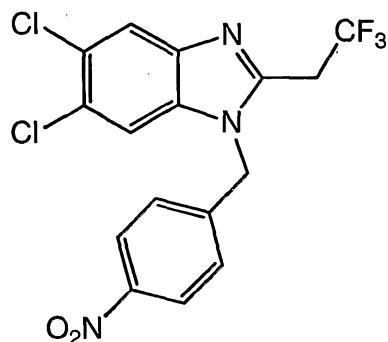
To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (423 mg) in DMF (5 mL) was added potassium carbonate powder (868 mg) and 3-(bromomethyl)pyridine hydrogen bromide (615 mg). The resulting mixture was

stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (15% - 60% EtOAc/hexanes) to yield the title compound as a green solid.

5

Example 26

5,6-Dichloro-1-(4-nitro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole



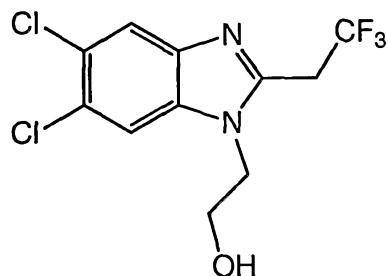
- To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole (355 mg) in
- 10 DMF (5 mL) was added sodium hydride (110 mg of 60% in oil) and 4-nitrobenzyl bromide (596 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title
- 15 compound as a light orange solid.

¹H NMR (300 MHz, CDCl₃): δ 8.20 (d, 2H, *J* = 8.8 Hz), 7.92 (s, 1H), 7.26 (s, 1H), 7.16 (d, 2H, *J* = 8.8 Hz), 5.50 (s, 2H), 3.75 (ABq, 2H, *J_{AB}* = 9.7 Hz, $\Delta\nu_{AB}$ = 23 Hz).

20

Example 27

2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-ethanol



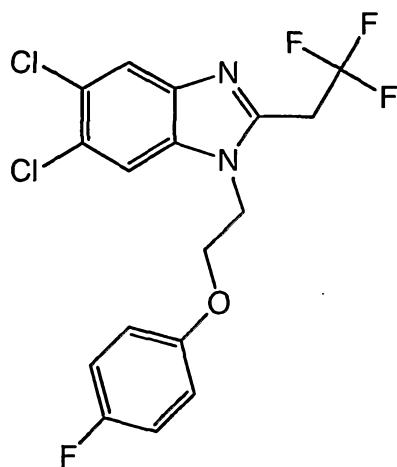
To [5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-benzimidazol-1-yl]-acetic acid ethyl ester (915 mg) in toluene (20 mL) at -78 °C was added DiBAI-H (3.43 mls of 1.5 M in toluene). The resulting mixture was stirred for 1 hour. The reaction mixture was quenched with Rochelle's salt (aq), extracted with EtOAc, and 5 dried over Na₂SO₄. The extracts were concentrated to a toluene solution and ethanol (10 mL) was added. To the resulting solution was added NaBH₄ (533 mg). The resulting mixture was stirred for 5 hour. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (15% - 60% EtOAc/hexanes) 10 to yield the title compound as a yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 7.41 (s, 1H), 7.37 (s, 1H), 4.37 (t, 1H, *J* = 5.1 Hz), 4.30 (t, 2H, *J* = 4.6 Hz), 3.99-4.03 (m, 2H), 3.86 (ABq, 2H, *J*_{AB} = 9.8 Hz, $\Delta\nu_{AB}$ = 17 Hz).

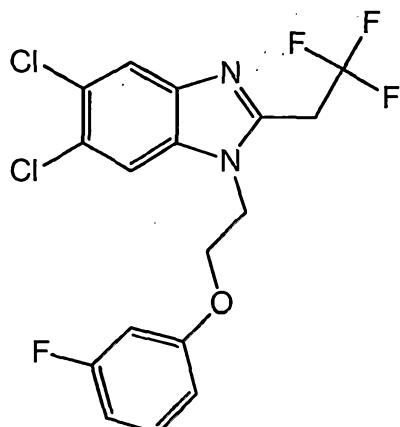
15

Example 28

5,6-Dichloro-1-[2-(4-fluoro-phenoxy)-ethyl]-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole



To a mixture of 2-[5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-benzimidazol-1-yl]-ethanol (171 mg), 4-fluorophenol (92 mg), and triphenylphosphine (158 mg) 20 in toluene (5 mL) at 0°C was added diethylazodicarboxylate (0.11 mls). The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with 1N HCl (aq), extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (4% - 25% EtOAc/hexanes) to yield the title compound as a white solid.

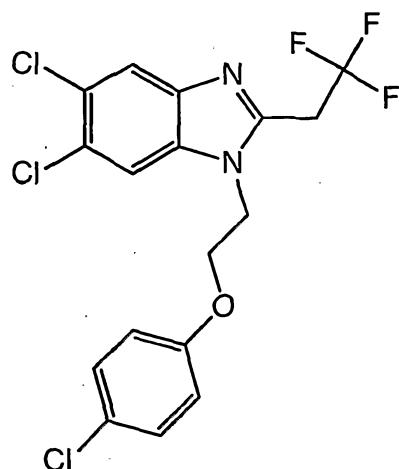
Example 295,6-Dichloro-1-[2-(3-fluoro-phenoxy)-ethyl]-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

5

To a mixture of 2-[5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-benzimidazol-1-yl]- ethanol (164 mg), 3-fluorophenol (88 mg), and triphenylphosphine (158 mg) in toluene (5 mL) at 0°C was added diethylazodicarboxylate (0.11 mls). The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with 1N HCl (aq), extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (4% - 25% EtOAc/hexanes) to yield the title compound as an off-white solid.

10 ¹H NMR (300 MHz, CDCl₃): δ 7.86 (s, 1H), 7.55 (s, 1H), 7.16-7.24 (m, 1H), 6.64-6.71 (m, 1H), 6.47-6.58 (m, 2H), 4.59 (t, 2H, *J* = 4.8 Hz), 4.25 (t, 2H, *J* = 5.0 Hz), 3.99 (ABq, 2H, *J_{AB}* = 9.9 Hz, $\Delta\nu_{AB}$ = 17 Hz).

Example 305,6-Dichloro-1-[2-(4-chloro-phenoxy)-ethyl]-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



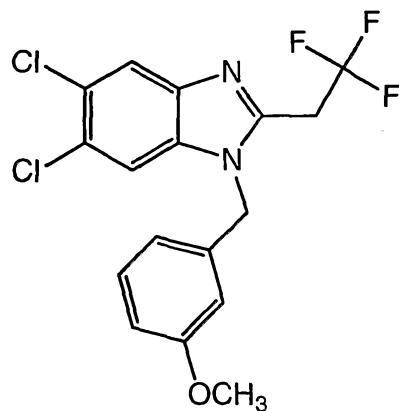
To a mixture of 2-[5,6-dichloro-2-(2,2,2-trifluoroethyl)-benzimidazol-1-yl]-ethanol (153 mg), 4-chlorophenol (94 mg), and triphenylphosphine (141 mg) in toluene (5 mL) at 0°C was added diethylazodicarboxylate (0.10 mls).

- 5 The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with 1N HCl (aq), extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (4% - 25% EtOAc/hexanes) to yield the title compound as a white foamy solid.

10

Example 31

5,6-Dichloro-1-(3-methoxy-benzyl)-2-(2,2,2-trifluoroethyl)-1H-benzimidazole



To 5,6-dichloro-2-(2,2,2-trifluoroethyl)-1H-benzimidazole (368 mg) in

- 15 DMF (5 mL) was added potassium carbonate powder (567 mg) and 3-methoxybenzyl bromide (825 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified

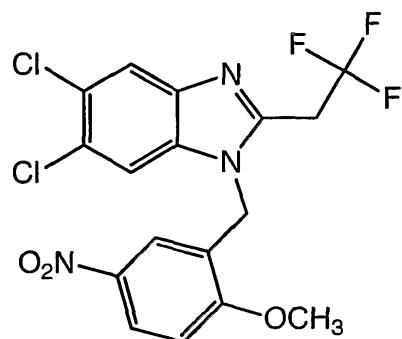
by silica gel chromatography (10% - 40% EtOAc/hexanes), followed by dissolution in CH_2Cl_2 and trituration with hexanes to yield the title compound as a peach solid.

5 ^1H NMR (300 MHz, CDCl_3): δ 7.91 (s, 1H), 7.37 (s, 1H), 7.26 (t, 1H, J = 6.7 Hz), 6.86 (dd, 1H, J = 8.3, 2.3 Hz), 6.55 (d, 1H, J = 7.6 Hz), 6.51 (s, 1H), 5.34 (s, 2H), 3.75 (s, 3H), 3.71 (ABq, 2H, J_{AB} = 9.8 Hz, $\Delta\nu_{\text{AB}}$ = 17 Hz).

Example 32

5,6-Dichloro-1-(2-methoxy-5-nitro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-

10 benzoimidazole



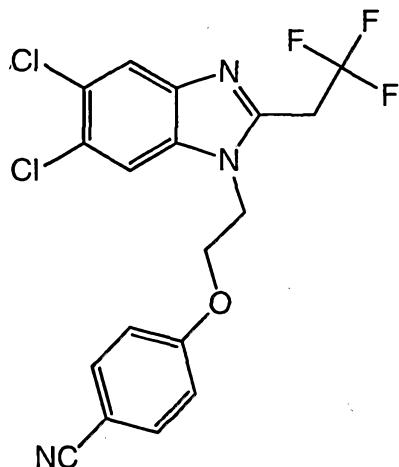
To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole (387 mg) in DMF (5 mL) was added potassium carbonate powder (596 mg) and 3-methoxy-5-nitro-benzyl bromide (1.06 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a peach-colored solid.

15 ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, 1H, J = 9.1, 2.7 Hz), 7.91 (s, 1H), 7.58 (d, 1H, J = 2.5 Hz), 7.33 (s, 1H), 7.03 (d, 1H, J = 9.1 Hz), 5.37 (s, 2H), 4.01 (s, 3H), 3.82 (ABq, 2H, J_{AB} = 9.7 Hz, $\Delta\nu_{\text{AB}}$ = 17 Hz).

Example 33

4-{2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-ethoxy}-

25 benzonitrile

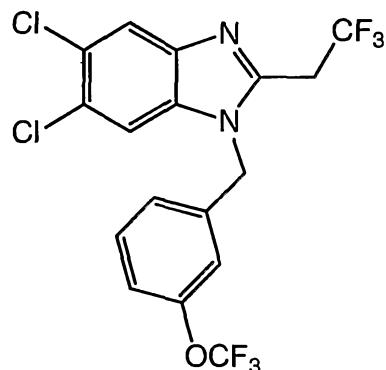


To a mixture of 2-[5,6-dichloro-2-(2,2,2-trifluoroethyl)-benzimidazol-1-yl]-ethanol (142 mg), 4-cyanophenol (81 mg), and triphenylphosphine (143 mg) in toluene (5 mL) at 0°C was added *ditert*-butylazodicarboxylate (125 mg). The 5 resulting mixture was stirred at ambient temperature overnight. To the mixture was added 2 drops of trifluoroacetic acid and stirred for 4 hours. The reaction mixture was quenched with 1N HCl (aq), extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 30% EtOAc/hexanes) to yield the title compound as a white foamy solid.

10 ¹H NMR (300 MHz, CDCl₃): δ 7.88 (s, 1H), 7.57 (s, 1H), 7.58 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.7 Hz), 4.63 (t, 2H, J = 4.8 Hz), 4.33 (t, 2H, J = 4.9 Hz), 3.97 (ABq, 2H, J_{AB} = 9.8 Hz, Δv_{AB} = 17 Hz).

Example 34

15 5,6-Dichloro-2-(2,2,2-trifluoroethyl)-1-(3-trifluoromethoxy-benzyl)-1H-benzoimidazole

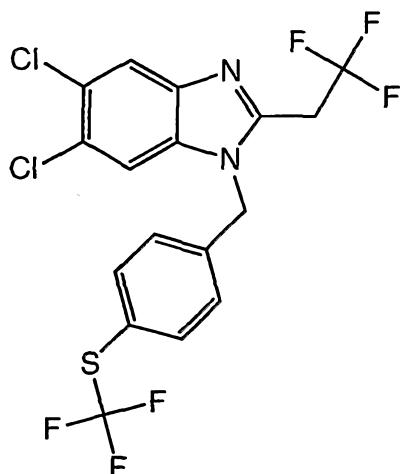


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (495 mg) in DMF (5 mL) was added potassium carbonate powder (763 mg) and 3-(trifluoromethoxy) benzyl bromide (1.41 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, 5 extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a brown solid.

¹H NMR (300 MHz, CDCl₃): δ 7.90 (s, 1H), 7.39 (t, 1H, *J* = 8.0 Hz), 7.31 (s, 1H), 7.20 (d, 1H, *J* = 8.3 Hz), 6.89 (s, 1H), 6.87 (d, 1H, *J* = 8.7 Hz), 5.40 (s, 10 2H), 3.73 (ABq, 2H, *J*_{AB} = 9.8 Hz, Δ*v*_{AB} = 17 Hz).

Example 35

5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1-(4-trifluoromethylsulfanyl-benzyl)-1*H*-benzoimidazole

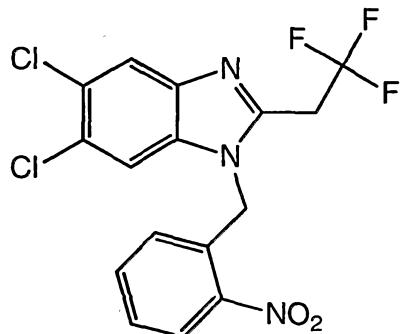


15

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (434 mg) in DMF (5 mL) was added potassium carbonate powder (669 mg) and 4-(trifluoromethylthio) benzyl bromide (596 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, 20 extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a brown solid.

¹H NMR (300 MHz, CDCl₃): δ 7.91 (s, 1H), 7.64 (d, 2H, *J* = 8.2 Hz), 7.31 (s, 1H), 7.03 (d, 2H, *J* = 8.3 Hz), 5.42 (s, 2H), 3.71 (ABq, 2H, *J_{AB}* = 9.8 Hz, $\Delta\nu_{AB}$ = 17 Hz).

5

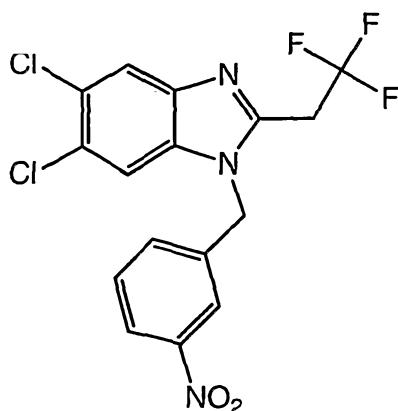
Example 365,6-Dichloro-1-(2-nitro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (319 mg) in DMF (5 mL) was added potassium carbonate powder (491 mg) I and 2-nitrobenzyl bromide (768 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 35% EtOAc/hexanes), followed by dissolution in CH₂Cl₂ and trituration with hexanes to yield the title compound as an orange solid.

¹H NMR (300 MHz, CDCl₃): δ 7.96 (s, 1H), 7.49-7.61 (m, 2H), 7.24 (s, 1H), 6.42-6.45 (m, 1H), 5.83 (s, 2H), 3.74 (ABq, 2H, *J_{AB}* = 9.7 Hz, $\Delta\nu_{AB}$ = 17 Hz).

20

Example 375,6-Dichloro-1-(3-nitro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole



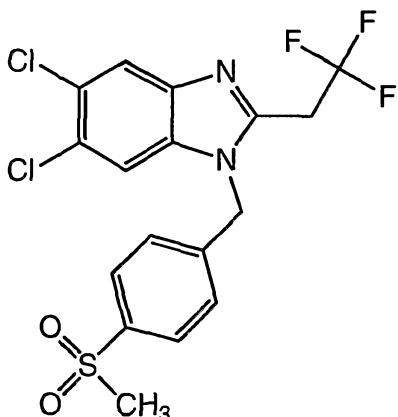
To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (355 mg) in DMF (5 mL) was added sodium hydride (110 mg of 60% in oil) and 3-nitrobenzyl bromide (596 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes) to yield the title compound as a red solid.

¹H NMR (300 MHz, CDCl₃): δ 8.22 (d, 1H, *J* = 7.8 Hz), 7.96 (d, 1H, *J* = 11.8 Hz), 7.94 (s, 1H), 7.56 (t, 1H, *J* = 7.9 Hz), 7.27 (s, 1H), 7.21 (s, 1H, *J* = 7.7 Hz), 5.50 (s, 2H), 3.76 (ABq, 2H, *J*_{AB} = 9.5 Hz, $\Delta\nu_{AB}$ = 17 Hz).

Example 38

5,6-Dichloro-1-(4-methanesulfonyl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole

benzoimidazole

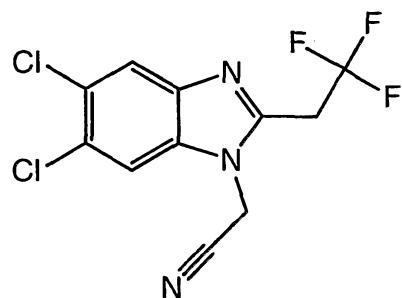


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (483 mg) in DMF (5 mL) was added potassium carbonate powder (744 mg) and 4-

methylsulphonylbenzyl bromide (1.68 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% - 75% EtOAc/hexanes) to yield the title compound as an off-white solid.

5 ^1H NMR (400 MHz, CDCl_3): δ 7.94 (s, 1H), 7.93 (d, 2H, $J = 7.9$ Hz), 7.27 (s, 1H), 7.17 (d, 2H, $J = 8.3$ Hz), 5.48 (s, 2H), 3.74 (ABq, 2H, $J_{\text{AB}} = 9.7$ Hz, $\Delta\nu_{\text{AB}} = 17$ Hz), 3.06 (s, 3H).

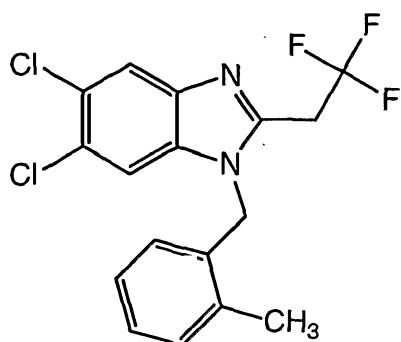
10

Example 39[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-acetonitrile

To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (356 mg) in DMF (5 mL) was added sodium hydride (79 mg of 60% in oil) and 15 iodoacetonitrile (331 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes), followed by washing solid with CH_2Cl_2 to yield the title compound as a peach-colored solid.

20 ^1H NMR (300 MHz, $d_6\text{-DMSO}$): δ 8.15 (s, 1H), 8.07 (s, 1H), 5.73 (s, 2H), 4.31 (ABq, 2H, $J_{\text{AB}} = 11$ Hz, $\Delta\nu_{\text{AB}} = 19$ Hz).

Example 405,6-Dichloro-1-(2-methyl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzimidazole



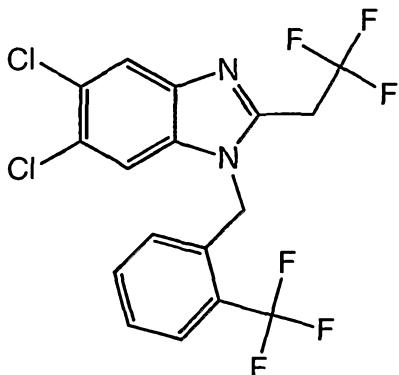
To 5,6-dichloro-2-(2,2,2-trifluoroethyl)-1*H*-benzimidazole (583 mg) in DMF (6 mL) was added potassium carbonate powder (900 mg) and 2-methylbenzyl bromide (1.2 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (10% - 40% EtOAc/hexanes), followed by washing solid with hexanes to yield the title compound as a tan solid.

10 ¹H NMR (300 MHz, CDCl₃): δ 7.93 (s, 1H), 7.29 (s, 1H), 7.22-7.26 (m, 2H), 7.04-7.10 (m, 1H), 6.31 (d, 1H, *J* = 7.9 Hz), 5.33 (s, 2H), 3.65 (ABq, 2H, *J_{AB}* = 9.8 Hz, $\Delta\nu_{AB}$ = 17 Hz).

Example 41

5,6-Dichloro-2-(2,2,2-trifluoroethyl)-1-(2-trifluoromethyl-benzyl)-1H-

15 benzoimidazole



To 5,6-dichloro-2-(2,2,2-trifluoroethyl)-1*H*-benzimidazole (577 mg) in DMF (6 mL) was added potassium carbonate powder (890 mg) and 2-(trifluoromethyl)benzyl bromide (1.54 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water,

extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (5% - 40% EtOAc/hexanes), followed by recrystallization with hexanes to yield the title compound as an orange-brown solid.

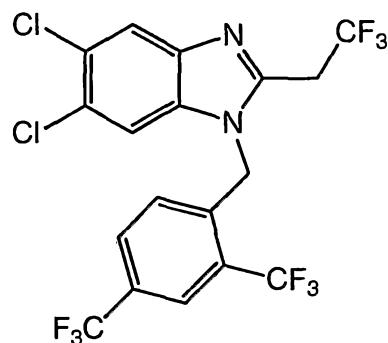
5 ^1H NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H), 7.80 (d, 1H, $J = 7.2$ Hz), 7.38-7.48 (m, 2H), 7.29 (s, 1H), 6.44 (d, 1H, $J = 7.5$ Hz), 5.58 (s, 2H), 3.68 (ABq, 2H, $J_{\text{AB}} = 9.7$ Hz, $\Delta\nu_{\text{AB}} = 17$ Hz).

MS (M+1) = 427.0

10

Example 42

1-(2,4-Bis-trifluoromethyl-benzyl)-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole (622 mg) in 15 DMF (7 mL) was added potassium carbonate powder (958 mg) and 2,4-bis(trifluoromethyl)-benzyl bromide (2.13 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na_2SO_4 . The crude product was purified by silica gel chromatography (5% - 40% EtOAc/hexanes), followed by recrystallization with hexanes to yield the title compound as an orange solid.

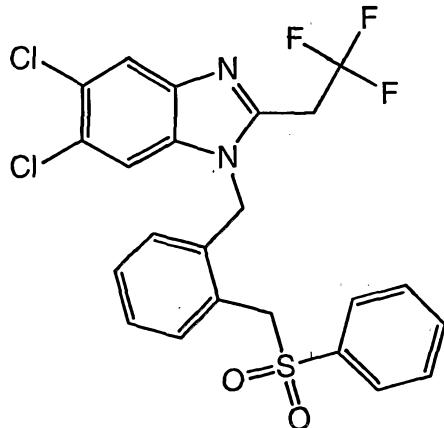
20 ^1H NMR (300 MHz, CDCl_3): δ 8.05 (s, 1H), 7.97 (s, 1H), 7.68 (d, 1H, $J = 8.1$ Hz), 7.25 (s, 1H), 6.59 (d, 1H, $J = 8.2$ Hz), 5.63 (s, 2H), 3.71 (ABq, 2H, $J_{\text{AB}} = 9.7$ Hz, $\Delta\nu_{\text{AB}} = 17$ Hz).

MS (M-1) = 492.9

25

Example 43

1-(2-Benzenesulfonylmethyl-benzyl)-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

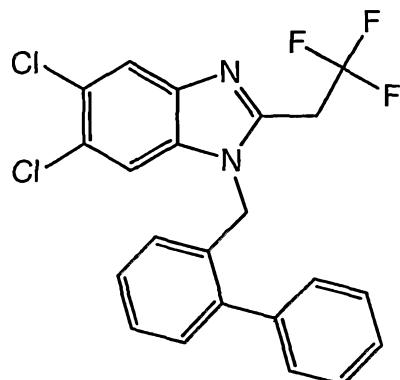


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (629 mg) in 5 DMF (7 mL) was added potassium carbonate powder (969 mg) and 1-bromomethyl-2-[phenylsulfonyl)methyl]benzyl bromide (2.28 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 40% EtOAc/hexanes), 10 followed by recrystallization with hexanes to yield the title compound as a yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 7.94 (s, 1H), 7.78 (d, 1H, *J* = 7.1 Hz), 7.69-7.77 (m, 1H), 7.59 (d, 2H, *J* = 7.9 Hz), 7.36 (s, 1H), 7.14-7.23 (m, 2H), 6.89 (dd, 1H, *J* = 6.8, 1.5 Hz), 6.32 (dd, 1H, *J* = 8.7, 6.8 Hz), 5.69 (s, 2H), 4.44 (s, 2H), 15 3.76 (ABq, 2H, *J*_{AB} = 9.8 Hz, Δ*v*_{AB} = 17 Hz).

Example 44

1-Biphenyl-2-ylmethyl-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

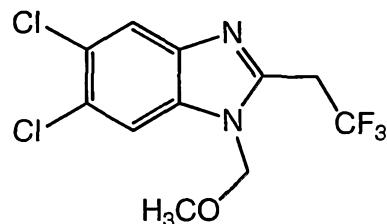


To 5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (521 mg) in DMF (5 mL) was added potassium carbonate powder (802 mg) and 2-phenyl benzyl bromide (1.43 g). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by silica gel chromatography (5% - 40% EtOAc/hexanes), followed by recrystallization with Et₂O/hexanes to yield the title compound as a white solid.

5 ¹H NMR (300 MHz, CDCl₃): δ 7.84 (s, 1H), 7.20-7.48 (m, 8H), 7.43 (s, 1H), 6.84 (d, 1H, *J* = 7.5 Hz), 5.25 (s, 2H), 3.40 (ABq, 2H, *J*_{AB} = 9.8 Hz, Δ*v*_{AB} = 10 17 Hz).

Example 46

5,6-Dichloro-1-methoxymethyl-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole



15 NaH (60%) (44.6 mg, 1.1153 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (200 mg, 0.7435 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. Bromomethyl methyl ether (139.4 mg, 0.09 ml, 1.1153 mmol) was added at 0°C. The reaction temperature was raised to 25°C and stirred for 18 hours.

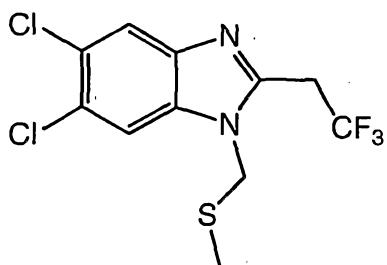
20 NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. Solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 30%) yielded the title compound as a brown solid.

MS m/z (M+H) 232

25

Example 47

5,6-Dichloro-1-methylsulfanylmethyl-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole



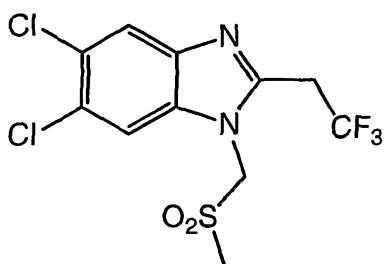
NaH (60%) (44.6 mg, 1.1153 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole (200 mg, 0.7435 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour.

- 5 Chloromethyl methyl sulfide (108 mg, 0.092 ml, 1.1153 mmol) was added at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. Solvent was distilled out under reduced pressure.
- 10 Column chromatography (silica gel, EtOAc / hexanes 0% to 30%) yield the title compound as a yellow solid.

MS m/z (M+H) 329, (M-H) 327

Example 48

- 15 5,6-Dichloro-1-methanesulfonylmethyl-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



- Oxone® (614.8 mg, 1 mmol) was dissolved in water (10 ml) and the pH was adjusted to pH7 with NaHCO₃. To the solution was then added
- 20 tetrabutylammonium hydrogen sulfate (20 mg). The resulting solution was added at room temperature to a solution of 5,6-dichloro-1-methanesulfonylmethyl-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole, prepared as in Example 47, (109.6 mg, 0.33 mmol) in EtOAc (4 mL). The Oxone® solution (608.87mg) was added until the reaction completed. The resulting mixture was

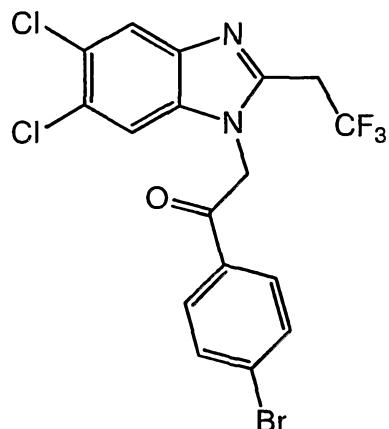
washed with 1N NaOH, then extracted with EtOAc. The organic layer was washed with 15% NaCl, dried over MgSO₄ and the solvent was distilled under reduced pressure to yield the title compound as a yellow solid.

MS m/z (M+H) 361

5

Example 49

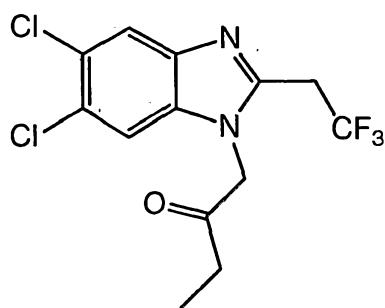
1-(4-Bromo-phenyl)-2-[5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-ethanone



- 10 NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2,4'-dibromoacetophenone (417 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 55%) yielded the title compound as a yellow solid.
- 15
- 20 MS m/z (M-H) 464.

Example 50

1-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-butan-2-one

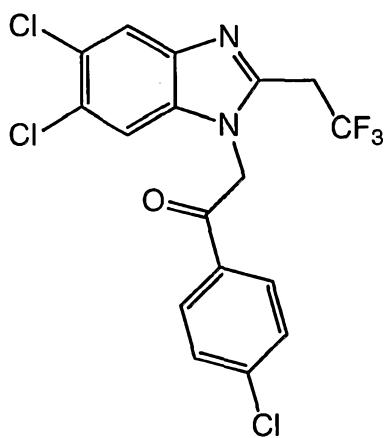


- NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoroethyl)-1H-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 1-bromo-2-butane (226.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure.
- 10 Column chromatography (silica gel, EtOAc / hexanes 0% to 55%) yielded the title compound as an off-white solid.

MS m/z (M+H) 339.

Example 51

- 15 1-(4-Chloro-phenyl)-2-[5,6-dichloro-2-(2,2,2-trifluoroethyl)-benzoimidazol-1-yl]-ethanone



- NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoroethyl)-1H-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-4'-

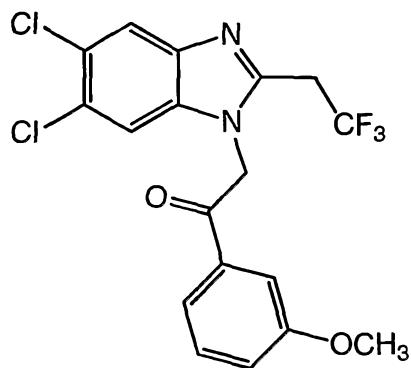
chloroacetophenone (350.25 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25 °C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, 5 then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 60%) yielded the title compound as a cream-colored solid.

MS m/z (M+H) 421, (M-H) 419.

10

Example 52

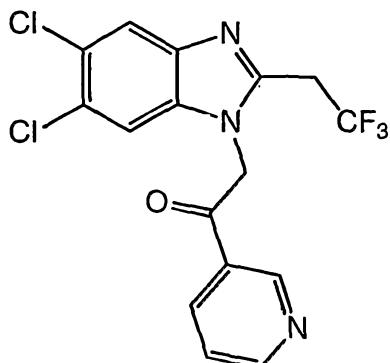
2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(3-methoxy-phenyl)-ethanone



NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-15 (2,2,2-trifluoro-ethyl)-1H-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-3'-methoxyacetophenone (343.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction 20 mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 60%) yielded the title compound as a yellow solid.

MS m/z (M-H) 415.

25

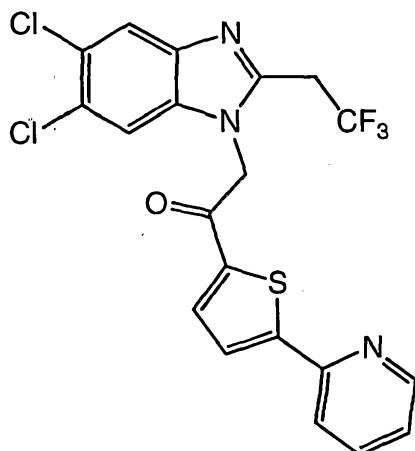
Example 532-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-pyridin-3-yl-ethanone

5 NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole) (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-1-pyridin-3-ylethan-1-one hydrobromide (421.43 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the 10 reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was then extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 30% to 100%) yielded the title compound as an off-white 15 solid.

MS m/z (M-H) 386.

Example 542-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(5-pyridin-2-yl-

20 thiophen-2-yl)-ethanone

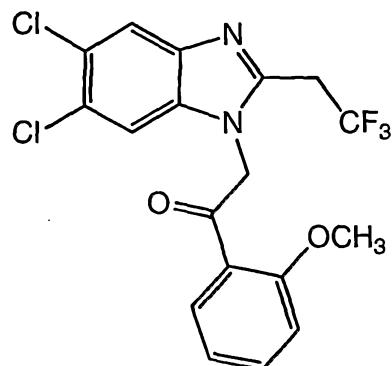


NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-1-[5-(2-pyridinyl)-2-thienyl]-1-ethanone (423.24 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was then extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 50% to 100%) yielded the title compound as a yellow solid.

MS m/z (M-H) 468.

Example 55

15 2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(2-methoxy-phenyl)-ethanone

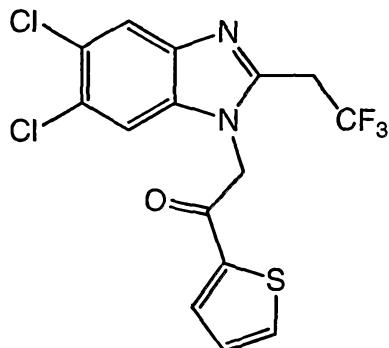


NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-2'-methoxy-acetophenone (350.25 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 5% to 60%) to yield the title compound as a yellow solid.

MS m/z (M-H) 415.

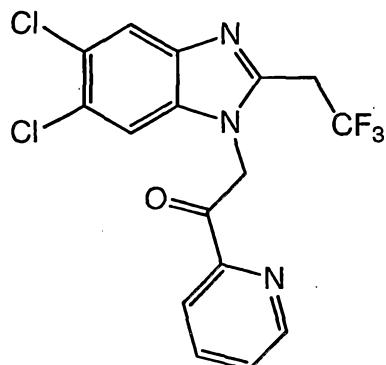
Example 56

2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-thiophen-2-yl-ethanone



NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-1-(2-thienyl)-1-ethanone (307.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 60%) yielded the title compound as a brown solid.

MS m/z (M+H) 393, (M-H) 391.

Example 572-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-pyridin-2-yl-
ethanone

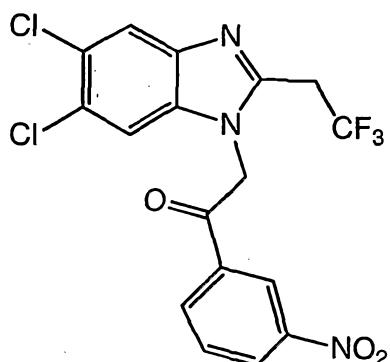
5

NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-1-(2-pyridinyl)-1-ethanone hydrobromide (421.4 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 70%) yielded the title compound as a yellow solid.

MS m/z (M+H) 388, (M-H) 386.

Example 582-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(3-nitro-phenyl)-
ethanone

20

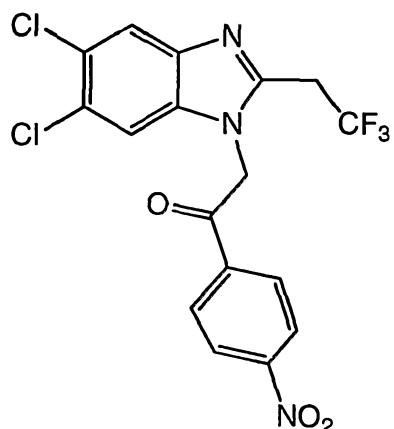


- NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-5 3'nitroacetophenone (366 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 70%) yielded the title 10 compound as a light brown solid.

MS m/z (M-H) 430.

Example 59

- 15 2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(4-nitro-phenyl)-ethanone



NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at

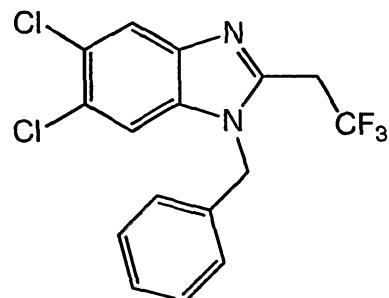
0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-4'nitroacetophenone (366 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and the reaction mixture was then stirred for 18 hours. NH₄Cl (aq.) was added and the reaction 5 mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 70%) yielded the title compound as a light brown solid.

MS m/z (M+H) 432, (M-H) 430.

10

Example 60

1-Benzyl-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



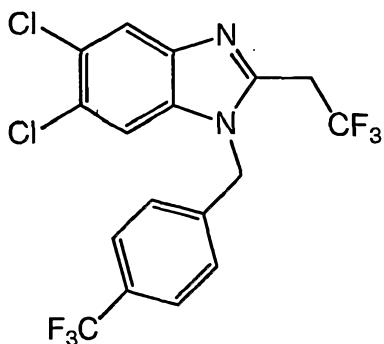
NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-15 (2,2,2-trifluoro-ethyl)-1H-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. Benzyl bromide (256.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The 20 organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 40%) yielded the title compound as a light brown solid.

MS m/z (M+H) 359, (M-H) 357.

25

Example 61

5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1-(4-trifluoromethyl-benzyl)-1H-benzoimidazole

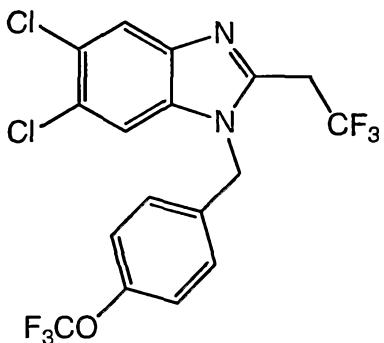


NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 4-(trifluoromethyl)-5 benzyl bromide (358.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes 0% to 50%) yielded the title compound as an off-white solid.

MS m/z (M+H) 427.

Example 62

15 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1-(4-trifluoromethoxy-benzyl)-1*H*-benzoimidazole



NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 4-(trifluoromethoxy)-benzyl bromide (382.5 mg, 1.5 mmol) was then added to the

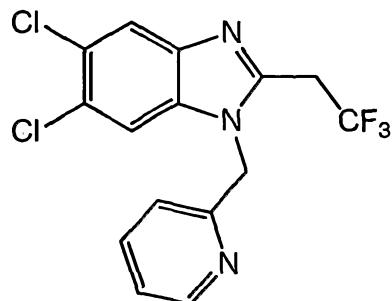
reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure.

5 Column chromatography (silica gel, EtOAc / hexanes 0% to 60%) yielded the title compound as a brown solid.

MS m/z (M+H) 443.

Example 63

10 5,6-Dichloro-1-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



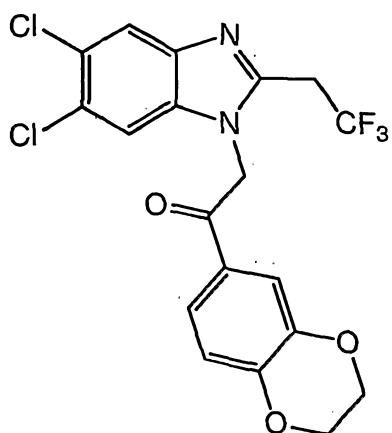
NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-(bromomethyl)-pyridine hydrobromide (379.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure.

15 Column chromatography (silica gel, EtOAc / hexanes 30% to 100%) yielded the title compound as a yellow solid.

MS m/z (M+H) 360.

Example 64

25 2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone

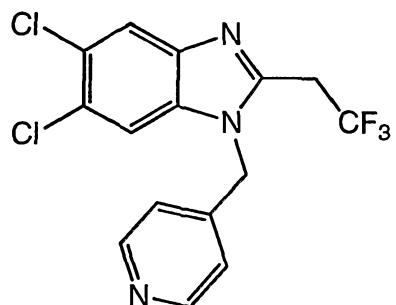


- NaH (60%) (60 mg, 1,5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethann-1-one (385.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. The residue was triturated with DCM to yield the title compound as a yellow solid.

MS m/z (M-H) 443.

Example 65

- 15 5,6-Dichloro-1-pyridin-4-ylmethyl-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



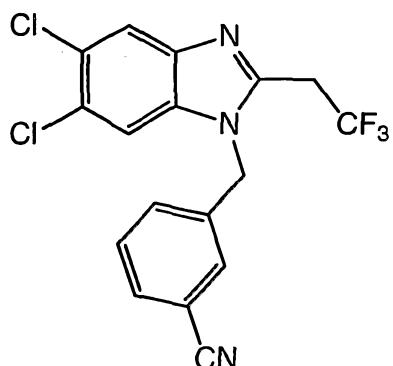
- NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 4-(bromomethyl)pyridine hydrobromide (379.5 mg, 1.5 mmol) was then added to the reaction

- mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure.
- 5 Column chromatography (silica gel, EtOAc / hexanes (30% to 100%) yielded the title compound as a white solid.

MS m/z (M+H) 360.

Example 66

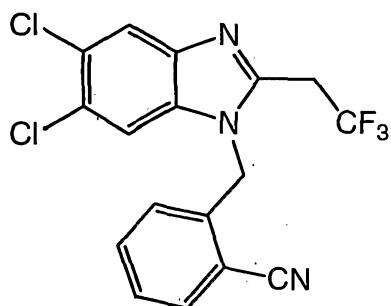
- 10 3-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzonitrile



- NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole, 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. α-bromo-m-tolunitrile (294 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure.
- 15 Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as an off-white solid.
- 20 MS m/z (M+H) 384; (M-H) 382.

Example 67

- 25 2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzonitrile

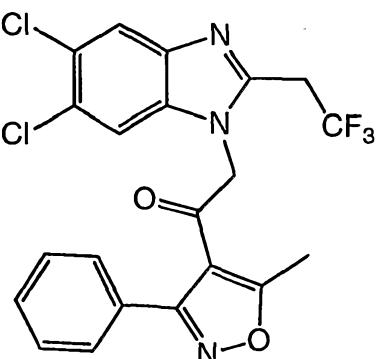


NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 5 stirred at 0°C for half hour. α -bromo-o-tolunitrile (294 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced 10 pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as an off-white solid.

MS m/z (M+H) 384.

Example 68

15 2-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-1-(5-methyl-3-phenyl-isoxazol-4-yl)-ethanone



NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 20 stirred at 0°C for half hours. 2-bromo-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-

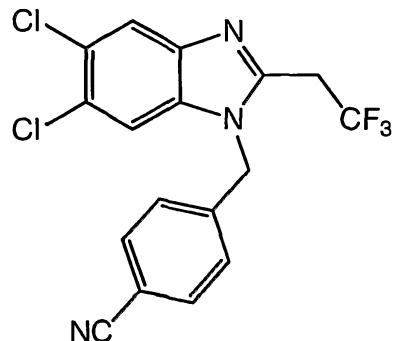
1-one (420 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a white solid.

5 MS m/z (M+H) 466.

10

Example 69

4-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzonitrile



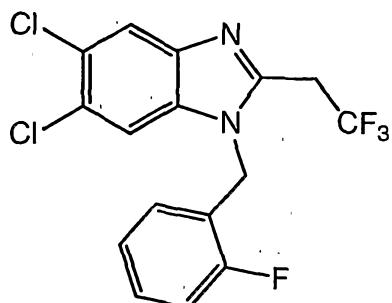
NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole, 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. α -bromo-p-tolunitrile (294 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a brown solid.

15 20 MS m/z (M-H) 381.

25

Example 70

5,6-Dichloro-1-(2-fluoro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole

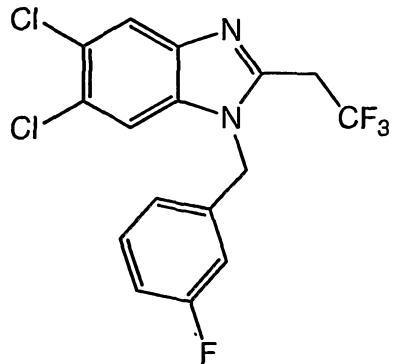


NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 5 stirred at 0°C for half hour. 2-fluorobenzyl bromide (283.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under 10 reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a light yellow solid.

MS m/z (M+H) 377.

Example 71

15 5,6-Dichloro-1-(3-fluoro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole



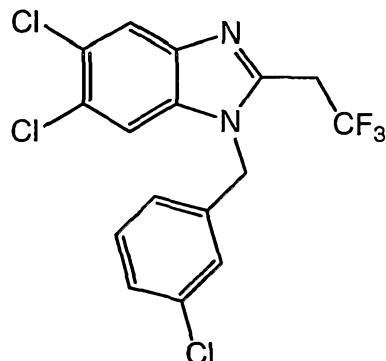
NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 20 stirred at 0°C for half hour. 3-fluorobenzyl bromide (283.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was

raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0%
5 to 60%) yielded the title compound as an off-white solid.

MS m/z (M+H) 377.

Example 72

5,6-Dichloro-1-(3-chloro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



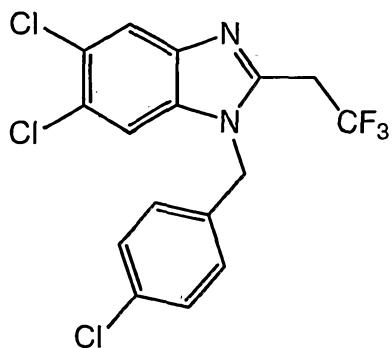
10

NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 3-chlorobenzyl bromide (308.25 mg, 1.5 mmol) was
15 then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0%
20 to 60%) yielded the title compound as a yellow solid.

MS m/z (M+H) 393.

Example 73

5,6-Dichloro-1-(4-chloro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

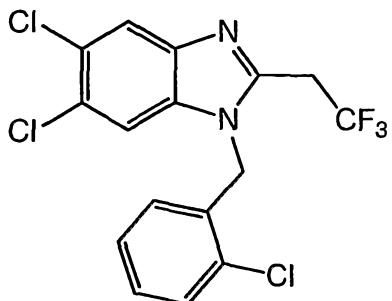


NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 5 stirred at 0°C for half hour. 4-chlorobenzyl bromide (308.25 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under 10 reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a yellow solid.

MS m/z (M-H) 393.

Example 74

15 5,6-Dichloro-1-(2-chloro-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 20 stirred at 0°C for half hour. 2-chlorobenzyl bromide (283.5 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was

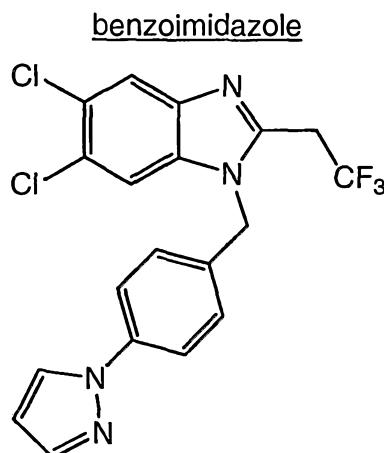
raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 5 60%) yielded the title compound as an off-white solid.

MS m/z (M+H) 393.

Example 75

5,6-Dichloro-1-(4-pyrazol-1-yl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-

10



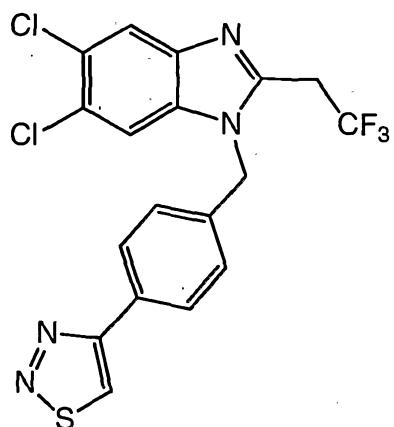
NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 15 stirred at 0°C for half hour. 1-[4-(bromomethyl)-phenyl]-1H-pyrazole (356 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was 20 distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a yellow solid.

MS m/z (M+H) 425.

Example 76

25 5,6-Dichloro-1-(4-[1,2,3]thiadiazol-4-yl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-

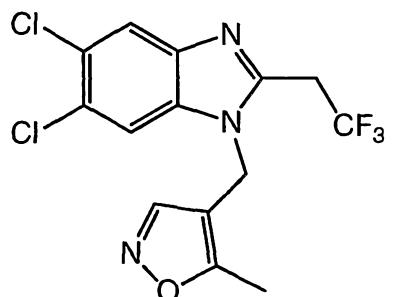
benzoimidazole



NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 5 stirred at 0°C for half hour. 4-[4-(bromomethyl)-phenyl]-1,2,3-thiazole (382.7 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was 10 distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a yellow solid. MS m/z (M+H) 443.

Example 77

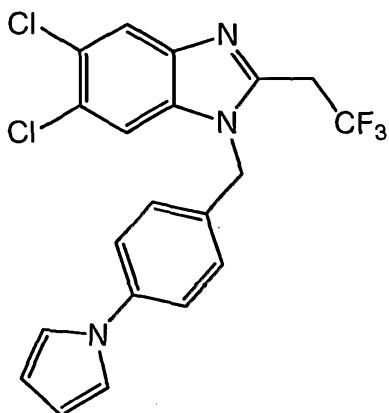
15 5,6-Dichloro-1-(5-methyl-isoxazol-4-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 20

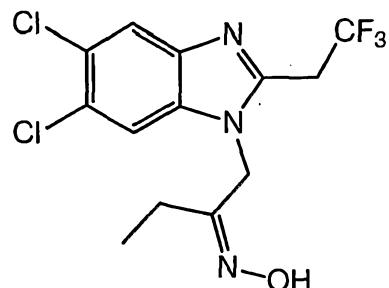
stirred at 0°C for half hour. 3-(bromomethyl)-5-methylisoxazole (264 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer 5 was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a yellow solid. MS m/z (M-H) 363.

10

Example 785,6-Dichloro-1-(4-pyrrol-1-yl-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

NaH (60%) (60 mg, 1.5 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-15 1H-indole (269 mg, 1 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 1-[4-(bromomethyl)phenyl]-1H-pyrrol (354 mg, 1.5 mmol) was then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer 20 was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 70%) yielded the title compound as a yellow solid.

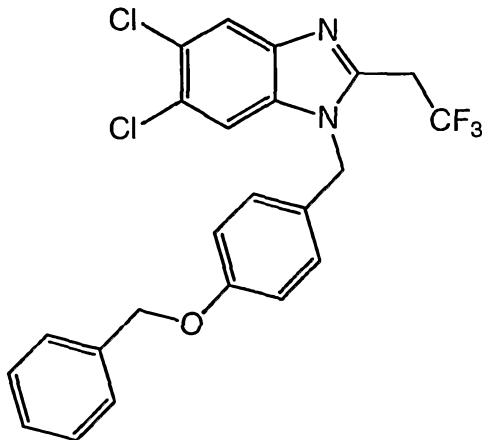
¹H- NMR (300 Hz, d₆-DMSO) δ 4.26 (ABq, 2H, J_{AB} = 10.7 Hz, Δv_{AB} = 18 Hz), 5.65 (s, 2H), 6.24 (t, 2H, J = 2.1 Hz), 7.20 (d, 2H, J = 8.6 Hz), 7.34 (t, 2H, J = 2.2 Hz), 7.55 (d, 2H, J = 8.6 Hz), 7.90 (s, 1H), 8.02 (s, 1H).

Example 791-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-butan-2-one oxime

5 1-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-butan-2-one (339 mg, 1 mmol), hydroxylamine hydrochloride (227.5 mg, 3.25 mmol) and pyridine (3 mL) in ethanol (3 mL) were heated to 70°C for 5 hours. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was washed with 15% NaCl, brine, then dried over anhydrous 10 MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a white solid.

MS m/z (M-H) 354.

15

Example 801-(4-Benzyloxy-benzyl)-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-20 1H-indole (538 mg, 2 mmol) in DMF (5 ml) at 0°C. The resulting mixture was

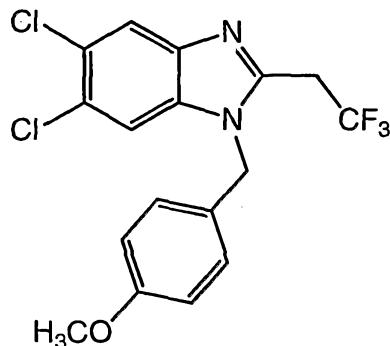
stirred at 0°C for half hour. 4-benzyloxy-benzyl chloride (698 mg, 3 mmol) and potassium iodide (498 mg, 3 mmol) were then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with 5 EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 70%) yielded the title compound as a yellow solid.

MS m/z (M-H) 463.

10

Example 81

5,6-Dichloro-1-(4-methoxy-benzyl)-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

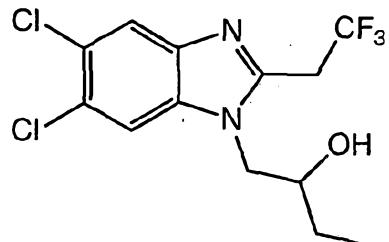


NaH (60%) (120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (538 mg, 2 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. 4-methoxy-benzyl chloride (470 mg, 3 mmol) and potassium iodide (498 mg, 3 mmol) were then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 70%), solvent was distilled under reduced pressure and the residue was dissolved in DCM. The resulting 15 solution was diluted with hexane. The precipitate was filtered and dried to yield the title compound as an off-white solid.

20

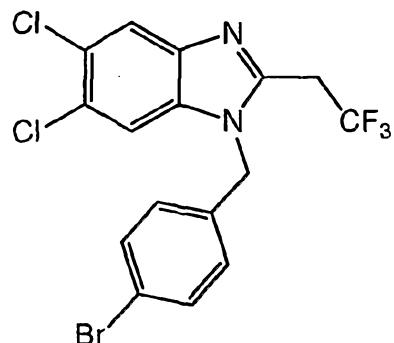
MS m/z (M+H) 389; (M-H) 387.

25

Example 821-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-yl]-butan-2-ol

5 Sodium borohydride (11.16 mg, 0.2949 mmol) was added into methanol (5 mL). After the bubbling ceased, 1-[5,6-dichloro-2-(2,2,2-trifluoroethyl)-benzoimidazol-1-yl]-butan-2-one (19170-168) (100 mg, 0.2949 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was poured into water and then extracted with EtOAc. The 10 organic layer was dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure to yield the title compound as an off-white solid.

MS m/z (M+H) 341.

Example 831-(4-Bromo-benzyl)-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole

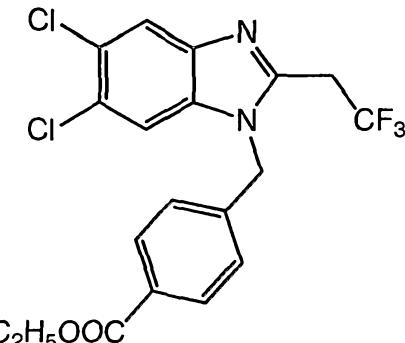
15 NaH (60%) 120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoroethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoroethyl)-1H-indole (538 mg, 2 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 20 stirred at 0°C for half hour. 4-bromo-benzyl bromide (749.8 mg, 3 mmol) and potassium iodide (498 mg, 3 mmol) were then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and then the reaction

mixture was extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. Solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a solid light brown solid.

5 MS m/z (M+H) 438.

Example 84

4-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzoic acid ethyl ester



10

NaH (60%) 120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1H-indole (538 mg, 2 mmol) in DMF (5 ml) at 0°C. The resulting mixture was stirred at 0°C for half hour. Ethyl 4-(bromomethyl)-benzoate (729.3 mg, 3 mmol) and potassium iodide (498 mg, 3 mmol) were then added to the reaction mixture at 0°C. The reaction temperature was raised to 25°C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure .

15 Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as an off-white solid.

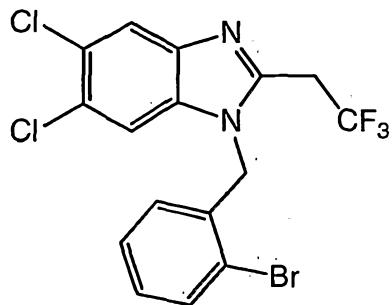
20

¹H- NMR (300 Hz, d₆-DMSO) δ 1.29 (t, 3H, J = 7.1 Hz), 4.22 (ABq, 2H, J_{AB} = 10.6 Hz, Δν_{AB} = 18.4 Hz), 4.29 (q, 2H, J = 7.1 Hz), 5.75 (s, 2H), 7.20 (d, 2H, J = 8.3 Hz), 7.84 (s, 1H), 7.92 (d, 2H, J = 8.4 Hz), 8.03 (s, 1H).

25

Example 85

1-(2-Bromo-benzyl)-5,6-dichloro-2-(2,2,2-trifluoro-ethyl)-1H-benzoimidazole



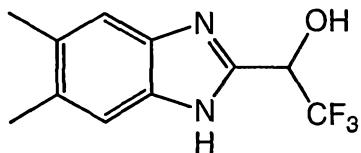
NaH (60%) 120 mg, 3 mmol) was added into a solution of dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzoimidazole. 5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-indole (538 mg, 2 mmol) in DMF (5 ml) at 0°C. The resulting mixture was 5 stirred at 0°C for half hour. Ethyl 4-(bromomethyl)-benzoate (729.3 mg, 3 mmol) and potassium iodide (498 mg, 3 mmol) were then added to the reaction mixture at 0°C. The reaction temperature was raised to 25 °C and then the reaction mixture was stirred for 18 hours. NH₄Cl (aq.) was added and extracted with EtOAc. The organic layer was washed with brine, then dried 10 over anhydrous MgSO₄. The solvent was distilled out under reduced pressure. Column chromatography (silica gel, EtOAc / hexanes (0% to 60%) yielded the title compound as a white solid.

MS m/z (M+H) 439.

15

Example 86

1-(5,6-Dimethyl-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol



4,5-Dimethyl-benzene-1,2-diamine (5.04 g; 37.0 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (8.01 g; 55.6 mmoles) were suspended in 6N 20 HCl (9 mL; 54 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (100 mL) and with ethyl acetate (100 mL), then sodium bicarbonate (6.90 g; 81.00 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and 25 extracted with ethyl acetate (3x40 mL). The extracts were combined, washed

with water (30 mL) and brine (30 mL), then dried over Na_2SO_4 . The filtrate was concentrated in vacuo to yield a crude brown solid which was purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as an off-white solid.

5 ^1H NMR (400 MHz, CD_3CN) δ 10.51 (br s, 1H), δ 7.37 (br d, 2H), δ 5.36 (q, J = 6.9 Hz, 1H), δ 5.16 (br s, 1H), δ 2.35 (s, 6H).
 MS calculated for $\text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$: 244.08
 MS Measured: 245 (M+H); 243 (M-H).

10

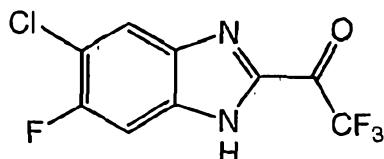
Example 871-(5-Chloro-6-fluoro-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol

4-Chloro-5-fluoro-benzene-1,2-diamine (5.20 g; 32.4 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (7.00 g; 48.6 mmoles) were suspended in 6N 15 HCl (9 mL; 54 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (100 mL) and with ethyl acetate (100 mL), then sodium bicarbonate (6.90 g; 81.00 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and 20 extracted with ethyl acetate (3x40 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over Na_2SO_4 . The filtrate was concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as an off-white solid.

25 ^1H NMR (400 MHz, CD_3CN) δ 7.74 (d, J = 6.7 Hz, 1H), δ 7.49 (d, J = 9.5, 1H), δ 5.41 (q, J = 6.8 Hz, 1H), δ 5.16 (br s, 1H), δ 2.35 (s, 6H)
 MS calculated for $\text{C}_9\text{H}_5\text{ClF}_4\text{N}_2\text{O}$: 268.00
 MS measured: 269 (M+H); 267 (M-H).

30

Example 88

1-(5-Chloro-6-fluoro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanone

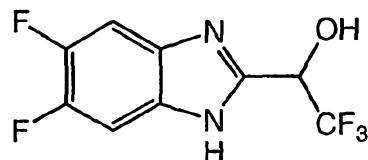
1-(5-Chloro-6-fluoro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol (.34 g; 1.3 mmoles), 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy free radical (4-5 mg; .03 mmoles), 4-methoxy-TEMPO free radical; 6.1 mg; .03 mmoles) and potassium bromide (KBr; 18 mg; .15 mmoles) were dissolved in THF (3.5 mL). The reaction mixture was stirred while cooled to -10°C, after 10 min. a sodium hypochlorite solution (bleach; 10-13% aqueous; 3.0 mL; 5.04 mmoles) was added and allowed to stir for 15 min., then warmed to room temperature and stirred for 15-10 min. The reaction mixture was diluted with water (20 mL) and ethyl acetate (30 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The extracts were combined and washed with water (30 mL) and brine (40 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo and purified by column chromatography (SiO₂; 100% diethyl ether) to yield the title compound as a light yellow solid.

¹H NMR (400 MHz, CD₃CN) δ 7.83 (d, *J* = 6.7 Hz, 1H), δ 7.77 (d, *J* = 9.5 Hz, 1H)

MS calculated for C₉H₃ClF₄N₂O: 265.99

MS Measured: 265, 267 (M-H).

20

Example 891-(5,6-Difluoro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol

4,5-Difluoro-benzene-1,2-diamine (4.98 g; 34.5 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (7.48 g; 51.9 mmoles) were suspended in 6N HCl (8 mL; 48 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (100 mL) and with ethyl acetate (100 mL),

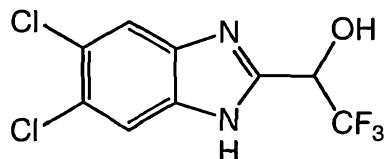
then sodium bicarbonate (6.05 g; 72.0 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x40 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over Na_2SO_4 . The filtrate was 5 concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as a pale orange solid.

10 ^1H NMR (400 MHz, CD_3CN) δ 7.35 (m, 1H), δ 7.21 (m, 1H), δ 5.44 (q, $J = 6.8$ Hz, 1H)

MS calculated for $\text{C}_9\text{H}_5\text{F}_5\text{N}_2\text{O}$: 252.03
 MS measured: 253 (M+H); 251 (M-H).

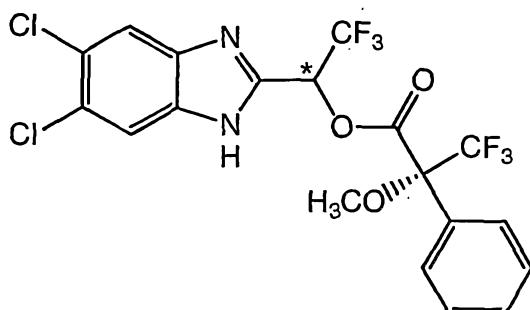
Example 90

1-(5,6-DiChloro-1*H*-benzimidazol-2-yl)-2,2,2-trifluoro-ethanol



15 4,5-Dichloro-benzene-1,2-diamine (8.50 g; 48.0 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (10.59 g; 73.52 mmoles) were suspended in 6N HCl (19 mL; 114 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room 20 temperature. The reaction was diluted with water (200 mL) and with ethyl acetate (200 mL), then sodium bicarbonate (6.05 g; 72.0 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x80 mL). The extracts were combined, washed with water (60 mL) and brine (60 mL), then dried over 25 Na_2SO_4 . The filtrate was concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as a brown solid.

30 ^1H NMR (400 MHz, CD_3CN) δ 7.80 (s, 2H), δ 5.43 (q, $J = 6.8$ Hz, 1H)
 MS calculated for $\text{C}_9\text{H}_5\text{Cl}_2\text{F}_3\text{N}_2\text{O}$: 283.97
 MS measured: 285, 287 (M+H); 283, 285 (M-H).

Example 91Diastereomers of 3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 1-(5,6-dichloro-1*H*-benzimidazol-2-yl)-2,2,2-trifluoro-1-methyl-ethyl ester

5

2-(5,6-Dichloro-1*H*-benzimidazol-2-yl)-1,1,1-trifluoro-propan-2-ol (2.24 g; 7.86 mmoles) was dissolved in pyridine (1.4 mL; 17 mmoles) and THF (20 mL), then stirred under a nitrogen atmosphere. (R)-(-)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride (1.85 mL; 9.91 mmoles) was added to the reaction mixture and stirred at room temperature for 18 hrs. The reaction mixture was concentrated in vacuo, and then dissolved in 50% diethyl ether/ethyl acetate (50 mL), then washed with water (30 mL). The aqueous layer was extracted with 50% diethyl ether/ethyl acetate (3x50 mL), the extracts were combined, washed with water (30 mL), brine (50 mL) and dried over Na₂SO₄. The filtrate was concentrated in vacuo then purified by column chromatography (SiO₂; 100% CH₂Cl₂) to yield the title compound as a yellow oil, as a mixture of diastereomers. The diastereomeric mixture was separated by chiral chromatography (Chiralpak AD; 30% isopropanol/heptane), to yield a white foam (peak 1; retention time: 9.04 min. (@ 100 mL/min)) and an off white solid (peak 2; retention time: 19.04 min. (@ 100 mL/min)).

Peak 1:

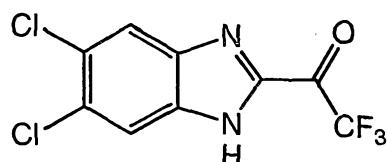
¹H NMR (300 MHz, CD₃CN) δ 11.19 (br s, 1H), δ 7.87 (br s, 1H), δ 7.77 (br s, 1H), δ 7.51–7.37 (series of m, 5H), δ 6.76 (q, *J* = 6.4, 1H), δ 3.61 (s, 3H)
 MS calculated for C₁₉H₁₂Cl₂F₆N₂O₃: 500.01

25 MS measured: 501, 503 (M+H); 499, 501 (M-H).

$[\alpha]_D^{20} = -22$; c = .306 in methanol.

Peak 2

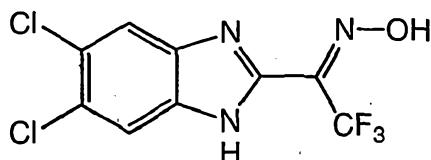
¹H NMR (300 MHz, CD₃CN) δ 11.18 (br s, 1H), δ 7.91 – 7.81 (br m, 2H),
 δ 7.58 – 7.45 (series of m; 5H), δ 6.78 (q, J = 6.3, 1H), δ 3.53 (s, 3H)
 MS calculated for C₁₉H₁₂Cl₂F₆N₂O₃: 500.01
 5 MS measured: 501, 503 (M+H); 499, 501 (M-H)
 [α]_D²⁰ = -49; c = .314 in methanol.

Example 921-(5,6-DiChloro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanone

10 1-(5,6-Dichloro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol (.29 g; 1.00 mmole), 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy free radical (4-methoxy-TEMPO free radical; 4.4 mg; .03 mmole) and potassium bromide (KBr; 13 mg; .11 mmole) were dissolved in THF (2.9 mL). The reaction
 15 mixture was stirred while cooled to -10°C, after 10 min. a sodium hypochlorite solution (bleach; 10-13% aqueous; 2.10 mL; 3.53 mmole) was added and allowed to stir for 15 min., then warmed to room temperature and stirred for 15 min. The reaction mixture was diluted with water (20 mL) and ethyl acetate (30 mL), the layers were separated and the aqueous layer was extracted with ethyl
 20 acetate (3x30 mL). The extracts were combined and washed with water (30 mL) and brine (40 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo and purified by column chromatography (SiO₂; 100% ether) to yield the title compound as a light yellow solid.

16 ¹H NMR (400 MHz, CD₃CN) δ 8.01 (s, 1H), δ 7.83 (br s, 2H)
 25 MS calculated for C₉H₈Cl₂F₃N₂O: 281.96
 MS measured: 281, 283 (M-H).

Example 931-(5,6-Dichloro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanone oxime



1-(5,6-Dichloro-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanone (.3005 g; 1.062 mmoles) and hydroxylamine hydrochloride (.2389 g, 3.438 mmoles) were suspended in pyridine (3 mL) and ethanol (3 mL), then heated to 70°C for 5 3 hrs. The reaction mixture was cooled to room temperature, water was added (50 mL) and the reaction mixture was then extracted with ethyl acetate (3x40 mL). The extracts were combined then washed with water (20 mL), brine (30 mL) and dried over Na₂SO₄. The filtrate was concentrated in vacuo and purified by column chromatography (SiO₂; 30% ethyl acetate/CH₂Cl₂) to yield the title 10 compound as an off-white solid, as a mixture of oxime E and Z isomers.

¹H NMR (400 MHz, d₆-DMSO) δ 8.33 – 7.64 (series of s, 2H)

MS calculated for C₉H₄Cl₂F₃N₂O: 296.96

MS measured: 296, 298 (M-H).

15

Example 94

1-(5-Chloro-6-methyl-1H-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol



4-Chloro-5-methyl-benzene-1,2-diamine (5.06 g; 32.3 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (7.11 g; 49.4 mmoles) were suspended 20 in 6N HCl (12 mL; 72 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (100 mL) and with ethyl acetate (100 mL), then sodium bicarbonate (9.12 g; 109 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was 25 separated and extracted with ethyl acetate (3x40 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude brown solid.

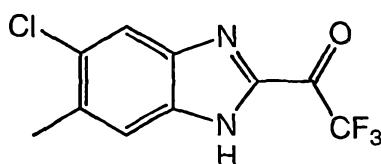
which was then purified by column chromatography (SiO₂; 30% ethyl acetate/CH₂Cl₂) to yield the title compound as a purple/brown solid.

¹H NMR (400 MHz, CD₃CN) δ 7.65 (s, 1H), δ 7.52 (s, 1H), δ 5.40 (q, *J* = 6.9 Hz, 1H), δ 2.46 (s, 3H)

5 MS calculated for C₁₀H₈ClF₃N₂O: 264.03
MS measured: 265, 267 (M+H); 263, 265 (M-H).

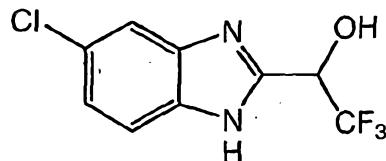
Example 95

1-(5-Chloro-6-methyl-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanone



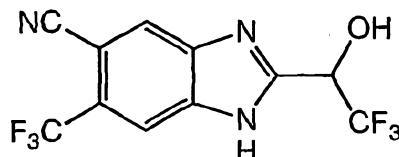
1-(5-Chloro-6-methyl-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol (.33 g; 1.2 mmole), 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy free radical (4-methoxy-TEMPO free radical; 5.6 mg; .03 mmole) and potassium bromide (KBr; 22 mg, .18 mmole) were dissolved in THF (3.5 mL). The reaction mixture was stirred while cooled to -10 °C, after 10 min. a sodium hypochlorite solution (bleach; 10-13% aqueous; 3.0 mL; 5.0 mmole) was added and the reaction mixture was allowed to stir for 15 min., then warmed to room temperature and stirred for 15 min. The reaction mixture was diluted with water (20 mL) and ethyl acetate (30 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The extracts were combined and washed with water (30 mL) and brine (40 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo and then purified by column chromatography (SiO₂; 100% diethyl ether) to yield the title compound as a white solid.

15 MS calculated for C₁₀H₈ClF₃N₂O: 262.01
MS measured: 261, 263 (M-H).

1-(5-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol

- 4-Chloro-benzene-1,2-diamine (2.02 g; 14.2 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (3.10g; 21.5 mmoles) were suspended in 6N HCl (5 mL; 30 mmoles) and water (4 mL) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (400 mL) and with ethyl acetate (500 mL), then sodium bicarbonate (3.83 g; 45.6 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x30 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO₂; 30% ethyl acetate/CH₂Cl₂) to yield the title compound as a tan solid.
- 15 ¹H NMR (400 MHz, CD₃CN) δ 7.65 (n d, *J* = 1.5, 1H), δ 7.58 (d, *J* = 8.6, 1H), δ 7.27 (dd, *J* = 6.6, 2.0, 3H) δ 5.42 (q, *J* = 6.9 Hz, 1H)
- MS calculated for C₉H₆ClF₃N₂O: 250.01
- MS measured: 251, 253 (M+H); 249, 251 (M-H).

20

Example 972-(2,2,2-Trifluoro-1-hydroxy-ethyl)-6-trifluoromethyl-1*H*-benzoimidazole-5-carbonitrile

- 4,5-Diamino-2-trifluoromethyl-benzonitrile (4.14 g; 20.6 mmoles) and 25 3,3,3-trifluoro-2-hydroxy-propionic acid (4.50 g; 31.2 mmoles) were suspended in 6N HCl (7 mL; 42 mmoles) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (100 mL) and with ethyl

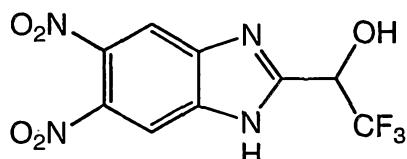
acetate (100 mL), then sodium bicarbonate (5.19 g; 62.0 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x40 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over 5 Na_2SO_4 . The filtrate was concentrated in vacuo to yield a crude dark solid which was then purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as a dark brown solid.

10 ^1H NMR (400 MHz, CD_3CN) δ 8.27 (s, 1H), δ 8.14 (s, 1H), δ 5.54 (q, J = 6.9 Hz, 1H)

15 MS calculated for $\text{C}_{11}\text{H}_5\text{F}_6\text{N}_3\text{O}$: 309.03
MS measured: 310 (M+H); 308 (M-H).

Example 98

1-(5,6-Dinitro-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol



15 4,5-Dinitro-benzene-1,2-diamine (2.01 g; 10.2 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (2.22 g; 15.4 mmoles) were suspended in 6N HCl (5 mL; 30 mmoles) and water (4 mL) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to 20 room temperature. The reaction was diluted with water (40 mL) and with ethyl acetate (40 mL), then sodium bicarbonate (3.79 g; 45.0 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x30 mL). The extracts were combined, washed with water (30 mL) and brine (40 mL), then dried over 25 Na_2SO_4 . The filtrate was concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO_2 ; 30% ethyl acetate/ CH_2Cl_2) to yield the title compound as a brown solid.

30 ^1H NMR (400 MHz, CD_3CN) δ 8.29 (s, 2H), δ 5.55 (q, J = 6.8, 1H)
MS calculated for $\text{C}_9\text{H}_5\text{F}_3\text{N}_4\text{O}_5$: 306.16
MS measured: 305 (M-H).

Example 991-(5,6-Dimethoxy-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol

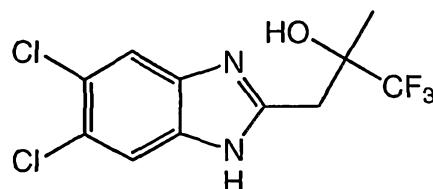
5 4,5-Dimethoxy-benzene-1,2-diamine (2.02 g; 12.0 mmoles) and 3,3,3-trifluoro-2-hydroxy-propionic acid (2.67 g; 18.5 mmoles) were suspended in 6N HCl (5 mL; 30 mmoles) and water (4 mL) under a nitrogen atmosphere. The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (40 mL) and with ethyl acetate (40 mL), then sodium bicarbonate (3.84 g; 46.0 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate (3x30 mL). The extracts were combined, washed with water (30 mL) and brine (40 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude dark orange solid which was then purified by column chromatography (SiO₂; 30% ethyl acetate/CH₂Cl₂) to yield the title compound as a bright orange solid.

10 15

1H NMR (400 MHz, CD₃CN) δ 7.15 (br s, 1H), δ 7.06 (br s, 1H), δ 5.34 (q, *J* = 6.8, 1H)

MS calculated for C₁₁H₁₁F₃N₂O₃: 267.07

20 MS measured: 277 (M+H); 275 (M-H).

Example 1003-(5,6-Dichloro-2-1*H*-benzoimidazol-2-yl)-1,1,1-trifluoro-2-methyl-propan-2-ol

25 4,5-Dichloro-benzene-1,2-diamine (.53 g; 3.0 mmoles) and 4,4,4-trifluoro-3-hydroxy-3-methyl-butyric acid (.78 g; 4.5 mmoles) were suspended in 6N HCl (4 mL; 24 mmoles) and water (4 mL) under a nitrogen atmosphere.

The reaction was stirred vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (25 mL) and with ethyl acetate (30 mL), then sodium bicarbonate (7.59g; 90.3 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was 5 separated and extracted with ethyl acetate (3x20 mL). The extracts were combined, washed with water (20 mL) and brine (20 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude brown solid which was then purified by column chromatography (SiO₂; 100% CH₂Cl₂) to yield the title compound as a light orange solid.

10 ¹H NMR (400 MHz, CD₃CN) δ 7.74 (s, 2H), δ 3.28 (d, *J* = 15, 1H), δ 3.15 (d, *J* = 15, 1H), δ 1.37 (s, 3H)

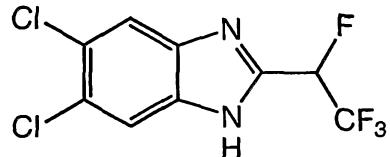
MS calculated for C₁₁H₁₉Cl₂F₃N₂O: 312.00

MS measured: 313, 315 (M+H); 311, 313 (M-H).

15

Example 101

5,6-Dichloro-2-(1,2,2,2-tetrafluoro-ethyl)-1*H*-benzoimidazole



4,5-Dichloro-benzene-1, 2-diamine (2.03 g; 11.5 mmoles) and 2,3,3,3-tetrafluoro-propionic acid (1.99 g; 13.6 mmoles) were suspended in 6N HCl (5 mL; 30 mmoles) under a nitrogen atmosphere. The reaction was stirred 20 vigorously and heated to 108°C for 18 hrs, then cooled to room temperature. The reaction was diluted with water (60 mL) and with ethyl acetate (60 mL), then sodium bicarbonate (4.02 g; 47.9 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was separated and 25 extracted with ethyl acetate (3x30 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude brown solid. A sample of the crude brown solid was purified by column chromatography (SiO₂; 100% CH₂Cl₂) to yield the title compound as a light orange solid.

¹H NMR (400 MHz, CD₃CN) δ 7.65 (s, 1H), δ 6.28 (dq, *J* = 37, 6.0 Hz, 1H)

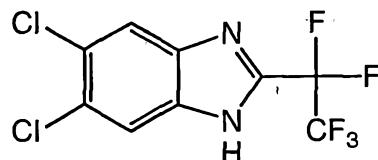
MS calculated for C₉H₅Cl₂F₄N₂: 285.97

MS measured: 287, 289 (M+H); 285, 287 (M-H).

5

Example 102

5,6-Dichloro-2-(pentafluoroethyl)-1*H*-benzoimidazole



4,5-Dichloro-benzene-1, 2-diamine (2.01 g; 11.4 mmoles) and 2,2,3,3,3-
10 pentafluoro-propionic acid (1.80 mL; 17.3 mmoles) were suspended in 6N HCl
(10 mL; 60 mmoles) under a nitrogen atmosphere. The reaction was stirred
vigorously and heated to 108°C for 18 hrs, then cooled to room temperature.
The reaction was diluted with water (60 mL) and with ethyl acetate (60 mL),
then sodium bicarbonate (7.59g; 90.3 mmoles) was added slowly and in
15 portions to quench the reaction. The aqueous layer was separated and
extracted with ethyl acetate (3x30 mL). The extracts were combined, washed
with water (30 mL) and brine (30 mL), then dried over Na₂SO₄. The filtrate was
concentrated in vacuo to yield a crude brown solid which was then purified by
column chromatography (SiO₂; 100% CH₂Cl₂) to yield the title compound as a
20 light tan solid.

¹H NMR (400 MHz, CD₃CN) δ 7.94 (s, 2H)

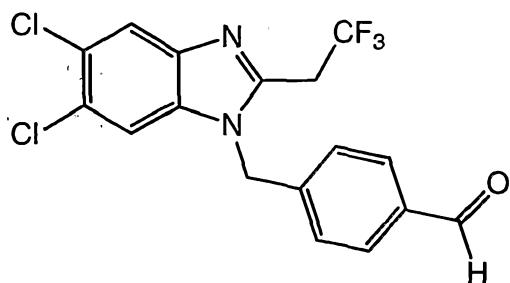
MS calculated for C₉H₃Cl₂F₅N₂: 303.96

MS measured: 305, 307 (M+H); 303, 305 (M-H).

25

Example 103

4-[5,6-Dichloro-2-(trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzaldehyde



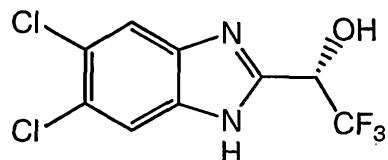
4-[5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-benzoimidazol-1-ylmethyl]-benzonitrile (.4079 g; 1.0617 mmoles) was suspended in CH_2Cl_2 (3 mL), treated with 1.5 M diisobutylaluminium hydride in toluene (1.42 mL; 2.13 mmoles) and stirred at room temperature for 3 hrs. The reaction mixture was quenched with saturated Rochelle's salt solution (1 mL) and stirred overnight, then filtered through a pad of Celite. The filtrate was diluted with ethyl acetate (30 mL), washed with water (20 mL), brine and dried over Na_2SO_4 . The filtrate was concentrated in vacuo and then purified by column chromatography (SiO_2 ; 100% CH_2Cl_2) to yield the title compound as a yellow oil.

MS calculated for $\text{C}_{17}\text{H}_{11}\text{Cl}_2\text{F}_3\text{N}_2\text{O}$: 389.02

MS measured: 389, 387 ($\text{M}+\text{H}$); 385, 387 ($\text{M}-\text{H}$).

Example 104

15 (+)-1-(5,6-DiChloro-1*H*-benzoimidazol-2-yl)-2,2,2-trifluoro-ethanol



A solution of "Peak 1" prepared as in Example 91 (136 mg; 0.27 mmoles) was suspended in a mixture of dioxane and water (10 mL, 4:1) and treated with NaOH (0.5 mL; 2 mmoles). The reaction was stirred vigorously and heated to 50°C for 30 min, then cooled to room temperature. The reaction was diluted with water (50 mL) and 1 N HCl (3 mL, 3 mmol). The resulting white precipitate was collected by suction filtration, dissolved in ethyl acetate and then purified by flash chromatography (SiO_2 , 30% ethyl acetate/dcm) to yield the title compound as a white solid.

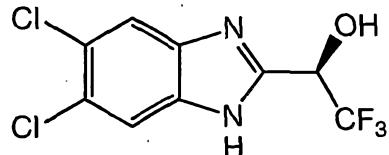
25 ^1H NMR (400 MHz, CD_3CN) δ 7.80 (s, 2H), δ 5.43 (q, $J = 6.8$ Hz, 1H)
MS calculated for $\text{C}_9\text{H}_5\text{Cl}_2\text{F}_3\text{N}_2\text{O}$: 283.97

MS measure: 285, 287 (M+H); 283, 285 (M-H).

$[\alpha]_D^{20} = +29$; $c = 0.196$ in MeOH.

Example 105

5 (-)-1-(5,6-DiChloro-1*H*-benzimidazol-2-yl)-2,2,2-trifluoro-ethanol



A solution of "Peak 2" prepared as in Example 91 (103 mg; 0.21 mmoles) was suspended in a mixture of dioxane and water (10 mL, 4:1) and treated with NaOH (0.5 mL; 2 mmoles). The reaction was stirred vigorously 10 and heated to 50°C for 30 min, then cooled to room temperature. The reaction was diluted with water (50 mL) and 1 N HCl (3 mL, 3 mmol). The resulting white precipitate was collected by suction filtration, dissolved in ethyl acetate and then purified by flash chromatography (SiO₂, 30% ethyl acetate/dcm) to yield the title compound as a white solid.

15 ¹H NMR (400 MHz, CD₃CN) δ 7.80 (s, 2H), δ 5.43 (q, *J* = 6.8 Hz, 1H)

MS calculated for C₉H₅Cl₂F₃N₂O: 283.97

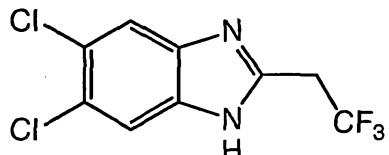
MS measured: 285, 287 (M+H); 283, 285 (M-H).

$[\alpha]_D^{20} = -27$; $c = 0.183$ in MeOH.

20

Example 106

5,6-Dichloro-2-(2,2,2-trifluoro-ethyl)-1*H*-benzimidazole



4,5-Dichloro-benzene-1,2-diamine (10.0114 g; 56.5520 mmoles) and 3,3,3-trifluoro-propionic acid (7.5 mL; 84.9 mmoles) were combined with 6N 25 HCl (20 mL; 120 mmoles) and heated to 108°C for 18hrs. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (200 mL) and water (200 mL), then sodium bicarbonate (15.15 g; 180.3 mmoles) was added slowly and in portions to quench the reaction. The aqueous layer was

separated and extracted with ethyl acetate (3x60 mL). The extracts were combined, washed with water (60 mL) and brine (60 mL), then dried over Na₂SO₄. The filtrate was concentrated in vacuo to yield a crude brown solid. A sample of the crude brown solid was purified by column chromatography (SiO₂;

5 100% CH₂Cl₂) to yield the title compound as a light brown solid.

¹H NMR (400 MHz, CD₃CN) δ 7.78 (s, 2H), δ 3.87 (q, *J* = 10.7 Hz, 2H)

MS calculated for C₉H₅Cl₂F₃N₂: 267.98

MS measured: 269, 271 (M+H); 267, 269 (M-H).

10

Example 107

Ventral Prostate and Seminal Vesicle Weight *in vivo* Assay

Immature (approximately 50 g) castrated male Sprague Dawley rats (Charles River) were treated once daily for five days with test compound (usually given orally at 40 mg/kg in a volume of 0.3 mL, in 30% cyclodextrin or

15 0.5% methylcellulose vehicle) and with testosterone propionate (given subcutaneously by injection at the nape of the neck at 2 mg/kg, in a volume of 0.1 mL in sesame oil). On the sixth day, the rats were euthanized by asphyxiation in carbon dioxide. Ventral prosataes and seminal vesicles were removed and their wet weights determined. Test compound activity was

20 determined as the percent inhibition of testosterone-enhanced tissue weights, with a vehicle-treated control group set to zero percent and a testosterone alone-treated control group set to 100%.

Representative compounds of the present invention were tested

25 according to the procedure described, with results as listed in Table 7 below. A test compound is listed as "active" if the non weight adjusted prostate weight was ≤ 40 mg or the % Inhibition prostate weight, body weight adjusted was ≥40% @ 2mg/day dosage. ID₅₀'s, if determined, of ≤ 15 mg/day also indicated an "active" compound. For the compounds listed in Table 7 as "inactive", one

30 skilled in the art will recognize that said compounds may or may not have shown an effect on prostate and / or vesical weight, rather they are listed herein as "inactive" as they did not meet the specified criteria defined above.

Table 7

ID No.	Activity
1	active
2	active
3	inactive
4	active
5	inactive
7	active
8	active
9	active
10	inactive
12	active
13	active
14	active
15	active
16	active
17	inactive
18	active
20	inactive
21	active
22	inactive
23	active
24	inactive
25	active
26	inactive
27	active
28	active
29	active
30	active
31	active
33	active
36	inactive
37	active
38	inactive
39	active
40	active
41	active
42	inactive
44	inactive
45	inactive
46	inactive
48	active
49	inactive
50	active
51	active
53	inactive
54	inactive

55	active
56	inactive
57	active
58	active
59	active
60	inactive
61	active
62	active
63	active
64	inactive
65	inactive
66	active
68	active
69	inactive
70	inactive
71	active
72	inactive
73	active
74	inactive
75	active
76	active
77	inactive
78	active
79	inactive
80	active
81	inactive
82	active
83	active
84	inactive
85	inactive
86	inactive
87	inactive
88	inactive
89	active
90	inactive
91	active
92	active
93	active
94	inactive
95	inactive
96	inactive
97	active
98	active
99	active
100	active
101	inactive
102	active
104	inactive

105	active
106	active
107	active
108	active
109	active
110	active
111	inactive
112	active
113	inactive
114	active
115	active
116	active
117	active
119	active
120	active
121	active
123	inactive
124	active
125	active
126	inactive
128	inactive
129	inactive
131	inactive
132	inactive
133	active
134	inactive
135	inactive
136	active
137	active
138	active
139	active
140	inactive
141	active
142	inactive
144	active
146	active
147	active
148	active
149	active
150	active
151	active
152	active
153	inactive
154	inactive
155	inactive
156	inactive
157	inactive
159	active

160	active
-----	--------

Example 108

Ventral Prostate and *Levator ani* Weight *in vivo* Assay

Mature (150 to 200 g) castrated male Sprague Dawley rats (Charles River) were treated once daily for 14 days with test compound (usually administered by oral gavage at up to the desired dosage, up to 30 mg/kg in a volume of 1 mL, in 30% cyclodextrin or 0.5% methylcellulose vehicle), or with testosterone propionate (administered subcutaneously by injection at the nape of the neck at 5 mg/kg, in a volume of 0.1 mL in sesame oil), or with vehicle (1 mL of 30% cyclodextrin or 0.5% methylcellulose, given orally). On the fifteenth day, the rats were euthanized by asphyxiation in carbon dioxide. Ventral prostates and *levator ani* muscles were removed and their wet weights determined.

Test compound activity was determined as the percent stimulation of tissue weight, with the vehicle-treated control group set to zero percent and the testosterone alone-treated control group set to 100%. A compound was designated as "active" if it produced greater than or equal to 25% stimulation of levator ani at 30 mg / kg.

Compound #7 was tested according to the above procedure described above, dosing at 30 mg/kg and was measured to be active, according to the above criteria.

Example 109

As a specific embodiment of an oral composition, 100 mg of the Compound #7 prepared as in Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual

variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound selected from
1-(5,6-dichloro-1H-benzimidazol-2-yl)-2,2,2-trifluoro-ethanol;
3-(5,6-dichloro-1H-benzimidazol-2-yl)-3-hydroxy-butyronitrile;
5 or a pharmaceutically acceptable salt thereof.
2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.
3. A pharmaceutical composition made by mixing a compound of claim 1 and a pharmaceutically acceptable carrier.
- 10 4. A method of treating a disorder mediated by an androgen receptor, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition of claim 2.
5. A method of treating a condition selected from the group consisting of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, 15 breast cancer, acne, AIDS, cachexia, male contraception, and male performance, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition of claim 2.
6. Use of a compound of claim 1 in the manufacture of a medicament for treating a disorder mediated by an androgen receptor.
- 20 7. Use of a compound of claim 1 in the manufacture of a medicament for treating a condition selected from the group consisting of prostate carcinoma, benign prostatic hyperplasia (BPH), hirsutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, male contraception, and male performance.
8. A compound according to claim 1; or a pharmaceutical composition according to 25 claim 2 or 3; or a method according to claim 4 or 5; or use according to claim 6 or 7, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.