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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2014 (03.04.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/052836 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2013/062309

(22) International Filing Date:
27 September 2013 (27.09.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/706,492 27 September 2012 (27.09.2012) US

(72) Inventors; and
(71) Applicants : **DUNMAN, Paul M.** [US/US]; 695 W. Bloomfield Road, Pittsford, New York 14534 (US). **KRYSAN, Damian J.** [US/US]; 54 Woodgreen Drive, Pittsford, New York 14534 (US). **FLAHERTY, Daniel P.** [US/US]; 13130 Hadley Street, Apt. 2024, Overland Park, Kansas 66213 (US).

(74) Agents: **PRATT, John S.** et al.; 1100 Peachtree Street, Suite 2800, Atlanta, Georgia 30309 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2014/052836 A2

(54) Title: METHODS AND COMPOSITIONS FOR TREATING INFECTION

(57) Abstract: Provided herein are compositions and methods for treating or preventing infection.

METHODS AND COMPOSITIONS FOR TREATING INFECTION

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/706,492, filed on September 27, 2012, which is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

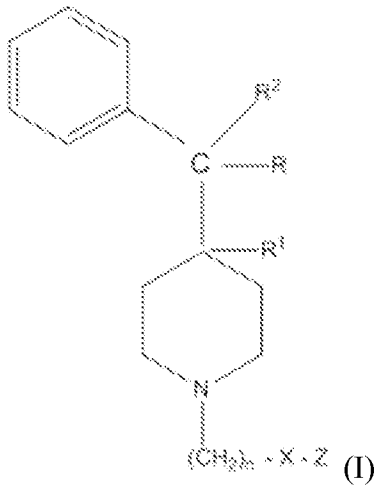
This invention was made with government funding under Grant Nos. 1R01AI1075033-03 and 5P50GM069663 from the National Institutes of Health. The government has certain rights in this invention.

BACKGROUND

Infectious diseases affect the health of people and animals around the world, causing serious illness and death. Thus, an urgent need exists for treatments for infections.

SUMMARY

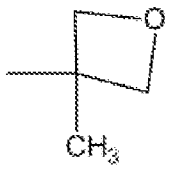
Provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound of Formula I



(I)

wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from

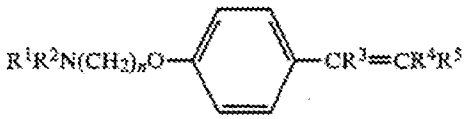
phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $-COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl or a pharmaceutically acceptable salt thereof.

Further provided is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject

a compound of Formula III

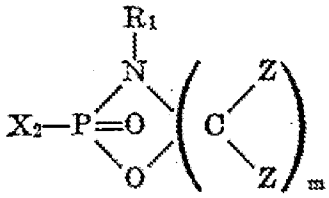


(III)

or a pharmaceutically acceptable salt thereof, wherein R^I and $R^2$are independently selected from ethyl or methyl, n 1 or 2, R^3 and R^4 are both phenyl or substituted phenyl, wherein the substituent can be halo (for example, fluoro-, chloro-, iodo- or bromo-), hydroxyl, a lower alkyl or a substituted lower alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy, and R^5 is hydrogen, a halogen, a lower alkyl from about 1 to 4 carbon atoms or a substituted alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy.

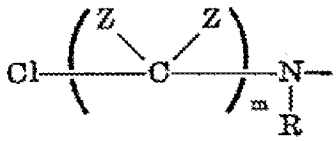
Also provided is a method of treating or preventing infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula V



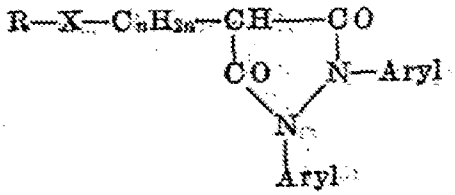
(V)

wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms being substituted with one or several halogen atoms, Z is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms, *m* is 2 or 3 and X_2 is the ethylene imino group or the group having the formula:



wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms which can be substituted with a chlorine atom or a hydroxy group, and Z and *m* have the above-given meaning,

a compound of Formula X



(X)

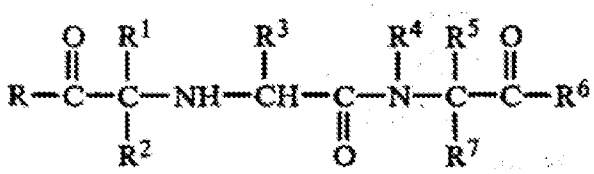
wherein R represents a lower alkyl or a lower alkenyl group, a phenyl group which can be substituted by halogen, methyl or lower alkoxy groups, or a benzyl group which can be nuclear substituted by halogen, methyl or lower alkoxy groups,

X represents –O-, -S-, -SO-, or $–SO_2$-,

n represents an integer from 1-4, and

Aryl represents a phenyl group which can be substituted by lower alkoxy or lower alkylmercapto groups;

a compound of Formula XII



(XII)

wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy (dimethylaminoethoxy), acylamino lower alkoxy (acetylaminoethoxy), acyloxy lower alkoxy (pivaloyloxymethoxy), aryloxy, such as phenoxy, arloweralkoxy, such as benzyloxy, substituted aryloxy or substituted arloweralkoxy wherein the substitutent is methyl, halo or methoxy, amino, loweralkylamino, diloweralkylamino, hydroxyamino, arloweralkylamino such as benzylamino;

R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms which include branched and cyclic and unsaturated (such as allyl) alkyl groups, substituted loweralkyl wherein the substituent can be halo, hydroxy, lower alkoxy, aryloxy such as phenoxy, amino, diloweralkylamino, acylamino, such as acetamido and benzamido, arylamino, guanidino, imidazolyl, indolyl, mercapto, loweralkylthio, arylthio such as phenylthio, carboxy or carboxamido, carboloweralkoxy, aryl such as phenyl or naphthyl, substituted aryl such as phenyl wherein the substituent is lower alkyl, lower alkoxy or halo, arloweralkyl, arloweralkenyl, heteroarlower alkyl or heteroarlower alkenyl such as benzyl, styryl or indolyl ethyl, substituted arloweralkyl, substituted arloweralkenyl, substituted heteroarlower alkyl, or substituted heteroarlower alkenyl, wherein the substituent(s) is halo, dihalo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, acylamino (acetyl amino or benzoylamino) diloweralkylamino, loweralkylamino, carboxyl, halologweralkyl, cyano or sulfonamido; arloweralkyl or heteroarloweralkyl substituted on the alkyl portion by amino or acylamino (acetylamino or benzoylamino);

R^2 and R^7 are the same or different and are hydrogen or lower alkyl;

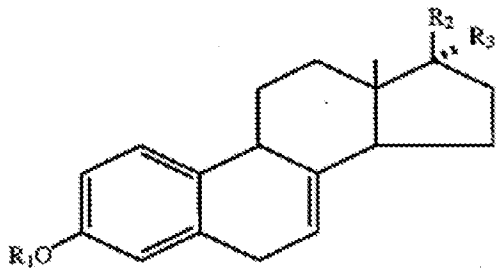
R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethyl phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl (such as benzoylamino lower alkyl, acetylamino lower alkyl), amino lower alkyl, dimethylamino lower alkyl, halo lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyllower alkyl, mercapto lower alkyl, lower alkyl thio lower alkyl;

R^4 is hydrogen or lower alkyl;

R^5 is hydrogen, lower alkyl, phenyl, phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, amino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, mercapto lower alkyl or lower alkyl thio lower alkyl;

R^4 and R^5 can be connected together to form an alkylene bridge of from 2 to 4 carbon atoms, an alkylene bridge of from 2 to 3 carbon atoms and one sulfur atom, an alkylene bridge of from 3 to 4 carbon atoms containing a double bond or an alkylene bridge as above substituted with hydroxy, loweralkoxy, loweralkylor diloweralky;

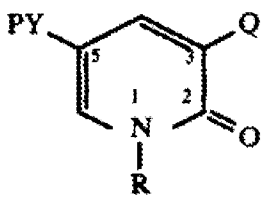
a compound of Formula XIII



(XIII)

wherein R_1 is H, alkyl, acyl or silyl(alkyl)$_3$; R_2 is H and R_3 is OH, O-acyl, O-alkyl or O-silyl (alkyl)$_3$ or R_3 is H and R_2 is OH. O-acyl, O-alkyl or O-silyl (alkyl)$_3$; or R_2 and R_3 together represent O; or R_2 and R_3 together represent acetal or cyclic acetal. R_1 might also represent a substituted alkyl such as e.g. methoxy ethoxy methyl;

a compound of Formula XIV

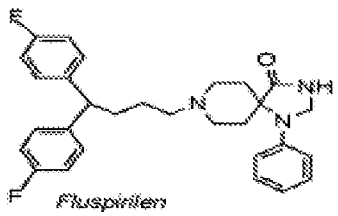


(XIV)

wherein PY is 4- or 3- or 2-pyridinyl or 4- or 3-or 2-pyridinyl having one or two lower-alkyl substituents, R is hydrogen, lower-alkyl or lower-hydroxyalkyl, and Q is nitro, carbamyl,

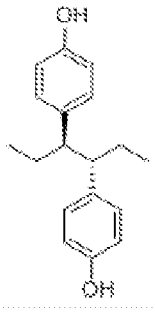
halo, amino, lower-alkylamino, di(lower-alkyl)amino, or NHAc where Ac is lower-alkanoyl or lower-carbalkoxy;

a compound of Formula XV



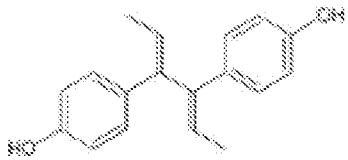
(XV)

a compound of Formula XVI



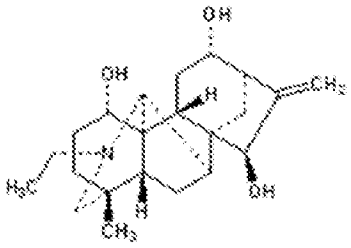
(XVI)

a compound of Formula XVII



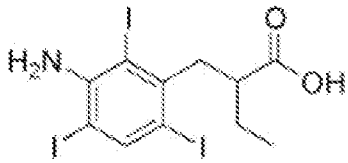
(XVII)

a compound of Formula XVIII



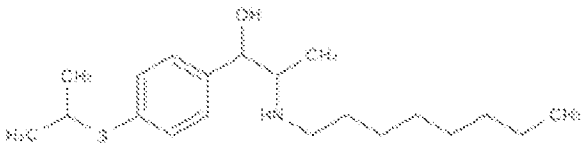
(XVIII)

a compound of Formula XIX



(XIX)

a compound of Formula (XX)



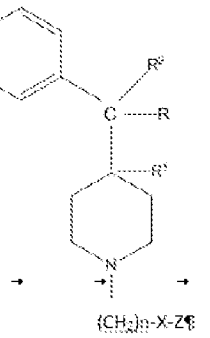
(XX)

or a pharmaceutically acceptable salt thereof.

Further provided is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of: Didanosine, Norcyclobenzaprine, Niridazole, Ifosfamide, Cefalonium, Tamoxifen citrate, Butoconazole, Suloctidil, Clomiphene, Sulconazole, Miconazole, Mefloquine, Sulfinpyrazone, Terfenadine, Lisinopril, Econzaole, Clofazimine, Equilin, Felodipine, Dacarbazine, Furazolidone, Perhexiline maleate, Oxethazaine, Pimozide, Trifluoperazine, Ellipticine, Fluspirilen, Hexestrol, Dienestrol, Zidovudine, Metoprolol, Napelline, Methimazole, Amrinone, Iopanoic acid, R-Propanolol, Rimexolone and Pyrvinium pamoate, wherein the infection is a bacterial infection.

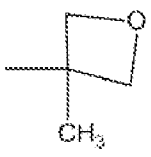
Also provided is a method of removing or preventing biofilm formation on a surface, the method comprising administering to a biofilm containing surface or a surface susceptible to biofilm formation an effective amount of a compound selected from the group consisting of:

a compound of Formula I



(I)

wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $-COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF DRAWINGS

Figure 1 depicts the adenylate kinase (AK) assay described in the Examples. Bactericidal agents compromise bacterial cell integrity, releasing cellular adenylate kinase. Extracellular AK is measured by the addition of a commercial ToxiLight AK cocktail containing ADP and luciferase, resulting in luminescence.

Figure 2 shows AK assay development. (A) AK assay measures of *E. coli* lysed cell supernatants. *E. coli* DH5α cells (1×10^9) were heat inactivated by boiling and diluted, and the AK assay was used to measure adenylate kinase release. Background signal is also shown (mock-treated cells (right-hand column in Figure 2A). "*" indicates a significant difference between results for boiled and mock treatment (Student's *t* test; $P \leq 0.05$). (B) AK assay results for colistin-treated *A. baumannii* strain 98-37-09. Cells were treated with the indicated concentration of colistin, and AK was measured; MIC (4 μg ml^{-1} is indicated. "*" indicates a significant increase in signal compared to that for mock treatment (0 μg ml^{-1}; Student's *t* test, $P \leq 0.05$).

Figure 3 shows AK assay measures of *S. aureus* strain RN4220 treatment with bacteriostatic and bactericidal antibiotics. Standard MIC testing determined the MIC of each antibiotic class (in parentheses). Graphed are the fold changes in AK signal of cells treated with 0.5× or 1.0× the MIC value (left hand column and right hand column, respsectively) for each antibiotic, in comparison to untreated control cells; "*" indicates a significant change in signal as determined by Student's *t* test; $P \leq 0.05$ (compared to results for untreated cells).

Figure 4 shows AK assay measures of antibiotic-treated biofilms and small-colony variants.(A) Graphed are AK signals generated by static biofilm-associated cells following mock or antibiotic treatment: colistin (*P. aeruginosa*) or ciprofloxacin (*S. aureus* and *A. baumannii*). (B) Fold change of AK measures of *S. aureus* SCV UAMS-1112 cells following treatment with 1× and 10× ciprofloxacin, meropenem, and vancomycin, compared to results for mock treated cells. "*" indicates a significant change in signal in comparison to results for mock-treated cells (Student's *t* test, $P \leq 0.05$).

Figure 5 shows AK-based HTS development and screening. (A) Z′ factor assay results for *Klebsiella pneumoniae*. Three-hundred-eighty-four-well microtiter plates were seeded with *K. pneumoniae*, and alternating rows were mock treated (DMSO) or treated with 50 μM colistin. Following 3 h of incubation, AK release was measured and plotted. DMSO-treated

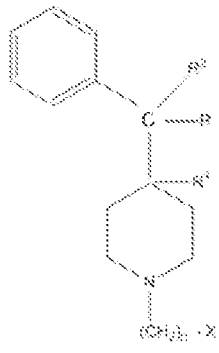
well measures are shown at the bottom of Figure 5A; colistin-treated wells are shown at the top of Figure 5A. (B) Prestwick library *Klebsiella pneumoniae* screening results. In total, 26 compounds were determined to result in a 3-fold increase in AK signal, in comparison to results for DMSO-treated cells. Included among this list were polymyxin, cephalosporins, aminoglycosides, fluoroquinolones, and detergents; the complete Prestwick screening results for *K. pneumoniae* and all other organisms screened are provided in Table 4.

Figure 6 shows antimicrobial properties of terfenadine and tamoxifen. (A) Fold changes in AK signal of terfenadine-treated (10× MIC) *S. aureus* strain UAMS-1 static biofilms and the SCV strain UAMS-1112, compared to those for mock (DMSO)-treated populations, are plotted. "*" indicates a significant increase in signal over that with mock-treated cells (Student's *t* test, $P \leq 0.05$). (B) Plotted are the percent survival of *G. mellonella* larvae at 48 h post-*E. faecium* inoculation. Groups of larvae ($n = 45$) were treated at 2 h and 24 h with either PBS (mock), DMSO, 80 mg kg^{-1} tamoxifen, 160 mg kg^{-1} tamoxifen, or 20 mg kg^{-1} vancomycin.

DETAILED DESCRIPTION

Provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

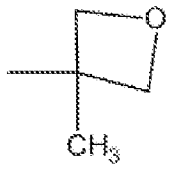
a compound of Formula I



(I)

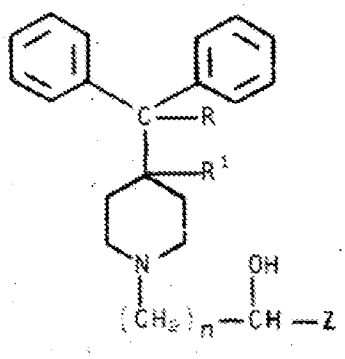
wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl

wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $-COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl. The substituents on the substituted phenyl may be attached at the ortho, meta or para positions of the phenyl ring.

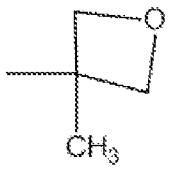
Compounds of Formula I include compounds of Formula II,



(II)

wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; *n* is zero or a positive whole integer of from 1 to 4; Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or

di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure – $COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or

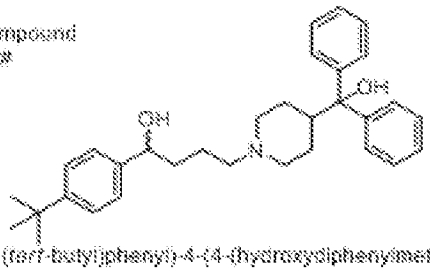


where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl

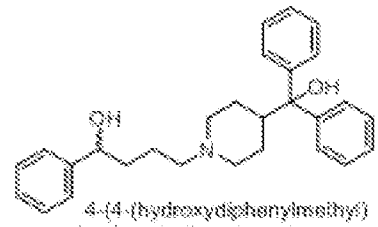
or a pharmaceutically acceptable salt thereof.

Compounds of Formula I also include terfenadine and derivatives thereof, including, but not limited to the following compounds. The compounds are identified by structure, name and registry number. The registry number for each compound is also set forth in Table 6 as an additional identifier for each compound.

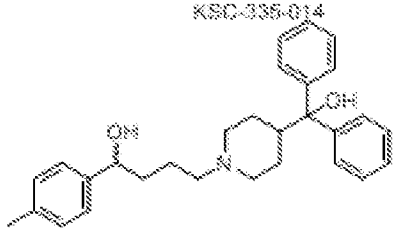
Compound Lists



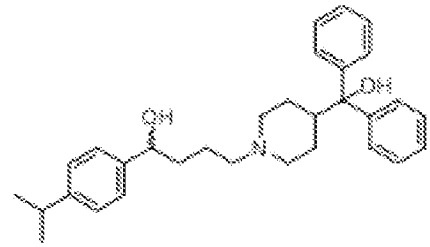
1-(4-(*tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol
Terfenadine
KSC-335-014



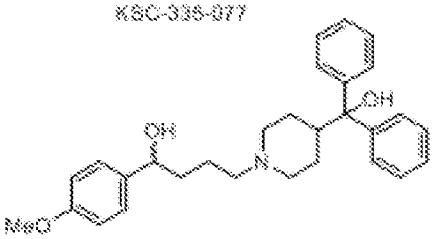
4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)-1-phenylbutan-1-ol
KSC-335-021



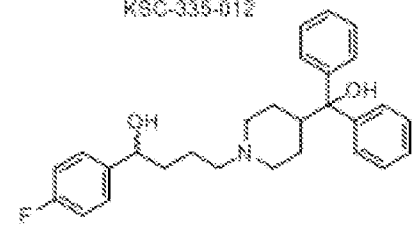
4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(*p*-tolyl)butan-1-ol
KSC-335-077



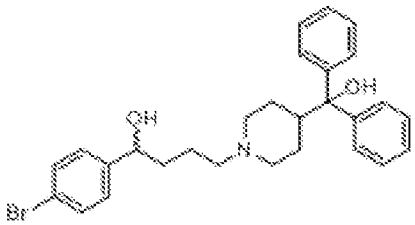
4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-ol
KSC-335-012



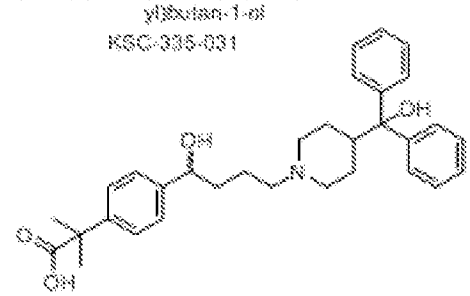
4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-ol
KSC-335-030



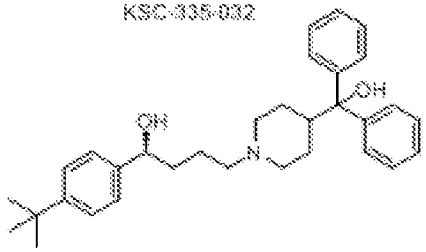
1-(4-fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol
KSC-335-031



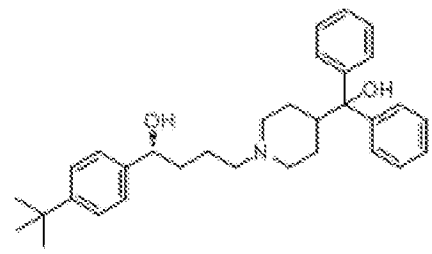
1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol
KSC-335-032



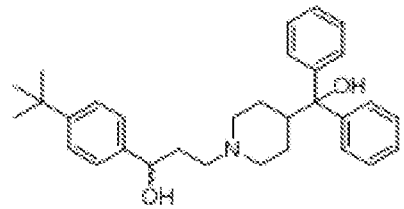
2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoic acid
KSC-335-081



(*S*)-1-(4-(*tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butan-1-ol
KSC-335-069

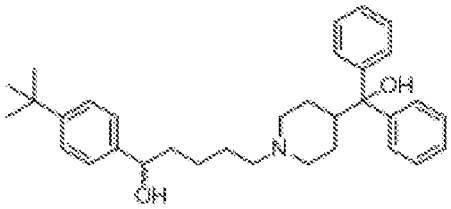


(*R*)-1-(4-(*tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol
KSC-335-070



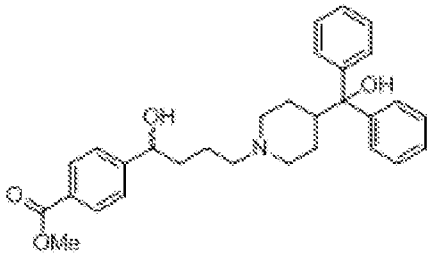
1-(4-(*tert*-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol

KSC-335-018



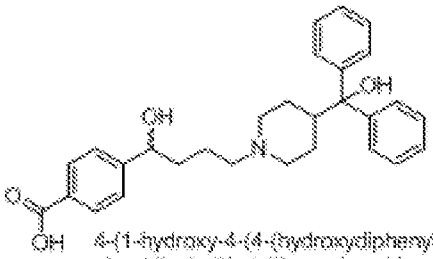
1-(4-(*tert*-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl) piperidin-1-yl)pentan-1-ol

KSC-335-013



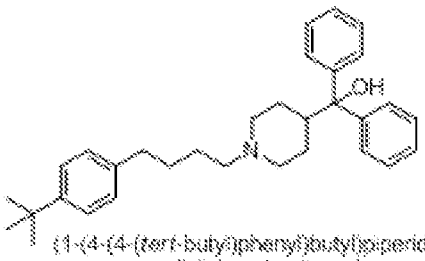
methyl 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butyl)benzoate

KSC-342-017



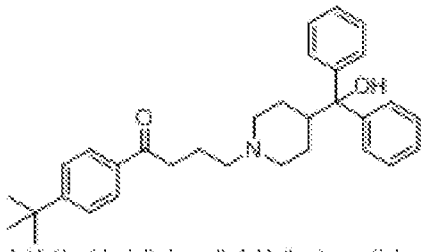
4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butyl)benzoic acid

KSC-342-021



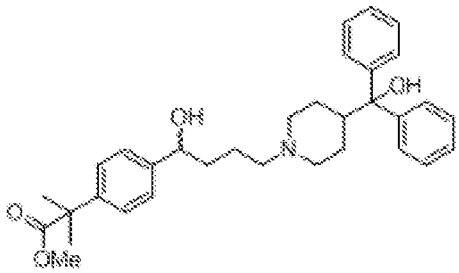
(1-(4-(4-(*tert*-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol

KSC-335-041



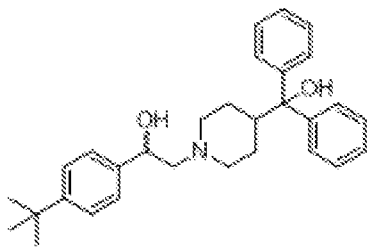
1-(4-(*tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butan-1-one

KSC-335-007



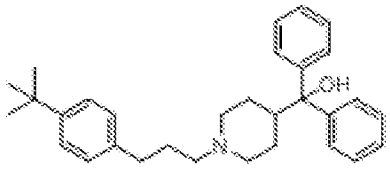
methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate

KSC-335-080

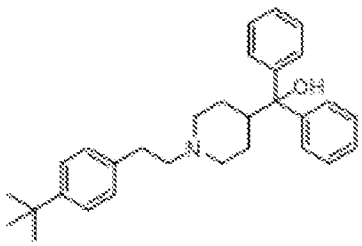


1-(4-(*tert*-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanol

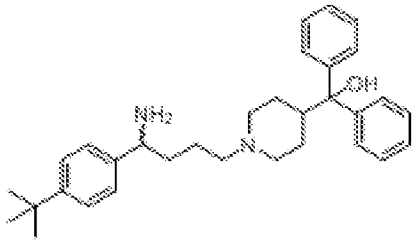
KSC-342-010



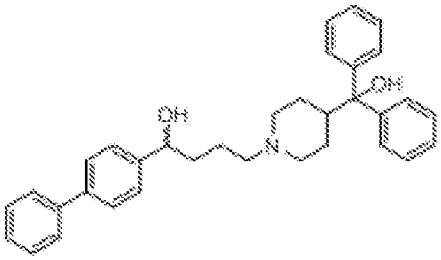
(1-(3-(4-(*tert*-butyl)phenyl)propyl)piperidin-4-yl)diphenylmethanol
KSC-342-080



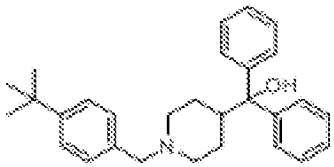
(1-(4-(*tert*-butyl)phenethyl)piperidin-4-yl)diphenylmethanol
KSC-342-081



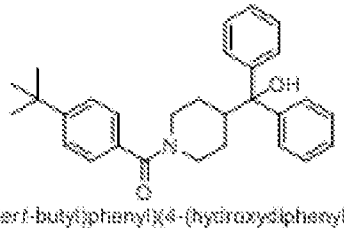
(1-(4-amino-4-(4-(*tert*-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol
KSC-342-088



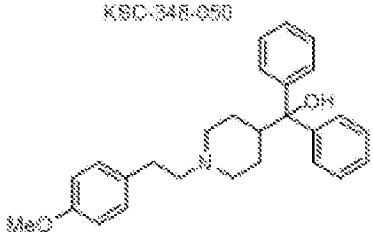
1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol
KSC-348-032



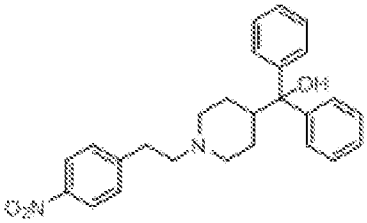
(1-(4-(*tert*-butyl)benzyl)piperidin-4-yl)diphenylmethanol
KSC-348-050



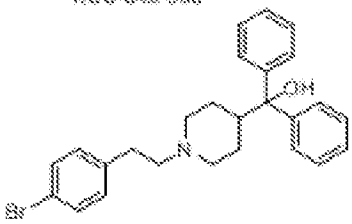
(4-(*tert*-butyl)phenyl)(4-(hydroxydiphenylmethyl)piperidin-1-yl)methanone
KSC-348-049



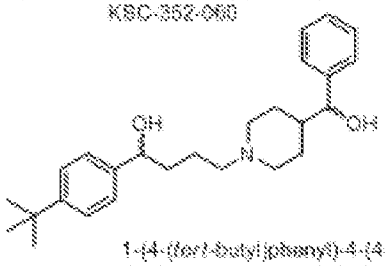
(1-(4-methoxyphenethyl)piperidin-4-yl)diphenylmethanol
KSC-348-058



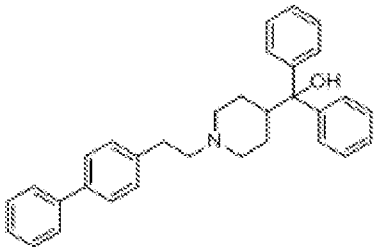
(1-(4-nitrophenethyl)piperidin-4-yl)diphenylmethanol
KSC-352-060



(1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol
KSC-352-061

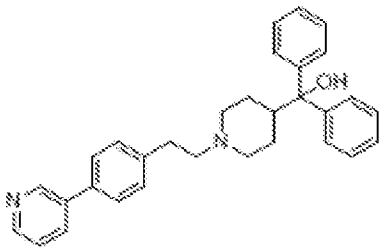


1-(4-((*tert*-butyl)phenyl)-4-(4-(hydroxy(phenyl)methyl)piperidin-1-yl)butan-1-ol
KSC-352-066



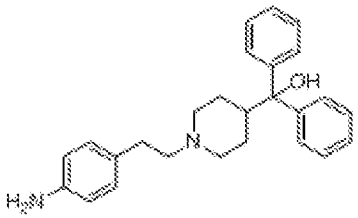
(1-(2-([1,1'-biphenyl]-4-yl)ethyl)piperidin-4-yl)diphenylmethanol

KSC-352-063



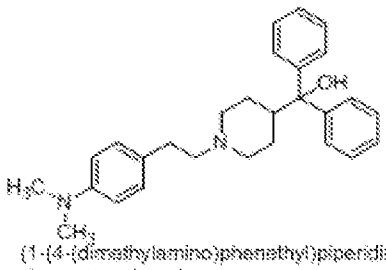
diphenyl(1-(4-(pyridin-3-yl)phenethyl)piperidin-4-yl)methanol

KSC-352-065



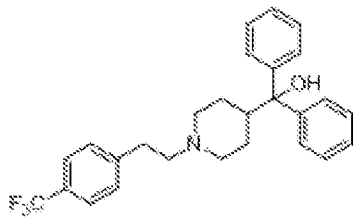
(1-(4-aminophenethyl)piperidin-4-yl)diphenylmethanol

KSC-352-069



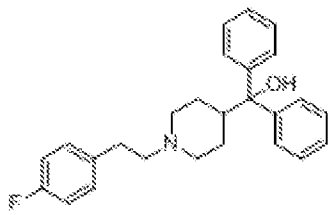
(1-(4-(dimethylamino)phenethyl)piperidin-4-yl) diphenylmethanol

KSC-352-075



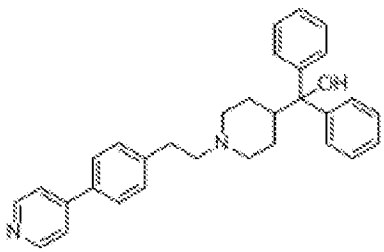
diphenyl(1-(4-(trifluoromethyl)phenethyl) piperidin-4-yl)methanol

KSC-352-082



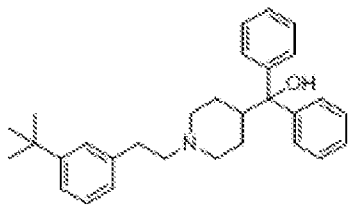
(1-(4-fluorophenethyl)piperidin-4-yl)diphenylmethanol

KSC-352-088



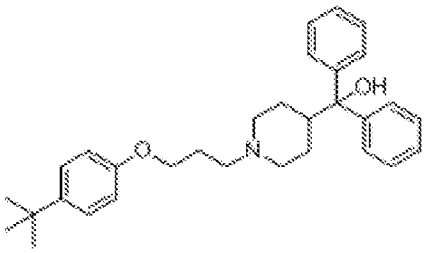
diphenyl(1-(4-(pyridin-4-yl)phenethyl)piperidin-4-yl)methanol

KSC-352-084

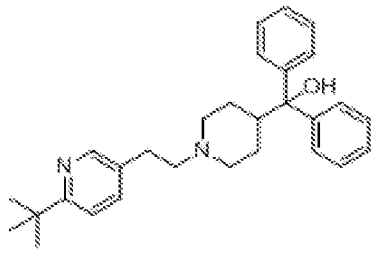


(1-(3-(*tert*-butyl)phenethyl)piperidin-4-yl) diphenylmethanol

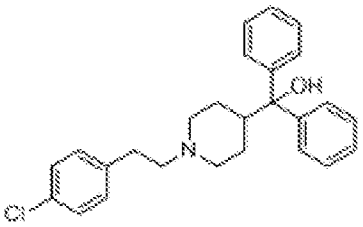
KSC-352-097



(1-(3-(4-(*tert*-butyl)phenoxy)propyl) piperidin-4-yl)diphenylmethanol
KSC-367-044

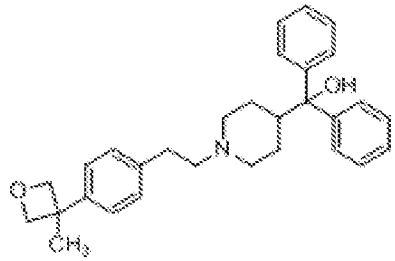


(1-(2-(6-(*tert*-butyl)pyridin-3-yl)ethyl) piperidin-4-yl)diphenylmethanol
KSC-367-052



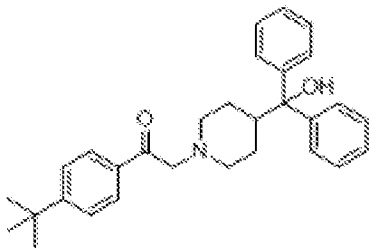
(1-(4-chlorophenethyl)piperidin-4-yl)diphenylmethanol

KSC-367-055

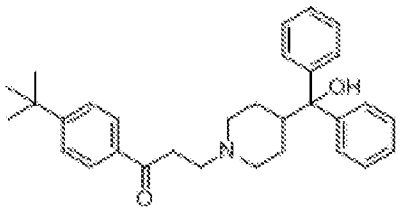


(1-(4-(3-methyloxetan-3-yl)phenethyl)piperidin-4-yl) diphenylmethanol

KSC-367-072

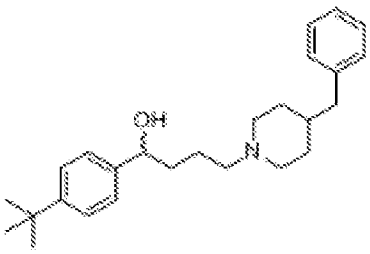


1-(4-(*tert*-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl) piperidin-1-yl)ethanone
KSC-342-006



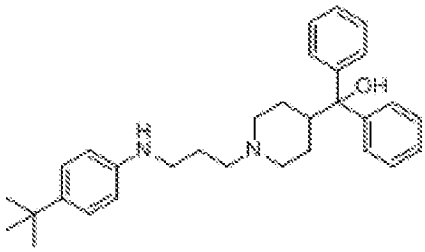
1-(4-(*tert*-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl) piperidin-1-yl)propan-1-one

KSC-335-008



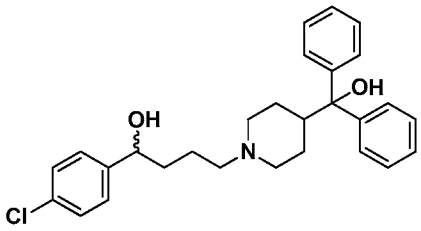
4-(4-benzylpiperidin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-ol

KSC-367-039



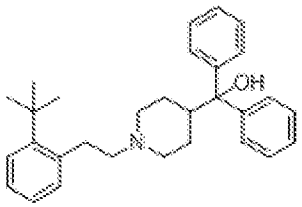
(1-(3-((4-(*tert*-butyl)phenyl)amino)propyl)piperidin-4-yl)diphenylmethanol

KSC-367-043



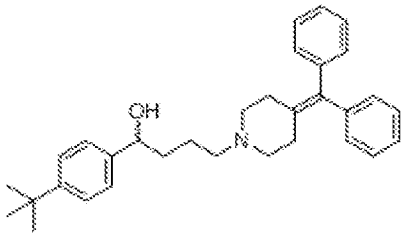
1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol

KSC-335-015



(1-(2-(*tert*-butyl)phenethyl)piperidin-4-yl)diphenylmethanol

KSC-381-020

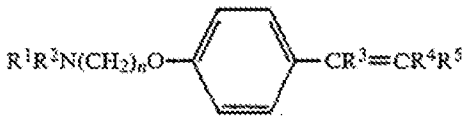


1-(4-(*tert*-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-ol

KSC-367-058

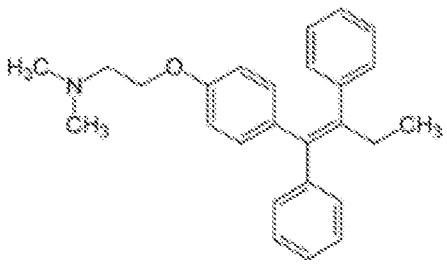
Also provided is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula III



(III)

or a pharmaceutically acceptable salt thereof, wherein R^I and $R^2$are independently selected from ethyl or methyl, n 1 or 2, R^3 and R^4 are both phenyl or substituted phenyl, wherein the substituent can be halo (for example, fluoro-, chloro-, iodo- or bromo-), hydroxyl, a lower alkyl or a substituted lower alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy, and R^5 is hydrogen, a halogen, a lower alkyl from about 1 to 4 carbon atoms or a substituted alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy. Examples of the compounds of Formula III include, tamoxifen and derivatives

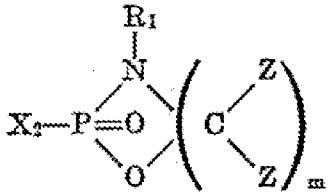


(IV)

thereof, including but not limited to tamoxifen (Formula IV), 4-hydroxy tamoxifen and clomiphene. In the methods provided herein, wherein a one or more compounds of Formula III are used to treat or prevent infection, the infection can be an infection, wherein the infection is not a fungal infection or a parasitic infection.

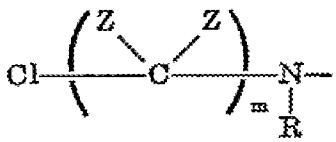
Further provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula V



(V)

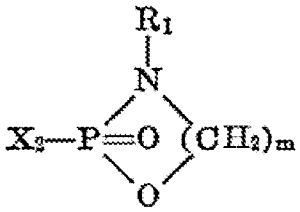
wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms being substituted with one or several halogen atoms, Z is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms, *m* is 2 or 3 and X_2 is the ethylene imino group or the group having the formula:



wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms which may be substituted with a chlorine atom or a hydroxy group, and Z and *m* have the above-given meaning, or a pharmaceutically acceptable salt thereof.

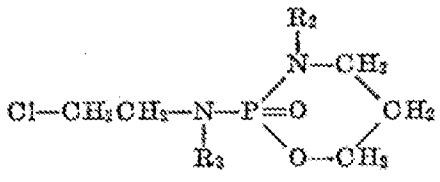
As used throughout, the term "lower alkyl group containing from 1 to 4 carbon atoms" means methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, and I-

methylpropyl. The term "halogen" means chlorine, bromine, fluorine, and iodine. Included herein are compounds of formula IV that correspond to formula VI:



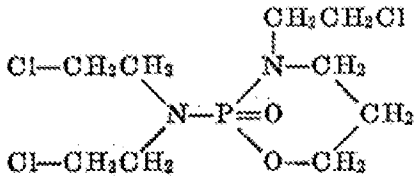
(VI)

wherein R_1, X_2 and *m* have the same meaning as in Formula IV. Additional compounds of formula IV, include the compounds of formula VII:

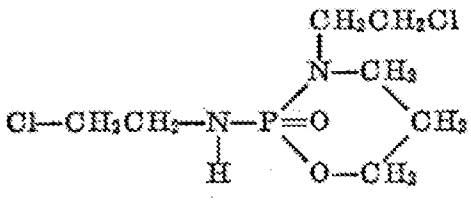


(VII)

wherein R_2 is a β-chloroethyl or a γ-chloropropyl group, and R_3 is hydrogen, a methyl group or an ethyl group, optionally substituted in the β-position with a chlorine atom or a hydroxy group. Among the compounds of formula VII, are the compounds of formula VIII and IX. The compound of formula VIII is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide or ifosfamide. Ifosfamide is also known as IFEX.



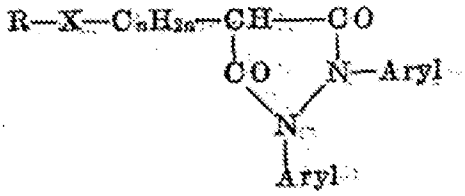
(VIII)



(IX)

Further provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula X



(X)

wherein R represents a lower alkyl or a lower alkenyl group, a phenyl group which can be substituted by halogen, methyl or lower alkoxy groups, or a benzyl group which can be nuclear substituted by halogen, methyl or lower alkoxy groups,

X represents –O-, -S-, -SO-, or $–SO_2$-,

n represents an integer from 1-4, and

Aryl represents a phenyl group which can be substituted by lower alkoxy or lower alkylmercapto groups;

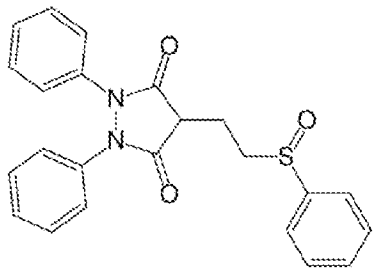
or a pharmaceutically acceptable salt thereof.

With respect to Formula X, R represents a lower alkyl or a lower alkenyl group, a phenyl group which can be substituted by halogen, methyl or lower alkoxy groups, or a benzyl group which can be nuclear substituted by halogen, methyl or lower alkoxy groups, X represents –O-, -S-, -SO-, or –SO2-, n represents an integer from 1-4, and aryl represents a phenyl group which can be substituted by lower alkoxy or lower alkylmercapto groups.

For example, -R-X-C_nH_{2n}- can represent the following groups: methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, allyloxy-, crotyloxy-. phenoxy-, o,-m- and p-methylphenoxy-, o,p-dimethylphenoxy-, m,p-dimethylphenoxy-, p-chlorophenoxy-, p-bromophenoxy-, -o, m and p-methoxyphenoxy-, p-ethoxyphenoxy-, benzyloxy-, o-, m-, and p-methylbenzyloxy-, p-chlorobenzyloxy-, p-bromobenzyloxy, o, m and p-methoxybenzyloxyand-, p- ethoxybenzyloxy-; methyl, -ethyl, -propyl, -isopropyl, and butyl radicals and ·analogous radicals with SO or SO_2 instead of O as divalent group X.

Besides the phenyl group, aryl can be, for example, the o- or p-methylmercaptophenyl group, the o- or p-ethyl mercaptophenyl group, the o-; m-, or p-methoxyphenyl group or the o-, m- or p-ethoxyphenyl group.

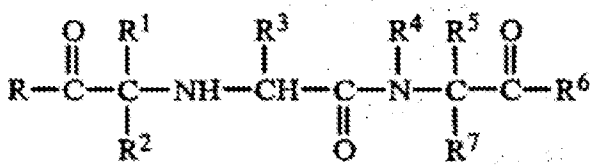
An example of the compound of formula X is set forth herein as formula XI. The compound of formula X is sulfinapyrazone. Sulfinapyrazone is also known as Anturane.



(XI)

Also provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula XII



(XII)

wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy (dimethylaminoethoxy), acylamino lower alkoxy (acetylaminoethoxy), acyloxy lower alkoxy (pivaloyloxymethoxy), aryloxy, such as phenoxy, arloweralkoxy, such as benzyloxy, substituted aryloxy or substituted arloweralkoxy wherein the substitutent is methyl, halo or methoxy, amino, loweralkylamino, diloweralkylamino, hydroxyamino, arloweralkylamino such as benzylamino;

R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms which include branched and cyclic and unsaturated (such as allyl) alkyl groups, substituted loweralkyl wherein the substituent can be halo, hydroxy, lower alkoxy, aryloxy such as phenoxy, amino, diloweralkylamino, acylamino, such as acetamido and benzamido, arylamino, guanidino, imidazolyl, indolyl,

mercapto, loweralkylthio, arylthio such as phenylthio, carboxy or carboxamido, carboloweralkoxy, aryl such as phenyl or naphthyl, substituted aryl such as phenyl wherein the substituent is lower alkyl, lower alkoxy or halo, arloweralkyl, arloweralkenyl, heteroarlower alkyl or heteroarlower alkenyl such as benzyl, styryl or indolyl ethyl, substituted arloweralkyl, substituted arloweralkenyl, substituted heteroarlower alkyl, or substituted heteroarlower alkenyl, wherein the substituent(s) is halo, dihalo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, acylamino (acetyl amino or benzoylamino) diloweralkylamino, loweralkylamino, carboxyl, halologweralkyl, cyano or sulfonamido; arloweralkyl or heteroarloweralkyl substituted on the alkyl portion by amino or acylamino (acetylamino or benzoylamino);

R^2 and R^7 are the same or different and are hydrogen or lower alkyl;

R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethyl phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl (such as benzoylamino lower alkyl, acetylamino lower alkyl), amino lower alkyl, dimethylamino lower alkyl, halo lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyllower alkyl, mercapto lower alkyl, lower alkyl thio lower alkyl;

R^4 is hydrogen or lower alkyl;

R^5 is hydrogen, lower alkyl, phenyl, phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, amino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, mercapto lower alkyl or lower alkyl thio lower alkyl;

R^4 and R^5 may be connected together to form an alkylene bridge of from 2 to 4 carbon atoms, an alkylene bridge of from 2 to 3 carbon atoms and one sulfur atom, an alkylene bridge of from 3 to 4 carbon atoms containing a double bond or an alkylene bridge as above substituted with hydroxy, loweralkoxy, loweralkylor diloweralky;

or a pharmaceutically acceptable salt thereof.

With respect to Formula XII, R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy (dimethylaminoethoxy), acylamino lower alkoxy (acetylaminoethoxy), acyloxy lower alkoxy (pivaloyloxymethoxy), aryloxy, such as phenoxy, arloweralkoxy, such as benzyloxy, substituted aryloxy or

substituted arloweralkoxy wherein the substitutent is methyl, halo or methoxy, amino, loweralkylamino, diloweralkylamino, hydroxyamino, arloweralkylamino such as benzylamino;

R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms which include branched and cyclic and unsaturated (such as allyl) alkyl groups, substituted loweralkyl wherein the substituent can be halo, hydroxy, lower alkoxy, aryloxy such as phenoxy, amino, diloweralkylamino, acylamino, such as acetamido and benzamido, arylamino, guanidino, imidazolyl, indolyl, mercapto, loweralkylthio, arylthio such as phenylthio, carboxy or carboxamido, carboloweralkoxy, aryl such as phenyl or naphthyl, substituted aryl such as phenyl wherein the substituent is lower alkyl, lower alkoxy or halo, arloweralkyl, arloweralkenyl, heteroarlower alkyl or heteroarlower alkenyl such as benzyl, styryl or indolyl ethyl, substituted arloweralkyl, substituted arloweralkenyl, substituted heteroarlower alkyl, or substituted heteroarlower alkenyl, wherein the substituent(s) is halo, dihalo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, acylamino (acetyl amino or benzoylamino) diloweralkylamino, loweralkylamino, carboxyl, halologweralkyl, cyano or sulfonamido; arloweralkyl or heteroarloweralkyl substituted on the alkyl portion by amino or acylamino (acetylamino or benzoylamino);

R^2 and R^7 are the same or different and are hydrogen or lower alkyl;

R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethyl phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl (such as benzoylamino lower alkyl, acetylamino lower alkyl), amino lower alkyl, dimethylamino lower alkyl, halo lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyllower alkyl, mercapto lower alkyl, lower alkyl thio lower alkyl;

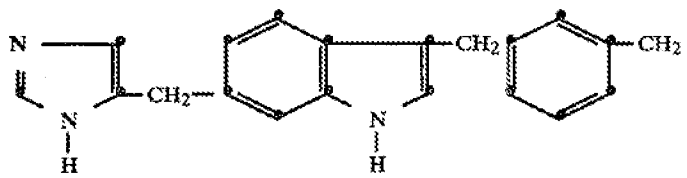
R^4 is hydrogen or lower alkyl;

R^5 is hydrogen, lower alkyl, phenyl, phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, amino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, mercapto lower alkyl or lower alkyl thio lower alkyl;

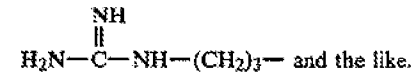
R^4 and R^5 may be connected together to form an alkylene bridge of from 2 to 4 carbon atoms, an alkylene bridge of from 2 to 3 carbon atoms and one sulfur atom, an alkylene

bridge of from 3 to 4 carbon atoms containing a double bond or an alkylene bridge as above substituted with hydroxy, loweralkoxy, loweralkylor diloweralky.

The loweralkyl or lower alkenyl groups except where noted otherwise represented by any of the variables include straight and branched chain hydrocarbon radicals from one to six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or vinyl, allyl, butenyl and the like. The aralkyl groups represented by any of the above variables have from one to four carbon atoms in the alkyl portion thereof and include for example, benzyl, p-methoxy benzyl and the like. Halo means chloro, bromo, iodo or fluoro. Aryl where it appears in any of the radicals except where noted represents phenyl or naphthyl. Heteroaryl groups where they appear include for example pyridyl, thienyl, furyl, indolyl, benzthienyl, imidazoyl and thiazolyl. The R^1, R^3 and R^5 substituted lower alkyl moieties are exemplified by groups such as

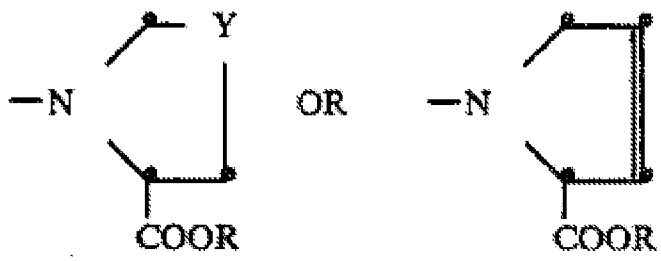


$HO—CH_2—$, $HS—CH_2—$, $H_2N—(CH_2)_4—$,
$CH_3—S—(CH_2)_2—$, $H_2N—(CH_2)_3—$,



and the like.

R^4 and R^5 when joined through the carbon and nitrogen atoms to which they are attached form a 4 to 6 membered ring which may contain one sulfur atom or a double bond. Preferred rings have the formulae:



where Y is CH_2, S, or $CHOCH_3$.

Compounds of Formula XI include compounds wherein:

R and R^6 can each independently be hydroxy, lower alkoxy, lower alkenoxy, arloweralkyloxy, amino, dilower alkylamino lower alkoxy, acylamino lower alkoxy, acyloxy lower alkoxy wherein the substituent is methyl, halo or methoxy;

R^2 and R^7 are hydrogen; R^3 is lower alkyl, amino lower alkyl, imidazoyllower alkyl, halo lower alkyl;

R^4 and R^5 are joined to form the preferred rings as defined above where Y is CH_2, S, or $CH\text{-}OCH_3$;

R^1 is as defined previously.

Other compounds include compounds of Formula XI wherein further R^1 is alkyl having from 1 to 8 carbon atoms, substituted lower alkyl wherein the alkyl group has 1-5 carbon atoms and the substituent is amino, arylthio, aryloxy or arylamino, aralkyl or heteroaralkyl wherein the alkyl portion has 1 to 3 carbon atoms such as phenethyl or indolylethyl or substituted arloweralkyl 65 (phenyl lower alkyl or naphthyl lower alkyl) and substituted heteroarloweralkyl wherein the alkyl groups have 1-3 carbons and wherein the substituent(s) is halo, dihalo, amino, aminoalkyl, hydroxy, lower alkoxy or lower alkyl.

Other compounds of Formula XI include compounds wherein Rand R^6 are hydroxy, lower alkoxy, aralkyloxy;

R^2 and R^7 are hydrogen;

R^3 is methyl or amino lower alkyl;

R^4 and R^5 are joined through the carbon and nitrogen atom to form proline, 4-thiaproline or 4-methoxy proline;

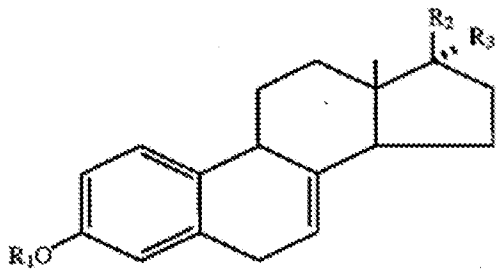
R^1 is alkyl having from 1 to 8 carbon atoms, substituted lower alkyl wherein the alkyl group has 1-5 carbon atoms and the substituent is amino, arylthio or aryloxy, aralkyl or heteroaralkyl wherein the alkyl portion has 1 to 3 carbon atoms such as phenethyl or indolylethyl or substituted aralkyl (phenyl lower alkyl or naphthyl lower alkyl) and substituted heteroaralkyl wherein the alkyl groups have 1-3 carbons and wherein the substituent(s) is halo, dihalo, amino, aminoalkyl, hydroxy, lower alkoxy or lower alkyl.

Further examples of compounds of Formula XII include, but are not limited to:

N-(1(S)-carboxy-3-phenylpropyl)-L-alanyl-L-proline;
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline and its maleate salt;
N-(1(S)-ethoxycarbonyl-4-methylpentyl)-L-alanyl-L-proline;
N-(1-carboxy-5-aminopentyl)-L-alanyl-L-proline;
N-.alpha.-(1(S)-carboxy-3-phenylpropyl)-L-lysyl-L-proline (lisinopril);
N-.alpha.(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-lysyl-L-proline;
N-.alpha.[1(S)-carboxy-3-(3-indolyl)propyl]-L-lysyl-L-proline;
N-.alpha.-[1(S)-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-L-proline;
N-.alpha.-[1(S)-carboxy-2-phenylthioethyl]-L-lysyl-L-proline;
N-.alpha.-[1(S)-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-L-4.alpha.-metho xyproline;
N-.alpha.-[1(S)-carboxy-5-aminopentyl]-L-lysyl-L-proline;
Ethyl N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinate hydrochloride;
and the like.

Also provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula XIII

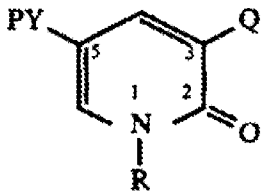


(XIII)

wherein R_1 is H, alkyl, acyl or silyl(alkyl)$_3$; R_2 is H and R_3 is OH, O-acyl, O-alkyl or O-silyl (alkyl)$_3$ or R_3 is H and R_2 is OH. O-acyl, O-alkyl or O-silyl (alkyl)$_3$; or R_2 and R_3 together represent O; or R_2 and R_3 together represent acetal or cyclic acetal. R_1 might also represent a substituted alkyl such as e.g. methoxy ethoxy methyl; or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula XIV



(XIV)

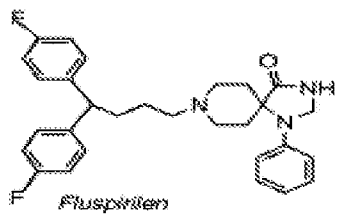
wherein PY is 4- or 3- or 2-pyridinyl or 4- or 3-or 2-pyridinyl having one or two lower-alkyl substituents, R is hydrogen, lower-alkyl or lower-hydroxyalkyl, and Q is nitro, carbamyl, halo, amino, lower-alkylamino, di(lower-alkyl)amino, or NHAc where Ac is lower-alkanoyl or lower-carbalkoxy;

or a pharmaceutically acceptable salt thereof.

With respect to Formula XIII, PY is 4- or 3- or 2-pyridinyl or 4- or 3-or 2-pyridinyl having one or two lower-alkyl substituents, R is hydrogen, lower-alkyl or lower-hydroxyalkyl, and Q is nitro, carbamyl, halo, amino, lower-alkylamino, di(lower-alkyl)amino, or NHAc where Ac is lower-alkanoyl or lower-carbalkoxy, or pharmaceutically-acceptable acid-addition salt thereof. Compounds of formula XIII where Q is amino, lower-alkylamino, di-(lower-alkyl) amino, or NHAc are provided herein. The compounds of formula XIII where Q is nitro or carbamyl are useful as intermediates for preparing the said compounds where Q is amino and those where Q is halo are useful as intermediates in the preparation of the compounds where Q is lower-alkylamino and di-(lower-alkyl)amino. Other compounds of Formula XIII include compounds where Q is amino, R is hydrogen and PY is 4-pyridinyl or 3-pyridinyl, for example, 3- amino-5-(4-pyridinyl)- 2(1H)-pyridinone (amrinone).

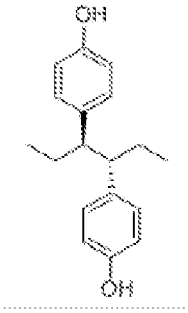
Further provided herein is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula XV



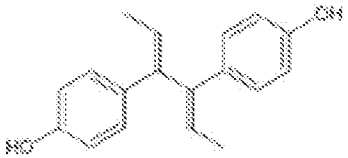
(XV)

a compound of Formula XVI



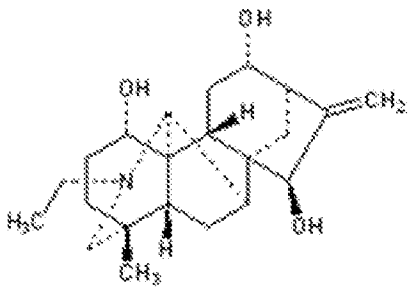
(XVI)

a compound of Formula XVII



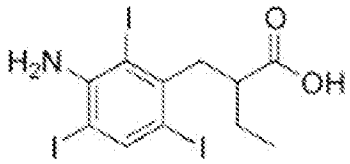
(XVII)

a compound of Formula XVIII



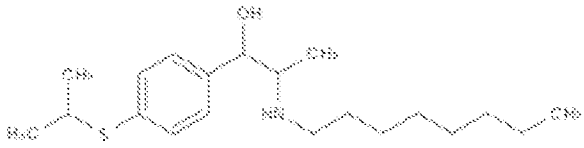
(XVIII)

a compound of Formula XIX



(XIX)

a compound of Formula (XX)



(XX)

or pharmaceutically acceptable salt thereof.

Formula XV is fluspirilen, Formula XVI is hexestrol, Formula XVII is dienestrol, Formula XVIII is napelline, Formula XIX is iopanoic acid and Formula XX is suloctodil.

Further provided is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of: Didanosine, Norcyclobenzaprine, Niridazole, Ifosfamide, Cefalonium, Tamoxifen citrate, Butoconazole, Suloctidil, Clomiphene, Sulconazole, Miconazole, Mefloquine, Sulfinpyrazone, Terfenadine, Lisinopril, Econzaole, Clofazimine, Equilin, Felodipine, Dacarbazine, Furazolidone, Perhexiline maleate, Oxethazaine, Pimozide, Trifluoperazine, Ellipticine, Fluspirilen, Hexestrol, Dienestrol, Zidovudine, Metoprolol, Napelline, Methimazole, Amrinone, Iopanoic acid, R-Propanolol, Rimexolone and Pyrvinium pamoate, or a pharmaceutically acceptable salt thereof.

Further provided is a method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of: Didanosine, Norcyclobenzaprine, Niridazole, Ifosfamide, Cefalonium, Tamoxifen citrate, Butoconazole, Suloctidil, Clomiphene, Sulconazole, Miconazole, Mefloquine, Sulfinpyrazone, Terfenadine, Lisinopril, Econzaole, Clofazimine, Equilin, Felodipine, Dacarbazine, Furazolidone, Perhexiline maleate, Oxethazaine, Pimozide, Trifluoperazine, Ellipticine, Fluspirilen, Hexestrol,

Dienestrol, Zidovudine, Metoprolol, Napelline, Methimazole, Amrinone, Iopanoic acid, R-Propanolol, Rimexolone and Pyrvinium pamoate, or a pharmaceutically acceptable salt thereof, wherein the infection is a bacterial infection selected from the group consisting of *Enterobacterium faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinebacter baumannii, Pseudomonas aeruginosa and Enterobacter sp.*

Further provided is a method of treating or preventing a bacterial infection in a subject with or at risk of developing a bacterial infection in a subject comprising administering to the subject a compound that inhibits bacterial DNA gyrase or topoisomerase IV. The compound can be, for example, a compound of Formula I. As set forth above, a compound of Formula I can be terfenadine or a derivative thereof. In the methods set forth herein an inhibitor of bacterial DNA gyrase or topoisomerase IV can be used to treat or prevent *Staphylococcus aureus* infection.

It is contemplated that one or more, for example, two, three, four, five, etc., of the compounds or derivatives of the compounds set forth herein can be administered to treat or prevent infection. Thus, combinations of the compounds set forth herein are also provided. Pharmaceutically acceptable salts of all of the compounds set forth herein are also provided. The term pharmaceutically acceptable salt as used herein refers to those salts of any of the compounds described herein or derivatives thereof that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds described herein. These salts can be prepared *in situ* during the isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not

limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

The infection can be a viral infection, bacterial infection, fungal infection or a parasitic infection, to name a few. All strains and types of pathogenic infection are contemplated herein. The infection can also be a respiratory infection, a gastrointestinal infection or a skin infection, to name a few.

In any of the methods of treating or preventing infection set forth herein, the infection can be any infection, wherein the infection is not a bacterial infection. In any of the methods of treating or preventing infection set forth herein, the infection can be any infection, wherein the infection is not a viral infection. In any of the methods of treating or preventing infection set forth herein, the infection can be any infection, wherein the infection is not a parasitic infection. In any of the methods of treating or preventing infection set forth herein, the infection can be any infection, wherein the infection is not a fungal infection. In any of the methods of treating or preventing infection set forth herein, the infection can be any infection, wherein the infection is not a protozoal infection.

Examples of bacterial infections include, but are not limited to infections caused by the Gram negative or Gram positive bacteria. For example, the infection can be caused by *Listeria* (*sp.*), *Franscicella tularensis*, *Enterobacter sp. Enterococcus faecium*, other *Enterococcus* species, *Klebsiella pneumonia*, *Acinetobacter baumannii, Mycobacterium tuberculosis*, *Rickettsia* (all types), *Ehrlichia* or *Chylamida*. Further examples of bacteria include *M. tuberculosis, Legionella pneumophila*, other *Legionella* species, *Salmonella typhi,* other *Salmonella* species, *Shigella* species, *Yersinia pestis, Pasteurella haemolytica, Pasteurella multocida,* other *Pasteurella species, Actinobacillus pleuropneumoniae, Listeria monocytogenes, Listeria ivanovii, Brucella abortus,* other *Brucella* species, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Coxiella burnetti*, other *Rickettsial* species, *Ehrlichia* species, *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae, Bacillus anthracis, Escherichia coli, Vibrio cholerae, Kingella kingae, Campylobacter* species, *Neiserria meningitidis, Neiserria gonorrhea, Pseudomonas aeruginosa,* other *Pseudomonas* species, *Haemophilus influenzae, Haemophilus ducreyi,* other *Hemophilus* species, *Clostridium tetani,* other *Clostridium* species, *Yersinia enterolitica,* and other *Yersinia* species. In the methods provided herein, one or more compounds set forth herein can treat or prevent one or more bacterial infections selected from the group consisting of *Enterobacterium faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinebacter baumannii, Pseudomonas aeruginosa and Enterobacter*

sp. In the methods set forth herein, the bacteria can be a small colony variant strain, for example a small colony strain of *Staphylococcus aureus*. In any of the methods set forth herein, the infection can be a bacterial infection, wherein the bacterial infection is not tuberculosis, for example, *Mycobacterium tuberculosis*. For example, and not to be limiting any of the compounds set forth herein, including compounds of Formula I and II can be used to treat or prevent infection in a subject with or at risk of developing an infection, wherein the infection is not tuberculosis.

Examples of parasitic infections include, but are not limited to infections caused by the following parasites: *Cryptosporidium*, *Plasmodium* (all species), American trypanosomes (*T. cruzi*), African trypanosomes, *Acanthamoeba*, *Entaoeba histolytica, Angiostrongylus, Anisakis, Ascaris, Babesia, Balantidium, Baylisascaris,* lice, ticks, mites, fleas, *Capillaria, Clonorchis, Chilomastix mesnili, Cyclspora, Diphyllobothrium, Dipylidium caninum, Fasciola, Giardia, Gnathostoma, Hetetophyes, Hymenolepsis, Isospora*, *Loa loa, Microsporidia, Naegleria, Toxocara, Onchocerca, Opisthorchis*, *Paragonimus*, *Baylisascaris*, *Strongyloides, Taenia, Trichomonas and Trichuris*. In any of the methods set forth herein, the infection can be a parasitic infection, wherein the parasitic infection is not malaria, for example, malaria caused by any species of *Plasmodium* including *Plasmodium falciparum.* For example, and not to be limiting any of the compounds set forth herein, including compounds of Formula I and II can be used to treat or prevent infection in a subject with or at risk of developing an infection, wherein the infection is not malaria.

Furthermore, examples of protozoan and fungal species contemplated within the present methods include, but are not limited to, *Plasmodium falciparum*, other *Plasmodium* species, *Toxoplasma gondii*, *Pneumocystis carinii*, *Trypanosoma cruzi*, other trypanosomal species, *Leishmania donovani*, other *Leishmania species*, *Theileria annulata,* other *Theileria* species, *Eimeria tenella,* other *Eimeria* species, *Histoplasma capsulatum, Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Penicillium marneffei*, and *Candida* species. In any of the methods set forth herein, the infection can be a protozoan infection, wherein the protozoan infection is not leishmaniasis, for example, leishmaniasis caused by a *Leishmania* species, for example, *Leishmania major.* For example, and not to be limiting any of the compounds set forth herein, including compounds of Formula I and III can be used to treat or prevent infection in a subject with or at risk of developing an infection, wherein the infection is not leishmaniasis.

Examples of viral infections include but are not limited to, infections caused by RNA viruses (including negative stranded RNA viruses, positive stranded RNA viruses, double stranded RNA viruses and retroviruses) and DNA viruses. All strains, types, subtypes of DNA and RNA viruses are contemplated herein.

Examples of RNA viruses include, but are not limited to picornaviruses, which include aphthoviruses (for example, foot and mouth disease virus O, A, C, Asia 1, SAT1, SAT2 and SAT3), cardioviruses (for example, encephalomycarditis virus and Theiller's murine encephalomyelitis virus), enteroviruses (for example polioviruses 1, 2 and 3, human enteroviruses A-D, bovine enteroviruses 1 and 2, human coxsackieviruses A1-A22 and A24, human coxsackieviruses B1-B5, human echoviruses 1-7, 9, 11-12, 24, 27, 29-33, human enteroviruses 68-71, porcine enteroviruses 8-10 and simian enteroviruses 1-18), erboviruses (for example, equine rhinitis virus), hepatovirus (for example human hepatitis A virus and simian hepatitis A virus), kobuviruses (for example, bovine kobuvirus and Aichi virus), parechoviruses (for example, human parechovirus 1 and human parechovirus 2), rhinovirus (for example, human rhinovirus 1-100 and bovine rhinoviruses 1-3) and teschoviruses (for example, porcine teschovirus).

Additional examples of RNA viruses include caliciviruses, which include noroviruses (for example, Norwalk virus), sapoviruses (for example, Sapporo virus), lagoviruses (for example, rabbit hemorrhagic disease virus and European brown hare syndrome) and vesiviruses (for example vesicular exanthema of swine virus and feline calicivirus).

Other RNA viruses include astroviruses, which include mamastorviruses and avastroviruses. Togaviruses are also RNA viruses. Togaviruses include alphaviruses (for example, Chikungunya virus, Sindbis virus, Semliki Forest virus, Western equine encephalitis, Getah virus, Everglades virus, Venezuelan equine encephalitis virus and Aura virus) and rubella viruses. Additional examples of RNA viruses include the the flaviviruses (for example, tick-borne encephalitis virus, Tyuleniy virus, Aroa virus, Dengue virus (types 1 to 4), Kedougou virus, Japanese encephalitis virus (JEV), West Nile virus (WNV), Kokobera virus, Ntaya virus, Spondweni virus, Yellow fever virus, Entebbe bat virus, Modoc virus, Rio Bravo virus, Cell fusing agent virus, pestivirus, GB virus A, GBV-A like viruses, GB virus C, Hepatitis G virus, hepacivirus (hepatitis C virus (HCV)) all six genotypes), bovine viral diarrhea virus (BVDV) types 1 and 2, and GB virus B).

Other examples of RNA viruses are the coronaviruses, which include, human respiratory coronaviruses such as SARS-CoV, HCoV-229E, HCoV-NL63 and HCoV-OC43. Coronaviruses also include bat SARS-like CoV, turkey coronavirus, chicken coronavirus, feline coronavirus and canine coronavirus. Additional RNA viruses include arteriviruses (for example, equine arterivirus, porcine reproductive and respiratory syndrome virus, lactate dehyrogenase elevating virus of mice and simian hemorraghic fever virus). Other RNA viruses include the rhabdoviruses, which include lyssaviruses (for example, rabies, Lagos bat virus, Mokola virus, Duvenhage virus and European bat lyssavirus), vesiculoviruses (for example, VSV-Indiana, VSV-New Jersey, VSV-Alagoas, Piry virus, Cocal virus, Maraba virus, Isfahan virus and Chandipura virus), and ephemeroviruses (for example, bovine ephemeral fever virus, Adelaide River virus and Berrimah virus). Additional examples of RNA viruses include the filoviruses. These include the Marburg and Ebola viruses (for example, EBOV-Z, EBOV-S, EBOV-IC and EBOV-R.

The paramyxoviruses are also RNA viruses. Examples of these viruses are the rubulaviruses (for example, mumps, parainfluenza virus 5, human parainfluenza virus type 2, Mapuera virus and porcine rubulavirus), avulaviruses (for example, Newcastle disease virus), respoviruses (for example, Sendai virus, human parainfluenza virus type 1 and type 3, bovine parainfluenza virus type 3), henipaviruses (for example, Hendra virus and Nipah virus), morbilloviruses (for example, measles, Cetacean morvilliirus, Canine distemper virus, Peste-des-petits-ruminants virus, Phocine distemper virus and Rinderpest virus), pneumoviruses (for example, human respiratory syncytial virus A2, B1 and S2, bovine respiratory syncytial virus and pneumonia virus of mice), metapneumoviruses (for example, human metapneumovirus and avian metapneumovirus). Additional paramyxoviruses include Fer-de-Lance virus, Tupaia paramyxovirus, Menangle virus, Tioman virus, Beilong virus, J virus, Mossman virus, Salem virus and Nariva virus. Additional RNA viruses include the orthomyxoviruses.

These viruses include influenza viruses and strains (*e.g.,* influenza A (H1N1 (including but not limited to A/WS/33 and A/California/04/2009 strains) H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3 and H10N7), B and C viruses, as well as avian influenza (for example, strains H5N1, H5N2, H7N1, H7N7 and H9N2) thogotoviruses and isaviruses. Orthobunyaviruses (for example, Akabane virus, California encephalitis, Cache Valley virus, Snowshoe hare virus,) nairoviruses (for example, Nairobi sheep virus, Crimean-Congo hemorrhagic fever virus Group and Hughes virus), phleboviruses (for example,

Candiru, Punta Toro, Rift Valley Fever, Sandfly Fever, Naples, Toscana, Sicilian and Chagres), and hantaviruses (for example, Hantaan, Dobrava, Seoul, Puumala, Sin Nombre, Bayou, Black Creek Canal, Andes and Thottapalayam) are also RNA viruses. Arenaviruses such as lymphocytic choriomeningitis virus, Lujo virus, Lassa fever virus, Argentine hemorrhagic fever virus, Bolivian hemorrhagic fever virus, Venezuelan hemorrhagic fever virus, SABV and WWAV are also RNA viruses. Borna disease virus is also an RNA virus. Hepatitis D (Delta) virus and hepatitis E are also RNA viruses. Any of the compounds set forth herein, including, but not limited to the compounds of Formula I and II can be used to treat or prevent a viral infection, wherein the viral infection is not a Lassa fever virus infection.

Additional RNA viruses include reoviruses, rotaviruses, birnaviruses, chrysoviruses, cystoviruses, hypoviruses partitiviruses and totoviruses. Orbiviruses such as African horse sickness virus, Blue tongue virus, Changuinola virus, Chenuda virus, Chobar Gorge Corriparta virus, epizootic hemorraghic disease virus, equine encephalosis virus, Eubenangee virus, Ieri virus, Great Island virus, Lebombo virus, Orungo virus, Palyam virus, Peruvian Horse Sickness virus, St. Croix River virus, Umatilla virus, Wad Medani virus, Wallal virus, Warrego virus and Wongorr virus are also RNA viruses.

Retroviruses include alpharetroviruses (for example, Rous sarcoma virus and avian leukemia virus), betaretroviruses (for example, mouse mammary tumor virus, Mason-Pfizer monkey virus and Jaagsiekte sheep retrovirus), gammaretroviruses (for example, murine leukemia virus and feline leukemia virus, deltraretroviruses (for example, human T cell leukemia viruses (HTLV-1, HTLV-2), bovine leukemia virus, STLV-1 and STLV-2), epsilonretriviruses (for example, Walleye dermal sarcoma virus and Walleye epidermal hyperplasia virus 1), reticuloendotheliosis virus (for example, chicken syncytial virus, lentiviruses (for example, human immunodeficiency virus (HIV) type 1, human immunodeficiency virus (HIV) type 2, human immunodeficiency virus (HIV) type 3, simian immunodeficiency virus, equine infectious anemia virus, feline immunodeficiency virus, caprine arthritis encephalitis virus and Visna maedi virus) and spumaviruses (for example, human foamy virus and feline syncytia-forming virus).

Examples of DNA viruses include polyomaviruses (for example, simian virus 40, simian agent 12, BK virus, JC virus, Merkel Cell polyoma virus, bovine polyoma virus and lymphotrophic papovavirus), papillomaviruses (for example, human papillomavirus, bovine papillomavirus, adenoviruses (for example, adenoviruses A-F, canine adenovirus type I,

canined adeovirus type 2), circoviruses (for example, porcine circovirus and beak and feather disease virus (BFDV)), parvoviruses (for example, canine parvovirus), erythroviruses (for example, adeno-associated virus types 1-8), betaparvoviruses, amdoviruses, densoviruses, iteraviruses, brevidensoviruses, pefudensoviruses, herpes viruses 1,2, 3, 4, 5, 6, 7 and 8 (for example, herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, Kaposi's sarcoma associated herpes virus, human herpes virus-6 variant A, human herpes virus-6 variant B and cercophithecine herpes virus 1 (B virus)), poxviruses (for example, smallpox (variola), cowpox, monkeypox, vaccinia, Uasin Gishu, camelpox, psuedocowpox, pigeonpox, horsepox, fowlpox, turkeypox and swinepox), and hepadnaviruses (for example, hepatitis B and hepatitis B-like viruses).

One or more of the compounds described herein can be contacted with a cell or populations of cells *in vitro*, *ex vivo* or *in vivo*. For example, the cell or population of cells can be in a subject, or in an *in vitro* culture. In another example, one or more compounds set forth herein can be used to inhibit bacterial growth, fungal growth, parasitic growth, protozoal growth or viral replication, *in vitro*, *ex vivo* or *in vivo*. Any of the compounds set forth herein can be used alone or in combination with other therapeutic agents such as antiviral compounds, antibacterial agents (for example, antibiotics), antifungal agents, antiparasitic agents, anti-inflammatory agents, anti-cancer agents, etc.

In the methods described herein, the level of infection, for example, in a cell, or a population of cells, or a cell culture, can be assessed by measuring an antigen or other product associated with a particular infection. The level of infection can also be measured in a tissue sample or a culture of cells from a subject, either before or after administration of one or more compounds disclosed herein. For example, the level of viral infection can be measured by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) assay (See for example, Payungporn et al. "Single step multiplex real-time RT-PCR for H5N1 influenza A virus detection." *J Virol Methods*. Sep 22, 2005; Landolt et la. "Use of real-time reverse transcriptase polymerase chain reaction assay and cell culture methods for detection of swine influenza A viruses" *Am J Vet Res*. 2005 Jan;66(1):119-24).

Methods of measuring bacterial growth and inhibition of bacterial growth are provided in the Examples. Further, one of skill in the art would know how to determine the concentration of a compound that inhibits bacterial infection (see, for example, Andrews, et al. "Determination of minimum inhibitory concentrations". *Journal of Antimicrobial Chemotherapy* 48 (suppl 1): 5–16 (2001)). Other methods for determining antifungal and

antibacterial activity are known in the art. See, for example, Hayhoe et al. "Screening for Antibacterial, Antifungal and Anti quorum Sensing Activity," *Methods Mol. Biol.* 1055: 219-225 (2013)); Doddanna et al. "Antimicrobial activity of plant extracts on *Candida albicans*: An in vitro study *Indian J. Dent. Res*. 24(4): 401-405 (2013), both of which are incorporated by this reference in their entireties.

As used throughout, by subject is meant an individual. Preferably, the subject is a mammal such as a primate, and, more preferably, a human. Non-human primates are subjects as well. The term subject includes domesticated animals, such as cats, dogs, etc., livestock (for example, cattle, horses, pigs, sheep, goats, etc.) and laboratory animals (for example, ferret, chinchilla, mouse, rabbit, rat, gerbil, guinea pig, etc.). Thus, veterinary uses and medical formulations are contemplated herein.

As used herein, a biological sample is a sample derived from a subject such as a mammal or human and includes, but is not limited to, any biological fluid, including a bodily fluid. Examples of bodily fluids include, but are not limited to, whole blood, plasma, serum, urine, saliva, ocular fluid, ascites, a stool sample, spinal fluid, tissue infiltrate, pleural effusions, lung lavage fluid, and the like. The biological fluid includes a cell culture medium or supernatant of cultured cells from the subject.

The methods and compounds as described herein are useful for therapeutic treatment. Use of one or more of the compounds set forth herein for the treatment or prevention of infection is also contemplated herein. One or more of the compounds set forth herein for use in a method of treating or preventing infection is also provided herein. Therapeutic treatment involves administering to a subject a therapeutically effective amount of one or more of the agents described herein, optionally, after diagnosis of an infection or risk of infection in the subject. Therefore, all of the methods disclosed herein, can optionally comprise the step of diagnosing a subject with an infection or diagnosing a subject in need of prophylaxis or prevention of infection.

As used herein, the terms treatment, treat, or treating refers to a method of reducing the effects of a disease or condition or symptom of the disease or condition. Thus, in the disclosed methods, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease or condition or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as

compared to a control. A control subject can be a subject that has not received a compound set forth herein. Thus, the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition.

As utilized herein, by preventing infection is meant a method of precluding, delaying, averting, obviating, forestalling, stopping, or hindering the onset, incidence, severity, or recurrence of infection. For example, the disclosed method is considered to be a prevention if there is about a 10% reduction in onset, incidence, severity, or recurrence of infection, or symptoms of infection (e.g., inflammation, fever, lesions, weight loss, etc.) in a subject exposed to an infection when compared to control subjects exposed to an infection that did not receive a composition for decreasing infection. Thus, the reduction in onset, incidence, severity, or recurrence of infection can be about a 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between as compared to a control subject. For example, and not to be limiting, if about 10% of the subjects in a population do not become infected as compared to subjects that did not receive preventive treatment, this is considered prevention.

The compounds set forth herein can also be used to decrease infection in a cell. A decrease or inhibition of infection can occur in a cell, *in vitro*, *ex vivo* or *in vivo*. As utilized throughout, the term "infection" encompasses all phases of pathogenic life cycles including, but not limited to, attachment to cellular receptors, entry, internalization, disassembly, replication, genomic integration of pathogenic sequences, transcription of pathogen RNA, translation of pathogen RNA, transcription of host cell mRNA, translation of host cell mRNA, proteolytic cleavage of pathogenic proteins or cellular proteins, assembly of particles, endocytosis, cell lysis, budding, and egress of the pathogen from the cells.

The compounds described herein can be provided in a pharmaceutical composition. Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include a therapeutically effective amount of the compound described herein or derivatives thereof in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically

acceptable is meant a material that is not biologically or otherwise undesirable, which can be administered to an individual along with the selected agent without causing unacceptable biological effects or interacting in a deleterious manner with the other components of the pharmaceutical composition in which it is contained.

As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, *e.g.*, Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers such as phosphate buffers, citrate buffer, and buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN® (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICS™ (BASF; Florham Park, NJ).

Compositions containing the compound(s) described herein suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be promoted by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Isotonic agents, for example, sugars, sodium

chloride, and the like may also be included. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration of the compounds described herein or derivatives thereof include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art. They may contain opacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration of the compounds described herein or derivatives thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol,

dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

Administration can be carried out using therapeutically effective amounts of the agents described herein for periods of time effective to treat or prevent infection in a subject. The effective amount may be determined by one of ordinary skill in the art and includes exemplary dosage amounts for a mammal of from about 0.5 to about 200mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.5 to about 150mg/kg of body weight of active compound per day, about 0.5 to 100mg/kg of body weight of active compound per day, about 0.5 to about 75mg/kg of body weight of active compound per day, about 0.5 to about 50mg/kg of body weight of active compound per day, about 0.5 to about 25mg/kg of body weight of active compound per day, about 1 to about 20mg/kg of body weight of active compound per day, about 1 to about 10mg/kg of body weight of active compound per day, about 20mg/kg of body weight of active compound per day, about 10mg/kg of body weight of active compound per day, or about 5mg/kg of body weight of active compound per day.

According to the methods taught herein, the subject is administered an effective amount of the compound. The terms effective amount and effective dosage are used interchangeably. The term effective amount is defined as any amount necessary to produce a desired physiologic response. Effective amounts and schedules for administering the agent may be determined empirically, and making such determinations is within the skill in the art. The dosage ranges for administration are those large enough to produce the desired effect in which one or more symptoms of the disease or disorder are affected (e.g., reduced or delayed). The dosage should not be so large as to cause substantial adverse side effects, such as unwanted cross-reactions, anaphylactic reactions, and the like. Generally, the dosage will vary with the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any contraindications.

Dosages can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products.

Any appropriate route of administration can be employed, depending on whether local or systemic treatment is desired, and on the area to be treated. The compositions are administered via any of several routes of administration, including topically, orally, parenterally, intravenously, intra-articularly, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally, intrahepatically, intracranially, nebulization/inhalation, or by installation via bronchoscopy. Optionally, the composition is administered by oral inhalation, nasal inhalation, or intranasal mucosal administration. Administration of the compositions by inhalant can be through the nose or mouth via delivery by spraying or droplet mechanism, for example, in the form of an aerosol. Pharmaceutical compositions can be delivered locally to the area in need of treatment, for example by topical application or local injection. Multiple administrations and/or dosages can also be used. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

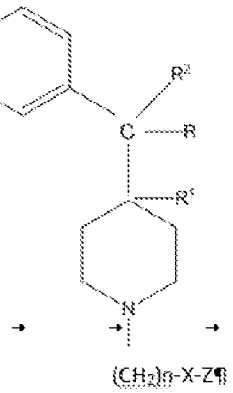
The disclosure also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. Instructions for use of the composition can also be included.

Also provided is a method of removing biofilm from a surface, comprising administering an effective amount of one or more of the compounds provided herein to a biofilm-containing surface, wherein the amount is effective to remove biofilm from the surface. Removal of the biofilm from this surface does not have to be complete as this can range from a reduction to complete removal of the biofilm. Thus, in the disclosed methods, removal can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the amount of biofilm on a surface. For example, a method for removing biofilm from a surface is considered to be removal if there is a 10% reduction in the amount of biofilm on the surface as compared to a control. A control surface can be a biofilm containing surface that has not received a compound set forth herein. Thus, the reduction can be a 10%, 20%,

30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to control.

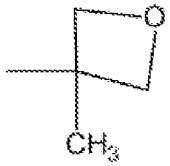
Further provided is a method of preventing biofilm formation on a surface comprising administering an effective amount of one or more of the compounds provided herein to the surface, wherein the amount is effective to prevent biofilm formation. The surface can be susceptible to biofilm formation. The biofilm can be produced by an organism selected from the group consisting of bacteria, algae, fungi and protozoa.

The compound can be, but is not limited to, a compound of Formula I



(I)

wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $-COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl

or a pharmaceutically acceptable salt thereof.

One or more of the compounds set forth herein can be combined with one or more biodegradable polymers to form a biodegradable antimicrobial composition. These compositions can be applied to a surface or used as a coating. The biodegradable polymers include but are not limited to polylactic acid, polyglycolic acid and copolymers and mixtures thereof such as poly(L-lactide) (PLLA), poly(D,L-lactide) (PLA), polyglycolic acid [polyglycolide (PGA)], poly(L-lactide-co-D,L-lactide) (PLLA/PLA), poly(L-lactide-co-glycolide) (PLLA/PGA), poly(D,L-lactide-co-glycolide) (PLA/PGA), poly(glycolide-co-trimethylene carbonate) (PGA/PTMC), poly(D,L-lactide-co-caprolactone) (PLA/PCL) and poly(glycolide-co-caprolactone) (PGA/PCL); polyethylene oxide (PEO), polydioxanone (PDS), polypropylene fumarate, poly(ethyl glutamate-co-glutamic acid), poly(tert-butyloxy-carbonylmethyl glutamate), polycaprolactone (PCL), polycaprolactone co-butylacrylate, polyhydroxybutyrate (PHBT) and copolymers of polyhydroxybutyrate, poly(phosphazene), polyphosphate ester), poly(amino acid), polydepsipeptides, maleic anhydride copolymers, polyiminocarbonates, poly[(97.5% dimethyl-trimethylene carbonate)-co-(2.5% trimethylene carbonate)], poly(orthoesters), tyrosine-derived polyarylates, tyrosine-derived polycarbonates, tyrosine-derived polyiminocarbonates, tyrosine-derived polyphosphonates, polyethylene oxide, polyethylene glycol, polyalkylene oxides, hydroxypropylmethylcellulose, polysaccharides such as hyaluronic acid, chitosan and regenerate cellulose, and proteins such as gelatin and collagen, and mixtures and copolymers thereof, among others as well as PEG derivatives or blends of any of the foregoing.

In the methods of removing or preventing biofilm formation, the surface can be a hard (for example, glass, metal, wood, chrome, plastic, vinyl or formica) or a soft surface (for example, cloth or upholstery). The methods set forth herein can be used to remove or prevent biofilm formation *in vitro*, *ex vivo* or *in vivo*. The methods set forth herein can also be used to

remove or prevent biofilm formation on a medical device or a part thereof. For example, the methods set forth herein can be used to remove or prevent biofilm formation on an implantable medical device such as a cardiac rhythm management device (for example, a pacemaker, a defibrillator, an implantable cardioverter defibrillator (ICD) and a cardiac resynchronization therapy defibrillator (CRT device), a neurostimulator, a pulse generator, a drug pump, an infusion device, a physiological monitoring device (for example, a glucose sensor), contact lenses, a stent, a catheter, tubing or a breast implant. Mesh, bandages, and implantable devices, for example, can be coated with a compositions comprising one or more of the compounds set forth herein. Further, organs can be treated with one or more of the compounds set forth herein prior to transplantation in a subject. One or more of the compounds set forth herein can be used to inhibit biofilm formation by one or more of *Staphylococcus aureus*, *Pseudomonas aeuroginosa*, *Staphylococcus epidermidis*, *Escherichia coli* or *Acinetobacter baummanii.*

As utilized herein, by preventing biofilm formation is meant a method of precluding, delaying, averting, obviating, forestalling, stopping, or hindering the onset, incidence, severity, or recurrence of biofilm formation. For example, the disclosed method is considered to be prevention if there is about a 10% reduction in onset, incidence, severity, or recurrence of biofilm formation on a surface when compared to a control surface that did not receive a composition for preventing biofilm formation. Thus, the reduction in onset, incidence, severity, or recurrence of biofilm can be about a 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between as compared to a control surface.

A biofilm can also exist or form in a biological subject, for example, on the teeth or gums of a subject. Therefore, one or more of the compounds set forth herein can be in a toothpaste, mouth rinse, gel, foam, varnish, polish, floss, dental strip, or copolymer membrane in order to remove or prevent biofilm formation on a dental surface.

Further provided herein is a method of identifying an antimicrobial agent comprising contacting a bacterial culture with a test agent and measuring adenylate kinase release in the supernatant of the bacterial culture, wherein an increase in adenylate kinase release as compared to a control indicates that the test compound is an antimicrobial agent. The control can be a bacterial culture that was not contacted with the test compound. The bacterial culture can be a culture of any bacterial strain, for example, a culture of any of the bacteria disclosed herein. The bacterial culture can also be small colony variant bacterial culture or a

biofilm associated bacterial culture. Examples of agents identified utilizing this method are provided in the Examples.

Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including in the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

Publications cited herein and the material for which they are cited are hereby specifically incorporated by reference in their entireties.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention except as and to the extent that they are included in the accompanying claims.

EXAMPLE I

Identification of antimicrobial compounds

Adenylate kinase (AK) is a ubiquitous intracellular enzyme that is released into the extracellular space upon cell lysis. As shown herein, AK release serves as a useful reporter of bactericidal agent activity and can be exploited for antimicrobial screening purposes. The AK

assay exhibits improved sensitivity over that of growth-based assays and can detect agents that are active against bacteria in clinically relevant growth states that are difficult to screen using conventional approaches, such as small colony variants (SCV) and bacteria within established biofilms. The usefulness of the AK assay was validated by screening a library of off-patent drugs for agents that exhibit antimicrobial properties toward a variety of bacterial species, including *Escherichia coli* and all members of the "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*). The assay detected antibiotics within the library that were expected to be active against the organism screened. Moreover, 38 drugs elicited AK release. Examples include, the antihistamine, terfenadine, which was active against *S. aureus* planktonic, SCV population, and biofilm-associated cells, to name a few. Tamoxifen, an estrogen receptor antagonist, was active toward *E. faecium in vitro* and also reduced *E. faecium* pathogenesis in a *Galleria mellonella* infection model. These data demonstrate that the AK assay provides an attractive screening approach for identifying new antimicrobial agents. Further, drugs identified using this screening approach, for example, terfenadine and tamoxifen, provide novel antimicrobial drug development scaffolds.

The ESKAPE pathogens frequently cause health care-associated bacterial infections and can escape the effects of most currently available antibiotics. The most successful and widely applied method to identify agents with antibacterial activity has been whole-cell, bacterial growth assays. In this approach, libraries of small molecules or natural products are screened for agents that limit bacterial growth. However, growth-based assays have limitations. For example, the growth or no-growth readout has a limited dynamic range. This is likely to be problematic because growth assays lack the sensitivity required to detect antimicrobial molecules that are present in low concentrations within complex natural product extract libraries or compounds with limited antimicrobial activity. While the latter would obviously not represent a molecule that could be directly translated to clinical use, these low-activity hits could provide structurally novel scaffolds suitable for medicinal chemistry-based optimization. In addition, traditional growth-based assays are not readily amenable to screening for agents that target bacteria within certain clinically relevant bacterial growth states, such as established biofilms and small-colony variants.

To address these limitations, provided herein is a high-throughput screen (HTS)-compatible whole-cell assay to detect agents that directly kill bacteria. The assay is based on the release of intracellular adenylate kinase (AK) into culture medium as a reporter of bacterial cell death. As shown herein, the AK assay exhibits improved sensitivity over that of conventional whole-cell growth assays and displays specificity for bactericidal agents. Further, the assay can be used to screen for agents that kill small-colony-variant bacteria and bacteria within established biofilms.

To validate the AK assay as an HTS-compatible screening platform, the Prestwick library of off-patent drugs was screened against *E. coli* and each of the ESKAPE pathogens. This library contains representative examples of nearly all classes of antibiotics, and the bactericidal agents within the library that were expected to be active against the organism screened were identified. Additionally, agents with no previously reported antibiotic activity were identified. Traditional MIC testing confirmed the antimicrobial properties of many of these molecules, showing that they could be repurposed as antimicrobials or serve as lead molecules for antibiotic development. Consistent with that prediction, it was shown that one of these compounds, tamoxifen, is active against *E. faecium* in a *Galleria mellonella* model of infection. Further, it was shown that terfenadine is active against planktonic, small-colony variant, and biofilm-associated *S. aureus*. Taken together, these data demonstrate that the AK assay provides a general approach to screening for new antimicrobial agents active against a variety of pathogens during planktonic and other disease-associated growth states.

Bacterial growth conditions- The bacterial species and strains used in these experiments are listed in Table 1. *S. aureus* strain UAMS-1112 (generous gift from M. Smeltzer, University of Arkansas Medical Center) is a stable small-colony variant of the common laboratory *S. aureus* strain 8325-4, which harbors a *hemB* deletion. Unless otherwise noted, bacteria were grown for 16 h in Mueller-Hinton (MH) (Becton, Dickinson, Franklin Lakes, NJ) or brain heart infusion (BHI) (Becton, Dickinson) medium at 37°C on a rotary shaker at 225 rotations per min (rpm) and then used to inoculate (1:100) fresh medium and processed, as described below.

Table 1-Bacterial Strains

Species	Strain	Relevant resistance[a]	Source or reference[b]
Enterococcus faecium	824-05	Amp, Cf, Cp, Cl, Mp, Tmp, Sul, Erm, Kan	Clinical isolate
Staphylococcus aureus	USA300-0114	Amp, Cf, Cl, Sul, Kan	6
	UAMS-1	ND	7
	UAMS-1112	Erm	Univ. of Arkansas
	RN4220	Cl	8
Klebsiella pneumoniae	cKP1	Amp, Cp, Sul, Erm, Van	9
Acinetobacter baumannii	98-37-09	Amp, Lz	10
Pseudomonas aeruginosa	PA01	Amp, Kan, Lz, Sul, Van	11
Enterobacter cloacae	PMD1001	Amp, Erm, Lz, Sul, Van	Clinical isolate
Escherichia coli	8295	Erm, Lz, Sul	Clinical isolate

[a] Abbreviations: ampicillin, Amp; colistin, Cl; ceftriaxone, Cf; ciprofloxacin, Cp; erythromycin, Erm; kanamycin, Kan; linezolid, Lz; meropenem, Mp; minocycline, Min; Sulfamethoxazole, Sul; vancomycin, Van; not determined, ND; Univ., university.

[b] Clinical isolates were obtained from the University of Rochester School of Medicine and Dentistry.

Chemicals- The Prestwick Chemical Library of molecules with known biological activities was acquired from Prestwick Chemical (Illkirch, France). ToxiLight BioAssay kits were obtained from Lonza (Basel, Switzerland). Terfenadine, suloctidil, clomiphene citrate, ceftriaxone, sulfamethoxazole, erythromycin, kanamycin, ciprofloxacin, rifampin, ampicillin, minocycline, tamoxifen, and trimethoprim were purchased from Sigma-Aldrich (St. Louis, MO). Meropenem, linezolid, and vancomycin were purchased from Thermo Fisher (Waltham, MA). Colistin was purchased from APP Pharmaceuticals (Schaumburg, IL).

MIC testing- MIC testing was performed to determine the antibiotic susceptibility profile of selected bacterial strains according to Clinical and Laboratory Standards (CLSI) protocols (Hindler et al. Antimicrobial susceptibility testing, section 5. Clinical microbiology procedures handbook, Vol. 1 America Society of Microbiology, Washington, DC (2010). Briefly, colonies of each bacterial species were collected from MH agar plates and suspended in individual tubes of MH medium to an optical density (600 nm) of 0.8. The resulting cultures were incubated at 37°C in a rotary shaker at 225 rpm to exponential phase (~1×10^8 CFU ml^{-1}) and then diluted in fresh MH medium to a cell density of ~3×10^7 CFU ml^{-1}. Ten microliters of the diluted cultures was added to 88 µl of MH medium in individual wells of a 96-well, round-bottom plate (Corning, Inc.), and 2 µl of a stock solution of the indicated reference antibiotic or test compound (0 to 256 µg ml^{-1}) was added to each well. The carrier solvent was either water or dimethyl sulfoxide (DMSO); final DMSO concentrations were less than or equal to 2%. Plates were incubated at 37°C for 24 h, and the MIC was defined as the lowest concentration of antibiotic in which there was no visible cell pellet in the wells.

Heat-killed bacterial AK release assays- Overnight cultures of *E. coli* strain 8295 or *S. aureus* RN4220 were used to inoculate (1:100 dilution) 25 ml of fresh MH medium and grown at 37°C on a rotary shaker at 225 rpm to exponential phase (~1×10^8 CFU ml^{-1}). Cells were pelleted by centrifugation (2,000 × *g*) and resuspended in 2.5 ml of sterile water. One milliliter of the resulting suspension was boiled for 3 min and filter sterilized (0.45-µm filter) to remove cell debris. The filtrate was serially diluted in sterile water, and 100 µl of each dilution was added to individual wells of a white-walled, 96-well plate (Corning, Inc., Corning, NY). To measure the AK activity in the supernatants at each dilution, 100 µl of ToxiLight AK reagent was added to each well, followed by incubation at room temperature for 30 min, and luminescence was measured using a SpectraMax M5 plate reader (Molecular Devices, Sunnyvale, CA). Cells were serially diluted and plated to enumerate CFU (CFU ml^{-1}) before and after boiling to correlate cell lysis with viability.

AK assay 96-well format- Overnight cultures of each bacterial species were used to inoculate (1:100 dilution) 25 ml of fresh MH medium and grown at 37°C on a rotary shaker at 225 rpm to exponential phase (~1×10^8 CFU ml^{-1}). Ninety-eight microliters of MH medium, 2 µl of the indicated antibiotic, and 5×10^6 bacteria were added to individual wells of a white-walled, 96-well microtiter plate. Well components were mixed by pipetting and incubated at 37°C for 3 h. The plate was equilibrated to room temperature for 30 min. Next,

100 µl of ToxiLight AK reagent was added to each well and incubated at room temperature for 30 min, and luminescence was measured using a SpectraMax M5 plate reader.

AK assay 384-well format and high-throughput screening- Overnight cultures of each bacterial species were used to inoculate (1:100 dilution) 25 ml of fresh medium and grown at 37°C on a rotary shaker at 225 rpm to exponential phase (~1×10^8 CFU ml^{-1}). In a white-walled, 384-well plate, 24 µl of MH medium, 0.3 µl (50 µM) of antibiotic or compound, and 5×10^6 bacteria were added to individual wells and incubated at 37°C for 3 h. The plates were equilibrated at room temperature for 1 h. Twenty-five microliters of ToxiLight AK reagent was then added to each well, followed by incubation at room temperature for 30 min, and luminescence was measured using a SpectraMax M5 plate reader.

AK assay of established biofilms- Biofilms were grown as previously described (Beenken et al. *Infect. Immun.* 71: 4206-4211 (2003); Musken et al. *Nat. Protoc.* 5: 1460-1459 (2010); Tomaras et al. *Microbiology* 149: 3473-3483 (2003)). Briefly, *P. aeruginosa* and *A. baumannii* were cultured overnight in Luria-Bertani medium and then used to seed 96-well, flat-bottom plates. Plates were incubated at 37°C in a humidified incubator for 48 h to allow the formation of static biofilms. Nonadherent cells were removed by aspiration and washing with sterile phosphate-buffered saline (PBS). Fresh LB medium supplemented with 0, 1×, 10×, or 100× MIC of antibiotic was added to each well and incubated overnight at 37°C. Following treatment, 100 µl of each biofilm supernatant was transferred to 96-well, white-walled plates, 100 µl of ToxiLight AK reagent was added to each well, mixtures were incubated for 30 min at room temperature, and luminescence was measured using a SpectraMax M5 plate reader. Biofilm-associated bacteria were enumerated by resuspending each biofilm in fresh PBS and plating. For *S. aureus* UAMS-1 biofilms, 96-well, flat-bottom plates were first coated with 100 µl of 20% human plasma in carbonate buffer overnight at 4°C. Following coating, the plasma solution was removed and cells were inoculated in each well 1:200 in 100 µl of tryptic soy broth supplemented with 3% glucose and 0.5% NaCl. Biofilms were cultured for 48 h in a humidified incubator at 37°C. Established *S. aureus* biofilms were washed once with PBS and then treated with a 100 µl of ToxiLight lysis buffer for 3 h, after which the amount of AK released into supernatants was measured, as described above.

Small-colony variant AK assays- Thirty-six-hour cultures of *S. aureus* strain UAMS-1112 were used to inoculate (1:100 dilution) 100 ml of fresh MH medium and grown at 37°C on a

rotary shaker at 225 rpm to an optical density (600 nm) of 0.1 to 0.2, corresponding to ~1 × 10^6 CFU ml^{-1}. Cells were pelleted by centrifugation and resuspended in 2 ml of fresh MH medium. Ninety-eight microliters of MH medium containing 5 × 10^6 bacteria and 2 µl of the indicated antibiotic were added to individual wells of a white-walled, 96-well microtiter plate. Well components were mixed by pipetting and incubated at 37°C for 3 h. The plate was equilibrated to room temperature for 30 min. Next, 100 µl of ToxiLight AK reagent was added to each well, followed by incubation at room temperature for 30 min, and luminescence was measured using a SpectraMax M5 plate reader.

***Galleria mellonella* model of *S. aureus* infection-** A *Galleria mellonella* model of infection was used to measure the putative antimicrobial properties of tamoxifen against *E. faecium* and terfenadine against *S. aureus*. To do so, overnight cultures of *E. faecium* strain 824-05 or *S. aureus strain* USA300-0114 were used to inoculate (1:100 dilution) 25 ml of fresh MH medium and grown at 37°C on a rotary shaker at 225 rpm to exponential phase (~1 × 10^8 CFU ml^{-1}). Cultures were pelleted by centrifugation (2,000 × *g*), washed with sterile PBS, and resuspended at ~1 × 10^9 CFU ml^{-1} in fresh PBS. *Galleria mellonella* larvae (Vanderhorst Wholesale, Inc.; St. Marys, OH) weighing 200 to 300 mg were inoculated with 5 µl of *E. faecium* or *S. aureus* (5 × 10^6 CFU) into the last left proleg using a 10-µl Hamilton syringe. Worms were then mock treated with either DMSO (negative control), vancomycin (20 mg kg^{-1}; positive control) at 2 h and 24 h postinoculation. For *E. faecium* studies, groups were also treated with the test compound tamoxifen at 80, 160, or 320 mg kg^{-1}, whereas groups were treated with the test compound terfenadine (80, 160, or 320 mg kg^{-1}) for *S. aureus* studies. Treatments were administered in the same manner as infection, except that each injection was in the next left proleg moving toward the head of the worm. Larvae were housed in petri dishes in the dark at 37°C and monitored for viability at the conclusion of the study (48 h postinoculation); worms were considered dead if they did not respond to physical stimuli. In addition to mock or compound treatment of infected larvae, studies included two additional noninfected negative-control groups: one group that did not receive injections and one group that was injected with PBS to control for the impact of physical trauma. All experimental groups contained 15 worms, and each experiment was repeated three times.

Rationale for adenylate kinase as a reporter of bacterial cell lysis- Adenylate kinase (AK) is a ubiquitous intracellular enzyme that catalyzes the conversion of 2 ADP ↔ ATP + AMP and is released into the extracellular space upon cell lysis. The premise of the assay is that

agents which disrupt cellular integrity, either directly through damage of the membrane/cell wall or indirectly following the death of the cell, will induce release of AK into the culture medium. Extracellular AK is subsequently detected by the addition of commercially available ToxiLight AK assay reporter cocktail (Lonza, Basel, Switzerland), which generates a luminescent signal by utilizing AK-generated ATP in the standard luciferase catalyzed reaction (see Fig. 1). As shown herein, an AK assay was developed as a high-throughput screening platform for antibacterial drug discovery.

The AK assay provides a sensitive measure of bacterial lysis- As an initial test of AK release as a reporter of bacterial cell death for Gram-positive and Gram-negative organisms, the sensitivity with which the assay measures AK in the culture supernatants of heat-killed *E. coli* and S. aureus was determined. Each bacterial species was grown to exponential phase, harvested, and resuspended at 1×10^9 CFU per ml in Mueller-Hinton (MH) medium. Bacterial suspensions were heat killed, and a 10-fold dilution series of supernatants was prepared; an aliquot of each heat-killed sample was plated to ensure ≥99% bacterial death. The AK activity of the dilution series was measured and compared to the AK activity of mock-treated (viable) bacteria by Student's *t* test. In comparison to untreated cells, a statistically significant increase in AK activity was detected at dilutions containing 1.7×10^3 or more heat-killed *E. coli* supernatants, compared to results for live bacteria (see Fig. 2A). AK activity increased ~433-fold and ~1,574-fold in cultures with 1×10^7 and 1×10^8 heat-killed *E. coli* supernatants, respectively, compared to results for mock-treated bacteria. A comparison of AK released from heat-killed *S. aureus* to that of mock-treated cells revealed a statistically significant difference in AK activity was detected at dilutions containing 1.8×10^4 or more heat-killed *S. aureus* supernatants, with a maximum 122-fold increase in AK activity observed for 1×10^8 lysed cells. Taken together, these results indicate that the AK assay reproducibly detects AK release following bacterial cell lysis and that the assay is extremely sensitive, allowing the identification of agents that cause lysis in 0.0001% or 0.001% of the starting inoculum of *E. coli* or *S. aureus* cells, respectively. Furthermore, the AK assay exhibited a dynamic range of nearly 3 orders of magnitude and an excellent signal-to-noise ratio.

The AK assay detects bactericidal molecules that are active against the ESKAPE pathogens- Next, ability of the AK assay to detect the activities of bactericidal antibiotics toward *E. coli* and each of the ESKAPE pathogens was examined. To do so, the MICs of six classes of bactericidal antibiotics (penicillin, cephalosporin, quinolone, glycopeptide,

carbapenem, and polymyxin) were determined for each organism (see Table 2). An AK assay was then performed at 0, 0.125×, 0.25×, 0.5×, 1×, and 2× MIC of each antibiotic. As discussed below, AK release was detected at antibiotic concentrations below the MIC for most antibiotics tested, showing that the AK assay is more sensitive than growth-based assays for detecting bactericidal agents. As a representative example, Fig. 2B presents the AK assay measured polymyxin (colistin)-mediated killing of *A. baumannii* strain 98-37-09. The MIC of colistin for this strain is 4 $\mu g\ ml^{-1}$, whereas AK release was robustly detected at 0.25×, 0.5×, and 1× MIC value.

TABLE 2

MIC and AK measures of bacterial species and antibiotic combinations[a]

Strain and parameter	Treatment (× MIC)	Value for agent										
		Bactericidal						Bacteriostatic				
		Ampicillin	Ceftriaxone	Ciprofloxacin	Vancomycin	Meropenem	Colistin	Sulfamethoxazole	Minocycline	Erythromycin	Kanamycin	Linezolid
Enterococcus faecium 824-05												
MIC		>256	>256	256	2	>256	>256	>256	1	>256	>256	16
Fold increase in AK signal	0.5	ND	ND	ND	1	ND	ND	ND	3	ND	ND	2
	1.0	ND	ND	ND	2	ND	ND	ND	4	ND	ND	2
Staphylococcus aureus												
USA300-0114												
MIC		>256	>256	2	1	4	>256	>256	1	64	>256	2
Fold increase in AK signal	0.5	ND	ND	3	11	13	ND	ND	1	1	ND	1
	1.0	ND	ND	5	3	17	ND	ND	1	1	ND	1
RN4220												
MIC		2	2	2	2	2	>256	2	8	2	16	2
Fold increase in AK signal	0.5	4	10	8	3	11	ND	2	1	1	1	1
	1.0	3	12	10	6	11	ND	3	1	1	1	1
Klebsiella pneumoniae cKP1												
MIC		>256	2	>256	>256	2	8	>256	64	>256	2	>256
Fold increase in AK signal	0.5	ND	50	ND	ND	128	34	ND	1	ND	1	ND
	1.0	ND	55	ND	ND	220	33	ND	1	ND	1	ND
Acinetobacter baumannii 98-37-09												
MIC		256	8	0.0625	64	2	4	8	1	16	2	256
Fold increase in AK signal	0.5	ND	5	2	2	79	17	6	23	3	3	ND
	1.0	ND	21	2	4	134	49	5	14	12	14	ND
Pseudomonas aeruginosa PA01												
MIC		>256	4	2	>256	2	4	256	32	32	256	>256

Strain and parameter	Treatment (× MIC)	Value for agent										
		Bactericidal						Bacteriostatic				
		Ampicillin	Ceftriaxone	Ciprofloxacin	Vancomycin	Meropenem	Colistin	Sulfamethoxazole	Minocycline	Erythromycin	Kanamycin	Linezolid
Fold increase in AK signal	0.5	ND	2	27	ND	45	5	ND	1	3	ND	ND
	1.0	ND	14	182	ND	39	12	ND	6	1	ND	ND
Enterobacter cloacae PMD1001												
MIC		>256	2	<1	>256	2	2	>256	4	256	2	>256
Fold increase in AK signal	0.5	ND	20	6	ND	99	10	ND	4	ND	1	ND
	1.0	ND	17	7	ND	296	32	ND	9	ND	1	ND
Escherichia coli 8295												
MIC		128	2	0.125	16	2	8	>256	16	256	32	>256
Fold increase in AK signal	0.5	50	51	17	1	60	15	ND	4	ND	55	ND
	1.0	74	76	39	2	85	22	ND	38	ND	70	ND
% increase expected	0.5	100	83.3	83.3	40	100	100	50	50	50	40	0
	1.0	100	100	83.3	60	100	100	100	62.5	25	40	0

a Shading indicates significant increase in AK signal (greater than or equal to threefold over vehicle-treated cells).

The MIC measures for each ESKAPE pathogen and each organism's corresponding fold increase in AK signal following treatment with 0.5× and 1.0× the MIC are provided in Table 2 (bactericidal agents). For four of the six bactericidal antibiotics tested, the AK assay proved to be superior to growth-based assays with respect to detecting the killing properties of bactericidal agents at sub-MIC values. More specifically, 100% of the organisms that were determined to be susceptible to the cell wall-active antibiotics ampicillin, meropenem, and colistin exhibited a significant increase in AK signal (≥3-fold over that for vehicle-treated cells) at both 0.5× and 1.0× their MICs. Eighty-three percent and 100% of ceftriaxone-susceptible species exhibited increased AK signal at 0.5× and 1× their MICs, respectively. Five of six (83%) ciprofloxacin-susceptible organisms exhibited AK signal at both 0.5× and 1.0× MIC. Interestingly, the cell wall-targeted glycopeptide, vancomycin, caused significant AK release at 0.5× and 1.0× their MICs in only 40% and 60% of susceptible species.

To evaluate the specificity of the assay for detecting bactericidal agents, measured AK release by each of the ESKAPE pathogens following exposure to five classes of bacteriostatic agents (sulfonamide, tetracycline, macrolide, aminoglycoside, and oxazolidine) was also measured. To do this, the MIC value of each bacteriostatic antibiotic/organism pair was measured by a conventional growth-based approach. AK release by each bacterial species following treatment with 0.5× or 1.0× MIC of each bacteriostatic agent was subsequently measured. As shown in Fig. 3, *S. aureus* strain RN4220 was susceptible to all agents tested but bacteriostatic agents generated very low AK release, whereas bactericidal antibiotics generated robust AK detection. In most instances, a similar trend was observed for the other ESKAPE pathogens, indicating that the assay enriches for the identification of bactericidal agents, which are arguably the most valuable antibiotics because they can be used to treat patients with immunological defects or rapidly lethal infections (Table 2, bacteriostatic agents). Two exceptions were noted. Surprisingly, *A. baumannii* generated significant AK signal in response to all the bacteriostatic agents evaluated, showing that AK release may be a feature of a more general stress response in this organism. Additionally, the bacteriostatic agent minocycline generated signal by five of the eight (63%) organisms tested.

Taken together, these results show that the AK assay provides a viable screening approach for identifying bactericidal agents at sub-MICs that could otherwise be missed by growth-based assays. Further, because the AK assay relies on bacterial killing as opposed to

growth changes to generate its readout, it was hypothesized that it would provide a format to develop screens that are not readily available by conventional, growth-based approaches.

Use of the AK assay to identify agents with antimicrobial activities against established biofilms and small colony variants- Established bacterial biofilms represent a particularly problematic disease state, in part because biofilm-associated bacteria are recalcitrant to conventional antibiotic therapy. Thus, they have been a focus of antibiotic development. As a result, a number of approaches to screening for molecules with activity toward bacterial biofilms have been developed recently (Benoit et al. *Environ. Microb.* 76: 4136-4142; Perez et al. *Lett. Appl. Microb.* 51:331-337 (2010)). Although each has its advantages, they also have a number of limitations, including reproducibility, reliance on specialized equipment, or low throughput. It was hypothesized that the AK assay would provide a solution to some of these problems because it is rapid, sensitive, and simple to perform and it detects bactericidal molecules, the type of antibiotics required to treat established biofilms.

To determine whether the AK assay could detect agents with activity against established biofilms, S. *aureus* strain UAMS-1, *A. baumannii* strain 98-37-09, and *P. aeruginosa* strain PAO1 static biofilms were formed in 96-well flat-bottom plates. Forty-eight hours postinoculation, one well corresponding to each organism was stained with crystal violet to verify that biofilm formation had occurred, whereas the remaining wells were treated with 10× the MIC value with either colistin (*A. baumannii* biofilms) or ciprofloxacin (*P. aeruginosa*, and *S. aureus* biofilms). Following overnight antibiotic treatment, biofilm-associated bacteria were enumerated by plating, and the corresponding supernatants were analyzed by the AK assay. Plating verified that 10× MIC antibiotic treatment resulted in a significant reduction in biofilm-associated *P. aeruginosa* (a 3.1-log decrease), *S. aureus* (a 0.7-log decrease), and *A. baumannii* (a 1.8-log decrease) compared to findings for untreated biofilms. As shown in Fig. 4A, corresponding AK measures indicated that the assay robustly detects the mild effects of these antibiotics on each bacterial species tested, showing that it represents a promising approach to identify agents that exhibit bactericidal activity toward established bacterial biofilms.

Another context in which the AK assay can be particularly valuable is in the identification of molecules that exhibit bactericidal activity toward bacterial small-colony variants (SCV). SCV are slow-growing populations of bacterial species that have been hypothesized to cause latent or recurrent infections and are tolerant of standard antibiotic

treatment regimens. Based on the aberrant SCV growth characteristics, typical growth-based HTS assays would be difficult to employ. Accordingly, the ability of the AK assay to identify agents that kill *S. aureus* SCV strain UAMS-1112 was tested. To do so, 1×10^6 UAMS-1112 cells were treated with 1× or 10× MIC ciprofloxacin, meropenem, or vancomycin for 3 h. Following treatment, suspensions were plated to measure the antimicrobial properties of each antibiotic, and the AK assay was performed to measure adenylate kinase release. Plating revealed that ciprofloxacin and vancomycin had no effect on SCV viability at any concentration tested and exhibited no change in AK release in comparison to results for mock-treated cells (Fig. 4B), supporting the observation that *S. aureus* small-colony variants are recalcitrant to antibiotic treatment. Meropenem treatment resulted in a 0.5-log decrease in SCV viability, which corresponded to a 2.5-fold increase in AK signal compared to that for mock-treated cells (Fig. 4B). Taken together, these results show that the AK assay provides the sensitivity needed to detect the slight antimicrobial effects of antibiotics, such as meropenem, toward *S. aureus* SCV.

Validation of AK as an HTS-compatible assay of antibacterial activity- To test the viability of the AK assay as a general tool in HTS-based antibacterial small-molecule discovery, optimized assay parameters, including inoculum, drug incubation time, and AK reaction time, for screening planktonic ESKAPE species as well as *E. coli* in a 384-well format were determined. Based on these experiments, a standardized assay, as described above, was developed. As part of this optimization process, control assays in a 384-well format were performed to measure the signal to noise and reproducibility of the assay in an HTS manner. For this, plates were seeded with *E. coli* or an ESKAPE pathogen. Alternating columns of the plate were then mixed with either 2% DMSO (negative control) or a bactericidal antibiotic (positive control), and AK signal was detected; a representative result for DMSO- and colistin-treated *K. pneumoniae* is shown in Fig. 5A. Comparisons of the variance in signal between positive- and negative-control measures indicated that the AK assay provides Z′-factor scores between 0.59 and 0.82 (depending on the specific organism), indicating that the assay is sufficiently robust for HTS.

AK-based screening of library of off-patent drugs and biologically active molecules- To further validate the AK assay protocol, *E. coli* and each of the ESKAPE pathogens was screened against the Prestwick library of FDA-approved drugs and biologically active molecules (1,120 compounds, total; 50 μM final drug concentration). The Prestwick library contains representatives of nearly all classes of antibiotics currently in clinical use, making it

an ideal library for testing the ability of the AK assay to detect bactericidal agents in a high-throughput screening format. Accordingly, the library was screened for antimicrobial agents that were active against planktonic *E. coli* and each of the ESKAPE pathogens using the AK assay; the cutoff for positive-scoring molecules was set at a 3-fold increase in extracellular AK activity, corresponding to the detection limit of statistically significant increases in AK activity for planktonic bacteria. The hit rates for the different organisms ranged from 1.4% to 4.8%; a representative example of raw screening data for *Klebsiella pneumoniae* is shown in Fig. 5B. Screening results for all ESKAPE pathogens are summarized in Table 3, whereas results for all compounds within the Prestwick library are provided in Table 4.

Table 3- Preswick library screening results

Compound	No. of active agents for species						
	E. coli	*E. faecium*	*S. aureus*[a]	*K. pneumoniae*	*A. baumannii*[a]	*P. aeruginosa*	*E. cloacae*
Bactericidal	45	4	25	19	17	21	16
Bacteriostatic	2	1	14	0	7	0	1
Detergent	2	2	2	2	2	1	0
Other	5	9	10	4	18	1	12
Total	54	16	51	25	44	23	29

[a] Tetracyclines were identified.

Table 4 AK-based Prestwick Library Screening Results.

E. coli	*E. faecium*	*S. aureus*	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*	*E. cloacae*	Chemical name	Mechanism	Therapeutic group
0.4	0.8	0.6	0.3	0.3	0.3	0.3	Azaguanine-8	Purine antimetabolite	Antineoplastic
0.4	0.8	0.4	0.4	0.4	0.3	0.3	Metronidazole	Bacterial DNA damage	Antibacterial
0.4	0.7	1.4	0.4	0.4	0.3	0.3	Allantoin	Precipitate proteins	Vulnerary
0.5	0.8	0.4	0.4	0.3	0.3	0.3	Cotinine (-)		Antidepressant
0.4	0.9	0.4	0.4	0.4	0.3	0.3	Acetazolamide	Carbonic anhydrase inhibitor	Diuretic
0.4	0.8	0.4	0.5	0.4	0.4	0.3	Edrophonium chloride	Cholinergic	Myasthenia Gravis test
0.5	0.8	0.4	0.4	0.4	0.3	0.3	Metformin hydrochloride	-	Antidiabetic
0.5	0.8	0.4	0.4	0.4	0.3	0.3	Moroxidine hydrochloride	-	Antiviral
0.5	0.8	0.5	0.5	0.4	0.4	0.3	Atracurium besylate	Neuromuscular blocking agent	Curarizing agent
0.5	0.8	0.4	0.6	0.4	0.3	0.3	Baclofen (R,S)	GABAb agonist	Antispasmodic
0.5	0.9	0.4	0.5	0.4	0.4	0.4	Isoflupredone acetate		Anti-inflammatory
0.5	0.9	0.5	0.5	0.4	0.4	0.3	Acyclovir	ADN polymerase inhibitor	Antiviral
0.5	0.8	0.4	0.4	0.4	0.3	0.4	Amiloride hydrochloride dihydrate	Antialdosteron	Diuretic
0.5	0.9	0.5	0.4	0.4	0.4	0.4	Diazoxide	Activator of ATP-dependent K+ channels	Antihypertensor
0.5	0.9	0.5	0.6	0.5	0.4	0.4	Amprolium hydrochloride	Thiamine transport inhibitor	Coccidiostatic
0.5	0.9	0.4	0.5	0.4	0.4	0.4	Amidopyrine	ACTH secretor	Antipyretic

0.5	1.1	0.5	0.6	0.5	0.5	0.4	Hydrochlorothiazide	Na+ Cl- transport inhibitor	Diuretic
0.4	2.8	0.1	0.4	0.5	0.4	0.5	Ursolic acid	-	Diuretic
0.5	1.0	0.5	0.6	0.5	0.5	0.4	Sulfaguanidine	Inhibitor of folic acid synthesis	Antibacterial
0.5	1.0	0.5	0.6	0.5	0.4	0.4	Pindolol	Beta adrenergic antagonist	Antiarrhythmic
0.6	1.0	0.7	0.6	0.6	0.6	0.6	Isoniazid	-	Antibacterial
0.6	0.9	0.7	0.6	0.5	0.7	0.7	Mexiletine hydrochloride	Na+ channel blocker	Antiarrhythmic
0.6	1.0	0.7	0.5	0.6	0.7	0.6	Pentylenetetrazole	GABA antagonist	CNS stimulant
0.5	0.9	0.6	0.6	0.5	0.6	0.6	Flavoxate hydrochloride	Phosphodiesterase inhibitor	Antispasmodic
0.6	0.9	0.5	0.5	0.6	0.6	0.6	Chlorzoxazone	-	Muscle relaxant
0.5	0.9	0.4	0.5	0.5	0.5	0.6	Bufexamac	-	Antiinflammatory
0.6	0.9	0.5	0.5	0.6	0.6	0.6	Ornidazole	Bacterial DNA damage	Antibacterial
0.5	0.9	0.5	0.6	0.6	0.6	0.5	Glutethimide, para-amino	Aromatase inhibitor	Antineoplasic
0.6	0.9	0.5	0.6	0.5	0.5	0.6	Ethosuximide	Ca++ channel inhibitor voltage dependant	Anticonvulsant
0.7	0.9	0.5	0.5	0.5	0.5	0.5	Dropropizine (R,S)	-	Antitussive
0.6	1.2	0.6	0.5	0.5	0.5	0.6	Mafenide hydrochloride	Inhibitor of folic acid biosynthesis	Antibacterial
0.5	0.9	0.5	0.5	0.5	0.5	0.6	Pinacidil	K+ channel Ca++ dependant activator	Vasodilatator
0.2	0.3	0.2	0.2	0.2	0.2	0.5	Riluzole hydrochloride	Glutamate antagonist	Neuroprotective
0.3	0.5	0.2	0.3	0.3	0.3	0.4	Albendazole		
0.4	1.0	0.4	0.8	0.5	0.4	0.6	Nitrofurantoin	Bacterial DNA damage	Urinary antiseptic

0.5	0.9	0.5	0.5	0.6	0.5	0.6	Clonidine hydrochloride	Alpha2 agonist	Antihypertensor
0.0	0.3	0.2	0.0	0.1	0.0	0.3	Hydralazine hydrochloride	Adrenergic antagonist	Antihypertensor
0.5	1.0	0.5	0.5	0.5	0.5	0.5	Bupropion hydrochloride	-	Antidepressant
0.5	0.8	0.5	0.6	0.5	0.5	0.5	Phenelzine sulfate	MAO inhibitor	Antidepressant
0.6	0.9	0.6	0.5	0.7	0.5	0.4	Alprenolol hydrochloride	Beta1 antagonist	Antihypertensor
0.6	0.9	0.8	0.5	0.8	0.6	0.7	Meticrane	Na+ channel blocker	Antihypertensor
0.6	0.9	0.7	0.6	0.7	0.7	0.7	Khellin	-	Phototherapeutic agent
0.7	0.8	0.7	0.6	0.7	0.6	0.7	Benzonatate		Antitussive
0.7	0.9	0.8	0.5	0.7	0.6	0.8	Zimelidine dihydrochloride monohydrate	5-HT uptake inhibitor	Antidepressant
0.7	0.9	0.5	0.5	0.7	0.5	0.7	Hydroflumethiazide	Na+ Cl- transport inhibitor	Antihypertensor
0.6	0.9	0.7	0.6	0.6	0.6	0.9	Azacyclonol	H1 antagonist	Anxiolytic
0.6	0.9	0.7	0.5	2.2	0.5	0.7	Sulfacetamide sodic hydrate		Antipsoriasic
0.6	0.8	0.7	0.5	0.7	0.6	0.8	Azathioprine	Antimetabolite	Immunosuppressant
0.8	0.9	0.7	0.5	0.6	0.5	0.7	Heptaminol hydrochloride	-	Antihypotensive
0.7	0.9	0.5	0.6	1.4	0.6	0.7	Lynestrenol	Antioestrogen	Progestogen
0.7	0.9	0.6	0.6	1.0	0.6	0.7	Sulfathiazole	Inhibitor of folic acid synthesis	Antibacterial
0.7	1.0	0.5	0.4	0.8	0.6	0.7	Guanabenz acetate	Alpha agonist	Antihypertensor
0.6	0.8	0.5	0.6	0.7	0.5	0.8	Levodopa	Tyrosine aminotransferase inhibitor	Antiparkinsonian
0.9	1.0	1.1	0.6	1.0	0.6	0.7	Disulfiram	Dopamine beta-hydroxylase inhibitor	Alcohol deterrent

0.7	1.0	0.7	0.6	0.7	0.6	0.8	Idoxuridine	Nucleic acid synthesis inhibitors	Antiviral
0.6	1.0	0.7	0.6	0.7	0.6	0.8	Acetylsalicylsalicylic acid	Cyclooxygenase inhibitor	Antiinflammatory
0.7	1.0	0.7	0.6	0.8	0.6	0.8	Captopril	Angiotensive converting enzyme inhibitor	Antihypertensor
0.7	0.9	0.7	0.6	0.8	0.8	0.7	Mianserine hydrochloride	5-HT antagonist	Antidepressant
0.6	1.0	0.7	0.6	0.8	0.6	0.7	Minoxidil	K+ channel activator	Antihypertensor
0.6	0.9	0.6	0.5	0.6	0.6	0.7	Nocodazole	Microtubule poison	Antineoplastic
0.8	1.1	0.7	0.7	0.8	0.9	0.9	Tranexamic acid	Plasminogen inhibitor	Hemostatic
0.9	1.0	0.8	0.7	0.9	0.9	0.9	Chlorothiazide	Na+ Cl- transport inhibitor	Antihypertensor
0.8	1.0	0.8	0.6	0.8	0.7	0.9	Etofylline	Phosphodiesterase inhibitor	Cardiac analeptic
0.8	1.0	0.7	0.7	0.7	0.8	0.8	Diphenidol hydrochloride	-	Antivertigo
0.8	1.0	0.8	0.6	0.9	0.8	0.9	Tranylcypromine hydrochloride	MAO inhibitor	Antidepressant
0.7	1.0	0.8	0.7	0.7	0.8	0.9	Norethindrone	-	Progestogen
0.9	0.9	0.7	0.7	0.9	0.8	0.9	Alverine citrate salt	Anticholinergic	Spasmolytic
0.9	0.9	1.0	0.7	0.9	0.8	0.9	Nortriptyline hydrochloride	Norepinephrine uptake inhibitor	Antidepressant
0.7	1.0	0.7	0.6	0.7	0.8	0.8	Aceclofenac	Cyclooxygenase inhibitor	Antiinflammatory
0.6	0.9	0.7	0.6	0.7	0.7	0.8	Niflumic acid	Prostaglandine synthesis inhibitor	Analgesic
0.8	1.0	1.0	0.7	0.7	0.7	0.8	Iproniazide phosphate	Monoamine oxydase inhibitor (non selective)	Antidepressant
0.7	1.0	0.6	0.6	0.7	0.8	0.9	Isotretinoin	-	Cystic acne

0.7	1.0	0.7	0.6	1.3	0.7	0.7	Sulfamethoxazole		
0.7	1.0	0.8	0.6	0.8	0.7	0.9	Retinoic acid	-	Keratolytic
0.7	1.0	0.8	0.7	0.8	0.6	0.8	Mephenesin	-	Muscle relaxant
0.7	1.0	0.8	0.6	0.8	0.7	0.8	Antazoline hydrochloride	H1 antagonist	Antihistaminic
0.8	1.0	0.7	0.6	0.8	0.7	0.8	Phenformin hydrochloride	Neoglucogenese inhibitor	Antidiabetic
0.7	1.3	1.4	0.6	0.8	0.7	0.8	Ethacrynic acid	Na+ Cl- uptake inhibitor	Diuretic
0.7	1.0	0.4	0.6	0.7	0.8	0.7	Flutamide	Androgenic receptor antagonist	Anticancer
0.9	1.0	0.8	0.6	0.7	0.6	0.7	Praziquantel	Modulates cell membrane permeability	Anthelmintic
0.8	0.8	0.8	0.7	1.4	0.8	0.8	Sulfaphenazole	Inhibitor of folic acid synthesis	Antibacterial
0.8	0.8	0.9	0.8	0.8	0.6	0.9	R(-) Apomorphine hydrochloride hemihydrate	D1 agonist	Emetic
0.9	0.8	0.6	0.7	0.8	0.7	1.0	Panthenol (D)	-	Vitamin
1.0	0.9	0.7	0.8	0.8	0.9	0.9	Amoxapine	Dopamine-reuptake inhibitor	Antidepressant
1.0	0.8	0.7	0.7	1.2	0.8	0.9	Sulfadiazine	Inhibitor of folic acid synthesis	Antibacterial
0.9	0.9	0.6	0.6	0.9	0.9	0.9	Cyproheptadine hydrochloride	5-HT antagonist	Antipruritic
0.9	0.9	0.7	0.7	0.7	0.8	1.0	Norethynodrel	-	Progestogen
0.9	0.8	0.5	0.8	0.8	0.8	1.0	Famotidine	H2 histaminic antagonist	Antiulcerative
0.9	0.9	0.7	0.4	0.9	0.8	1.4	Thiamphenicol	Ribosomal protein synthesis inhibitor	Antibacterial

0.7	0.9	0.6	0.6	0.9	0.8	0.9	Danazol	Estrogen antagonist	Antigonadotropin
0.9	0.9	0.8	0.7	0.8	0.8	1.0	Cimetidine	H2 antagonist	Antiulcer
0.9	0.9	0.6	0.8	0.8	0.7	0.9	Nicorandil		Antihypertensor
0.8	0.9	0.7	0.6	0.8	0.8	1.0	Doxylamine succinate	H1 antagonist	Antihistaminic
0.9	1.0	0.8	0.7	1.0	0.8	1.1	Tomatine		Antifungal
0.9	0.9	0.6	0.7	0.8	0.7	1.1	Ethambutol dihydrochloride	Chelating agent	Antibacterial
0.9	0.9	0.7	0.8	0.8	0.8	1.0	Nomifensine maleate	Dopamine uptake inhibitor	Antidepressant
0.9	1.0	0.7	0.7	1.0	0.8	1.0	Antipyrine	-	Analgesic
0.9	0.9	0.7	0.7	0.8	0.9	1.0	Dizocilpine maleate	Probe for NMDA receptors	-
0.9	1.0	0.7	0.7	0.8	0.8	1.0	Antipyrine, 4-hydroxy	-	Antipyrine metabolite
0.9	1.0	0.8	0.7	0.8	0.9	0.9	Acenocoumarol	Vitamin K antagonist	Anticoagulant
0.9	1.0	0.8	0.7	0.9	1.0	1.0	Ampyrone	-	Analgesic
1.0	0.9	0.8	0.8	0.9	1.0	1.1	Ethisterone	-	Progestogen
1.0	1.0	0.9	0.7	1.1	1.0	1.0	Levamisole hydrochloride	Alkaline phosphatase inhibitor	Immunomodulator
1.0	1.0	0.6	0.7	0.9	1.0	1.0	Triprolidine hydrochloride	H1 antagonist	Antihistaminic
1.0	0.9	0.8	0.8	0.9	1.0	0.9	Pargyline hydrochloride	Monoamine oxidase inhibitor	Antihypertensor
1.1	1.0	0.9	0.8	0.9	1.1	1.0	Doxepin hydrochloride	Adrenaline uptake inhibitor	Anticonvulsant
0.9	0.9	0.8	0.6	0.9	0.9	1.0	Methocarbamol	-	Muscle relaxant
1.0	1.0	0.9	0.7	0.9	1.0	1.1	Dyclonine hydrochloride	Na+ channel blocker	Local anesthesic
15.9	1.0	0.6	2.6	5.4	9.1	18.4	Aztreonam	Bacterial transpeptidase	Antibacterial

								inhibitor	
1.0	1.0	0.8	0.7	0.8	1.0	1.2	Dimenhydrinate	H1 antogonist	Antihistaminic
1.0	1.0	5.3	0.7	1.3	1.0	1.0	Cloxacillin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.9	0.9	2.7	0.6	0.9	0.9	1.0	Disopyramide	Na+ channel blocker	Antiarrhythmic
1.0	1.0	0.8	0.8	0.8	0.7	1.0	Catharanthine		
1.0	1.3	2.0	1.0	3.3	1.0	1.0	Clotrimazole	Specific inhibitor of Ca2+ activated K+ channels	Antibacterial
0.8	0.9	0.7	0.7	1.0	1.0	1.1	Pentolinium bitartrate	Glanglionic blocking agent	Antihypertensor
0.9	1.0	0.8	0.8	0.9	1.0	1.0	Vinpocetine	Phosphodiesterase inhibitor	Nootropic drug
0.9	0.9	0.7	0.8	0.8	0.9	1.1	Aminopurine, 6-benzyl	Inhibitor of respiratory kinase in plants	
1.1	1.1	0.8	0.7	1.0	0.9	1.0	Clomipramine hydrochloride	Noradrenaline reuptake inhibitor	Antidepressant
0.8	1.0	0.7	0.8	0.9	0.9	1.0	Tolbutamide	K+ channel ATP dependant inhibitor	Hypoglycemic
1.0	1.1	0.8	0.8	1.5	1.1	0.9	Fendiline hydrochloride	Ca++ channel activator	Antianginal
0.7	0.8	9.7	0.2	1.0	0.8	1.5	Chloramphenicol	Ribosomal peptidyltransferase inhibitor	Antibacterial
0.9	0.8	0.7	0.6	0.8	0.8	1.1	Naloxone hydrochloride	Opiate antagonist	Opioate antidote
1.0	0.8	2.2	0.7	0.9	0.8	1.2	Epirizole		Antiinflammatory
0.8	0.8	0.7	0.6	0.8	0.7	1.0	Metolazone	-	Diuretic
1.0	0.9	0.7	0.6	0.8	0.7	1.1	Diprophylline	Phosphodiesterase inhibitor	Cardiac analeptic
33.6	1.2	1.5	0.8	2.2	29.7	4.7	Ciprofloxacin hydrochloride		Anti-bacterial

0.6	0.7	0.6	0.5	1.1	0.6	1.2	Triamterene	Non competitive aldosterone antagonist	Diuretic
12.2	1.1	0.5	0.6	1.6	0.7	3.5	Ampicillin trihydrate		Antibacterial
0.8	0.9	0.6	0.7	1.3	0.8	1.1	Dapsone	Folic acid antagonist	Antiinflammatory
0.9	0.9	0.8	0.6	1.0	0.9	1.1	Haloperidol	Dopamine antagonist	Antipsychotic
0.9	1.0	6.5	0.6	0.8	0.7	1.1	Troleandomycin	Ribosomal protein synthesis inhibitor	Antibacterial
0.9	1.0	0.7	0.6	0.9	0.8	1.3	Naltrexone hydrochloride dihydrate	Opioid antagonist	Analgesic
1.4	1.0	0.7	0.7	2.5	0.9	1.3	Pyrimethamine		Antimalarial
1.0	0.9	0.8	0.7	0.9	0.8	1.1	Chlorpheniramine maleate	H1 antagonist	Antihistaminic
0.9	0.9	0.7	0.7	0.9	0.8	1.2	Hexamethonium dibromide dihydrate	Ganglion blocking agent	Antihypertensor
0.9	0.9	0.7	0.7	0.9	0.8	1.2	Nalbuphine hydrochloride	Opioid ligand	Analgesic
0.7	0.9	0.6	0.6	0.7	0.6	1.2	Diflunisal	Cyclooxygenase inhibitor	Antiinflammatory
0.9	0.9	0.7	0.8	0.9	0.8	1.2	Picotamide monohydrate	Eicosenoid receptor antagonist	Antithrombotic
0.1	0.1	0.4	0.1	0.2	0.1	0.5	Niclosamide	Helmintic DNA damage	Anthelmintic
1.0	1.0	0.8	0.7	0.9	0.7	1.2	Triamcinolone	-	Antiinflamatory
1.0	1.0	0.9	0.7	0.9	0.9	1.0	Midodrine hydrochloride	Alpha adrenergic	Hypotensor
0.9	0.9	0.7	0.7	0.9	1.0	1.2	Vincamine	-	Cerebral antianoxic
1.0	1.0	1.0	0.8	0.9	0.9	1.1	Thalidomide	-	Immunosuppressant
0.9	0.9	0.6	0.8	1.0	0.9	1.2	Indomethacin	Cyclooxygenase inhibitor	Antiinflammatory

13.1	1.1	1.0	1.6	2.3	1.0	4.3	Oxolinic acid	Topoisomerase II inhibitor	Antibacterial
0.9	0.9	0.8	0.8	1.0	1.0	1.2	Cortisone		Antiinflammatory
0.9	0.8	0.7	0.7	0.9	0.9	1.4	Nimesulide	Cyclooxygenase 2 inhibitor	Antiinflammatory
1.0	1.0	0.8	0.7	1.0	1.0	1.3	Prednisolone	-	Glucocorticoid
1.0	0.9	0.7	0.8	0.9	0.9	1.2	Hydrastinine hydrochloride	Dopamine receptor blocker	Cardiotonic
0.8	0.8	0.8	0.6	0.7	0.8	1.2	Fenofibrate	Lipoprotein lipase activator	Hypolipidemiant
0.8	0.9	0.8	0.7	0.9	0.8	1.1	Pentoxifylline	Phosphodiesterase inhibitor	Vasodilatator
0.9	0.9	0.7	0.7	0.8	0.8	1.3	Bumetanide	Vascular cyclooxygenase activator	Diuretic
1.0	1.0	0.7	0.8	0.9	0.8	1.3	Metaraminol bitartrate	Adrenergic agonist	Vasoconstrictor
0.9	0.9	0.8	0.7	0.9	0.9	1.3	Labetalol hydrochloride		
0.9	1.0	0.8	0.7	0.9	0.8	1.4	Salbutamol	Beta adrenergic agonist	Bronchodilatator
0.9	1.0	1.0	0.8	2.3	0.9	1.2	Cinnarizine	H1 antagonist	Antihistaminic
0.9	0.9	0.8	0.7	0.9	0.9	1.3	Prilocaine hydrochloride	Na+ channel blocker	Local anesthesic
0.8	1.0	0.8	0.7	0.9	0.9	1.3	Methylprednisolone, 6-alpha		Glucocorticoid
0.9	0.9	0.7	0.8	0.8	0.8	1.1	Camptothecine (S,+)	Topoisomerase I inhibitor	Antitumor agent
1.0	1.0	0.9	0.8	0.9	0.9	1.1	Quinidine hydrochloride monohydrate	Heme polymerase inhibitor	Antiarrhythmic
1.2	0.9	1.2	1.0	1.1	1.0	1.4	Procaine hydrochloride	Na+ channel blocker	Local anesthesic
1.3	0.9	0.6	1.1	1.4	1.1	1.4	Bromocryptine mesylate	Prolactin inhibitor	Antiparkinsonian
1.2	0.9	1.1	1.0	1.1	1.1	1.6	Moxisylyte hydrochoride	Alpha antagonist	Vasodilatator
1.3	1.0	1.2	1.0	1.1	1.1	1.3	Metanephrine hydrochloride DL	Isoprenaline uptake inhibitor	

								extraneuronal	
1.3	1.0	1.2	0.9	1.2	1.0	1.4	Betazole hydrochloride	Histamine analog	Gastric secretion stimulant
1.3	1.0	1.0	0.8	1.0	1.0	1.4	Dehydrocholic acid	-	Choleretic
1.2	1.0	1.0	1.0	1.0	1.0	1.4	Isoxicam	Cyclooxygenase inhibitor	Antiinflammatory
1.1	0.9	0.5	0.9	1.1	0.9	1.3	Hesperetin	P450 inhibitor	
1.2	1.0	0.8	0.9	1.1	1.0	1.4	Naproxen	Cyclooxygenase inhibitor	Antiinflammatory
1.5	1.2	0.9	1.3	1.6	1.1	1.4	Perphenazine	Dopamine antagonist	Antipsychotic
1.3	1.1	1.0	0.8	1.1	1.0	1.5	Naphazoline hydrochloride	Adrenergic ligand	Vasoconstrictor
1.3	1.0	3.2	1.3	2.6	1.1	1.2	Mefloquine hydrochloride	Heme polymerase inhibitor	Antimalarial
1.3	1.0	0.8	1.0	1.1	1.1	2.0	Ticlopidine hydrochloride	ADP antagonist	Platelet antiaggregant
1.8	1.8	5.2	1.4	5.6	1.3	1.7	Isoconazole	Sterol 14-demethylase inhibitor	Antibacterial
1.2	1.1	1.0	0.9	1.3	1.2	1.5	Dicyclomine hydrochloride	Anticholinergic	Antispasmodic
1.4	1.0	1.2	1.0	1.1	1.0	1.3	Spironolactone	Aldosterone antagonist	Diuretic
1.4	1.1	1.1	0.8	1.1	0.9	1.2	Amyleine hydrochloride	Na+ channel blocker	Local Anesthesic
1.4	1.1	1.0	1.0	1.1	1.0	1.4	Pirenzepine dihydrochloride	M1 antagonist	Antiulcerative
1.3	1.2	1.1	1.1	1.1	1.1	1.3	Lidocaïne hydrochloride	Na+ channel blocker	Local anesthesic
1.4	1.2	1.2	1.1	1.1	1.0	1.2	Dexamethasone acetate		Antiinflammatory
1.4	1.1	1.2	0.9	1.1	1.3	1.5	Ranitidine hydrochloride	H2 antagonist	Antiulcerative
1.3	1.1	1.0	1.0	1.2	1.2	1.4	Fludrocortisone acetate	-	Mineralocorticoid
1.1	1.3	0.4	1.0	1.1	1.2	1.5	Tiratricol, 3,3',5-triiodothyroacetic acid	-	Hypocholesterolemic drug

1.3	1.1	1.0	0.9	1.3	1.1	1.4	Fenoterol hydrobromide	Beta adrenergic agonist	Bronchodilatator
1.0	1.0	0.5	1.0	1.3	1.1	1.8	Flufenamic acid	Cyclooxygenase inhibitor	Analgesic
1.5	1.2	1.0	1.1	1.2	1.2	1.8	Homochlorcyclizine dihydrochloride	H1 antagonist	Antihistaminic
13.6	1.5	2.2	2.2	2.9	1.4	24.4	Flumequine	Topoisomerase II inhibitor	Antibacterial
1.3	1.2	1.1	0.9	1.1	1.1	1.7	Diethylcarbamazine citrate	Lipoxygenase inhibitor	Antihelmintic
1.0	1.1	0.5	0.8	1.4	1.2	1.6	Tolfenamic acid	Cyclooxygenase inhibitor	Antiinflammatory
1.2	1.0	1.7	0.8	1.0	1.2	1.5	Chenodiol	Detergent	Anticholelithogenic
1.1	1.2	0.6	1.0	1.2	1.2	1.4	Meclofenamic acid sodium salt monohydrate	Cyclooxygenase inhibitor	Antiinflammatory
1.8	1.2	0.8	1.6	3.4	1.4	1.5	Perhexiline maleate	Ca2+ blocking agent	Vasodilatator
1.1	1.1	1.0	1.0	1.2	1.0	1.4	Kawain	Ca++ channel blocker	Antiaggregant
1.4	1.1	1.2	0.9	1.1	1.0	1.6	Oxybutynin chloride	Anticholinergic	Spasmolytic
1.2	1.1	1.0	0.8	3.1	1.1	7.2	Trimethoprim	Folic acid antagonist	Antibacterial
1.3	1.2	1.0	0.9	1.2	1.2	1.3	Spiperone	D2 antagonist	Antipsychotic
1.3	1.2	0.9	0.9	1.2	1.1	1.6	Metoclopramide monohydrochloride	5-HT3 antagonist	Antiemetic
1.4	1.2	1.4	1.0	1.1	1.1	1.4	Pyrilamine maleate	H1 antagonist	Antihistaminic
0.9	0.9	0.6	0.7	0.9	0.9	1.3	Fenbendazole	Microtubule formation inhibitor	Antihelmintic
1.3	1.1	3.5	1.0	1.2	1.0	1.2	Sulfinpyrazone	-	Uricosuric
1.2	0.8	1.1	1.1	0.9	1.0	1.5	Trichlorfon	Cholinesterase inhibitor	Antihelminthic
1.2	0.9	1.2	0.8	1.0	1.0	1.3	Glipizide		

1.0	0.8	1.0	0.9	0.9	1.0	1.5	Carbamazepine	Cholinergic antagonist	Anticonvulsivant
1.0	0.9	1.1	1.0	1.0	0.9	1.3	Loxapine succinate	Dopamine antagonist	Anxiolytic
1.1	0.9	1.1	1.0	1.5	1.0	1.6	Triflupromazine hydrochloride	Dopaminergic antagonist ?	Antipsychotic
1.0	0.9	0.9	0.8	1.0	1.0	1.6	Hydroxyzine dihydrochloride	H1 antogonist	Antihistaminic
0.9	0.9	0.7	0.8	1.2	0.9	1.6	Mefenamic acid	Cyclooxygenase inhibitor	Antiinflammatory
1.0	0.9	0.8	1.0	1.0	0.9	1.5	Diltiazem hydrochloride	Ca2+ channel inhibitor (L-Type)	Antianginal
1.2	0.9	1.1	0.8	1.1	1.2	1.7	Acetohexamide	Blocking of ATP-sensitive K+ channel	Antidiabetic (type II, noninsulin-dependent)
1.1	0.8	0.9	0.8	1.0	1.0	1.3	Methotrexate		
1.0	1.0	1.1	1.0	1.0	1.1	1.6	Sulpiride	D2 antagonist	Antipsychotic
1.3	1.0	2.2	1.1	1.6	1.0	1.6	Astemizole	H1 antagonist	Antihistaminic
1.3	0.9	1.0	1.0	1.1	0.9	1.4	Benoxinate hydrochloride	Na+ channel blocker	Local anesthesic
0.8	1.2	8.4	0.5	1.0	1.1	1.7	Clindamycin hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial
1.4	1.0	1.0	1.5	4.2	1.0	1.5	Oxethazaine	Na+ channel blocker	Local anesthesic
1.7	1.5	###	1.1	3.1	1.0	1.2	Terfenadine	H1 antagonist	Antihistaminic
1.4	1.0	1.0	1.0	1.0	1.0	1.7	Pheniramine maleate	H1 antagonist	Antihistaminic
21.9	1.0	2.9	5.5	2.2	10.0	22.0	Cefotaxime sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
1.4	1.0	1.2	1.0	1.3	1.1	1.5	Tolazoline hydrochloride	Alpha antagonist	Vasodilatator
0.8	1.0	9.2	0.2	4.4	0.5	1.0	Tetracycline hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial

1.2	1.1	1.4	1.0	1.0	1.2	1.4	Piroxicam	Cyclooxygenase inhibitor	Antiinflammatory
1.0	1.0	1.1	0.9	1.1	1.2	1.5	Dantrolene sodium salt	Blocker of Ca2+ release	Skeletal muscle relaxant
1.3	1.1	1.2	0.9	1.1	1.2	1.4	Pyrantel tartrate	Neuromuscular depolarizing agent	Anthelmintic
0.9	1.0	0.9	1.0	1.0	1.2	1.3	Trazodone hydrochloride	5-HT uptake inhibitor	Antidepressant
1.3	1.0	1.1	1.0	1.2	1.1	1.6	Fenspiride hydrochloride	Bradykinin antagonist	Antiinflammatory
1.2	1.1	1.1	1.0	1.1	1.2	1.5	Glafenine hydrochloride	-	Analgesic
1.3	1.0	0.9	0.9	1.3	1.2	1.5	Gemfibrozil	-	Antihyperlipoproteinemic
1.4	1.1	0.9	1.2	1.1	1.1	1.4	Pimethixene maleate	Anticholinergic	Antihistaminic
1.2	1.0	0.9	0.9	1.0	1.1	1.3	Mefexamide hydrochloride	-	Psychoanaleptic
1.3	1.0	1.0	0.8	1.3	1.0	1.4	Pergolide mesylate	Dopaminergic agonist	Antiparkinsonian
1.4	1.1	1.0	0.9	1.1	1.2	1.5	Tiapride hydrochloride	Dopamine antagonist	Antidyskinetic
1.2	1.0	1.1	0.9	1.1	1.1	1.3	Acemetacin	Cyclooxygenase inhibitor	Antiinflammatory
0.8	0.9	0.9	0.8	0.7	0.8	1.2	Mebendazole		
1.3	1.1	1.1	1.0	1.0	1.2	1.2	Benzydamine hydrochloride	5-HT receptor antagonist	Analgesic
0.8	0.8	0.7	0.8	1.0	0.8	1.6	Fenbufen	Cyclooxygenase inhibitor	Antiinflammatory
1.3	1.1	0.9	1.1	1.0	1.0	1.3	Fipexide hydrochloride	Glutamatergic	Nootropic
1.1	0.9	1.0	1.1	1.0	1.0	1.5	Ketoprofen	Cyclooxygenase inhibitor	Antiinflammatory
1.3	1.1	0.7	0.9	1.1	1.0	1.4	Mifepristone	Progesterone receptor antagonist	Abortifacient
1.1	1.1	1.0	1.1	1.0	1.1	1.7	Indapamide		Diuretic
1.4	1.1	1.2	0.9	1.1	1.1	1.4	Diperodon hydrochloride	-	Local anesthesic

1.4	0.8	1.2	0.9	1.1	1.2	1.3	Morantel tartrate	Fumarate reductase inhibitor	Anthelmintic
1.3	0.9	1.2	0.9	1.5	1.2	1.2	Verapamyl hydrochloride	Alpha1 antagonist	Antyhypertensive
1.4	0.8	1.1	0.9	1.3	1.1	1.4	Homatropine hydrobromide (R,S)	Muscarinic antagonist	Antispasmodic
1.3	0.9	0.8	0.9	1.2	1.1	1.4	Dipyridamole		
1.4	0.9	0.5	0.9	1.5	1.0	1.4	Nifedipine	L-type Ca2+ channels blocker	Antihypertensor
50.1	4.0	###	18.8	12.3	23.6	1.8	Chlorhexidine	Detergent	Bacteriostatic
1.4	1.0	1.4	1.1	1.5	1.1	1.4	Chlorpromazine hydrochloride	Dopamine antagonist	Antiemetic
1.4	0.9	1.0	0.9	1.5	1.2	1.5	Loperamide hydrochloride	Ca2+ channel antagonist	Antidiarrhoeic
1.3	0.9	1.1	1.0	1.3	1.0	1.4	Diphenhydramine hydrochloride	H1 receptor antagonist	Antihistaminic
0.8	0.9	6.8	0.2	3.9	0.7	1.0	Chlortetracycline hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial
1.3	0.8	1.0	0.9	1.3	1.1	1.3	Minaprine dihydrochloride	Dopamine agonist	Antidepressant
1.9	4.0	2.1	2.1	6.6	1.4	1.3	Tamoxifen citrate	Oestrogen receptor antagonist	
1.4	2.5	2.2	1.4	4.7	1.2	1.6	Miconazole	Sterol 14-demethylase inhibitor	Antifungal
1.3	1.0	1.4	1.0	1.4	1.2	1.2	Nicergoline	Alpha agonist	Vasodilatator
1.1	1.0	1.1	1.0	1.5	1.1	1.5	Isoxsuprine hydrochloride	beta adrenergic agonist	Vasodilatator
1.4	1.0	1.1	0.9	1.5	1.3	1.2	Canrenoic acid potassium salt	Detergent	Antihypercholesterolemic
1.3	1.1	1.1	0.9	1.3	1.1	1.2	Acebutolol hydrochloride	Beta1 antagonist	Antianginal
1.5	1.0	1.0	1.1	1.7	1.1	1.3	Thioproperazine dimesylate	Dopamine antagonist	Antipsychotic
1.1	1.0	1.3	0.9	1.5	1.0	1.2	Tolnaftate	-	Antifungal

1.3	1.0	1.0	0.9	1.5	1.2	1.3	Dihydroergotamine tartrate	Serotonine antagonist	Antimigraine
33.1	1.5	1.8	0.8	3.1	31.3	3.1	Norfloxacin	Topoisomerase II inhibitor	Antibacterial
1.2	1.0	4.3	1.0	1.3	1.2	1.5	Lisinopril	Converting enzyme inhibitor	Antihypertensor
1.3	1.1	1.0	1.0	1.4	1.1	1.3	Antimycin A	Inhibitor of mitochondrial electron transport	Antifungal
0.9	1.3	7.9	0.9	1.2	1.2	1.3	Lincomycin hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	1.0	1.2	0.9	1.3	1.2	1.4	Xylometazoline hydrochloride		Vasoconstrictor
1.5	1.1	1.3	1.0	1.6	1.2	1.4	Telenzepine dihydrochloride	M1 muscarinic antagonist	Antiulcerative
1.1	1.0	1.1	1.1	1.4	1.2	1.3	Oxymetazoline hydrochloride	Partial alpha2A agonist	Vasoconstrictor
1.3	1.5	3.7	1.3	6.7	1.3	1.3	Econazole nitrate	Ergosterol synthesis inhibition	Antifungal
1.2	1.0	1.3	1.0	1.6	1.2	1.2	Nifenazone	Cyclooxygenase inhibitor	Analgesic
1.3	1.0	1.1	1.0	1.4	1.2	1.5	Bupivacaine hydrochloride	Na+ channel blocker	Local anesthesic
1.3	1.1	1.4	0.9	1.4	1.3	1.3	Griseofulvin	Enzymatic inductor	Antifungal
1.4	1.0	1.2	1.1	1.5	1.2	1.2	Clemastine fumarate	H1 antagonist	Antihistaminic
1.2	1.2	1.6	1.0	1.6	1.2	1.4	Clemizole hydrochloride	H1 antagonist	Antihistaminic
1.0	0.9	3.4	0.2	5.3	0.5	1.1	Oxytetracycline dihydrate	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	1.0	1.1	1.1	1.5	1.2	1.4	Tropicamide	Muscarinic antagonist	Mydriatic
1.7	1.3	2.3	1.3	8.7	1.3	1.2	Pimozide	Dopamine antagonist ?	Antipsychotic
1.2	1.0	1.1	0.9	1.4	1.2	1.4	Nefopam hydrochloride	-	Analgesic
1.2	1.1	1.3	0.9	1.5	1.2	1.4	Amodiaquin dihydrochloride	Heme polymerase inhibitor	Antimalarial

							dihydrate		
1.4	1.0	1.1	1.1	1.4	1.2	1.2	Phentolamine hydrochloride	Alpha adrenergic antagonist	Antihypertensor
1.3	1.0	1.1	1.0	1.4	1.1	1.3	Mebeverine hydrochloride	Antispasmodic	
1.3	0.8	1.3	1.0	1.1	1.1	1.7	Todralazine hydrochloride	-	Antihypertensor
1.0	1.0	8.2	1.0	1.5	0.7	1.6	Erythromycin	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	0.9	1.2	1.0	1.3	1.1	1.7	Imipramine hydrochloride	5-HT transport inhibitor	Antidepressant
1.1	1.0	3.6	1.0	1.1	1.0	1.6	Oleandomycin phosphate	Ribosomal protein synthesis inhibitor	Antibacterial
1.1	0.9	0.8	1.0	1.1	0.8	1.5	Sulindac	Cyclooxygenase inhibitor	Antiinflammatory
4.7	0.9	1.2	0.9	1.5	1.0	4.2	Didanosine	Transrcriptase inverse inhibitor	Antiviral
1.2	1.0	1.4	1.1	1.3	1.0	1.8	Amitryptiline hydrochloride	Alpha 1 antogonist	Antidiabetic
1.3	1.0	8.4	1.0	1.1	0.9	1.4	Josamycin	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	1.0	1.3	1.0	1.3	0.9	1.5	Adiphenine hydrochloride	Anticholinergic	Local anesthesic
1.1	1.0	1.0	1.0	1.3	1.0	1.6	Paclitaxel	Tubuline inhibitor	Antineoplastic
1.3	0.9	1.3	1.1	1.3	1.1	1.7	Dibucaine	Na+ channel blocker	Local anesthesic
1.3	1.2	2.1	1.0	1.5	1.0	1.6	Ivermectin	GABA ligand	Anthelmintic
1.2	0.9	1.1	0.9	1.2	0.9	1.4	Prednisone	-	Glucocorticoid
1.3	1.0	1.1	1.1	1.2	1.0	1.5	Gallamine triethiodide	M2 antagonist allosteric	Muscle relaxant
1.6	1.0	1.3	1.3	2.9	1.1	1.5	Thioridazine hydrochloride	Ca2+ channel antagonist	Neuroleptic
1.2	1.0	1.1	1.0	1.4	0.9	1.3	Neomycin sulfate	Ribosomal protein synthesis	Antibacterial

								inhibitor	
1.2	1.1	1.5	1.1	1.3	1.0	1.6	Diphemanil methylsulfate	Anticholinergic	Bronchodilatator
1.2	1.0	1.2	0.7	1.2	0.9	1.3	Dihydrostreptomycin sulfate	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	1.1	1.2	1.1	1.2	1.0	1.3	Trimethobenzamide hydrochloride	D2 antagonist	Antiemetic
1.3	1.0	1.1	1.0	1.5	0.9	1.4	Gentamicine sulfate	Ribosomal protein synthesis inhibitor	Antibacterial
1.2	1.1	1.0	1.3	1.4	1.5	1.2	Etodolac	Cyclooxygenase inhibitor	Antiinflammatory
1.2	1.0	1.1	1.3	1.4	1.2	1.3	Ifenprodil tartrate	Adrenergic antagonist	Vasodilatator
1.2	1.1	1.4	1.2	1.4	1.3	1.5	Scopolamin-N-oxide hydrobromide	Anticholinergic	Antiparkinsonian
1.7	1.3	1.1	1.4	2.6	1.3	1.6	Flunarizine dihydrochloride	Na+ channel blocker	Vasodilatator
1.3	1.0	1.2	1.2	1.4	1.2	1.5	Hyoscyamine (L)	Cholinergic	Antispasmodic
1.7	1.1	1.2	1.5	3.4	1.4	1.3	Trifluoperazine dihydrochloride	Dopamine antagonist	Psycholeptic
1.2	0.9	1.0	1.1	1.3	1.1	1.4	Chlorphensin carbamate	-	Muscle relaxant
1.2	1.1	1.3	1.2	1.3	1.2	1.3	Enalapril maleate	Converting enzyme inhibitor	Antihypertensor
16.8	1.6	1.3	1.0	1.1	1.3	4.3	Metampicillin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
2.3	1.1	6.9	0.6	3.9	0.7	0.9	Minocycline hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial
1.5	1.1	1.2	1.4	1.4	1.3	1.1	Dilazep dihydrochloride	Adenosine uptake inhibitor	Vasodilatator
1.2	1.0	0.9	1.1	1.3	1.2	1.4	Glibenclamide	ATP-dependent K+ channel inhibitor	Antidiabetic

15.7	1.4	2.8	1.0	3.7	20.0	4.1	Ofloxacin	Topoisomerase II inhibitor	Antibacterial
1.4	1.1	1.1	1.1	1.3	1.4	1.4	Guanethidine sulfate	Catecholamine depletor	Antihypertensor
26.8	1.5	3.4	1.0	3.8	30.2	3.5	Lomefloxacin hydrochloride	Topoisomerase II inhibitor	Antibacterial
1.2	1.0	1.2	1.0	1.3	0.9	1.4	Quinacrine dihydrochloride dihydrate	Monoamine oxydase inhibitor	Antimalarial
1.3	1.0	1.0	1.2	1.3	1.1	1.2	Orphenadrine hydrochloride	H1 antogonist	Antihistaminic
1.5	1.4	1.2	1.5	1.6	1.3	1.2	Clofilium tosylate	K+ channel blocker	Antiarrhythmic
1.3	1.0	1.1	1.2	1.3	1.1	1.5	Proglumide	Gastrin inhibitor	Antiulcerative
1.3	1.1	1.0	1.5	1.6	1.1	1.6	Fluphenazine dihydrochloride	Dopamine antagonist	Antipsychotic
0.5	0.9	0.4	0.3	0.4	0.4	0.3	Streptomycin sulfate	Ribosomal protein synthesis inhibitor	Antibacterial
0.5	0.9	0.3	0.4	0.5	0.4	0.3	Testosterone propionate	-	Androgen
0.5	0.9	0.3	0.4	0.4	0.4	0.4	Alfuzosin hydrochloride	Alpha 1- adrenergic antagonist	Antihypertensor
0.4	0.9	0.4	0.4	0.4	0.4	0.3	Arecoline hydrobromide	Cholinergic	Anthelmintic
0.4	0.9	0.4	0.4	0.3	0.3	0.3	Chlorpropamide	Glucagon secretogen, somatostatin secretogen	Antidiabetic
0.5	1.0	0.2	0.4	0.4	0.4	0.3	Thyroxine (L)	Thyroid hormone	Hypocholesterolemic drug
0.5	0.8	0.3	0.5	0.4	0.4	0.4	Phenylpropanolamine hydrochloride	Alpha adrenergic agonist	Decongestant
0.6	0.9	0.4	0.4	0.4	0.4	0.4	Tocopherol (R,S)	-	Anti-oxidant
0.5	0.9	0.4	0.5	0.4	0.3	0.4	Ascorbic acid	-	Vitamin
0.5	0.8	0.4	0.5	0.4	0.4	0.4	Pepstatin A	Aspartic proteases irreversible inhibitor	Antiviral

0.6	0.9	0.4	0.6	0.5	0.4	0.5	Methyldopa (L,-)	L-aromatic aminoacid decarboxylase inhibitor	Antihypertensor
0.5	0.8	0.4	0.5	0.5	0.4	0.4	SR-95639A	M1 agonist receptor	
16.5	0.9	0.7	2.1	0.7	5.2	12.0	Cefoperazone dihydrate	Bacterial transpeptidase inhibitor	Antibacterial
0.5	0.9	0.4	0.5	0.5	0.4	0.4	Adamantamine fumarate	Inhibition of viral uncoating and viral assembly, alteration of dopamine release and reuptake	Antiviral
0.7	0.8	0.4	0.6	0.4	0.4	0.4	Zoxazolamine	Uric acid uptake inhibitor	Muscle relaxant
0.7	3.3	0.6	0.7	2.0	0.5	0.5	Butoconazole nitrate	Ergosterol inhibitor	Antifungal
0.5	0.9	0.5	0.4	0.5	0.5	0.4	Tacrine hydrochloride hydrate	Cholinesterase inhibitor	Cognition enhancer
0.7	1.7	0.7	0.6	2.2	0.5	0.5	Amiodarone hydrochloride	Na+ channel blocker, K+ channel blocker, non-competitive beta-adrenergic blocker	Antiarrhythmic
0.5	0.9	0.6	0.5	0.5	0.5	0.6	Bisoprolol fumarate	Beta1 antagonist	Antihypertensor
0.5	0.9	0.5	0.7	0.5	0.4	0.5	Amphotericin B	Ergosterol ligand	Antibacterial
0.8	0.9	0.6	0.6	0.6	0.6	0.6	Serotonin hydrochloride	5-HT agonist	Neurotransmitter
0.7	0.9	0.5	0.6	0.7	0.6	0.6	Tubocurarine chloride pentahydrate (+)	Curarising	Muscle relaxant
23.9	0.9	2.3	7.8	0.9	0.6	15.6	Cefotiam hydrochloride		Antibacterial
0.7	0.9	0.5	0.6	0.7	0.6	0.6	Dihydroergocristine mesylate	5-HT antagonist, partial adrenergic agonist, partial dopaminergic agonist	Vasodilatator
0.6	0.9	0.4	0.5	0.5	0.6	0.6	Azathymine, 6	Antimetabolite	Anticancer

0.6	0.9	0.5	0.5	0.6	0.5	0.6	Noscapine	Inhibitor of carbachol-stimulated phosphoinositide turnover	Antitussive
0.6	1.0	0.5	0.5	0.5	0.6	0.6	Benperidol	Dopamine antagonist, 5-HT antagonist	Antipsychotic
0.6	0.9	0.3	0.5	0.6	0.5	0.6	Syrosingopine	Catecholamine depletor	-
10.7	0.9	0.5	2.5	1.5	0.5	0.7	Cefaclor	Bacterial transpeptidase inhibitor	Antibacterial
0.6	0.8	0.5	0.5	0.5	0.5	0.5	Atropine sulfate monohydrate	Muscarinic antagonist	Anticholinergic
42.2	1.0	0.6	24.1	10.0	23.6	0.7	Colistin sulfate	Performs membrane ionophores	Antibacterial
0.7	0.9	0.4	0.5	0.5	0.6	0.7	Eserine sulfate, physostigmine sulfate	Cholinesterase inhibitor	Ophtalmic agent
0.9	2.3	2.1	0.5	0.6	0.5	0.6	Daunorubicin hydrochloride	DNA intercaling	Antineoplastic
0.6	0.9	0.5	0.5	0.6	0.5	0.6	Aconitine	Open TTX-Na+ channel	Analgesic
0.6	0.9	0.5	0.5	0.5	0.5	0.5	Dosulepin hydrochloride	-	Antidepressant
0.7	1.0	0.3	0.6	1.1	0.4	0.6	Rescinnamin	Catecholamine depletor	Antihypertensor
11.5	0.9	0.4	3.2	0.5	7.8	12.9	Ceftazidime pentahydrate		Antibacterial
0.6	0.8	0.4	0.5	0.5	0.4	0.6	Dihydroergotoxine mesylate	High affinity GABA A receptor Cl- channel, prolactin inhibitor	Anticonvulsant
0.5	0.9	0.5	0.5	0.5	0.4	0.6	Iobenguane sulfate	-	Antineoplastic if radiolabeled
0.5	0.9	0.5	0.6	0.5	0.5	0.5	Emetine dihydrochloride	Protein synthesis inhibitor, 5-HT ligand	Antiamebic
0.7	1.0	0.5	0.6	0.7	0.6	0.7	Tremorine dihydrochloride	Cholinergic	Convulsant

0.6	1.0	0.5	0.5	0.7	0.6	0.7	Androsterone	-	Antihypertensor
0.7	0.9	0.6	0.5	0.7	0.6	0.8	Practolol	Beta antagonist	Antihypertensor
0.7	1.0	0.7	0.5	0.7	0.7	0.7	Anisomycin	Acetylcholine esterase inhibitor	Antiprotozoal
2.1	0.9	0.6	1.2	1.8	0.6	4.2	Zidovudine, AZT	Transcriptase reverse inhibitor	Antiviral
0.6	1.0	0.6	0.5	0.6	0.6	0.7	Carbarsone		Antiamebic
0.7	0.9	0.5	0.5	1.0	0.6	0.7	Sulfisoxazole	Inhibitor of folic acid biosynthesis, Eta endothelin receptor antagonist	Antibacterial
0.2	0.3	0.0	0.2	0.2	0.2	0.5	Apigenin	MAP kinase inhibitor	Antiproliferative
0.7	1.0	0.6	0.5	0.6	0.7	0.8	Zaprinast	cGMP phosphodiesterase inhibitor, phosphodiesterase 5 inhibitor	Erectogen
0.6	0.9	0.5	0.5	0.6	0.6	0.7	Aspartic acid, N-acetyl (R,S)	-	-
0.7	1.0	0.7	0.6	0.7	0.6	0.7	Chlormezanone	-	Skeletal muscle relaxant
11.9	1.1	0.5	0.6	1.3	0.6	0.6	Bacampicillin hydrochloride	Bacterial transpeptidase inhibitor	Antibacterial
0.6	1.0	0.6	0.6	0.7	0.6	0.9	Procainamide hydrochloride	Alpha antagonist, antinuclear antibodies, anticholinergic	Antiarrhythmic
0.6	0.9	0.1	0.5	0.6	0.6	0.7	Betulinic acid	Apoptosis inducer, PLA2 inhibitor	Antimalarial
0.6	0.9	0.5	0.5	0.6	0.6	0.7	N6-methyladenosine	Antimetabolite	Anticancer
0.6	0.9	1.4	0.6	0.8	0.7	0.8	Biotin	-	Vitamin H

0.8	1.1	0.6	0.5	0.7	0.7	0.9	Guanfacine hydrochloride	Alpha 2A agonist	Antihypertensor
0.6	1.0	0.5	0.6	0.8	0.6	0.9	Bisacodyl	Na+ uptake inhibitor	Cathartic
0.6	0.9	0.8	0.6	0.7	0.6	0.8	Domperidone	Dopamine Antagonists	Antiemetic
0.8	0.9	0.5	0.7	0.7	0.7	0.7	Calciferol	Stimulator of calcium and phosphate absorption	Vitamin D
0.9	1.0	0.7	0.8	1.0	0.8	0.8	Metixene hydrochloride	Anticholinergic	Antiparkinsonian
0.9	0.9	0.6	0.6	0.8	0.8	0.9	Tetracaïne hydrochloride		Local anesthesic
0.7	1.0	0.5	0.2	1.0	0.8	0.8	Nitrofural	Bacterial DNA damage	Antibacterial
0.9	1.0	0.4	0.7	0.9	0.6	0.9	Mometasone furoate	-	Antiinflammatory
0.7	0.8	0.2	0.6	0.8	0.6	0.8	Omeprazole	Non competitive ATPase H+ pump inhibitor	Antiulcerative
0.7	1.2	0.5	0.6	0.7	0.7	1.0	Tomatidine	Cholinesterase activity	Antifungal
0.7	1.0	0.7	0.6	0.8	0.7	1.1	Propylthiouracil	Antimetabolite	Antihyperthyroid
2.0	1.1	0.7	3.8	1.6	0.9	0.8	Dacarbazine	Alkylating agent	Antineoplastic
0.9	1.0	0.6	0.7	0.8	0.8	0.9	Terconazole	Sterol 14-demethylase inhibitor	Antifungal
0.6	0.9	0.7	0.6	0.6	0.8	0.8	Ipratropium bromide	Antimuscarinic agent	Bronchodilatator
0.6	0.8	0.5	0.5	0.7	0.6	0.8	Tiaprofenic acid	Cyclooxygenase inhibitor	Antiinflammatory
0.8	1.0	0.8	0.6	0.8	0.7	0.8	Acetopromazine maleate salt	Dopaminergic antagonist ?	Tranquilizer
1.2	1.5	###	0.8	1.1	0.9	0.9	Vancomycin hydrochloride	Bacterial mucopeptide biosynthesis inhibitor	Antibacterial
0.7	1.0	0.7	0.6	0.8	0.6	0.8	Rauwolscine hydrochloride	Alpha2 antagonist	Antidepressant
0.5	0.9	0.5	0.6	0.7	0.6	0.7	Artemisinin	Oxidant	Antimalarial

0.7	1.0	0.7	0.6	0.6	0.7	0.8	Corynanthine hydrochloride	Alpha1-adrenoreceptor antagonist	Anti-leishmania drug
1.0	1.0	0.7	0.6	0.7	0.7	0.8	Propafenone hydrochloride	Beta adrenergic antagonist	Antiarrhythmic
0.7	1.0	0.8	0.5	0.7	0.7	0.9	Palmatine chloride	Anticholinestrase activity	Uterine contractant
0.6	1.0	0.6	0.6	0.9	0.6	0.9	Ethamivan	-	Respiratory analeptic
0.8	1.2	0.6	0.7	1.0	0.7	0.8	Trimethylcolchicinic acid	Tubuline inhibitor ?	Anticancer agent
1.0	0.9	0.7	0.7	0.8	0.9	0.8	Furosemide	Na+ Cl- uptake inhibitor, carbonic anhydrase inhibitor	Diuretic
1.9	5.4	2.0	2.5	4.1	6.8	0.9	Suloctidil	-	Vasodilatator
0.9	1.0	0.5	0.6	0.9	0.9	0.8	Methapyrilene hydrochloride	Histamine H1 antagonist	Antihistaminic
0.8	0.9	0.7	0.6	0.8	0.8	0.8	Carcinine	-	Anti-oxidant
0.9	0.8	0.7	0.7	0.7	0.9	0.8	Desipramine hydrochloride	Adrenergic transport inhibitor, 5-HT transport inhibitor	Antidepressant
0.9	0.9	0.7	0.6	0.8	0.9	0.8	Carisoprodol	-	Muscle relaxant
0.7	0.7	0.5	0.5	0.6	0.7	0.8	Clorgyline hydrochloride	Monoamine oxidase A inhibitor	Antidepressant
0.9	0.9	0.6	0.7	0.8	0.8	0.8	Cephalosporanic acid, 7-amino	Bacterial transpeptidase inhibitor	Antibacterial
0.8	0.9	0.7	0.7	0.8	0.8	0.9	Clenbuterol hydrochloride	Beta adrenergic agonist	Bronchodilatator
0.5	0.5	0.0	0.3	0.4	0.4	0.9	Chicago sky blue 6B	Competitive glutamate uptake inhibitor	-
0.8	0.8	1.1	0.6	0.8	0.9	0.9	Maprotiline hydrochloride	Noradrenaline uptake inhibitor, 5-HT uptake inhibitor	Antidepressant

0.8	0.8	0.6	0.6	0.7	0.8	0.9	Buflomedil hydrochloride	-	Vasodilatator
0.8	0.9	0.5	0.7	0.9	0.8	0.9	Thioguanosine	Antimetabolite	Anticancer
0.8	0.9	0.5	0.7	0.8	0.7	0.8	Chlorogenic acid	Glucose-6-phosphate translocase inhibitor	Antiinflammatory
1.0	1.0	0.6	0.8	1.2	0.9	1.0	Chlorprothixene hydrochloride	D2 dopamine receptor antagonist, GABAA receptors antagonist	Neuroleptic
0.8	1.0	0.6	0.7	0.8	0.7	0.9	Roxatidine Acetate HCl		Antiulcerative
0.8	0.9	0.5	0.7	0.8	0.9	0.9	Ritodrine hydrochloride	Beta2 agonist	Tocolytic
1.0	0.9	0.7	0.7	0.8	0.9	1.0	Cholecalciferol	-	Vitamin
0.9	0.9	0.7	0.8	0.9	1.0	1.0	Clozapine	5-HT antagonist, dopamine antagonist, GABA ligand	Antipsychotic
0.9	0.9	0.6	0.7	1.1	0.9	0.9	Cisapride	5-HT antagonist	Peristaltic stimulant
1.0	0.9	0.7	0.8	1.1	0.9	0.8	Vigabatrin	GABA transaminase inhibitor	Anticonvulsant
0.9	1.0	0.6	0.8	1.0	0.9	0.9	Hydrastine hydrochloride	GABAa antagonist	Hypotensor
1.0	0.9	0.6	0.8	0.8	0.8	0.9	Biperiden hydrochloride	Anticholinergic	Antiparkinsonian
1.0	0.9	0.6	0.8	1.0	1.0	1.0	Lobelanidine hydrochloride	Nicotinic ligand	_
0.9	0.9	0.7	0.7	1.1	0.9	0.9	Cetirizine dihydrochloride	H1 antagonist	Antihistaminic
0.9	1.0	0.6	0.8	0.8	1.0	0.9	Papaverine hydrochloride	Phosphodiesterase inhibitor	Vasodilator
1.1	0.9	0.5	0.8	0.9	0.9	1.0	Etifenin	Chelating agent	Diagnostic agent
0.8	0.9	0.6	0.8	0.8	0.9	1.0	Yohimbine hydrochloride	Alpha antagonist	Mydriatic
1.0	0.9	0.6	0.7	0.9	0.9	1.0	Metaproterenol sulfate, orciprenaline sulfate	Beta-adrenergic agonist	Bronchodilatator

1.0	0.9	0.8	0.7	0.8	0.9	1.0	Lobeline alpha (-) hydrochoride	Nicotinic receptor ligand	Respiratory stimulant
0.8	0.9	0.6	0.6	0.9	0.9	1.0	Sisomicin sulfate	Ribosomal protein synthesis inhibitor	Antibacterial
1.0	1.0	0.7	0.7	0.9	0.9	1.1	Berberine chloride	Anti-HIV reverse transcriptase, cholinesterase inhibitor	Antibacterial
0.7	0.8	0.1	0.6	0.4	0.6	0.9	Quercetine dihydrate	Lipoxygenase inhibitor	Antimalarial
0.9	0.9	0.8	0.7	0.9	0.9	0.9	Cilostazol		Antithrombotic
0.0	0.0	0.0	0.0	0.0	0.0	0.1	Resveratrol		Antiinflammatory
0.9	0.9	0.8	0.8	0.8	0.8	1.0	Galanthamine hydrobromide	Cholinesterase inhibitor, nicotinic receptor agonist	Alzheimer treatment
0.8	0.9	0.7	0.7	1.0	1.1	1.1	Bromperidol	Dopamine antagonist	Antipsychotic
0.8	0.9	0.6	0.8	0.8	0.9	0.9	Bicuculline (+)	GABAa receptor antagonist	Convulsant
0.9	1.0	0.9	0.8	1.0	0.9	0.9	Cyclizine hydrochloride	H1 antagonist	Antiemetic
0.9	0.9	0.7	0.7	0.8	0.9	0.9	Yohimbinic acid monohydrate	-	-
0.9	0.9	0.7	0.6	0.8	0.8	1.0	Chlorthalidone	Na+ uptake inhibitor, carbonic anhydrase inhibitor	Diuretic
0.9	0.9	0.4	0.6	0.8	0.8	1.1	Coralyne chloride hydrate	Topoisomerase I inhibitor	Anti-leukemic
0.8	0.8	0.1	0.8	0.7	0.6	1.1	Dobutamine hydrochloride	Beta1, Beta2 agonist	Bronchodilatator
0.9	0.9	0.6	0.7	0.9	0.8	1.2	Corticosterone	-	Glucocorticoid
0.9	0.9	0.6	0.6	0.7	0.8	1.2	Moclobemide	Mono amine oxidase inhibitor (Type A)	Antidepressant
0.8	0.8	0.5	0.6	0.8	0.7	1.2	Cyanocobalamin	-	Vitamin
0.8	0.9	0.7	0.7	0.8	0.8	1.0	Clopamide	Gonad stimuling agent	Antihypertensor

0.9	0.8	0.5	0.8	0.9	0.8	1.2	Cefadroxil	Bacterial transpeptidase inhibitor	Antibacterial
0.9	1.2	0.8	0.7	0.8	0.8	1.1	Hycanthone	DNA intercaling agent	Anthelmintic
0.9	0.9	0.6	0.7	0.9	0.8	1.4	Cyclosporin A	IL 2 synthesis inhibitor, calcineurine phosphatase inhibitor	Immunosuppressant
0.8	0.8	0.6	0.6	0.7	0.8	1.2	Adenosine 5'-monophosphate monohydrate	Ca++ channel block, adenosine receptor activation, activation of outward K+ current	Nutrient
0.9	0.9	0.6	0.7	0.8	0.8	1.2	Digitoxigenin	Na+ K+ ATPase inhibitor	Cardiotonic
10.6	1.4	0.4	0.7	1.7	0.7	1.0	Amoxicillin	Bacterial transpeptidase inhibitor	Antibacterial
0.8	0.9	0.8	0.7	0.9	0.8	1.2	Digoxin	Na+ K+ ATPase inhibitor	Cardiotonic
0.8	0.9	0.7	0.7	0.9	0.8	1.4	Cephalexin monohydrate	Bacterial transpeptidase inhibitor	Antibacterial
1.0	1.7	0.9	0.7	1.0	0.6	1.2	Doxorubicin hydrochloride	DNA intercalant	Antibacterial
0.8	0.9	0.7	0.7	0.8	0.8	1.1	Dextromethorphan hydrobromide monohydrate	Opioid ligand	Antitussive
0.8	0.9	0.6	0.7	0.8	0.7	1.2	Carbimazole	Iodine oxidazing inhibitor	Antityroidic hormone
0.9	1.0	0.9	0.7	1.0	0.7	1.2	Droperidol	Alpha adrenergic antagonist, 5-HT antagonist, dopamine antagonist	Antipsychotic
0.9	1.0	0.6	0.7	0.8	0.8	1.1	Epiandrosterone	-	Anabolic steroid
1.0	0.9	1.1	0.8	1.0	0.9	1.1	Fluoxetine hydrochloride	5-HT uptake inhibitor	Antidepressant
1.0	0.9	0.7	0.7	0.9	0.9	1.3	Laudanosine (R,S)	-	Convulsant

1.0	0.9	0.7	0.7	0.9	0.8	1.1	Iohexol	-	Diagnostic aid
0.9	0.9	0.5	0.7	0.9	0.9	1.2	Ajmalicine hydrochloride	Alpha antagonist	Antihypertensor
6.3	0.8	0.6	0.9	1.1	1.0	1.3	Norcyclobenzaprine	-	Antiulcerative
0.9	0.9	0.8	0.7	0.9	0.8	1.2	Trigonelline	Antihyperglycaemic agent	
0.9	0.8	0.7	0.8	0.9	0.8	1.2	Pyrazinamide	-	Antibacterial
0.9	0.9	0.8	0.7	0.8	0.9	1.2	Diclofenac sodium	Cyclooxygenase inhibitor	Antiinflammatory
1.0	0.9	0.7	0.7	0.9	0.8	1.4	Trimethadione	Ca++ channel blocker voltage dependant ?	Anticonvulsant
0.9	0.8	0.6	0.7	0.8	0.8	1.2	Calycanthine	Calcium channel blocker	
1.0	1.0	0.3	0.8	1.0	0.8	1.2	Lovastatin	HMG CoA reductase inhibitor	Antihypercholesterolemic
1.1	0.9	0.6	0.7	1.0	0.8	1.3	Convolamine hydrochloride	Cholinergic ligand	Vasodilatator
1.0	0.8	0.7	0.8	0.9	0.8	1.4	Nystatine	Performs membrane ionophores	Antifungal
0.9	0.9	0.7	0.7	0.9	0.8	1.3	Isocorydine (+)	Ganglioblocker	Hypotensor
0.9	0.9	0.6	0.7	0.9	0.9	1.4	Budesonide	-	Antiinflammatory
0.8	0.9	0.8	0.7	0.9	0.9	1.4	Xylazine	Alpha-2 adrenergic agonist	Antinociceptive
12.1	0.9	2.5	1.7	1.2	1.0	2.4	Imipenem	Bacterial transpeptidase inhibitor	Antibacterial
0.9	0.9	0.8	0.7	0.8	0.8	1.2	Seneciphylline	-	Antitumor activity
0.8	0.9	0.8	0.7	1.1	0.8	1.1	Sulfasalazine	15- hydroxydéhydrogenase inhibitor	Treatment of ulcerative colitis
0.9	0.9	0.8	0.7	0.8	0.9	1.2	Boldine	Smooth muscle relaxant	Choleretic

1.3	1.1	1.2	0.9	1.0	1.2	1.2	Bambuterol hydrochloride	Beta2 adrenergic receptor agonist	Bronchodilatator
1.1	0.9	0.8	0.8	0.8	1.0	1.3	Estradiol-17 beta	-	Estrogen
1.1	1.1	1.1	0.9	0.9	1.1	1.3	Betamethasone	-	Glucocorticoid
0.8	1.1	0.9	0.9	0.9	1.1	1.2	Fusaric acid	Dopamine beta hydroxylase inhibitor	Antibacterial
1.2	1.0	1.0	0.9	1.0	1.0	1.1	Colchicine	Tubulin polymerisation inhibitor	Antiinflammatory
1.0	1.1	1.1	0.8	1.1	1.0	1.3	Gabazine	Antagonist GABA	
1.2	1.0	1.1	1.0	1.3	1.1	1.3	Metergoline	5-HT1 antagonist, D2 agonist, 5-HT2 antagonist	Antiprolactin
1.3	1.0	1.1	1.0	1.0	1.1	1.2	Ginkgolide A	Cholinergic antagonist	Alzheimer treatment
1.1	1.4	1.0	0.9	1.1	1.1	1.5	Brinzolamide	Carbonic anhydrase inhibitor	Antiglaucoma drug
1.3	1.0	1.0	0.9	1.2	1.1	1.2	Cyclobenzaprine hydrochloride	-	Muscle relaxant
1.0	1.0	1.0	1.0	1.2	1.2	1.5	Ambroxol hydrochloride	-	Expectorant
1.2	1.0	1.1	0.8	1.0	1.1	1.1	Carteolol hydrochloride		Antihypertensor
1.4	0.9	1.2	1.1	1.0	1.1	1.4	Benfluorex hydrochloride	Increase of glucose penetration and use by cells, decrease of triglyceride intestinal absorption	Hypolipedimic
1.1	1.0	1.3	0.9	1.3	1.1	1.4	Hydrocortisone base	-	Glucocorticoid
1.3	1.1	1.6	1.0	1.5	1.2	1.4	Bepridil hydrochloride	Ca++ channel blocker	Antianginal
1.3	1.0	3.0	1.0	1.0	1.0	1.3	Hydroxytacrine maleate (R,S)	Acetylcholine esterase inhibitor	
1.0	0.9	2.0	0.8	0.9	0.9	1.2	Meloxicam	Cyclooxygenase inhibitor	Anti-inflammatory

1.0	1.1	1.3	0.9	1.0	1.0	1.5	Pilocarpine nitrate	Cholinergic	Antiglaucoma drug
1.1	1.2	0.4	0.9	1.4	1.5	1.4	Benzbromarone	Uric acid transport inhibitor	Coronarodilatator
1.2	1.0	7.1	0.9	1.5	1.4	1.2	Dicloxacillin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
1.1	1.1	1.2	1.0	1.1	1.1	1.4	Glycocholic acid	Detergent	Anticholelithogenic
1.2	1.0	1.0	1.0	1.3	1.1	1.6	Scoulerine	Dopamine antagonist, alpha1 antagonist	Antiemetic
1.3	1.0	0.4	1.0	1.1	0.9	1.4	Thiostrepton		Antibacterial
1.2	1.1	1.0	0.9	1.1	1.1	1.6	Ajmaline	Inhibitor of glucose uptake by heart tissue	Antihypertensor
1.3	1.0	1.1	0.9	1.0	1.2	1.5	Methionine sulfoximine (L)	Glutamine synthetase inhibitor	-
1.3	1.1	1.0	1.0	1.2	1.2	1.3	Monocrotaline	-	For inducing pulmonary diseases in rats
0.6	0.5	0.6	0.4	0.5	0.6	1.3	Tiabendazole	Microtubule inhibitor	Anthelmintic
1.2	1.0	1.0	1.0	1.0	1.1	1.6	Piperlongumine	-	Antifungal
1.3	0.8	0.8	0.7	3.0	0.6	1.4	Rifampicin	RNA polymerase inhibitor	Antibacterial
1.2	1.0	1.0	0.9	1.3	1.2	1.4	Hydrocotarnine hydrobromide	-	Hemostatic
1.1	1.0	1.3	1.0	1.2	1.1	1.4	Ethionamide		Antibacterial
1.3	1.0	0.9	0.8	1.1	1.1	1.6	(-)-Cinchonidine		Antimalarial
1.3	1.0	1.2	0.9	1.0	1.1	1.6	Tenoxicam	Cyclooxygenase inhibitor	Antiinflammatory
1.2	1.1	1.0	1.0	1.1	1.3	1.4	Eburnamonine (-)	-	Cerebral vasodilatator
1.2	1.0	1.4	0.9	1.0	1.2	1.3	Triflusal	Cyclooxygenase inhibitor	Antithrombotic

1.2	1.1	1.6	1.0	1.1	1.1	1.5	Cinchonine	Heme polymerase inhibitor	Antimalarial
1.1	1.1	1.3	1.0	1.0	1.2	1.3	Mesoridazine besylate	D antagonist	Antipsychotic
1.2	1.1	1.6	0.9	1.1	1.1	1.4	Canavanine sulfate monohydrate (L,+)	Nitric oxide inductible synthetase inhibitor	Anticancer agent
1.1	1.1	1.6	1.1	1.1	1.1	1.6	Trolox	-	Vitamin E analog
1.1	1.0	1.4	0.9	1.0	1.0	1.3	Harmaline hydrochloride dihydrate	Monoamine oxydase inhibitor	Antihelminthic
1.3	1.0	1.1	0.9	1.1	1.1	1.7	Ketotifen fumarate	H1 antagonist	Antihistaminic
1.0	1.0	1.0	0.9	1.1	1.1	1.4	Alizapride HCl		Antiemetic
1.2	1.0	0.9	0.8	0.9	1.0	1.7	Debrisoquin sulfate	Catecholamine depletor	Antihypertensor
1.0	1.0	0.8	0.9	1.1	1.0	1.2	Lactobionic acid	-	Antithrombonic
1.1	0.9	1.0	0.8	0.9	1.1	1.3	Amethopterin (R,S)	Dehydrofolate reductase inhibitor	Antineoplastic
1.1	1.0	0.9	1.0	1.2	1.1	1.4	Lumicolchicine gamma	Microtubule depolymerizating agent	–
1.0	0.9	0.8	1.0	0.9	0.9	1.6	Methylergometrine maleate	5-HT antagonist, alpha adrenergic agonist	Oxytocic
1.1	0.9	0.9	0.8	1.0	1.1	1.6	Lysergol	5-HT antagonist	Antipsychotic
1.4	1.0	1.3	1.3	1.5	1.1	1.8	Methiothepin maleate	5-HT autoreceptor antagonist, 5-HT1c antagonist, 5-HT release inhibitor electrical or K+ induced	-
1.1	1.0	0.9	0.8	0.9	1.1	1.5	Mebhydroline 1,5-naphtalenedisulfonate	H1 antagonist	Antihistaminic

1.2	1.0	4.6	1.1	5.0	1.0	1.8	Clofazimine	-	Antileprosy
0.8	1.0	4.3	0.3	3.2	0.5	2.1	Meclocycline sulfosalicylate	Ribosomal protein synthesis inhibitor	Antibacterial
1.0	1.0	0.9	1.0	1.0	1.1	1.4	Nafronyl oxalate	Phosphodiesterase inhibitor ?, 5-HT antagonist, bradykinine antagonist	Vasodilatator
1.2	1.2	2.1	0.9	1.9	1.2	1.4	Meclozine dihydrochloride	Histamine antagonist	Antiemetic
0.9	0.8	1.1	0.7	0.8	1.0	1.5	Bezafibrate	Lipoprotein lipase activator	Antihyperlipoproteinemic
0.9	1.0	1.3	0.8	1.2	1.1	1.4	Melatonin	Melatonin receptor ligand	Immunostimulant
1.0	1.0	1.4	0.9	0.9	1.1	1.5	Mimosine	Cell cycle blocker, apoptosis inducer	Anticancer agent
1.0	1.1	1.4	1.0	1.0	1.2	1.5	Menadione	-	Vitamin K3
1.0	1.1	1.2	1.0	1.0	0.9	1.6	Clebopride maleate	-	Spasmolytic
1.0	1.0	1.4	1.0	1.2	1.0	1.1	Dinoprost trometamol	Protaglandin agonist	Smooth muscle activator
1.1	1.1	1.1	1.0	1.2	1.2	1.5	Pirenperone	5-HT2 antagonist	
1.2	1.0	0.8	0.8	1.1	1.2	1.6	Harmalol hydrochloride dihydrate	-	Vasorelaxant
1.3	0.9	1.0	1.0	1.0	1.2	1.5	Isoquinoline, 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro, hydrochloride	-	-
1.4	1.0	0.9	0.9	1.1	1.1	1.6	Harmol hydrochloride monohydrate	Liver conjugation probe	Anxiolytic
1.2	0.9	0.8	0.9	1.1	0.9	1.4	Phenacetin	Cyclooxygenase inhibitor	Analgesic
1.1	1.1	0.9	0.7	1.0	1.2	1.5	Harmine hydrochloride	Topoisomerase II inhibitor	Antibacterial
1.1	1.0	1.2	0.8	1.2	1.0	1.4	Atovaquone		Antipneumocystic

1.3	1.3	0.8	1.0	4.1	1.2	1.8	Ellipticine	Intercaling agent	Anticancer
1.1	1.0	0.9	1.0	1.0	1.2	1.4	Methoxamine hydrochloride	Alpha adrenergic agonist	Antihypotensive
1.1	0.9	0.1	0.8	0.8	1.0	1.4	Chrysene-1,4-quinone	-	-
1.2	1.0	1.2	0.9	1.1	1.1	1.7	(S)-(-)-Atenolol	Blokage of the action of adrenergic mediators on beta receptors	Antihypertensor
1.4	1.0	0.8	1.0	1.1	1.3	2.0	Demecarium bromide		Cholinergic (ophtalmic)
1.1	0.9	1.0	1.0	0.9	1.1	1.4	Piracetam	-	Nootropic drug
1.1	1.0	1.0	0.8	1.0	1.2	1.3	Quipazine dimaleate salt	5-HT agonist, 5-HT3 ligand	
1.2	0.9	1.1	1.1	1.1	0.9	1.3	Phenindione	Antivitamin K	Anticoagulant
1.3	1.0	1.1	1.0	1.0	1.0	1.7	Sparteine (-)	Ganglioplegic	Antiarrhythmic
1.0	1.1	1.2	0.8	0.9	1.0	1.7	Thiocolchicoside	GABA agonist ?	Muscle relaxant
1.1	1.1	1.1	1.0	0.9	1.0	1.4	Diflorasone Diacetate		Anti-inflammatory (topical)
1.0	1.4	1.5	1.0	1.0	1.1	1.7	Clorsulon		Anthelmintic
1.1	1.0	1.3	0.6	1.0	0.9	1.4	Harmane hydrochloride	Imidazoline receptors ligand	Vasorelaxant
1.4	1.0	1.4	1.1	2.9	1.3	1.4	Lidoflazine	Ca++ channel activator	Coronary vasodilatator
1.1	1.0	0.9	0.8	1.3	1.1	1.3	Tropisetron HCl	5 HT3 antagonist	Antiemetic
1.2	0.9	0.9	1.0	1.4	1.1	1.6	Betaxolol hydrochloride	Beta adrenergic antagonist	Antihypertensor
18.5	1.1	1.2	4.6	1.8	11.7	21.9	Cefixime		Antibacterial
1.2	1.1	0.6	1.0	1.3	1.1	1.4	Nicardipine hydrochloride	Ca2+ channel antagonist	Antihypertensor
1.2	1.0	1.2	1.0	1.3	1.2	1.3	Metrizamide	-	Contrasting product
1.1	0.9	0.6	0.9	1.4	1.1	1.3	Probucol	-	Antihyperlipoproteinemic

1.1	1.0	1.0	1.0	1.5	1.1	1.4	Muramic acid, N-acetyl	Constituent of bacterial peptidoglycan	
1.5	0.8	0.7	1.0	1.5	0.9	1.2	Mitoxantrone dihydrochloride	DNA topoisomerase II inhibitor	Antineoplastic
0.9	0.8	0.5	0.9	0.8	0.9	1.2	Myricetin	Neutral endopeptidase inhibitor	–
1.4	1.3	1.5	1.0	2.2	1.2	1.5	GBR 12909 dihydrochloride	Dopamine reuptake inhibitor	Antidepressant
1.1	0.9	0.5	0.9	1.2	1.0	1.5	Naringenine		Antiestrogenic
1.4	1.0	1.1	1.0	1.4	1.2	1.4	Carbetapentane citrate	Sigma1 receptor ligand	Antitussive
1.3	1.0	1.2	0.9	1.2	1.3	1.2	Naringin hydrate	-	Anti-oxidant
3.0	1.1	1.2	1.6	3.2	2.3	1.8	Dequalinium dichloride	Blocker of the apamin-sensitive small conductance Ca2+ activated K+ channel, detergent	Antibacterial
1.3	1.0	1.2	1.0	1.3	1.1	1.2	Neostigmine bromide	Cholinesterase inhibitor	Spinal analgesic
1.3	0.9	1.2	1.2	1.5	1.1	1.5	Ketoconazole	Cytochrome P450c17 inhibitor, sterol 14-demethylase inhibitor	Antifungal
13.2	1.0	1.8	6.0	1.4	1.2	6.1	Niridazole	Helminthic DNA damage	Anthelmintic
1.1	1.1	4.2	1.1	1.3	1.1	1.4	Fusidic acid sodium salt	Protein synthesis inhibitor GTPase coupled	Antibacterial
12.2	1.0	1.8	3.1	1.8	1.2	1.9	Ceforanide		Antibacterial
1.1	1.6	0.7	0.9	1.2	1.0	1.2	Ciclopirox ethanolamine	Cell membrane proteins synthesis inhibitor	Antifungal
1.4	1.0	0.8	1.0	1.3	1.2	1.4	Methoxy-6-harmalan	Benzodiazepine receptor ligand	Psoriasis treatment

1.4	1.0	1.0	1.1	1.3	1.2	1.4	Probenecid	Uric acid uptake inhibitor	Uricosuric
1.4	1.0	1.0	1.1	1.4	1.2	1.5	Stachydrine hydrochloride	Potent inhibitor of tyrosinase	
1.4	0.9	0.9	1.1	1.2	1.1	1.3	Betahistine mesylate	H1 agonist, H3 antagonist	Vasodilatator
1.4	1.0	1.3	1.1	1.4	1.2	1.7	Pyridoxine hydrochloride	-	Vitamin
7.5	0.9	1.1	2.0	5.7	17.1	1.5	Tobramycin	Ribosomal protein synthesis inhibitor	Antibacterial
1.3	1.0	1.0	1.2	1.4	1.2	1.5	Cytisine (-)	Partial nicotinic receptor antagonist	Antiinflammatory
1.3	1.0	1.1	1.1	1.4	1.2	1.4	Tetramisole hydrochloride	Alkaline phosphatase inhibitor	Antihelminthic
1.4	0.9	1.0	1.2	1.2	1.1	1.5	Pseudopelletierine hydrochloride	-	-
1.4	1.1	1.1	1.1	1.3	1.1	1.5	Pregnenolone		Estrogen
1.2	1.0	1.9	1.1	1.3	1.2	1.5	Racecadotril	Enkephalinase inhibitor	Antidiarrhoeic
1.4	0.9	0.9	1.0	1.2	1.1	1.5	Molsidomine	NO° production ?	Vasodilatator
1.3	1.1	1.0	1.0	1.3	1.1	1.3	Folic acid	-	Vitamin Bc or M
1.2	0.9	1.1	1.1	1.3	1.1	1.6	Chloroquine diphosphate	Heme polymerase inhibitor	Antipaludic
1.2	1.0	1.1	1.2	1.2	1.1	1.5	Salsolinol hydrobromide	Dopamine analog	-
1.4	1.0	1.2	1.1	1.2	1.1	1.7	Trimetazidine dihydrochloride	-	Antianoxic
1.2	1.0	1.3	1.0	1.3	1.1	1.5	Gramine	Cholinesterase inhibitor	Antibacterial
1.5	1.0	1.3	1.1	1.3	1.2	1.4	Parthenolide	MAP kinase inhibitor	Antiinflammatory
1.3	1.0	1.3	1.2	1.5	1.2	1.5	Dimethisoquin hydrochloride		Local anesthesic
1.2	1.0	1.1	1.3	1.1	1.1	1.4	Terbutaline hemisulfate	Beta-2 adrenergic agonist	Bronchodilatator

1.2	1.0	1.1	0.9	1.2	1.1	1.7	Strophantine octahydrate	Na+ K+ ion dependant ATPase inhibitor	Cardiotonic
1.3	1.0	1.0	1.0	1.2	1.0	1.4	Ketanserin tartrate hydrate	5-HT1, 5-HT2, 5-HT2A antagonist	Antihypertensor
1.1	1.1	1.1	1.0	1.1	1.0	1.4	Pantothenic acid calcium salt monohydrate	-	Nutritional factor
1.1	0.9	1.0	1.0	1.2	0.9	2.0	Hemicholinium bromide	Acetylcholine stores depleter, acetylcholine uptake inhibitor	-
22.1	1.2	2.5	8.4	2.0	1.2	25.3	Cefotetan		Antibacterial
1.2	0.9	2.5	1.0	1.1	1.0	1.9	Kanamycin A sulfate	Ribosomal protein synthesis inhibitor	Antibacterial
0.4	0.3	0.2	0.3	0.4	0.4	1.6	Piperine	Enzyme inhibitor	Antidiarrhoeic
22.1	1.0	1.3	6.2	7.6	14.2	4.9	Amikacin hydrate	Ribosomal protein synthesis inhibitor	Antibacterial
1.4	1.0	1.1	1.1	1.2	1.1	2.0	Brompheniramine maleate	H1 Antagonist, anticholinergic	Antihistaminic
1.2	1.1	1.4	1.0	1.2	1.0	1.4	Etoposide	Topoisomerase II inhibitor, kinase inhibitor	Antineoplastic
1.2	0.9	2.1	1.0	1.1	1.0	1.4	Primaquine diphosphate	Heme polymerase inhibitor	Antimalarial
1.8	4.4	2.0	1.6	5.4	1.4	1.9	Clomiphene citrate (Z,E)	Antioestrogen, gonad-stimulating agent	Ovulation inductor
1.0	1.1	1.1	1.1	1.1	1.0	1.7	Progesterone	-	Progestogen
1.1	1.0	1.3	1.0	1.1	1.0	1.8	Oxantel pamoate	Fumarate reductase inhibitor, neuromuscular depolarizing agent	Anthelmintic

1.2	1.3	2.5	1.0	3.0	1.0	1.7	Felodipine	L-type Ca2+ channels blocker	Antihypertensor
1.2	1.1	1.1	1.2	1.6	1.2	2.0	Prochlorperazine dimaleate	Dopamine antagonist	Antiemetic
1.1	1.1	1.0	0.9	1.0	1.0	1.5	Methoxy-8-psoralen	Apoptosis inducer with UV	Psoriasis treatment
1.1	1.1	1.3	1.0	1.2	1.0	1.4	Hesperidin	-	Anticancer
1.1	1.1	1.1	1.1	1.6	1.0	1.4	Puromycin dihydrochloride	Antimetabolite	Antiprotozoal
1.5	1.1	1.2	1.4	3.0	1.1	1.6	Hexetidine	Detergent	Antifungal
1.4	1.0	1.1	1.4	1.3	1.3	1.3	Thiamine hydrochloride	-	Vitamin
1.3	1.0	1.1	1.2	1.1	1.2	1.6	Selegiline hydrochloride	Monoamine B oxydase inhibitor	Antiparkinsonian
1.4	1.0	1.2	1.3	1.4	1.3	1.6	Dipivefrin hydrochloride		Antiglaucoma drug
1.4	1.4	1.9	1.2	1.2	1.2	1.4	Pentamidine isethionate	-	Antiparasitic
1.2	1.0	1.3	1.3	1.2	1.2	1.5	Thiorphan	Neutral endopeptidase inhibitor	Antinociceptive
1.5	1.0	1.0	1.4	1.2	1.4	1.6	Tolazamide	ATP-sensitive K+ ion channels blocker	Antidiabetic
1.1	1.0	0.9	1.6	1.2	1.2	1.5	Riboflavine	-	Vitamin
1.2	1.0	0.7	1.8	1.1	1.2	1.5	Nifuroxazide	Bacterial DNA damage	Antibacterial
1.2	1.1	1.0	1.3	1.2	1.2	1.6	Hydroquinine hydrobromide hydrate	-	Preventor of muscular cramp
1.2	1.1	1.1	1.5	1.2	1.2	1.3	Mycophenolic acid	Inosine monophosphate dehydrogenase inhibitor	Antineoplastic
1.3	1.0	1.0	1.2	1.2	1.2	1.6	Epivincamine		Antiaggregant
1.1	1.2	2.1	1.2	1.8	0.9	1.5	Dirithromycin	Ribosomal protein synthesis inhibitor	Antibacterial

1.3	1.0	1.2	1.2	1.2	1.2	1.5	Retrorsine	-	Antineoplastic
1.2	1.0	1.0	1.2	1.3	1.2	1.8	Gliclazide	K+ channel voltage dependant inhibitor	Antidiabetic
1.5	1.1	1.2	1.2	1.4	1.2	1.6	Conessine		Antiamebic
1.4	1.0	1.1	1.3	1.2	1.3	1.7	DO 897/99	D3 antagonist	-
1.1	1.0	1.2	1.2	1.2	1.1	1.3	Protoveratrine A	Acetylcholinesterase release stimulant	Antihypertensor
1.6	1.2	1.6	1.3	1.9	1.3	1.6	Prenylamine lactate	Ca++ channel activator	Vasodilatator
1.2	1.0	1.2	1.2	1.3	1.2	1.7	Solanine alpha	Butyrylcholinesterase inhibitor	Antifungal
0.3	0.9	0.4	0.5	0.3	0.3	0.3	Sulmazole	Phosphodiesterase III inhibitor	Cardiotonic
0.4	1.0	0.4	0.4	0.4	0.4	0.3	Althiazide	Na+ Cl- transport inhibitor	Diuretic
0.4	0.9	0.3	0.4	0.3	0.3	0.3	Epicatechin-(-)	-	Antidiarrhoeic
0.4	0.8	0.4	0.4	0.3	0.4	0.3	Isopyrin hydrochloride	Cyclooxygenase inhibitor	Antipyretic
0.5	0.9	0.4	0.5	0.4	0.3	0.3	Flunisolide	-	Glucocorticoid
0.5	1.0	0.6	0.5	0.8	0.4	0.3	Phenethicillin potassium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.5	0.8	0.4	0.4	0.4	0.3	0.7	N-Acetyl-DL-homocysteine Thiolactone	Disulfure bridge breaker	Expectorant
0.5	0.9	0.4	0.5	0.7	0.3	0.3	Sulfamethoxypyridazine	Inhibitor of folic acid synthesis	Antibacterial
0.5	0.8	0.4	0.5	0.5	0.4	0.3	Flurandrenolide		Glucocorticoid
0.4	0.9	0.4	0.5	0.4	0.4	0.4	Deferoxamine mesylate	Iron chelating agent	

0.5	0.9	0.4	0.5	0.4	0.4	0.4	Helveticoside	Inhibitor of membrane ATP	Cardiotonic
0.5	0.8	0.4	0.5	0.4	0.4	0.4	Mephentermine hemisulfate	Alpha-adrenergic receptor agonist	Antihypotensive
0.5	0.9	0.4	0.5	0.5	0.4	0.4	Myosmine	Cholinergic	-
0.4	0.7	0.2	0.5	0.5	0.4	0.4	Ergocryptine-alpha		Vasoconstrictor
0.4	0.9	0.4	0.6	0.4	0.4	0.4	Betonicine	-	-
0.6	0.9	0.5	0.5	0.9	0.4	0.4	Sulfadimethoxine	Inhibitor of folic acid biosynthesis	Antibacterial
0.5	0.8	0.4	0.5	0.5	0.4	0.4	Etanidazole	DNA damage	Antineoplastic adjunct (radiosensitizer)
0.5	0.9	0.4	0.6	1.5	0.5	0.4	Sulfanilamide	Inhibitor of folic acid biosynthesis	Antibacterial
0.5	0.8	0.5	0.5	0.5	0.5	0.4	Butirosin disulfate salt	Ribosomal protein synthesis inhibitor	Antibacterial
0.5	0.9	0.4	0.7	0.5	0.5	0.4	Balsalazide Sodium		Anti-inflammatory
0.7	0.8	0.6	0.6	0.7	0.6	0.7	Carbinoxamine maleate salt	Histamine antagonist	Antihistaminic
0.7	0.9	0.6	0.5	0.6	0.6	0.7	Niacin		Antihyperlipoproteine-mic
0.5	1.5	0.6	0.5	0.5	0.6	0.7	Methazolamide	Anhydrase carbonic inhibitor	Diuretic
0.6	0.9	0.7	0.6	0.7	0.6	0.6	Bemegride		Respiratory stimulant
0.7	0.8	0.6	0.6	0.5	0.6	0.7	Pyrithyldione	-	Sedative
0.7	0.8	0.6	0.6	0.6	0.5	0.7	Digoxigenin	Mainly used as a non-isotopic label for DNA	Diagnosis
0.6	1.0	0.6	0.2	0.5	0.5	0.6	Spectinomycin dihydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial

0.5	0.8	0.5	0.7	0.5	0.5	0.6	Meglumine		Expectorant
0.6	0.9	0.7	0.6	0.5	0.5	0.6	Piromidic acid	Topoisomerase II inhibitor	Antibacterial
0.6	0.8	0.5	0.6	0.5	0.5	0.6	Cantharidin		Aphrodisiac
0.6	0.9	0.5	0.6	0.6	0.6	0.6	Trimipramine maleate salt	noradrednaline and 5-HT uptake inhibitor, alpha antagonist, anticholinergic, Dopamine and Histamine antagonist	
0.5	0.9	0.2	0.6	1.1	0.4	0.5	Clioquinol		Anti-infective
0.7	0.9	0.5	0.6	0.6	0.5	0.6	Chloropyramine hydrochloride	H1 antagonist	Antihistaminic
0.5	0.7	0.4	0.4	0.4	0.5	0.6	Oxybenzone		Ultraviolet screen
0.8	0.9	0.8	3.2	0.4	0.6	0.6	Furazolidone	Monoamine oxidase inhibitor and protozoal DNA damage	Antiinfective
0.6	0.8	0.5	0.5	0.6	0.6	0.5	Promethazine hydrochloride		Antihistaminic
0.6	1.1	0.5	0.5	0.5	0.5	0.5	Dichlorphenamide	Carbonic anhydrase inhibitor	
0.2	0.3	0.2	0.2	0.2	0.1	0.6	Chrysin	5-lipoxygenase inhibitor	Antifungal
0.8	3.5	0.7	0.9	2.6	0.5	0.6	Sulconazole nitrate	Ergosterol synthesis inhibition	Antifungal
0.5	0.9	0.5	0.5	0.6	0.5	0.5	Proxyphylline		Vasodilator
0.5	1.4	0.5	0.7	0.7	0.7	0.9	Glimepiride		Antidiabetic
0.6	0.9	0.7	0.6	1.0	0.6	0.8	Sulfaquinoxaline sodium salt	Inhibitor of folic acid synthesis	Antibacterial
0.6	1.0	0.6	0.6	0.7	0.6	0.7	Picrotoxinin	GABA channel blocker	Analeptic
0.7	2.6	1.2	1.4	0.7	0.7	0.7	Streptozotocin		Antineoplastic

0.6	1.0	0.6	0.6	0.7	0.6	0.7	Mepenzolate bromide	Anticholinergic and muscarinic antagonist	
0.6	0.9	0.6	0.5	0.7	0.7	7.0	Metoprolol-(+,-) (+)-tartrate salt	Beta adrenergic antagonist	
0.7	0.9	0.5	0.6	0.7	0.6	0.8	Benfotiamine		Vitamin
0.6	0.9	0.6	0.6	0.7	0.7	0.8	Flumethasone		Antiinflammatory
0.6	0.9	0.6	0.5	0.7	0.7	0.8	Halcinonide		Antiinflammatory
0.6	0.9	0.7	0.6	0.8	0.6	0.7	Flecainide acetate		Antiarrhythmic
0.6	0.9	0.7	0.6	0.8	0.6	1.0	Lanatoside C	Na+ K+ ATPase inhibitor	Cardiotonic
16.5	0.9	3.1	3.6	0.5	0.7	0.9	Cefazolin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.6	1.1	0.7	0.6	0.6	0.6	0.7	Benzamil hydrochloride	Na+ channel blocker and blocker of Na+/Ca++ exchanger	
0.7	0.9	0.7	0.6	0.8	0.6	0.8	Atractyloside potassium salt	Nucleotide transport inhibitor	Anticancer
0.6	0.9	0.6	0.6	0.8	0.6	0.8	Suxibuzone	-	Antiinflammatory
0.7	1.0	0.7	0.6	0.7	0.6	0.7	Folinic acid calcium salt	-	Antianemic
0.7	0.9	0.6	0.5	0.7	0.7	0.9	6-Furfurylaminopurine	-	Plant growth accelerator
0.7	1.0	0.6	0.8	0.8	0.7	0.7	Levonordefrin	Adrenergic receptor agonist	Vasoconstrictor
0.8	1.2	1.7	0.6	0.8	0.6	0.9	Avermectin B1	Ligand GABA receptors	Antihelmetic
0.6	0.9	0.5	0.6	0.7	0.6	0.7	Ebselen	Cyclooxygenase inhibitor	Antiinflammatory
0.7	0.9	0.9	0.8	0.9	0.8	1.1	Bergenin monohydrate	-	Antiarrhythmic
0.7	0.9	0.6	0.6	0.8	0.8	1.1	3-Acetylcoumarin		

0.7	0.9	0.7	0.7	0.9	0.8	1.0	Cromolyn disodium salt	-	Antiasthmatic
0.7	0.9	0.7	0.6	0.8	0.8	0.9	Esculin Hydrate		Skin protectant
0.7	0.9	0.7	0.6	0.8	0.8	0.9	Bucladesine sodium salt	Adenylate cyclase modulator	Cardiotonic
0.7	0.9	0.6	0.6	0.8	0.7	1.0	Felbinac		Analgesic
0.9	0.9	1.0	0.7	1.1	8.6	0.9	Cefsulodin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.5	0.5	0.7	0.4	0.6	0.6	1.0	Butylparaben		Antifungal
0.7	0.9	0.7	0.6	0.8	0.7	0.8	Fosfosal	Cyclooxygenase inhibitor	Analgesic
0.7	0.9	0.6	0.6	0.7	0.7	0.8	Aminohippuric acid		Diagnostic aid (renal function)
0.7	0.9	0.6	0.7	0.8	0.7	0.9	Suprofen	Cyclooxygenase inhibitor	Analgesic
0.7	0.9	0.7	0.6	0.7	0.7	0.9	N-Acetyl-L-leucine		Vertigo
0.7	0.9	0.7	0.6	0.7	0.6	1.0	Catechin-(+,-) hydrate		Antidiarrhoeic
14.7	1.1	0.7	1.7	0.9	0.9	1.0	Pipemidic acid		Antibacterial
0.8	0.9	0.7	0.6	0.7	0.6	0.8	Nadolol	Adrenergic beta antagonist	Antihypertensor
0.8	0.8	0.5	0.7	0.6	0.7	1.0	Dioxybenzone		Ultraviolet screen
18.1	1.3	4.4	3.3	0.6	0.6	0.8	Moxalactam disodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.7	0.9	0.6	0.6	0.8	0.6	1.2	Adrenosterone		Androgenic activity
0.6	0.9	0.6	0.6	0.7	0.8	0.8	Aminophylline	Mastocytes degranulation inhibitor and benzodiazepines antagonist	Vasodilatator
0.7	1.0	0.6	0.6	0.7	0.7	0.8	Methylatropine nitrate		Mydriatic
0.8	1.0	0.7	0.8	0.7	0.8	0.8	Vitexin		Antiviral

0.9	0.9	0.6	0.7	0.8	0.8	0.9	Nadide	Coenzyme nicotinamide adenine dinucleotide	-
0.9	0.9	0.7	0.7	0.7	0.9	0.9	Gelsemine		Tumour inhibitor
1.0	0.9	0.7	0.7	1.4	0.8	0.9	Sulfamethizole	Inhibitor of folic acid synthesis	Antibacterial
1.0	0.9	0.6	0.7	0.7	1.0	0.9	Solasodine		Cytotoxic
0.7	1.0	0.6	0.7	0.7	0.8	1.0	Medrysone	-	Glucocorticoid
0.8	0.9	0.7	0.7	0.9	0.9	1.2	Delcorine	Nicotinic ligand	Antiarrhythmic
0.6	0.6	0.5	0.5	0.5	0.6	1.0	Flunixin meglumine		Analgesic
0.7	0.8	0.6	0.7	0.7	0.8	1.1	Evoxine	Glycine receptor antagonist	Sedative
0.9	1.0	6.6	0.8	0.9	0.7	1.2	Spiramycin	Ribosomal protein synthesis inhibitor	Antibacterial
0.9	0.9	0.4	0.7	1.4	0.8	1.0	Nisoldipine		Antihypertensive
0.9	0.9	0.7	0.8	0.8	0.9	1.1	Glycopyrrolate		Antispasmodic
0.9	0.9	0.7	0.8	0.8	0.8	1.0	Foliosidine	-	Anticonvulsant
10.5	0.9	1.3	2.3	0.6	0.7	0.9	Cefamandole sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.6	0.6	0.6	0.5	0.5	0.6	1.1	Skimmianine	5-HT ligand	Sedative
0.9	1.1	0.7	0.6	0.7	0.9	1.1	Monensin sodium salt	Performs membrane ionophores	Antibacterial
1.0	0.9	0.6	0.8	0.8	0.9	1.0	Anabasine		Insecticide
0.9	0.9	0.6	1.4	0.8	0.6	0.9	Isoetharine mesylate salt	Beta adrenergic agonist	Bronchodilator
0.9	1.0	0.9	0.9	0.9	0.9	1.1	Tetrandrine		Analgesic

1.0	1.0	0.9	0.8	0.9	0.8	0.9	Mevalonic-D, L acid lactone	HMG CoA substrate	-
12.3	0.9	0.4	0.7	2.1	9.7	1.0	Azlocillin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.9	1.0	1.0	0.7	0.8	1.0	1.1	Hymecromone		Antispasmodic
1.0	0.9	0.9	0.8	1.1	1.1	1.3	Clidinium bromide	Anticholinergic	Spasmolytic
1.0	0.9	0.8	0.8	0.8	0.9	1.0	Caffeic acid		Antineoplastic
0.9	0.9	0.7	0.8	1.6	1.0	1.1	Sulfamonomethoxine	Inhibitor of folic acid synthesis	Antiseptic
1.0	0.8	0.7	0.7	0.9	1.0	1.2	Diloxanide furoate		Antiamebic
0.9	1.4	0.8	0.8	0.9	0.9	1.1	Benzthiazide	Na+ Cl- transport inhibitor	Diuretic
0.9	0.8	0.8	0.7	1.0	1.0	1.2	Metyrapone		Diagnostic aid (pituitary function)
0.8	1.4	1.3	0.8	1.0	0.8	1.2	Trichlormethiazide	Na+ Cl- transport inhibitor	Diuretic
1.0	0.9	0.9	0.7	1.0	1.0	1.1	Urapidil hydrochloride		Antihypertensor
0.9	0.8	0.8	0.7	0.8	0.9	1.2	Oxalamine citrate salt	-	Antiinflammatory
1.3	1.3	1.4	1.1	6.6	0.8	1.0	Fluspirilen		Antipsychotic
0.9	0.8	0.8	0.8	1.0	0.9	1.3	Propantheline bromide	Muscarinic antagonist	Antiulcerative
0.9	0.9	0.8	0.7	0.8	0.9	1.3	S-(+)-ibuprofen		Analgesic
1.0	0.9	3.7	0.7	2.6	0.7	1.0	Lasalocid sodium salt	Membrane ionophores producer	Antibacterial
0.8	0.9	0.5	0.7	0.9	0.9	1.1	Ethynodiol diacetate		Progestogen
0.9	0.9	0.7	0.8	0.8	0.8	1.0	Dimethadione	-	Anticonvulsant
0.5	0.4	0.4	0.5	0.4	0.6	1.0	Nabumetone		Analgesic

0.9	1.0	0.5	0.7	0.9	0.9	1.0	Ethaverine hydrochloride		Antispasmodic
0.9	1.0	0.7	0.7	0.8	0.9	0.9	Nisoxetine hydrochloride	Inhibitor of noradrenaline	
0.9	1.0	0.7	0.8	0.8	0.9	1.2	Dydrogesterone		Progestogen
0.8	0.8	0.8	0.7	0.7	0.6	1.2	Terazosin hydrochloride	Alpha adrenergic antagonist	Treatment of benign prostatic hyperplasia
0.8	0.9	0.7	0.7	0.9	0.8	1.3	(d,l)-Tetrahydroberberine	-	Sedative
0.1	0.1	0.3	0.1	0.1	0.1	1.4	Phenazopyridine hydrochloride	-	Analgesic
0.9	0.9	0.8	0.7	0.8	0.8	1.1	Deltaline	Nicotinic receptor ligand	Antiarrhythmic
0.5	0.9	7.1	0.2	3.4	0.4	1.3	Demeclocycline hydrochloride	Ribosomal protein synthesis inhibitor	Antibacterial
0.8	0.8	0.7	0.6	0.8	0.8	1.2	Graveoline	topoisomerase II inhibitor? and CNS stimulant	Antihypotensive
0.8	0.9	0.8	0.7	0.8	0.8	1.4	Fenoprofen calcium salt dihydrate	Cyclooxygenase inhibitor	Antiinflammatory
0.9	0.9	0.7	0.6	0.8	0.9	1.4	Hippeastrine hydrobromide	-	Hypotensor
12.6	0.9	0.4	2.3	3.3	8.7	1.3	Piperacillin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.9	0.9	0.8	0.7	0.8	0.7	1.4	Beta-Escin		Peripheral vascular disorders
0.9	1.1	0.6	0.7	1.8	0.8	1.4	Diethylstilbestrol		Estrogen
0.6	1.3	0.2	0.3	0.4	0.5	1.5	Gossypol	Ca2+ uptake inhibitor	Local contraceptive
0.9	1.0	0.8	0.8	0.8	0.8	1.4	Chlorotrianisene	Nuclear receptor ligand	Non-steroidal estrogen
0.8	0.9	0.9	0.8	0.8	0.7	1.3	Ricinine		
0.9	0.9	0.8	0.7	0.8	0.8	1.2	Ribostamycin sulfate salt	Ribosomal protein synthesis inhibitor	Antibacterial

0.9	0.9	0.8	0.7	0.9	0.8	1.3	Delsoline	Nicotinic receptor antagonist and Ganglioblocker	
0.9	0.9	0.7	0.7	0.8	0.9	1.3	Methacholine chloride	Cholinergic agonist	
0.9	0.9	0.8	0.7	0.9	0.8	1.4	Fluorocurarine chloride		Muscle relaxant
0.9	0.9	0.8	0.7	0.7	0.8	0.9	Pipenzolate bromide	Nicotinic receptor antagonist	Spasmolytic
0.9	0.9	0.8	0.8	0.9	1.0	1.4	Butacaine	Na+ channel blocker	Local anesthesic
0.9	0.9	0.8	1.0	0.8	0.8	1.4	(+)-Isoproterenol (+)-bitartrate salt		Sympathomimetic (VET)
20.1	1.0	3.4	3.2	1.3	0.8	1.2	Cefoxitin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
0.7	0.6	0.6	0.5	0.5	0.7	1.4	Monobenzone		Depigmentor
5.0	0.8	0.8	0.7	0.8	0.9	1.4	Ifosfamide		Antineoplastic
1.1	0.9	0.8	0.7	0.9	0.9	1.4	2-Aminobenzenesulfonamide	Ligand and potent inhibitor of carbonic anhydrase B	
3.2	1.5	4.5	0.7	1.1	1.0	1.6	Novobiocin sodium salt	DNA topoisomerase IV inhibitor	Antibacterial
0.8	0.8	0.7	0.7	0.8	0.8	1.4	Estrone		Estrogen
0.9	0.9	0.8	0.8	1.1	0.9	1.3	Tetrahydroxy-1,4-quinone monohydrate	-	Keratolytic
0.9	1.0	0.3	0.7	0.8	0.9	1.3	Lorglumide sodium salt	CCKa ligand	
0.2	0.1	0.2	0.1	0.2	0.2	1.5	Indoprofen	Cyclooxygenase inhibitor	Analgesic
0.8	0.9	0.4	0.8	0.9	0.9	1.4	Nitrendipine		Antihypertensor
0.8	0.9	1.6	0.7	1.1	0.9	1.4	Carbenoxolone disodium salt	Mucus stimulating synthesis	Antiulcerative
0.8	0.9	0.6	0.7	0.9	0.8	1.6	Flurbiprofen		Anti-inflammatory

0.9	0.9	0.8	0.8	0.8	0.9	1.4	Iocetamic acid		Diagnostic aid (radiopaque medium)
0.9	1.0	0.7	0.7	1.0	0.9	1.4	Nimodipine		Vasodilator
0.9	0.9	0.9	0.7	0.8	0.9	1.4	Ganciclovir	Antimetabolite	Antiviral
1.0	1.3	0.4	0.8	1.1	0.8	1.2	Bacitracin		Antibacterial
0.9	0.9	0.7	0.8	1.0	1.0	1.3	Ethopropazine hydrochloride	Anticholinergic	Antiparkinsonian
0.8	0.9	0.8	0.7	0.8	0.8	1.2	L(-)-vesamicol hydrochloride	Potent inhibitor of vesicular acetylcholine storage	
1.2	1.1	1.2	1.0	1.0	1.1	1.3	Austricine hydrate		Antiatherosclerotic
0.8	0.8	1.1	0.6	0.7	0.9	1.7	Butamben	Na+ channel blocker	Anesthetic
1.2	1.0	1.3	0.9	1.0	1.2	1.3	beta- Belladonnine dichloroethylate	Muscarinic receptor and nicotinic receptor lignad	
1.2	1.0	1.4	0.9	2.2	1.1	1.6	Sulfapyridine		Antibacterial
1.1	1.0	1.1	1.0	1.1	1.1	1.5	Pempidine tartrate	Nicotinic acetylcholine receptor antagonist	Antihypertensor
1.2	1.0	1.2	1.0	1.0	1.1	1.4	Meclofenoxate hydrochloride	Acetylcholine precursor	Cerebral stimulant
1.2	1.0	1.4	1.0	1.0	1.0	1.7	Heliotrine	Model for hepatitis and cirrhosis in liver	
0.9	1.1	0.7	2.6	1.0	1.1	1.7	Furaltadone hydrochloride	Bacterial DNA damage	Antibacterial
1.2	1.0	1.3	1.1	1.0	1.1	1.4	Nitrarine dihydrochloride	-	Hypotensor
1.1	0.9	1.1	0.9	0.9	1.1	1.4	Ethoxyquin	-	Antifungal
1.0	1.0	1.4	0.8	1.0	1.1	1.5	Lycorine hydrochloride	Inhibitor of protein translation	Antitumoral
1.2	0.9	1.2	0.8	1.0	1.1	1.5	Tinidazole	Protozoal and bacterial DNA	Antiprotozoal

								damage	
1.0	1.0	1.2	0.9	1.0	1.1	1.3	Karakoline	Inhibitor of ACE	Hypotensor
1.3	1.0	1.2	0.7	1.0	1.1	1.4	Guanadrel sulfate		Antihypertensor
1.1	1.0	1.1	1.0	1.0	1.1	1.3	Estropipate		Menopause
1.1	1.1	1.5	0.7	1.0	1.0	1.8	Vidarabine	Adenosine antimetabolite	Antiviral
1.3	1.0	1.2	1.0	1.1	1.1	1.4	Ungerine nitrate	Enhancer of analgesics	Sedative
1.3	1.0	1.2	1.0	2.3	1.1	1.2	Sulfameter	Inhibitor of folic acid synthesis	Antibacterial
1.3	1.0	1.4	1.0	1.0	1.1	3.6	Napelline	Anticholinergic agent	Antiarrhythmic
1.3	1.1	1.2	1.1	1.0	1.2	1.5	Isopropamide iodide	Anticholinergic	
1.3	1.0	1.1	0.8	1.1	1.2	1.6	Securinine	-	CNS stimulant
1.3	1.0	1.2	0.9	1.0	1.2	1.7	Nizatidine	H2 antagonist	Antiulcerative
1.2	1.0	1.1	0.9	1.1	1.2	1.5	Trimeprazine tartrate	Histamine antagonist	Antipruritic
1.2	1.0	1.1	1.0	1.0	1.3	1.6	Thioperamide maleate	H3 antagonist	Antiemetic
1.2	1.0	6.5	1.0	1.5	1.3	1.4	Nafcillin sodium salt monohydrate	Bacterial transpeptidase inhibitor	Antibacterial
1.3	1.0	1.1	0.8	1.0	1.2	1.8	Xamoterol hemifumarate	beta1-Adrenoceptor selective partial agonist	Cardiotonic
1.4	1.1	1.2	0.9	1.1	1.2	1.8	Procyclidine hydrochloride	Muscarinic antagonist	Antiparkinsonian
1.1	1.0	1.3	1.0	1.2	1.2	1.7	Rolipram		Nootropic drug
1.3	1.1	1.3	0.9	1.2	1.1	1.5	Amiprilose hydrochloride	-	Immunomodulator
3.2	7.5	###	4.7	5.6	1.5	1.8	Thonzonium bromide	Detergent	

1.2	0.9	0.8	0.8	1.1	1.1	1.5	Ethynylestradiol 3-methyl ether	-	Estrogen
1.1	1.0	1.1	1.0	1.1	1.2	1.5	Idazoxan hydrochloride	Alpha2 agonist	Antiparkinsonian
1.3	1.0	1.0	1.0	1.0	1.2	1.9	(-) -Levobunolol hydrochloride	Adrenergic beta antagonist	Antiglaucoma drug
1.2	1.1	1.2	1.0	1.2	1.2	1.6	Quinapril HCl		Angiotensin
1.3	1.1	1.3	1.0	1.0	1.2	1.5	Iodixanol		Diagnostic aid (radiopaque medium)
1.2	1.0	1.3	1.0	1.2	1.2	1.4	Nilutamide		Antineoplastic
1.1	1.0	1.1	1.0	1.2	1.1	1.7	Rolitetracycline	Ribosomal protein synthesis inhibitor	Antibacterial
1.3	1.0	1.1	1.0	1.0	1.0	1.4	Ketorolac tromethamine		Analgesic
1.3	1.0	3.3	0.9	1.0	1.1	1.4	Equilin	-	Estrogen
1.2	1.0	2.8	1.1	1.1	1.2	1.4	Protriptyline hydrochloride		Antidepressant
1.2	1.0	1.0	0.8	0.9	1.2	1.8	Fillalbin	-	-
1.1	1.0	1.1	1.1	0.9	1.0	1.2	Alclometasone dipropionate	Corticoïde	Anti-inflammatory
1.0	1.0	1.0	0.9	0.9	1.2	1.5	Citalopram Hydrobromide	5HT uptake inhibitor	
0.8	0.7	0.6	0.6	0.8	0.8	1.5	Leflunomide	Inhibitor of T and B cell proliferation	Immunosuppressive
1.2	1.0	1.4	0.8	0.9	1.1	1.7	Promazine hydrochloride	Dopamine receptor antagonist	Antipsychotic
1.0	1.0	1.1	1.1	1.1	1.1	1.7	Norgestrel-(-)-D	Progestogen	Oral contraceptive
1.1	1.0	0.9	1.0	2.1	1.0	1.9	Sulfamerazine	Inhibitor of folic acid synthesis	Antibacterial
1.0	1.0	1.1	0.9	0.9	1.2	1.7	Fluocinonide		Antiinflammatory

0.7	0.5	0.7	0.6	0.3	0.6	1.6	Acacetin	Inhibitor of glutathione reductase and of topoisomerase I	Antitumor agent
1.0	1.0	1.4	1.0	1.6	1.1	1.4	Sulfamethazine sodium salt	Inhibitor of folic acid synthesis	Antibacterial
1.2	1.0	1.2	1.0	1.1	0.9	1.6	Ethotoin		Anticonvulsant
1.1	1.0	1.2	0.8	1.0	1.1	1.6	Guaifenesin	-	Expectorant
1.2	1.0	1.0	0.9	0.9	1.1	1.9	3-alpha-Hydroxy-5-beta-androstan-17-one		
43.3	7.4	###	23.4	12.3	19.2	1.5	Alexidine dihydrochloride	Detergent	Antibacterial
1.4	1.0	1.1	0.9	1.0	1.0	1.4	Tetrahydrozoline hydrochloride	Adrenergic	Vasoconstrictor
1.2	1.1	0.8	0.8	1.1	1.1	1.7	Proadifen hydrochloride	Cytochrome P450 mono-oxygenases inhibitor, Na+ channel blocker	Local anesthesic
1.4	1.2	0.7	0.7	3.0	1.1	1.6	Hexestrol	Nuclear receptor ligand	Estrogen antineoplastic
1.1	1.1	0.9	1.0	1.1	0.9	1.6	Zomepirac sodium salt	Cyclooxygenase inhibitor	
20.0	1.4	5.0	4.6	1.4	1.0	1.6	Cefmetazole sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
10.3	1.1	1.3	2.1	1.3	1.2	1.4	Cinoxacin	Topoisomerase II inhibitor	Antibacterial
1.4	0.9	1.4	1.2	1.3	1.3	1.6	Paroxetine Hydrochloride	5-HT uptake inhibitor	
1.3	1.0	1.2	1.1	1.0	1.0	1.7	Propofol		Anesthetic (intravenous)
2.0	1.1	9.4	0.3	3.4	0.7	1.5	Doxycycline hyclate	Ribosomal protein synthesis inhibitor	Antibacterial
0.9	1.0	1.6	1.1	1.0	1.3	1.8	S(-)Eticlopride hydrochloride		
1.2	1.1	1.0	0.9	1.1	1.1	1.6	Liothyronine	Thyroid hormone	Thyroidic drug

1.0	0.9	1.3	0.9	1.2	1.2	1.8	Primidone		Anticonvulsant
0.9	1.4	2.8	1.1	1.0	0.9	1.5	Roxithromycin	Ribosomal protein synthesis inhibitor	Antibacterial
1.1	0.9	1.1	0.8	1.2	1.1	1.8	Flucytosine		Antifungal
1.1	1.0	0.5	0.9	1.0	1.0	1.5	Beclomethasone dipropionate	-	Antiinflammatory
1.2	1.0	1.1	1.0	1.1	1.3	1.9	(-)-MK 801 hydrogen maleate	NMDA antagonist	Anticonvulsant
0.9	0.8	0.9	0.6	0.8	1.0	2.0	Tolmetin sodium salt dihydrate	Cyclooxygenase inhibitor	Antiinflammatory
1.2	1.0	1.2	1.0	0.9	1.0	2.0	Bephenium hydroxynaphthoate		Antihelmintic
1.2	0.9	1.3	0.9	0.9	1.2	1.5	(+) -Levobunolol hydrochloride	Beta adrenergic antagonist	Antiglaucoma drug
1.0	1.1	0.8	0.9	1.1	1.1	1.7	Dehydroisoandosterone 3-acetate		Menopausal syndrome
1.4	1.1	1.2	0.9	1.3	1.1	1.5	Doxazosin mesylate	Alpha 1 adrenergic antagonist	Antihypertensor
1.3	0.9	1.4	1.2	1.0	1.1	1.8	Benserazide hydrochloride	Inhibitor of L-aromatic amino acid decarboxylase	In combination with levodopa as antiparkinsonian
1.3	1.0	1.0	0.9	0.9	1.0	1.7	Fluvastatin sodium salt	HMG CoA reductase inhibitor	Anti- hyperlipoproteinemic
1.2	1.0	1.0	1.0	1.2	1.1	1.6	Iodipamide		Diagnostic aid (radiopaque medium-cholecystographic)
1.4	1.1	1.3	1.0	1.0	1.1	2.0	Methylhydantoin-5-(L)	-	_
1.4	1.0	1.1	1.2	1.1	0.9	1.4	Esculetin		Antifungal
1.2	1.1	1.4	1.1	1.4	1.3	1.5	Trihexyphenidyl-D,L Hydrochloride	Anticholinergic	Antiparkinsonian
1.2	1.0	0.9	1.0	1.3	1.1	1.3	Clobetasol propionate	-	Glucocorticoid
1.4	1.0	1.3	1.1	1.3	1.1	1.4	Succinylsulfathiazole	Inhibitor of folic acid	Antibacterial

								synthesis	
1.2	0.9	1.0	1.2	1.2	1.1	1.3	Podophyllotoxin		Antiviral
1.2	1.0	0.8	1.1	1.1	1.2	1.5	Famprofazone		Antipyretic
1.2	1.1	1.4	1.1	1.3	1.2	1.5	Clofibric acid	Lipoproteine lipase activator ?	Antihyperlipoproteinemic
1.3	0.9	1.3	1.0	1.3	1.1	1.3	Bromopride	Dopamine antagonist	Antiemetic
1.3	1.2	1.3	1.1	1.3	1.1	1.5	Bendroflumethiazide	Na+ Cl- transport inhibitor	Diuretic
5.1	7.4	###	7.4	5.8	8.9	1.3	Methyl benzethonium chloride	Detergent	Antibacterial
1.1	1.3	1.3	1.1	1.3	1.2	1.5	Dicumarol	Vitamin K antagonist	Anticoagulant
1.3	1.0	1.2	1.1	1.5	1.1	1.6	Chlorcyclizine hydrochloride	Histamine antagonist	Antihistaminic
1.2	0.9	1.0	1.0	1.4	1.0	27.1	Methimazole	Iodine oxidazing inhibitor	Antihyperthyroid
1.3	1.1	1.2	1.0	1.3	1.1	1.4	Diphenylpyraline hydrochloride	H1 antagonist	Antihistaminic
0.5	0.6	0.2	0.4	0.7	0.4	1.4	Merbromin	-	Antibacterial
2.9	6.2	###	5.7	5.4	5.8	1.3	Benzethonium chloride	Detergent	Antibacterial
1.2	1.0	1.3	1.0	1.3	1.1	1.4	Hexylcaine hydrochloride		Local anesthesic
1.2	0.9	0.9	1.0	1.2	1.0	1.3	Trioxsalen	-	Pigmentation agent (photosensitizer)
1.5	1.0	1.5	1.2	1.3	1.2	1.5	Drofenine hydrochloride	-	Spasmolytic
1.4	1.0	1.3	1.1	1.3	1.1	1.3	Strophanthidin	ATPase inhibitor	Cardiotonic
1.3	1.0	1.1	1.0	1.2	1.1	0.9	Cycloheximide	-	Antibacterial
1.4	1.0	1.5	1.1	1.4	1.3	1.6	Gabapentin	GABA receptor ligand	Anticonvulsant
1.3	1.0	1.4	1.1	1.3	1.2	1.5	Pentetic acid	Chelating agent (iron)	

1.5	0.9	1.2	1.1	1.5	1.2	1.3	Raloxifene hydrochloride		
1.3	1.0	1.3	1.1	1.3	1.2	1.6	Bretylium tosylate		Antiadrenergic
1.3	1.0	1.2	1.0	1.2	1.1	1.4	Etidronic acid, disodium salt	-	Calcium regulator
1.3	1.0	1.3	1.0	1.4	1.2	1.5	Pralidoxime chloride		
1.2	1.0	1.2	1.1	1.3	1.2	1.5	Methylhydantoin-5-(D)	-	_
1.4	0.9	1.1	1.2	1.3	1.1	1.4	Phenoxybenzamine hydrochloride	Nonselective alpha-adrenergic blockade	Antihypertensor
1.6	1.0	0.4	1.2	2.5	1.1	1.5	Simvastatin	HMG-CoA reductase inhibitor	Antihyperlipidemic
1.4	1.0	1.9	1.1	1.5	1.2	1.5	Salmeterol	beta 2 adrenergic agonist	Bronchodilator
2.2	1.0	1.2	0.9	1.4	1.2	1.5	Azacytidine-5	Antimetabolite	Antineoplastic
1.3	1.0	1.1	1.0	1.3	1.2	1.4	Altretamine		
1.4	0.9	1.3	1.0	1.5	1.0	1.4	Paromomycin sulfate	Ribosomal protein synthesis inhibitor	Antiamebic
1.2	1.1	1.4	0.9	1.4	1.1	1.5	Prazosin hydrochloride		Antihypertensor
1.4	1.0	1.6	1.2	1.5	1.1	1.6	Acetaminophen	Cyclooxygenase inhibitor	Antipyretic
1.3	1.0	1.3	1.1	1.5	1.1	1.4	Timolol maleate salt		Antiglaucoma drug
1.4	1.0	1.4	1.0	1.4	1.0	1.2	Phthalylsulfathiazole	Inhibitor of folic acid synthesis	Antibacterial
1.3	1.0	1.3	1.1	1.3	1.0	1.4	(+,-)-Octopamine hydrochloride	beta-3 Adrenergic receptor agonist	Adrenergic
0.4	0.5	0.2	0.5	0.3	0.5	1.6	Luteolin	-	Expectorant
1.4	1.0	1.3	1.2	1.3	1.0	1.3	(±)-Nipecotic acid	Activates GABA-like ion	

								channels	
1.1	1.1	1.2	1.1	2.8	1.1	1.6	Sulfabenzamide	Inhibitor of folic acid synthesis	Antibacterial
1.1	1.0	1.0	1.0	1.1	1.0	1.7	(R) -Naproxen sodium salt	Cyclooxygenase inhibitor	Antiinflammatory
1.1	1.0	1.2	0.9	1.2	1.1	1.6	Benzocaine	Na+ channel blocker	Anesthetic
1.3	0.8	1.4	0.8	1.1	1.0	1.6	Propidium iodide	Detergent	Antibacterial
1.1	1.0	1.4	1.1	1.1	1.1	1.4	Dipyrone	Cyclooxygenase inhibitor	Antipyretic
1.2	1.1	1.3	1.2	1.4	1.2	2.0	Cloperastine hydrochloride	Histamine antagonist	Antitussive
1.1	1.0	1.2	1.0	1.1	1.0	1.8	Isosorbide dinitrate	Nitric oxide (NO) donor	Antianginal
1.2	1.1	1.3	0.9	1.1	1.1	1.6	Eucatropine hydrochloride	Anticholinergic	
1.0	1.0	1.1	1.1	2.1	1.0	1.5	Sulfachloropyridazine	Inhibitor of folic acid synthesis	Antibacterial
1.1	1.0	1.5	1.1	1.1	1.1	1.5	Isocarboxazid		Antidepressant
1.1	1.0	1.3	1.1	1.1	1.2	1.5	Pramoxine hydrochloride		Local anesthesic
0.8	1.2	1.1	0.8	1.0	1.0	1.7	Lithocholic acid	Anticholelithogenic, gastrointestinal agent	Cholagogue
1.1	1.1	1.0	0.9	1.2	1.1	1.8	Finasteride		Antialopecia agent
1.3	1.0	1.2	1.0	1.1	1.1	1.8	Methotrimeprazine maleat salt	-	Analgesic
1.1	1.0	1.2	1.0	1.3	1.1	1.7	Fluorometholone	-	Glucocorticoid
1.1	1.3	0.4	0.9	3.2	1.1	21.9	Dienestrol	Nuclear receptor ligand	Non-steroidal estrogen
11.8	1.0	5.3	3.2	1.1	1.1	2.0	Cephalothin sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
1.1	1.1	1.2	0.9	1.1	1.1	1.6	Pridinol methanesulfonate salt	Anticholinergic	Antiparkinsonian

12.1	1.0	3.4	2.4	1.4	1.6	1.6	Cefuroxime sodium salt	Bacterial transpeptidase inhibitor	Antibacterial
1.3	1.0	1.1	1.1	1.2	1.0	44.0	Amrinone	TNF production inhibitor	
1.2	1.0	1.3	1.2	1.2	1.2	1.4	Iopamidol		Diagnostic aid (radiopaque medium)
1.5	1.1	1.3	1.1	1.3	1.3	1.3	Crotamiton		Scabicide
1.2	1.0	1.3	1.1	1.1	1.2	1.4	Iopromide	Contrast molecule	
1.2	1.1	1.4	1.1	1.2	1.2	1.4	Propranolol hydrochloride	Beta blocking agent	Antiarrhythmic
1.2	1.0	1.3	1.1	1.2	1.2	1.3	Theophylline monohydrate	Mastocyte degranulation inhibitor in vitro	Bronchodilatator
1.3	1.0	1.2	1.2	1.3	1.2	1.3	(R)-(+)-Atenolol		
1.2	1.1	1.3	1.2	1.1	1.2	1.4	Theobromine	Adenosine receptor antagonist	Cardiotonic
1.4	1.0	1.4	1.5	1.3	1.2	1.2	Tyloxapol		Mucolytic
1.3	1.1	1.3	1.2	1.5	1.4	1.5	Reserpine		
1.2	1.0	###	0.3	1.2	1.4	1.4	Florfenicol		Antibacterial
0.7	0.6	0.9	0.7	0.8	0.8	1.2	Arcaine sulfate	Lowers blood sugar	
1.1	1.2	0.9	1.0	1.2	1.2	1.6	Megestrol acetate		Progestogen
1.2	1.0	1.2	1.1	1.2	1.1	1.5	Scopolamine hydrochloride	Non-selective muscarinic antagonist	Antiemetic
1.2	1.2	1.6	1.2	1.3	1.3	1.3	Deoxycorticosterone	Corticoide	Antiinflammatory
1.2	1.0	1.2	1.2	1.3	1.2	1.4	Ioversol		Diagnostic aid (radiopaque medium)
1.2	1.0	1.2	1.0	1.3	1.2	1.4	Urosiol		Anticholelithogenic

1.3	1.1	1.2	1.0	1.2	1.1	1.5	Capsaicin	Vanilloid receptor ligand	Topical analgesic
1.3	1.0	1.2	1.1	1.4	1.1	1.2	Proparacaine hydrochloride		Local anesthesic (VET)
1.2	1.1	1.4	1.2	1.3	1.2	1.2	Carbachol	Cholinergic agonist, Cholinesterase inhibitor ?	Myotic
1.2	1.1	1.2	1.2	1.3	1.1	1.6	Aminocaproic acid		Antiallergic
0.5	0.9	0.4	0.4	0.3	0.4	0.4	Denatonium benzoate	Bittering agent to prevent poisoning	
0.5	0.9	0.3	0.4	0.3	0.4	0.3	Etomidate		Hypnotic
0.4	0.9	0.3	0.4	0.4	0.4	0.3	Scopoletin	Eicosanoid release inhibitor	Antispasmodic
0.4	0.8	0.4	0.4	0.4	0.4	0.3	Tridihexethyl chloride		Antispasmodic
0.5	1.1	0.4	0.5	0.4	0.4	0.4	Enilconazole		Antifungal
0.5	0.8	0.4	0.5	0.4	0.5	0.4	Penbutolol sulfate		Antiarrhythmic
3.2	0.9	1.9	0.2	4.2	0.2	0.4	Methacycline hydrochloride		Antibacterial
0.4	0.9	0.4	0.5	0.4	0.4	0.3	Prednicarbate		Glucocorticoid (topical)
0.5	0.8	0.4	0.5	0.4	0.4	0.4	Gibberellic acid		Plant growth regulator
0.7	2.8	0.7	0.7	2.4	0.5	0.4	Sertaconazole nitrate		Antibacterial
0.4	0.8	0.4	0.5	0.5	0.4	0.4	Sotalol hydrochloride	Beta-blocker	
0.4	0.9	0.3	0.4	0.4	0.4	0.4	Repaglinide		Antidiabetic
0.5	0.9	0.4	0.5	0.5	0.4	0.4	6-Hydroxytropinone		
0.5	0.8	0.4	0.5	0.4	0.4	0.4	Piretanide		Antihypertensor
0.5	0.9	0.4	0.5	0.5	0.4	0.5	Decamethonium bromide		Muscle relaxant (skeletal)
0.5	0.9	0.5	0.5	0.6	0.5	0.4	Piperacetazine		Antipsychotic

0.5	0.8	0.4	0.4	0.4	0.4	0.4	3-Acetamidocoumarin		Antiinflammatory
0.5	0.9	0.4	0.5	0.5	0.5	0.5	Oxyphenbutazone	Inhibition of cyclo-oxygenase	Anti-inflammatory
0.4	0.8	0.6	0.4	0.5	0.5	0.5	Roxarsone		Control of enteric infections. To improve growth and feed efficiency (VET)
0.6	0.9	0.4	0.6	0.5	0.5	0.4	Quinethazone		Diuretic
0.7	0.9	0.6	0.6	0.7	0.7	0.8	Remoxipride Hydrochloride	Dopaminergic antagonist	Antipsychotic
0.6	1.0	0.6	0.6	0.6	0.6	0.7	Moricizine hydrochloride		Antiarrhythmic
0.6	1.0	0.6	0.6	0.6	0.6	0.8	THIP Hydrochloride	GABAergic Agonist	
0.6	0.9	0.4	0.6	0.6	0.6	0.6	Iopanoic acid	Contrast molecule	
0.7	0.9	0.6	0.6	0.7	0.7	0.7	Pirlindole mesylate	Highly selective reversible inhibitor of monoamine oxidase type A	Anti depressant Seizures
0.7	0.9	0.6	0.5	1.1	0.6	0.8	Pivmecillinam hydrochloride		Antibacterial
0.7	0.9	0.6	0.6	0.6	0.6	0.9	Pronethalol hydrochloride		Antihypertensor
0.6	1.0	0.6	0.6	0.7	0.7	0.7	Levopropoxyphene napsylate		Antitussive
0.9	0.8	0.5	0.6	0.7	0.7	0.9	Naftopidil dihydrochloride	Alpha1 agonist	Antihypertensor
0.7	1.0	0.6	0.6	0.6	0.7	0.7	Piperidolate hydrochloride		Antispasmodic
0.5	1.1	0.5	0.6	0.8	0.6	0.7	Tracazolate hydrochloride	GABA receptor ligand	
0.9	0.9	0.7	1.1	1.1	0.6	0.7	Trifluridine		Antiviral (ophthalmic)
0.6	1.0	0.6	0.7	0.7	0.7	0.9	Zardaverine	Phosphodiesterase III & IV inhibitor	
0.7	0.9	0.6	0.6	0.6	0.6	0.9	Oxprenolol hydrochloride	Blocking beta-adrenergic receptors	Antiarrhythmic

0.6	0.9	0.6	0.5	0.7	0.6	0.7	Memantine Hydrochloride	NMDA receptor antagonist	Altzheimer disease
0.7	1.1	0.6	0.6	0.7	0.7	0.8	Ondansetron Hydrochloride	Antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT 3) receptors	Antiemetic
0.6	0.9	0.5	0.5	0.7	0.6	0.9	Ozagrel hydrochloride	Thromboxane synthase inhibitor	Antianginal
0.6	1.0	0.7	0.6	0.8	0.7	0.8	Propoxycaine hydrochloride		Local anesthesic
0.6	0.9	0.6	0.5	0.7	0.6	1.0	Piribedil hydrochloride	Dopaminergic agonist	Vasodilator (peripheral)
0.6	1.1	0.5	0.6	0.7	0.7	0.9	Oxaprozin		Analgesic
0.9	0.9	0.6	0.7	0.7	0.8	1.2	Nitrocaramiphen hydrochloride		Muscarinic antagonist
1.0	0.9	0.7	0.8	0.8	0.7	1.1	Phensuximide		Anticonvulsant
0.9	1.0	0.7	0.7	0.8	0.9	1.0	Nandrolone		Anabolic
0.9	0.9	0.6	0.8	0.8	0.8	1.1	Ioxaglic acid	Low-osmolar, ionic contrast medium	Diagnostic aid (radiopaque medium)
0.8	0.9	0.7	0.7	0.8	0.8	1.0	Dimaprit dihydrochloride	Histamine H2 receptor agonist	
1.0	1.0	0.8	0.7	1.1	0.8	1.0	Naftifine hydrochloride		Antifungal
0.9	0.9	0.6	0.7	0.8	0.8	1.0	Reserpinic acid hydrochloride		
0.9	0.9	0.6	0.7	0.8	0.9	0.8	Meprylcaine hydrochloride		Local anesthesic
0.8	0.9	0.7	0.8	0.8	0.8	1.1	Beta-sistosterol		Anticholesteremic
0.8	0.9	0.7	0.8	0.8	0.9	0.9	Milrinone		Cardiotonic
0.9	0.8	0.6	0.7	0.8	0.9	0.9	Proscillaridin A		Glucoside cardiotonic
0.9	0.9	0.7	0.8	0.8	0.9	1.1	Methantheline bromide		Antispasmodic

0.6	0.3	0.1	0.2	0.7	0.3	0.9	Sanguinarine	Potent cytotoxic	Antimicrobial drug
12.8	1.2	0.7	0.7	2.6	0.8	1.4	Ticarcillin sodium		Antibacterial
0.8	0.9	0.8	0.7	0.9	0.8	0.9	Harpagoside		Antiinflammatory
1.1	1.0	0.8	1.0	2.1	0.8	1.0	Thiethylperazine malate	adrenergic antagonist	Antiemetic
0.8	0.9	0.8	0.7	0.8	0.8	1.0	Asiaticoside		Antibiotic
0.9	0.9	0.7	0.7	0.9	0.9	1.0	Mesalamine		Anti-inflammatory (gastrointestinal)
0.8	0.9	0.3	0.7	0.8	0.7	1.3	Betulin		Antineoplastic
0.8	1.0	0.9	0.7	0.8	0.9	0.9	alpha-Santonin		Anthelmintic
0.8	0.9	0.5	0.7	0.7	0.8	1.1	Gliquidone		Antidiabetic
0.9	0.9	0.7	0.7	0.8	0.8	1.2	Imidurea		
1.0	1.0	0.7	0.7	0.8	0.8	1.3	Pizotifen malate		Antihistaminic
0.6	0.6	0.2	0.5	0.6	0.7	1.0	Lansoprazole		Antiulcerative
0.8	0.9	0.7	0.7	0.9	1.1	1.2	Ribavirin		Antiviral
1.0	0.9	0.7	0.7	0.8	0.7	0.9	Bethanechol chloride		Cholinergic
0.8	0.9	0.7	0.8	0.8	0.8	1.2	Cyclopenthiazide		Diuretic
0.8	1.0	0.6	0.7	0.8	0.8	1.4	Cyproterone acetate		Antiandrogen
0.9	0.8	0.7	0.7	0.9	0.8	1.1	Fluvoxamine maleate		Antidepressant
0.8	0.9	0.8	0.7	0.9	0.8	17.3	(R)-Propranolol hydrochloride	Beta-adrenergic receptor blocking agent	Antihypertensor
16.6	0.9	1.6	3.8	1.5	0.8	1.4	Cefalonium		Prophylactic use in mastitis and dry udder therapy

0.8	0.9	0.7	0.8	0.8	0.7	1.2	Ciprofibrate		Antihyperlipoproteine-mic
0.8	0.9	0.7	0.7	0.8	0.8	1.5	Fluticasone propionate		Anti-inflammatory
0.9	0.9	0.7	0.8	0.8	0.8	1.2	Tropine		
1.2	1.0	0.7	1.0	1.9	0.9	1.3	Zuclopenthixol hydrochloride	Blocking of D1 and D2 dopaminergic receptors	Schizophrenia
1.2	1.7	0.8	0.6	2.9	0.7	1.2	Benzylpenicillin sodium		Antibacterial
0.9	0.8	0.9	0.7	0.9	0.8	1.1	Proguanil hydrochloride	Inhibition of dihydrofolate reductase	
0.9	0.9	0.8	0.7	0.9	0.8	1.2	Chlorambucil		Antineoplastic
0.8	1.0	0.7	0.7	0.8	0.7	1.2	Lymecycline		Antibiotic
0.4	0.5	1.3	0.4	0.5	0.5	1.3	Methiazole		
1.2	1.1	1.0	0.9	1.0	1.0	1.4	Alfadolone acetate		In combination with alfaxalone as anesthesic (intravenous)
1.2	1.1	1.0	1.0	1.0	1.1	1.6	(S)-propranolol hydrochloride	Beta-adrenergic blocking agent	Antihypertensor
1.2	1.1	1.2	1.0	1.0	1.2	1.7	Alfaxalone		In combination with alfadolone acetate as anesthetic (intravenous)
1.0	1.1	0.9	0.9	0.9	0.8	1.4	(-)-Eseroline fumarate salt	Anti-acetylcholinesterase activity & opiate agonist activity	Potent analgesic
1.1	1.0	0.8	0.9	0.9	1.0	1.5	Azapropazone	Cyclooxygenase inhibitor	Analgesic
1.1	1.1	1.1	1.0	1.1	1.0	1.2	Condelphine		
1.3	1.1	0.9	0.9	1.1	1.1	1.4	Meptazinol hydrochloride		Analgesic (narcotic)
1.3	1.1	0.9	1.0	1.0	1.1	1.6	Leucomisine		

1.2	1.0	0.9	0.8	1.0	1.1	1.4	Apramycin		Antibacterial
1.4	1.0	2.4	0.9	1.1	1.0	1.3	Dubinidine		
1.2	1.0	0.9	0.9	1.1	1.1	1.3	Epitiostanol		Antineoplastic
1.4	1.2	1.4	1.1	1.0	1.2	1.2	D-cycloserine	Competitive inhibition of alanin racenase and D-alanin synthase (bacterial cell wall)	
1.4	1.1	1.0	1.0	1.3	1.1	1.2	Fursultiamine Hydrochloride		Altzheimer's disease
1.0	1.1	1.1	0.9	1.2	1.0	1.4	2-Chloropyrazine		Cardiotonic
1.1	1.1	1.3	0.9	1.1	1.1	1.4	Gabexate mesilate		Anticoagulant
1.3	1.1	1.0	1.0	1.1	1.1	1.3	(+,-)-Synephrine		Hypertensive
1.5	1.1	0.4	0.9	1.8	0.9	1.2	Pivampicillin		Antibacterial
1.3	1.1	1.1	1.0	1.1	1.1	1.6	(S)-(-)-Cycloserine		Tuberculosis
15.2	1.4	1.2	0.8	0.8	1.1	1.6	Talampicillin hydrochloride		Antibacterial
1.3	1.1	1.2	1.1	1.8	1.1	1.5	Homosalate	Tool for uv screen	
1.3	1.0	6.1	1.1	1.5	1.2	1.3	Flucloxacillin sodium		Antibacterial
1.4	1.1	1.0	0.9	0.9	1.1	1.6	Spaglumic acid	NMDA receptor ligands	
1.3	1.1	0.9	0.9	1.0	1.0	1.5	Trapidil		Vasodilator (coronary)
1.2	0.9	1.0	0.9	1.2	1.0	1.4	Ranolazine		Antianginal
1.5	1.1	1.1	0.9	1.3	1.0	1.6	Deptropine citrate		Chronic bronchitis
1.1	1.0	1.2	1.0	1.0	0.9	1.7	(-)-Quinpirole hydrochloride	D2-dopamine receptor agonist, some selectivity for D3 sites	
1.6	1.1	1.6	1.4	2.9	1.2	1.5	Sertraline	5-HT uptake inhibitor	

1.0	1.0	0.9	1.0	2.9	1.0	1.3	Sulfadoxine	Inhibition of dihydropteroate synthase	Antibacterial
1.2	0.9	1.0	1.1	1.2	1.0	0.8	Ethamsylate		Retinopathy
1.2	1.0	1.1	1.0	1.0	1.1	1.3	Cyclopentolate hydrochloride		Mydriatic
1.1	0.9	1.0	1.1	1.1	1.1	1.8	Moxonidine	Imidazoline receptor ligand	Antihypertensor
1.1	1.1	1.2	0.8	1.2	1.0	1.4	Estriol		Estrogen
1.0	1.0	1.1	0.8	1.4	1.1	1.5	Etilefrine hydrochloride	Adrenergic agonist	Antihypotensive
1.2	0.9	0.9	1.2	0.9	1.1	2.3	(-)-Isoproterenol hydrochloride	Beta Adrenergic Agonist	Cardiovascular drug (Sick Sinus Syndrome)
1.3	1.0	1.1	1.1	1.0	1.1	1.4	Alprostadil		Vasodilator
0.5	1.0	0.2	0.6	0.5	0.6	1.6	Kaempferol	Topoisomerase I inhibitor, tyrosin kinase, xanthin oxidase	Anti-inflammatory
0.9	1.1	0.6	0.9	1.7	1.1	1.5	Tribenoside		Antihaemorrhoidic drug
1.2	1.1	1.2	0.9	1.0	1.2	1.4	Nialamide		Antidepressant
0.9	0.9	1.1	0.8	0.9	1.0	4.9	Rimexolone	Corticoid	Anti-inflammatory (local)
0.9	1.0	1.8	0.8	1.1	1.1	1.6	Vitamin K2		Dietary factor for controlling blood pressure
1.1	1.1	0.7	1.1	1.2	1.1	1.4	Isradipine		Antianginal
1.2	1.0	1.1	1.1	1.4	1.2	1.3	Perindopril		Antihypertensive
1.2	1.0	1.1	1.1	1.6	1.1	1.4	Tiletamine hydrochloride		Anesthetic
1.2	1.0	1.1	1.1	1.3	1.0	1.3	Fexofenadine HCl		Antihistaminic
1.2	1.0	1.2	1.1	1.5	1.1	1.2	Isometheptene mucate	Adrenergic	Sympathomimetic (VET)

1.2	1.0	1.2	1.3	1.4	1.1	1.2	Quinic acid		
1.1	1.0	0.8	1.2	1.5	1.1	1.3	Nifurtimox		Antiprotozoal (Trypanosoma)
1.0	0.9	1.2	1.1	1.4	1.0	1.5	Clonixin Lysinate		Analgesic
1.2	1.0	1.2	1.1	1.3	1.0	1.4	Letrozole		Antineoplastic
0.7	1.2	0.5	0.8	0.9	0.8	1.6	Verteporfin		Treatment of age-related macular degeneration
1.2	0.9	1.1	1.2	1.5	1.1	1.4	Arbutin	Tyrosinase inhibitor and Melanin biosynthesis inhibitor	Antibacterial
13.4	1.0	3.9	3.6	1.5	14.8	1.2	Meropenem		Antibacterial
1.2	1.0	1.1	1.1	1.6	1.1	1.4	Tocainide hydrochloride		Antiarrhythmic
1.1	1.0	1.2	1.0	1.3	1.2	1.1	Ramipril	Converting enzyme inhibitor	Antihypertensor
15.6	1.6	1.0	1.0	5.9	1.1	1.6	Benzathine benzylpenicillin		Antibacterial
1.1	1.0	1.1	1.0	1.3	1.0	1.3	Mephenytoin		Anticonvulsant
1.1	1.0	1.3	1.1	1.5	1.1	1.3	Risperidone	5-HT2 antagonist	Antipsychotic
1.3	1.2	0.7	1.3	3.3	0.6	1.6	Rifabutin	Inhibition of RNA-polymerase DNA-dependent	Antibacterial
1.1	1.0	1.5	1.3	1.6	1.1	1.4	Torsemide		Diuretic
0.7	0.6	0.7	0.7	0.8	0.7	1.2	Parbendazole		Anthelmintic (VET)
1.0	1.0	1.2	1.1	1.3	1.1	1.3	Halofantrine hydrochloride		Antimalarial
1.4	1.1	1.4	1.0	1.2	1.1	1.6	Mecamylamine hydrochloride		Antihypertensor
1.1	1.2	1.1	1.1	1.2	1.0	1.6	Articaine hydrochloride		Local Anesthesic
1.0	1.0	1.1	1.1	1.1	0.9	1.7	Procarbazine hydrochloride	DNA depolymerization	

1.1	1.2	1.0	1.1	1.1	1.1	1.5	Nomegestrol acetate		Progestin
1.0	1.0	1.3	0.9	1.1	0.9	1.6	Viomycin sulfate		Antibacterial
1.1	1.0	1.1	1.0	1.1	0.9	1.6	Pancuronium bromide	Competitive antagonist of autonomic cholinergic receptors	Neuromuscular blocking agent
1.3	1.2	0.9	1.1	1.5	1.0	1.8	Saquinavir mesylate	Protease inhibitor	
1.1	1.0	1.1	1.0	1.1	0.9	1.7	Molindone hydrochloride		Antipsychotic
1.1	1.1	1.3	1.7	1.6	1.0	1.6	Ronidazole		Antimicrobial
1.4	1.0	1.2	1.0	1.4	1.0	2.2	Alcuronium chloride		Neuromuscular blocking agent
1.1	2.3	1.0	1.1	1.2	0.9	1.3	Dorzolamide hydrochloride		Antiglaucoma drug
1.3	1.1	1.1	1.1	1.2	1.0	1.8	Zalcitabine	Reverse transcriptase inhibitor	Antiviral (HIV)
1.1	1.0	1.2	1.0	1.2	1.0	1.9	Azaperone		Tranquilizer
1.2	1.1	1.2	1.2	1.4	1.1	1.8	Methyldopate hydrochloride		Antihypertensor
19.3	1.0	3.1	4.9	3.4	15.6	1.9	Cefepime hydrochloride		Antibacterial
1.1	1.0	1.1	1.1	1.2	1.0	1.6	Levocabastine hydrochloride		Antihistaminic
1.0	1.1	1.1	1.0	1.2	1.0	1.6	Clocortolone pivalate		Glucocorticoid
0.8	1.5	1.4	0.8	0.9	0.7	13.2	Pyrvinium pamoate		Anthelmintic (Nematodes, enterobiasis)
13.4	2.8	4.3	5.2	2.9	17.7	1.7	Nadifloxacin		Antibacterial

Consistent with expectations, a detailed assessment of the hits revealed that AK screening enriches for the identification of bactericidal compounds (Table 3). More specifically, 100% of the antibiotics that were identified to be active against *P. aeruginosa* or *K. pneumoniae* represented bactericidal agents. Similarly, 96%, 94%, and 80% of the antibiotics that were active against *E. coli*, *E. cloacae*, and *E. faecium*, respectively, were bactericidal antibiotics. The assay identified 71% and 64% bactericidal antibiotics for *A. baumannii* and *S. aureus*.

Among the bactericidal antibiotics detected, β-lactam, cephalosporin, polymyxin, and fluoroquinolone antibiotics were active against Gram-negative pathogens (*E. coli* and the ESKAPE pathogens *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*), and penicillins, cephalosporins, quinolines, glycopeptides, and carbapenems were active toward *S. aureus* (see Table 4). It was also determined that clofazimine, which was initially developed as an antimycobacterial agent and was recently shown to exhibit bactericidal activity toward *S. aureus*, was indeed active against *S. aureus*. Bacteriostatic compounds, such as clindamycin, and macrolides, such as erythromycin, were not identified as being active toward any of the species tested. Interestingly, many tetracyclines were identified as killing *S. aureus* strain USA300-0114 and *A. baumannii* strain 98-37-09. In addition, the library contains membrane-active antiseptics, such as chlorhexidine, and with the exception of *E. cloacae*, these were also strong hits against all organisms tested. Screening results also revealed that the *E. faecium* strain tested proved to be resistant to most classes of antibiotics within the Prestwick library by MIC testing (Table 2), and this was also observed in the AK assay, indicating that the assay exhibits a low false-positive rate. Interestingly, the assay also detected 38 drugs with no known antimicrobial properties (denoted as "other" in Table 3) that were active against each organism; see Table 4 for a complete list of these compounds.

Antimicrobial activities of nonantibiotic drugs that induce AK release- Recently, the exploration of the so-called "off-target" activities of previously developed drugs has emerged as an approach to identify chemical scaffolds that could be exploited for new therapeutic indications. In that regard, Prestwick library screening results revealed that 4% to 56% (depending on the organism) of the members that generated significant AK signal were compounds with no previously reported antimicrobial activity (see Table 4).

To determine whether the 38 nonantibiotics identified in the screen have potential for repurposing as anti-infectives, 4 nonantibiotic drugs that were commercially available were further evaluated by two secondary assays. First, dose-response assays were performed to validate that they induced AK activity, and all were reconfirmed. Second, the *in vitro* antimicrobial activity for each drug was measured by standard MIC testing. With the exception of one drug/organism pair, all drugs exhibited *in vitro* activity toward each organism. More specifically, tamoxifen, suloctidil, and clomiphene exhibited MICs of 8 μg ml^{-1} against *E. faecium*. *S. aureus* and *A. baumannii* were susceptible to terfenadine (16-μg ml^{-1} MIC and 64-μg ml^{-1} MIC, respectively). Suloctidil was also detected to be active against *P. aeruginosa* by both primary and confirmatory AK screens, but the drug did not elicit an antimicrobial response by MIC measures. Some strains of *P. aeruginosa* secrete AK at high cell density, and it is possible that suloctidil may trigger a similar response.

Terfenadine and tamoxifen, which exhibited antimicrobial properties toward planktonic *S. aureus* and *E. faecium* cells, respectively, were characterized further. Terfenadine was evaluated for activity against *S. aureus* biofilms and small-colony variants using the AK assays described above. Treatment of 48-h *S. aureus* strain UAMS-1 biofilms with 10×-MIC terfenadine elicited a modest 2.7-fold increase in AK release (see Fig. 6A); plating-based viability assays determined that this correlated with a 1.1-log reduction in biofilm cell viability, which was comparable to the activity of ciprofloxacin under the same assay conditions (see Fig. 4A). Similarly, treatment of *S. aureus* small-colony-variant UAMS-1112 cells with 10× MIC terfenadine elicited a 3.3-fold increase in AK signal in comparison to that for mock-treated cells (see Fig. 6A). Conventional MIC testing subsequently verified that terfenadine is active against UAMS-1112 at 2 μg ml^{-1}.

Next, the *in vivo* antimicrobial properties of terfenadine and tamoxifen were evaluated using a *Galleria mellonella* model of *S. aureus* and *E. faecium* infection, respectively. For terfenadine, groups of larvae ($n = 45$) were infected with 1.0×10^6 *S. aureus* USA300-1114 cells. Worms were then treated at 2 h and 24 h with a range of terfenadine concentrations (20 to 160 mg kg^{-1}), vehicle (DMSO; negative control), or 20 mg kg^{-1} vancomycin (positive control), and larval survival was assessed 48 h postinoculation. For tamoxifen studies, experiments were performed exactly as described above except that larvae were inoculated with 1.4×10^6 *E. faecium* strain 824-05 cells and larvae were treated with either 80 or 160 mg kg^{-1} tamoxifen. Terfenadine-treated larvae did not reproducibly exhibit increased survival

relative to vehicle-treated larvae. However, tamoxifen treatment of *E. faecium*-infected larvae resulted in a dose-dependent increase in survival. As shown in Fig. 6B, treatment with 80 or 160 mg kg^{-1} resulted in a 4.2-fold- or 7-fold-higher survival, respectively, than was found with vehicle-treated controls. Taken together, these results indicate that terfenadine exhibits *in vitro* activity toward *S. aureus* planktonic, SCV, and biofilm populations and that tamoxifen is active toward planktonic *E. faecium* and against the organism in a simple animal model of infection. As discussed below, these data show that tamoxifen and terfenadine represent attractive new chemical scaffolds for antibacterial optimization.

As set forth herein, Prestwick library screening revealed that each bacterial species studied was susceptible to members of the library with no previously reported antimicrobial activity. The antimicrobial properties of two of these drugs was studied in more detail: terfenadine and tamoxifen. Terfenadine is a nonsedating antihistamine based on a 4-substituted piperidine scaffold. Based on further studies, it was determined that terfenadine acts as a topoisomerase inhibitor and is structurally similar to certain topoisomerase inhibitors, including for example novel bacterial topoisomerase II inhibitor (NBTI). Based on the structural similarity between terfenadine and these molecules, it is likely that terfenadine is acting as a DNA gyrase and topoisomerase inhibitor. More specifically, terfenadine and derivatives thereof act as topoisomerase 4 inhibitors. Furthermore, it was found that terfenadine has activity against *S. aureus* small-colony variants and biofilms, properties not previously reported for this scaffold.

A screen of *E. faecium* identified two structurally related nonsteroid estrogen receptor antagonists, tamoxifen and clomiphene. Tamoxifen is used to treat some forms of estrogen-receptor-positive breast cancer, while clomiphene is used in fertility treatment regimens. These two compounds are members of the triarylethylene class of estrogen receptors.

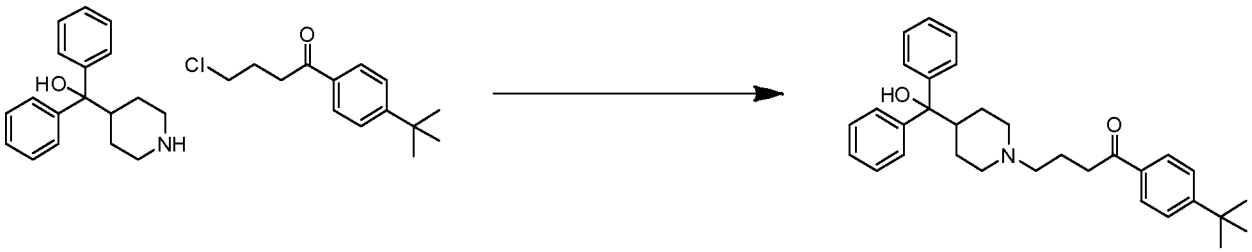
Since the number of agents with activity toward enterococcus is quite limited, tamoxifen's *in vivo* activity was investigated using a *Galleria* model of enterococcus infection. Although it was not as active as vancomycin, tamoxifen did impart a survival benefit, indicating that it has *in vivo* antimicrobial activity. High-dose tamoxifen therapy has been used in experimental treatment of refractory human cancers, and dosing results in micromolar serum concentrations of tamoxifen corresponding to the levels of drug associated with antienterococcal activity observed in the studies provided herein.

In addition to providing a powerful new HTS approach to identify antimicrobial agents active against planktonic bacteria, an AK assay that is easily amenable to screening bacteria in disease states that cannot be readily screened via conventional approaches is provided herein. In that regard, the AK assay is capable of measuring the killing properties of bactericidal agents administered to biofilms formed by both Gram-negative and Gram-positive representatives of the ESKAPE pathogens. Similarly, the AK assay can detect the bactericidal properties of antibiotics toward a phenotypically stable *S. aureus* small-colony variant. These features can be exploited to develop corresponding high-throughput screening assays for the identification of agents that kill established biofilms and small-colony variants or provide powerful secondary assays aimed at characterizing the potential antimicrobial properties of molecules of interest.

EXAMPLE II

Antimicrobial properties of terfenadine and terfenadine derivaties.

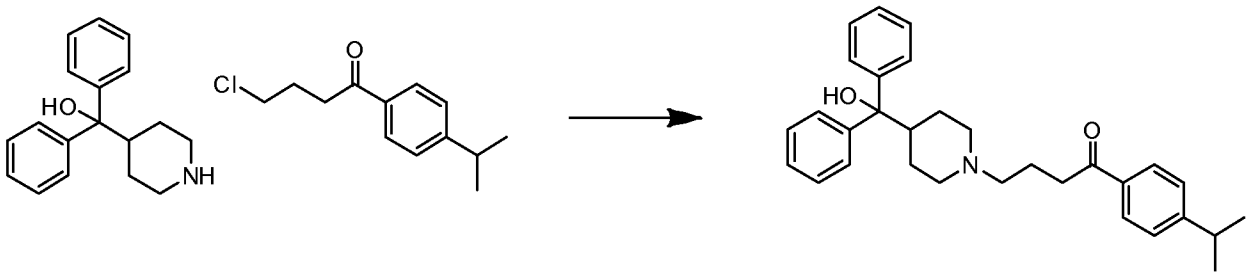
Terfenadine derivatives were synthesized as described below.



General Method A

KSC-335-007

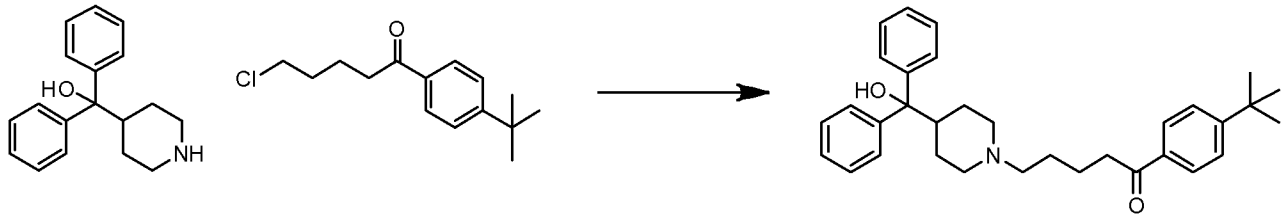
1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one. To a vial was added the diphenyl(piperidin-4-yl)methanol (1.190 g, 4.45 mmol), 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (1.012 g, 4.24 mmol), sodium bicarbonate (0.427 g, 5.09 mmol) with water:2-butanone (18 mL, 1:5). The reaction stirred at 85 °C for 16 h and was then cooled to rt and water (50 mL) was added. The reaction was extracted with EtOAc (3 x 50 mL). The EtOAc layer was dried with $MgSO_4$, filtered, concentrated and purified by MPLC (20 min, 0 - 10% MeOH:DCM) to produce pure 1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butan-1-one (1.37 g, 2.92 mmol, 69% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 2H), 7.49 – 7.45 (m, 6H), 7.31 – 7.25 (m, 4H), 7.20 – 7.14 (m, 2H), 2.97 – 2.92 (m, 4H), 2.45 – 2.36 (m, 3H), 2.09 (br s, 1H), 2.00 – 1.87 (m, 4H), 1.49 – 1.32 (m, 4H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 156.5, 146.0, 134.5, 128.1, 128.0, 126.4, 125.7, 125.4, 79.4, 57.9, 43.9, 43.4, 44.1, 36.2, 35.0, 31.0, 26.2, 21.9. LCMS Retention time: 4.207 min. LCMS purity 99.5%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO_2$ $[M+H]^+$ 470.2981, found 470.3054.



KSC-335-005

4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.620 g, 2.317 mmol), 4-chloro-1-(4-

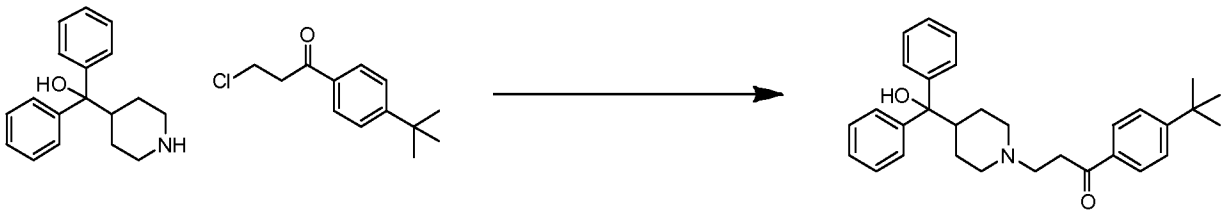
isopropylphenyl)butan-1-one (0.496 g, 2.207 mmol), sodium bicarbonate (0.222 g, 2.65



mmol) with water (3 mL) and 2-butanone (15 mL, Ratio: 5). to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-one (0.481 g, 1.056 mmol, 48% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 2H), 7.49 – 7.45 (m, 4H), 7.31 – 7.26 (m, 6H), 7.20 – 7.14 (m, 2H), 2.98 – 2.91 (m, 4H), 2.45 – 2.35 (m, 1H), 2.38 (t, J = 6.8 Hz, 2H), 2.08 (br s, 1H), 1.99 – 1.89 (m, 4H), 1.61 (br s, 1H), 1.48 – 1.33 (m, 4H), 1.27 (d, J = 6.8 Hz, 6H).

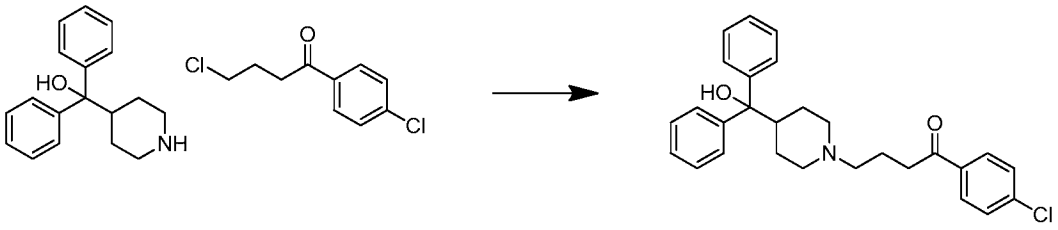
KSC-335-006

1-(4-(tert-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.544 g, 2.035 mmol), 1-(4-(tert-butyl)phenyl)-5-chloropentan-1-one (0.490 g, 1.938 mmol), sodium bicarbonate (0.195 g, 2.326 mmol) with water:2-butanone (18 mL, 1:5) to produce pure 1-(4-(tert-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-one (0.600 g, 1.240 mmol, 64.0 % yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 2H), 7.49 – 7.45 (m, 6H), 7.32 – 7.26 (m, 4H), 7.20 – 7.14 (m, 2H), 2.98 – 2.92 (m, 4H), 2.48 – 2.32 (m, 3H), 2.14 (br s, 1H), 1.99 – 1.89 (m, 2H), 1.77 – 1.62 (m, 2H), 1.60 – 1.42 (m, 6H), 1.34 (s, 9H).



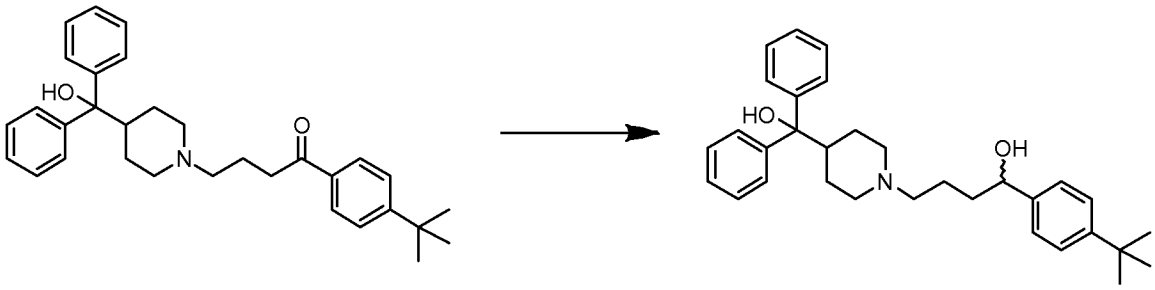
KSC-335-008

1-(4-(tert-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.543 g, 2.032 mmol), 1-(4-(tert-butyl)phenyl)-3-chloropropan-1-one (0.435 g, 1.936 mmol), sodium bicarbonate (0.195 g, 2.323 mmol) with water:2-butanone (18 mL, 1:5) to produce pure 1-(4-(tert-butyl)phenyl)-3-(4-(hydroxydiphenyl methyl)piperidin-1-yl)propan-1-one (0.838 g, 1.84 mmol, 95% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 2H), 7.50 – 7.45 (m, 6H), 7.32 – 7.25 (m, 4H), 7.21 – 7.14 (m, 2H), 3.15 (t, J = 7.1 Hz, 2H), 3.01 – 2.96 (m, 2H), 2.81 (t, J = 7.1 Hz, 2H), 2.49 – 2.42 (m, 1H), 2.15 – 2.04 (m, 3H), 1.56 – 1.46 (m, 4H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 171.1, 156.8, 145.8, 134.3, 128.2, 128.0, 126.5, 125.8, 125.5, 79.4, 60.4, 54.2, 53.4, 44.0, 36.3, 35.1, 31.1, 26.4, 21.1, 14.2. LCMS Retention time: 3.968 min. LCMS purity 98.1%. HRMS (ESI): *m/z* calcd for $C_{31}H_{37}NO_2$ $[M+H]^+$ 456.2824, found 456.2897.



KSC-335-009

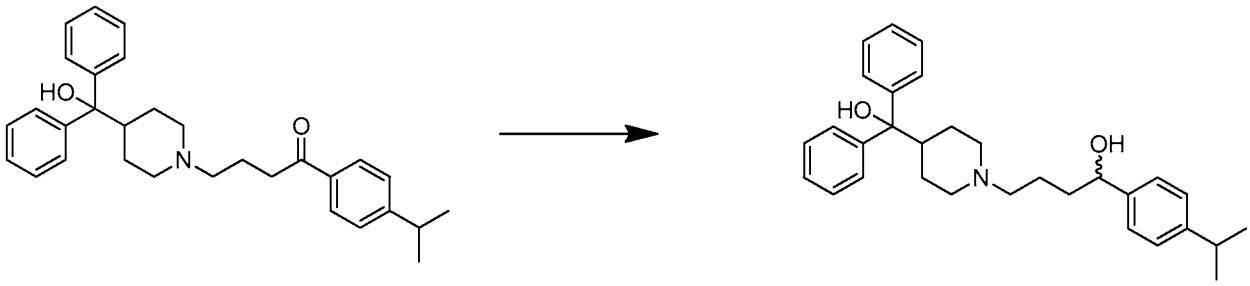
1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.626 g, 2.341 mmol), 4-chloro-1-(4-chlorophenyl) butan-1-one (0.484 g, 2.229 mmol), sodium bicarbonate (0.225 g, 2.68 mmol) with water:2-butanone (18 mL, 1:5) to produce pure 1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.394 g, 0.879 mmol, 39.4 % yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 2H), 7.48 – 7.44 (m, 4H), 7.42 (d, J = 8.6 Hz, 2H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 3.96 – 2.89 (m, 4H), 2.45 – 2.34 (m, 3H), 2.08 (br s, 1H), 1.99 – 1.87 (m, 4H), 1.50 – 1.30 (m, 4H).



General Method B

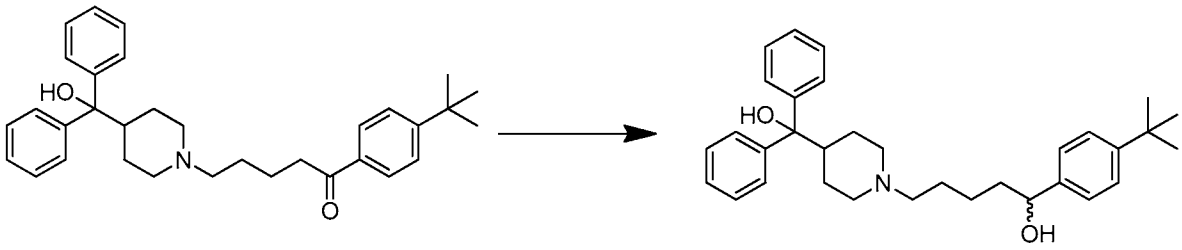
KSC-335-014, Terfenadine

1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. To a vial was added the 1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (KSC-335-007 (0.198 g, 0.422 mmol) and MeOH (2 mL). The sodium borohydride (0.032 g, 0.844 mmol) was then added and the reaction stirred at rt for 3 h. The reaction was concentrated to dryness, water (5 mL) was added and a white precipitate formed. The precipitate was filtered out and then dissolved in DCM (10 mL), dried with $MgSO_4$, filtered and concentrated to produce pure 1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.151 g, 0.320 mmol, 76% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.33 – 7.25 (m, 8H), 7.21 – 7.15 (m, 2H), 4.61 – 4.56 (m, 1H), 3.16 – 3.11 (br m, 1H), 3.00 – 2.94 (m, 1H), 2.51 – 2.34 (m, 4H), 2.10 – 1.88 (m, 4H), 1.83 – 1.75 (m, 1H), 1.70 – 1.45 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.4, 126.3, 125.7, 125.6, 125.3, 125.0, 79.2, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.0, 25.9, 24.1. LCMS Retention time: 4.137 min. LCMS purity 97.5%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3144, found 472.3219.



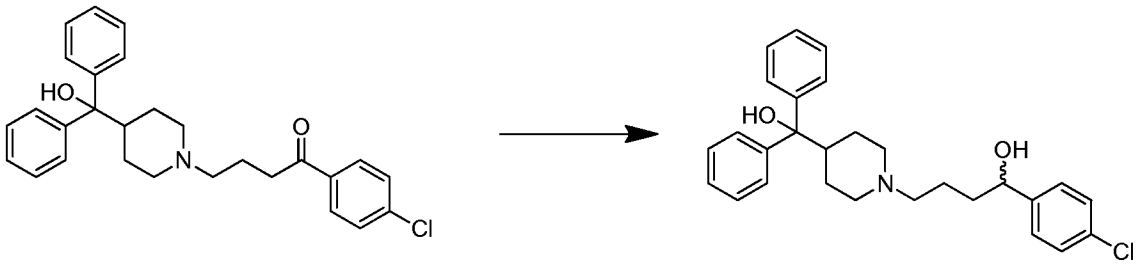
KSC-335-012

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-ol. Method B: 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-one (KSC-335-005) (0.154 g, 0.338 mmol) and MeOH (2 mL) sodium borohydride (0.026 g, 0.676 mmol) to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-ol (0.146 g, 0.319 mmol, 94% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.32 – 7.23 (m, 6H), 7.20 – 7.14 (m, 4H), 4.61 – 4.58 (m, 1H), 3.18 – 3.11 (br m, 1H), 3.00 – 2.94 (br m, 1H), 2.87 (septet, J = 6.9 Hz, 1H), 2.50 – 2.33 (m, 3H), 2.29 (br s, 1H), 2.10 – 1.89 (m, 3H), 1.82 – 1.44 (m, 8H), 1.22 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2, 146.1, 146.0, 128.2, 128.1, 126.5, 126.4, 126.1, 125.7, 125.7, 79.2, 73.5, 58.9, 54.7, 53.3, 44.2, 39.9, 33.7, 26.0, 25.9, 24.2, 24.1, 24.0. LCMS Retention time: 4.056 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO_2$ $[M+H]^+$ 458.2986, found 458.3062.



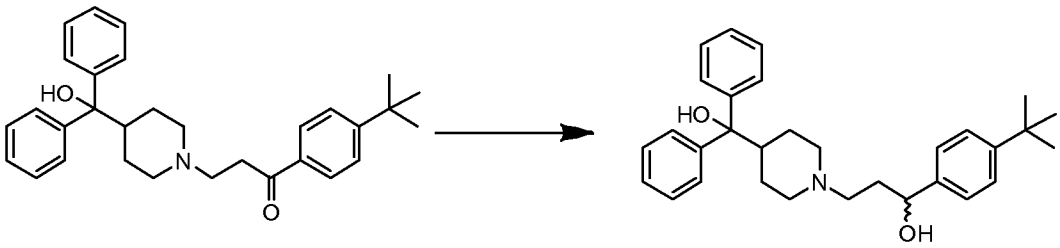
KSC-335-013

1-(4-(tert-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-ol. Method B: 1-(4-(tert-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-one (KSC-335-006) (0.204 g, 0.422 mmol) and MeOH (2 mL) and sodium borohydride (0.032 g, 0.844 mmol) to produce pure 1-(4-(tert-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-ol (0.156 g, 0.321 mmol, 76 % yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 4H), 7.36 (d, J = 8.4 Hz, 2H), 7.31 – 7.24 (m, 6H), 7.19 – 7.14 (m, 2H), 4.65 – 4.60 (m, 1H), 2.98 – 2.90 (br m, 1H), 2.48 – 2.38 (m, 1H), 2.30 (t, J = 7.2 Hz, 2H), 2.23 (br s, 1H), 1.97 – 1.87 (m, 2H), 1.84 – 1.60 (m, 4H), 1.55 – 1.35 (m, 8H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 146.0, 142.0, 128.1, 126.4, 125.8, 125.5, 125.3, 79.4, 74.1, 58.4, 54.1, 54.0, 44.2, 38.5, 34.5, 31.4, 31.3, 26.5, 26.3, 26.2, 23.7. LCMS Retention time: 4.254 min. LCMS purity 96.4%. HRMS (ESI): *m/z* calcd for $C_{33}H_{43}NO_2$ $[M+H]^+$ 486.3294, found 486.3370.



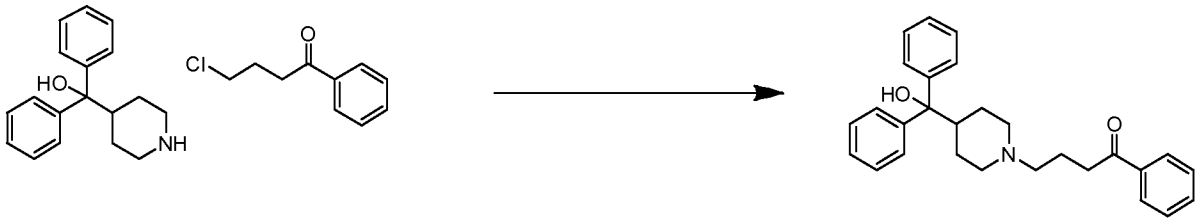
KSC-335-015

1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. Method B: 1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (KSC-335-009) (0.156 g, 0.348 mmol) and MeOH (2 mL) sodium borohydride (0.026 g, 0.696 mmol) to produce pure 1-(4-chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.118 g, 0.262 mmol, 75% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.32 – 7.24 (m, 8H), 7.20 – 7.15 (m, 2H), 4.61 – 4.56 (m, 1H), 3.16 – 3.10 (br m, 1H), 2.97 – 2.91 (m, 1H), 2.51 – 2.33 (m, 4H), 2.12 – 1.88 (m, 3H), 1.83 – 1.75 (m, 1H), 1.78 – 1.46 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 144.5, 139.1, 128.19, 128.18, 128.1, 127.1, 126.49, 126.45, 125.62, 125.57, 79.2, 72.9, 58.8, 54.7, 53.2, 44.2, 40.2, 26.0, 25.9, 24.1. LCMS Retention time: 3.845 min. LCMS purity 98.4%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}ClNO_2$ $[M+H]^+$ 450.2122, found 450.2194.



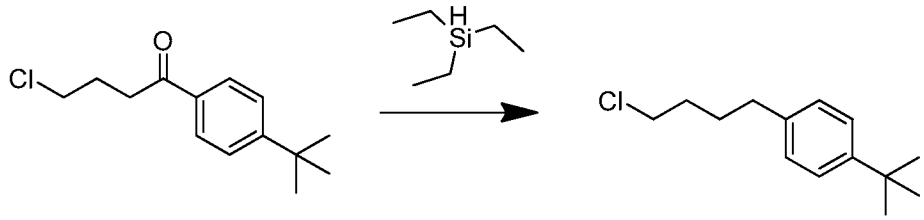
KSC-335-016

1-(4-(tert-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol. Method B: 1-(4-(tert-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-one (KSC-335-008) (0.116 g, 0.255 mmol) and MeOH (2 mL) and sodium borohydride (0.019 g, 0.509 mmol) to produce pure 1-(4-(tert-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol (0.106 g, 0.232 mmol, 91% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 4H), 7.36 – 7.25 (m, 8H), 7.22 – 7.16 (m, 2H), 6.72 (br s, 1H), 4.90 – 4.85 (m, 1H), 3.21 – 3.15 (br m, 1H), 3.11 – 3.05 (br m, 1H), 2.70 – 2.62 (m, 1H), 2.57 – 2.40 (m, 2H), 2.14 – 2.06 (m, 2H), 1.91 – 1.79 (m, 3H), 1.57 – 1.45 (m, 4H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 145.8, 145.7, 141.9, 128.2, 128.1, 126.6, 126.5, 125.8, 125.7, 125.2, 125.0, 79.4, 75.3, 57.3, 55.2, 53.2, 44.1, 34.4, 33.7, 31.4, 26.7, 26.4. LCMS Retention time: 4.006 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO_2$ $[M+H]^+$ 458.2991, found 458.3066.



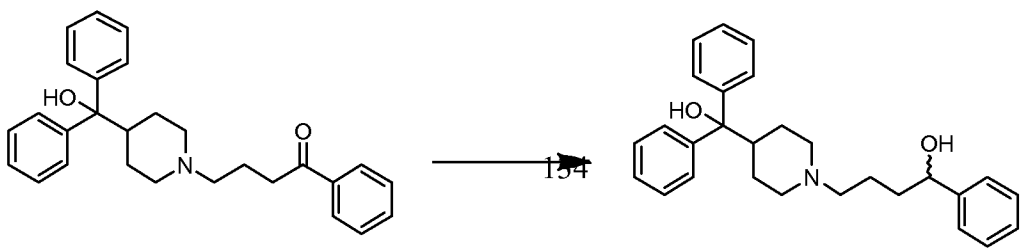
KSC-335-018

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-phenylbutan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.524 g, 1.961 mmol), 4-chloro-1-phenylbutan-1-one (0.300 ml, 1.868 mmol), sodium bicarbonate (0.188 g, 2.241 mmol) with water:2-butanone (18 mL, 1:5) to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-phenylbutan-1-one (0.177 g, 0.428 mmol, 23% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 – 7.94 (m, 2H), 7.57 – 7.52 (m, 1H), 7.49 – 7.42 (m, 6H), 7.32 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 3.00 – 2.90 (m, 4H), 2.46 – 2.35 (m, 3H), 2.09 (br s, 1H), 2.00 – 1.87 (m, 4H), 1.50 – 1.33 (m, 4H).



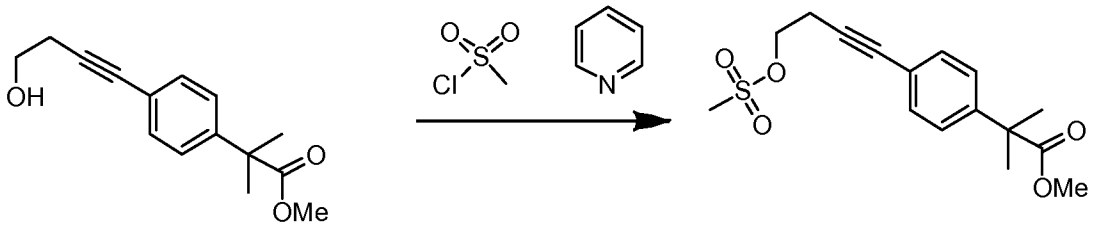
KSC-335-020

1-(tert-butyl)-4-(4-chlorobutyl)benzene. To a vial was added the 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.266 g, 1.114 mmol) and triethylsilane (0.518 g, 0.712 ml, 4.46 mmol) with TFA (4 mL). The reaction stirred at 75 °C for 18 h, was cooled to rt and concentrated in vacuo. The residue was then dissolved in DCM (5 mL) and washed with water (4 mL). The DCM layer was collected and washed with water (1 x 5 mL), dried with $MgSO_4$, filtered and adsorbed to silica and purified by Teledyne ISCO Combiflash chromatography (20 min, 0 - 40% EtOAc:Hex) and fractions 4 and 5 were collected to produce pure 1-(tert-butyl)-4-(4-chlorobutyl)benzene (0.155 g, 0.690 mmol, 61.9 % yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.87 – 1.74 (m, 4H), 1.32 (s, 9H).



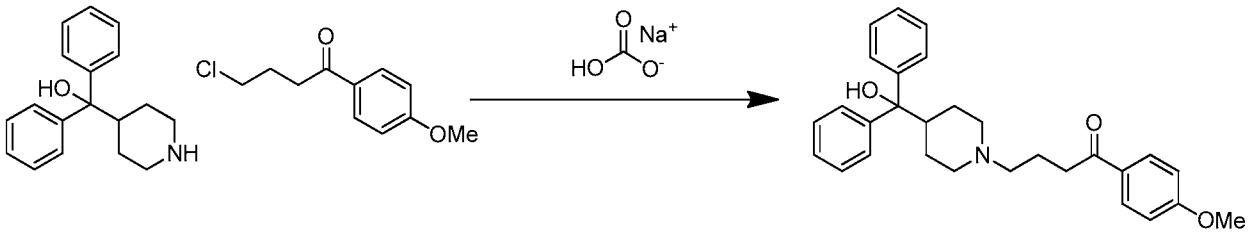
KSC-335-021

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-phenylbutan-1-ol. Method B: 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-phenylbutan-1-one (KSC-335-018) (0.065 g, 0.157 mmol) and MeOH (2 mL) and sodium borohydride (0.012 g, 0.314 mmol) to produce pure 4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)-1-phenylbutan-1-ol (0.048 g, 0.116 mmol, 73% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.37 – 7.33 (m, 2H), 7.32 – 7.26 (m, 5H), 7.23 – 7.14 (m, 3H), 4.65 – 4.61 (m, 1H), 3.15 (d, *J* = 11.7 Hz, 1H), 2.96 (d, *J* = 11.7 Hz, 1H), 2.52 – 2.31 (m, 4H), 2.11 – 1.90 (m, 3H), 1.84 – 1.74 (m, 2H), 1.70 – 1.44 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 145.8, 128.2, 128.1, 128.0, 126.6, 126.5, 126.4, 125.6, 125.6, 79.2, 73.6, 58.9, 54.7, 53.3, 44.2, 40.1, 26.0, 25.9, 24.1. LCMS Retention time: 3.711 min. LCMS purity 99.8%. HRMS (ESI): *m/z* calcd for $C_{28}H_{33}NO_2$ $[M+H]^+$ 416.2517, found 416.2592.



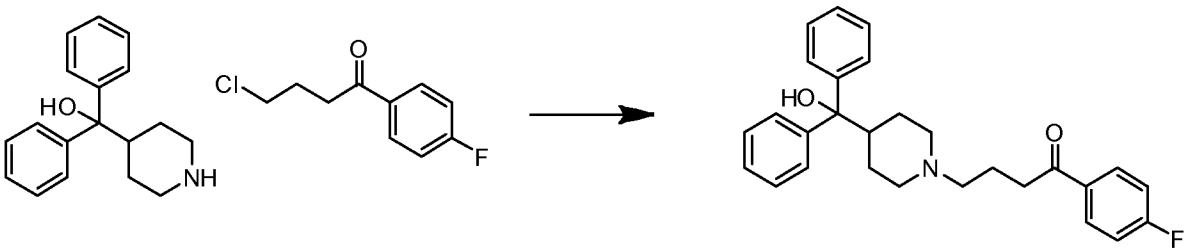
KSC-335-022

Methyl 2-methyl-2-(4-(4-((methylsulfonyl)oxy)but-1-yn-1-yl)phenyl)propanoate. To a vial was added the methyl 2-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-methylpropanoate (0.051 g, 0.207 mmol) and dry DCM (2 mL). The methanesulfonyl chloride (0.047 g, 0.032 mL, 0.414 mmol) and pyridine (0.147 g, 0.151 mL, 1.864 mmol) were each added and the reaction and stirred at rt for 16 h. The reaction was then diluted with DCM (5 mL) and washed with 1% w/v sulfuric acid in water (3 x 7 mL), saturated $NaHCO_3$ (7 mL) and brine (7 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to produce methyl 2-methyl-2-(4-(4-((methylsulfonyl) oxy)but-1-yn-1-yl)phenyl)propanoate (0.063 g, 0.194 mmol, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.64 (s, 3H), 3.06 (s, 3H), 2.87 (t, *J* = 6.8 Hz, 2H), 1.56 (s, 6H).



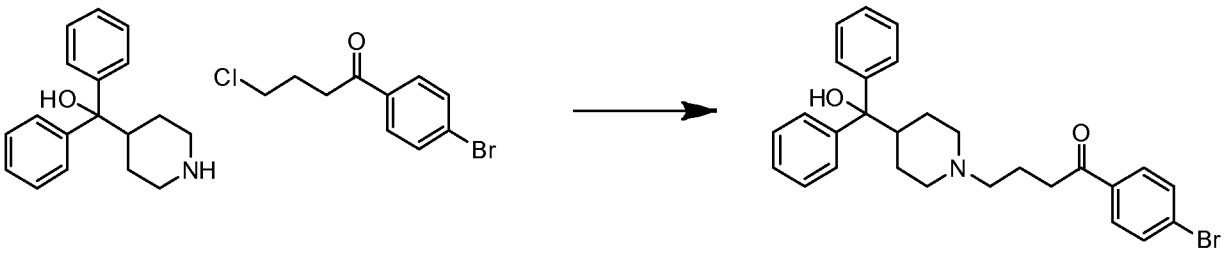
KSC-335-023

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.490 g, 1.832 mmol), 4-chloro-1-(4-methoxyphenyl)butan-1-one (0.371 g, 1.744 mmol), sodium bicarbonate (0.176 g, 2.093 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-one (0.282 g, 0.636 mmol, 36% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 9.0 Hz, 2H), 7.49 – 7.45 (m, 4H), 7.31 – 7.26 (m, 4H), 7.17 (tt, J_1 = 7.3 Hz, J_2 = 1.3 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.97 (br s, 1H), 2.93 (t, J = 7.3 Hz, 2H), 2.48 – 2.35 (m, 3H), 2.02 – 1.88 (m, 4H), 1.63 – 1.40 (m, 4H).



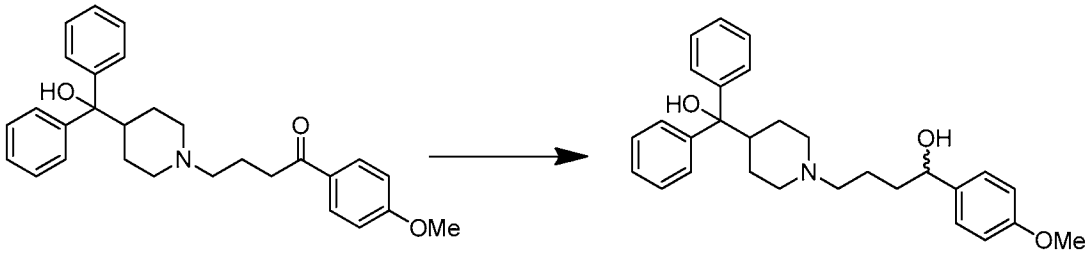
KSC-335-024

1-(4-Fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.385 g, 1.439 mmol), 4-chloro-1-(4-fluorophenyl)butan-1-one (0.275 g, 1.371 mmol), sodium bicarbonate (0.138 g, 1.645 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure 1-(4-fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.174 g, 0.403 mmol, 29% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.96 (m, 2H), 7.48 – 7.44 (m, 4H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 7.14 – 7.08 (m, 2H), 2.97 – 2.94 (m, 4H), 2.46 – 2.36 (m, 3H), 2.15 (br s, 1H), 2.01 – 1.88 (m, 4H), 1.52 – 1.35 (m, 4H).



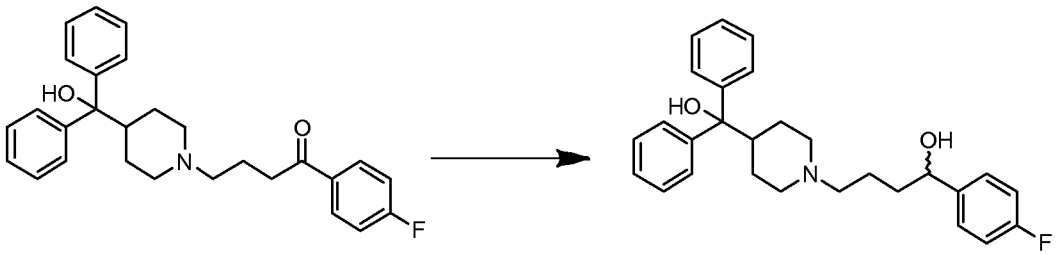
KSC-335-025

1-(4-Bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one. Method A: diphenyl(piperidin-4-yl)methanol (0.439 g, 1.642 mmol), 1-(4-bromophenyl)-4-chlorobutan-1-one (0.409 g, 1.564 mmol), sodium bicarbonate (0.158 g, 1.877 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.245 g, 0.498 mmol, 32% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 2H), 7.60 – 7.56 (m, 2H), 7.48 – 7.45 (m, 4H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 2.95 – 2.90 (m, 4H), 2.45 – 2.35 (m, 3H), 2.17 (br s, 1H), 2.00 – 1.88 (m, 4H), 1.51 – 1.33 (m, 4H).



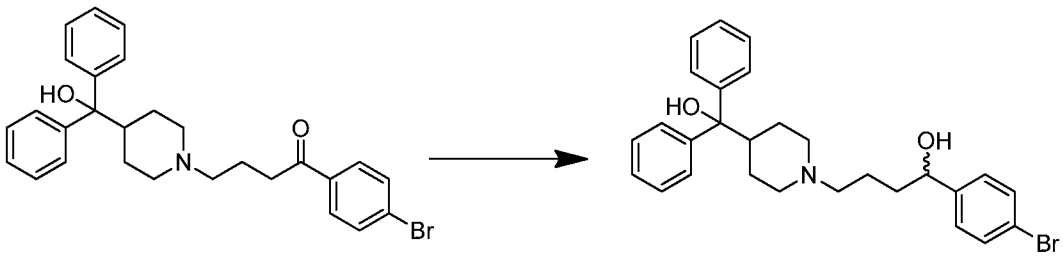
KSC-335-030

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-ol. Method B: 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-one (KSC-335-023) (0.113 g, 0.255 mmol) and MeOH (2 mL) and sodium borohydride (0.019 g, 0.509 mmol) to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-methoxyphenyl)butan-1-ol (0.062 g, 0.139 mmol, 55% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.32 – 7.24 (m, 6H), 7.20 – 7.15 (m, 2H), 6.84 (d, J = 7.0 Hz, 2H), 4.60 – 4.56 (m, 1H), 3.78 (s, 3H), 3.14 (d, J = 11.7 Hz, 1H), 2.95 (d, J = 11.7 Hz, 1H), 2.50 – 2.35 (m, 4H), 2.10 – 2.02 (m, 1H), 1.99 – 1.86 (m, 2H), 1.80 – 1.73 (m, 1H), 1.69 – 1.45 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 146.1, 146.0, 138.1, 128.1, 128.1, 126.7, 126.4, 126.4, 125.7, 125.6, 113.5, 79.2, 73.2, 58.9, 55.2, 54.7, 53.2, 44.2, 40.0, 26.0, 25.9, 24.1. LCMS Retention time: 3.620 min. LCMS purity 98.3%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO_3$ $[M+H]^+$ 446.2652, found 446.2728.



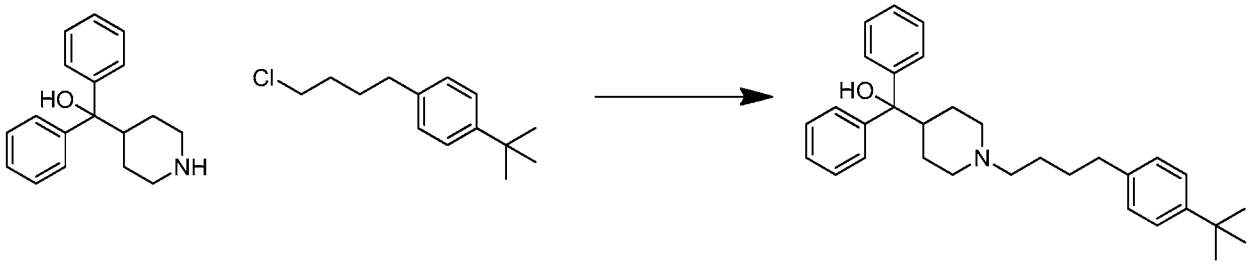
KSC-335-031

1-(4-fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. Method B: 1-(4-fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (KSC-335-024) (0.064 g, 0.148 mmol) and MeOH (2 mL) and sodium borohydride (0.011 g, 0.297 mmol) to produce pure 1-(4-fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.059 g, 0.136 mmol, 92% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.33 – 7.25 (m, 6H), 7.20 – 7.14 (m, 2H), 6.96 (t, *J* = 8.8 Hz, 2H), 4.61 – 4.57 (m, 1H), 3.14 (d, *J* = 11.7 Hz, 1H), 2.94 (d, *J* = 11.7 Hz, 1H), 2.51 – 2.35 (m, 4H), 2.13 – 2.02 (m, 1H), 2.02 – 1.86 (m, 2H), 1.78 – 1.45 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 160.7, 146.0, 145.9, 141.7, 141.6, 128.2, 128.1, 127.2, 127.1, 126.5, 126.4, 125.6, 125.5, 114.9, 114.7, 79.2, 73.0, 58.8, 54.8, 53.1, 44.2, 40.3, 30.9, 26.0, 25.9, 24.1. LCMS Retention time: 3.691 min. LCMS purity 98.5%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}FNO_2$ $[M+H]^+$ 434.2406, found 434.2482.



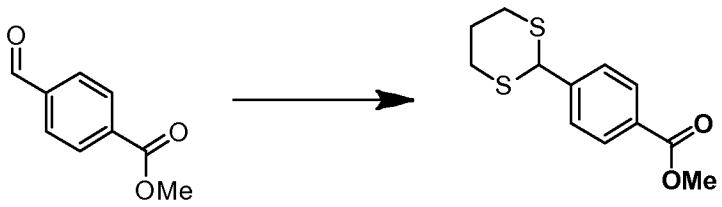
KSC-335-032

1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. Method B: 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (KSC-335-025) (0.083 g, 0.169 mmol) and MeOH (2 mL) and sodium borohydride (0.013 g, 0.337 mmol) to produce pure 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.053 g, 0.107 mmol, 63.6 % yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.41 (d, *J* = 6.8 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.22 (d, *J* = 6.6 Hz, 2H), 7.20 – 7.15 (m, 2H), 4.60 – 4.56 (m, 1H), 3.14 (d, *J* = 11.7 Hz, 1H), 2.93 (d, *J* = 11.7 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.41 – 2.34 (m, 2H), 2.11 – 2.05 (m, 1H), 2.01 – 1.95 (m, 1H), 1.94 – 1.86 (m, 1H), 1.78 – 1.45 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 145.1, 131.1, 128.2, 128.1, 127.5, 126.5, 126.4, 125.6, 125.6, 120.2, 79.2, 72.9, 58.8, 54.7, 53.2, 44.1, 40.1, 26.0, 25.9, 24.1. LCMS Retention time: 3.902 min. LCMS purity 99.1%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}BrNO_2$ $[M+H]^+$ 494.1614, found 494.1673.



KSC-335-041

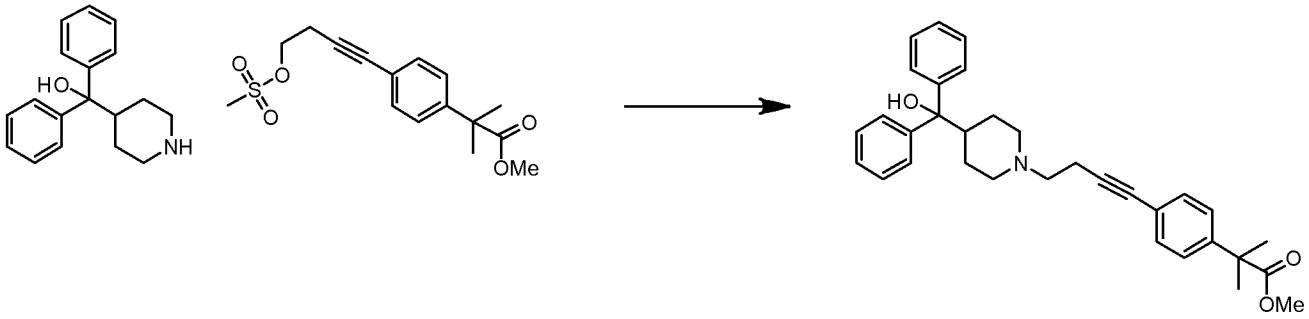
(1-(4-(4-(tert-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.153 g, 0.571 mmol), 1-(tert-butyl)-4-(4-chlorobutyl)benzene (KSC-335-020) (0.154 g, 0.685 mmol) and potassium carbonate (0.473 g, 3.43 mmol) in acetonitrile. The reaction stirred overnight at 85 °C and for 18 h and was then cooled to rt and filtered. The filtrate was then diluted with brine and extracted with diethyl ether (3 x 15 mL). The ether layers were combined, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:H_2O) to produce pure (1-(4-(4-(tert-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol (0.180 g, 0.395 mmol, 69% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.34 (m, 4H), 7.19 – 7.14 (m, 6H), 7.07 – 7.02 (m, 2H), 6.99 – 6.95 (m, 2H), 2.86 – 2.80 (m, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.35 – 2.26 (m, 1H), 2.22 – 2.17 (m, 2H), 1.84 – 1.76 (m, 3H), 1.52 – 1.30 (m, 8H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 148.4, 146.0, 139.4, 128.1, 128.0, 126.4, 125.8, 125.1, 79.5, 60.4, 58.8, 54.1, 44.2, 35.2, 34.3, 31.4, 29.5, 26.8, 26.4, 21.0, 14.2. LCMS Retention time: 3.928 min. LCMS purity 97.8%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO$ $[M+H]^+$ 456.3188, found 456.3261.



KSC-335-053

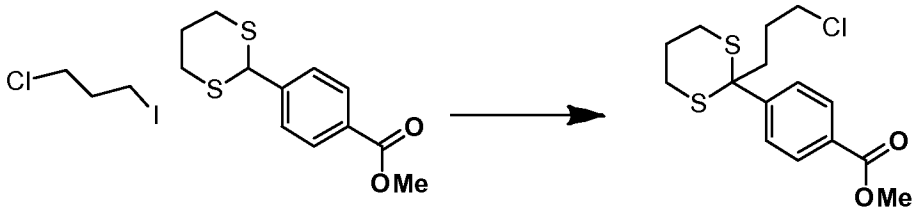
Methyl 4-(1,3-dithian-2-yl)benzoate. A flame dried vial was evaporated 3 times with argon and methyl 4-formylbenzoate (0.50 g, 3.05 mmol) was added with anhydrous DCM (8.70 mL) followed by 1,3-propanedithiol (0.339 mL, 3.35 mmol). The reaction began to stir at rt for 1.5 h. The reaction was then cooled to 0 °C and the $BF3{\cdot}OEt_2$ (0.425 ml, 3.35 mmol) was added dropwise. The reaction was then warmed slowly to rt and stirred overnight. The reaction was then diluted with DCM (15 mL) and quenched with saturated $NaHCO_3$ (15 mL) and the DCM layer was dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (20 min, 0 - 35% EtOAc:Hex) to produce methyl 4-(1,3-dithian-2-yl)benzoate (0.669

g, 2.63 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 3.91 (s, 3H), 3.12 – 3.03 (m, 2H), 2.96 – 2.90 (m, 2H), 2.23 – 2.16 (m, 1H), 2.01 – 1.89 (m, 1H), 1.55 (s, 2H).



KSC-335-054

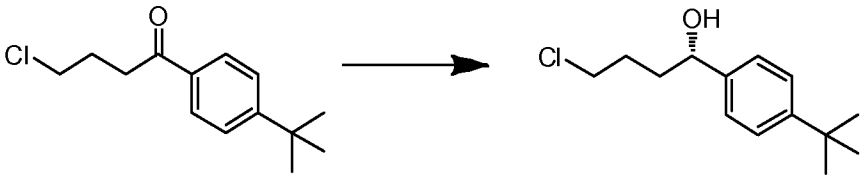
Methyl 2-(4-(4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)but-1-yn-1-yl)phenyl)-2-methylpropanoate. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.528 g, 1.974 mmol), methyl 2-methyl-2-(4-(4-((methylsulfonyl)oxy)but-1-yn-1-yl)phenyl)propanoate (KSC-335-022) (0.582 g, 1.794 mmol) and potassium carbonate (0.744 g, 5.38 mmol) with acetonitrile (10 mL). The reaction stirred at 70 °C for 18 h and cooled to rt and filtered to remove the potassium carbonate. The filtrate was adsorbed to silica gel and purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:H_2O) to produce pure methyl 2-(4-(4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)but-1-yn-1-yl)phenyl)-2-methylpropanoate (0.434 g, 0.876 mmol, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 4H), 7.34 – 7.27 (m, 6H), 7.25 – 7.15 (m, 4H), 3.64 (s, 3H), 3.03 – 2.97 (m, 2H), 2.68 – 2.63 (m, 2H), 2.59 – 2.54 (m, 2H), 2.48 – 2.40 (m, 1H), 2.14 – 2.06 (m, 2H), 1.63 (br s, 1H), 1.55 (s, 6H), 1.55 – 1.45 (m, 4H).



KSC-335-056

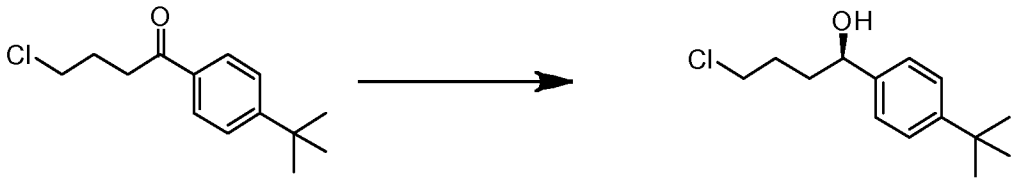
Methyl 4-(2-(3-chloropropyl)-1,3-dithian-2-yl)benzoate. To a dry vial was added the methyl 4-(1,3-dithian-2-yl)benzoate (KSC-335-053) (0.256 g, 1.01 mmol) and this was evacuated with argon 3 times. The dry THF (7 mL) was added and the reaction was cooled to -78 °C at and the NaHMDS (1.258 mL, 1.258 mmol) was added. After 30 minutes the 1-chloro-3-iodopropane (0.531 mL, 5.03 mmol) was added. The reaction was then allowed to warm to rt overnight. The mixture was quenched with the addition of saturated NH_4Cl (10 mL) at and diluted with EtOAc (15 mL) and shaken. The EtOAc layer was collected, dried

with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (20 min, - 25% EtOAc:Hex) to produce pure methyl 4-(2-(3-chloropropyl)-1,3-dithian-2-yl)benzoate (0.102 g, 0.308 mmol, 31% yield).). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 – 8.03 (m, 2H), 8.01 – 7.98 (m, 2H), 3.93 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.62 (m, 4H), 2.19 – 2.13 (m, 2H), 1.99 – 1.92 (m, 2H), 1.78 – 1.70 (m, 2H).



KSC-335-059

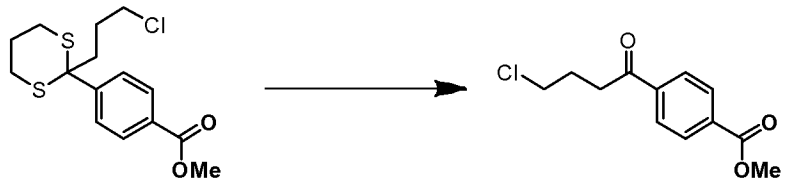
(*S*)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol. To a flame-dried vial was added dry THF (2 mL) and then cooled to 0 °C. The 1.0 M *R*-5,5-Diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.105 mL, 0.105 mmol) in THF was added followed by the 2.0 M borane-methyl sulfide complex (0.654 mL, 1.309 mmol) in THF. The reaction began to stir at 0 °C for 30 minutes. To another flame-dried vial was added the 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.250 g, 1.047 mmol) and this was evacuated with argon 3 times then dissolved in dry THF (5 mL) and the oxazaborlidine solution was added dropwise at 0 °C and the reaction was allowed to warm to rt stirred for 2 h. The reaction was quenched with MeOH (10 mL) extracted with EtOAc (20 mL) then was washed with 1.0 M HCl (3 x 25 mL). The EtOAc layer was dried with $MgSO_4$, filtered and concentrated to produce pure (S)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol (0.248 g, 1.030 mmol, 98% yield). $[\alpha]^{25}_{589}$ = -24.0° (c = 10 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4, 2H), 4.71 – 4.67 (m, 1H), 3.61 – 3.53 (m, 2H), 1.98 – 1.79 (m, 4H), 1.32 (s, 9H).



KSC-335-060

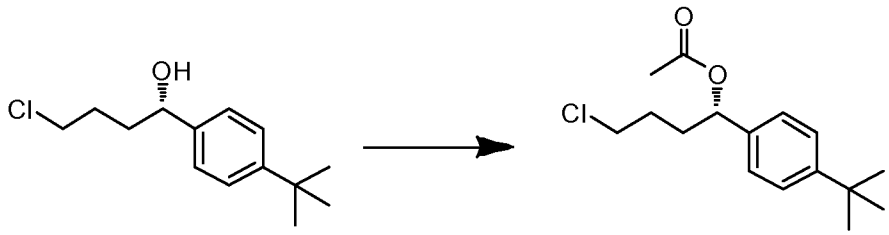
(*R*)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol. Prepared the same as KSC-335-059 with 1.0 M (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.105 ml, 0.105 mmol), 2.0 M Borane-methyl sulfide complex (0.654 ml, 1.309 mmol) and 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.250 g, 1.047 mmol) to produce pure (R)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol (0.216 g, 0.897 mmol, 86% yield). $[\alpha]^{25}_{589}$ = +23.1° (c = 10 in

$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4, 2H), 4.71 – 4.67 (m, 1H), 3.61 – 3.53 (m, 2H), 1.98 – 1.79 (m, 4H), 1.32 (s, 9H).



KSC-335-061

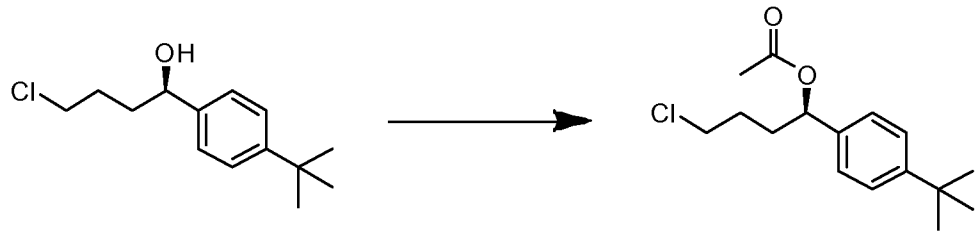
Methyl 4-(4-chlorobutanoyl)benzoate. To a vial was added the methyl 4-(2-(3-chloropropyl)-1,3-dithian-2-yl)benzoate (KSC-335-056) (0.102 g, 0.308 mmol) and acetonitrile (1.5 mL) with water (0.2 mL). The (bis(trifluoroacetoxy)iodo)benzene (0.199 g, 0.462 mmol) was then added and the reaction stirred at rt for 1 h. The reaction was quenched with saturated $NaHCO_3$ (7 mL) then diluted with EtOAc (10 mL) and extracted. The EtOAc was collected and washed with water (2 x 8 mL) and then dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (20 min, 0 - 25% EtOAc:hex to produce pure methyl 4-(4-chlorobutanoyl)benzoate (0.0512 g, 0.213 mmol, 69% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.00 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H), 3.67 (t, J = 6.1 Hz, 2H), 3.19 (t, J = 6.1 Hz, 2H), 2.22 (quintet, J = 6.3 Hz, 2H).



KSC-335-062

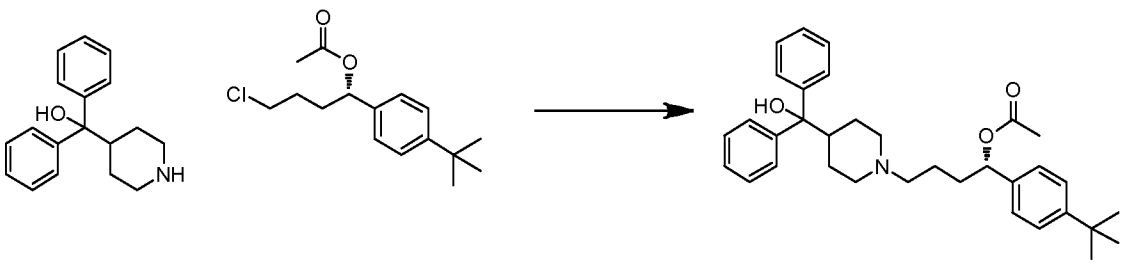
(S)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate. To a vial was added the (S)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol (KSC-335-059) (0.248 g, 1.030 mmol) and diethyl ether (5.15 ml). The TEA (0.215 mL, 1.545 mmol) was added followed by the acetyl chloride (0.073 mL, 1.030 mmol) and the reaction began to stir at rt for 2 h. A white precipiate formed immediately. Water (5 mL) was added the reaction after 2 h and the ether layer was extracted. The aqueous was extracted again with more ether and the combined organics were dried with $MgSO_4$, filtered and concentrated to produce pure (S)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (0.250 g, 0.884 mmol, 86 % yield). $[alpha]^{25}_{589}$ = -42.11, (c = 10,

CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.78 – 5.73 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.06 (s, 3H), 2.02 – 1.68 (m, 4H), 1.31 (s, 9H).



KSC-336-063

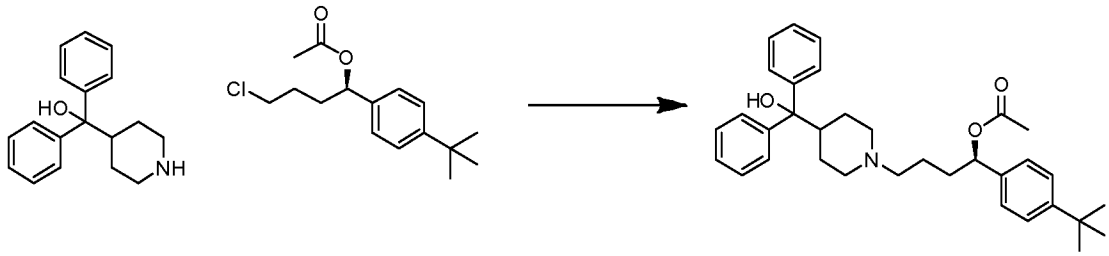
(R)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate. Prepared the same as KSC-335-062 with (R)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol (KSC-335-060) (0.216 g, 0.897 mmol) and diethyl ether (4.5 mL), TEA (0.188 ml, 1.346 mmol) and acetyl chloride (0.064 ml, 0.897 mmol) to produce pure (R)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (0.249 g, 0.880 mmol, 98% yield). [alpha]$^{25}_{589}$ = +54.57, (c = 10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.78 – 5.73 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.06 (s, 3H), 2.02 – 1.68 (m, 4H), 1.31 (s, 9H).



KSC-335-064

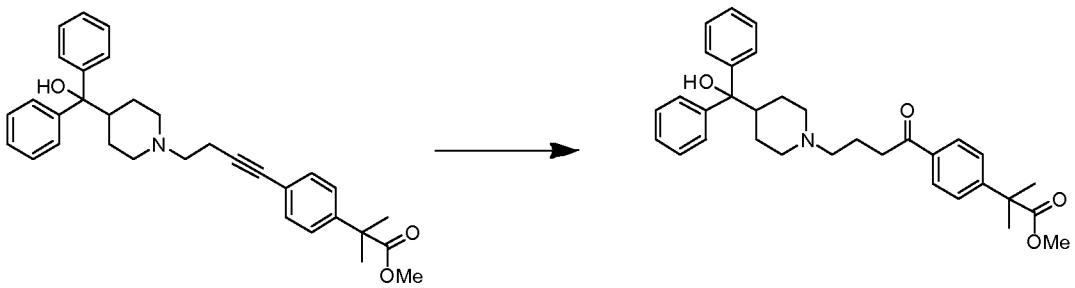
(S)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.154 g, 0.578 mmol), (S)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (0.196 g, 0.693 mmol) (KSC-335-062) and potassium carbonate (0.319 g, 2.310 mmol) in acetonitrile (10 mL). The reaction stirred overnight at 70 °C for 18 h and was then cooled to rt and filtered. The filtrate was then diluted with DCM and washed with water (10 mL) and brine (10 mL). The DCM layers were combined, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:water) to produce pure (S)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (0.135 g, 0.263 mmol, 46% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.45 (m, 4H), 7.35 – 7.14 (m, 10H), 5.73 –

5.68 (m, 1H), 2.93 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.87 (t, J = 7.7 Hz, 2H), 2.11 (br s, 1H), 2.04 (s, 3H), 1.95 – 1.84 (m, 3H), 1.80 – 1.72 (m, 1H), 1.53 – 1.38 (m, 6H), 1.29 (s, 9H).



KSC-335-065

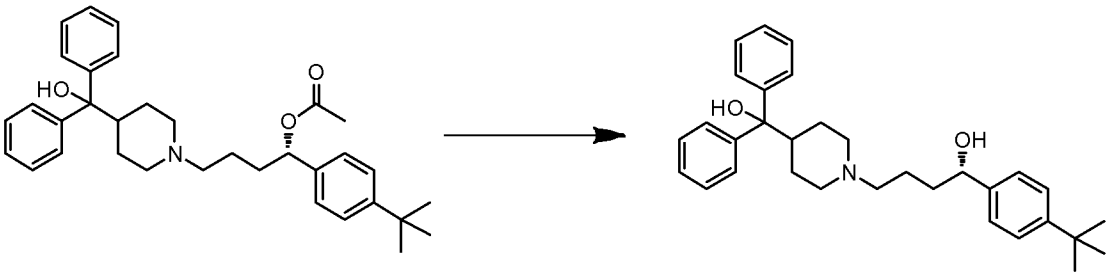
(R)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate. Prepared the same way as KSC-335-064 with diphenyl(piperidin-4-yl)methanol (0.196 g, 0.734 mmol), (R)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (KSC-335-063) (0.249 g, 0.880 mmol) and potassium carbonate (0.406 g, 2.93 mmol) in acetonitrile to produce pure (R)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (0.237 g, 0.461 mmol, 63% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.45 (m, 4H), 7.35 – 7.14 (m, 10H), 5.73 – 5.68 (m, 1H), 2.93 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.87 (t, J = 7.7 Hz, 2H), 2.11 (br s, 1H), 2.04 (s, 3H), 1.95 – 1.84 (m, 3H), 1.80 – 1.72 (m, 1H), 1.53 – 1.38 (m, 6H), 1.29 (s, 9H).



KSC-335-066

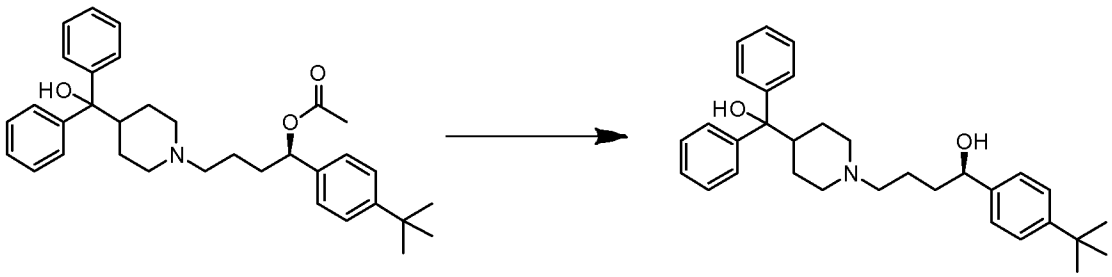
Methyl 2-(4-(4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butanoyl)phenyl)-2-methylpropanoate. To a vial was added the methyl 2-(4-(4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)but-1-yn-1-yl)phenyl)-2-methylpropanoate (KSC-335-054) (0.074 g, 0.149 mmol). The mercuric oxide (1.493 ml, 0.045 mmol) was made into a 0.03 M solution in 4% w/v sulfuric acid and added to the starting material then heated to 55 °C and stirred for 3.5 h. The reaction turned a milky white color upon addition of the mercuric oxide solution. The reaction was removed from heat and diluted with saturated $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The DCM layers were combined and dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce methyl 2-(4-(4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butanoyl)phenyl)-2-methylpropanoate (0.0217 g, 0.042 mmol, 28.3 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.91 (m, 2H), 7.48 – 7.45 (m, 4H), 7.42 – 7.39 (m, 2H), 7.30 –

7.26 (m, 4H), 7.19 – 7.14 (m, 2H), 3.63 (s, 3H), 2.96 – 2.88 (m, 4H), 2.44 – 2.34 (m, 3H), 2.08 (br s, 1H), 1.60 (s, 6H), 1.62 – 1.56 (m, 4H), 1.46 – 1.30 (m, 4H).



KSC-335-069

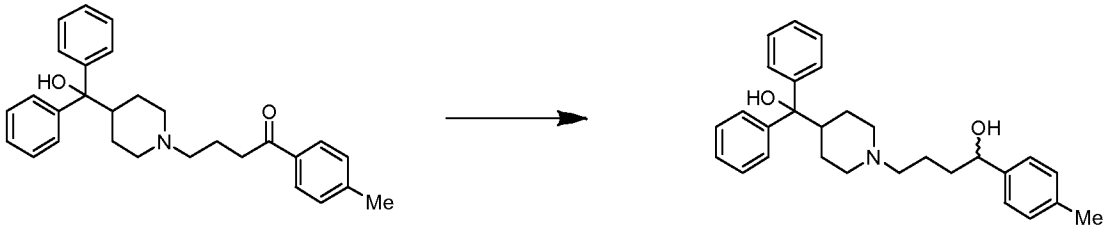
(*S*)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. To a vial was added the (S)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (0.135 g, 0.263 mmol) and this vial was evacuated with nitrogen 3 times. The dry THF (9 mL) was then added. The 1.0 M lithium aluminum hydride (0.263 mL, 0.263 mmol) in THF was added dropwise at rt and the reaction stirred for 5 h. The reaction was quenched slowly with water (10 mL) and then extracted with diethyl ether (2 x 10 mL). The ether layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (20 min, 10 - 100%, MeCN:H_2O) to produce pure (S)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.100 g, 0.212 mmol, 81 % yield). [alpha]$^{25}_{589}$ = - 38.8°. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.33 – 7.24 (m, 8H), 7.20 – 7.14 (m, 2H), 4.59 (dd, *J* = 8.2 Hz, 2.8 Hz, 1H), 3.13 (br d, *J* = 11.2 Hz, 1H), 2.97 (br d, *J* = 11.2 Hz, 1H), 2.50 – 2.34 (m, 3H), 2.10 – 1.88 (m, 4H), 1.84 – 1.74 (m, 1H), 1.68 – 1.44 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.45, 126.43, 125.7, 125.6, 125.4, 125.0, 79.3, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.1, 26.0, 24.1. LCMS Retention time: 4.159 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3137, found 472.3210.



KSC-335-070

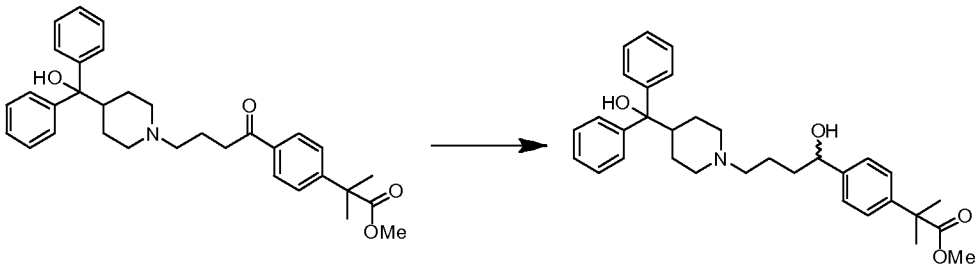
(*R*)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. To a vial was added the (*R*)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (0.237 g, 0.461 mmol) and this vial was evacuated with nitrogen 3 times. The dry THF (Volume: 4.61 ml) was added and then the 1.0 M lithium aluminum hydride

(0.461 mL, 0.461 mmol) in THF was added portionwise at rt for 5 h. The reaction was quenched slowly with water (10 mL) and then extracted with diethyl ether (2 x 10 mL). The ether layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (20 min, 10 - 100%, MeCN:H_2O) to produce pure (R)-1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butan-1-ol (0.116 g, 0.246 mmol, 53% yield). [alpha]$^{25}_{589}$ = + 38.6°. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.33 – 7.24 (m, 8H), 7.20 – 7.14 (m, 2H), 4.59 (dd, *J* = 8.2 Hz, 2.8 Hz, 1H), 3.13 (br d, *J* = 11.2 Hz, 1H), 2.97 (br d, *J* = 11.2 Hz, 1H), 2.50 – 2.34 (m, 3H), 2.10 – 1.88 (m, 4H), 1.84 – 1.74 (m, 1H), 1.68 – 1.44 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.45, 126.43, 125.7, 125.6, 125.4, 125.0, 79.3, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.1, 26.0, 24.1. LCMS Retention time: 4.156 min. LCMS purity 97.8%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3137, found 472.3210.



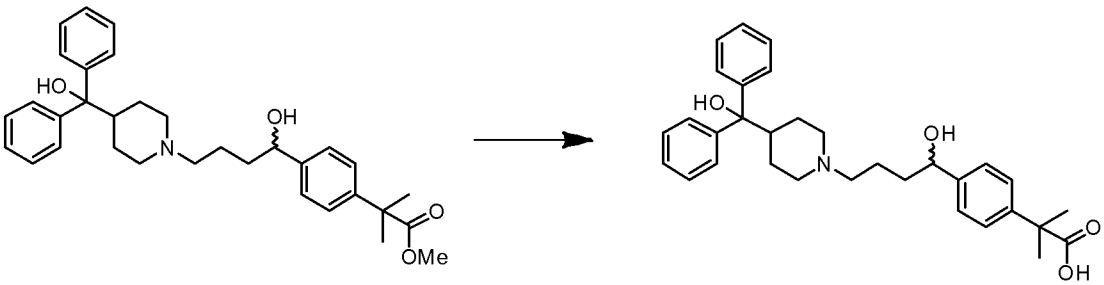
KSC-335-077

4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(p-tolyl)butan-1-ol. Method B: 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(p-tolyl)butan-1-one (0.073 g, 0.171 mmol) and MeOH (Volume: 2 mL) and SODIUM BOROHYDRIDE (0.013 g, 0.341 mmol) to produce pure 4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(p-tolyl)butan-1-ol (0.070 g, 0.163 mmol, 95% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 4H), 7.32 – 7.09 (m, 10H), 4.59 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.15 – 3.09 (m, 1H), 2.99 – 2.92 (m, 1H), 2.52 – 2.32 (m, 6H), 2.32 (s, 3H), 2.09 – 1.87 (m, 3H), 1.82 – 1.73 (m, 1H), 1.68 – 1.44 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 146.0, 142.9, 136.0, 128.7, 128.11, 128.10, 128.06, 126.39, 126.37, 125.7, 125.6, 125.5, 79.2, 73.3, 58.9, 54.6, 53.4, 53.3, 44.2, 39.9, 30.9, 26.0, 25.9, 26.0, 21.0. LCMS Retention time: 3.809 min. LCMS purity 94.1%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO_2$ $[M+H]^+$ 430.2668, found 430.2741.



KSC-335-080

Methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate. Method B: methyl 2-(4-(4-(4-(hydroxydiphenylmethyl) piperidin-1-yl)butanoyl)phenyl)-2-methylpropanoate (KSC-335-066)(0.148 g, 0.288 mmol) and MeOH (1 mL) and sodium borohydride (0.016 g, 0.432 mmol) to produce pure methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate (0.108 g, 0.209 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.49 (m, 4H), 7.35 – 7.27 (m, 8H), 7.23 – 7.17 (m, 2H), 4.62 (dd, J = 8.0, 2.8 Hz, 1H), 3.65 (s, 3H), 3.16 (d, J = 11.7 Hz, 1H), 2.98 (d, J = 11.7 Hz, 1H), 2.53 – 2.40 (m, 3H), 2.29 (br s, 1H), 2.14 – 2.06 (m, 1H), 2.01 – 1.93 (m, 2H), 1.84 – 1.50 (m, 14H). LCMS Retention time: 3.786 min. LCMS purity 98.2%. HRMS (ESI): *m/z* calcd for $C_{33}H_{41}NO_4$ $[M+H]^+$ 516.3036, found 516.3108.



KSC-335-081

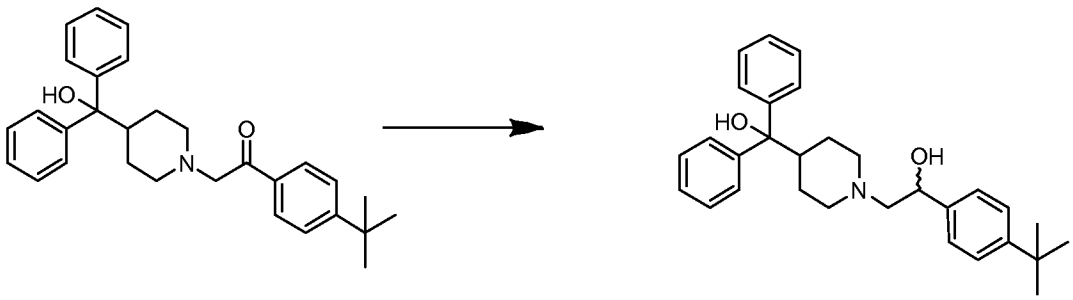
2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoic acid. To a vial was added the methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate (KSC-335-080) (0.094 g, 0.182 mmol) and THF (Volume: 3 mL,). The LiOH (0.022 g, 0.911 mmol) was dissolved in water (3.00 mL) and then added to the reaction stirred at 80°C for 18 h. The reaction was removed from heat and cooled to rt and 1.0 M HCl in water was added to adjust to pH to 4 and a gummy off-white solid formed. DCM (5 mL) was added to the mixture and it was sonicated to break up the solid. The DCM layer was removed and the aqueous was extracted with DCM (2 x 5 mL). The DCM layer was concentrated and the residue was purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:water) to produce the product with impurities. This was submitted to the purification core. The pure sample was recovered to produce 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoic acid (0.0378 g, 0.075 mmol, 41% yield). ^{1}H NMR (400 MHz, DMSO-d_6):

δ 8.22 (s, 1H), 7.52 – 7.49 (m, 4H), 7.29 – 7.26 (m, 8H), 7.15 7.10 (m, 2H), 4.47 (t, *J* = 5.9 Hz, 1H), 2.94 – 2.86 (m, 3H), 2.35 – 2.30 (m, 2H), 2.05 – 1.95 (m, 2H), 1.60 – 1.35 (m, 12H), 1.28 – 1.22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 163.7, 147.2, 144.4, 143.4, 127.8, 125.8, 125.7, 125.6, 125.1, 78.4, 71.8, 57.7, 53.4, 53.2, 45.5, 43.1, 37.3, 26.5, 25.6, 22.6. LCMS Retention time: 2.612 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO_4$ $[M+H]^+$ 502.2879, found 502.2952.



KSC-342-006

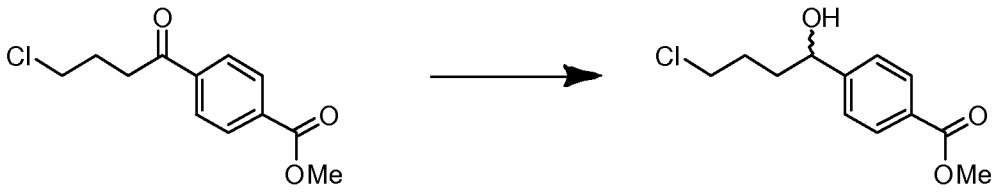
1-(4-(tert-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanone. Method A: diphenyl(piperidin-4-yl)methanol (0.4 g, 1.496 mmol), 1-(4-(tert-butyl)phenyl)-2-chloroethanone (0.300 g, 1.425 mmol), sodium bicarbonate (0.144 g, 1.710 mmol) with water (3 mL) and 2-butanone (Volume: 15 mL) to produce pure 1-(4-(tert-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanone (0.452 g, 1.024 mmol, 71.8 % yield) as a colorless oil. . ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.50 – 7.43 (m, 6H), 7.32 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 3.78 (s, 2H), 3.07 – 3.01 (m, 2H), 2.47 (tt, *J* = 11.8 Hz, 3.5 Hz, 1H), 2.26 – 2.18 (m, 2H), 1.66 – 1.45 (m, 5H), 1.33 (s, 9H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 157.0, 145.8, 133.5, 129.8, 128.2, 128.0, 126.5, 125.8, 125.5, 125.1, 79.5, 64.2, 54.2, 43.8, 35.1, 31.2, 31.0, 26.2. LCMS Retention time: 3.987 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_2$ $[M+H]^+$ 442.2668, found 442.2741.



KSC-342-010

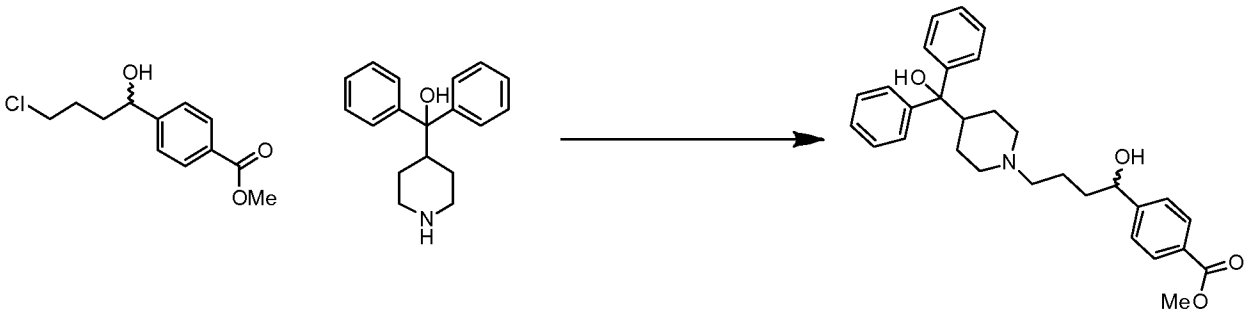
1-(4-(tert-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanol. Methon B: 1-(4-(tert-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanone (0.113 g, 0.256 mmol) and MeOH (1 mL) and SODIUM BOROHYDRIDE (0.019 g, 0.512 mmol) to produce pure 1-(4-(tert-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanol

(0.106 g, 0.239 mmol, 93% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.37 – 7.26 (m, 8H), 7.22 – 7.17 (M, 2H), 4.67 (m, 1H), 4.01 (br s, 1H), 3.20 (m, 1H), 2.86 (m, 1H), 2.50 – 2.45 (m, 3H), 2.37 – 2.30 (m, 1H), 2.10 – 2.02 (m, 1H), 1.60 – 1.45 (m, 5H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 145.82, 145.78, 139.1, 128.20, 128.19, 126.59, 126.57, 125.7, 125.6, 125.2, 79.5, 68.6, 66.3, 55.8, 53.4, 52.2, 44.1, 34.5, 31.3, 26.8, 26.5. LCMS Retention time: 4.083 min. LCMS purity 94.2%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO_2$ $[M+H]^+$ 444.2824, found 444.2897.



KSC-342-014

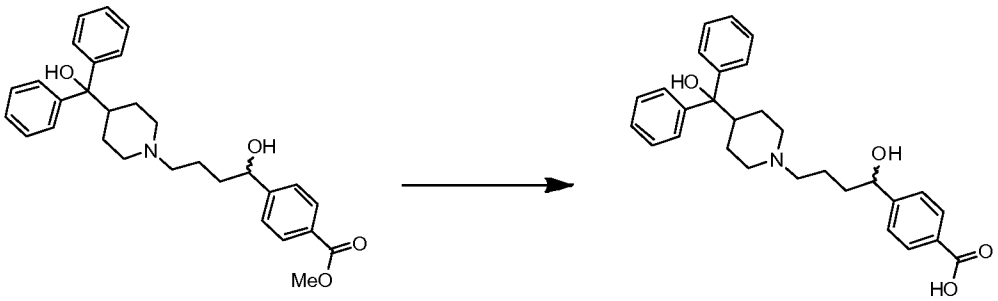
Methyl 4-(4-chloro-1-hydroxybutyl)benzoate. Method B: methyl 4-(4-chlorobutanoyl)benzoate (KSC-335-061) (0.042 g, 0.175 mmol) and MeOH with sodium borohydride (0.013 g, 0.349 mmol). to produce methyl 4-(4-chloro-1-hydroxybutyl)benzoate (0.037 g, 0.152 mmol, 87 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 4.8 – 4.6 (m, 1H), 3.90 (s, 3H), 3.58 – 3.52 (m, 2H), 2.19 (br s, 1H), 1.96 – 1.78 (m, 4H)



KSC-342-017

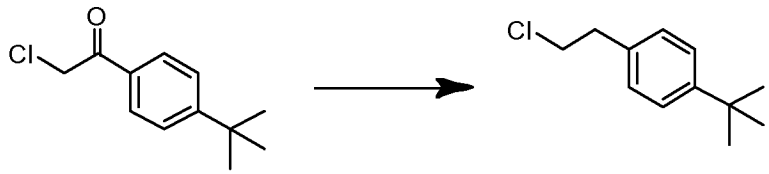
Methyl 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoate. To a vial was added the methyl 4-(4-chloro-1-hydroxybutyl)benzoate (KSC-342-014) (0.037 g, 0.152 mmol), diphenyl(piperidin-4-yl)methanol (0.122 g, 0.457 mmol), SODIUM BICARBONATE (0.026 g, 0.305 mmol), SODIUM IODIDE (1.143 mg, 7.62 µmol) and the vial was evacuated with argon 3 times. Dry acetonitrile (2 ml) was added and the reaction stirred overnight at reflux and was then cooled to rt after 18 h and the solvent was concentrated. The residue was dissolved in DCM (5 mL) and washed with 0.1 N HCl (5 mL), water (5 mL) and brine (5 mL). The product was purified by MPLC (0 - 10 % MeOH:DCM) to produce pure methyl 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoate (0.0268 g, 0.057 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97

(d, J = 8.4 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.42 (d, J = 7.9 Hz, 2H), 7.32 – 7.29 (m, 4H), 7.20 – 7.14 (m, 2H), 4.66 (m, 1H), 3.90 (s, 3H), 3.14 (m, 1H), 2.94 (m, 1H), 2.78 (br s, 1H), 2.52 – 2.43 (m, 1H), 2.39 (t, J = 4.8 Hz, 2H), 2.13 – 2.06 (m, 1H), 2.04 – 1.92 (m, 2H), 1.77 – 1.47 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 151.4, 146.0, 145.9, 129.5, 128.4, 128.2, 128.2, 126.51, 126.48, 125.64, 125.59, 79.2, 73.2, 58.8, 54.7, 51.9, 44.2, 40.0, 26.0, 25.9, 24.0. LCMS Retention time: 3.652 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_4$ $[M+H]^+$ 474.2566, found 474.2639.



KSC-342-021

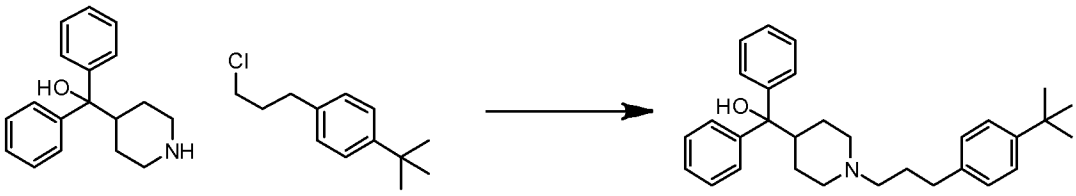
4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoic acid. To a vial was added the methyl 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoate (0.0195 g, 0.041 mmol) and THF (1 mL). The LiOH (6.90 mg, 0.288 mmol) was dissolved in water (1 mL) and added to the reaction. The reaction stirred at overnight and was then acidified with 1.0 M HCl to pH 2 - 3 then extracted with DCM (3 x 5 mL). The DCM layer was concentrated and purified by reverse-phase MPLC (10 - 100 % MeCN:water) to produce pure 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoic acid (0.009 g, 0.020 mmol, 47% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.85 (d, J = 8.2 Hz, 2H), 7.53 – 7.49 (m, 4H), 7.34 – 7.26 (m, 6H), 7.19 – 7.14 (m, 2H), 4.70 (m, 1H), 3.46 (m, 1H), 3.35 (s, 2H), 3.01 – 2.96 (m, 2H), 2.92 – 2.77 (m, 3H), 1.84 – 1.64 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD): δ 174.7, 148.2, 147.2, 137.6, 130.4, 129.1, 127.6, 127.0, 126.4, 79.9, 74.0, 53.9, 49.8, 36.9, 25.5, 21.8. LCMS Retention time: 2.490 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_4$ $[M+H]^+$ 460.2410, found 460.2482.



KSC-342-074

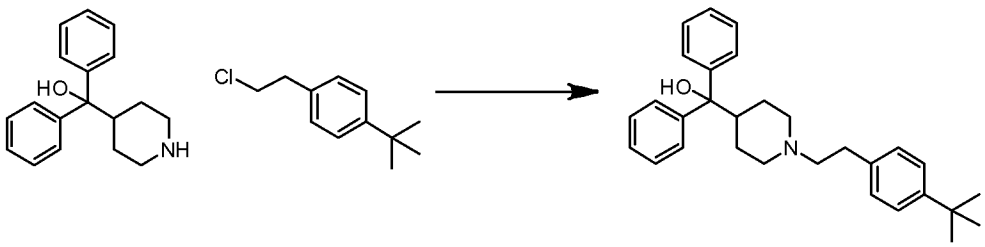
1-(Tert-butyl)-4-(2-chloroethyl)benzene. To a vial was added the 1-(4-(tert-butyl)phenyl)-2-chloroethanone (0.171 g, 0.812 mmol) and triethylsilane (0.519 mL, 3.25 mmol) with TFA (4 mL). The reaction stirred at 75 °C for 17 h and was then concentrated in vacuo. The residue was dissolved in DCM (5 mL) and washed with water (4 mL). The DCM layer was

collected and washed with water (1 x 5 mL), dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (20 min, 0 - 40% EtOAc:hex) to produce pure 1-(tert-butyl)-4-(2-chloroethyl)benzene (0.114 g, 0.580 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 3.71 (t, J = 7.5 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 1.32 (s, 9H).



KSC-342-080

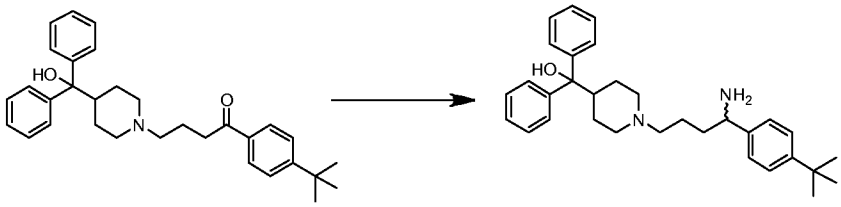
(1-(3-(4-(Tert-butyl)phenyl)propyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.142 g, 0.530 mmol), 1-(tert-butyl)-4-(3-chloropropyl)benzene (0.134 g, 0.636 mmol) and POTASSIUM CARBONATE (0.439 g, 3.18 mmol) in acetonitrile. The reaction stirred overnight at 85 °C for 18 h and then filtered. The filtrate was then diluted with brine and extracted with diethyl ether (3 x 15 mL). The ether layers were combined, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:water) to produce pure (1-(3-(4-(tert-butyl)phenyl)propyl)piperidin-4-yl)diphenylmethanol (0.152 g, 0.344 mmol, 65% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.45 (m, 4H), 7.31 – 7.24 (m, 6H), 7.19 – 7.14 (m, 2H), 7.11 – 7.08 (m, 2H), 2.96 (m, 2H), 2.57 (t, J = 7.7 Hz, 2H), 2.48 – 2.32 (m, 3H), 2.22 (br s, 1H), 1.97 – 1.90 (m, 2H), 1.83 – 1.75 (m, 2H), 1.53 – 1.45 (m, 4H), 1.29 (s, 9H). LCMS Retention time: 2.965 min. LCMS purity 97.2%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO$ $[M+H]^+$ 442.3032, found 442.3104.



KSC-342-081

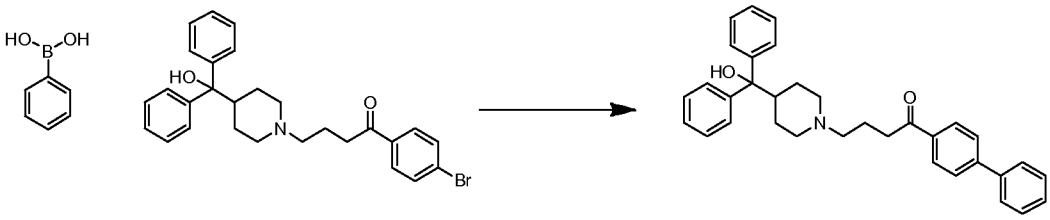
(1-(4-(Tert-butyl)phenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.150 g, 0.561 mmol), 1-(tert-butyl)-4-(2-chloroethyl)benzene (KSC-342-074) (0.110 g, 0.561 mmol) and potassium carbonate (0.465 g, 3.37 mmol) in acetonitrile. The reaction stirred overnight at 85 °C for 18 h and then filtered. The filtrate was then diluted with brine and extracted with diethyl ether (3 x 15 mL). The ether layers were combined, dried with MgSO4, filtered and purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:water) to produce pure (1-(4-(tert-

butyl)phenethyl)piperidin-4-yl)diphenylmethanol (0.180 g, 0.421 mmol, 75% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.33 – 7.27 (m, 6H), 7.21 – 7.16 (m, 2H), 7.14 – 7.11 (m, 2H), 3.09 – 3.03 (m, 2H), 2.80 – 2.74 (m, 2H), 2.60 – 2.55 (m, 2H), 2.51 – 2.42 (m, 1H), 2.28 (br s, 1H), 2.08 – 2.00 (m, 2H), 1.57 – 1.50 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 145.9, 137.3, 128.3, 128.1, 126.5, 125.8, 125.2, 79.5, 60.8, 54.0, 44.2, 40.9, 34.3, 33.1, 31.4, 26.4. LCMS Retention time: 4.384 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2875, found 428.2948.



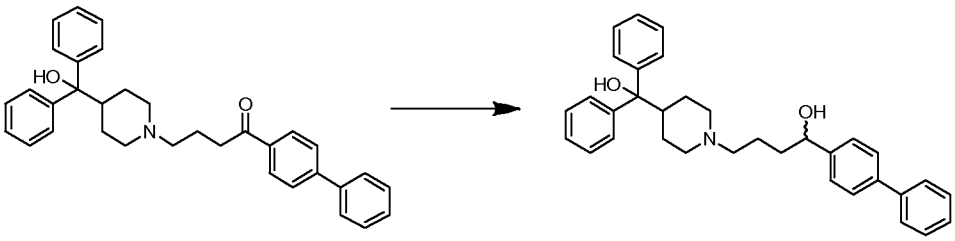
KSC-342-088

(1-(4-amino-4-(4-(tert-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol. To a vial was added the 1-(4-(tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.200 g, 0.426 mmol), Ammonium acetate (0.328 g, 4.26 mmol) and Sodium cyanoborohydride (0.040 g, 0.639 mmol) with MeOH (Volume: 4 ml). The reaction stirred at rt at 2:56:22 PM. The reaction was stirred overnight and then concentrated and diluted with dilute aqueous ammonium hydroxide and extracted with DCM. The DCM layer was concentrated and the crude NMR showed product and starting material. The reaction then purified by reverse-phase Teledyne ISCO Combiflash chromatography (10 - 100% MeCN:basic water) and fractions 5 and 6 were collected. These were then subjected to normal phase purification (0 - 10% MeOH (5% NH_3OH):DCM) to produce pure (1-(4-amino-4-(4-(tert-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol (0.010 g, 0.021 mmol, 5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.44 (m, 4H), 7.34 – 7.26 (m, 6H), 7.22 – 7.14 (m, 4H), 3.84 (t, J = 6.7 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.28 (t, J = 7.6 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.70 – 1.60 (m, 5H), 1.55 – 1.40 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 146.0, 143.3, 128.1, 126.5, 125.9, 125.8, 125.3, 79.5, 58.7, 55.8, 54.2, 54.0, 44.2, 37.5, 34.4, 31.4, 26.4, 24.2. LCMS Retention time: 2.397 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{32}H_{42}N_2O$ $[M+H]^+$ 471.3297, found 471.3370.



KSC-348-001

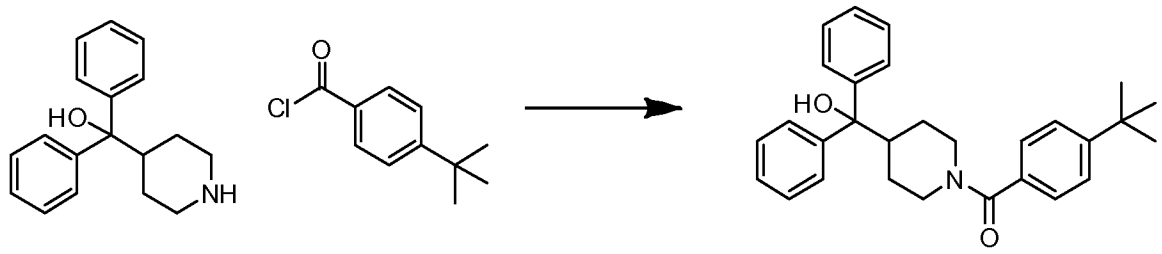
1-([1,1'-Biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one. To a vial was added the 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.098 g, 0.199 mmol), 1,1'-bis (di-t-butylphosphino)ferrocene palladium dichloride, (2.71 mg, 3.98 μmol) and phenylboronic acid (0.029 g, 0.239 mmol) followed by acetonitrile (1.5 mL). The potassium carbonate (0.041 g, 0.299 mmol) was dissolved in water (1.5 mL) and added the reaction. The reaction stirred at 60 °C for 18 h. The reaction was stopped and the organic layer was diluted with EtOAc and extracted then washed with brine. The EtOAc layer was collected, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce the desired 1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.035 g, 0.071 mmol, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.61 (m, 2H), 7.50 – 7.45 (m, 6H), 7.42 – 7.38 (m, 1H), 7.31 – 7.26 (m, 4H), 7.19 – 7.14 (m, 2H), 3.02 – 2.91 (m, 4H), 2.46 – 2.37 (m, 3H), 2.10 (br s, 1H), 1.97 – 1.92 (m, 4H), 1.50 – 1.35 (m, 4H).



KSC-348-002

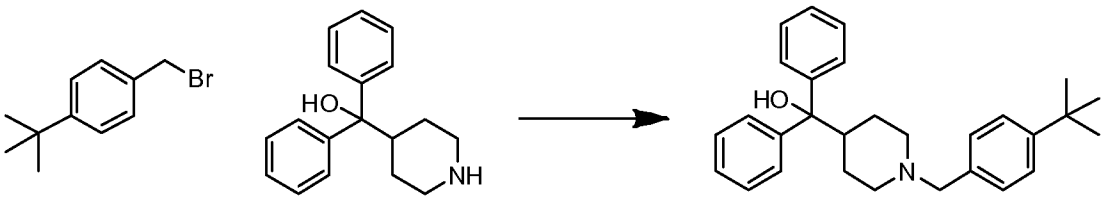
1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol. Method B: 1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (KSC-348-001) (0.035 g, 0.071 mmol) and MeOH (2 mL) and sodium borohydride (5.41 mg, 0.143 mmol) to produce pure 1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (0.033 g, 0.067 mmol, 94% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.55 (m, 2H), 7.53 – 7.46 (m, 6H), 7.43 – 7.38 (m, 4H), 7.34 – 7.25 (m, 5H), 7.19 – 7.13 (m, 2H), 4.65 (dd, *J* = 8.2 Hz, 2.7 Hz, 1H), 3.16 – 3.10 (m, 1H), 2.99 – 2.93 (m, 1H), 2.56 (br s, 1H), 2.50 – 2.34 (m, 3H), 2.10 – 1.92 (m, 3H), 1.86 – 1.76 (m, 1H), 1.70 – 1.45 (m, 6H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 146.0, 145.0, 141.1, 139.4, 128.6, 128.2, 128.1, 127.01, 126.96, 126.8, 126.44, 126.41, 126.1, 125.7, 125.6, 79.2, 73.3, 58.9, 54.7,

53.3, 44.2, 40.0, 26.0, 25.9, 24.1. LCMS Retention time: 4.049 min. LCMS purity 97.6%. HRMS (ESI): *m/z* calcd for $C_{34}H_{37}NO_2$ $[M+H]^+$ 492.2824, found 492.2897.



KSC-348-049

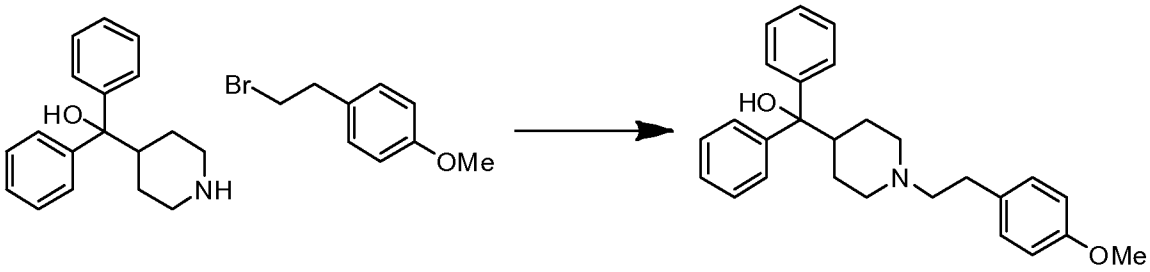
(4-(tert-butyl)phenyl)(4-(hydroxydiphenylmethyl)piperidin-1-yl)methanone. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.232 g, 0.868 mmol), acetonitrile (3 mL) and TEA (0.181 ml, 1.30 mmol). The 4-(tert-butyl)benzoyl chloride (0.173 mL, 0.954 mmol) was added and the reaction stirred at 70 °C for 6 h and was diluted with EtOAc (15 mL) and washed with saturated $NaHCO_3$ (15 mL). The EtOAc was collected, dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (20 min, 0 - 30 % EtOAc:Hex) to produce pure (4-(tert-butyl)phenyl)(4-(hydroxydiphenylmethyl)piperidin-1-yl)methanone (0.304 g, 0.711 mmol, 82% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.44 (m, 4H), 7.38 – 7.14 (m, 10H), 4.77 (br s, 1H), 3.84 (br s, 1H), 3.05 – 2.63 (m, 3H), 2.25 – 2.17 (m, 1H), 1.75 – 1.35 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 152.7, 145.4, 133.2, 128.3, 126.7, 125.7, 125.2, 79.5, 44.5, 34.7, 31.2. LCMS Retention time: 3.774 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_2$ $[M+H]^+$ 428.2511, found 428.2584.



KSC-348-050

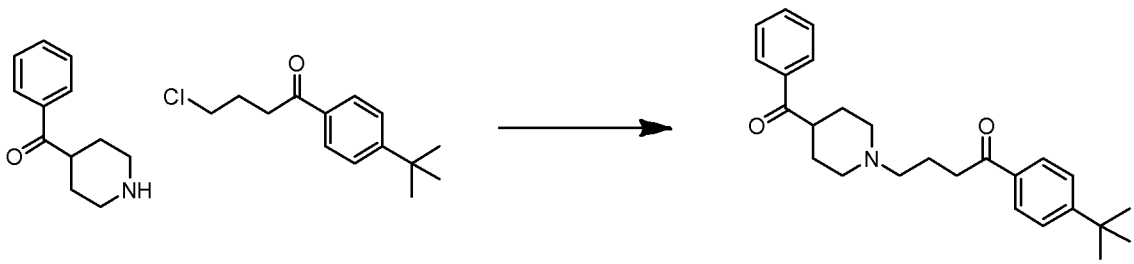
(1-(4-(tert-butyl)benzyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.085 ml, 0.393 mmol), acetonitrile (2 mL) and TEA (0.082 ml, 0.589 mmol). The p-tert-butylbenzyl bromide (0.098 g, 0.432 mmol) was then added and the reaction stirred at 70 °C and stirred for 5 h then diluted with EtOAc (15 mL) and washed with saturated $NaHCO_3$ (15 mL). The EtOAc was collected, dried with $MgSO_4$, filtered and adsorbed to silica and purified by reverse phase MPLC (20 min, 10 - 100 % MeCN:water) to produce pure (1-(4-(tert-butyl)benzyl)piperidin-4-yl)diphenylmethanol (0.131 g, 0.317 mmol, 81% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.45 (m, 4H), 7.32 – 7.25 (m, 6H), 7.22 – 7.14 (m, 4H), 3.47 (s, 2H), 2.96 – 2.90 (m, 2H), 2.46 –

2.38 (m, 1H), 2.02 – 1.95 (m, 1H), 1.51 – 1.44 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 146.0, 135.1, 128.9, 128.1, 126.4, 125.8, 125.0, 79.5, 62.8, 53.9, 44.2, 34.4, 31.4, 26.5, 21.0. LCMS Retention time: 4.186 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO$ $[M+H]^+$ 414.2719, found 414.2791.



KSC-348-058

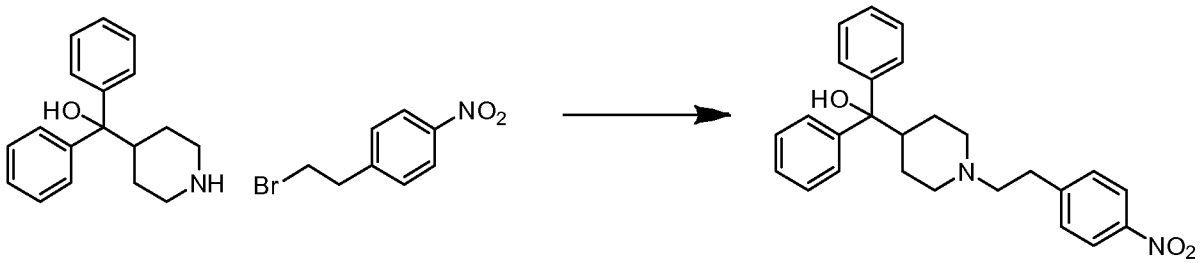
(1-(4-methoxyphenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.381 g, 1.425 mmol), acetonitrile (5 mL) and TEA (0.298 ml, 2.138 mmol). The 1-(2-bromoethyl)-4-methoxybenzene (0.245 ml, 1.568 mmol) was then added and the reaction stirred at 75 °C and the stirred for 16 h then was quenched with saturated $NaHCO_3$, extracted with EtOAc, dried with $MgSO_4$, filtered and adsorbed to silica. The product was purified by MPLC (20 min, 0 - 10% MeOH:DCM) to produce pure (1-(4methoxyphenethyl) piperidin-4-yl)diphenylmethanol (0.289 g, 0.720 mmol, 50% yield) as a sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 4H), 7.32 – 7.28 (m, 4H), 7.19 (tt, J = 7.3 Hz, 1.9 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.29 – 3.24 (m, 2H), 2.95 – 2.90 (m, 2H), 2.80 – 2.75 (m, 2H), 2.58 – 2.50 (m, 1H), 2.42 – 2.30 (m, 3H), 1.90 – 1.77 (m, 2H), 1.65 – 1.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 145.5, 129.6, 128.3, 126.7, 125.6, 114.0, 79.3, 55.3, 53.6, 53.4, 43.4, 31.5, 25.1. LCMS Retention time: 3.695 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{27}H_{31}NO_2$ $[M+H]^+$ 402.2355, found 402.2353.



KSC-352-055

4-(4-Benzoylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one. To a vial was added the 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.060 g, 0.252 mmol) and potassium iodide (0.063 g, 0.377 mmol) with acetonitrile (2 mL). The reaction stirred at 85 °C for 1 h then the phenyl(piperidin-4-yl)methanone (0.050 g, 0.264 mmol) along with potassium carbonate

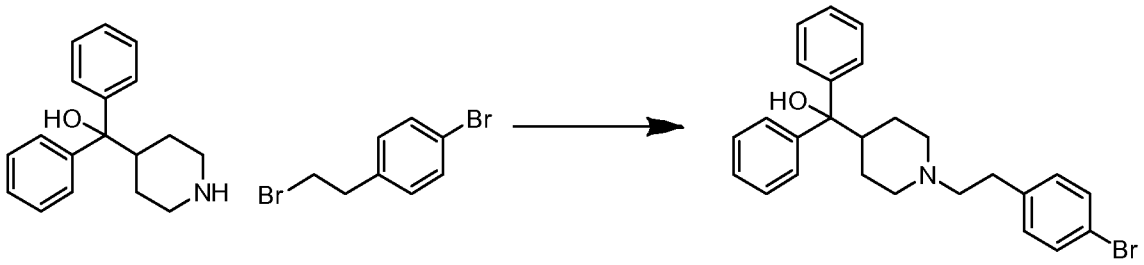
(0.052 g, 0.377 mmol) was added. The reaction was then heated back to 85 °C for 48 h. The reaction was cooled to rt and diluted with water then extracted with EtOAc (3 x 15 mL). The EtOAc layer was dried with $MgSO_4$, filtered and adsorbed to silica. The product was purified by reverse-phase MPLC (20 min, 10 - 100% MeCN:water) to produce 4-(4-benzoylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (0.026 g, 0.066 mmol, 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 4H), 7.57 – 7.53 (m, 1H), 7.49 – 7.44 (m, 4H), 3.27 – 3.18 (m, 1H), 3.03 – 2.96 (m, 4H), 2.44 (t, J = 7.04 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.98 – 1.91 (m,



2H), 1.85 – 1.76 (m, 4H), 1.34 (s, 9H).

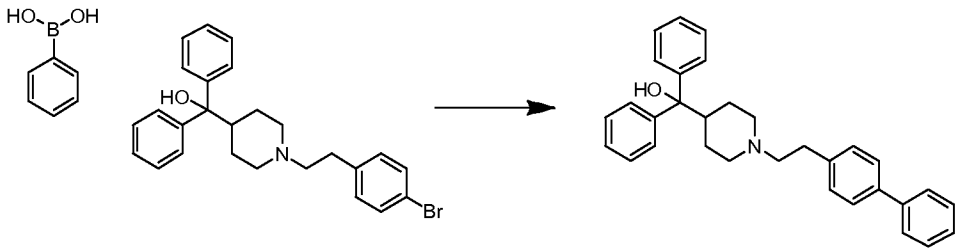
KSC-352-060

(1-(4-nitrophenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin -4-yl)methanol (0.513 g, 1.919 mmol), 1-(2-bromoethyl)-4-nitrobenzene (0.401 g, 1.744 mmol) and acetonitrile (10 mL). The TEA (0.365 ml, 2.62 mmol) was then added and the reaction stirred at 85 °C for 18 h then cooled to rt. The reaction was diluted with water and extracted with EtOAc (3 x 15 mL). The EtOAc layer was collected and dried with MgSO4, filtered and adsorbed to silica then purified by MPLC (15 min, 0 - 10 % MeOH:DCM). to produce pure (1-(4-nitrophenethyl)piperidin-4-yl)diphenylmethanol (0.145 g, 0.348 mmol, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 2H), 7.49 – 7.46 (m, 4H), 7.35 (d, J = 8.7 Hz, 2H), 7.32 – 7.27 (m, 4H), 7.21 – 7.16 (m, 2H), 3.11 – 3.05 (m, 2H), 2.97 – 2.91 (m, 2H), 2.69 – 2.63 (m, 2H), 2.52 – 2.43 (m, 1H), 2.25 (br s, 1H), 2.20 – 2.10 (m, 2H), 1.63 – 1.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.9, 146.5, 145.7, 129.5, 128.2, 126.6, 125.7, 123.7, 79.4, 59.4, 53.9, 43.9, 33.2, 26.1, 21.1. LCMS Retention time: 3.654 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_2O_3$ $[M+H]^+$ 417.2162, found 417.2173.



KSC-352-061

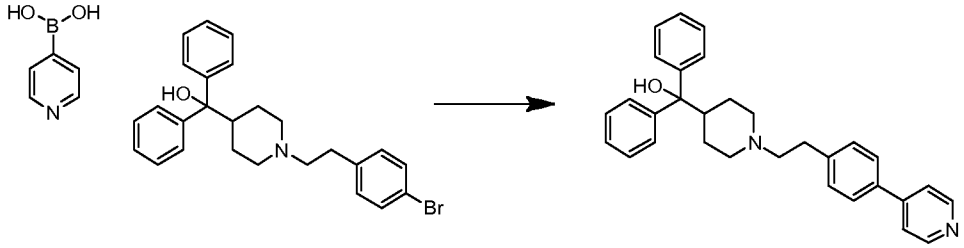
(1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.496 g, 1.855 mmol), 1-bromo-4-(2-bromoethyl)benzene (0.258 ml, 1.69 mmol) and acetonitrile (10 mL). The TEA (0.353 mL, 2.53 mmol) was then added and the reaction stirred at 85 °C for 18 h then cooled to rt. The reaction was diluted with water and extracted with EtOAc (3 x 15 mL). The EtOAc layer was collected and dried with $MgSO_4$, filtered and adsorbed to silica then purified by MPLC (15 min, 0 - 10 % MeOH:DCM). to produce pure (1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol (0.488 g, 1.083 mmol, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.38 (d, J = 8.3 Hz, 2H), 7.34 – 7.27 (m, 4H), 7.18 (tt, J = 7.3 Hz, 1.8 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 3.06 – 3.00 (m, 2H), 2.77 – 2.72 (m, 2H), 2.58 – 2.52 (m, 2H), 2.50 – 2.41 (m, 1H), 2.15 – 2.00 (m, 3H), 1.56 – 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 139.3, 131.4, 130.4, 128.2, 126.6, 125.8, 119.8, 79.5, 60.4, 54.0, 44.1, 33.1, 26.4, 21.1 LCMS Retention time: 3.969 min. LCMS purity 99.8%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}BrNO$ $[M+H]^+$ 450.1354, found 450.1427.



KSC-352-063

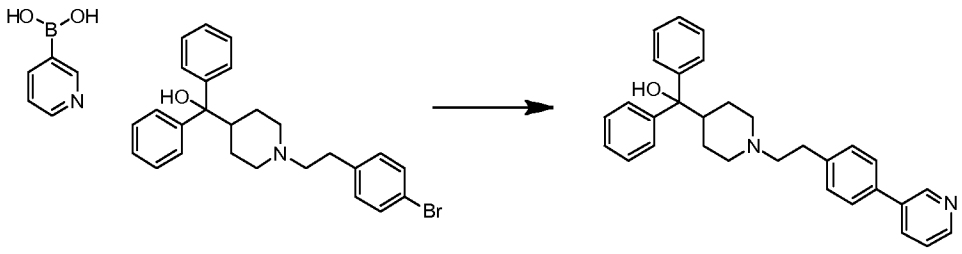
(1-(2-([1,1'-biphenyl]-4-yl)ethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the phenylboronic acid (0.019 g, 0.152 mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (4.12 mg, 6.33 µmol), (1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol (KSC-352-061) (0.057 g, 0.127 mmol) and potassium carbonate (0.035 g, 0.253 mmol). The vial was then evacuated with argon 3 times and acetonitrile (1 mL) was added followed by water (1 mL). The reaction then stirred at 60 °C for 18 h then was diluted with EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The EtOAc layer was collected and the aqueous layer was extracted with more EtOAc (2 x 5 mL). The EtOAc layers were combined and dried with $MgSO_4$, filtered and concentrated. The reaction was purified by MPLC (10 - 100% MeCN:water) to produce pure (1-(2-([1,1'-biphenyl]-4-yl)ethyl)piperidin-4-yl)diphenylmethanol (0.045 g, 0.101 mmol, 79% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.45 (m, 2H), 7.53 – 7.48 (m, 6H), 7.45 – 7.40 (m, 2H), 7.35 – 7.25 (m,

7H), 7.22 – 7.16 (m, 2H), 3.11 – 3.05 (m, 2H), 2.87 – 2.81 (m, 2H), 2.65 – 2.59 (m, 2H), 2.53 – 2.44 (m, 1H), 2.22 (br s, 1H), 2.12 – 2.04 (m, 2H), 1.59 – 1.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 141.0, 139.5, 139.0, 129.1, 128.7, 128.2, 127.1, 127.03, 126.96, 126.5, 125.8, 79.5, 60.7, 54.0, 50.8, 44.2, 33.3, 26.4. LCMS Retention time: 4.086 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{32}H_{33}NO$ $[M+H]^+$ 448.2562, found 448.2635.



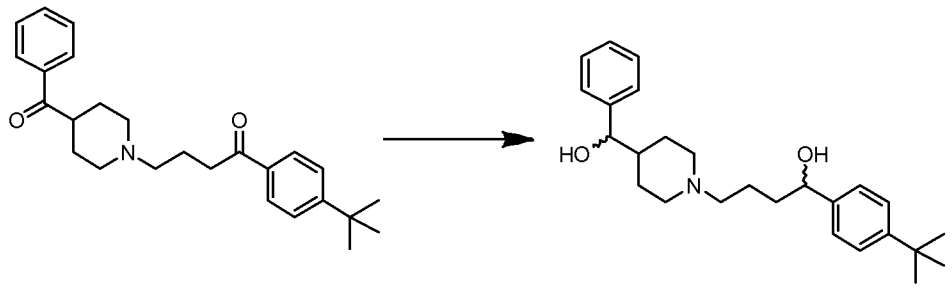
KSC-352-064

Diphenyl(1-(4-(pyridin-4-yl)phenethyl)piperidin-4-yl)methanol. To a vial was added the (1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol (KSC-352-061) (0.050 g, 0.111 mmol), pyridin-4-ylboronic acid (0.018 g, 0.133 mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.62 mg, 5.55 μmol) and potassium carbonate (0.031 g, 0.222 mmol). The vial was evacuated 3 times with argon and then acetonitrile (1 mL) followed by water (1 mL) was added. The reaction stirred at 60 °C for 18 h and was then cooled to rt and diluted with EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The EtOAc layer was collected and the aqueous layer was extracted with more EtOAc (2 x 5 mL). The EtOAc layers were combined and dried with $MgSO_4$, filtered and concentrated. The reaction was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce pure diphenyl(1-(4-(pyridin-4-yl)phenethyl)piperidin-4-yl)methanol (0.015 g, 0.033 mmol, 30% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 – 8.62 (m, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.51 – 7.46 (m, 6H), 7.32 – 7.28 (m, 6H), 7.18 (tt, J = 7.3 Hz, 1.8 Hz, 2H), 3.10 – 3.04 (m, 2H), 2.88 – 2.82 (m, 2H), 2.65 – 2.58 (m, 2H), 2.51 – 2.43 (m, 1H), 2.19 (br s, 1H), 2.12 – 2.03 (m, 2H), 1.58 – 1.51 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 148.1, 145.9, 141.7, 135.8, 129.5, 128.2, 127.0, 126.5, 125.8, 121.4, 79.5, 60.5, 54.1, 44.1, 41.0, 33.4, 26.4. LCMS Retention time: 3.585 min. LCMS purity 93.3%. HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_2O$ $[M+H]^+$ 449.2515, found 449.2587.



KSC-352-065

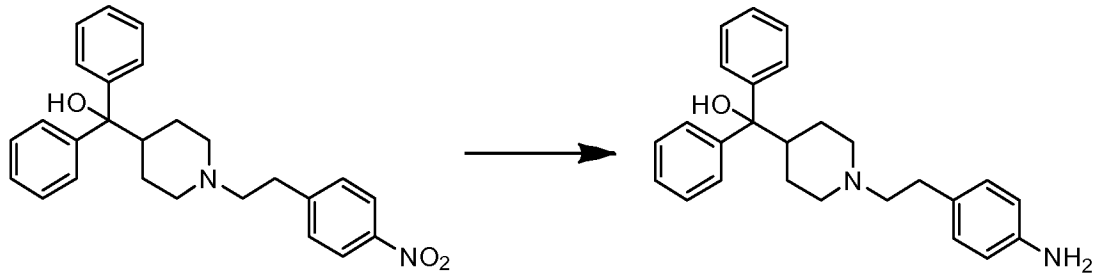
Diphenyl(1-(4-(pyridin-3-yl)phenethyl)piperidin-4-yl)methanol. To a vial was added the (1-(4-bromophenethyl)piperidin-4-yl)diphenylmethanol (0.057 g, 0.127 mmol), pyridin-3-ylboronic acid (0.019 g, 0.152 mmol), 1,1'-Bis(di-tert-butylphosphino)ferrocene palladium dichloride (4.12 mg, 6.33 μmol) and potassium carbonate (0.035 g, 0.253 mmol). The vial was evacuated with argon 3 times and then acetonitrile (1 mL) followed by water (1 mL) was added. The reaction stirred at 60 °C for 18 h and then cooled to rt and diluted with EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The EtOAc layer was collected and the aqueous layer was extracted with more EtOAc (2 x 5 mL). The EtOAc layers were combined and dried with $MgSO_4$, filtered and concentrated. The reaction was purified by RP MPLC (10 - 100% MeCN:water) to produce pure diphenyl(1-(4-(pyridin-3-yl)phenethyl)piperidin-4-yl)methanol (0.05 g, 0.111 mmol, 88% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (dd, J = 2.4 Hz, 0.9 Hz, 1H), 8.53 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 7.86 – 7.83 (m, 1H), 7.51 – 7.47 (m, 6H), 7.36 – 7.27 (m, 7H), 7.20 – 7.15 (m, 2H), 3.10 – 3.03 (m, 2H), 2.87 – 2.81 (m, 2H), 2.71 (br s, 1H), 2.63 – 2.58 (m, 2H), 2.51 – 2.43 (m, 1H), 2.11 – 2.03 (m, 2H), 1.58 – 1.52 (m, 4H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.04, 147.97, 146.0, 140.5, 136.5, 135.5, 134.3, 129.4, 128.1, 127.1, 126.4, 125.8, 123.5, 79.4, 60.5, 54.1, 44.1, 33.2, 26.2. LCMS Retention time: 3.582 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_2O$ $[M+H]^+$ 449.2515, found 449.2587.



KSC-352-066

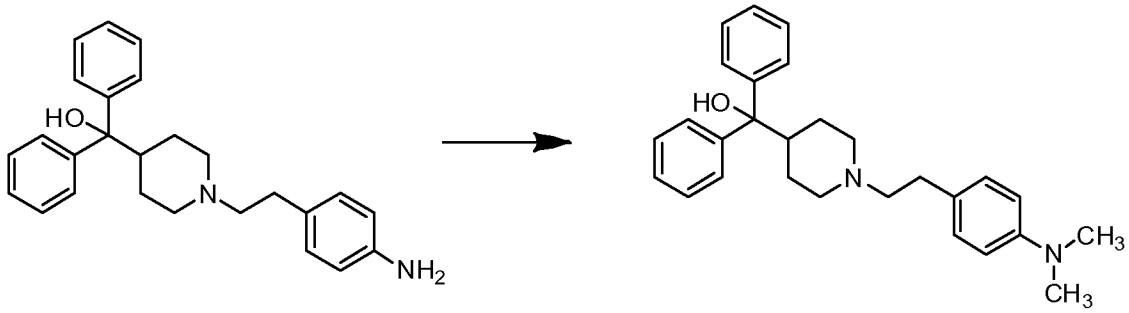
1-(4-(tert-butyl)phenyl)-4-(4-(hydroxy(phenyl)methyl)piperidin-1-yl)butan-1-ol. Method B: 4-(4-benzoylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (KSC-352-055) (0.026 g, 0.066 mmol) and MeOH (2 mL) and sodium borohydride (10.05 mg, 0.266 mmol) to produce pure 1-(4-(tert-butyl)phenyl)-4-(4-(hydroxy(phenyl)methyl)piperidin-1-yl)butan-1-ol (0.019 g, 0.048 mmol, 72% yield) as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.36 – 7.24 (m, 9H), 4.63 – 4.57 (m, 1H), 4.33 (d, J = 7.6 Hz, 1H), 3.23 – 2.83 (m, 2H), 2.42 – 2.35 (m, 2H), 2.13 – 1.89 (m, 3H), 1.86 – 1.52 (m, 6H), 1.46 – 1.16 (m, 4H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 143.4, 142.8, 128.3, 127.63, 127.61, 126.6, 125.4, 125.0, 78.74, 78.67, 73.4, 58.9, 54.30, 54.26, 52.8, 52.7, 43.21, 43.2, 39.9, 34.4, 31.4, 28.4, 28.3, 28.2, 24.2, 24.1. LCMS Retention time: 3.707 min. LCMS purity 97.1%. HRMS (ESI): m/z calcd for $C_{26}H_{37}NO_2$ $[M+H]^+$ 396.2824, found 396.2897.



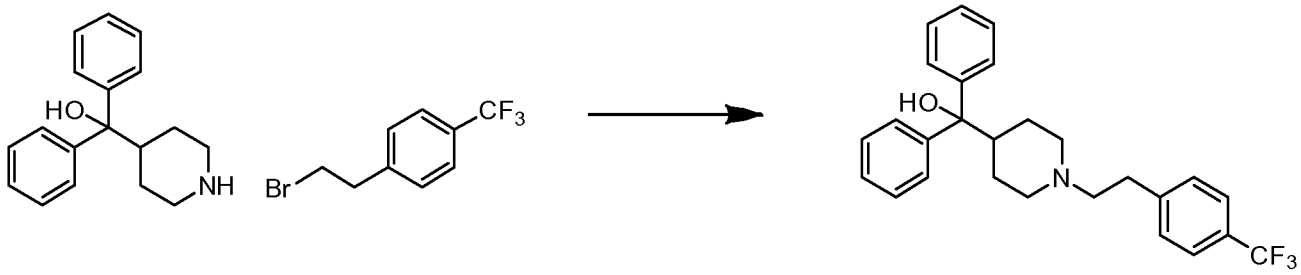
KSC-352-069

(1-(4-aminophenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the (1-(4-nitrophenethyl) piperidin-4-yl)diphenylmethanol (KSC-352-060) (0.135 g, 0.324 mmol) with MeOH (1 mL) and DCM (1 mL). The reaction was cooled to 0 °C and the Raney Nickel (1.902 mg, 0.032 mmol) was added. The sodium borohydride (0.031 g, 0.810 mmol) was then added portionwise and the reaction stirred at rt for 28 h and the Raney Nickel filtered through celite. The reaction was diluted with DCM and washed with water and the DCM layer was dried with $MgSO_4$, filtered and adsorbed to silica then purified by MPLC (0 - 15% MeOH:DCM) to produce pure (1-(4-aminophenethyl)piperidin-4-yl)diphenylmethanol (0.077 g, 0.199 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.32 – 7.27 (m, 4H), 7.18 (tt, J = 7.3 Hz, 1.8 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 6.61 (d, J = 8.3 Hz, 2H), 3.52 (br s, 2H), 3.07 – 3.01 (m, 2H), 2.70 – 2.65 (m, 2H), 2.54 – 2.41 (m, 3H), 2.22 (br s, 1H), 2.07 – 1.98 (m, 2H), 1.56 – 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.4, 130.4, 129.4, 128.1, 126.5, 125.8, 115.2, 79.5, 61.2, 54.1, 44.2, 32.8, 26.4, 21.0. LCMS Retention time: 3.328 min. LCMS purity 93.1%. HRMS (ESI): m/z calcd for $C_{26}H_{30}N_2O$ $[M+H]^+$ 387.2358, found 387.2431.



KSC-352-075

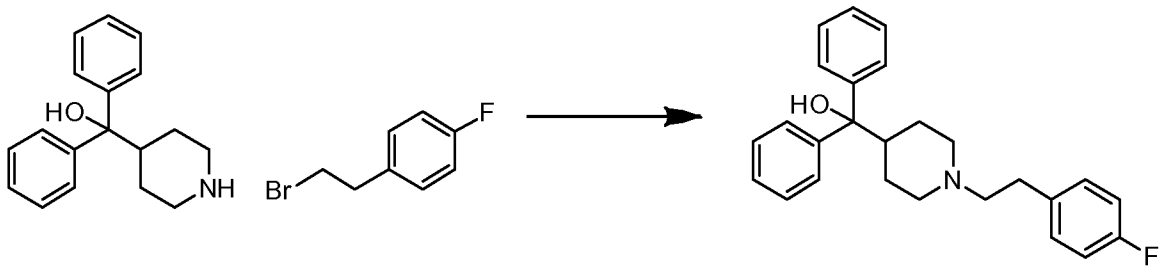
(1-(4-(Dimethylamino)phenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the (1-(4-aminophenethyl)piperidin-4-yl)diphenylmethanol (KSC-352-069) (0.030 g, 0.078 mmol) and acetic acid (1 mL). The paraformaldehyde (0.058 mL, 0.776 mmol) solution in water followed by sodium cyanoborohydride (0.015 g, 0.233 mmol) was then added and the reaction stirred at rt for 20 h. The reaction was concentrated and diluted with saturated $NaHCO_3$ and extracted with EtOAc (3 x 5 mL). The EtOAc layer was dried with $MgSO_4$, filtered and concentrated. The product was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce (1-(4-(dimethylamino)phenethyl)piperidin-4-yl)diphenylmethanol (0.027 g, 0.065 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.31 – 7.26 (m, 4H), 7.17 (tt, *J* = 7.3 Hz, 1.8 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 3.08 – 3.02 (m, 2H), 2.90 (s, 6H), 2.72 – 2.67 (m, 2H), 2.56 – 2.50 (m, 2H), 2.48 – 2.42 (m, 1H), 2.30 (br s, 1H), 2.07 – 2.00 (m, 2H), 1.56 – 1.51 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.1, 146.0, 129.2, 128.4, 128.1, 126.4, 125.8, 112.9, 79.4, 61.1, 54.0, 44.2, 41.0, 40.8, 32.6, 26.4. LCMS Retention time: 2.50 min. LCMS purity 96.1%. HRMS (ESI): *m/z* calcd for $C_{28}H_{34}N_2O$ $[M+H]^+$ 415.2671, found 415.2744.



KSC-352-082

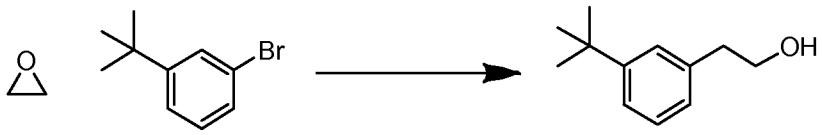
Diphenyl(1-(4-(trifluoromethyl)phenethyl)piperidin-4-yl)methanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.100 g, 0.374 mmol), 1-(2-bromoethyl)-4-(trifluoromethyl)benzene (0.057 ml, 0.340 mmol) and acetonitrile (10 mL). The TEA (0.071 mL, 0.510 mmol) was then added and the reaction stirred at 85 °C for 18 h. The reaction was diluted with water and extracted with EtOAc (3 x 15 mL). The EtOAc layer was collected and dried with $MgSO_4$, filtered and adsorbed to silica then purified by MPLC (15 min, 0 - 10 % MeOH:DCM) to produce pure diphenyl(1-(4-(trifluoromethyl)phenethyl)piperidin-4-yl)methanol (0.074 g, 0.168 mmol, 49% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54

– 7.47 (m, 4H), 7.33 – 7.27 (m, 6H), 7.19 (tt, J = 7.3 Hz, 1.8 Hz, 2H), 3.06 – 3.00 (m, 2H), 2.86 – 2.80 (m, 2H), 2.60 – 2.55 (m, 2H), 2.51 – 2.42 (m, 1H), 2.14 (br s, 1H), 2.10 – 2.03 (m, 2H), 1.57 – 1.47 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.6, 129.0, 128.3 (q, J = 32 Hz), 128.2, 126.5, 125.8, 125.2 (q, 3.8 Hz), 124.2 (q, J = 271.8 Hz), 79.5, 60.2, 54.1, 44.1, 33.6, 26.4, 21.0. LCMS Retention time: 3.877 min. LCMS purity 99.1%. HRMS (ESI): m/z calcd for $C_{27}H_{28}F_3NO$ $[M+H]^+$ 440.2123, found 440.2196.



KSC-352-088

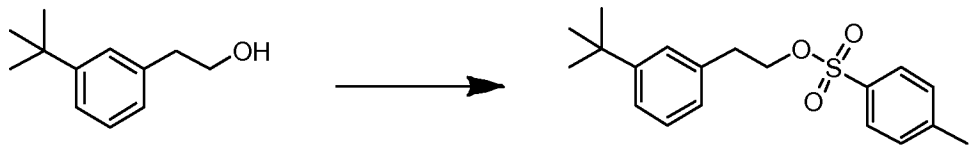
(1-(4-Fluorophenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.099 g, 0.370 mmol), 1-(2-bromoethyl)-4-fluorobenzene (0.047 mL, 0.337 mmol) and acetonitrile (10 mL). The TEA (0.070 mL, 0.505 mmol) was then added and the reaction stirred at 85 °C at for 19 h and was cooled to rt. The reaction was diluted with water and extracted with EtOAc (3 x 15 mL). The EtOAc layer was collected and dried with $MgSO_4$, filtered and adsorbed to silica then purified by MPLC (15 min, 0 - 10 % MeOH:DCM) to produce pure (1-(4-fluorophenethyl)piperidin-4-yl)diphenylmethanol (0.123 g, 0.316 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.32 – 7.27 (m, 4H), 7.21 – 7.11 (m, 4H), 6.98 – 6.92 (m, 2H), 3.06 – 3.00 (m, 2H), 2.78 – 2.72 (m, 2H), 2.56 – 2.51 (m, 2H), 2.50 – 2.42 (m, 1H), 2.21 (br s, 1H), 2.08 – 1.99 (m, 2H), 1.57 – 1.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2 (d, J = 243.6 Hz), 145.9, 136.5 (d, J = 3.2 Hz), 129.9 (d, J = 7.9 Hz), 128.1, 126.5, 125.8, 115.0 (d, J = 21.2 Hz), 79.5, 60.8, 54.1, 44.2, 33.0, 26.4, 21.0. LCMS Retention time: 3.733 min. LCMS purity 96.8%. HRMS (ESI): m/z calcd for $C_{26}H_{28}FNO$ $[M+H]^+$ 390.2155, found 390.2228.



KSC-352-090

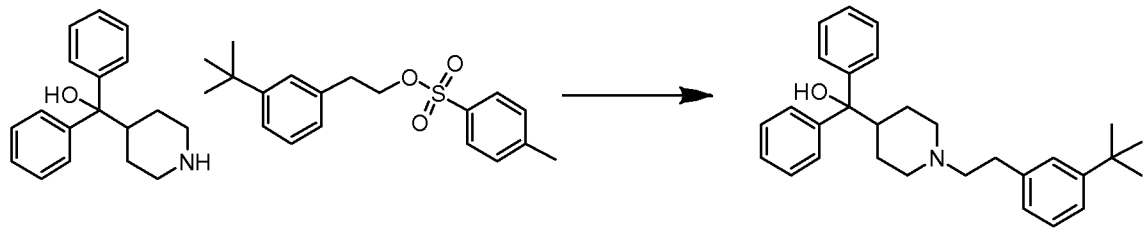
2-(3-(Tert-butyl)phenyl)ethanol. To a vial was added the 1-bromo-3-(tert-butyl)benzene (0.107 g, 0.502 mmol) and dry THF. The reaction was then cooled to -78 °C and the BuLi (0.221 mL, 0.552 mmol) (2.5 M in hexanes) was added dropwise and the reaction stirred for 30 min at -78 °C and then ethylene oxide (0.502 mL, 1.255 mmol) (2.5 - 3.3M solution in THF) was added dropwise and the reaction stirred for 10 minutes at -78 °C then warmed to rt

and stirred for 1 h. The reaction was then quenched with 1.0 M HCl (2 mL) and extracted with EtOAc (3 x 5 mL). The EtOAc layer was combined, concentrated and purified by reverse-phase MPLC (10 - 100 % MeCN:water) to produce pure 2-(3-(tert-butyl)phenyl)ethanol (0.035 g, 0.196 mmol, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 3H), 7.10 -7.07 (m, 1H), 3.90 (t, J = 6.6 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 1.52 (br s, 1H), 1.36 (s, 9H).



KSC-352-093

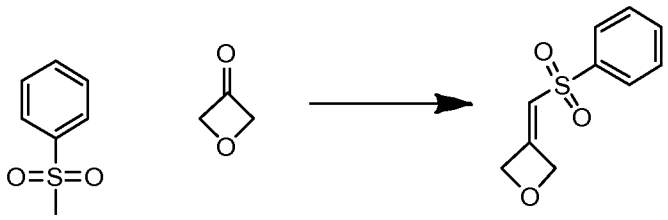
3-(Tert-butyl)phenethyl 4-methylbenzenesulfonate. To a vial was added the 2-(3-(tert-butyl)phenyl)ethanol (KSC-352-090) (0.035 g, 0.196 mmol), TEA (0.082 mL, 0.589 mmol) and DCM (2 mL) followed by p-toluenesulfonyl chloride (0.056 g, 0.294 mmol). The reaction began to stir at rt for 20 h and was then diluted with saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc was then dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% MeCN:water) to provide pure 3-(tert-butyl)phenethyl 4-methylbenzenesulfonate (0.060 g, 0.180 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 2H), 7.30 – 7.24 (m, 3H), 7.19 (t, J = 7.52 Hz, 1H), 7.14 – 7.12 (m, 1H), 4.22 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.29 (s, 9H).



KSC-352-097

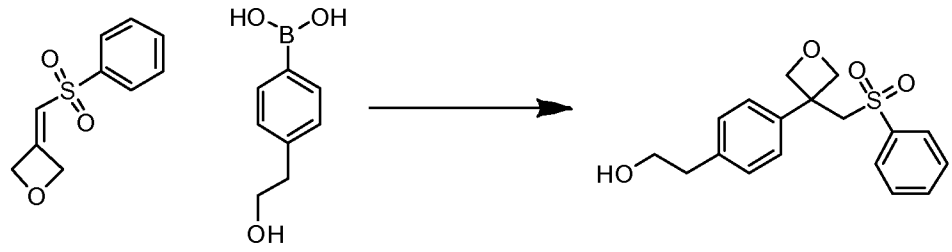
(1-(3-(Tert-butyl)phenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the 3-(tert-butyl)phenethyl 4-methylbenzenesulfonate (KSC-352-093) (0.060 g, 0.180 mmol), diphenyl(piperidin-4-yl)methanol (0.048 g, 0.180 mmol) and acetonitrile (1 mL). The TEA (0.038 mL, 0.271 mmol) was added and the reaction stirred at 85 °C for 18 h and was cooled to rt then diluted with water and extracted with EtOAc. The EtOAc layer was concentrated

and the crude product was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce the pure (1-(3-(tert-butyl)phenethyl)piperidin-4-yl)diphenylmethanol (0.065 g, 0.152 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.32 – 7.27 (m, 4H), 7.23 – 7.16 (m, 5H), 7.01 – 6.98 (m, 1H), 3.09 – 3.04 (m, 2H), 2.81 – 2.76 (m, 2H), 2.61 – 2.55 (m, 2H), 2.51 – 2.43 (m, 1H), 2.28 (br s, 1H), 2.10 – 2.02 (m, 2H), 1.30 (s, 9H), 1.32 – 1.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2, 145.9, 140.0, 128.1, 128.0, 126.5, 125.8, 125.71, 125.68, 123.0, 79.5, 54.1, 44.2, 34.6, 34.0, 31.6, 31.4, 26.4, 22.6. LCMS Retention time: 4.214 min. LCMS purity 96.4%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2875, found 428.2948.



KSC-352-099

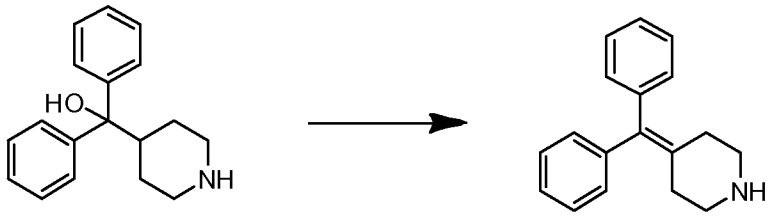
3-((Phenylsulfonyl)methylene)oxetane. To an oven-dried vial was added (methylsulfonyl)benzene (0.570 g, 3.65 mmol) and the vial was evacuated with argon 3 times. The dry THF (17 mL) was added and the reaction was cooled to 0 °C. The 2.5 M BuLi in hexanes (3.21 mL, 8.03 mmol) was added dropwise and the reaction began to stir at 0 °C and stirred for 45 minutes. The diethyl chlorophosphate (0.528 mL, 3.65 mmol) was then added at 0 °C and the reaction stirred for 30 minutes. The reaction was then cooled to -78 °C and the oxetan-3-one (0.330 mL, 5.15 mmol) was then added dropwise and the reaction stirred for 2 h. The reaction was then warmed to rt and filtered through a silica plug. The reaction was then concentrated onto silica and purified by MPLC (20 min, 0 - 40% EtOAc:hex) to provide pure 3-((phenylsulfonyl)methylene)oxetane (0.579 g, 2.75 mmol, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.87 (m, 2H), 7.69 – 7.64 (m, 1H), 7.60 – 7.55 (m, 2H), 6.12 (quintet, J = 2.3 Hz, 1H), 5.66 – 5.63 (m, 2H), 5.30 – 5.27 (m, 2H).



KSC-367-003

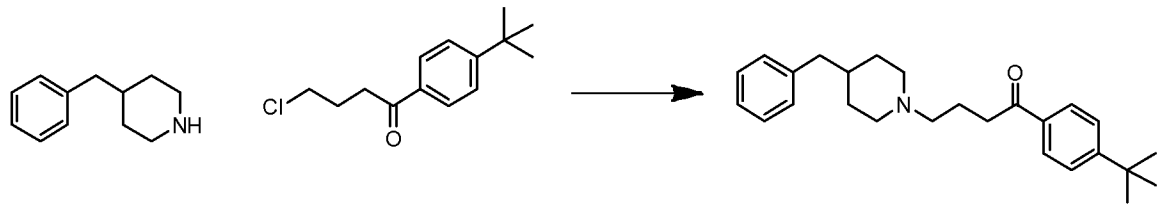
2-(4-(3-((Phenylsulfonyl)methyl)oxetan-3-yl)phenyl)ethanol. To a vial was added the chloro(1,5-cyclooctadiene)rhodium(I), dimer (0.012 g, 0.025 mmol) and 1,4-dioxane (10 mL). The 1.5 M aqueous KOH (0.496 mL, 0.745 mmol) was then added and the reaction

stirred for 1 minute at rt. Then the (4-(2-hydroxyethyl)phenyl)boronic acid (0.103 g, 0.621 mmol) and 3-((phenylsulfonyl)methylene)oxetane (KSC-352-099) (0.052 g, 0.248 mmol) in 1 mL dioxane was added and the reaction stirred for 30 minutes at 100 °C in μwaves. The reaction was then cooled to rt and diluted with EtOAc and washed with 1.0 M HCl. The water layer was extracted with EtOAc (3 x 15 mL). The EtOAc layer was collected and the water was extracted with EtOAc again. The EtOAc layers were combined and dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (30 min, 10 - 100% MeCN:water) to produce pure 2-(4-(3-((phenylsulfonyl)methyl) oxetan-3-yl)phenyl)ethanol (0.063 g, 0.190 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.52 (m, 2H), 7.50 – 7.46 (m, 1H), 7.36 – 7.31 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.03 (d, *J* = 6.4 Hz, 2H), 4.93 (d, *J* = 6.4 Hz, 2H), 4.03 (s, 2H), 3.82 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H).



KSC-367-027

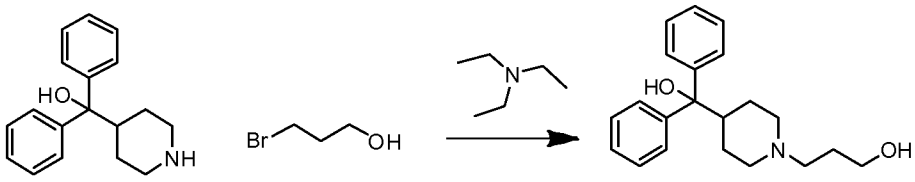
4-(diphenylmethylene)piperidine. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.514 g, 1.922 mmol) and TFA (4 mL). The reaction stirred at 75 °C at for 24 h and was concentrated in vacuo. The residue was then dissolved in DCM (5 mL) and washed with water (4 mL). The DCM layer was collected and washed with water (1 x 5 mL), dried with $MgSO_4$, filtered concentrated then purified by reverse-phase MPLC (10 - 100% MeCN:Hex) to produce pure 4-(diphenylmethylene)piperidine (0.296 g, 1.187 mmol, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 2H), 7.18 – 7.14 (m, 4H), 2.96 – 2.92 (m, 4H), 2.37 – 2.33 (m, 4H), 1.75 (br s, 1H).



KSC-367-032

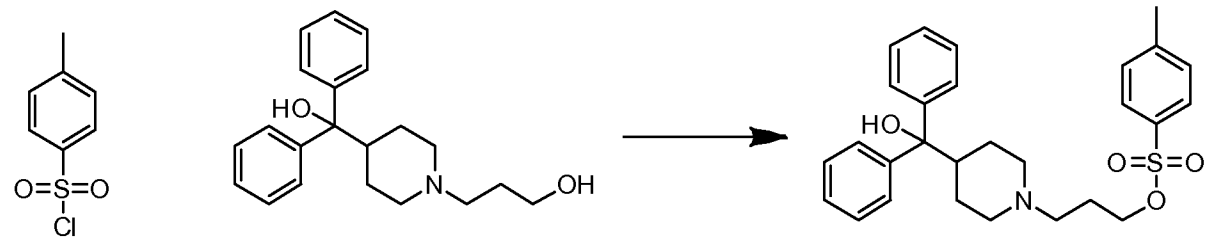
4-(4-Benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one. To a vial was added the 4-benzylpiperidine (0.25 ml, 1.422 mmol), 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.407 g, 1.707 mmol), acetonitrile and TEA (0.297 mL, 2.133 mmol). The reaction stirred at 85 °C for 17 h. The reaction was cooled to rt and diluted with saturated $NaHCO_3$ then extracted with EtOAc. The EtOAc was dried with $MgSO_4$, filtered and concentrated. The

crude material was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce 4-(4-benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (0.291 g, 0.771 mmol, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.20 – 7.16 (m, 1H), 7.14 – 7.11 (m, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.90 – 2.84 (m, 2H), 2.50 (d, J = 7.0 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.96 – 1.82 (m, 4H), 1.63 – 1.56 (m, 2H), 1.53 – 1.46 (m, 1H), 1.34 (s, 9H), 1.28 – 1.18 (m, 2H).



KSC-367-033

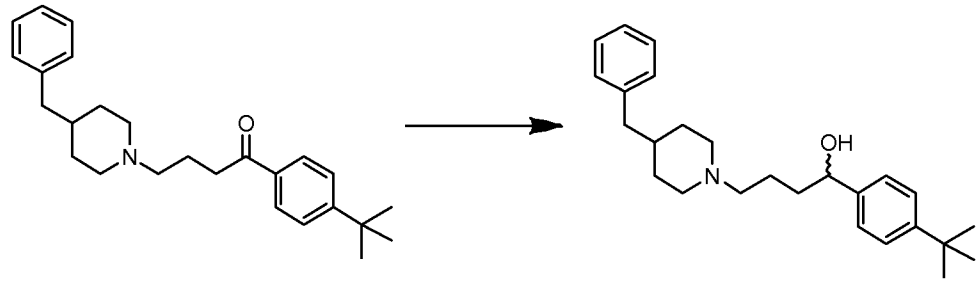
3-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.502 g, 1.878 mmol), 3-bromopropan-1-ol (0.204 mL, 2.253 mmol), acetonitrile and TEA (0.393 mL, 2.82 mmol). The reaction stirred at 85 °C for 3 h. The reaction was cooled to rt and diluted with saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc layer was concentrated and purified by reverse-phase MPLC (10 - 100 % MeCN:water) to provide 3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol (0.395 g, 1.214 mmol, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.44 (m, 4H), 7.31 – 7.27 (m, 4H), 7.20 – 7.15 (m, 2H), 5.45 (br s, 1H), 3.75 (t, J = 5.2 Hz, 2H), 3.12 – 3.06 (m, 2H), 2.57 (t, J = 5.7 Hz, 2H), 2.47 – 2.36 (m, 1H), 1.98 – 1.91 (m, 2H), 1.70 – 1.65 (m, 3H), 1.54 – 1.42 (m, 4H).



KSC-367-036

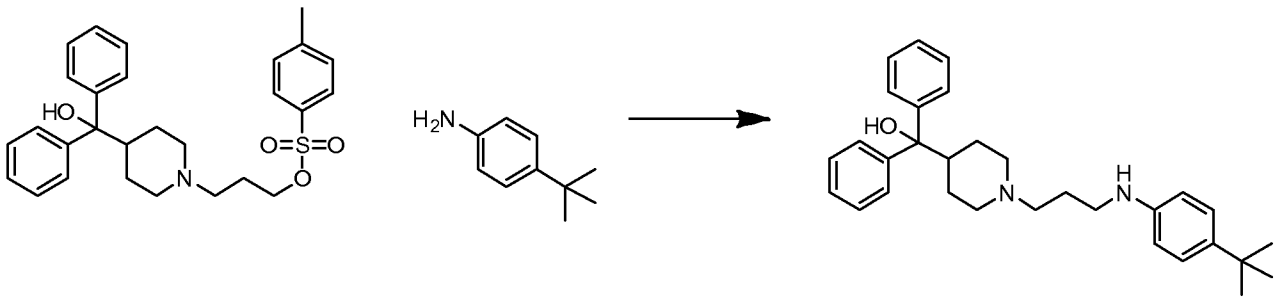
3-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)propyl 4-methylbenzenesulfonate. Prepared with same method at KSC-352-093 using 3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol (KSC-367-033) (0.395 g, 1.214 mmol), 4-methylbenzene-1-sulfonyl chloride (0.347 g, 1.821 mmol), DCM (5 mL) and TEA (0.508 mL, 3.64 mmol) to produce pure 3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propyl 4-methylbenzenesulfonate (0.193 g, 0.402 mmol, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.66 (m, 2H), 7.46 – 7.41 (m, 4H), 7.24 – 7.19 (m, 4H), 7.15 – 7.05 (m, 4H), 4.26 – 4.12 (m, 4H), 3.73 – 3.65 (m, 2H), 3.27 –

3.18 (m, 2H), 2.68 – 2.60 (m, 1H), 2.47 – 2.37 (m, 2H), 2.30 (s, 3H), 1.88 – 1.76 (m, 2H), 1.52 – 1.43 (m, 2H).



KSC-367-039

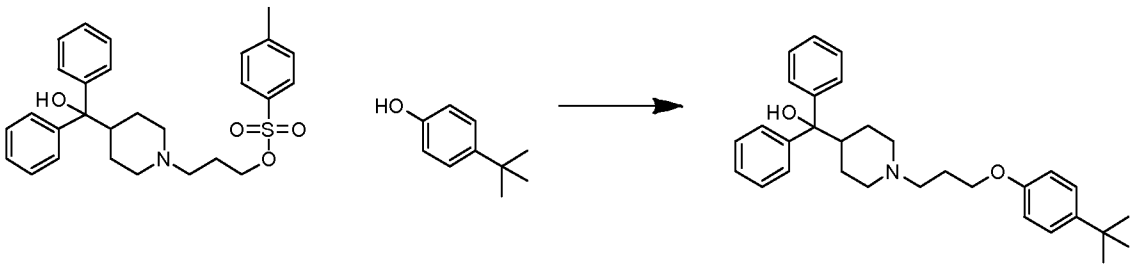
4-(4-Benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-ol. Method B: 4-(4-benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (KSC-367-032) (0.291 g, 0.771 mmol) and MeOH (5 mL) and sodium borohydride (0.117 g, 3.08 mmol) to produce pure 4-(4-benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-ol (0.232 g, 0.611 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 6H), 7.21 – 7.12 (m, 3H), 4.64 – 4.60 (m, 1H), 3.13 – 3.07 (m, 1H), 2.94 – 2.88 (m, 1H), 2.54 (d, J = 7.0 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.03 – 1.93 (m, 2H), 1.90 – 1.38 (m, 10H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 142.9, 140.7, 129.1, 128.2, 125.8, 125.4, 125.0, 73.5, 59.0, 54.6, 52.9, 42.9, 40.1, 38.0, 34.4, 31.8, 31.6, 31.4, 24.3. LCMS Retention time: 4.330 min. LCMS purity 99.1%. HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO$ $[M+H]^+$ 380.2875, found 380.2948.



KSC-367-043

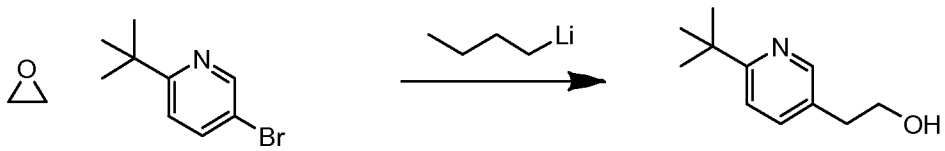
(1-(3-((4-(Tert-butyl)phenyl)amino)propyl)piperidin-4-yl)diphenylmethanol. To a vial was added the 3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propyl 4-methylbenzenesulfonate (KSC-367-036) (0.088 g, 0.183 mmol), 4-(tert-butyl)aniline (0.035 mL, 0.220 mmol) and TEA (0.038 mL, 0.275 mmol) with acetonitrile (3 mL). The reaction began to stir at 85 °C for 18 h and was then cooled to rt and diluted with saturated $NaHCO_3$ then extracted with EtOAc. The EtOAc was concentrated and purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce pure (1-(3-((4-(tert-butyl)phenyl)amino) propyl)piperidin-4-yl)diphenylmethanol (0.038 g, 0.083 mmol, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.33 – 7.28 (m, 4H), 7.21 – 7.16 (m, 4H), 6.51 (d, J = 8.7 Hz, 2H), 3.13 (t, J

= 6.4 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.49 – 2.41 (m, 3H), 2.15 (br s, 1H), 2.00 – 1.93 (m, 2H), 1.80 – 1.73 (m, 2H), 1.57 – 1.43 (m, 5H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.4, 145.9, 139.7, 128.2, 126.5, 125.9, 125.8, 112.4, 79.6, 57.4, 54.2, 44.2, 43.7, 33.8, 31.5, 26.6, 26.2. LCMS Retention time: 4.208 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{30}H_{38}N_2O$ $[M+H]^+$ 457.6620, found 457.3194.



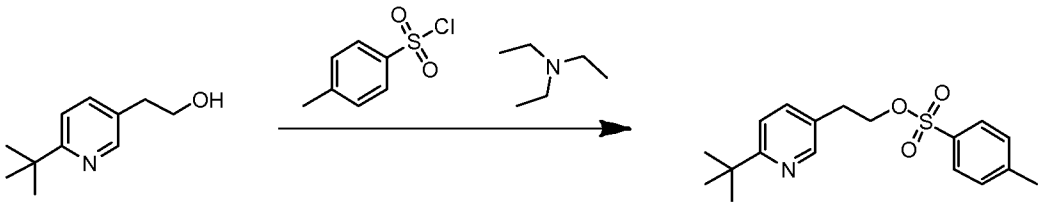
KSC-367-044

(1-(3-(4-(Tert-butyl)phenoxy)propyl)piperidin-4-yl)diphenylmethanol. To a vial was added the 3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propyl 4-methylbenzenesulfonate (KSC-367-036) (0.105 g, 0.219 mmol), 4-(tert-butyl)phenol (0.039 g, 0.263 mmol) and TEA (0.046 mL, 0.328 mmol) with acetonitrile (3 mL). The reaction stirred at 85 °C for 18 h then diluted with saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc layer was concentrated and purified by RP MPLC (10 - 100% MeCN:water) to produce pure (1-(3-(4-(tert-butyl)phenoxy)propyl)piperidin-4-yl)diphenylmethanol (0.015 g, 0.033 mmol, 15 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 4H), 7.31 – 7.26 (m, 6H), 7.19 – 7.14 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.01 – 2.94 (m, 2H), 2.51 – 2.40 (m, 3H), 1.99 – 1.89 (m, 5H), 1.52 – 1.45 (m, 4H), 1.28 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 145.9, 143.2, 128.1, 126.5, 126.1, 125.7, 116.3, 113.9, 79.5, 66.3, 60.4, 55.4, 54.1, 44.1, 34.0, 31.5, 29.7, 27.0, 26.4. LCMS Retention time: 4.293 min. LCMS purity 95.2%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO_2$ $[M+H]^+$ 458.6470, found 458.3068.



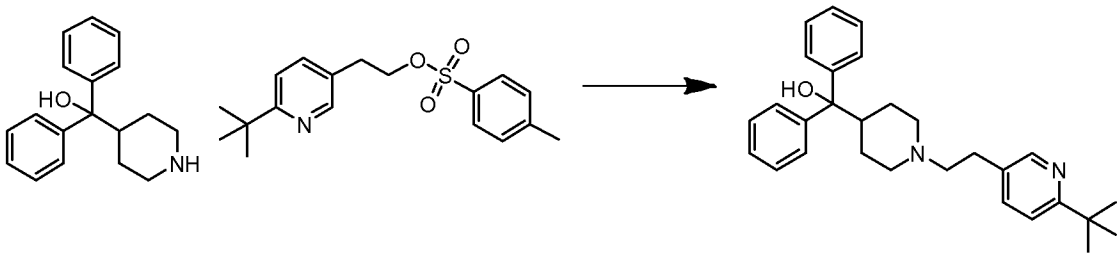
KSC-367-047

2-(6-(tert-butyl)pyridin-3-yl)ethanol. Prepared by same method as KSC-352-090 with 5-bromo-2-(tert-butyl)pyridine (0.303 g, 1.415 mmol), dry THF (10 mL), 2.5 M BuLi in hexanes (0.623 mL, 1.557 mmol) and ethylene oxide (1.415 ml, 3.54 mmol) (2.5 - 3.3M solution in THF) to produce pure 2-(6-(tert-butyl)pyridin-3-yl)ethanol (0.211 g, 1.177 mmol, 83% yield).). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (br d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.2 Hz, 2.4 Hz, 1H), 7.26 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 3.85 (br t, *J* = 6.0 Hz, 2H), 2.82 (t, *J* = 6.5 Hz, 2H), 2.29 (br s, 1H), 1.33 (s, 9H).



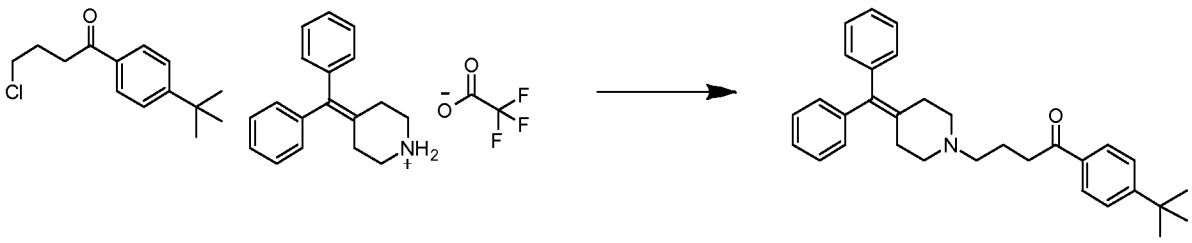
KSC-367-049

2-(6-(tert-butyl)pyridin-3-yl)ethyl 4-methylbenzenesulfonate. Prepared by same method at KSC-352-093 with 2-(6-(tert-butyl)pyridin-3-yl)ethanol (KSC-367-047) (0.211 g, 1.177 mmol), TEA (0.492 mL, 3.53 mmol) and DCM (2 mL) followed by p-toluenesulfonyl chloride (0.337 g, 1.766 mmol) to provide pure 2-(6-(tert-butyl)pyridin-3-yl)ethyl 4-methylbenzenesulfonate (0.260 g, 0.780 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (br d, J = 2.4 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.40 (dd, J = 8.2 Hz, 2.4 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.23 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 4.19 (t, J = 6.9 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 1.34 (s, 9H).



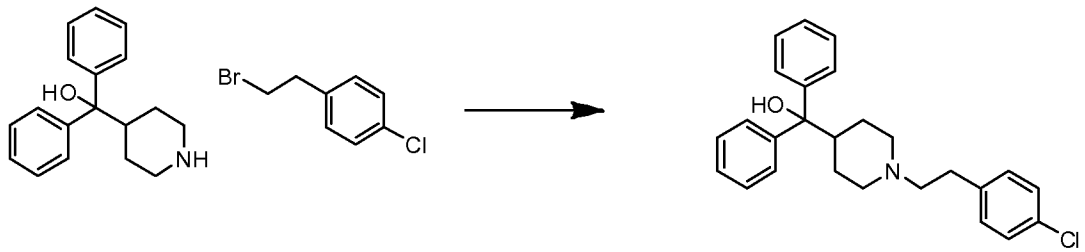
KSC-367-052

(1-(2-(6-(Tert-butyl)pyridin-3-yl)ethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.250 g, 0.936 mmol), 2-(6-(tert-butyl)pyridin-3-yl)ethyl 4-methylbenzenesulfonate (KSC-367-049) (0.260 g, 0.780 mmol) and acetonitrile (5 mL). The TEA (0.163 mL, 1.170 mmol) was then added and the reaction stirred at 50 °C for 20 h and was then cooled to rt and diluted with saturated $NaHCO_3$ then extracted with DCM. The DCM layer was concentrated and purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce pure (1-(2-(6-(tert-butyl)pyridin-3-yl)ethyl)piperidin-4-yl)diphenylmethanol (0.308 g, 0.719 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 – 8.38 (m, 1H), 7.51 – 7.48 (m, 4H), 7.42 (dd, J = 8.1 Hz, 2.4 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.25 – 7.22 (m, 1H), 7.20 – 7.15 (m, 2H), 3.07 – 3.01 (m, 2H), 2.76 – 2.71 (m, 2H), 2.57 – 2.52 (m, 2H), 2.50 – 2.42 (m, 1H), 2.31 (br s, 1H), 2.09 – 2.01 (m, 2H), 1.57 – 1.48 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 148.7, 145.9, 136.3, 132.3, 128.1, 126.5, 125.8, 118.6, 79.4, 60.2, 54.0, 44.1, 37.0, 30.3, 30.2, 26.4. LCMS Retention time: 3.802 min. LCMS purity 99.5%. HRMS (ESI): *m/z* calcd for $C_{29}H_{36}N_2O$ $[M+H]^+$ 429.2828, found 429.2900.



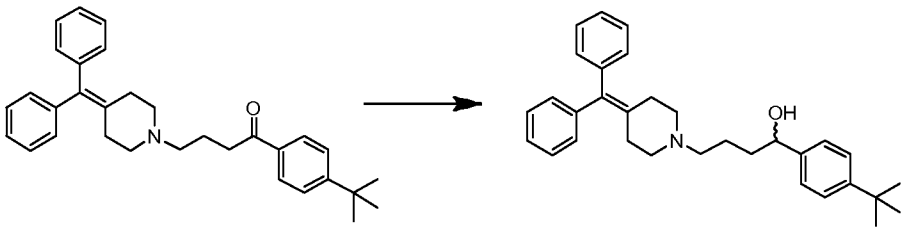
KSC-367-053

1-(4-(Tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-one. To a vial was added the 4-(diphenylmethylene)piperidin-1-ium 2,2,2-trifluoroacetate (KSC-367-027) (0.0475 g, 0.131 mmol), 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.037 g, 0.157 mmol) and TEA (0.046 mL, 0.327 mmol) in acetonitrile. The reaction stirred at 75 °C for 20 h. The reaction was removed from heat and diluted with saturated $NaHCO_3$, extracted with EtOAc. The EtOAc layer was concentrated and purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce pure 1-(4-(tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-one (0.019 g, 0.042 mmol, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.21 – 7.17 (m, 2H), 7.13 – 7.10 (m, 4H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.51 – 2.32 (m, 10H), 1.98 – 1.91 (m, 2H), 1.34 (s, 9H).



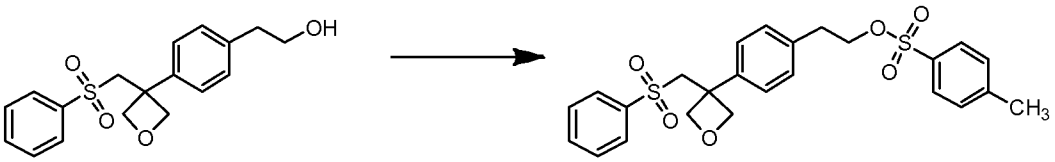
KSC-367-055

(1-(4-Chlorophenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(piperidin-4-yl)methanol (0.221 g, 0.827 mmol), 1-(2-bromoethyl)-4-chlorobenzene (0.165 g, 0.752 mmol), acetonitrile (4 mL) and TEA (0.157 mL, 1.128 mmol). The reaction stirred at 75 °C for 18 h then was cooled to rt and diluted with saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc layer was concentrated and purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce pure (1-(4-chlorophenethyl)piperidin-4-yl)diphenylmethanol (0.224 g, 0.552 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 4H), 7.20 – 7.15 (m, 4H), 7.12 – 7.09 (m, 2H), 7.08 – 7.03 (m, 2H), 6.99 – 6.96 (m, 2H), 2.92 – 2.87 (m, 2H), 2.64 – 2.58 (m, 2H), 2.43 – 2.38 (m, 2H), 2.37 – 2.30 (m, 1H), 2.22 (br s, 1H), 1.95 – 1.88 (m, 2H), 1.44 – 1.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 145.8, 138.9, 131.6, 129.9, 128.3, 128.0, 126.4, 125.7, 79.4, 79.3, 60.4, 57.0, 44.1, 33.0, 26.4. LCMS Retention time: 3.903 min. LCMS purity 99.6%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}ClNO$ $[M+H]^+$ 406.1859, found 406.1932.



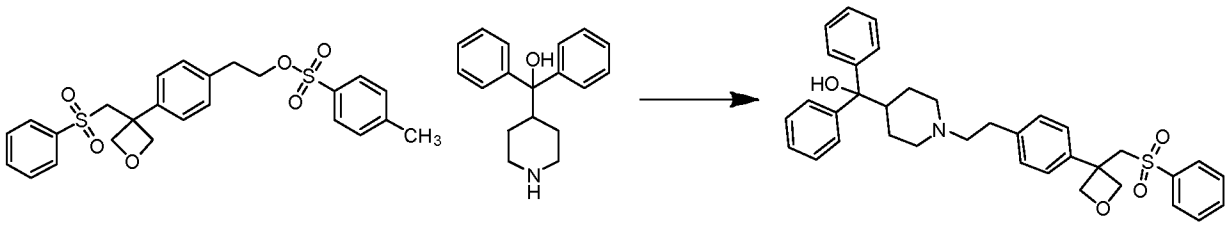
KSC-367-058

1-(4-(Tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-ol. Method B: 1-(4-(tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-one (KSC-367-053) (0.019 g, 0.042 mmol) and sodium borohydride (6.37 mg, 0.168 mmol) to produce pure 1-(4-(tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-ol (0.010 g, 0.022 mmol, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.26 (m, 8H), 7.23 – 7.18 (m, 2H), 7.13 – 7.10 (m, 4H), 4.68 – 4.65 (m, 1H), 2.66 – 2.60 (m, 2H), 2.55 – 2.42 (m, 8H), 2.00 – 1.94 (m, 1H), 1.90 – 1.81 (m, 1H), 1.73 – 1.63 (m, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 142.7, 142.3, 136.4, 134.6, 129.7, 128.0, 126.4, 125.3, 125.0, 73.3, 58.7, 55.0, 39.6, 34.4, 31.6, 31.4, 31.1, 24.0, 22.6. LCMS Retention time: 4.454 min. LCMS purity 97.1%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO$ $[M+H]^+$ 454.3032, found 454.3104.



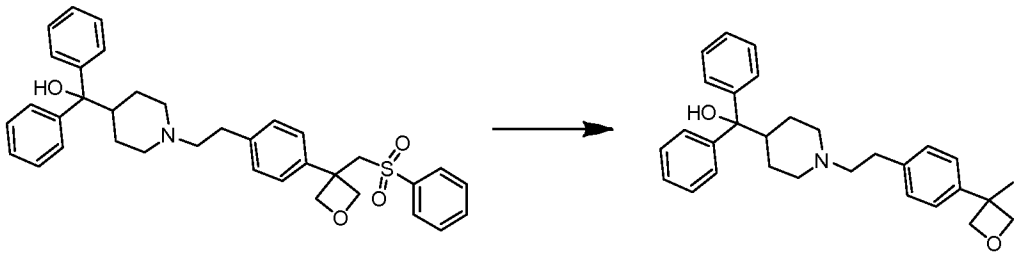
KSC-367-066

4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenethyl 4-methylbenzenesulfonate. Prepared by the same method as KSC-352-093 with 2-(4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenyl)ethanol (KSC-367-003) (0.104 g, 0.313 mmol), TEA (0.131 mL, 0.939 mmol) and DCM (2 mL) followed by p-toluenesulfonyl chloride (0.089 g, 0.469 mmol) to produce 4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenethyl 4-methylbenzenesulfonate (0.041 g, 0.084 mmol, 27% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.3 Hz, 2H), 7.57 – 7.46 (m, 4H), 7.36 – 7.32 (m, 4H), 7.02 – 6.96 (m, 3H), 5.00 (d, J = 6.4 Hz, 2H), 4.93 (d, J = 6.4 Hz, 2H), 4.17 (t, J = 7.0 Hz, 2H), 4.01 (s, 2H), 2.90 (t, J = 7.0 Hz, 2H), 2.45 (s, 3H).



KSC-367-069

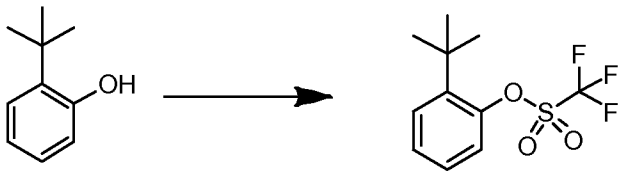
Diphenyl(1-(4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenethyl)piperidin-4-yl)methanol. To a vial was added the 4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenethyl 4-methylbenzenesulfonate (KSC-367-066) (0.041 g, 0.084 mmol) and diphenyl(piperidin-4-yl)methanol (0.025 g, 0.093 mmol) in acetonitrile. The TEA (0.018 ml, 0.126 mmol) was then added and the reaction stirred at 50 °C for 18 h. The reaction was removed from heat and cooled to rt then diluted with saturated $NaHCO_3$. The reaction was then extracted with EtOAc (3 x 5 mL) and the EtOAc layer was dried with $MgSO_4$, filtered and concentrated. The crude residue was purified by reverse-phase MPLC (15 min, 10 - 100% MeCN:water) to produce diphenyl(1-(4-(3 ((phenylsulfonyl) methyl)oxetan-3-yl)phenethyl)piperidin-4-yl)methanol (0.024 g, 0.041 mmol, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.43 (m, 6H), 7.33 – 7.27 (m, 7H), 7.21 – 7.16 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 5.02 (d, J = 6.4 Hz, 2H), 4.92 (d, J = 6.4 Hz, 2H), 4.01 (s, 2H), 3.08 – 3.02 (m, 2H), 2.74 – 2.69 (m, 2H), 2.56 – 2.44 (m, 3H), 2.10 – 2.02 (m, 2H), 1.60 – 1.50 (m, 5H).



KSC-367-072

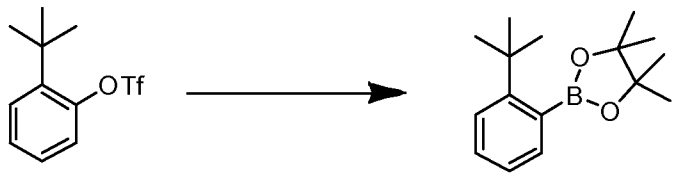
(1-(4-(3-Methyloxetan-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the diphenyl(1-(4-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenethyl)piperidin-4-yl)methanol (KSC-367-069) (0.024 g, 0.041 mmol) and MeOH (10 mL) and the reaction as heated to 50 °C. The magnesium was added in 3 additions (0.016 g, 0.066 mmol, 16 equiv) 1.5 h apart. The reaction was removed from heat 1.5 h after the final magnesium addition, cooled to rt and poured into 1.0 M HCl with ice. The aqueous layer was then extracted with DCM (3 x 10 mL) and the organic layers were combined and dried with $MgSO_4$, filtered and concentrated then purifed by reverse-phase MPLC (15 min, 10 - 100% MeCN:water). To produce (1-(4-(3-methyloxetan-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol (0.0045 g, 10.19 µmol, 24.70 % yield) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.47 (m, 4H), 7.32 - 7.27 (m, 4H), 7.21 - 7.16 (m, 4H), 7.13 - 7.10 (m, 2H), 4.95 (d, J = 5.5 Hz, 2H), 4.61 (d, J = 5.5 Hz, 2H), 3.09 - 3.02 (m, 2H), 2.81 - 2.75 (m, 2H), 2.59 - 2.54 (m, 2H), 2.50 - 2.42 (m, 1H), 2.16 (br s, 1H), 2.09 - 2.00 (m, 2H), 1.71 (s, 3H), 1.56 - 1.48 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.1, 138.4, 128.8, 128.2, 126.5, 125.8, 125.1, 83.8, 79.5, 60.7, 54.1, 44.1, 43.1, 33.3, 27.8, 26.4. LCMS Retention time: 3.652 min. LCMS purity 97.9%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_2$ $[M+H]^+$ 442.2668, found 442.2741.



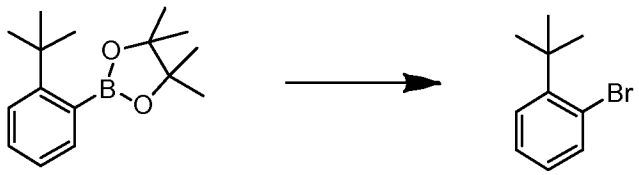
KSC-367-088

2-(Tert-butyl)phenyl trifluoromethanesulfonate. To a vial was added the 2-(tert-butyl)phenol (1.0 ml, 6.51 mmol) and DCM (4 mL) followed by pyridine (1.053 mL, 13.02 mmol). The reaction was then cooled to 0 °C and the triflic anhydride (1.320 mL, 7.81 mmol) was added dropwise and the reaction stirred for 2 h. The reaction was then allowed to warm to rt and was diluted with DCM and quenched with 1.0 M HCl. The DCM layer was collected and washed with saturated $NaHCO_3$ and brine. The organic layer was then dried ($MgSO_4$), filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hex) to produce pure 2-(tert-butyl)phenyl trifluoromethanesulfonate (1.66 g, 5.88 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.31 – 7.27 (m, 2H), 1.43 (s, 9H).



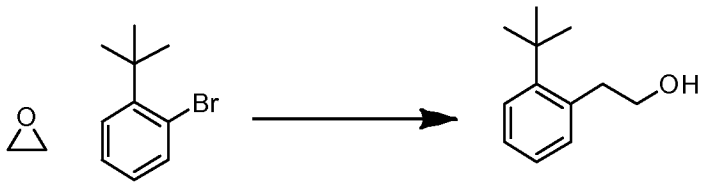
KSC-381-009

2-(2-(Tert-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To a flame-dried vial was added molecular sieves and 2-(tert-butyl)phenyl trifluoromethanesulfonate (KSC-367-088) (0.475 g, 1.683 mmol) and 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.042 g, 0.050 mmol). The vial was evacuated with argon 3 times and then dioxane (1 mL), TEA (0.704 mL, 5.05 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.732 mL, 5.05 mmol) were added via syringe. The reaction stirred at reflux (100 °C) for 2 h. The reaction was then removed from heat and diluted with water then extracted with DCM (3 x 5 mL). The DCM layer was then washed again with water (3 x 10 mL). The DCM layer was dried with $MgSO_4$, filtered and concentrated. The residue was diluted with hexanes and filtered through $MgSO_4$ to remove the residual Pd complex. The hexanes layer was then concentrated to produce pure 2-(2-(tert-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.093 g, 0.357 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.29 (td, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.14 (td, *J* = 7.6 Hz, 2.0 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 12H).



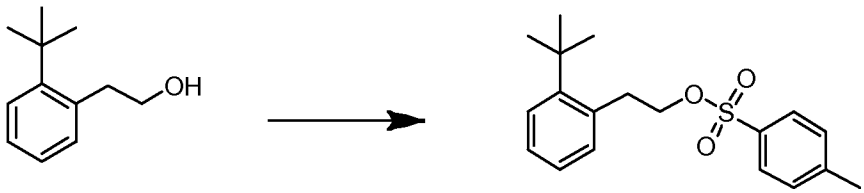
KSC-381-011

1-Bromo-2-(tert-butyl)benzene. To a vial was added the 2-(2-(tert-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (KSC-381-009) (0.180 g, 0.692 mmol) and MeOH (1.5 mL). The copper (II) bromide (0.464 g, 2.075 mmol) was then dissolved in water and added to the reaction then stirred at 80 °C for 24 h. The reaction was then removed from heat and diluted with water and extracted with EtOAc. The EtOAc was dried with $MgSO_4$, filtered and concentrated to produce 1-bromo-2-(tert-butyl)benzene (0.103 g, 0.483 mmol, 70% yield) as a brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.44 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.24 (td, J = 7.6 Hz, 2.0 Hz, 1H), 7.02 (td, J = 7.6 Hz, 2.0 Hz, 1H), 1.51 (s, 9H).



KSC-381-015

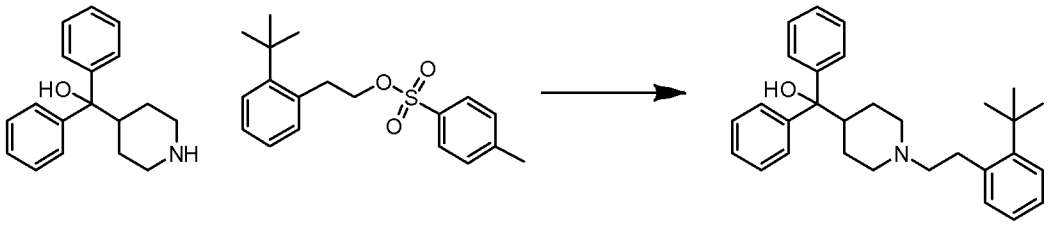
2-(2-(Tert-butyl)phenyl)ethanol. Prepared by same method as KSC-352-090 with 1-bromo-2-(tert-butyl)benzene (KSC-381-011) (0.147 g, 0.690 mmol), dry THF, 2.5 M BuLi in hexanes (0.303 ml, 0.759 mmol) and then ethylene oxide (0.690 ml, 1.724 mmol) (2.5 - 3.3M solution in THF) to produce pure 2-(2-(tert-butyl)phenyl)ethanol (0.018 g, 0.101 mmol, 14.64 % yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 - 7.37 (m, 1H), 7.23 - 7.19 (m, 1H), 7.18 - 7.14 (m, 2H), 3.90 (t, J = 7.6 Hz, 2H), 3.19 (t, J = 7.6 Hz, 2H), 1.44 (s, 9H).



KSC-381-018

2-(Tert-butyl)phenethyl 4-methylbenzenesulfonate. Prepared according to same procedure as KSC-352-093 with 2-(2-(tert-butyl)phenyl)ethanol (KSC-381-015) (0.018 g, 0.101 mmol), TEA (0.042 mL, 0.303 mmol) and DCM (2 mL) followed by p-toluenesulfonyl chloride (0.029 g, 0.151 mmol) to provide pure 2-(tert-butyl)phenethyl 4-

methylbenzenesulfonate (0.022 g, 0.066 mmol, 66% yield) and a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.37 - 7.31 (m, 3H), 7.17 - 7.04 (m, 3H), 4.19 (t, *J* = 7.6 Hz, 2H), 3.25 (t, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.33 (s, 9H).



KSC-381-020

(1-(2-(Tert-butyl)phenethyl)piperidin-4-yl)diphenylmethanol. To a vial was added the 2-(tert-butyl)phenethyl 4-methylbenzenesulfonate (KSC-381-018) (0.022 g, 0.066 mmol), diphenyl(piperidin-4-yl)methanol (0.018 g, 0.066 mmol) and acetonitrile. The TEA (0.014 mL, 0.099 mmol) was added and the reaction stirred at 85 °C for 20 h. The reaction was cooled to rt and diluted with water then extracted with EtOAc. The EtOAc layer was concentrated and the crude product was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce the pure (1-(2-(tert-butyl)phenethyl) piperidin-4-yl)diphenylmethanol (0.013 g, 0.030 mmol, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.48 (m, 4H), 7.37 – 7.28 (m, 5H), 7.21 – 7.09 (m, 5H), 3.15 – 3.04 (m, 4H), 2.65 – 2.60 (m, 2H), 2.52 – 2.42 (m, 1H), 2.17 – 2.08 (m, 3H), 1.60 – 1.53 (m, 4H), 1.41 (s. 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7, 145.9, 138.5, 132.1, 128.2, 126.5, 126.1, 125.9, 125.84, 125.79, 79.5, 61.7, 54.2, 44.2, 35.7, 31.7, 29.7, 26.4. LCMS Retention time: 4.200 min. LCMS purity 99.3%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2875, found 428.2948.

Bacterial Strains and Conditions

All strains used to evaluate the antimicrobial activity of terfenadine and corresponding structural derivatives are shown below in Table 5. *S. aureus* strain UAMS-1 is an osteomyelitis clinical isolate (Gillaspy et al. "Role of the accessory gene regulator (agr) in pathogenesis of staphylococcal osteomyelitis. *Infect. Immun.* 63:3373–3380 (1995)), whereas ciprofloxacin-resistant strains CRC118 and CRC61 are spontaneous ciprofloxacin-resistant derivatives of UAMS-1 that were selected by growth on Mueller-Hinton agar (MHA) (Becton, Dickinson & Company, Franklin Lakes, NJ) at 1.5X MIC ciprofloxacin (0.75 μg/ml).

Table 5. Bacterial Strains Used in Terfenadine Study

Species	Strain	Source
S. aureus	UAMS-1	1
	CRC61	Dunman Lab, URMC
	CRC118	Dunman Lab, URMC

Minimum Inhibitory Concentration (MIC) Testing

Minimum Inhibitory Concentration (MIC) testing was performed to determine the minimum concentration of test compound that is necessary to inhibit visible growth of bacteria according to Clinical and Laboratory Standards (CLSI) guidelines (Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Ninth Edition. CLSI document M07-A9. 2012. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.) To do so, 10^5 colony forming units of an overnight bacterial culture were seeded into individual wells of 96-well round-bottom microtiter plates containing 88 μl of MHB medium. To the first column, 2 μl of the test compound's corresponding solvent was also added to each well (negative control). To the next ten columms, 2 μl of the test compound (dissolved in DMSO for terfenadine and its derivatives or sterile water for ciprofloxacin) was added in increasing 2-fold increments of 0.5 μg/ml to 256 μg/ml to each successive well. Each test compound was evaluated in duplicate. Plates were incubated at 37°C incubator for 16 h at which point the minimum inhibitory concentration was determined to be the lowest concentration of test compound that inhibited bacterial growth, as judged by the unaided eye.

***S. aureus* DNA Gyrase Supercoiling Assay (TopoGEN)**

The gyrase supercoiling assays were performed to determine if test compounds interfered with *S. aureus* DNA gyrase activity, following the manufacturer's

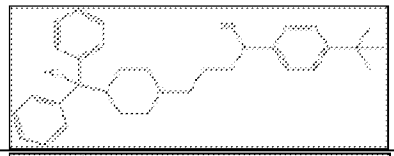
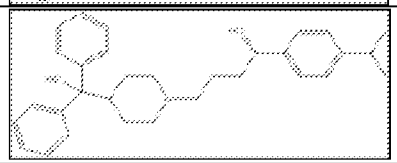
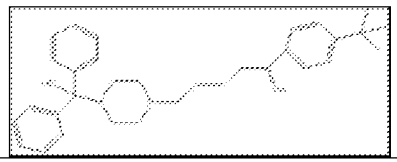
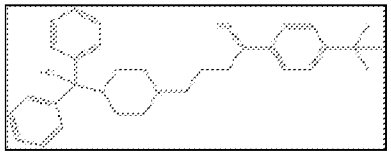
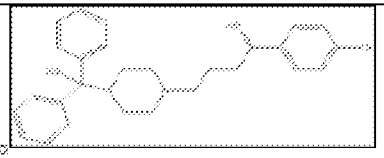
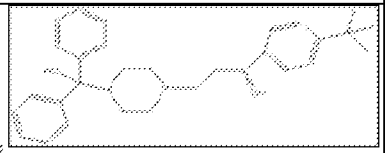
recommendations (TopoGEN). Reactions (20 µl) contained kit provided assay buffer, ATP, potassium glutamate, relaxed plasmid DNA (0.4 µg/ml), 2 Units of *S. aureus* DNA gyrase, and various amounts of test compound. Reactions were incubated at 37°C for 30 min and then stopped by the addition of 10% SDS, filtered through 0.025 µm Millipore membrane filters in a 10 mM Tris-HCl buffer (pH 8), and electrophoresed in a 1% agarose TAE gel. Gels were stained with 0.5 µg/ml ethidium bromide and images were analyzed using densitometry (Image J, NIH). The IC_{50} values for each test compound was determined to be the compound concentration that inhibited S. aureus DNA gyrase activity by 50%.

***S. aureus* Topoisomerase IV Decatenation Assay (Inspiralis)**

A Topoisomerase IV assay was performed on test compounds to determine if they interfered with the ability of *S. aureus* topoisomerase IV to decatenate kDNA, according to the recommendations of the manufacturer (Inspiralis). To do so, 0.25 U S. aureus topoisomerase IV enzyme was mixed with 200 ng kDNA in kit provided reaction buffer, in the absence or presence of various concentrations of test compounds at 37°C for 30 min. The reaction was stopped by the addition of STEB stop buffer and 30 µl of 24:1 chlorform:isoamyl alcohol (total volume 90 µl). Reaction products then electrophoresed in a 1% agarose TAE gel, stained with 0.5 µg/ml ethidium bromide and images were analyzed using densitometry (Image J, NIH). The IC_{50} value for each test compound was determined as the compound concentration that inhibited *S. aureus* topoisomerase IV activity by 50%.

The results are set forth in Table 6.

Table 6

Compound #¤	KUC Registry Number¤	Molecular Weight (g/mol)¤	Structure¤	MIC (μg/mL)¤	Gyrase IC50 (μM)¤	Topoisomerase iv IC50 (μM)¤
Terfenzine¤	N/A¤	471.673¤		16¤	190.00¤	206.67¤
1¤	KSC-335-012¤	457.647¤		16¤	126.67¤	273.33¤
2¤	KSC-335-013¤	485.7¤		16¤	100.00¤	133.33¤
3¤	KSC-335-014¤	471.673¤		8¤	330.00¤	103.33¤
4¤	KSC-335-015¤	450.012¤		64¤	133.33¤	>333¤
5¤	KSC-335-016¤	457.647¤		8¤	133.33¤	333.00¤

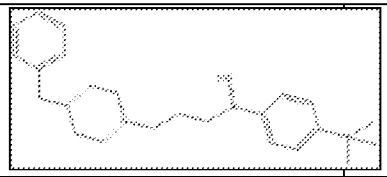
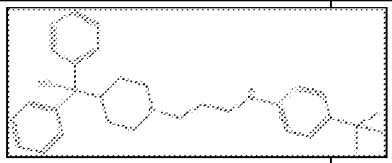
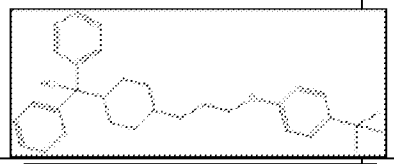
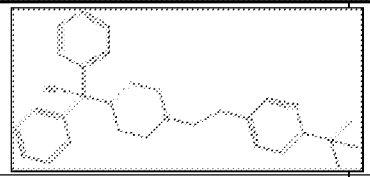
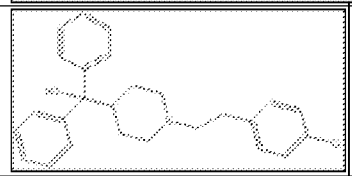
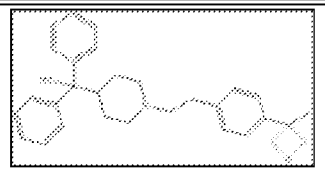
6	KSC-335-021	415.567		256	>500	>333	
7	KSC-335-030	445.593		256	>500	>333	
8	KSC-335-031	433.558		128	>500	>333	
9	KSC-335-032	494.465		32	>500	>333	
10	KSC-335-041	455.674		8	93.33	320.00	
11	KSC-335-007	469.658		8	93.33	110.00	
12	KSC-335-069	471.673		16	126.67	100.00	

13	KSC-335-070	471.673		16	410.00	110.00
14	KSC-335-077	429.594		128	>500	>333
15	KSC-335-080	515.683		128	>500	>333
16	KSC-335-081	501.656		>256	>500	>333
17	KSC-342-010	443.62		16	73.33	100.00
18	KSC-342-017	473.603		256	440.00	>333

19	KSC-342-021	459.577		>256	>300	>333
20	KSC-342-006	441.604		>256	73.33	246.67
21	KSC-333-008	455.631		32	90.00	133.33
22	KSC-342-080	441.647		8	93.33	100.00
23	KSC-342-081	427.621		8	93.33	146.67
24	KSC-342-088	470.689		16	>500	>333
25	KSC-348-002	421.663		8	13.33	100.00

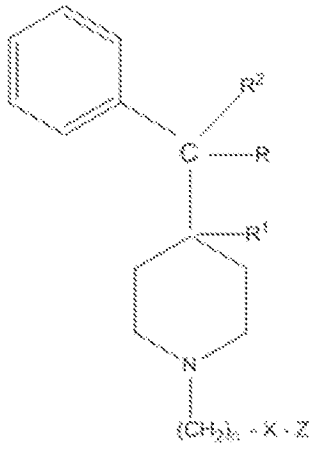
26	KSC-348-050	413.594		8	90.000	213.33
27	KSC-348-049	427.578		>256	93.33	>333
28	KSC-348-058	401.541		256	>333	>333
29	KSC-352-060	416.512		64	263.33	>333
30	KSC-352-061	430.411		16	246.67	260.00
31	KSC-352-066	395.577		128	>333	>333
32	KSC-352-063	447.611		8	80.00	133.33

33	KSC-352-064	448.589		32	93.33	226.67
34	KSC-352-069	386.529		256	93.33	>333
35	KSC-352-065	448.599		32	250.00	280.00
36	KSC-352-075	414.582		256	>333	>333
37	KSC-352-082	439.513		16	16.67	>333
38	KSC-352-088	389.505		128	>333	>333
39	KSC-352-097	427.621		16	93.33	>333

40	KSC-367-039	379.578		64	>333	>333
41	KSC-367-043	456.662		8	193.33	250.00
42	KSC-367-044	457.647		8	100.00	>333
43	KSC-367-052	428.609		64	>333	>333
44	KSC-367-055	405.96		32	260.00	266.67
45	KSC-367-072	441.604		>256	>333	>333

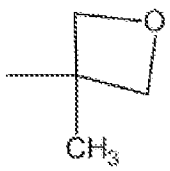
What is claimed is:

1. A method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a a compound of Formula I



(I)

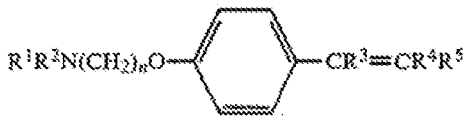
wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $–COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl

or a pharmaceutically acceptable salt thereof.

2. A method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound of Formula III

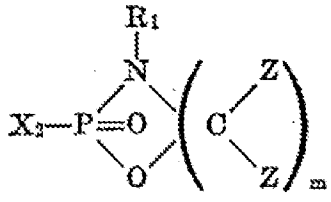


(III)

or a pharmaceutically acceptable salt thereof, wherein R^I and R^2 are independently selected from ethyl or methyl, n 1 or 2, R^3 and R^4 are both phenyl or substituted phenyl, wherein the substituent can be halo (for example, fluoro-, chloro-, iodo- or bromo-), hydroxyl, a lower alkyl or a substituted lower alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy, and R^5 is hydrogen, a halogen, a lower alkyl from about 1 to 4 carbon atoms or a substituted alkyl wherein the substituent can be halo, hydroxy, or lower alkoxy.

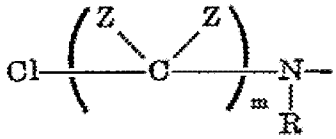
3. A method of treating or preventing infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of:

a compound of Formula V



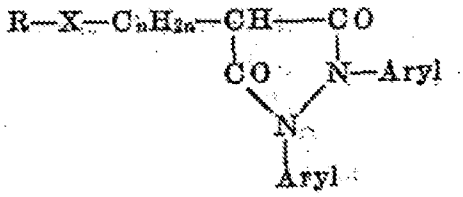
(V)

wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms being substituted with one or several halogen atoms, Z is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms, *m* is 2 or 3 and X_2 is the ethylene imino group or the group having the formula:



wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms which may be substituted with a chlorine atom or a hydroxy group, and Z and *m* have the above-given meaning,

a compound of Formula X



(X)

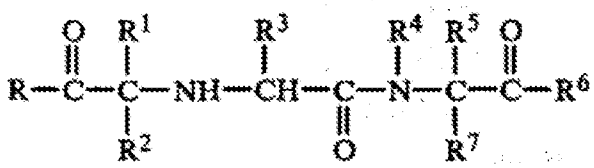
wherein R represents a lower alkyl or a lower alkenyl group, a phenyl group which can be substituted by halogen, methyl or lower alkoxy groups, or a benzyl group which can be nuclear substituted by halogen, methyl or lower alkoxy groups,

X represents –O-, -S-, -SO-, or $–SO_2$-,

n represents an integer from 1-4, and

Aryl represents a phenyl group which can be substituted by lower alkoxy or lower alkylmercapto groups;

a compound of Formula XII



(XII)

wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy (dimethylaminoethoxy), acylamino lower alkoxy (acetylaminoethoxy), acyloxy lower alkoxy (pivaloyloxymethoxy), aryloxy, such as phenoxy, arloweralkoxy, such as benzyloxy, substituted aryloxy or substituted

arloweralkoxy wherein the substitutent is methyl, halo or methoxy, amino, loweralkylamino, diloweralkylamino, hydroxyamino, arloweralkylamino such as benzylamino;

R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms which include branched and cyclic and unsaturated (such as allyl) alkyl groups, substituted loweralkyl wherein the substituent can be halo, hydroxy, lower alkoxy, aryloxy such as phenoxy, amino, diloweralkylamino, acylamino, such as acetamido and benzamido, arylamino, guanidino, imidazolyl, indolyl, mercapto, loweralkylthio, arylthio such as phenylthio, carboxy or carboxamido, carboloweralkoxy, aryl such as phenyl or naphthyl, substituted aryl such as phenyl wherein the substituent is lower alkyl, lower alkoxy or halo, arloweralkyl, arloweralkenyl, heteroarlower alkyl or heteroarlower alkenyl such as benzyl, styryl or indolyl ethyl, substituted arloweralkyl, substituted arloweralkenyl, substituted heteroarlower alkyl, or substituted heteroarlower alkenyl, wherein the substituent(s) is halo, dihalo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, acylamino (acetyl amino or benzoylamino) diloweralkylamino, loweralkylamino, carboxyl, halologweralkyl, cyano or sulfonamido; arloweralkyl or heteroarloweralkyl substituted on the alkyl portion by amino or acylamino (acetylamino or benzoylamino);

R^2 and R^7 are the same or different and are hydrogen or lower alkyl;

R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethyl phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl (such as benzoylamino lower alkyl, acetylamino lower alkyl), amino lower alkyl, dimethylamino lower alkyl, halo lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyllower alkyl, mercapto lower alkyl, lower alkyl thio lower alkyl;

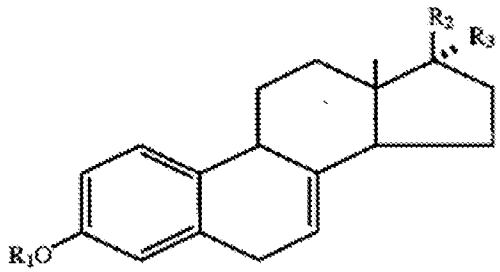
R^4 is hydrogen or lower alkyl;

R^5 is hydrogen, lower alkyl, phenyl, phenyl lower alkyl, hydroxy phenyl lower alkyl, hydroxy lower alkyl, amino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, mercapto lower alkyl or lower alkyl thio lower alkyl;

R^4 and R^5 may be connected together to form an alkylene bridge of from 2 to 4 carbon atoms, an alkylene bridge of from 2 to 3 carbon atoms and one sulfur atom, an

alkylene bridge of from 3 to 4 carbon atoms containing a double bond or an alkylene bridge as above substituted with hydroxy, loweralkoxy, loweralkylor diloweralky;

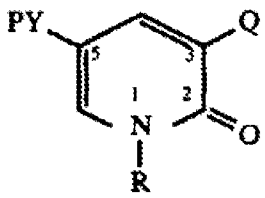
a compound of Formula XIII



(XIII)

wherein R_1 is H, alkyl, acyl or silyl(alkyl)$_3$; R_2 is H and R_3 is OH, O-acyl, O-alkyl or O-silyl (alkyl)$_3$ or R_3 is H and R_2 is OH. O-acyl, O-alkyl or O-silyl (alkyl)$_3$; or R_2 and R_3 together represent O; or R_2 and R_3 together represent acetal or cyclic acetal. R_1 might also represent a substituted alkyl such as e.g. methoxy ethoxy methyl;

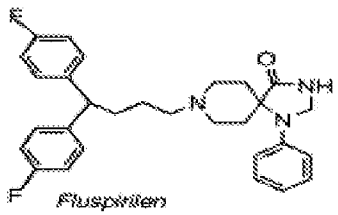
a compound of Formula XIV



(XIV)

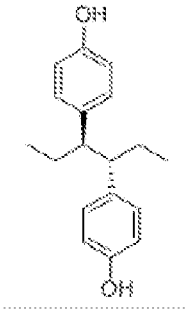
wherein PY is 4- or 3- or 2-pyridinyl or 4- or 3-or 2-pyridinyl having one or two lower-alkyl substituents, R is hydrogen, lower-alkyl or lower-hydroxyalkyl, and Q is nitro, carbamyl, halo, amino, lower-alkylamino, di(lower-alkyl)amino, or NHAc where Ac is lower-alkanoyl or lower-carbalkoxy;

a compound of Formula XV



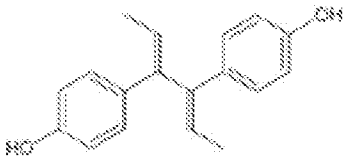
(XV)

a compound of Formula XVI



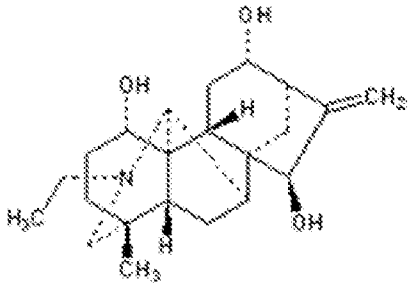
(XVI)

a compound of Formula XVII



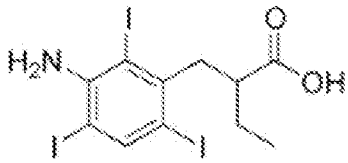
(XVII)

a compound of Formula XVIII



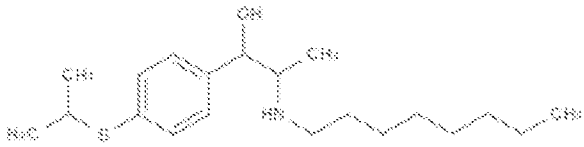
(XVIII)

a compound of Formula XIX



(XIX)

a compound of Formula (XX)

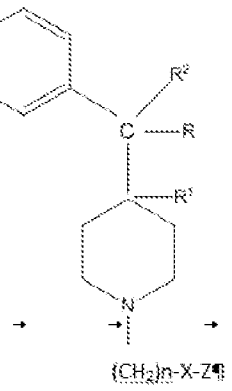


(XX)

or a pharmaceutically acceptable salt thereof.

4. The method of claim 3, wherein the compound is selected from the group consisting of ifosfamide, sulfinpyrazone, lisinopril, equilin, fluspirilen, hexestrol, dienestrol, napelline, amrinone and iopanoic acid.
5. The method of any of claims 1-4, wherein the infection is a bacterial infection, a viral infection, a parasitic infection or a fungal infection.
6. The method of any one of claims 1-5, wherein the infection is a respiratory infection.
7. The method of any one of claims 1-5, wherein the infection is a gastrointestinal infection.
8. The method of any one of claims 1-5, wherein the infection is a skin infection.
9. The method of claim 5 wherein the bacterial infection is selected from the group consisting of *Enterobacterium faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinebacter baumannii, Pseudomonas aeruginosa and Enterobacter sp.*

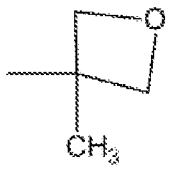
10. The method of claim 5, wherein the bacterial infection is a small colony variant bacterial infection.
11. A method of treating or preventing an infection in a subject with or at risk of developing an infection, the method comprising administering to the subject a compound selected from the group consisting of: Didanosine, Norcyclobenzaprine, Niridazole, Ifosfamide, Cefalonium, Tamoxifen citrate, Butoconazole, Suloctidil, Clomiphene, Sulconazole, Miconazole, Mefloquine, Sulfinpyrazone, Terfenadine, Lisinopril, Econzaole, Clofazimine, Equilin, Felodipine, Dacarbazine, Furazolidone, Perhexiline maleate, Oxethazaine, Pimozide, Trifluoperazine, Ellipticine, Fluspirilen, Hexestrol, Dienestrol, Zidovudine, Metoprolol, Napelline, Methimazole, Amrinone, Iopanoic acid, R-Propanolol, Rimexolone and Pyrvinium pamoate, wherein the infection is a bacterial infection.
12. The method of claim 11, wherein the bacterial infection is selected from the group consisting of *Enterobacterium faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinebacter baumannii, Pseudomonas aeruginosa and Enterobacter sp.*
13. A method of removing or preventing biofilm formation on a surface, the method comprising administering to a biofilm containing surface or a surface susceptible to biofilm formation an effective amount of a compound of Formula I



(I)

wherein R represents hydrogen or hydroxyl and R^1 represents hydrogen, or R and R^1 taken together form a second bond between the carbon atoms bearing R and R^1; R^2 represents hydrogen or phenyl; *n* is zero or a positive whole integer of from 1 to 4; X represents CH_2, CHOH, NH, C=O, $CHNR^3R^4$, where R^3 and R^4 independently are hydrogen or lower alkyl; and Z represents thienyl, pyridinyl, substituted pyridinyl, phenyl or substituted phenyl wherein the substituents on the substituted pyridinyl or

substituted phenyl are selected from phenyl, pyridinyl, nitro, a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, amino, a mono or di(lower)alkylamino group, a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower)alkylpiperazino, or a group having the structure $-COOR^5$, $-CR^6R^7COOR^5$, $-CF_3$, CHF_2, CH_2F, or



where R^5 is hydrogen or lower alkyl, and R^6 and R^7 independently are hydrogen or methyl

or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the biofilm comprises one or more of *Staphylococcus aureus*, *Pseudomonas aeuroginosa*, *Staphylococcus epidermidis*, *Escherichia coli* or *Acinetobacter baummanii.*
15. A method of identifying an antimicrobial agent comprising:
    a) contacting a bacterial culture with a test agent;
    b) and measuring adenylate kinase release in the supernatant of the bacterial culture, wherein an increase in adenylate kinase release as compared to a control indicates that the test compound is an antimicrobial agent.
16. The method of claim 15, wherein the bacterial culture is selected from the group consisting of *Staphylococcus aureus*, *Pseudomonas aeuroginosa*, *Staphylococcus epidermidis*, *Escherichia coli* or *Acinetobacter baummanii.*

FIGURE 1

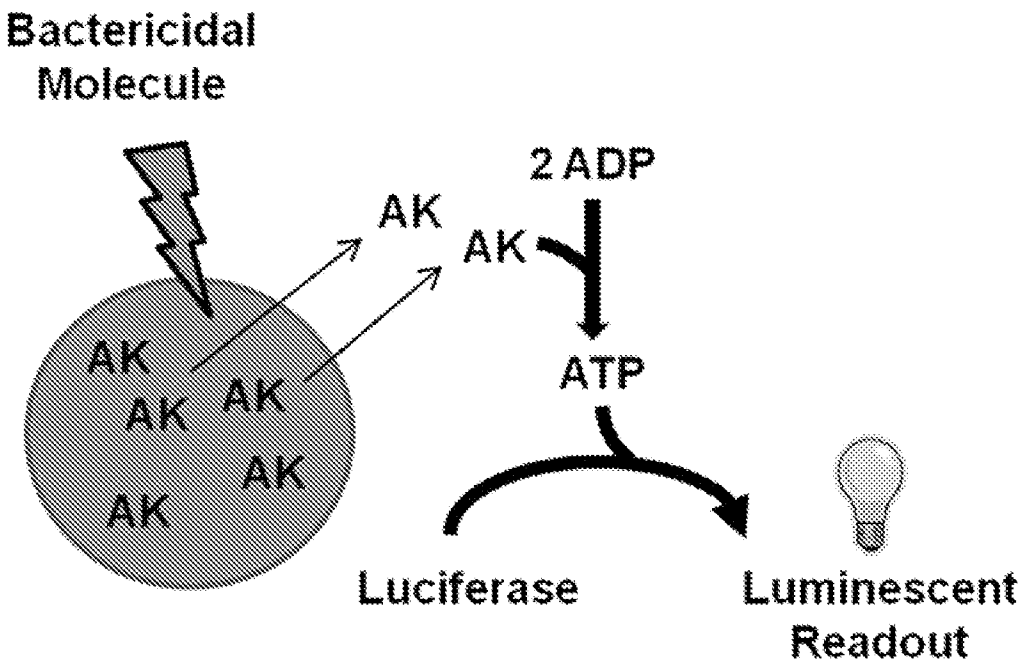

Bactericidal Molecule
AK
AK
AK
AK
AK
AK
2 ADP
AK
ATP
Luciferase
Luminescent Readout

FIGURE 2

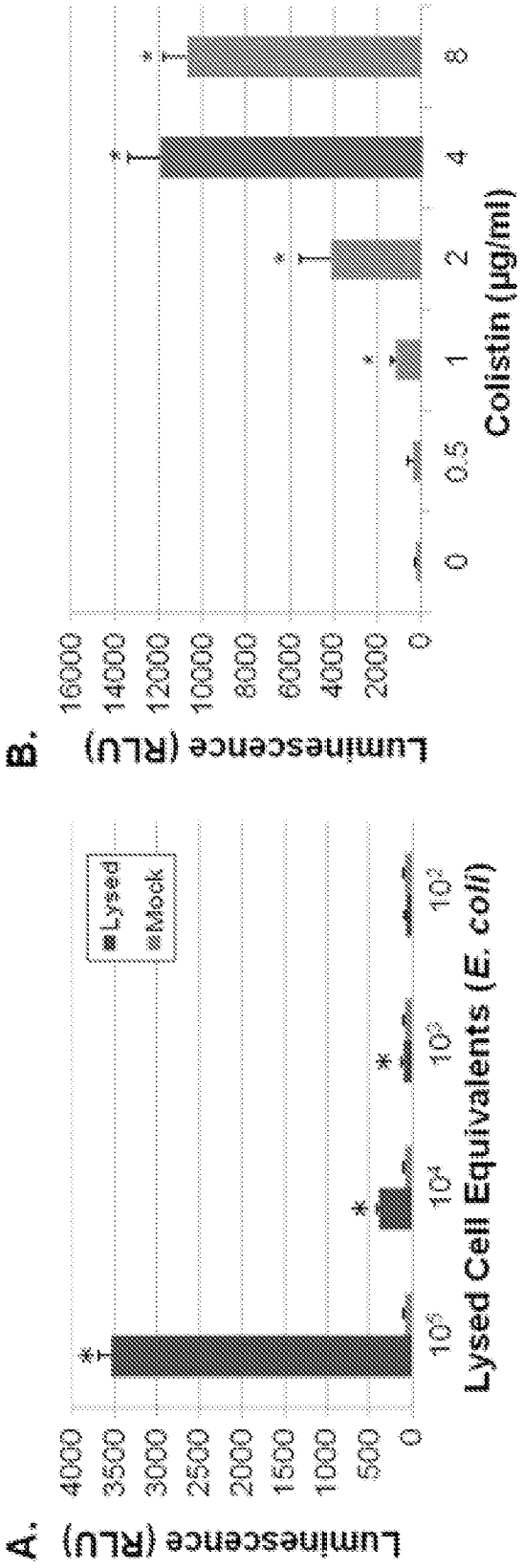

A.
Luminescence (RLU)
4000
3500
3000
2500
2000
1500
1000
500
0
Lysed
Mock
*
*
*
10^5
10^4
10^3
10^2
Lysed Cell Equivalents (E. coli)
B.
Luminescence (RLU)
16000
14000
12000
10000
8000
6000
4000
2000
0
*
*
*
*
0
0.5
1
2
4
8
Colistin (µg/ml)

FIGURE 3

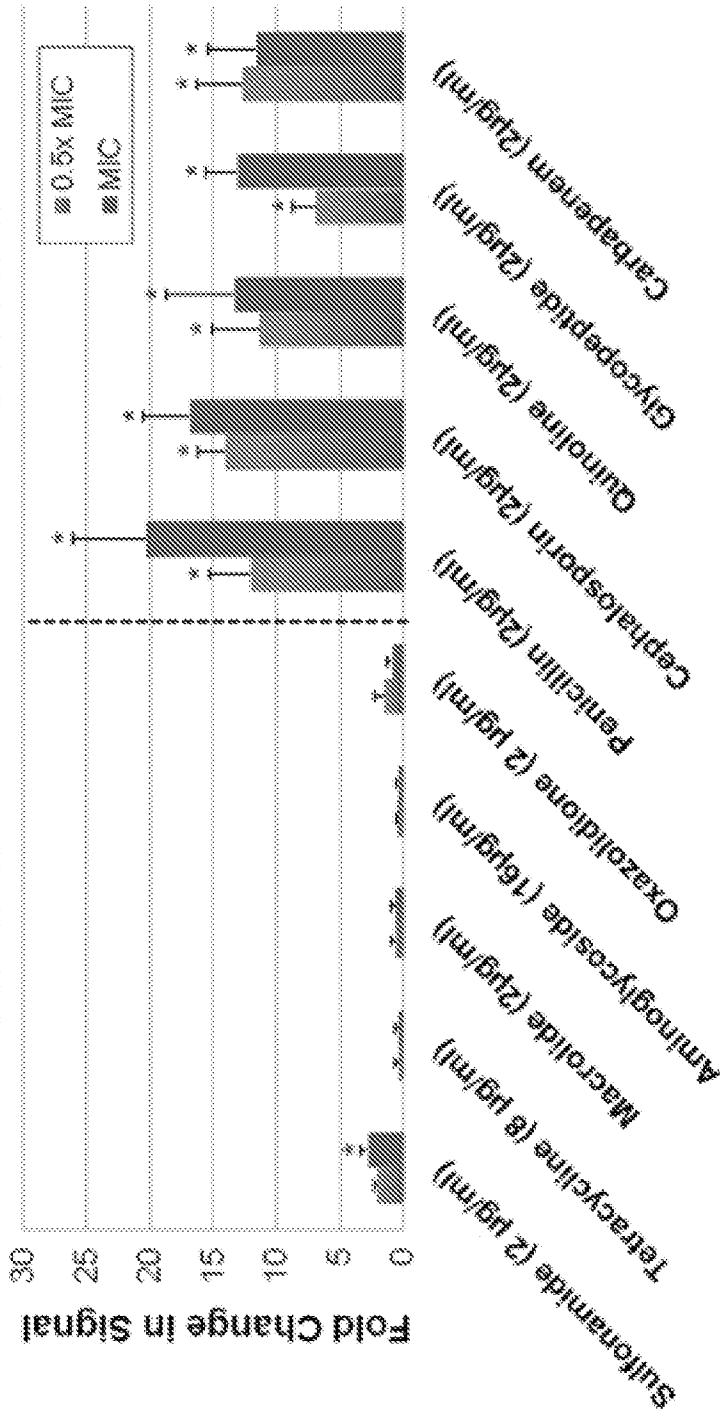

Bacteriostatic
Bactericidal
0.5x MIC
MIC
Fold Change in Signal
0
5
10
15
20
25
30
Sulfonamide (2 μg/ml)
Tetracycline (8 μg/ml)
Macrolide (2μg/ml)
Aminoglycoside (16μg/ml)
Oxazolidione (2 μg/ml)
Penicillin (2μg/ml)
Cephalosporin (2μg/ml)
Quinolone (2μg/ml)
Glycopeptide (2μg/ml)
Carbapenem (2μg/ml)

FIGURE 4

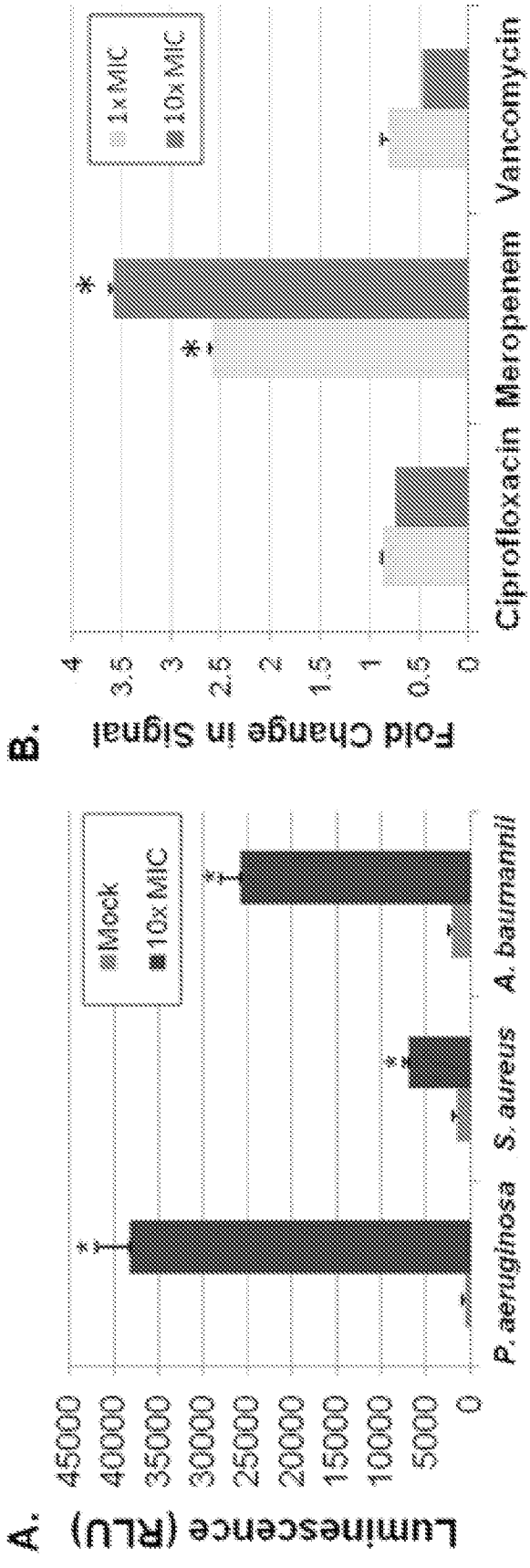

A.
Luminescence (RLU)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Mock
10x MIC
P. aeruginosa
S. aureus
A. baumannii
B.
Fold Change in Signal
4
3.5
3
2.5
2
1.5
1
0.5
0
1x MIC
10x MIC
Ciprofloxacin
Meropenem
Vancomycin

FIGURE 5

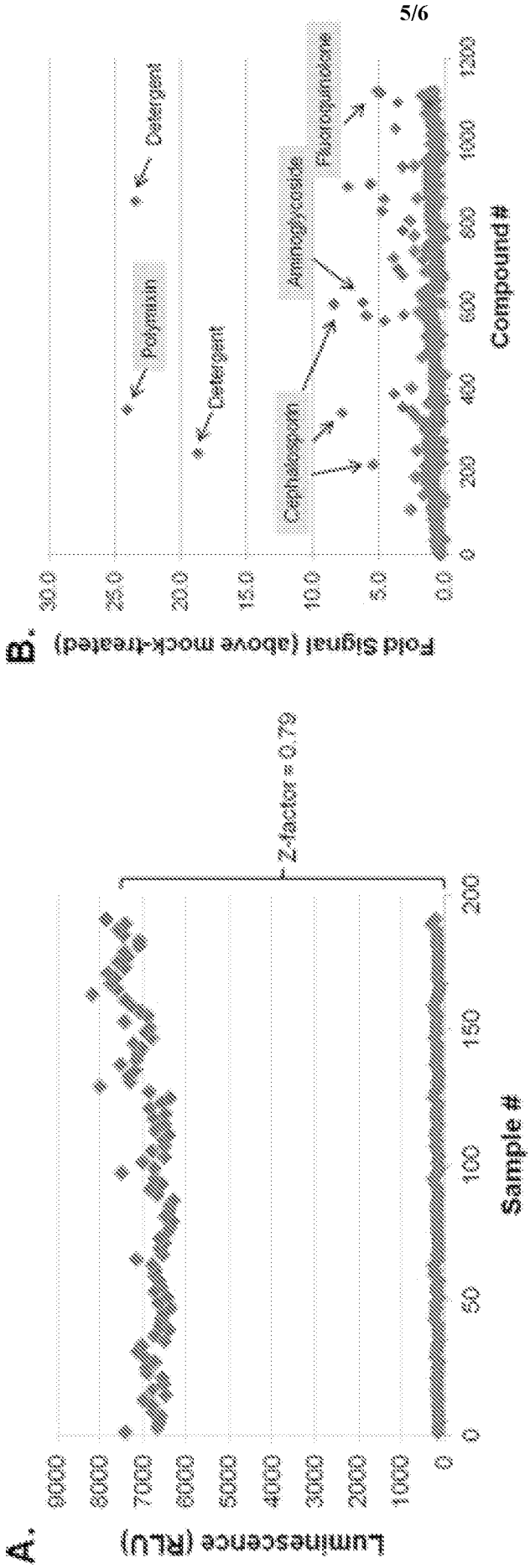
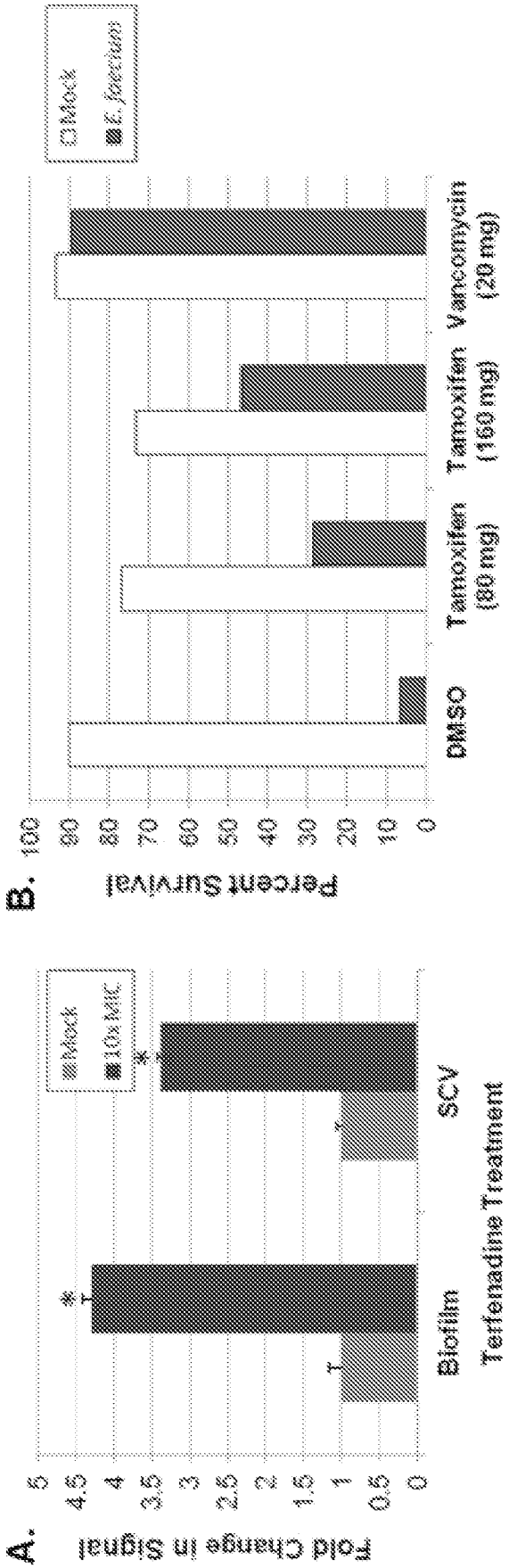

A.
Luminescence (RLU)
Sample #
Z-factor = 0.79
B.
Fold Signal (above mock-treated)
Compound #
Detergent
Polymyxin
Detergent
Cephalosporin
Aminoglycoside
Fluoroquinolone

FIGURE 6


A.
Fold Change in Signal
Mock
10x MIC
Biofilm
SCV
Terfenadine Treatment
B.
Percent Survival
Mock
E. faecium
DMSO
Tamoxifen (80 mg)
Tamoxifen (160 mg)
Vancomycin (20 mg)