

(43) International Publication Date
8 June 2017 (08.06.2017)(10) International Publication Number
WO 2017/093545 A1

(51) International Patent Classification:

C07F 9/50 (2006.01) **C07F 9/6533** (2006.01)
C07F 9/572 (2006.01) **C07F 9/6539** (2006.01)
C07F 9/58 (2006.01) **C07F 9/6544** (2006.01)
C07F 9/59 (2006.01) **C07F 9/6558** (2006.01)
C07F 9/6503 (2006.01) **C07F 9/6568** (2006.01)
C07F 9/6506 (2006.01) **C07F 9/6571** (2006.01)
C07F 9/6518 (2006.01) **A61K 33/24** (2006.01)
C07F 9/6524 (2006.01) **A61L 29/00** (2006.01)
C07F 9/653 (2006.01)

(21) International Application Number:

PCT/EP2016/079681

(22) International Filing Date:

2 December 2016 (02.12.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1521240.0 2 December 2015 (02.12.2015) GB

(71) **Applicant:** AUSPHERIX LIMITED [GB/GB]; Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2FX (GB).

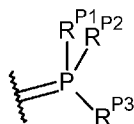
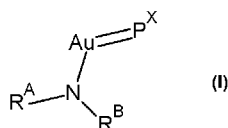
(72) **Inventors:** **HOLMES, Ian**; C/O Auspherix Limited, Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2FX (GB). **NAYLOR, Alan**; 1 Limekiln Close, Royston, Hertfordshire SG8 9XP (GB). **ALBER, Dagmar**; 77 London Road, Markyate, Hertfordshire AL3 8JP (GB). **POWELL, Jonathan Ray-**

mond; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB). **MAJOR, Meriel Ruth**; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB). **NEGOITA-GIRAS, Gabriel**; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB). **ALLEN, Daniel Rees**; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB). **GUETZOYAN, Lucie Juliette**; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB). **KING, Nigel Paul**; C/O Auspherix Limited, Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2FX (GB). **CHAPMAN, Nicholas Andrew**; C/O Domainex Ltd, 162 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0GH (GB).

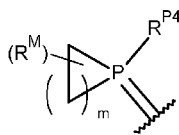
(74) **Agents:** **WATSON, Robert** et al.; Mewburn Ellis LLP, City Tower, 40 Basinghall Street, London, Greater London EC2V 5DE (GB).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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,

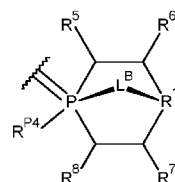
[Continued on next page]

(54) **Title:** ANTI-BACTERIAL COMPOUNDS BASED ON AMINO-GOLD PHOSPHINE COMPLEXES

(P1)



(P2)



(P3).

(57) **Abstract:** A compound of formula (I) for use in the prevention or treatment of a bacterial infection wherein: P^X is selected from the group consisting of (P1), (P2) and (P3).



TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(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, ST, 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,

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

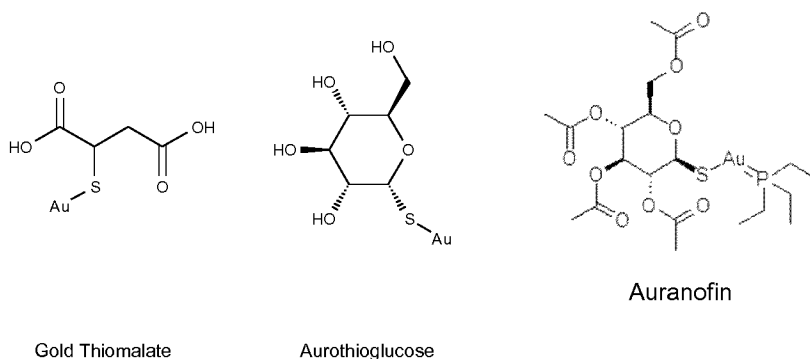
ANTI-BACTERIAL COMPOUNDS BASED ON AMINO-GOLD PHOSPHINE COMPLEXES

The present invention relates to gold(I)-phosphine compounds, and their use as inhibitors of growth of Gram-positive and/or Gram-negative bacteria. The present invention also relates to using such compounds for the prevention and/or treatment of bacterial infection.

The global rise of bacteria and other microorganisms resistant to antibiotics and antimicrobials in general, poses a major threat. Deployment of massive quantities of antimicrobial agents into the human ecosphere during the past 60 years has introduced a powerful selective pressure for the emergence and spread of antimicrobial-resistant bacterial pathogens. The World Health Organization has highlighted antimicrobial resistance (AMR) as an issue of global concern in 2014. AMR is now present in all parts of the world with the incidence of antibiotic resistance (ABR) in bacteria that cause common infections (e.g. pneumonia, bloodstream infections and urinary tract infections) rendering many historically efficacious antibiotics ineffective. Of particular concern are hospital-acquired infections caused by highly resistant bacteria such as the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), *Escherichia coli*, Coagulase-negative staphylococci and *Clostridium difficile*. Additionally, failure of last resort third-generation cephalosporins for the treatment of gonorrhea has now been reported in 10 countries raising the possibility that gonorrhea may soon become untreatable in the absence of new antibacterial agents.

The biological activity of gold(I) and gold(III) complexes has been studied historically and salts of both have been demonstrated to possess antimicrobial activity against a range of pathogens. Gold(I) complexes have historically been reported as having antibacterial activity against Gram positive organisms. (Glišić, B.D. & Djuran M.I., *Dalton Trans.*, 2014, 43, 5950-5969). For example, Nomiya (Nomiya, K., *et al.*, *J. Inorganic Biochem.*, 2003, 95, 208-220) discloses triphenyl phosphine compounds with a variety of ligands with antibacterial activity against Gram positive organisms, and Aguinagalde, L., *et al.*, *J. Antimicrob. Chemother.*, 2015, 70(9), 2608-2617 discloses six triethyl phosphine compounds with antibacterial activity against Gram positive organisms.

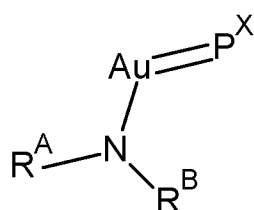
Gold(I) is a soft Lewis acid and preferentially complexes with soft donor atoms such as sulfur, selenium and phosphorous. Examples of such complexes used clinically include gold thiomalate, aurothioglucose and auranofin:



Auranofin, a second generation orally bioavailable gold(I) based treatment for rheumatoid arthritis (RA), has been identified as inhibiting the *in vitro* growth of *S. aureus* (Oxford strain) with an MIC of 0.6-0.9 µg/mL and *V. cholerae* with an MIC of 2.5 µg/mL. These observations reinforce multiple literature reports of the antimicrobial activity of auranofin and other gold(I) compounds against a range of bacterial pathogens (Madeira, JM., *Inflammopharmacology*, 2012, 20, 297-306; Jackson-Rosario, S, *J. Biol. Inorg. Chem.*, 2009, 14(4), 507-519; Novelli, F., *Farmaco*, 1999, 54, 232-236; Shaw, CF, *Chem Rev.*, 1999, 99(9), 2589-2600; Rhodes, MD, *J. Inorg. Biochem.*, 1992, 46, 129-142 and Fricker, SP, *Transition Met. Chem.*, 1996, 21, 377-383). Auranofin has not been shown to have any significant activity against the majority of Gram negative bacteria.

Co-pending applications PCT/GB2015/051551 and PCT/GB2015/051550 describe certain gold(I) phosphine compounds and their use as inhibitors of growth of Gram-positive and/or Gram-negative bacteria.

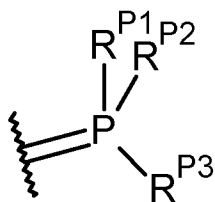
A first aspect of the present invention provides a compound of formula (I):



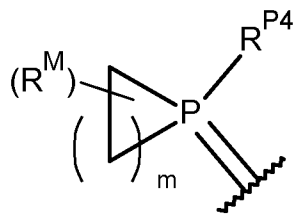
Formula (I)

for use in the prevention or treatment of a bacterial infection wherein:

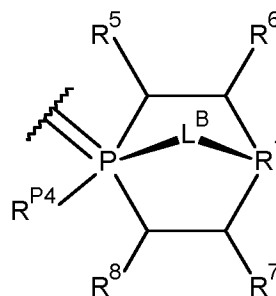
P^X is selected from the group consisting of (P1), (P2) and (P3);



(P1)



(P2)



(P3)

wherein

- 5 R^{P1} and R^{P2} are each independently selected from

methyl, ethyl, isopropyl and phenyl;

R^{P3} is selected from the group consisting of

methyl and ethyl,

isopropyl, t-butyl,

- 10 cyclopentyl,

phenyl,

4-membered or 5-membered heterocycloalkyl group linked to phosphorus via a carbon atom in the ring, including a single heteroatom independently selected from NR^Z , O and S,

- 15 $-CF_3$, $-CH_2CF_3$, $-CH_2CF_2H$, $-CH_2CH_2OR^{PB}$,
 $-CH_2Q$ and $-(CH_2)_2Q$;

wherein Q is a C_{5-6} heteroaryl group, optionally substituted with one or more groups R^{PA} ;

R^{P4} is selected from methyl and ethyl;

m is an integer selected from 1, 2 or 3;

- 20 R^M is one or more optional substituents on the ring independently selected from

R^{PC} when attached to a carbon atom adjacent the phosphorus atom, or

$-OH$, $-OC_{1-3}alkyl$ and R^{PC} , when attached to other ring carbons;

$-L^B$ is methylene, ethylene or is absent;

when $-L^B$ is present, R^{P4} is absent and R^1 is selected from N, CH and CR^{PC} ;

- 25 when $-L^B$ is absent, R^1 is selected from the group consisting of

O,

NR^Z ,

SO_2 ,

CH_2 , CHF , CF_2 and CHR^{PC} ;

- 30 wherein R^Z is selected from the group consisting of

H, C₁₋₃alkyl, COC₁₋₃alkyl and SO₂C₁₋₃alkyl;

R⁵ and R⁸ are each independently selected from H and R^{PC};

R⁶ and R⁷ are each independently selected from H and R^{PC};

5 wherein R^{PC} is selected from the group consisting of

C₁₋₃alkyl, optionally substituted with one or more groups R^{PD};

wherein R^{PA} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AL},

10 -F, -Cl, -Br, -CN

-OH, -OR^{PE},

-CF₃, -CF₂H,

-COR^{PE},

-CH₂OH, -CH₂OR^{PE},

15 -COOH, -COOR^{PE}, -CONH₂, -CONHR^{PE}, -CONR^{PE}₂,

-OCOR^{PE}, -OCONH₂, -OCONHR^{PE}, -OCONR^{PE}₂,

-NH₂, -NHR^{PE}, -NR^{PE}₂,

-SO₂NH₂, -SO₂NHR^{PE}₂, -SO₂NR^{PE}₂,

-SO₂R^{PE},

20 -NHCOH, -NHCOR^{PE}, -NR^{PE}COH and -NR^{PE}COR^{PE};

and R^{PB} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AT},

C₃₋₆cycloalkyl, C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl or C₅₋₆heterocycloalkenyl

25 optionally substituted with one or more groups R^{AT},

phenyl optionally substituted with one or more groups R^{AR}, and

C₅₋₆heteroaryl optionally substituted with one or more groups R^{AR};

R^{PE} is selected from

linear or branched C₁₋₄alkyl optionally substituted with one or more groups R^{PD};

30 and R^{PD} is selected from the group consisting of

F,

OH and OC₁₋₃alkyl;

R^A is selected from the group consisting of

H;

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl,
C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl and C₅₋₆heterocycloalkenyl optionally
substituted with one or more groups R^{AL},

C₅₋₆heteroaryl, optionally substituted with one or more groups R^{A1},

5 C₁₋₃alkyl substituted by phenyl or C₅₋₆heteroaryl, which groups may optionally
substituted with one or more groups R^{A1},

R^B is selected from -COR^{A2} and -SO₂R^{A2};

or R^A and R^B together with the nitrogen atom to which they are attached form

a 5- or 6-membered heteroaryl, heterocycloalkyl or heterocycloalkenyl group

10 optionally substituted with one or more groups selected from

oxo,

=NH;

phenyl optionally substituted with one or more groups R^{A1},

R^{A2}, and

15 R^{A1};

an 8- to 10-membered heterobicycyl group optionally substituted with one or more
groups selected from

oxo,

-NO₂;

20 -C(=O)N(R^{N1})₂, wherein each R^{N1} is independently selected from

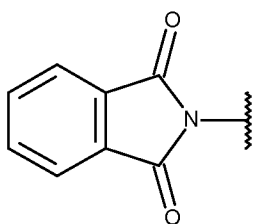
R^{N2} and -OR^{N3}, wherein R^{N2} and R^{N3} are each independently selected from
linear unsubstituted C₁₋₆alkyl;

phenyl optionally substituted with one or more groups R^{A1},

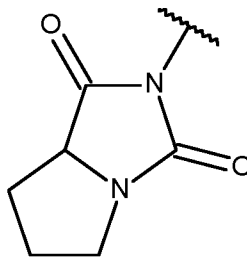
R^{A2} and

25 R^{A1};

with the proviso that when P^X is P(C₂H₅)₃, -NR^AR^B is not selected from the groups (X1) or
(X6)



(X1)



(X6)

30 wherein

R^{A1} is selected from the group consisting of

linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with one or more groups R^{AL} ,

-F, -Cl, -Br, -CN

-OH, -OR^{A2},

-CF₃, -CF₂H,

-COR^{A2},

-CH₂OH, -CH₂OR^{A2}, -CHR^{A2}OH, CHR^{A2}OR^{A2}

-COOH, -COOR^{A2}, -CONH₂, -CONHR^{A2}, -CONR^{A2}₂,

-OCOR^{A2}, -OCONH₂, -OCONHR^{A2}, -OCONR^{A2}₂,

-NH₂, -NHR^{A2}, -NR^{A2}₂,

-SO₂NH₂, -SO₂NHR^{A2}₂, -SO₂NR^{A2}₂,

-SO₂R^{A2},

-NHCOH, -NHCOR^{A2}, -NR^{A2}COH and -NR^{A2}COR^{A2};

R^{A2} is selected from the group consisting of

linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with one or more groups R^{AT} ,

C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl, C_{5-6} cycloalkenyl or C_{5-6} heterocycloalkenyl

optionally substituted with one or more groups R^{AT} ,

phenyl optionally substituted with one or more groups R^{AR} , and

C_{5-10} heteroaryl optionally substituted with one or more groups R^{AR} ;

where N is substituted by 2 R^{A2} groups, the N and the R^{A2} groups may together form a N-containing C_{5-6} heterocycloalkyl group;

R^{AL} is selected from the group consisting of

linear or branched C_{1-6} alkyl optionally substituted with one or more groups R^{AT} ;

-F, -CN

-OH, -OR^{A2},

-CF₃, -CF₂H,

-COR^{A2},

-COOH, -COOR^{A2}, -CONH₂, -CONHR^{A2}, -CONR^{A2}₂,

-OCOR^{A2}, -OCONH₂, -OCONHR^{A2}, -OCONR^{A2}₂,

-NH₂, -NHR^{A2}, -NR^{A2}₂,

-SO₂NH₂, -SO₂NHR^{A2}₂, -SO₂NR^{A2}₂,

-SO₂R^{A2},

-NHCOH, -NHCOR^{A2}, -NR^{A2}COH and -NR^{A2}COR^{A2}; and

wherein R^{AR} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AL},

-F, -Cl, -Br, -CN

-OH, -OR^{1A1},

5 -CF₃, -CF₂H,

-COR^{1A1},

-CH₂OH, -CH₂OR^{1A1}, -CHR^{1A1}OH, CHR^{1A1}OR^{1A1}

-COOH, -COOR^{1A1}, -CONH₂, -CONHR^{1A1}, -CONR^{1A1}₂,

-OCOR^{1A1}, -OCONH₂, -OCONHR^{1A1}, -OCONR^{1A1}₂,

10 -NH₂, -NHR^{1A1}, -NR^{1A1}₂,

-SO₂NH₂, -SO₂NHR^{1A1}₂, -SO₂NR^{1A1}₂,

-SO₂R^{1A1},

-NHCOH, -NHCOR^{1A1}, -NR^{1A1}COH and -NR^{1A1}COR^{1A1};

R^{AT} is selected from the group consisting of

15 -F, -CN

-OH, -OC₁₋₃alkyl,

-CF₃, -CF₂H,

-COC₁₋₃alkyl,

-COOH, -COOC₁₋₃alkyl, -CONH₂, -CONHC₁₋₃alkyl, -CON(C₁₋₃alkyl)₂,

20 -OCOC₁₋₃alkyl, -OCONH₂, -OCONHC₁₋₃alkyl, -OCON(C₁₋₃alkyl)₂,

-NH₂, -NHC₁₋₃alkyl, -N(C₁₋₃alkyl)₂,

-SO₂NH₂, -SO₂NH(C₁₋₃alkyl)₂, -SO₂N(C₁₋₃alkyl)₂,

-SO₂(C₁₋₃alkyl),

-NHCOH, -NHCO(C₁₋₃alkyl), -N(C₁₋₃alkyl)COH and -N(C₁₋₃alkyl)CO(C₁₋₃alkyl);

25 and pharmaceutically acceptable salts and solvates thereof.

In some embodiments of the first aspect,

R^{P1} and R^{P2} are each independently selected from

methyl and ethyl;

30 R^{P3} is selected from the group consisting of

methyl and ethyl,

4-membered or 5-membered heterocycloalkyl group linked to phosphorus via a carbon atom in the ring, including a single heteroatom independently selected from N, O and S,

35 -CF₃, -CH₂CF₃, -CH₂CF₂H, -CH₂CH₂OR^{PB},

-CH₂Q and -(CH₂)₂Q;

R^A and R^B together with the nitrogen atom to which they are attached form a 5- or 6-membered heteroaryl, heterocycloalkyl or heterocycloalkenyl group optionally substituted with one or more groups selected from

oxo,

- 5 phenyl optionally substituted with one or more groups R^{A1},
 R^{A2}, and
 R^{A1};

or an 8- to 10-membered heterobicycyl group optionally substituted with one or more groups selected from

- 10 oxo,
 phenyl optionally substituted with one or more groups R^{A1},
 R^{A2} and
 R^{A1}.

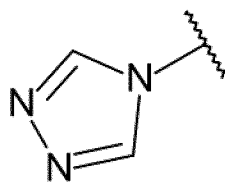
- 15 The first aspect of the invention also provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prevention of a bacterial infection. The first aspect of the invention further provides the treatment of a human or animal patient afflicted with a bacterial infection, comprising administering to said patient an effective amount of a pharmaceutical composition containing a compound of formula (I).

- 20 In the first aspect, the bacterial infection prevented and/or treated may be infection by one or more Gram-positive bacteria. The bacterial infection prevented and/or treated may be infection by one or more Gram-negative bacteria. In the first aspect, the bacterial infection prevented and/or treated may be infection by one or more multi-drug resistant
25 bacteria.

The first aspect may also relate to the treatment of fungal infection, e.g. by providing a compound of formula (I) for use in the prevention or treatment of a fungal infection.

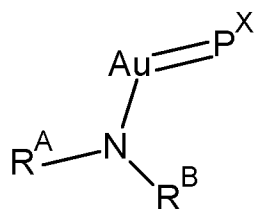
- 30 Compounds of the present invention may also be used to treat conditions by interaction, e.g. binding to thioredoxin reductase (TrxR), glutathione peroxidase (GSPx), IκB kinase (IKK) complex, cathepsins and type I iodothyronine deiodinase.

- 35 In some embodiments of the first aspect, when P^X is P(CH₃)₃, -NR^AR^B is not selected from the group (X15):

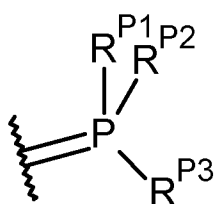


(X15)

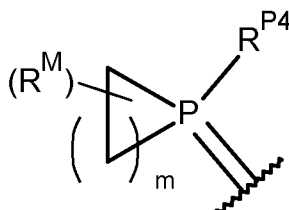
A second aspect of the present invention provides a compound of formula (I):

**Formula (I)**

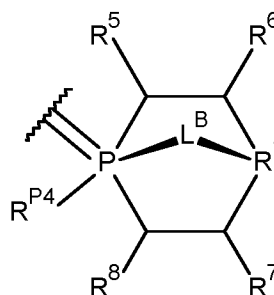
P^X is selected from the group consisting of (P1), (P2) and (P3);



(P1)



(P2)



(P3)

wherein

R^{P1} and R^{P2} are each independently selected from

methyl, ethyl, isopropyl and phenyl;

R^{P3} is selected from the group consisting of

methyl and ethyl,

isopropyl, t-butyl,

cyclopentyl,

phenyl,

4-membered or 5 membered heterocycloalkyl group linked to phosphorus via a

carbon atom in the ring, including a single heteroatom independently

selected from N, O and S,

$-CF_3$, $-CH_2CF_3$, $-CH_2CF_2H$, $-CH_2CH_2OR^{PB}$,

$-\text{CH}_2\text{Q}$ and $-(\text{CH}_2)_2\text{Q}$;

wherein Q is a C₅₋₆ heteroaryl group, optionally substituted with one or more groups R^{PA};

R^{P4} is selected from methyl and ethyl;

m is an integer selected from 1, 2 or 3;

5 R^M is one or more optional substituents on the ring independently selected from

R^{PC} when attached to a carbon atom adjacent the phosphorus atom, or

$-\text{OH}$, $-\text{OC}_{1-3}\text{alkyl}$ and R^{PC}, when attached to other ring carbons;

$-\text{L}^{\text{B-}}$ is methylene, ethylene or is absent;

when $-\text{L}^{\text{B-}}$ is present, R^{P4} is absent and R¹ is selected from N, CH and CR^{PC};

10 when $-\text{L}^{\text{B-}}$ is absent, R¹ is selected from the group consisting of

O,

NR^Z,

SO₂,

CH₂, CHF, CF₂ and CHR^{PC};

15 wherein R^Z is selected from the group consisting of

$-\text{H}$, $-\text{C}_{1-3}\text{alkyl}$, $-\text{COC}_{1-3}\text{alkyl}$ and $-\text{SO}_2\text{C}_{1-3}\text{alkyl}$;

R⁵ and R⁸ are each independently selected from H and R^{PC};

R⁶ and R⁷ are each independently selected from H and R^{PC};

wherein R^{PC} is selected from the group consisting of

20 C₁₋₃alkyl, optionally substituted with one or more groups R^{PD};

wherein R^{PA} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AL},

$-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{CN}$

25 $-\text{OH}$, $-\text{OR}^{\text{PE}}$,

$-\text{CF}_3$, $-\text{CF}_2\text{H}$,

$-\text{COR}^{\text{PE}}$,

$-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OR}^{\text{PE}}$,

$-\text{COOH}$, $-\text{COOR}^{\text{PE}}$, $-\text{CONH}_2$, $-\text{CONHR}^{\text{PE}}$, $-\text{CONR}^{\text{PE}}_2$,

30 $-\text{OCOR}^{\text{PE}}$, $-\text{OCONH}_2$, $-\text{OCONHR}^{\text{PE}}$, $-\text{OCONR}^{\text{PE}}_2$,

$-\text{NH}_2$, $-\text{NHR}^{\text{PE}}$, $-\text{NR}^{\text{PE}}_2$,

$-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHR}^{\text{PE}}_2$, $-\text{SO}_2\text{NR}^{\text{PE}}_2$,

$-\text{SO}_2\text{R}^{\text{PE}}$,

$-\text{NHCOH}$, $-\text{NHCOR}^{\text{PE}}$, $-\text{NR}^{\text{PE}}\text{COH}$ and $-\text{NR}^{\text{PE}}\text{COR}^{\text{PE}}$;

35 and R^{PB} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AT},

C₃₋₆cycloalkyl, C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl or C₅₋₆heterocycloalkenyl optionally substituted with one or more groups R^{AT},

5 phenyl optionally substituted with one or more groups R^{AR}, and

C₅₋₆heteroaryl optionally substituted with one or more groups R^{AR};

R^{PE} is selected from

linear or branched C₁₋₄alkyl optionally substituted with one or more groups R^{PD};

and R^{PD} is selected from the group consisting of

10 F,

OH and OC₁₋₃alkyl;

R^A is selected from the group consisting of

H;

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₂₃₋₆cycloalkyl,

15 C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl and C₅₋₆heterocycloalkenyl optionally substituted with one or more groups R^{AL},

C₅₋₆heteroaryl, optionally substituted with one or more groups R^{A1},

C₁₋₃alkyl substituted by phenyl or C₅₋₆heteroaryl, which groups may optionally substituted with one or more groups R^{A1},

20 R^B is selected from -COR^{A2} and -SO₂R^{A2};

or R^A and R^B together with the nitrogen atom to which they are attached form

a 5- or 6-membered heteroaryl, heterocycloalkyl or heterocycloalkenyl group optionally substituted with one or more groups selected from

oxo,

25 =NH;

phenyl optionally substituted with one or more groups R^{A1},

R^{A2} and

R^{A1};

an 8- to 10-membered heterobicycyl group optionally substituted with one or more groups selected from

30 oxo,

-NO₂;

-C(=O)N(R^{N1})₂, wherein each R^{N1} is independently selected from

R^{N2} and -OR^{N3}, wherein R^{N2} and R^{N3} are each independently selected from

35 linear unsubstituted C₁₋₆alkyl;

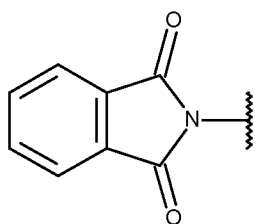
phenyl optionally substituted with one or more groups R^{A1},

R^{A2} and

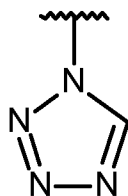
 R^{A1} ;

with the proviso that when P^X is $P(CH_3)_3$, $-NR^A R^B$ is not selected from any of the groups (X1) to (X5) and (X7);

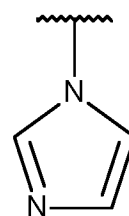
- 5 and with the proviso that when P^X is $P(C_2H_5)_3$, $-NR^A R^B$ is not selected from the groups (X1), and (X6) to (X11)



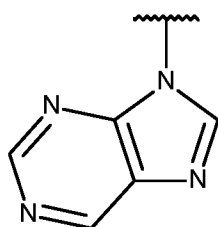
(X1)



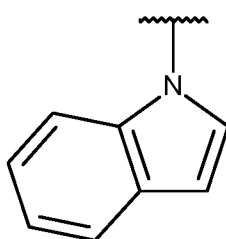
(X2)



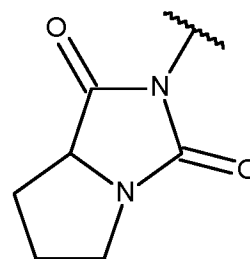
(X3)



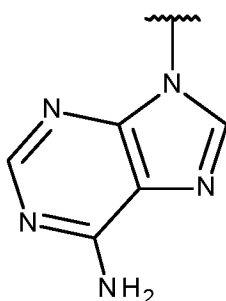
(X4)



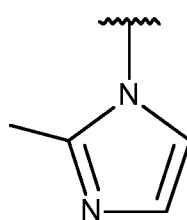
(X5)



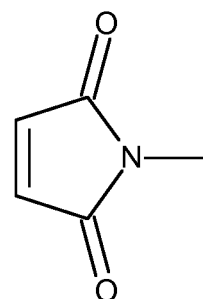
(X6)



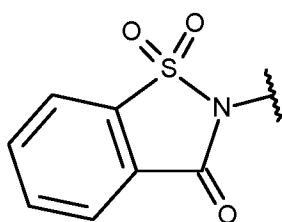
(X7)



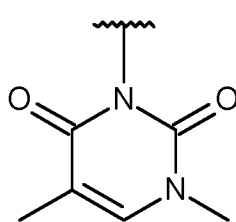
(X8)



(X9)



(X10)



(X11)

wherein

R^{A1} is selected from the group consisting of

linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with one or more groups R^{AL} ,

-F, -Cl, -Br, -CN

-OH, -OR^{A2},

-CF₃, -CF₂H,

-COR^{A2},

-CH₂OH, -CH₂OR^{A2}, -CHR^{A2}OH, CHR^{A2}OR^{A2}

-COOH, -COOR^{A2}, -CONH₂, -CONHR^{A2}, -CONR^{A2}₂,

-OCOR^{A2}, -OCONH₂, -OCONHR^{A2}, -OCONR^{A2}₂,

-NH₂, -NHR^{A2}, -NR^{A2}₂,

-SO₂NH₂, -SO₂NHR^{A2}₂, -SO₂NR^{A2}₂,

-SO₂R^{A2},

-NHCOH, -NHCOR^{A2}, -NR^{A2}COH and -NR^{A2}COR^{A2};

R^{A2} is selected from the group consisting of

linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with one or more groups R^{AT} ,

C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl, C_{5-6} cycloalkenyl or C_{5-6} heterocycloalkenyl

optionally substituted with one or more groups R^{AT} ,

phenyl optionally substituted with one or more groups R^{AR} , and

C_{5-10} heteroaryl optionally substituted with one or more groups R^{AR} ;

where N is substituted by 2 R^{A2} groups, the N and the R^{A2} groups may together form a N-containing C_{5-6} heterocycloalkyl group;

R^{AL} is selected from the group consisting of

linear or branched C_{1-6} alkyl optionally substituted with one or more groups R^{AT} ;

-F, -CN

-OH, -OR^{A2},

-CF₃, -CF₂H,

-COR^{A2},

-COOH, -COOR^{A2}, -CONH₂, -CONHR^{A2}, -CONR^{A2}₂,

-OCOR^{A2}, -OCONH₂, -OCONHR^{A2}, -OCONR^{A2}₂,

-NH₂, -NHR^{A2}, -NR^{A2}₂,

-SO₂NH₂, -SO₂NHR^{A2}₂, -SO₂NR^{A2}₂,

-SO₂R^{A2},

-NHCOH, -NHCOR^{A2}, -NR^{A2}COH and -NR^{A2}COR^{A2}; and

wherein R^{AR} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AL},

-F, -Cl, -Br, -CN

-OH, -OR^{1A1},

-CF₃, -CF₂H,

-COR^{1A1},

-CH₂OH, -CH₂OR^{1A1}, -CHR^{1A1}OH, CHR^{1A1}OR^{1A1}

-COOH, -COOR^{1A1}, -CONH₂, -CONHR^{1A1}, -CONR^{1A1}₂,

-OCOR^{1A1}, -OCONH₂, -OCONHR^{1A1}, -OCONR^{1A1}₂,

-NH₂, -NHR^{1A1}, -NR^{1A1}₂,

-SO₂NH₂, -SO₂NHR^{1A1}₂, -SO₂NR^{1A1}₂,

-SO₂R^{1A1},

-NHCOH, -NHCOR^{1A1}, -NR^{1A1}COH and -NR^{1A1}COR^{1A1};

R^{AT} is selected from the group consisting of

-F, -CN

-OH, -OC₁₋₃alkyl,

-CF₃, -CF₂H,

-COC₁₋₃alkyl,

-COOH, -COOC₁₋₃alkyl, -CONH₂, -CONHC₁₋₃alkyl, -CON(C₁₋₃alkyl)₂,

-OCOC₁₋₃alkyl, -OCONH₂, -OCONHC₁₋₃alkyl, -OCON(C₁₋₃alkyl)₂,

-NH₂, -NHC₁₋₃alkyl, -N(C₁₋₃alkyl)₂,

-SO₂NH₂, -SO₂NH(C₁₋₃alkyl)₂, -SO₂N(C₁₋₃alkyl)₂,

-SO₂(C₁₋₃alkyl),

-NHCOH, -NHCO(C₁₋₃alkyl), -N(C₁₋₃alkyl)COH and -N(C₁₋₃alkyl)CO(C₁₋₃alkyl);

and pharmaceutically acceptable salts and solvates thereof.

In some embodiments of the second aspect,

R^{P1} and R^{P2} are each independently selected from

methyl and ethyl;

R^{P3} is selected from the group consisting of

methyl and ethyl,

4-membered or 5 membered heterocycloalkyl group linked to phosphorus via a carbon atom in the ring, including a single heteroatom independently selected from N, O and S,

-CF₃, -CH₂CF₃, -CH₂CF₂H, -CH₂CH₂OR^{PB},

-CH₂Q and -(CH₂)₂Q;

R^A and R^B together with the nitrogen atom to which they are attached form a 5- or 6-membered heteroaryl, heterocycloalkyl or heterocycloalkenyl group optionally substituted with one or more groups selected from

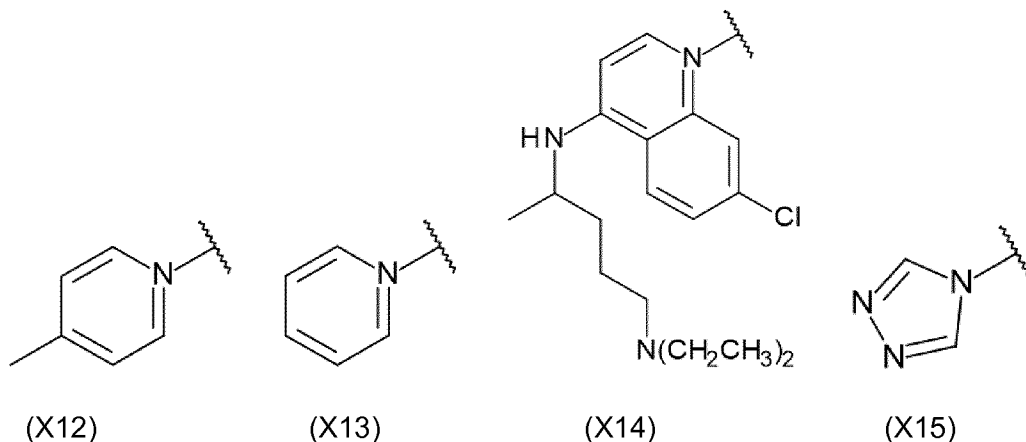
oxo,

- 5 phenyl optionally substituted with one or more groups R^{A1} ,
 R^{A2} , and
 R^{A1} ;

or an 8- to 10-membered heterobicycyl group optionally substituted with one or more groups selected from

- 10 oxo,
 phenyl optionally substituted with one or more groups R^{A1} ,
 R^{A2} and
 R^{A1} .

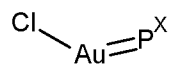
- 15 In some embodiments of the second aspect, when P^X is $P(CH_3)_3$, $-NR^A R^B$ is not selected from any of the groups (X1) to (X5), (X7) and (X12) to (X15);
 and when P^X is $P(C_2H_5)_3$, $-NR^A R^B$ is not selected from the groups (X1), (X6) to (X11), (X13) and (X14)



- A third aspect of the present invention provides a pharmaceutical composition comprising a compound of the second aspect of the invention. The pharmaceutical composition may also comprise a pharmaceutically acceptable diluent or excipient. The third aspect of the present invention also provides the use of a compound of the second aspect of the invention in a method of therapy.
- 25

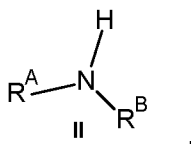
Another aspect of the invention is a compound obtained by a method of synthesis as described herein.

For example, in some embodiments a compound is provided which is obtained by a method of reacting gold(I) complexes of formula III:



III

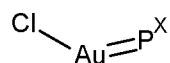
5 with a nitrogen containing derivative of general formula II:



wherein P^{X} , R^{A} and R^{B} are as defined under the first aspect.

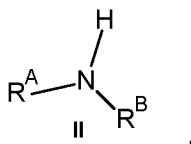
Another aspect of the invention is a compound obtainable by a method of synthesis as
10 described herein.

For example, in some embodiments a compound is provided which is obtainable by a method of reacting gold(I) complexes of formula III:



III

15 with a nitrogen containing derivative of general formula II:



wherein P^{X} , R^{A} and R^{B} are as defined under the first aspect.

Further aspects of the invention relate generally to the use of the compounds of the
20 present invention to inhibit microbial growth, sensitize the inhibition of microbial growth, inhibit biofilm formation or development, disrupt existing biofilms, reduce the biomass of a biofilm, and sensitize a biofilm and microorganisms within the biofilm to an antimicrobial agent.

In one aspect the invention relates to a method for inhibiting biofilm formation, comprising exposing a biofilm-forming microorganism to an effective amount of a compound of the invention. In some embodiments a compound of the invention is coated, impregnated or otherwise contacted with a surface or interface susceptible to biofilm formation. In some
5 embodiments, the surface is a surface of a medical device such as: medical or surgical equipment, an implantable medical device or prosthesis (for example, venous catheters, drainage catheters (e.g. urinary catheters), stents, pacemakers, contact lenses, hearing-aids, percutaneous glucose sensors, dialysis equipment, drug-pump related delivery cannula, prostheses such as artificial joints, implants such as breast implants, heart
10 valves, medical fixation devices such as rods, screws, pins, plates, or devices for wound repair such as sutures, and wound dressings such as bandages). In particular embodiments, the biofilm or biofilm-forming microorganism is on a bodily surface of a subject and exposure of the biofilm or biofilm-forming microorganism to a compound of the invention is by administration of the compound of the invention to the subject. In such
15 instances, the biofilm or biofilm-forming microorganism may be associated with an infection, disease or disorder suffered by the subject or to which the subject is susceptible. In a related aspect of the invention, a medical device (such as those exemplified above) coated or impregnated with a compound of the invention is provided.

20 In another aspect the invention relates to a method for reducing the biomass of a biofilm and/or promoting the dispersal of microorganisms from a biofilm, comprising exposing the biofilm to an effective amount of a compound of the invention.

In yet another aspect the invention relates to a method for dispersing or removing,
25 removing, or eliminating a biofilm, comprising exposing the biofilm to an effective amount of a compound of the invention. In some embodiments the biofilm is an existing, preformed or established biofilm.

In a further aspect the invention relates to a method for killing microorganisms within a
30 biofilm, comprising exposing the biofilm to an effective amount of a compound of the invention. In some embodiments the biofilm is an existing, preformed or established biofilm.

In a yet further aspect the invention relates to a method of sensitizing a microorganism in
35 a biofilm to an antimicrobial agent by exposing the biofilm to an effective amount of a compound of the invention. In some embodiments the antimicrobial agent is an antibiotic

(e.g. rifampicin, gentamicin, erythromycin, lincomycin, linezolid or vancomycin) or an antifungal agent.

In one aspect the invention relates to a compound of the invention for use in a method of dispersing, removing or eliminating an existing biofilm, inhibiting biofilm formation, reducing the biomass of a biofilm, promoting the dispersal of microorganisms from a biofilm, killing microorganisms within a biofilm, sensitizing a microorganism in a biofilm to an antimicrobial agent, treating or preventing an infection, disease or disorder caused by a biofilm, inhibiting the growth of a microbial persister cell, killing a microbial persister cell, or treating or preventing an infection, disease or disorder caused by or associated with a microbial persister cell.

In another aspect the invention relates to a compound of the invention for use in a method of treating or preventing an infection, disease or disorder treatable by dispersing, removing or eliminating an existing biofilm, inhibiting biofilm formation, reducing the biomass of a biofilm, promoting the dispersal of microorganisms from a biofilm, killing microorganisms within a biofilm, sensitizing a microorganism in a biofilm to an antimicrobial agent, inhibiting the growth of a microbial persister cell, killing a microbial persister cell, or treating or preventing an infection, disease or disorder caused by or associated with a microbial persister cell.

In some aspects, the biofilm comprises bacteria, such as, for example, multi-drug resistant bacteria. In some aspects the bacteria are Gram positive bacteria. In some aspects the bacteria are Gram negative bacteria. In particular examples, the biofilm comprises, consists essentially of, or consists of *S. aureus*. In some aspects, the *S. aureus* is methicillin-resistant *S. aureus* (MRSA). In some embodiments, the biofilm comprises, consists essentially of, or consists of *A. baumannii*. In other embodiments, the biofilm comprises, consists essentially of, or consists of *K. pneumoniae*. In other embodiments, the biofilm comprises, consists essentially of, or consists of one or more of the bacteria listed in Table 1 herein. In further embodiments, the biofilms comprise bacterial species, including but not limited to, *Staphylococcus spp.*, *Streptococcus spp.*, *Enterococcus spp.*, *Listeria spp.* and *Clostridium spp.*, *Klebsiella spp.*, *Acinetobacter spp.*, *Pseudomonas spp.*, *Burkholderia spp.*, *Erwinia spp.*, *Haemophilus spp.*, *Neisseria spp.*, *Escherichia spp.*, *Enterobacter spp.*, *Vibrio spp.* and/or *Actinobacillus spp.*

In some aspects, biofilm comprises lower eukaryotes, such as yeast, fungi, and filamentous fungi, including, but not limited to *Candida spp.*, *Pneumocystis spp.*, *Coccidioides spp.*, *Aspergillus spp.*, *Zygomycetes spp.*, *Blastoschizomyces spp.*, *Saccharomyces spp.*, *Malassezia spp.*, *Trichosporon spp.* and *Cryptococcus spp.*

- 5 Example species include *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. dubliniensis*, *C. krusei*, *C. tropicalis*, *A. fumigatus*, and *C. neoforms*.

- The biofilm may comprise one species of microorganism, or comprise two or more species of microorganism, i.e. be a mixed species biofilm. The mixed species biofilms
10 may include two or more species of bacteria, two or more species of lower eukaryote (e.g. two or more fungal species, such as unicellular fungi, filamentous fungi and/or yeast), and/or both bacteria and lower eukaryotes, such as one or more species of bacteria and one or more species of lower eukaryotes. For example, the methods, uses and compositions provided herein are applicable to biofilms comprising one or more species
15 of bacteria and one or more species of fungi, such as a yeast, unicellular fungi and/or filamentous fungi. The mixed species biofilm may thus comprise 2, 3, 4, 5, 10, 15, 20 or more species of microorganism, and the microorganisms within the biofilm may be bacteria and/or lower eukaryotes, such as unicellular fungi, filamentous fungi and/or yeast.

20

In one aspect the invention relates to a method for killing persister cells or inhibiting the growth of a microbial persister cell, comprising exposing the persister cell to an effective amount of a compound of the invention.

- 25 In another aspect the invention relates to a method for reducing the number, density or proportion of persister cells in a microbial population, comprising exposing the persister cell to an effective amount of a compound of the invention. In some embodiments the number, density or proportion of persister cells in a microbial population is reduced by at least 10% compared to an otherwise identical population not exposed to a compound of
30 the invention; for example, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.9%, or at least 99.99%.

- In a further aspect the invention relates to a method of preventing the formation of
35 microbial persister cells in a microbial population, the method comprising exposing the population to an effective amount of a compound of the invention.

In some aspects the persister cell is a bacterial or fungal persister cell. In some examples, the persister cell is a Gram negative bacterium. In some examples, the persister cell is a Gram positive bacterium. In some examples, the persister cell is a small colony variant. In particular embodiments, the persister cells are *Staphylococcus* spp. (including Staphylococcal SCVs), such as *S. aureus* (including methicillin resistant *S. aureus* (MRSA)), *S. epidermidis*, and *S. capitis*. In further embodiments, the persister cells are *Pseudomonas* spp. such as *P. aeruginosa*; *Burkholderia* spp. such as *B. cepacia* and *B. pseudomallei*; *Salmonella* serovars, including *Salmonella* Typhi; *Vibrio* spp. such as *V. cholerae*; *Shigella* spp.; *Brucella* spp. such as *B. melitensis*; *Escherichia* spp. such as *E. coli*; *Lactobacillus* spp. such as *L. acidophilus*; *Serratia* spp. such as *S. marcescens*; *Neisseria* spp. such as *N. gonorrhoeae*, or *Candida* spp., such as *C. albicans*.

The compounds of the invention can act together with other antimicrobial agents, allowing for increased efficacy of anti-microbial action. Accordingly, for any aspect described herein comprising exposing a biofilm, biofilm-forming microorganism, or a microbial persister cell to a compound of the invention, the present invention provides a corresponding further aspect comprising exposing the biofilm or biofilm-forming microorganism to a combination of compounds of the invention and at least one additional antimicrobial agent, such as, for example, an antibiotic or an anti-fungal agent. In particular examples, the antibiotic is selected from rifampicin, gentamicin, erythromycin, lincomycin and vancomycin.

The methods described herein may be performed, for example, *in vivo*, *ex vivo*, or *in vitro*.

Definitions

Microbe / Microorganism: The terms “microbe / microorganism” as used herein pertain to bacteria and lower eukaryotes, such as fungi, including yeasts, unicellular fungi and filamentous fungi.

Antimicrobial agent: The term “antimicrobial agent” as used herein pertains to any agent that, alone or in combination with another agent, is capable of killing or inhibiting the growth of one or more species of microorganism. Antimicrobial agents include, but are not limited to, antibiotics, antifungals, detergents, surfactants, agents that induce oxidative stress, bacteriocins and antimicrobial enzymes (e.g. lipases, proteinases, pronases and lyases) and various other proteolytic enzymes and nucleases, peptides and phage.

Reference to an antimicrobial agent includes reference to both natural and synthetic antimicrobial agents. Examples of antimicrobial agents include fluoroquinolones, aminoglycosides, glycopeptides, lincosamides, cephalosporins and related beta-lactams, macrolides, nitroimidazoles, penicillins, polymyxins, tetracyclines, and any combination thereof. For example, the methods of the present invention can employ acedapsone; acetosulfone sodium; alamecin; alexidine; amdinocillin; amdinocillin pivoxil; amicycline; amifloxacin; amifloxacin mesylate; amikacin; amikacin sulfate; aminosalicyclic acid; aminosalicylate sodium; amoxicillin; amphomycin; ampicillin; ampicillin sodium; apalcillin sodium; apramycin; aspartocin; astromicin sulfate; avilamycin; avoparcin; azithromycin; azlocillin; azlocillin sodium; bacampicillin hydrochloride; bacitracin; bacitracin methylene disalicylate; bacitracin zinc; bambarmycins; benzoylpas calcium; berythromycin; betamicin sulfate; biapenem; biniramycin; biphenamine hydrochloride; bispyrithione magsulfex; butikacin; butirosin sulfate; capreomycin sulfate; carbadox; carbenicillin disodium; carbenicillin indanyl sodium; carbenicillin phenyl sodium; carbenicillin potassium; carumonam sodium; cefaclor; cefadroxil; cefamandole; cefamandole nafate; cefamandole sodium; cefaparole; cefatrizine; cefazaflur sodium; cefazolin; cefazolin sodium; cefbuperazone; cefdinir; cefepime; cefepime hydrochloride; cefetecol; cefixime; cefmenoxime hydrochloride; cefmetazole; cefmetazole sodium; cefonicid monosodium; cefonicid sodium; cefoperazone sodium; ceforanide; cefotaxime sodium; cefotetan; cefotetan disodium; cefotiam hydrochloride; cefoxitin; cefoxitin sodium; cefpimizole; cefpimizole sodium; cefpiramide; cefpiramide sodium; cefpirome sulfate; cefpodoxime proxetil; cefprozil; cefroxadine; cefsulodin sodium; ceftazidime; ceftibuten; ceftizoxime sodium; ceftriaxone sodium; cefuroxime; cefuroxime axetil; cefuroxime pivoxetil; cefuroxime sodium; cephaetrile sodium; cephalixin; cephalixin hydrochloride; cephaloglycin; cephaloridine; cephalothin sodium; cephapirin sodium; cephradine; cetocycline hydrochloride; cetophenicol; chloramphenicol; chloramphenicol palmitate; chloramphenicol pantothenate complex; chloramphenicol sodium succinate; chlorhexidine phosphanilate; chloroxylenol; chlortetracycline bisulfate; chlortetracycline hydrochloride; cinoxacin; ciprofloxacin; ciprofloxacin hydrochloride; cirolemycin; clarithromycin; clinafloxacin hydrochloride; clindamycin; clindamycin hydrochloride; clindamycin palmitate hydrochloride; clindamycin phosphate; clofazimine; cloxacillin benzathine; cloxacillin sodium; chlorhexidine, cloxyquin; colistimethate sodium; colistin sulfate; coumermycin; coumermycin sodium; cyclacillin; cycloserine; dalfopristin; dapsone; daptomycin; demeclocycline; demeclocycline hydrochloride; demecycline; denofungin; diaveridine; dicloxacillin; dicloxacillin sodium; dihydrostreptomycin sulfate; dipyrithione; dirithromycin; doxycycline; doxycycline calcium; doxycycline fosfatex; doxycycline hyclate; droxacin

sodium; enoxacin; epicillin; epitettracycline hydrochloride; erythromycin; erythromycin acistrate; erythromycin estolate; erythromycin ethylsuccinate; erythromycin gluceptate; erythromycin lactobionate; erythromycin propionate; erythromycin stearate; ethambutol hydrochloride; ethionamide; fleroxacin; floxacillin; fludalanine; flumequine; fosfomycin; 5 fosfomycin tromethamine; fumoxicillin; furazolium chloride; furazolium tartrate; fusidate sodium; fusidic acid; ganciclovir and ganciclovir sodium; gentamicin sulfate; gloximonam; gramicidin; haloprogin; hetacillin; hetacillin potassium; hexedine; ibafloxacin; imipenem; isoconazole; isepamicin; isoniazid; josamycin; kanamycin sulfate; kitasamycin; levofuraltadone; levopropylcillin potassium; lexithromycin; lincomycin; lincomycin 10 hydrochloride; lomefloxacin; lomefloxacin hydrochloride; lomefloxacin mesylate; loracarbef; mafenide; meclocycline; meclocycline sulfosalicylate; megalomicin potassium phosphate; mequidox; meropenem; methacycline; methacycline hydrochloride; methenamine; methenamine hippurate; methenamine mandelate; methicillin sodium; metioprime; metronidazole hydrochloride; metronidazole phosphate; mezlocillin; mezlocillin 15 sodium; minocycline; minocycline hydrochloride; mirincamycin hydrochloride; monensin; monensin sodium; nafcillin sodium; nalidixate sodium; nalidixic acid; natainycin; nebramycin; neomycin palmitate; neomycin sulfate; neomycin undecylenate; netilmicin sulfate; neutramycin; nifuradene; nifuraldezone; nifuratel; nifuratrone; nifurdazil; nifurimide; nifiupirinol; nifurquinazol; nifurthiazole; nitrocyline; nitrofurantoin; nitromide; 20 norfloxacin; novobiocin sodium; ofloxacin; onnetoprim; oxacillin and oxacillin sodium; oximonam; oximonam sodium; oxolinic acid; oxytetracycline; oxytetracycline calcium; oxytetracycline hydrochloride; paldimycin; parachlorophenol; paulomycin; pefloxacin; pefloxacin mesylate; penamecillin; penicillins such as penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin G sodium, penicillin V, penicillin V benzathine, 25 penicillin V hydrabamine, and penicillin V potassium; pentizidone sodium; phenyl aminosalicylate; piperacillin sodium; pirbenicillin sodium; piridicillin sodium; pirlimycin hydrochloride; pivampicillin hydrochloride; pivampicillin pamoate; pivampicillin probenate; polymyxin b sulfate; porfiromycin; propikacin; pyrazinamide; pyrithione zinc; quindecamine acetate; quinupristin; racephenicol; ramoplanin; ranimycin; relomycin; 30 repromycin; rifabutin; rifametan; rifamexil; rifamide; rifampin; rifapentine; rifaximin; rolitettracycline; rolitettracycline nitrate; rosaramicin; rosaramicin butyrate; rosaramicin propionate; rosaramicin sodium phosphate; rosaramicin stearate; rosoxacin; roxarsone; roxithromycin; sancycline; sanfetrinem sodium; sarmoxicillin; sarpicillin; scopafungin; sisomicin; sisomicin sulfate; sparfloxacin; spectinomycin hydrochloride; spiramycin; 35 stallimycin hydrochloride; steffimycin; streptomycin sulfate; streptonicozid; sulfabenz; sulfabenzamide; sulfacetamide; sulfacetamide sodium; sulfacytine; sulfadiazine;

sulfadiazine sodium; sulfadoxine; sulfalene; sulfamerazine; sulfameter; sulfamethazine; sulfamethizole; sulfamethoxazole; sulfamonomethoxine; sulfamoxole; sulfanilate zinc; sulfanitran; sulfasalazine; sulfasomizole; sulfathiazole; sulfazamet; sulfisoxazole; sulfisoxazole acetyl; sulfisboxazole diolamine; sulfomyxin; sulopenem; sultamricillin; 5 suncillin sodium; talampicillin hydrochloride; teicoplanin; temafloxacin hydrochloride; temocillin; tetracycline; tetracycline hydrochloride; tetracycline phosphate complex; tetroxoprim; thiamphenicol; thiphencillin potassium; ticarcillin cresyl sodium; ticarcillin disodium; ticarcillin monosodium; ticlatone; tiodonium chloride; tobramycin; tobramycin sulfate; tosufloxacin; trimethoprim; trimethoprim sulfate; trisulfapyrimidines; 10 troleandomycin; trospectomycin sulfate; tyrothricin; vancomycin; vancomycin hydrochloride; virginiamycin; zorbamycin; bifonazole; butoconazole; clotrimazole; econazole; fenticonazole; isoconazole; ketoconazole; miconazolel omoconazolel oxiconazolel sertaconazolel sulconazolel tioconazolel; albaconazole; fluconazole; isavuconazole; itraconazole; posaconazole; ravuconazole; terconazole; voriconazole;. 15 abafungin; amorolfine; butenafine; naftifine; terbinafine; anidulafungin; caspofungin; and micafungin.

Biofilm: The term “biofilm” as used herein pertains to any three-dimensional, matrix-encased microbial community displaying multicellular characteristics. Accordingly, the 20 term biofilm includes surface-associated biofilms as well as biofilms in suspension, such as flocs and granules. Biofilms may comprise a single microbial species or may be mixed species complexes, and may include bacteria as well as fungi, algae, protozoa, or other microorganisms.

25 Reducing the biomass of a biofilm: The term “reducing the biomass of a biofilm” is used herein to mean reducing the biomass of an area of a biofilm exposed to an effective amount of a compound of the invention as compared to the biofilm biomass of the area immediately before exposure to a compound of the invention. In some embodiments the “biomass” is the mass of cells present in the area of biofilm in addition to the extracellular 30 polymeric substance (EPS) of the biofilm matrix. In some embodiments the “biomass” is only the mass of cells present in the area of biofilm (that is, the mass of the EPS is not counted as “biomass”). In some embodiments the biomass of the area of a biofilm exposed to an effective amount of a compound of the invention is at least 10% less than the biofilm biomass of the area immediately before exposure to a compound of the 35 invention, the mass of the otherwise identical area of a biofilm which has not been exposed to a compound of the invention, for example, at least 20%, at least 30%, at least

40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% less than the biofilm biomass of the area immediately before exposure to a compound of the invention. In some embodiments the area of biofilm compared is 10^{-6} m²; in other embodiments the area of biofilm compared is 10^{-5} m², 10^{-4} m², or 10^{-3} m². In some embodiments a biofilm whose biomass has been reduced by at least 95% is deemed to have been “eliminated”, “dispersed” or “removed”. In some embodiments a biofilm whose biomass has been reduced by at least 99% is deemed to have been “eliminated”, “dispersed” or “removed”. In some embodiments a biofilm whose biomass has been reduced by at least 99.9% is deemed to have been “eliminated”, “dispersed” or “removed”. In some embodiments the change in biofilm biomass is assessed by a method comprising the steps of: i) washing the area of biofilm to remove non-adherent (planktonic) microorganisms, ii) assessing the area of biofilm biomass (i.e. the biomass “immediately before exposure to a compound of the invention”), iii) exposing the area of biofilm (or an otherwise identical area) to an effective amount of a compound of the invention for a period of time (for example, 24 hours), iv) washing the biofilm to remove non-adherent (planktonic) microorganisms, and v) assessing the area of biofilm biomass to obtain the ‘post-exposure’ biomass.

Promoting the dispersal of microorganisms from a biofilm: The term “promoting the dispersal of microorganisms from a biofilm” is used herein to mean reducing the number of microorganisms present in an area of a biofilm exposed to an effective amount of a compound of the invention as compared to the number of microorganisms present in the area immediately before exposure to a compound of the invention. In some embodiments the number of microorganisms in the area of a biofilm exposed to an effective amount of a compound of the invention is at least 10% less than the number of microorganisms present in the area immediately before exposure to a compound of the invention, for example, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% less than the number of microorganisms present in the area immediately before exposure to a compound of the invention. In some embodiments the change in number of microorganisms in an area of biofilm is assessed by a method comprising the steps of: i) washing the biofilm to remove non-adherent (planktonic) microorganisms, ii) counting the remaining microorganisms to obtain a ‘pre-exposure’ microorganism count (i.e. the count “immediately before exposure to a compound of the invention”), iii) exposing the biofilm to an effective amount of a compound of the invention for a period of time (for example, 24

hours), iv) washing the biofilm to remove non-adherent (planktonic) microorganisms, and v) counting the remaining microorganisms to obtain the 'post-exposure' microorganism count. In some embodiments a biofilm where number of microorganisms in an area has been reduced by at least 95% is deemed to have been "eliminated", "dispersed" or "removed". In some embodiments a biofilm where number of microorganisms in an area has been reduced by at least 99% is deemed to have been "eliminated", "dispersed" or "removed". In some embodiments a biofilm where number of microorganisms in an area has been reduced by at least 99.9% is deemed to have been "eliminated", "dispersed" or "removed".

Killing microorganisms within a biofilm: The term "killing microorganisms within a biofilm" is used herein to mean reducing the number of live microorganisms present in an area of a biofilm exposed to an effective amount of a compound of the invention as compared to the number of live microorganisms present in the area immediately before exposure to a compound of the invention. In some embodiments the biofilm is an existing, preformed or established biofilm. In some embodiments the number of live microorganisms in the area of a biofilm exposed to an effective amount of a compound of the invention is at least 10% less than the number of live microorganisms present in the area immediately before exposure to a compound of the invention, for example, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% less than the number of live microorganisms present in the area immediately before exposure to a compound of the invention. In some embodiments the change in number of microorganisms in an area of biofilm is assessed by a method comprising the steps of: i) washing the area biofilm to remove non-adherent (planktonic) microorganisms, ii) manually disperse the biofilm into solution (using, for example, scraping, sonication, and vortexing), iii) prepare serial dilutions, plate, and culture to estimate the number of colony forming unit (cfu) in the area of biofilm, iv) provide an otherwise identical area of biofilm and expose it to an effective amount of a compound of the invention for a period of time (for example, 24 hours), v) manually disperse the biofilm and estimate cfu as described above to obtain the 'post-exposure' microorganism count. The viability of the biofilm can be also assessed by allowing the biofilm to re-grow in compound free medium and assessing planktonic growth.

Dispersal: The term "dispersal" as used herein pertains to any to a biofilm and microorganisms making up a biofilm means the process of detachment and separation of cells and a return to a planktonic phenotype or behaviour of the dispersing cells.

Exposing: The term "exposing" as used herein means generally bringing into contact with. Exposure of a biofilm or biofilm-forming microorganism to an agent (e.g. a compound of the invention) includes administration of the agent to a subject harbouring the

5 microorganism or biofilm, or otherwise bringing the microorganism or biofilm into contact with the agent itself, such as by contacting a surface on which the biofilm or biofilm-forming microorganism are present with the agent. In some embodiments, the biofilm or biofilm-forming microorganisms are exposed to a compound of the invention by coating, impregnating or otherwise contacting a surface or interface susceptible to biofilm

10 formation to an effective amount of the compound. Surfaces that may be exposed, coated, or impregnated with a compound of the invention include those present in a range of industrial and domestic settings, including but not limited to, domestic, medical or industrial settings (e.g. medical and surgical devices, and surfaces within hospitals, processing plants and manufacturing plants), as well as internal and external surfaces of

15 the body of a subject. In the present disclosure the terms "exposing", "administering" and "contacting" and variations thereof may, in some contexts, be used interchangeably.

Inhibiting: The term "inhibiting" and variations thereof such as "inhibition" and "inhibits" as used herein in relation to microbial growth refers to any microbiocidal or microbiostatic

20 activity of an agent (e.g. a compound of the invention) or composition. Such inhibition may be in magnitude and/or be temporal or spatial in nature. Inhibition of the growth of a microorganism by an agent can be assessed by measuring growth of the microorganism in the presence and absence of the agent. The growth can be inhibited by the agent by at least or about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%,

25 75%, 80%, 85%, 90%, 95% or more compared to the growth of the same microorganism that is not exposed to the agent.

The term "inhibiting" and variations thereof such as "inhibition" and "inhibits" as used herein in relation to biofilms means complete or partial inhibition of biofilm formation

30 and/or development and also includes within its scope the reversal of biofilm development or processes associated with biofilm formation and/or development. Further, inhibition may be permanent or temporary. The inhibition may be to an extent (in magnitude and/or spatially), and/or for a time, sufficient to produce the desired effect. Inhibition may be prevention, retardation, reduction or otherwise hindrance of biofilm formation or

35 development. Such inhibition may be in magnitude and/or be temporal or spatial in nature. Inhibition of the formation or development of a biofilm by a compound of the

invention can be assessed by measuring biofilm mass or microbial growth in the presence and absence of a compound of the invention. The formation or development of a biofilm can be inhibited by a compound of the invention by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more compared to the formation or development of a biofilm that is not exposed to a compound of the invention.

Sensitize: The terms "sensitize" or "sensitizing" as used herein mean making a biofilm or microorganisms within a biofilm more susceptible to an antimicrobial agent. The sensitizing effect of a compound of the invention, on a biofilm or microorganisms within the biofilm can be measured as the difference in the susceptibility of the biofilm or microorganisms (as measured by, for example, microbial growth or biomass of the biofilm) to a second antimicrobial agent with and without administration of the compound. The sensitivity of a sensitized biofilm or microorganism (i.e. for example, a biofilm or microorganism exposed to an agent such as a compound of the invention) to an antimicrobial agent can be increased by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500% or more compared to the sensitivity of an unsensitized biofilm or microorganism (i.e. a biofilm or microorganism not exposed to the agent). In some embodiments sensitizing effect of a compound of the invention on a biofilm or microorganisms within the biofilm can be measured by the difference in Minimum Inhibitory Concentration (MIC) of a second antimicrobial administered either in combination with a compound of the invention, or alone. For example, in some embodiments the MIC of a combination of a compound of the invention and the second antimicrobial is at least 10% lower than the MIC of the second antimicrobial administered alone; such as at least 20% lower, at least 30% lower, at least 40% lower, at least 50% lower, at least 60% lower, at least 70% lower, at least 80% lower, at least 90% lower, at least 95% lower, at least 99% lower, or at least 99.9% lower than the MIC of the second antimicrobial administered alone. The sensitization of a microorganism may also occur outside of a biofilm.

Surface: The term "surface" as used herein includes both biological surfaces and non-biological surfaces. Biological surfaces typically include surfaces both internal (such as organs, tissues, cells, bones and membranes) and external (such as skin, hair, epidermal appendages, seeds, plant foliage) to an organism. Biological surfaces also include other natural surfaces such as wood or fibre. A non-biological surface may be any artificial surface of any composition that supports the establishment and development of a biofilm.

Such surfaces may be present in industrial plants and equipment, and include medical and surgical equipment and medical devices, both implantable and non-implantable. Further, for the purposes of the present disclosure, a surface may be porous (such as a membrane) or non-porous, and may be rigid or flexible.

5

Infection, disease or disorder caused by a biofilm / infection, disease or disorder caused by or associated with a microbial persister cell: The term "Infection, disease or disorder caused by a biofilm" as used herein is used to describe conditions, diseases and disorders associated with, characterised by, or caused by biofilms and biofilm-forming microorganisms. Similarly, the term "Infection, disease or disorder caused by or associated with a microbial persister cell" as used herein is used to describe conditions, diseases and disorders associated with, characterised by, or caused by microbial persister cells. For example, a variety of microbial infections are known to be associated with biofilm formation and/or persister cells, such as cellulitis, impetigo, mastitis, otitis media, bacterial endocarditis, sepsis, toxic shock syndrome, urinary tract infections, pulmonary infections (including pulmonary infection in patients with cystic fibrosis), pneumonia, dental plaque, dental caries, periodontitis, bacterial prostatitis and infections associated with surgical procedures or burns. For example, *S. aureus* and *S. epidermidis* cause or are associated with cellulitis, impetigo, mastitis, otitis media, bacterial endocarditis, sepsis, toxic shock syndrome, urinary tract infections, pulmonary infections (including pulmonary infection in patients with cystic fibrosis), pneumonia, dental plaque, dental caries and infections associated with surgical procedures or burns. In other examples, *K. pneumoniae* can cause or be associated with pneumonia, sepsis, community-acquired pyogenic liver abscess (PLA), urinary tract infection, and infections associated with surgical procedures or burns. In further examples, *A. baumannii* can cause or be associated with bacteremia, pneumonia, meningitis, urinary tract infection, and infections associated with wounds. In still further examples, *P. aeruginosa* can cause or be associated with respiratory tract infections (including pneumonia), skin infections, urinary tract infections, bacteremia, infection of the ear (including otitis media, otitis externa and otitis interna), endocarditis and bone and joint infections such as osteomyelitis. *Candida* spp. such as *C. albicans*, *Cryptococcus* spp. such as *C. neoformans*, as well as other fungi such as *Trichosporon* spp., *Malassezia* spp., *Blastoschizomyces* spp., *Coccidioides* spp. and *Saccharomyces* spp. (e.g. *S. cerevisiae*) may cause or be associated with infections related to the implantation or use of medical or surgical devices, such as catheterization or implantation of heart valves.

Persister cell(s): The term “persister cell(s)” as used herein pertains to metabolic variants of wild type microbial cells that are phenotypically characterized by their slow growth rate, which is typically 30%, 25%, 20%, 15%, 10%, 5% or less of the growth rate of the wild-type counterpart. In some embodiments, the persister cells are dormant and have, for example, no detectable cell division in a 24 hour period. Further, persister cells typically form colonies that are approximately 30%, 25%, 20%, 15%, 10%, 5% or less of the size of the colonies formed by their wild-type counterparts. Reference to persister cells includes reference to persister cells of any microbial genera or species, including, but not limited to, bacterial and lower eukaryotic, such as fungal, including yeast, persister cells. In some examples, the persister cell is a Gram negative bacterium. In some examples, the persister cell is a Gram positive bacterium. Exemplary persister cells include, but are not limited to, those of *Staphylococcus* spp., such as *S. aureus*, *S. epidermidis*, and *S. capitis*; *Pseudomonas* spp. such as *P. aeruginosa*; *Burkholderia* spp. such as *B. cepacia* and *B. pseudomallei*; *Salmonella* serovars, including *Salmonella* Typhi; *Vibrio* spp. such as *V. cholerae*; *Shigella* spp.; *Brucella* spp. such as *B. melitensis*; *Escherichia* spp. such as *E. coli*; *Lactobacillus* spp. such as *L. acidophilus*; *Serratia* spp. such as *S. marcescens*; *Neisseria* spp. such as *N. gonorrhoeae*, as well as *Candida* spp., such as *C. albicans*.

C₁₋₆ alkyl: The term “C₁₋₆ alkyl” as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated hydrocarbon compound having from 1 to 6 carbon atoms.

Examples of saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄), pentyl (C₅) and hexyl (C₆).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), n-propyl (C₃), n-butyl (C₄), n-pentyl (C₅) and n-hexyl (C₆).

Examples of saturated branched alkyl groups include iso-propyl (C₃), iso-butyl (C₄), sec-butyl (C₄), tert-butyl (C₄), iso-pentyl (C₅), neopentyl (C₅), iso-hexyl (C₆) and neohexyl (C₆).

C₂₋₆ alkenyl: The term “C₂₋₆ alkenyl” as used herein, pertains to a C₂₋₆ alkyl group having one or more carbon-carbon double bonds. Examples of unsaturated alkenyl groups

include, but are not limited to, ethenyl (vinyl, $-\text{CH}=\text{CH}_2$), 1-propenyl ($-\text{CH}=\text{CH}-\text{CH}_3$), 2-propenyl (allyl, $-\text{CH}-\text{CH}=\text{CH}_2$) and isopropenyl (1-methylvinyl, $-\text{C}(\text{CH}_3)=\text{CH}_2$).

5 C_{2-6} alkynyl: The term " C_{2-6} alkynyl" as used herein, pertains to a C_{2-6} alkyl group having one or more carbon-carbon triple bonds. Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl ($-\text{C}\equiv\text{CH}$) and 2-propynyl (propargyl, $-\text{CH}_2-\text{C}\equiv\text{CH}$).

10 C_{3-6} cycloalkyl: the term " C_{3-6} cycloalkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated cyclic core having 3, 4, 5 or 6 atom in the cyclic core all of which are carbon atoms. Examples of C_{3-6} cycloalkyl include, but are not limited to, cyclopropyl, cyclohexyl and cyclopentyl.

15 C_{5-6} cycloalkenyl: The term " C_{5-6} cycloalkenyl" as used herein, pertains to a C_{3-6} cycloalkyl group having one or more carbon-carbon double bonds.

20 C_{4-6} heterocycloalkyl: The term " C_{4-6} heterocycloalkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 4 to 6 ring atoms, of which from 1 to 3 are ring heteroatoms selected from O, S and N. In this context, the prefixes denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms

Examples of monocyclic heterocycloalkyl groups include, but are not limited to, those derived from:

25 N_1 : azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6);
 O_1 : oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6);
30 S_1 : thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6);
 O_2 : dioxolane (C_5), dioxane (C_6);
 N_2 : imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine (C₆);

N₁S₁: thiazoline (C₅), thiazolidine (C₅), thiomorpholine (C₆);

5 N₂O₁: oxadiazine (C₆);

O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,

N₁O₁S₁: oxathiazine (C₆).

10 C₅₋₆ heterocycloalkenyl: The term "C₅₋₆ heterocycloalkenyl" as used herein, pertains to a C₅₋₆ heterocycloalkyl group having one or more carbon-carbon or carbon-nitrogen double bonds.

15 Heterobicycyl: The term "heterobicycyl" as used herein, pertains to a bicyclic ring, wherein 1, 2, or 3 ring carbons are replaced with a heteroatom selected from the group consisting of O, S and N. In some embodiments, one of the rings is aromatic. The bicyclic rings may be spiro or fused. Examples of a heterobicyclic group include, but are not limited to, 2,5-diaza-bicyclo[2.2.1]hept-2-yl, 7-aza-bicyclo[2.2.1]hept-7-yl, 1,3-dihydro-isoindolyl, 3,4-dihydro-1*H*-isoquinolyl, octahydro-cyclopenta[c]pyrrolyl and the like

20 C₅₋₆ heteroaryl: the term C₅₋₆ heteroaryl as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of an aromatic structure having between one and three atoms that are not carbon forming part of said ring. Wherein, those atoms that are not carbon can be chosen independently from the list nitrogen, oxygen and sulphur.

25 Examples of C₅₋₆ heteroaryl groups include, but are not limited to, groups derived from:

N₁: pyridine (C₆);

N₁O₁: oxazole (C₅), isoxazole (C₅);

N₂O₁: oxadiazole (furazan) (C₅);

30 N₂S₁: thiadiazole (C₅)

N₂: imidazole (1,3-diazole) (C₅), pyrazole (1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆), pyrimidine (1,3-diazine) (C₆) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C₆);

N₃: triazole (C₅).

35 Further embodiments

In some embodiments, P^x is P1.

In some embodiments, R^{P1} is methyl. In other embodiments, R^{P1} is ethyl.

In some embodiments, R^{P2} is methyl. In other embodiments, R^{P2} is ethyl.

5 In some embodiments, both R^{P1} and R^{P2} are methyl. In other embodiments, both R^{P1} and R^{P2} are ethyl. In further embodiments, R^{P1} is methyl and R^{P2} is ethyl.

In some embodiments, R^{P1} is isopropyl. In some embodiments, R^{P1} is phenyl. In some embodiments, both R^{P1} and R^{P2} are isopropyl. In some embodiments, both R^{P1} and R^{P2} are phenyl.

10

In some embodiments, R^{P1} is methyl, R^{P2} is phenyl and R^{P3} is selected from methyl and phenyl.

In some embodiments, R^{P3} is methyl. In other embodiments, R^{P3} is ethyl.

15

In some embodiments, R^{P3} is isopropyl. In some embodiments, R^{P3} is t-butyl. In some embodiments, R^{P3} is cyclopentyl. In some embodiments, R^{P3} is phenyl.

In some embodiments, P^X is PEt_3 .

20 In some embodiments, P^X is PEt_2Me .

In some embodiments, P^X is $PEtMe_2$.

In some embodiments, P^X is PMe_3 .

In some embodiments, P^X is $P(Ph)_3$.

In some embodiments, P^X is $P(i-Pr)_3$.

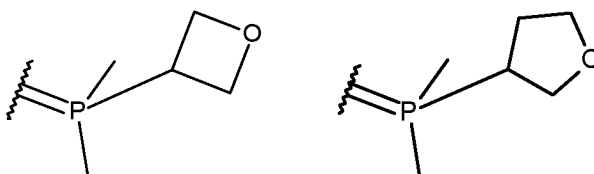
25 In some embodiments, P^X is $P(Me)(Ph)_2$.

In some embodiments, P^X is $P(Ph)(Me)_2$.

In some embodiments, R^{P3} is a 4-membered or 5-membered heterocycloalkyl group linked to phosphorus via a carbon atom in the ring, including a single heteroatom

30

independently selected from N, O and S. In these embodiments, R^{P3} may be selected from azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl and thiolanyl. In some of these embodiments, R^{P3} may be oxetanyl or tetrahydrofuranyl.



In some embodiments, P^X is:

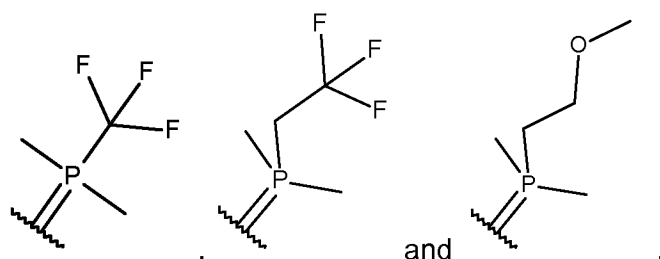
or

.

In some embodiments, R^{P3} is selected from the group consisting of $-CF_3$, $-CH_2CF_3$, $-CH_2CF_2H$ and $-CH_2CH_2OR^{PB}$. In some of these embodiments, R^{PB} may be a linear or

5 branched C_{1-6} alkyl, e.g. methyl.

In some embodiments, P^X is selected from:



and

.

10 In some embodiments, R^{P3} is selected from the group consisting of $-CH_2Q$ and $-(CH_2)_2Q$. In some of these embodiments, R^{P3} is $-CH_2Q$. In other of these embodiments, R^{P3} is $-(CH_2)_2Q$.

In any of these embodiments, Q is a C_{5-6} heteroaryl group, optionally substituted with one

15 or more groups R^{PA} . In some of these embodiments, Q may be unsubstituted. In other of these embodiments, Q may be substituted, and in particular, if Q comprises a N ring atom, this may be substituted by a methyl group.

In some embodiments, Q is independently selected from



and

20

wherein

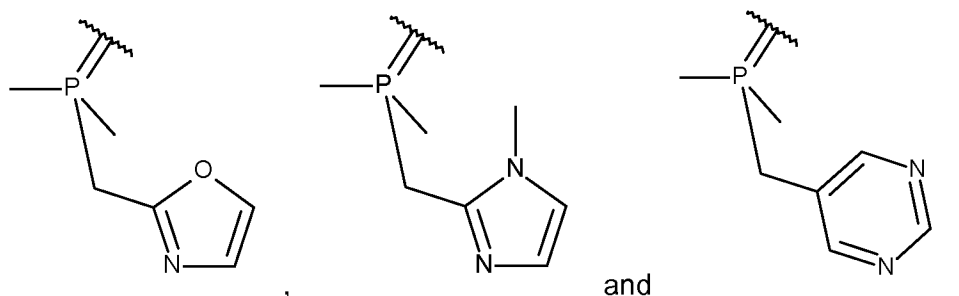
Q^1 is independently selected from O, S and NR^{PE} ;

each of Q^2 to Q^4 is independently selected from N and CR^{PA} ;

two of Q^5 to Q^9 is selected from CR^{PA} , one other of Q^5 to Q^9 is selected from N and the remainder are selected from N, CH and CR^{PA} .

In some embodiments, P^X is selected from:

5



In some embodiments, P^X is $P2$.

10

In some embodiments, R^{P4} is methyl. In other embodiments, R^{P4} is ethyl.

In some embodiments, m is 1. In other embodiments, m is 2. In further embodiments, m is 3.

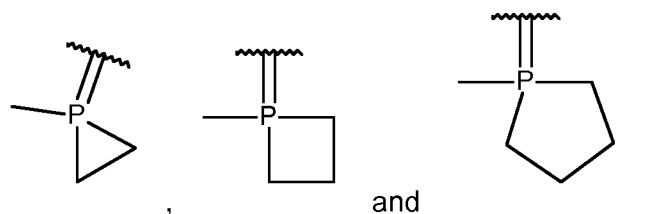
15

In some embodiments, the ring in $P2$ is not substituted. In other embodiments, there is one R^M substituent on the ring in $P2$. In further embodiments, there are two R^M substituents on the ring in $P2$.

20

In some embodiments, R^M is R^{PC} and R^{PC} may be methyl. In other embodiments, R^M is OH. In further embodiments, R^{PC} is OMe.

In some embodiments, P^X is selected from:



25

In some embodiments, P^X is $P3$.

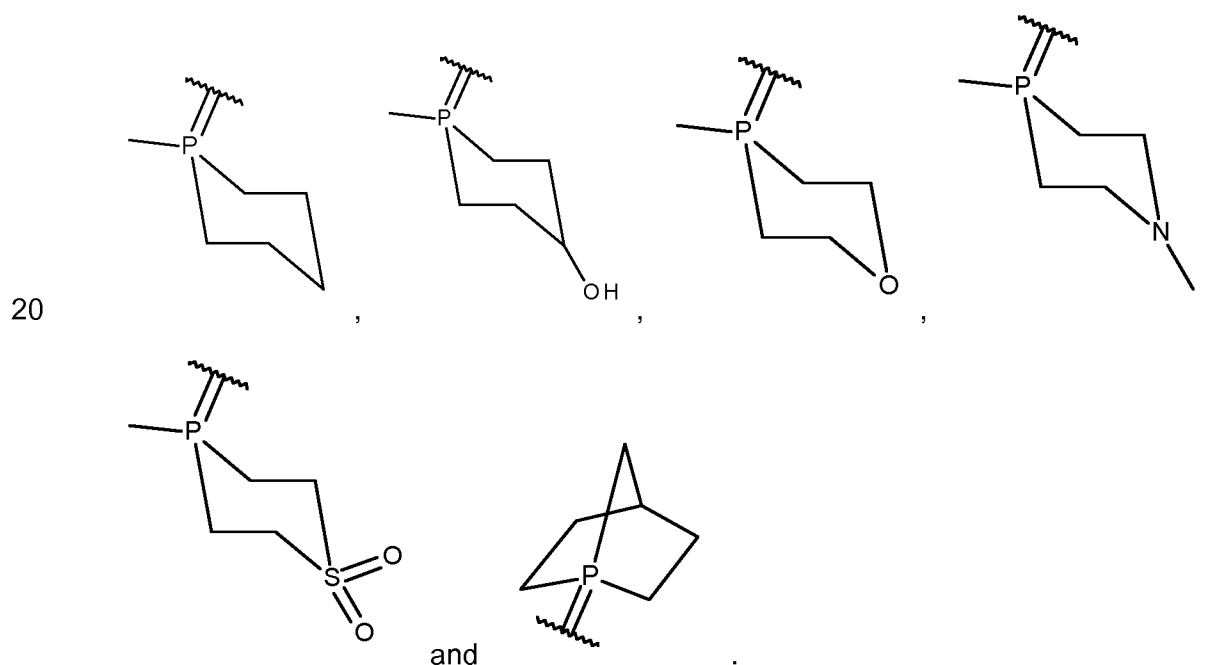
In some embodiments, $-L^B$ is methylene. In other embodiments, $-L^B$ is ethylene.

When $-L^B$ is present, R^{P4} is absent and R^1 is selected from N, CH and CR^{PC} . In some of these embodiments, R^1 is N. In other of these embodiments, R^1 is CH. In further of these
 5 embodiments, R^1 is CR^{PC} . In some embodiments, R^{PC} is unsubstituted C_{1-3} alkyl, e.g. methyl.

When L^B is absent, in some embodiments R^1 is selected from the group consisting of O,
 10 NR^Z , and SO_2 . In these embodiments, R^Z may be selected from H and C_{1-3} alkyl e.g. methyl.

When L^B is absent, in some embodiments R^1 is selected from the group consisting of CH_2 ,
 CHF, CF_2 and CHR^{PC} . In some of these embodiments, R^1 is CH_2 . In other of these
 15 embodiments, R^1 is CHF. In other of these embodiments, R^1 is CF_2 . In further of these
 embodiments, R^1 is CHR^{PC} . In some embodiments, R^{PC} is unsubstituted C_{1-3} alkyl, e.g. methyl.

In some embodiments, P^X is selected from:



R^A, R^B

In some embodiments R^A is linear or branched C_{1-6} alkyl optionally substituted with one or more groups R^{AL} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

5 In some embodiments R^A is linear or branched C_{1-6} alkyl optionally substituted with one or more groups R^{AL} ; and R^B is selected from $-CO(C_{1-6}alkyl)$ and $-SO_2R^{A2}$.

In some embodiments R^A is unsubstituted linear or branched C_{1-6} alkyl; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

10 In some embodiments R^A is unsubstituted linear or branched C_{1-6} alkyl; and R^B is selected from $-CO(C_{1-6}alkyl)$ and $-SO_2R^{A2}$.

In the above embodiments, R^{AL} may be selected from

15 $-F$, $-CN$
 $-OH$, $-OR^{A2}$,
 $-NH_2$, $-NHR^{A2}$, $-NR^{A2}_2$,
 $-NHCOH$, $-NHCOR^{A2}$, $-NR^{A2}COH$ and $-NR^{A2}COR^{A2}$.

In the above embodiments, R^{AL} may be selected from

20 $-F$,
 $-OH$, $-OR^{A2}$,
 $-NH_2$, $-NHR^{A2}$ and $-NR^{A2}_2$.

25 In some embodiments R^A is C_{5-6} heteroaryl, optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

In some embodiments, R^A is C_5 heteroaryl, optionally substituted with one or more groups R^{A1} (e.g. C_{1-6} alkyl, such as methyl); and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

30 In some embodiments R^A is C_6 heteroaryl, optionally substituted with one or more groups R^{A1} (e.g. C_{1-6} alkyl, such as methyl); and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

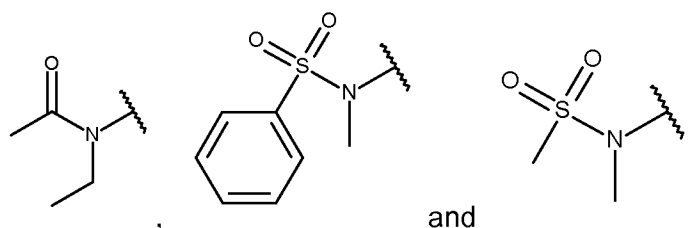
35 In some embodiments R^A is C_{1-3} alkyl substituted by phenyl or C_{5-6} heteroaryl, which groups may optionally be substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

In some embodiments R^A is C_{1-3} alkyl (e.g. methyl) substituted by C_5 heteroaryl which is optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

- 5 In some embodiments R^A is C_{1-3} alkyl (e.g. methyl) substituted by C_6 heteroaryl which is optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

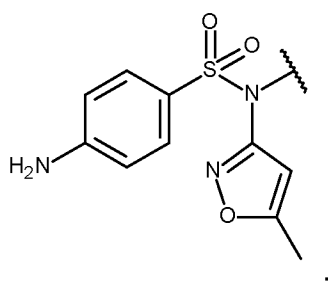
- 10 In some embodiments R^A is C_{1-3} alkyl (e.g. methyl) substituted by phenyl which is optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

In some embodiments, $-NR^A R^B$ is selected from



15

In some embodiments, $-NR^A R^B$ is selected from



$NR^A R^B$

- 20 In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group optionally substituted with one or more groups selected from
 oxo,
 phenyl optionally substituted with one or more groups R^{A1} ,
 R^{A2} , and
 25 R^{A1} .

In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group containing up to two heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; optionally substituted with one or more groups selected from

5 oxo,
 phenyl optionally substituted with one or more groups R^{A1} ,
 R^{A2} , and
 R^{A1} .

10 In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group containing up to two heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; substituted with one or two oxo groups and optionally further substituted with one or more groups selected from
 phenyl optionally substituted with one or more groups R^{A1} , and
15 R^{A1} .

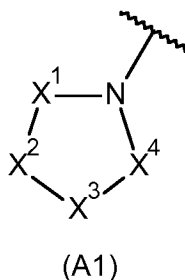
In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group containing one heteroatom in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; substituted with one or two oxo groups and optionally
20 further substituted with one or more groups selected from
 phenyl optionally substituted with one or more groups R^{A1} , and
 R^{A1} .

In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or
25 heterocycloalkenyl group containing one heteroatom in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; substituted with one or two oxo groups and optionally further substituted with one or more groups selected from
 linear or branched C_{1-6} alkyl; and
 phenyl optionally substituted with one or more groups selected from F, Cl, Br, CN,
30 OH, $O(C_{1-6}$ alkyl), COOH and $COO(C_{1-6}$ alkyl).

In some embodiments, $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group containing one heteroatom in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; substituted with one or two oxo groups and optionally
35 further substituted with one or more groups selected from
 C_{1-3} alkyl; and

phenyl optionally substituted with one or more groups selected from F, Cl, OH and O(C₁₋₆alkyl).

In some embodiments, -NR^AR^B is the group (A1)



wherein

X¹ is selected from C=O and CR^{4A}R^{4B};

X² is selected from O, CR^{4A}R^{4B} and NR^X; and

10 one of X³ and X⁴ is selected from C=O, CR^{4A}R^{4B} and SO₂, with the other group of X³ and X⁴ being selected from CR^{4A}R^{4B};

wherein R^X is selected from -H and -R^{A5};

each R^{4A} and R^{4B} is independently selected from

-H,

15 linear or branched C₁₋₄alkyl optionally substituted with one or more groups R^{AL},
phenyl, optionally substituted with one or more groups R^{A1},

C₅₋₆heteroaryl optionally substituted with one or more groups R^{A1},

independently geminal R^{4A} and R^{4B} groups may be joined to form a 5- or

6-membered alicyclic or 5- or 6- membered heteroalicyclic group optionally

20 substituted with one or more groups R^{AL}, and

independently two vicinal R^{4A} groups may be joined to form a 5- or 6-membered

alicyclic, heteroalicyclic, aromatic or heteroaromatic group optionally

substituted with one or more groups R^{A1};

and R^{A5} is selected from the group consisting of

25 linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with
one or more groups R^{AL},

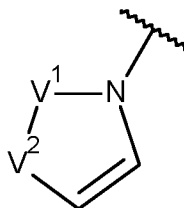
C₃₋₆cycloalkyl or C₄₋₆heterocycloalkyl optionally substituted with one or more
groups R^{AT},

phenyl, optionally substituted with one or more groups R^{A1},

30 C₅₋₆heteroaryl optionally substituted with one or more groups R^{A1}, or

except when each of R^{P1} to R^{P3} is selected from ethyl, R^{A5} may be joined to a vicinal R^{4A} or R^{4B} group to form a 5- or 6-membered heterocyclic or heteroaromatic group optionally substituted with one or more groups R^{A1} ;

- 5 In some embodiments, $-NR^A R^B$ is the group (A2)



(A2)

wherein

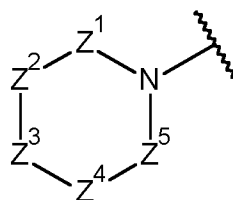
V^1 is selected from $C=O$ and SO_2 ;

- 10 V^2 is selected from O , NR^X and $CR^{4A}R^{4B}$;

with the proviso that when V^1 is SO_2 , V^2 cannot be O ;

wherein R^X , R^{4A} and R^{4B} are as defined above.

In some embodiments, $-NR^A R^B$ is the group (A4)



(A4)

wherein

Z^1 is selected from $C=O$ and $CR^{4A}R^{4B}$;

Z^2 and Z^3 are each independently selected from the group consisting of

- 20 O ,
 $CR^{4A}R^{4B}$, $C=O$ and
 NR^X ,

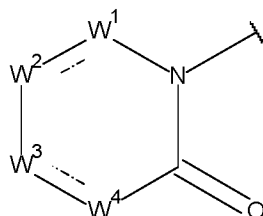
with the proviso that any two adjacent groups of Z^1 to Z^4 cannot both be O , cannot both be $C=O$ and cannot both be NR^X ;

- 25 Z^4 is selected from $CR^{4A}R^{4B}$, and NR^X ;

and Z^5 is selected from $C=O$ and SO_2 ;

with R^{4A} , R^{4B} and R^X being as defined above.

In some embodiments, $-NR^A R^B$ is the group (A5)

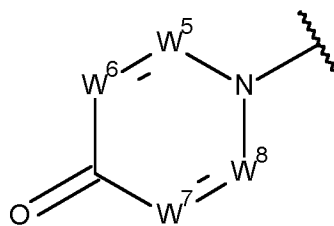


(A5)

wherein

- 5 a dotted line indicates that a bond may be present or absent; and W^1 to W^4 are each independently selected from CH and CR^{A1} .

In some embodiments, $-NR^A R^B$ is the group (A6)

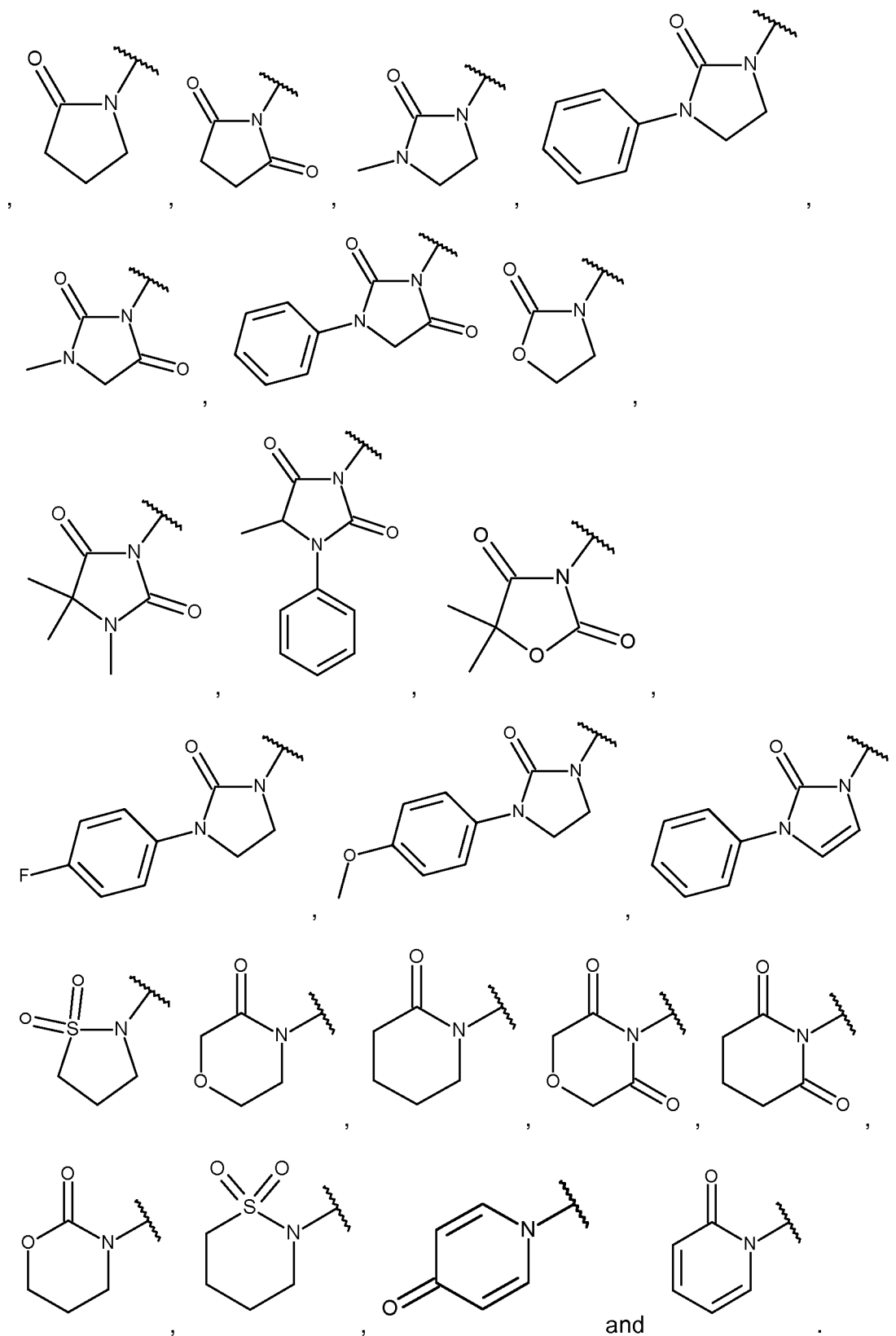


(A6)

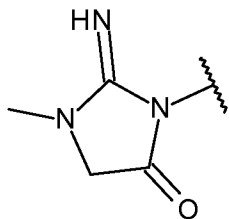
wherein

- 10 W^5 to W^8 are each independently selected from CH and CR^{A1} .

In some embodiments, $-NR^A R^B$ is selected from



In some embodiments, -NR^AR^B is selected from



5 In some embodiments, $-NR^A R^B$ is selected from a 5- or 6-membered heteroaryl group optionally substituted with one or more groups selected from

phenyl optionally substituted with one or more groups R^{A1} ,

R^{A2} , and

R^{A1} .

10

In some embodiments, $-NR^A R^B$ is selected from a 5- or 6-membered heteroaryl group containing up to three heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; optionally substituted with one or more groups selected from

phenyl optionally substituted with one or more groups R^{A1} ,

15

R^{A2} , and

R^{A1} .

In some embodiments, $-NR^A R^B$ is selected from a 5-membered heteroaryl group containing up to three heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$; optionally substituted with one or more groups selected from

20

phenyl optionally substituted with one or more groups R^{A1} ,

R^{A2} , and

R^{A1} .

25 In some embodiments, $-NR^A R^B$ is selected from a 5-membered heteroaryl group containing up to three N atoms in the ring in addition to the N atom of $-NR^A R^B$; optionally substituted with one or more groups R^{A1} .

In some embodiments, $-NR^A R^B$ is selected from a 5-membered heteroaryl group
30 containing one or two heteroatoms in the ring in addition to the N atom of $-NR^A R^B$, the

heteroatoms being N atoms; wherein the heteroaryl group is optionally substituted with one or more groups selected from

linear or branched C₁₋₆alkyl,

F, Cl, Br,

5 -CN,

-CF₃, -CF₂H, -CH₂F,

-OH, -O(C₁₋₆alkyl),

-COOH, -COO(C₁₋₆alkyl) and -CON(C₁₋₆alkyl)₂.

10 In some embodiments, -NR^AR^B is selected from a 5-membered heteroaryl group containing one heteroatom in the ring in addition to the N atom of -NR^AR^B, wherein both heteroatoms are N atoms; and wherein the heteroaryl group is optionally substituted with one or more groups selected from

linear or branched C₁₋₆alkyl,

15 F, Cl, Br,

-CN,

-CF₃, -CF₂H, -CH₂F,

-OH, -O(C₁₋₆alkyl),

-COOH, -COO(C₁₋₆alkyl) and -CON(C₁₋₆alkyl)₂.

20

In some embodiments, -NR^AR^B is selected from a 5-membered heteroaryl group containing two heteroatoms in the ring in addition to the N atom of -NR^AR^B, wherein both heteroatoms are N atoms; and wherein the heteroaryl group is optionally substituted with one or more groups selected from

25 linear or branched C₁₋₆alkyl,

F, Cl, Br,

-CN,

-CF₃, -CF₂H, -CH₂F,

-OH, -O(C₁₋₆alkyl),

30 -COOH, -COO(C₁₋₆alkyl) and -CON(C₁₋₆alkyl)₂.

In some embodiments, -NR^AR^B is selected from a 5-membered heteroaryl group containing one or two heteroatoms in the ring in addition to the N atom of -NR^AR^B, the heteroatoms being N atoms; wherein the heteroaryl group is optionally substituted with

35 one or more groups selected from

linear or branched C₁₋₆alkyl,

- F, Cl, Br,
 -CN,
 -CF₃, -CF₂H, -CH₂F,
 -OH, -O(C₁₋₆alkyl),
 5 -COOH, -COO(C₁₋₆alkyl) and -CON(C₁₋₆alkyl)₂.

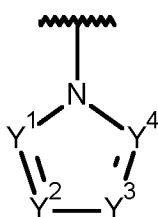
In some embodiments, -NR^AR^B is selected from a 5-membered heteroaryl group containing up to three N atoms in the ring in addition to the N atom of -NR^AR^B; optionally substituted with one or more groups selected from

- 10 linear or branched C₁₋₆alkyl,
 F, Cl, Br,
 -CN
 -CF₃, -CF₂H, -CH₂F,
 -OH, -O(C₁₋₆alkyl),
 15 -COOH and -COO(C₁₋₆alkyl).

In some embodiments, -NR^AR^B is selected from a 5-membered heteroaryl group containing up to three N atoms in the ring in addition to the N atom of -NR^AR^B; optionally substituted with one or more groups selected from

- 20 linear or branched C₁₋₆alkyl,
 -CN
 -CF₃, -CF₂H and -CH₂F.

In some embodiments, -NR^AR^B is the group (A3)



25

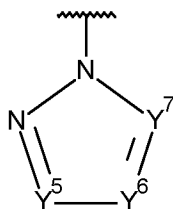
(A3)

wherein

one group from Y¹ to Y⁴ is CR³, another is N and the remainder are independently selected from CR³ and N.

30

In some embodiments, -NR^AR^B is the group (A7)



wherein one of Y^5 , Y^6 and Y^7 is selected from N and CR^{Y1} ; and the other two of Y^5 , Y^6 and Y^7 are each independently selected from CR^{Y1} ; wherein R^{Y1} is selected from

-H;

5 C_{1-6} linear or branched unsubstituted alkyl;

-F, -Cl, -Br,

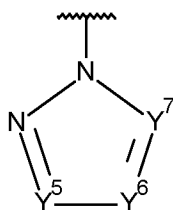
-CN,

-CF₃, -CF₂H, -CH₂F,

-OH, -O(C_{1-6} alkyl),

10 -COOH, -COO(C_{1-6} alkyl) and -CON(C_{1-6} alkyl)₂.

In some embodiments, -NR^AR^B is the group (A7)



wherein one of Y^5 , Y^6 and Y^7 is selected from N and CH; a second of Y^5 , Y^6 and Y^7 is CH
15 and the third of Y^5 , Y^6 and Y^7 is selected from CH and CR^{Y1} ; wherein R^{Y1} is selected from

-H;

C_{1-6} linear or branched unsubstituted alkyl;

-F, -Cl, -Br,

-CN,

20 -CF₃, -CF₂H, -CH₂F,

-OH, -O(C_{1-6} alkyl),

-COOH, -COO(C_{1-6} alkyl) and -CON(C_{1-6} alkyl)₂.

In some embodiments, P^X is (P1); R^{P1} and R^{P2} are each independently selected from
25 methyl and ethyl;

R^{P3} is selected from

methyl, ethyl, n-propyl,

-Q^A, -CH₂Q^A, -(CH₂)₂Q^A,

wherein Q^A is selected from

cyclopropyl,

4- or 5-membered heterocycloalkyl groups containing one or two

5 heteroatoms selected from NR^Z, O and S, and

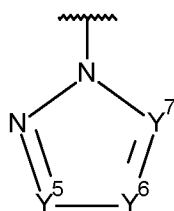
4- or 5-membered cycloalkyl groups;

wherein R^Z is selected from the group consisting of

H, C₁₋₃alkyl, COC₁₋₃alkyl and SO₂C₁₋₃alkyl;

and

10 -NR^AR^B is the group (A7)



wherein one of Y⁵, Y⁶ and Y⁷ is selected from N and CR^{Y1}; and the other two of Y⁵, Y⁶ and Y⁷ are each independently selected from CR^{Y1}; wherein R^{Y1} is selected from

-H;

15 C₁₋₆ linear or branched unsubstituted alkyl;

-F, -Cl, -Br,

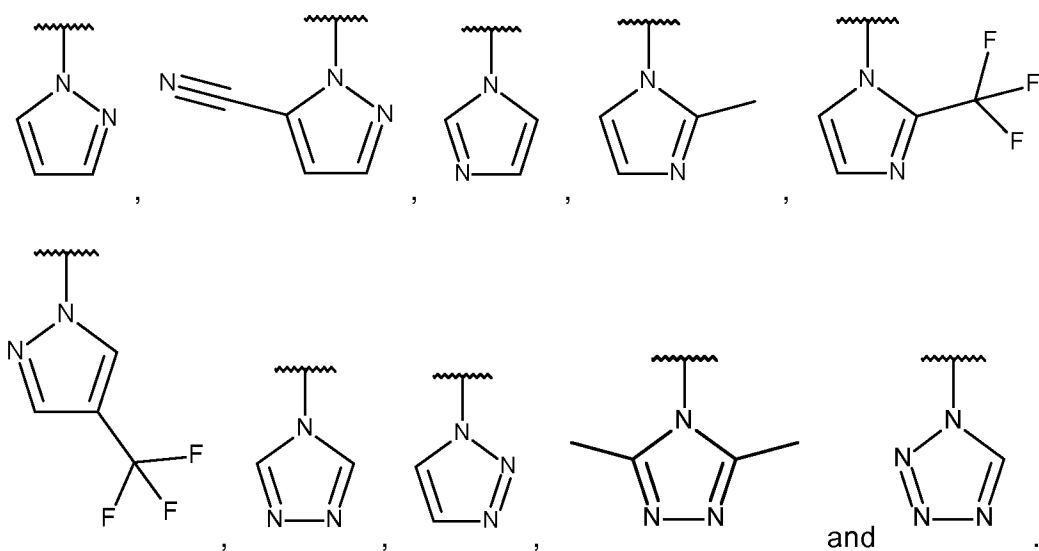
-CN,

-CF₃, -CF₂H, -CH₂F,

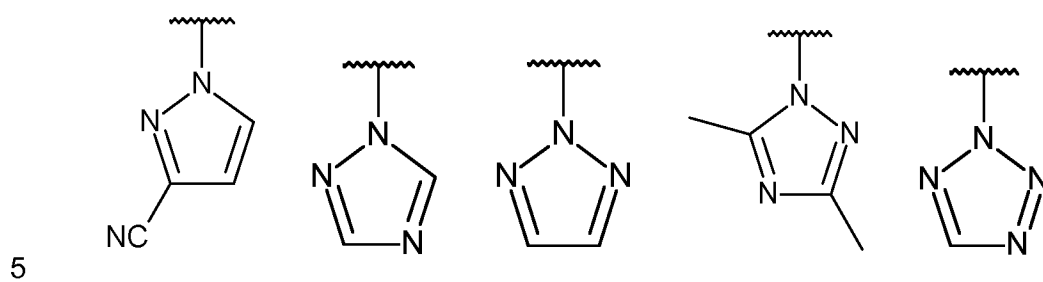
-OH, -O(C₁₋₆alkyl),

20 -COOH, -COO(C₁₋₆alkyl) and -CON(C₁₋₆alkyl)₂.

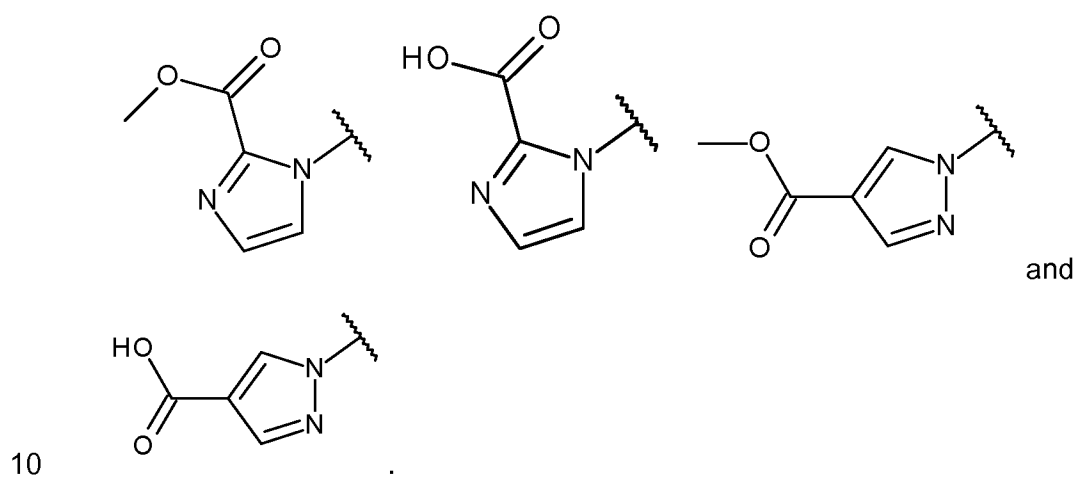
In some embodiments, -NR^AR^B is selected from



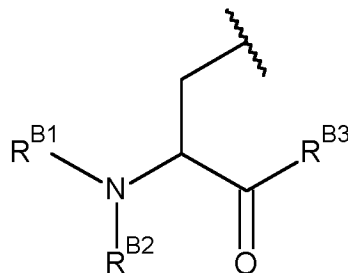
In some embodiments, $-NR^A R^B$ is selected from



In some embodiments, $-NR^A R^B$ is selected from



In some embodiments, $\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is an imidazolyl group, bearing a C substituent which is the group (B1)



(B1)

(i.e. ethyl substituted by COR^{B3} and $\text{NR}^{\text{B1}}\text{R}^{\text{B2}}$) wherein

R^{B1} is selected from the group consisting of

- H,
- $-\text{COR}^{\text{A2}}$, $-\text{CONR}^{\text{A2}}$, $\text{CO}_2\text{R}^{\text{A2}}$, and
- $-\text{SO}_2\text{R}^{\text{A2}}$;

R^{B2} is selected from -H, and linear or branched C_{1-4} alkyl; and

R^{B3} is selected from the group consisting of

- OH, $-\text{OR}^{\text{A2}}$,
- $-\text{NH}_2$, $-\text{NHR}^{\text{A2}}$ and $-\text{NR}^{\text{A2}}_2$.

In some embodiments, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is selected from an 8- to 10-membered heterobicycyl group optionally substituted with one or more groups selected from

- oxo,
- phenyl optionally substituted with one or more groups R^{A1} ,
- R^{A2} and
- R^{A1} .

In some embodiments, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is a 9-membered heterobicycyl group optionally substituted with one or more groups selected from

- oxo,
- phenyl optionally substituted with one or more groups R^{A1} ,
- R^{A2} and
- R^{A1} .

In some embodiments, $-NR^A R^B$ is a 9-membered 5,6 fused heterobicycyl group optionally substituted with one or more groups selected from

oxo,

phenyl optionally substituted with one or more groups R^{A1} ,

5 R^{A2} and

R^{A1} .

Herein, a "5,6" fused ring system indicates that the N of $-NR^A R^B$ lies within a 5-membered ring which is fused to a 6-membered ring.

10

In some embodiments, $-NR^A R^B$ is a 9-membered 5,6 fused heterobicycyl group optionally substituted with one or more groups selected from

oxo,

linear or branched C_{1-6} alkyl,

15 -F, -Cl, -Br,

-CN,

-OH, -O(C_{1-6} alkyl),

-COOH and -COO(C_{1-6} alkyl).

20 In some embodiments, $-NR^A R^B$ is a 9-membered 5,6 fused heterobicycyl group optionally substituted with one or more groups selected from

oxo,

linear or branched C_{1-6} alkyl,

-OH and -O(C_{1-6} alkyl).

25

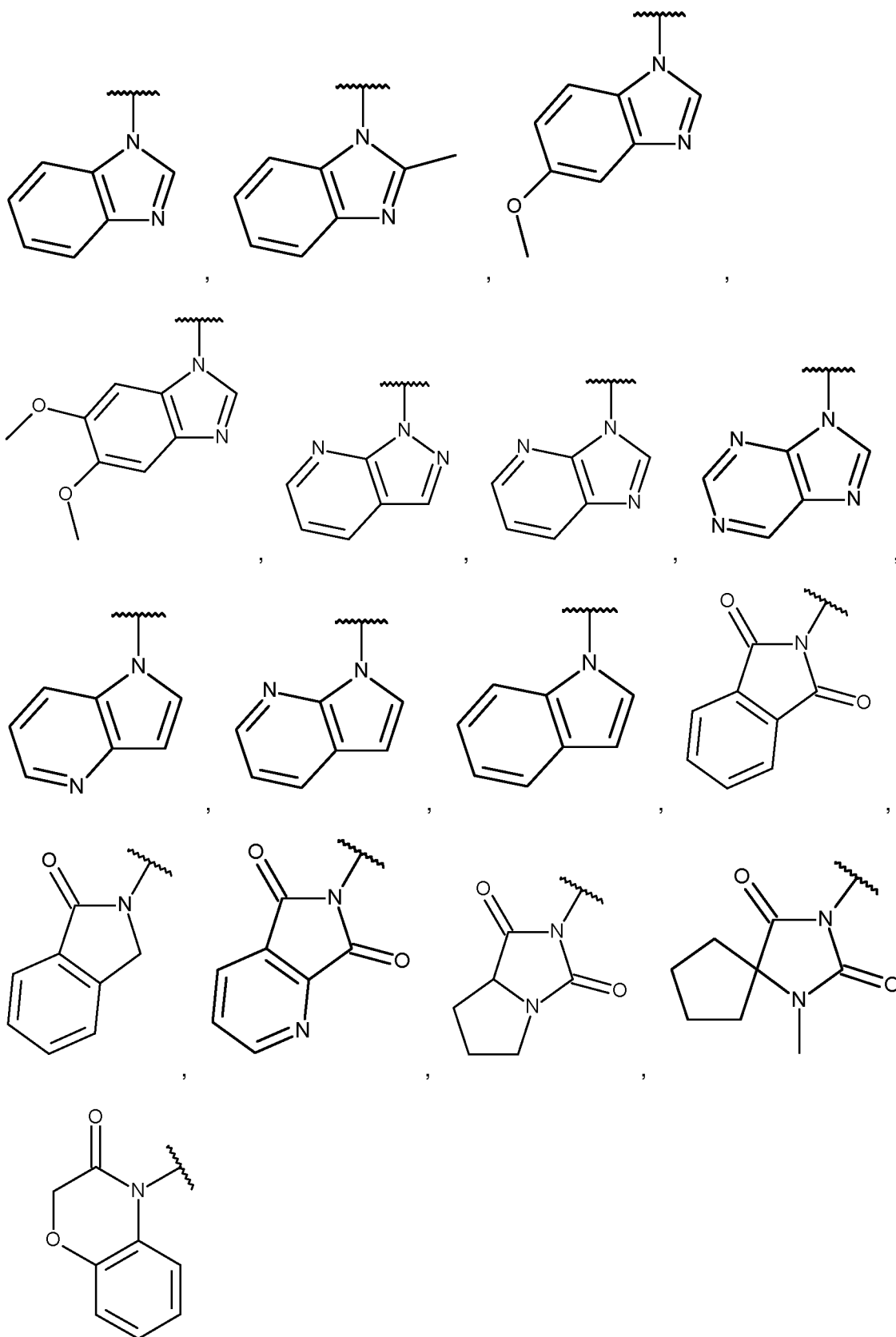
In some embodiments, $-NR^A R^B$ is a 10-membered 6,6 fused heterobicycyl group optionally substituted with one or more groups selected from

oxo, and

R^{A1} .

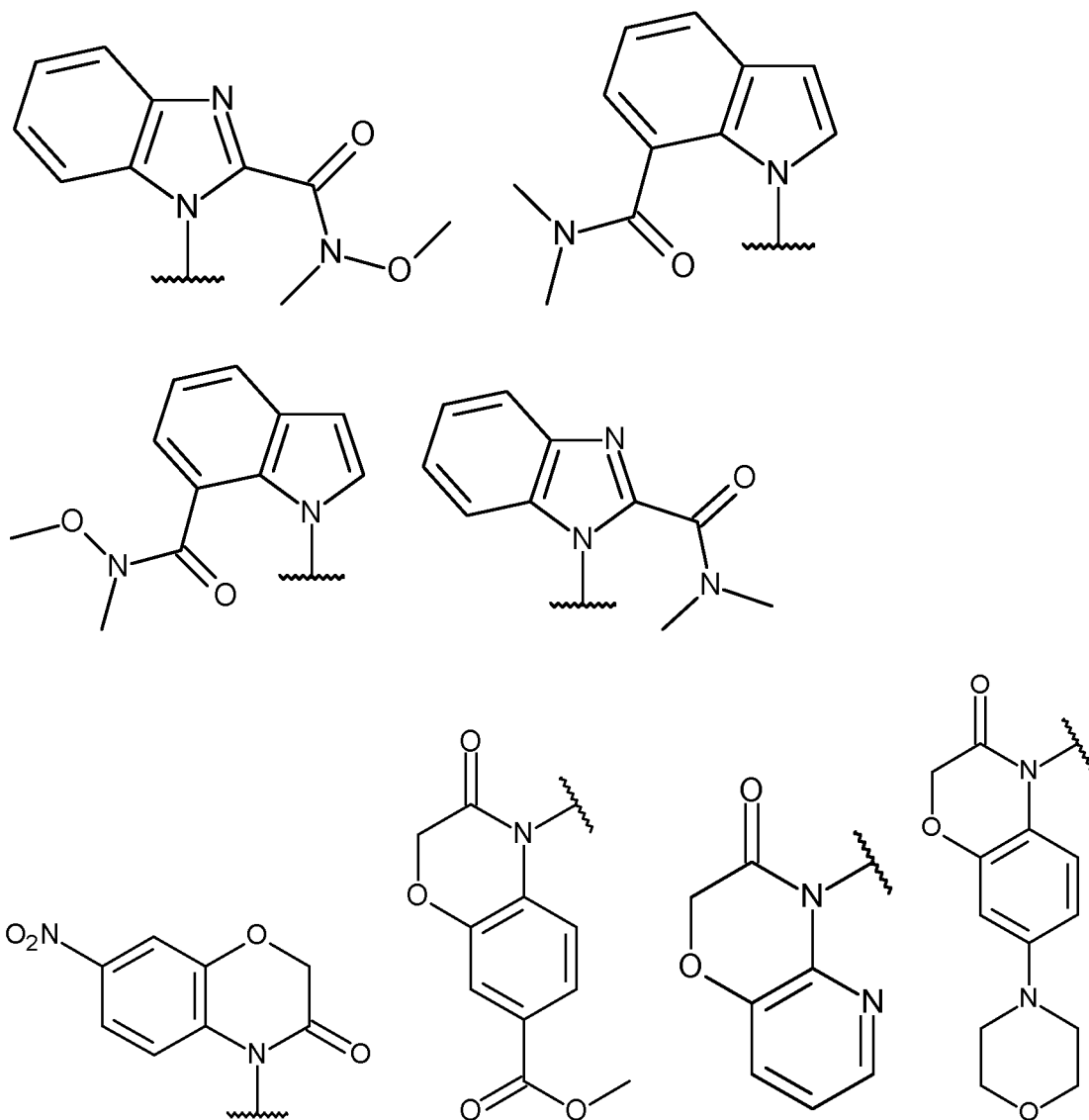
30

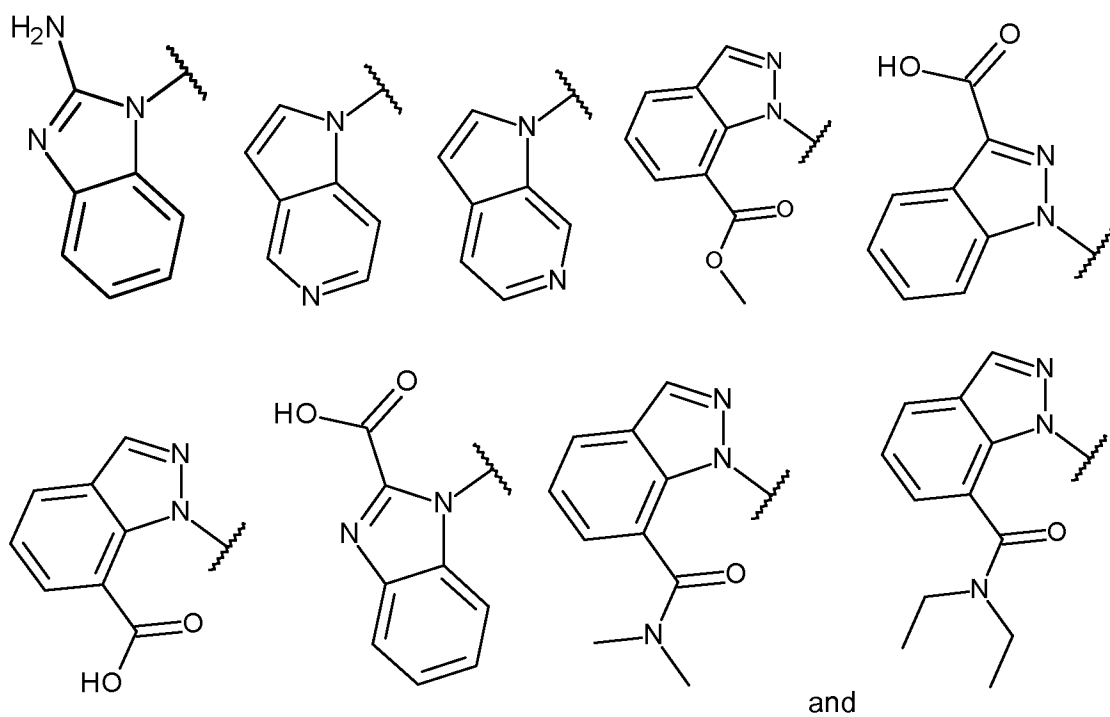
In some embodiments, $-NR^A R^B$ is selected from



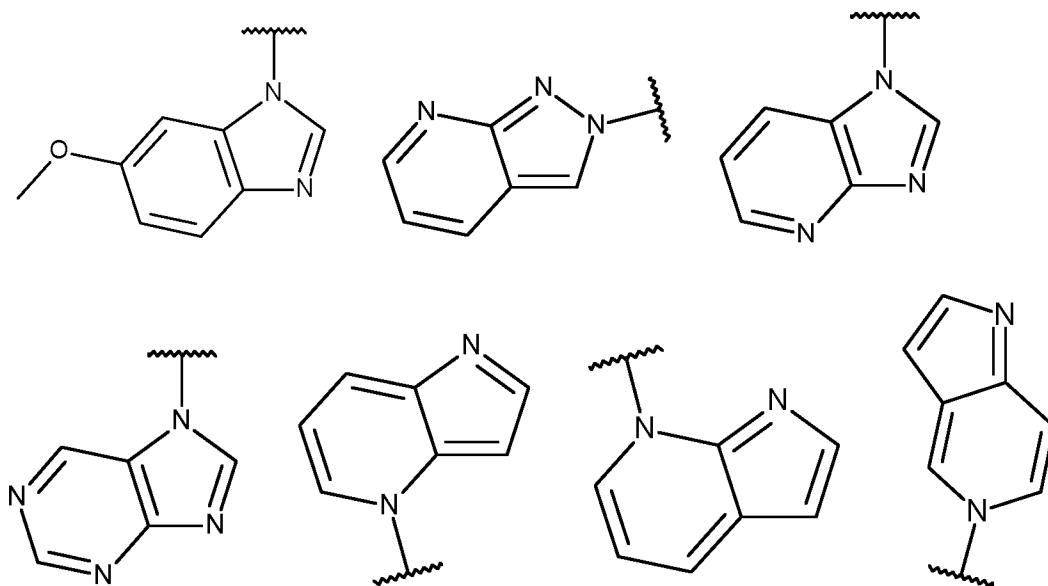
5 and

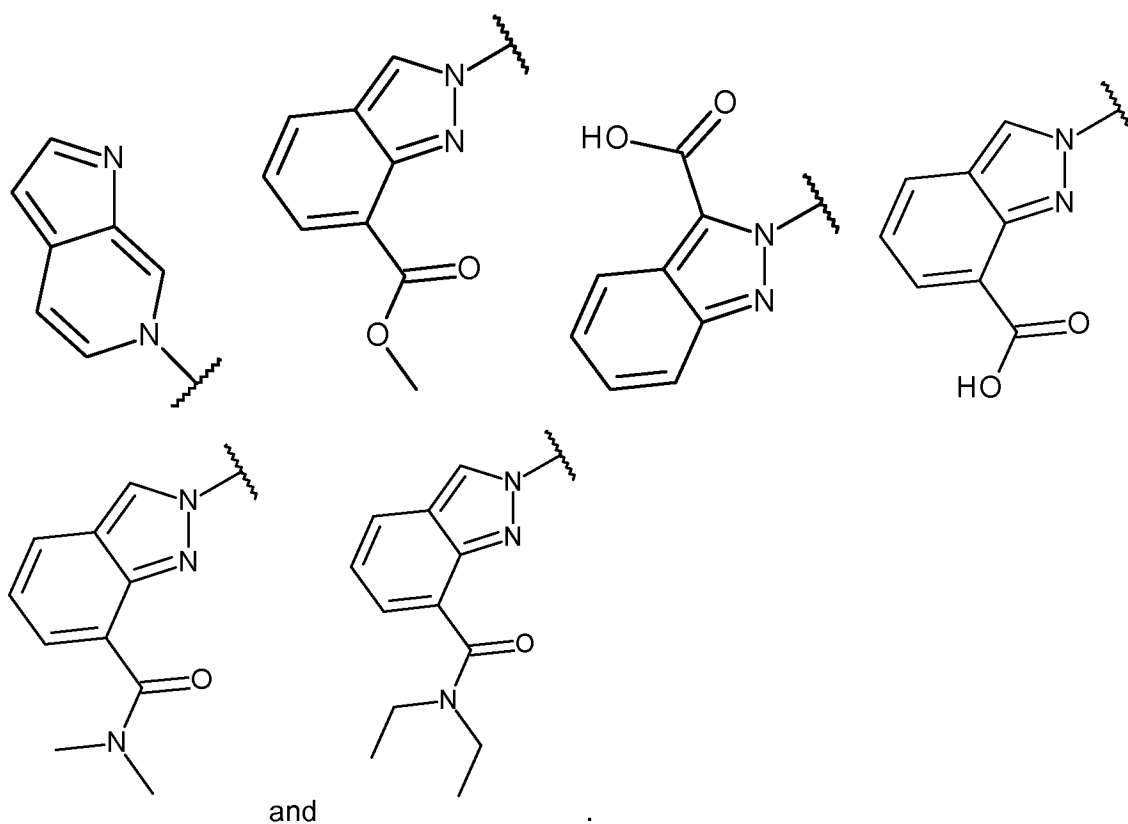
In some embodiments, $-NR^A R^B$ is selected from



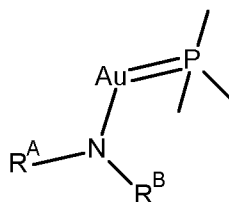


5 In some embodiments, $-NR^A R^B$ is selected from





In some embodiments, the compound is a compound according to formula (Ia)

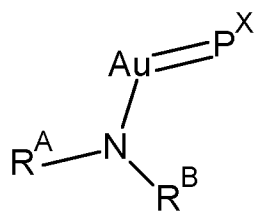


5

Formula (Ia)

wherein R^A and R^B are as defined above.

In some embodiments, the compound is a compound according to formula (Ib)

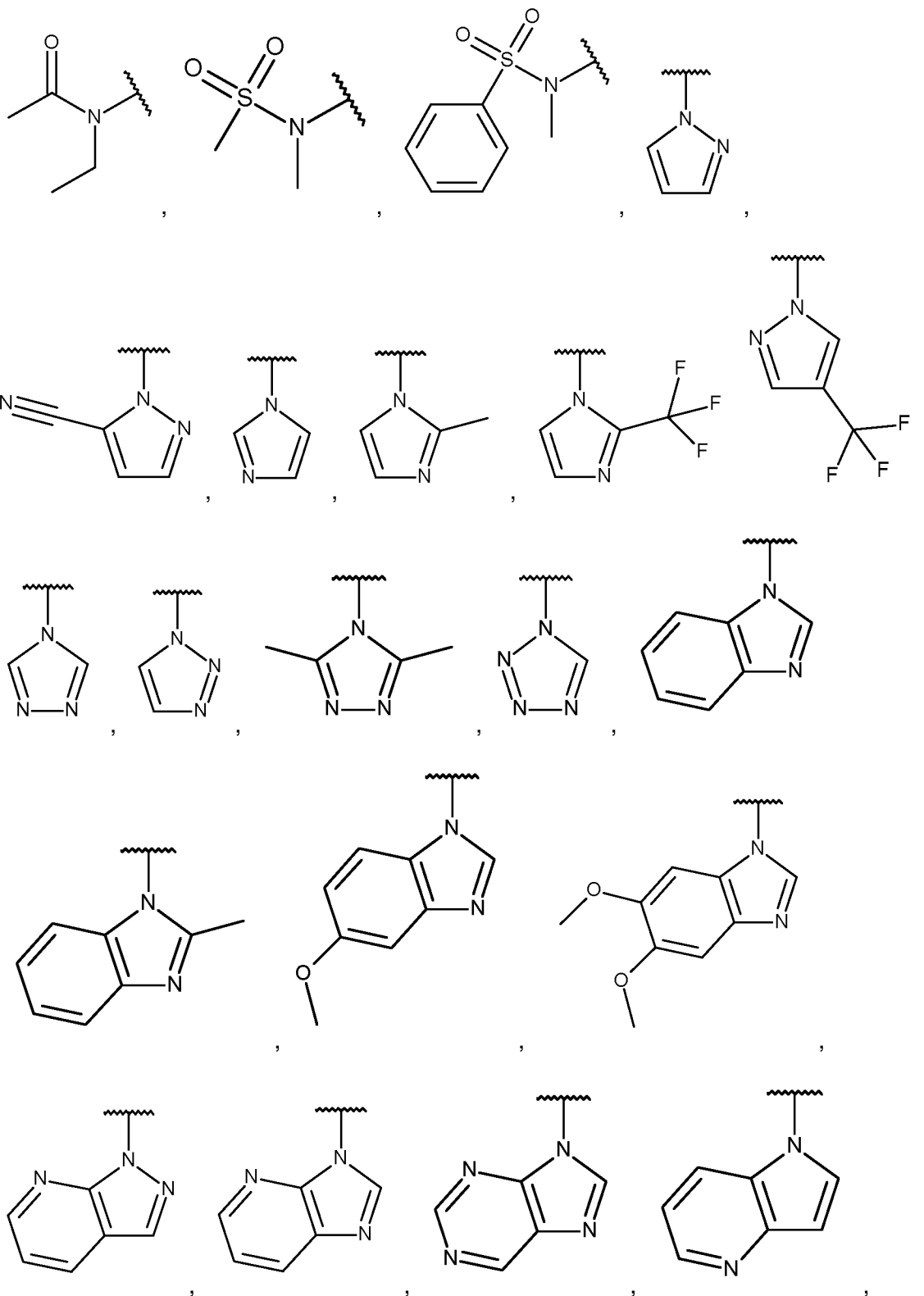


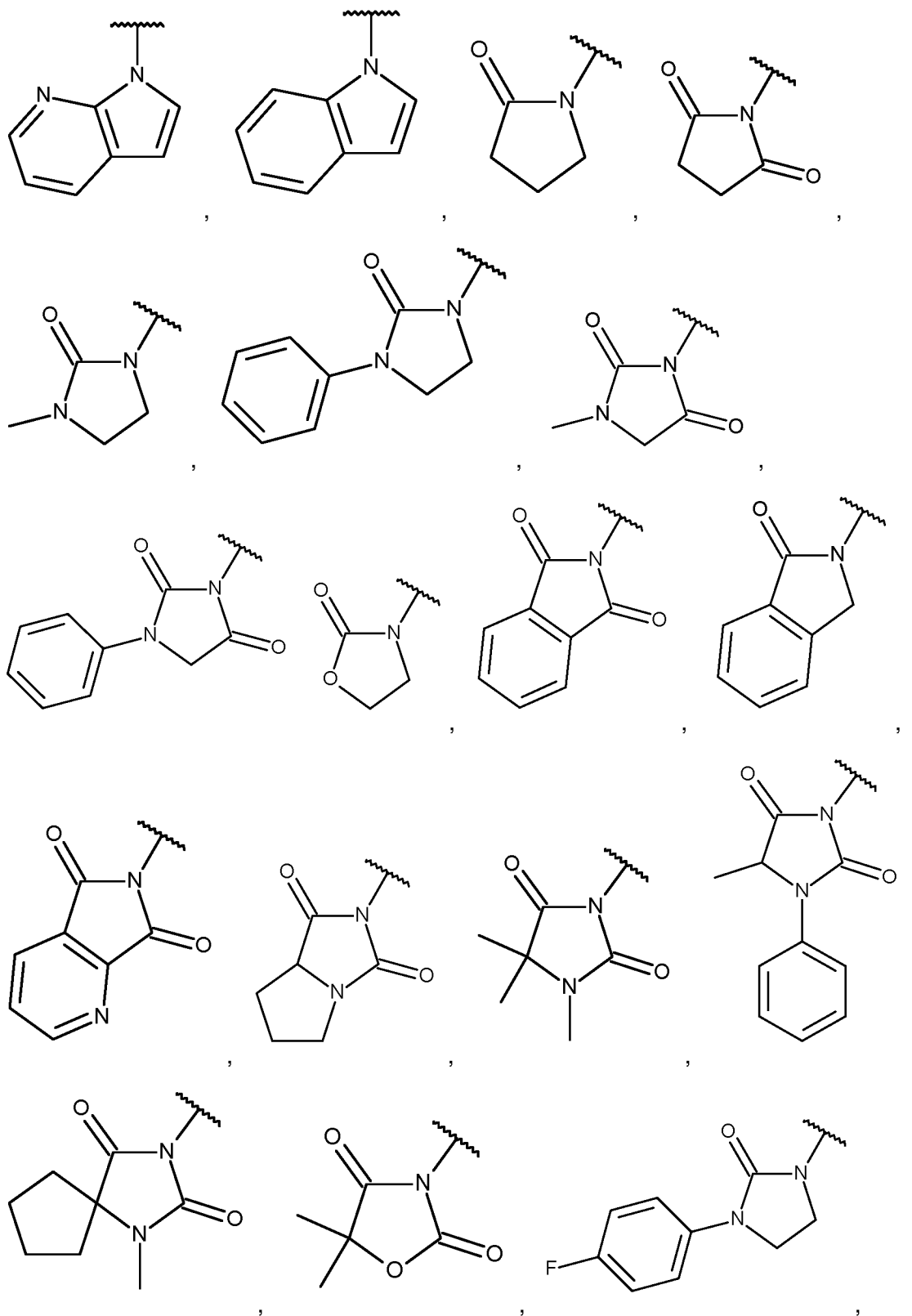
10

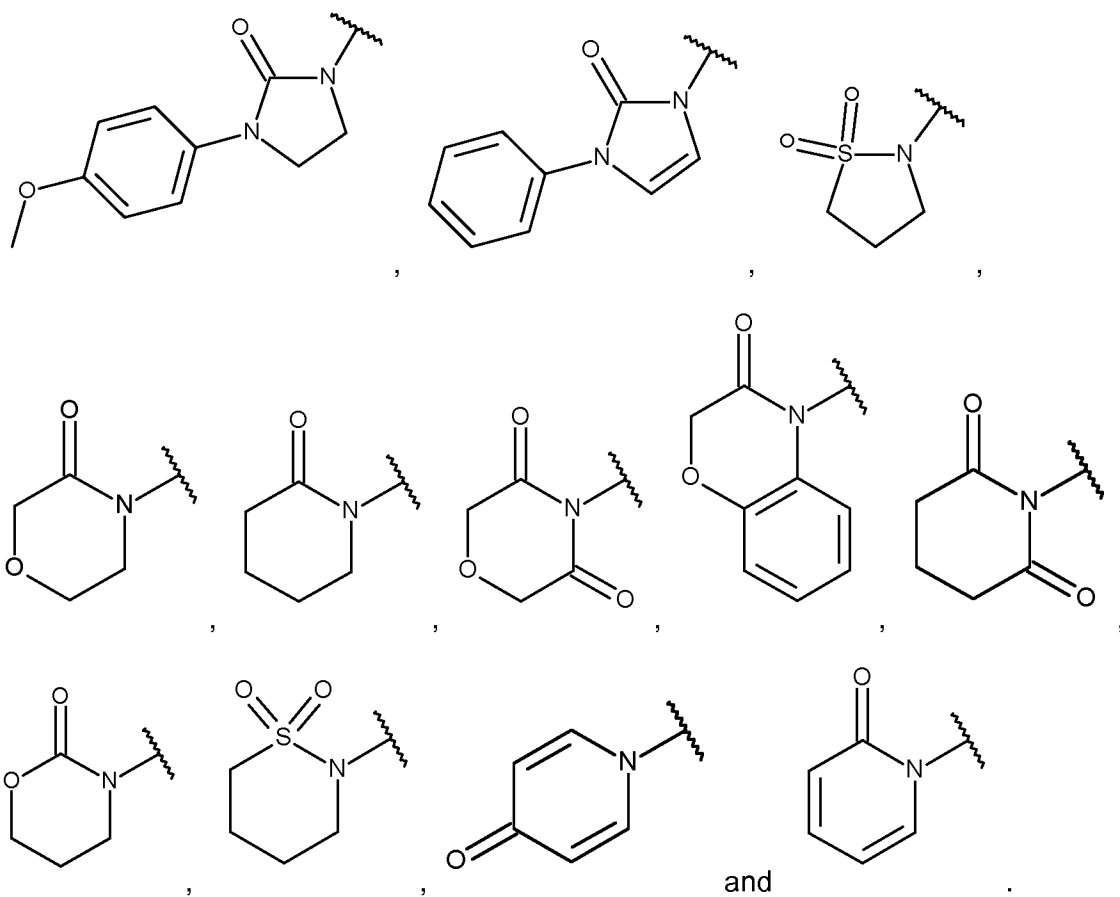
Formula (Ib)

wherein P^X is as defined above;

and $\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is selected from:

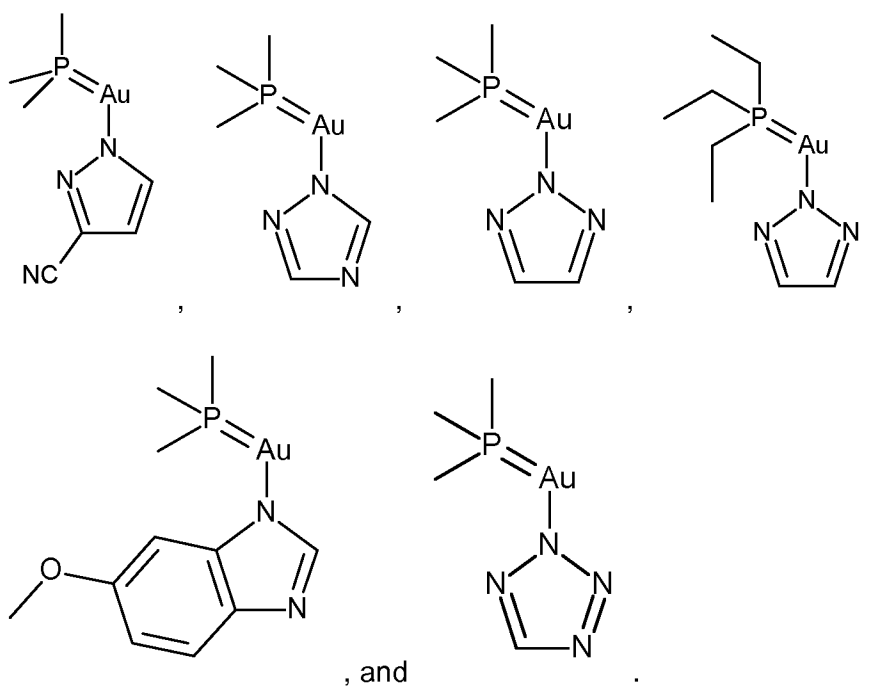






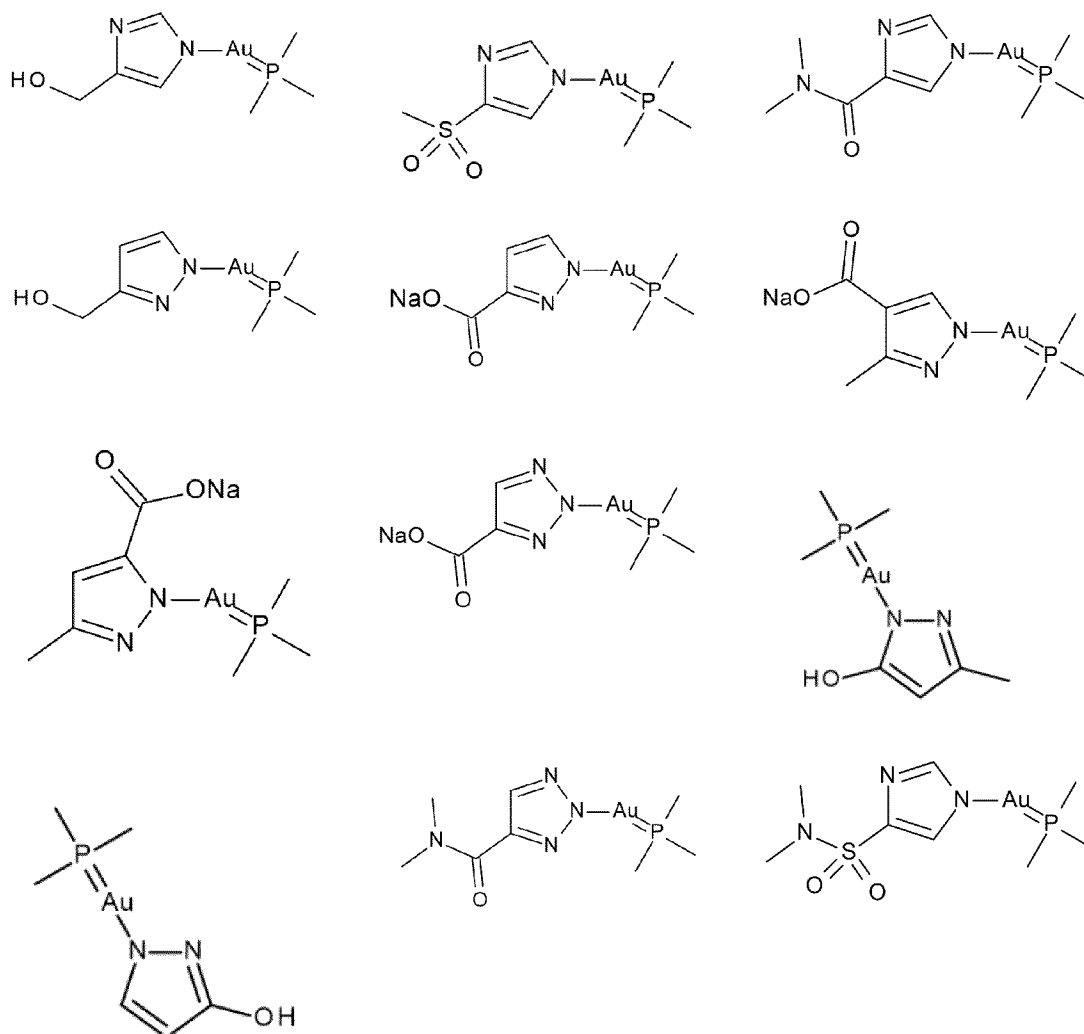
5

In some embodiments, the compound is selected from:



Particular embodiments of the invention are shown in the examples.

5 Further compounds of the invention include:



Bacterial infections

Bacteria that cause infection of humans include, but are not limited to, those set out below in Table 1.

Genus	Important species	Gram negative/positive
<i>Bordetella</i>	<i>Bordetella pertussis</i>	Gram-negative
<i>Borrelia</i>	<i>Borrelia burgdorferi</i>	Gram-negative
<i>Brucella</i>	<i>Brucella abortus</i> <i>Brucella canis</i> <i>Brucella melitensis</i> <i>Brucella suis</i>	Gram-negative
<i>Burkholderia</i>	<i>Burkholderia cepacia</i>	Gram-negative
<i>Campylobacter</i>	<i>Campylobacter jejuni</i>	Gram-negative
<i>Chlamydia</i> and <i>Chlamydophila</i>	<i>Chlamydia pneumoniae</i> <i>Chlamydia trachomatis</i> <i>Chlamydophila psittaci</i>	(not Gram-stained)
<i>Clostridium</i>	<i>Clostridium botulinum</i> <i>Clostridium difficile</i> <i>Clostridium perfringens</i> <i>Clostridium tetani</i>	Gram-positive
<i>Corynebacterium</i>	<i>Corynebacterium diphtheriae</i>	Gram-positive
<i>Enterobacter</i>	<i>Enterobacter cloacae</i>	Gram-negative
<i>Enterococcus</i>	<i>Enterococcus faecalis</i> <i>Enterococcus faecium</i>	Gram-positive
<i>Escherichia</i>	<i>Escherichia coli</i>	Gram-negative
<i>Francisella</i>	<i>Francisella tularensis</i>	Gram-negative
<i>Haemophilus</i>	<i>Haemophilus influenzae</i>	Gram-negative
<i>Helicobacter</i>	<i>Helicobacter pylori</i>	Gram-negative
<i>Klebsiella</i>	<i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i>	Gram-negative
<i>Legionella</i>	<i>Legionella pneumophila</i>	Gram-negative
<i>Leptospira</i>	<i>Leptospira interrogans</i>	Gram-negative
<i>Listeria</i>	<i>Listeria monocytogenes</i>	Gram-positive
<i>Moraxella</i>	<i>Moraxella catarrhalis</i>	Gram-negative
<i>Mycobacteriae</i>	<i>Mycobacterium tuberculosis</i>	Gram-indeterminate
<i>Neisseria</i>	<i>Neisseria gonorrhoeae</i> <i>Neisseria meningitidis</i>	Gram-negative
<i>Proteus</i>	<i>Proteus vulgaris</i>	Gram-negative
<i>Pseudomonas</i>	<i>Pseudomonas aeruginosa</i>	Gram-negative
<i>Rickettsia</i>	<i>Rickettsia rickettsii</i>	Gram-negative
<i>Salmonella</i>	<i>Salmonella typhi</i> <i>Salmonella typhimurium</i>	Gram-negative

<i>Shigella</i>	<i>Shigella sonnei</i>	Gram-negative
<i>Staphylococcus</i>	<i>Staphylococcus aureus</i>	Gram-positive
	<i>Staphylococcus epidermidis</i>	
	<i>Staphylococcus saprophyticus</i>	
<i>Streptococcus</i>	<i>Streptococcus agalactiae</i>	Gram-positive
	<i>Streptococcus pneumoniae</i>	
	<i>Streptococcus pyogenes</i>	
<i>Treponema</i>	<i>Treponema pallidum</i>	Gram-negative
<i>Vibrio</i>	<i>Vibrio cholerae</i>	Gram-negative
<i>Yersinia</i>	<i>Yersinia pestis</i>	Gram-negative
	<i>Yersinia enterocolitica</i>	
	<i>Yersinia pseudotuberculosis</i>	

Table 1

The bacterial infection prevented and/or treated by compounds of the present invention may be infection by one or more Gram-positive bacteria. Furthermore, the compounds of the present invention may be selective for one or more Gram-positive bacteria over Gram-negative bacteria. Thus, compounds of the present invention may show no significant inhibition of growth of Gram-negative bacteria.

The bacterial infection prevented and/or treated by compounds of the present invention may be infection by one or more Gram-negative bacteria. Furthermore, the compounds of the present invention may be selective for one or more Gram-negative bacteria over Gram-positive bacteria. Thus, compounds of the present invention may show no significant inhibition of growth of Gram-positive bacteria.

Furthermore, the compounds of the present invention may inhibit the growth of both Gram-positive bacteria and Gram-negative bacteria.

Therapeutic index is the ratio of the dose that produces growth inhibition in 50% of CHO or HepG22 cells divided by the dose where 50% of *S.aureus* growth is inhibited. In some embodiments, compounds have a therapeutic index of greater than 1. In other embodiments, compounds have a therapeutic index of greater than 4. In other embodiments, compounds have a therapeutic index of greater than 8.

Representative examples of Gram-positive bacteria include *Staphylococcus* (e.g. *S. aureus*, *S. epidermis*), *Enterococci* (e.g. *E. faecium*, *E. faecalis*), *Clostridia* (e.g. *C. difficile*), *Propionibacteria* (e.g. *P. acnes*) and *Streptococcus*.

- 5 Bacterial infections in animals are, for example, described in “Pathogenesis of Bacterial Infections in Animals”, edited by Carlton L. Gyles, John F. Prescott, J. Glenn Songer, and Charles O. Thoen, published by Wiley-Blackwell (Fourth edition, 2010 - ISBN 978-0-8138-1237-3), which is hereby incorporated by reference. Many are the same as listed above for humans.

10

Combinations

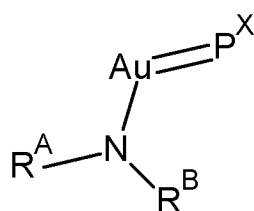
Treatments as described herein may be in combination with one or more known antibiotics, examples of which are described below:

- (a) Aminoglycosides: Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin,
 15 Tobramycin, Paromomycin, Streptomycin; Spectinomycin;
 (b) Ansamycins: Geldanamycin, Herbimycin, Rifaximin;
 (c) Carbacephem: Loracarbef;
 (d) Carbapenems: Ertapenem, Doripenem, Imipenem/Cilastatin, Meropenem;
 (e) 1st generation Cephalosporins: Cefadroxil, Cefazolin, Cefalotin or Cefalothin, Cefalexin;
 20 (f) 2nd generation Cephalosporins: Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime;
 (g) 3rd generation Cephalosporins: Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone;
 (h) 4th generation Cephalosporins: Cefepime;
 (i) 5th generation Cephalosporins: Ceftaroline fosamil, Ceftobiprole, Ceftolozane-
 25 tazobactam, Ceftaroline;
 (j) Glycopeptides: Teicoplanin, Vancomycin, Telavancin, Dalbavancin, Oritavancin;
 (k) Lincosamides: Clindamycin, Lincomycin
 (l) Lipopeptide: Daptomycin
 (m) Macrolides: Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin,
 30 Troleandomycin, Telithromycin, Spiramycin, Rifabutin; Fidaxomicin;
 (n) Monobactams: Aztreonam;
 (o) Nitrofurans: Furazolidone, Nitrofurantoin;
 (p) Oxazolidinones: Linezolid, Posizolid, Radezolid, Torezolid, Tedizolid, Tedizolid phosphate;

- (q) Penicillins: Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Methicillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin, Temocillin, Ticarcillin;
- (r) Polypeptides: Bacitracin, Colistin, Polymyxin B, Polymyxin E (colistin);
- 5 (s) Quinolones: Ciprofloxacin, Enoxacin, Gatifloxacin, Gemifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin, Temafloxacin;
- (t) Sulfonamides: Mafenide, Sulfacetamide, Sulfadiazine, Silver sulfadiazine, Sulfadimethoxine, Sulfamethizole, Sulfamethoxazole, Sulfanilimide, Sulfasalazine,
- 10 Sulfisoxazole, Trimethoprim-Sulfamethoxazole, Sulfonamidochrysoidine;
- (u) Tetracyclines: Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, Tetracycline;
- (v) Antibodies: bezlotoxumab;
- (w) Non- β -lactam β -lactamase inhibitors: avibactam;
- (x) Quinolines: Bedaquiline; and
- 15 (y) Combinations: ceftazidime-avibactam, colistin-ceftazidime, colistin-rifabutin.

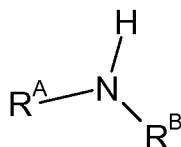
General Experimental

The invention also provides a process for the preparation of a compound of formula I:



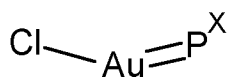
(I)

which comprises reacting a compound of general formula II:



(II)

with chloro(trialkyl phosphine) gold(I) complexes of general formula III:



(III)

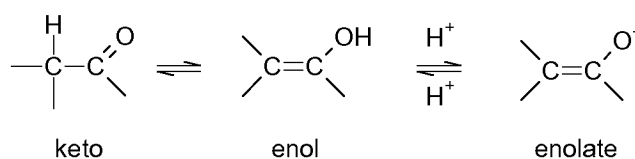
Isomers, Salts and Solvates

Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as “isomers” (or “isomeric forms”).

Note that, except as discussed below for tautomeric forms, specifically excluded from the term “isomers”, as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-\text{OCH}_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-\text{CH}_2\text{OH}$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7} alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



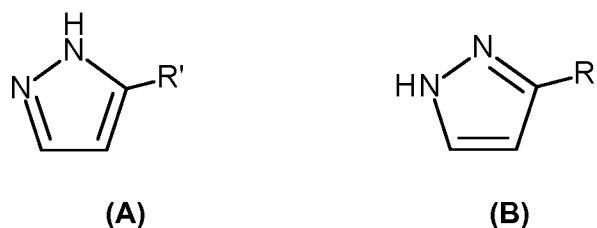
Note that specifically included in the term “isomer” are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D), and ^3H (T); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; Au may be in any isotopic forms, including ^{197}Au and

^{195}Au ; S may be in any isotopic forms, including ^{32}S , ^{33}S , ^{34}S and ^{36}S ; P may be in any isotopic forms, including ^{31}P , ^{33}P and ^{32}P ; and the like.

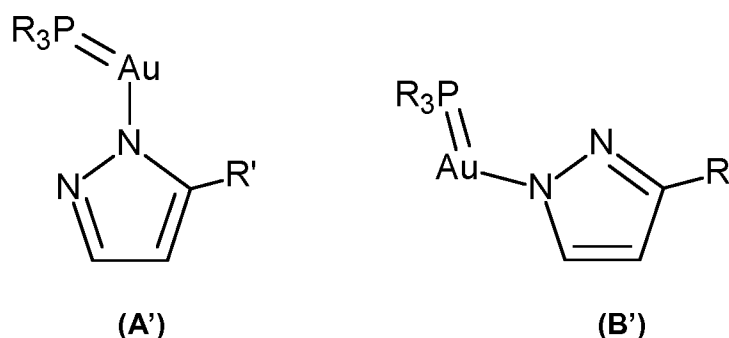
Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Regioisomers

In some cases, the structural assignments for compounds described herein may be unconfirmed due to regioisomerism. When a reactant exists in multiple interchangeable tautomeric forms, the product may be one of a number of regioisomers (each regioisomer resulting from the reaction of a different tautomeric form), or a mixture of these forms. For example, the substituted pyrazole compound below exists in the tautomeric forms (A) and (B) shown:



, where R' represents a group that is not H. When this substituted pyrazole compound reacts with a gold(I) phosphine chloride reactant Cl-Au=PR_3 , reaction may occur with either tautomer, producing the following two distinct regioisomeric products (A') and (B'):



It is possible that these may interconvert in solution (as described in Nomiya, 1998) – any analytical approach used may indicate only one of the possible regioisomers, although the

actual product formed may more correctly be assigned as (A'), (B') or a mixture of the two.

Thus, when a structure is assigned herein as a compound which could exist as multiple regioisomers due to reaction of a gold(I) phosphine chloride with a reactant which exists in multiple interchangeable tautomeric forms, the skilled person will understand that the actual product may in fact be one or more of the regioisomers, and the disclosure of such compounds herein extends to all such regioisomers individually and as mixtures in any relative amount.

The specific compounds described herein which may exist as multiple regioisomers for this reason are indicated below.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, *et al.*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO⁻), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na⁺ and K⁺, alkaline earth cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺.

Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH₃)₄⁺.

If the compound is cationic, or has a functional group which may be cationic (e.g., -NH₂ may be -NH₃⁺), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, gluheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Unless otherwise specified, a reference to a particular compound also include salt forms thereof.

15 *Solvates*

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

Unless otherwise specified, a reference to a particular compound also include solvate forms thereof.

25 **The Subject/Patient**

The subject/patient may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a fetus. In one preferred embodiment, the subject/patient is a human.

Dosage and Formulation

The dosage administered to a patient will normally be determined by the prescribing physician and will generally vary according to the age, weight and response of the individual patient, as well as the severity of the patient's symptoms and the proposed route of administration. However, in most instances, an effective therapeutic daily dosage will be in the range of from about 0.05 mg/kg to about 100 mg/kg of body weight and, preferably, of from 0.05 mg/kg to about 5 mg/kg of body weight administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The formulations, both for veterinary and for human medical use, of the present invention comprise a compound of formula (I) in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Conveniently, unit doses of a formulation contain between 0.1 mg and 1 g of the active ingredient. Preferably, the formulation is suitable for administration from one to six, such as two to four, times per day. For topical administration, the active ingredient preferably comprises from 1% to 2% by weight of the formulation but the active ingredient may comprise as much as 10% w/w. Formulations suitable for nasal or buccal administration, such as the self-propelling powder-dispensing formulations described hereinafter, may comprise 0.1 to 20% w/w, for example about 2% w/w of active ingredient.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, vaginal, intraperitoneal, intramuscular and intravenous), intra-articular, topical, nasal or buccal administration. The toxicity of certain of the compounds in accordance with the present invention will preclude their administration by systemic routes, and in those, and other, cases ophthalmic, topical or buccal administration, and in particular topical administration, is preferred for the treatment of local infection.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the

form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary or paste. For such formulations, a range of dilutions of the active ingredient in the vehicle is suitable, such as from 1% to 99%, preferably 5% to 50% and more preferably 10% to 25% dilution.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration comprise a solution, suspension or emulsion, as described above, conveniently a sterile aqueous preparation of the active ingredient that is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient, which may be in a microcrystalline form, for example, in the form of an aqueous microcrystalline suspension or as a micellar dispersion or suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient particularly for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions or applications; oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented in the form of aqueous eye drops, as for example, a 0.1-1.0% solution.

Drops according to the present invention may comprise sterile aqueous or oily solutions. Preservatives, bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric salts (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide or preservative prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten

drying and to cool the skin, such as an alcohol, or a softener or moisturiser such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid

5 formulations of the active ingredient in a base for external application. The base may comprise one or more of a hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil such as a vegetable oil, eg almond, corn, arachis, castor or olive oil; wool fat or its derivatives; or a fatty acid ester of a fatty acid together with an alcohol such as propylene glycol or macrogols. The formulation may also comprise a suitable surface-
10 active agent, such as an anionic, cationic or non-ionic surfactant such as a glycol or polyoxyethylene derivatives thereof. Suspending agents such as natural gums may be incorporated, optionally with other inorganic materials, such as siliceous silicas, and other ingredients such as lanolin.

15 Formulations suitable for administration to the nose or buccal cavity include those suitable for inhalation or insufflation, and include powder, self-propelling and spray formulations such as aerosols and atomisers. The formulations, when dispersed, preferably have a particle size in the range of 10 to 200µm.

20 Such formulations may be in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations, where the active ingredient, as a finely comminuted powder, may comprise up to 99.9% w/w of the formulation.

25 Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredient, and a liquid propellant having a boiling point of below 18°C at atmospheric pressure. Generally, the propellant constitutes 50 to 99.9% w/w of the formulation whilst the active ingredient constitutes 0.1 to 20% w/w. for example, about 2% w/w, of the formulation.

30 The pharmaceutically acceptable carrier in such self-propelling formulations may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Especially valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. The liquid non-ionic surfactant may constitute from 0.01 up to 20%
35 w/w of the formulation, though preferably it constitutes below 1% w/w of the formulation.

The solid anionic surfactants may constitute from 0.01 up to 20% w/w of the formulation, though preferably below 1% w/w of the composition.

Formulations of the present invention may also be in the form of a self-propelling

5 formulation wherein the active ingredient is present in solution. Such self-propelling formulations may comprise the active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. Suitable co-solvents are lower alkyl alcohols and mixtures thereof. The co-solvent may constitute 5 to 40% w/w of the formulation, though preferably less than 20% w/w of the formulation. Antioxidant stabilisers may be
10 incorporated in such solution-formulations to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulphites. They are preferably present in an amount of up to 0.25% w/w of the formulation.

Formulations of the present invention may also be in the form of an aqueous or dilute
15 alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution.

In addition to the aforementioned ingredients, the formulations of this invention may
20 include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives eg methylhydroxybenzoate (including anti-oxidants), emulsifying agents and the like. A particularly preferred carrier or diluent for use in the formulations of this invention is a lower alkyl ester of a C₁₈ to C₂₄ mono-unsaturated fatty acid, such as oleic acid, for
25 example ethyl oleate. Other suitable carriers or diluents include capric or caprylic esters or triglycerides, or mixtures thereof, such as those caprylic/capric triglycerides sold under the trade name Miglyol, eg Miglyol 810.

Embodiments of the invention will now be described by way of example only.

30

Examples

Preparative HPLC Methods

Reverse Phase Preparative HPLC-MS: Mass-directed purification by preparative LC-MS
35 using a preparative C-18 column (Phenomenex Luna C18 (2) 5 µm, 100 x 21.2 mm).

Generic Acidic Conditions:

A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 20°C; %B: 0.0 min Initial between 2% and 50%, 0.1 min % as per Initial, 7.0 min between 40% and 95%, 9.0 min 95%, 10.0 min 95%, 10.1 min back to Initial %; 12.0 min Initial %; 20.0 mL/min.

5 Generic Basic Conditions:

A = water pH 9 (Ammonium Bicarbonate 10 mM); B = MeOH; 20°C; %B: 0.0 min Initial between 2% and 50%, 0.1 min % as per Initial, 7.0 min between 40% and 95%, 9.0 min 95%, 10.0 min 95%, 10.1 min back to Initial %; 12.0 min Initial %; 20.0 mL/min.

10 NMR was also used to characterise final compounds. NMR spectra were obtained Bruker Advance 400, Bruker DRX 400 or Jeol 400 ECS at room temperature unless otherwise stated. ¹H NMR spectra are reported in ppm and referenced to either tetramethylsilane (0.00 ppm), DMSO-d₆ (2.50 ppm), CDCl₃ (7.26 ppm) or CD₃OD (3.31 ppm).

15 **Abbreviations Used**

For the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

20	°C	Degrees Centigrade
	aq.	Aqueous
	br	Broad
	d	Doublet
	DABCO	1,4-Diazabicyclo[2.2.2]octane
25	DavePhos	2-Dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl
	DCM	Dichloromethane
	DIPEA	<i>N,N</i> -Diisopropylethylamine
	DMF	Dimethylformamide
	DMSO	Dimethyl sulfoxide
30	Et	Ethyl
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	Et ₂ O	Diethyl ether
	FA	Formic acid

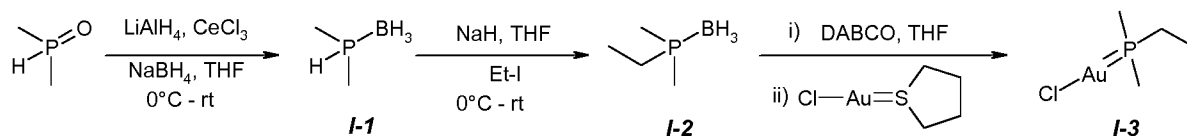
	g	Gram
	h	Hour(s)
	HATU	2-(7-Aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
5	<i>i</i> Pr	Isopropyl
	<i>J</i>	Coupling constant
	LC-MS	Liquid chromatography-mass spectrometry
	LiHMDS	Lithium bis(trimethylsilyl)amide
	Me	Methyl
10	MeCN	Acetonitrile
	MeOH	Methanol
	mg	Milligram
	min	Minute(s)
	mL	Millilitre
15	mmol	Millimole
	NaOMe	Sodium methoxide
	O/N	Overnight
	ppm	Parts per million
	ppt	Precipitate
20	q	Quartet
	quint	Quintet
	rt	Room temperature
	s	Singlet
	sext	sextet
25	TEA	Triethylamine
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	t	Triplet
	WIPE	Water / isopropanol / Ethyl acetate (1:2:9)

30

Chemical Synthesis

Several of the requisite gold(I) phosphine chloride complexes **III**, necessary for coupling with precursors **II**, required synthesis from commercial starting materials. Other precursors used were commercially available.

35

Dimethylethylphosphine gold(I) chloride I-3*(a) Dimethylphosphine borane I-1*

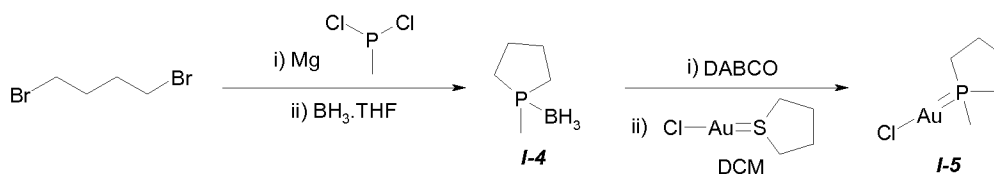
- 5 Cerium(III) chloride (25 g, 101.4 mmol) was suspended in THF (100 mL) and stirred at rt for 1 h. Sodium borohydride (3.8 g, 101.4 mmol) was then added and the suspension stirred at rt for a further 1 h. The reaction was cooled to 0°C at which point dimethylphosphine oxide (2.6 g, 33.8 mmol) was added dropwise followed by lithium aluminium hydride (1M in THF, 40.7 mL, 40.7 mmol) also dropwise. The reaction was stirred at rt O/N before diluting with toluene (50 mL) then quenching with water (25 mL) and aqueous HCl (6N, 25 mL). The suspension was filtered through celite and the layers separated. The aqueous phase was extracted with DCM (3 x 40 mL) and the combined organic extracts washed with brine (1 x 40 mL) and passed through a phase separator cartridge (Biotage). Concentration *in vacuo* gave the crude product as a yellow oil which
- 10 was purified by column chromatography (Biotage Isolera Four, 25 g KP-Sil column eluting with isohexane to 20% EtOAc / isohexane to provide the title compound as a colourless oil (1.49 g, 19.6 mmol, 58%).

(b) Dimethylethylphosphine borane I-2

- 20 Dimethylphosphine borane **I-1** (100 mg, 1.3 mmol) was dissolved in THF (3 mL) and the colourless solution cooled to 0°C . NaH (60% dispersion in mineral oil, 53 mg, 1.3 mmol) was added in one portion, whereupon effervescence was observed. The opaque reaction was stirred at rt for 10 min then cooled back down to 0°C whereupon iodoethane (0.12 mL, 1.4 mmol) was added in one portion. When TLC had indicated completion of the reaction, water (10 mL) and Et_2O (10 mL) were added and the phases separated. The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic extracts washed with brine (1 x 20 mL) before passing through a phase separator cartridge (Biotage). Concentration *in vacuo* gave the crude material as a colourless gum.
- 25 Purification by column chromatography (Biotage Isolera Four, 10 g KP-Sil column eluting with a gradient of isohexane to 20% EtOAc / isohexane provided the title compound as a
- 30 white solid (122 mg, 1.1 mmol, 90%).

(c) Dimethylethylphosphine gold(I) chloride I-3

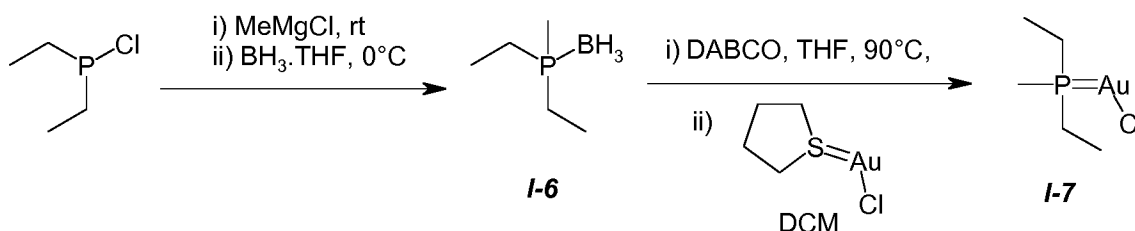
Dimethylethylphosphine borane **I-2** (225 mg, 2.0 mmol) was dissolved in THF (5 mL) and the colourless solution degassed with nitrogen for 5 min. DABCO (640 mg, 6.0 mmol) was added and the reaction sealed with a Teflon screw cap. The reaction was heated to 100°C and stirred at this temperature for 4 h before cooling in an ice bath and adding a solution of chloro(tetrahydrothiophene)gold(I) (640 mg, 2.0 mmol) in DCM (5 mL). After stirring at rt O/N the reaction was diluted with DCM (10 mL) and water (10 mL) and the phases separated. The aqueous phase was extracted with DCM (2 x 20 mL) and the combined organic extracts washed with brine (20 mL) before passing through a phase separator cartridge (Biotage). Concentration *in vacuo* gave the crude product as a brown oil which was purified by column chromatography (Biotage SP1, 25 g KP-Sil eluting with 25% EtOAc / isohexane to 60% EtOAc / isohexane to provide the title compound as a white solid (265 mg, 0.82 mmol, 41%).

1-Methylphospholane gold(I) chloride I-5*(a) 1-Methylphospholaneborane I-4*

The *bis*-Grignard reagent was prepared by treating magnesium (1.0 g, 0.04 mol) with 1,4-dibromobutane (4.3 g, 20 mmol) in dry THF (50 mL) at 65°C for 3 h. The reaction mixture was cooled to 0°C before adding a cooled (10°C) solution of dichloromethyl phosphine (2.3 g, 20 mmol) in dry THF (25 mL) dropwise maintaining a temperature of 10°C. The mixture was stirred O/N at rt. Borane-THF complex (1.0M in THF, 20 mL, 20 mmol) was added dropwise and the reaction mixture stirred for additional 4 h. The reaction mixture was poured onto a mixture of ice (200 g) and aqueous HCl (2M, 100 mL) with vigorous stirring. The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic extracts dried over MgSO₄. Concentration *in vacuo* gave the crude product as a yellow oil which was purified by flash column chromatography (Biotage SP1, 50 g KP-Sil column, eluting with isohexane to DCM) to provide the title compound as a colourless oil (700 mg, 6.0 mmol, 30%).

(b) 1-Methylphospholane gold(I) chloride I-5

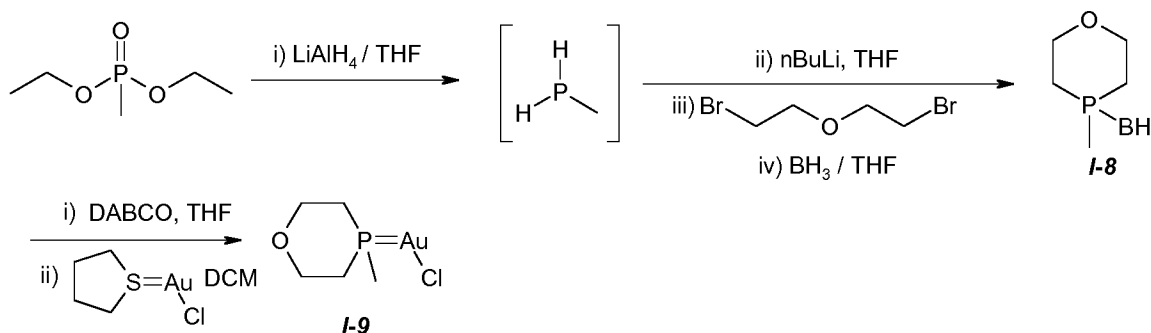
Procedure similar to that described for dimethylethylphosphine gold(I) chloride **I-3** starting from 1-methylphospholaneborane **I-4** (116 mg, 1.0 mmol) to provide the title compound as an off-white solid (200 mg, 0.6 mmol, 60%).

Diethylmethylphosphine gold(I) chloride I-7*(a) Diethylmethylphosphine borane I-6*

To a cold (0°C) solution of diethylchlorophosphine (1.0 g, 8.0 mmol) in THF (20 mL) under an inert atmosphere was slowly added methylmagnesium chloride (3M in THF, 2.7 mL, 8.1 mmol). After warming to rt and being stirred for 4 h, the reaction was cooled to 0°C prior to the addition of borane-THF complex (1M in THF, 8 mL, 8.0 mmol). The reaction mixture was allowed to warm up to rt O/N, then was diluted with Et₂O (30 mL) and water (20 mL). The phases were separated and the organic layer was washed with water (2 x 10 mL) and brine (10 mL) before being dried over MgSO₄ and concentrated *in vacuo* to provide the title compound as a colourless oil (388 mg, 3.2 mmol, 40%).

(b) Diethylmethylphosphine gold(I) chloride I-7

Procedure similar to that described for dimethylethylphosphine gold(I) chloride **I-3** starting from diethylmethylphosphine borane **I-6** (385 mg, 3.2 mmol) to provide the title compound as a white solid (475 mg, 1.4 mmol, 44%).

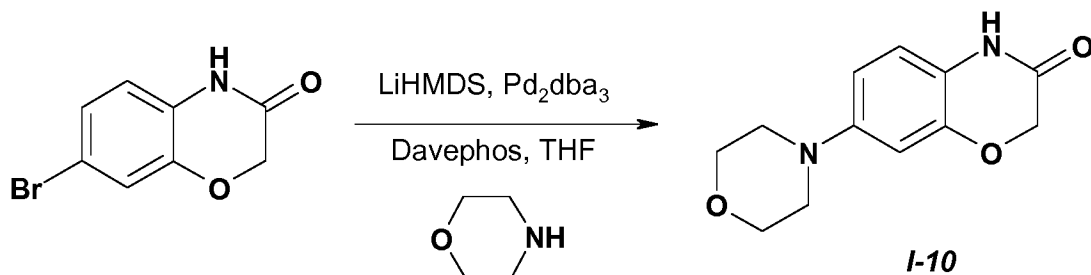
4-Methyl-[1,4]oxaphosphinane gold(I) chloride I-9**(a) 4-Methyl-[1,4]oxaphosphinaneborane I-8**

- 5 To a solution of diethyl methylphosphonate (1.5 g, 10.0 mmol) in dry THF (30 mL) was added lithium aluminium hydride (1M in THF, 15 mL, 15.0 mmol) at 0°C, and the mixture allowed to warm to rt and stirred for 4 h. The reaction mixture was cooled to 0°C whereupon BuLi (1.6M in hexanes, 12.5 mL, 20 mmol) was added over 5 min and stirring continued at 0°C for 45 min. 1-Bromo-2-(2-bromoethoxy)ethane (2.3 g, 10 mmol) was then added in one portion and the reaction mixture stirred for further 4 h. Borane-THF complex (1M in THF, 20 mL, 20 mmol) was added and the reaction mixture stirred at rt for an additional 72 h before being diluted with water (60 mL) and 2M HCl (aq., 160 mL) with vigorous stirring. The aqueous phase was extracted with DCM and the combined organic extracts dried over MgSO₄. Concentration *in vacuo* gave the crude product which was
- 10 purified by flash column chromatography (Biotage SP1, 25 g KP-Sil column, eluting with isohexane to EtOAc) to provide the title compound as a colourless oil (220 mg, 1.7 mmol, 17%).

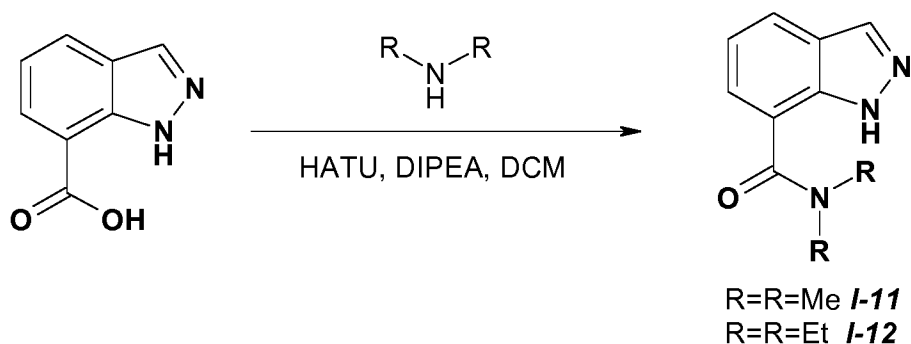
(b) 4-Methyl-[1,4]oxaphosphinane gold(I) chloride I-9

- 20 Procedure similar to that described for dimethylethylphosphine gold(I) chloride **I-3** starting from 4-methyl-[1,4]oxaphosphinaneborane **I-8** (220 mg, 1.7 mmol) to provide the title compound as an off-white solid (186 mg, 0.5 mmol, 32%).

- A number of the requisite precursors **II**, necessary for coupling with chloro(trialkyl phosphine) gold(I) complexes **III**, required synthesis from commercial starting materials.
- 25 Other precursors used were commercially available.

7-Morpholin-4-yl-4H-benzo[1,4]oxazin-3-one **I-10**

7-Bromo-4H-benzo[1,4]oxazin-3-one (300 mg, 1.3 mmol), morpholine (140 μ L, 1.6 mmol), tris(dibenzylideneacetone)dipalladium(0) (11.9 mmol, 0.013 mmol) and DavePhos (15.3 mg, 0.039 mmol) were combined in THF (5 mL). The reaction was degassed with nitrogen and LiHMDS (3.3 mL, 3.3 mmol) was added and the reaction heated under nitrogen at 70°C O/N. The reaction mixture was cooled to rt, diluted with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to afford a brown solid. The residue was purified by column chromatography (Biotage Isolera Four, 25 g, KP-Sil column, eluting with isohexane to EtOAc) to afford the title compound as a brown solid (125 mg, 0.53 mmol, 41%).

1H-Indazole-7-carboxylic acid dimethylamide **I-11** and 1H-indazole-7-carboxylic acid diethylamide **I-12**(a) 1H-Indazole-7-carboxylic acid dimethylamide **I-11**

1H-Indazole-7-carboxylic acid (100 mg, 0.62 mmol) was suspended in anhydrous DCM (10 mL). DIPEA (430 μ L, 2.47 mmol) was added followed by HATU (281 mg, 0.74 mmol) and the reaction was stirred at rt for 20 min. Dimethylamine hydrochloride (100 mg, 1.23 mmol) was added and the reaction stirred at rt O/N. Additional dimethylamine hydrochloride (100 mg, 1.23 mmol), DIPEA (1 mL, 5.74 mmol) and HATU (281 mg, 0.74 mmol) were added and the reaction stirred for a further 18 h. The reaction was diluted

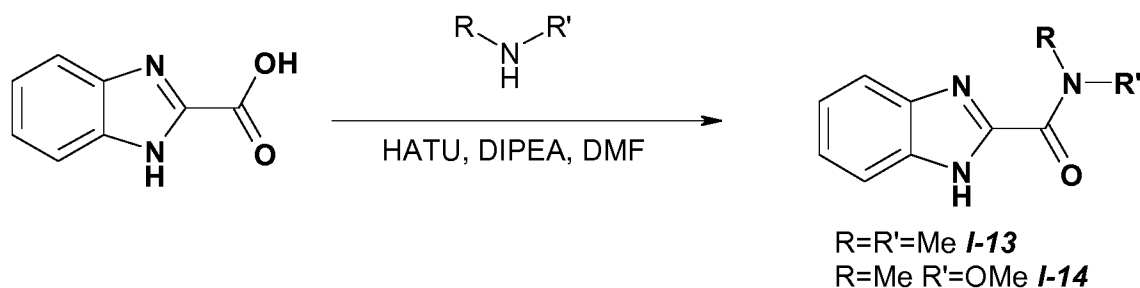
with DCM and washed with water and saturated aqueous sodium hydrogen carbonate. The organic fraction was dried and concentrated *in vacuo*. Initial purification by column chromatography (Biotage Isolera Four, 10 g, KP-Sil column, eluting with isohexane to EtOAc) afforded impure title compound. Final purification by preparative HPLC (acidic conditions) afforded the title compound as a white solid, (43 mg, 0.23 mmol, 37%).

An alternative procedure can be employed using 1*H*-indazole-7-carboxylic acid (198 mg, 0.62 mmol) and TEA (6.1 mmol) as base. The crude product was purified directly by preparative HPLC (basic conditions) to afford the title compound as a white solid, (108 mg, 0.57 mmol, 47%).

(b) 1*H*-Indazole-7-carboxylic acid diethylamide **I-12**

Procedure similar to that described for 1*H*-indazole-7-carboxylic acid dimethylamide **I-11** starting from diethylamine (191 μ L, 1.85 mmol) to provide the title compound as a white solid (93 mg, 0.43 mmol, 49%).

1*H*-Benzoimidazole-2-carboxylic acid dimethylamide **I-13** and 1*H*-benzoimidazole-2-carboxylic acid methoxy-methyl-amide **I-14**

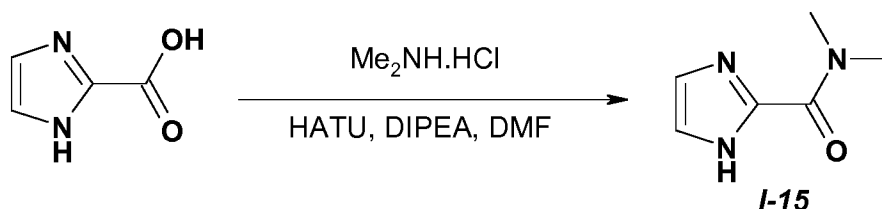


(a) 1*H*-Benzoimidazole-2-carboxylic acid dimethylamide **I-13**

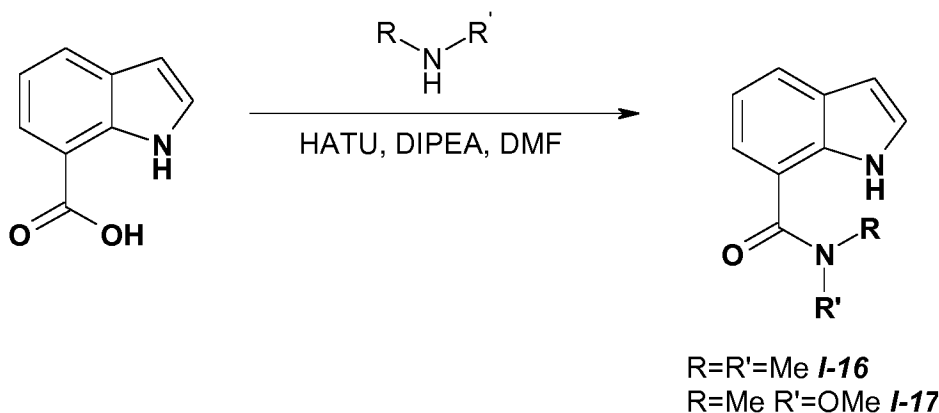
1*H*-Benzoimidazole-2-carboxylic acid (150 mg, 0.93 mmol) was suspended in anhydrous DMF (10 mL). DIPEA (480 μ L, 2.76 mmol) was added followed by HATU (530 mg, 1.39 mmol) and the reaction was stirred at rt for 20 min. Dimethylamine hydrochloride (157 mg, 1.86 mmol) was added and the reaction stirred at rt O/N. The reaction was diluted with saturated aqueous sodium hydrogen carbonate and extracted with DCM. The organic fraction was dried and concentrated *in vacuo*. Purification by column chromatography (Biotage Isolera Four, 25 g KP-Sil column, eluting with isohexane to EtOAc) afforded impure title compound as a white solid, (80 mg, 0.42 mmol, 46%).

(b) 1H-benzoimidazole-2-carboxylic acid methoxy-methyl-amide I-14

Procedure similar to that described for 1H-benzoimidazole-2-carboxylic acid dimethylamide **I-13** starting from *N*-methyl,*O*-methyl hydroxylamine hydrochloride (181 mg, 1.86 mmol) to provide the title compound as an off-white solid (103 mg, 0.5 mmol, 54%).

1H-imidazole-2-carboxylic acid dimethylamide I-15

Procedure similar to that described for 1H-benzoimidazole-2-carboxylic acid dimethylamide **I-13** starting from imidazole-2-carboxylic acid (218 mg, 2.67 mmol) to provide the title compound as a yellow oil (256 mg, 1.83 mmol, 54%).

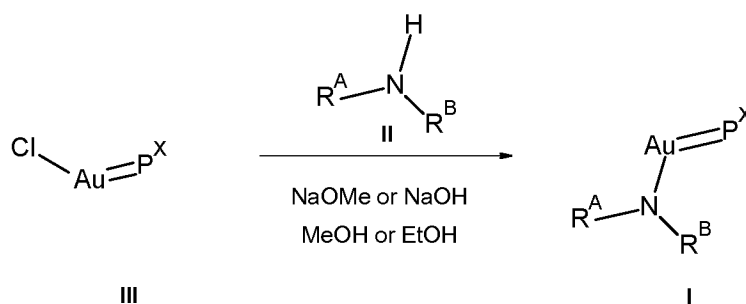
1H-indole-7-carboxylic acid dimethylamide I-16 and 1H-indole-7-carboxylic acid methoxy-methylamide I-17*(a) 1H-Indole-7-carboxylic acid dimethylamide I-16*

Procedure similar to that described for 1H-benzoimidazole-2-carboxylic acid dimethylamide **I-13** starting from 7-indole carboxylic acid (200 mg, 1.24 mmol) to provide the title compound as a white solid (194 mg, 1.03 mmol, 83%).

(b) *1H-Indole-7-carboxylic acid methoxy-methylamide I-17*

Procedure similar to that described for 1H-benzimidazole-2-carboxylic acid dimethylamide **I-13** starting from 7-indole carboxylic acid (200 mg, 1.24 mmol) and N-methyl,O-methyl hydroxylamine hydrochloride (240 mg, 2.45 mmol) to provide the title compound as a white solid (262 mg, 1.28 mmol, 100%).

Compounds of the formula **I** were synthesised *via* the coupling of gold(I) phosphine chloride complexes of formula **III** with nitrogen containing derivatives of general formula **II**:

10 *Example 1:*

Method A: To a stirred suspension of the appropriate nitrogen derivative **II** (0.16 mmol) and chlorophosphine gold(I) compound **III** (0.16 mmol) in MeOH (2 mL) was added dropwise NaOMe (0.5 M in MeOH, 0.18 mmol). The reaction was stirred at rt for 16 h before concentrating *in vacuo* to give a solid residue which was suspended in DCM (2 mL) and filtered. The filtrate was concentrated *in vacuo* giving an oily residue which after trituration with Et₂O (x 3) and drying under high vacuum for 16 h, provided the title compound **I**.

Method B: As Method A, except NaOH was used instead of NaOMe and EtOH instead of MeOH. The reaction was stirred at 0°C for 75 min before the reaction mixture was concentrated *in vacuo*, re-suspended in water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were passed through a phase separator cartridge (Biotage) and concentrated *in vacuo* to give a residue which was trituated with Et₂O (x 3) to provide the title compound **I**.

Method C: As Method A, except NaOH was used instead of NaOMe.

Method D: As Method A except 2 equivalents of chlorophosphine gold(I) compound **III** and 2.2 equivalents of NaOMe were used.

Method E: As Method A except the reaction mixture was heated at 50 °C for 18 h.

Method F: As Method A except workup and isolation as Method B.

5

Method G: As Method A except the order of addition of reagents was changed such that the base was added prior to addition of chlorophosphine gold(I) compound **III**.

10

Method H: To a stirred solution of the appropriate nitrogen derivative **II** (0.1 mmol) in THF (10 mL) was added sodium hydride (60% dispersion in mineral oil, 0.1 mmol). The reaction mixture was stirred at rt for 15 min whereupon chlorophosphine gold(I) compound **III** (0.1 mmol) was added. The reaction mixture was stirred at rt for 18 h before concentrating *in vacuo*. The resulting residue was suspended in DCM (2 mL) and filtered. The filtrate was concentrated *in vacuo*, triturated with Et₂O and isohexane, and dried under high vacuum for 16 h to provide the title compound **I**.

15

Method I: As Method A except 2 equivalents of NaOMe were used and after 16 h, the reaction was concentrated *in vacuo* to afford the title compound **I**.

20

Method J: As Method A except after 16h, the reaction was concentration *in vacuo*, the resulting solid was triturated with DCM and then dissolved in MeOH. The solution was filtered, concentrated *in vacuo* and the resulting solid triturated further with Et₂O and dried under high vacuum to provide the title compound **I**.

25

Method K: To a stirred solution of the appropriate nitrogen derivative **II** (0.3 mmol) in EtOH (3 mL) was added aqueous K₂CO₃ (10% w/v, 1 mL) followed by chlorophosphine gold(I) compound **III** (0.3 mmol). The reaction mixture was stirred at RT for 18 h before it was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were passed through a phase separator cartridge (Biotage) and the solvent evaporated to provide the title compound **I**.

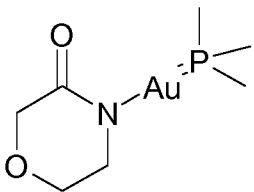
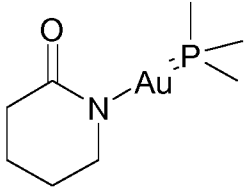
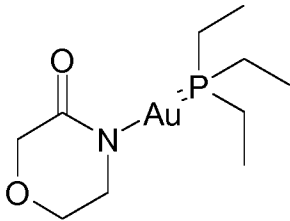
30

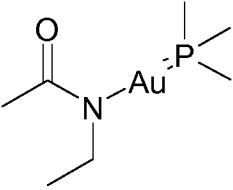
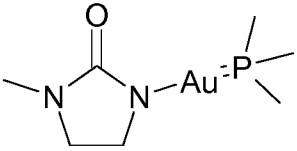
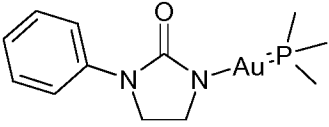
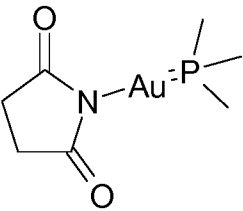
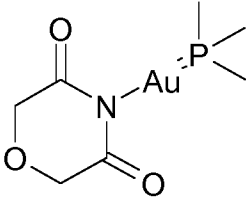
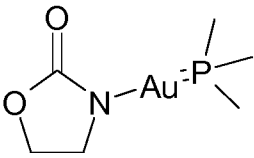
For compounds **94**, **95**, **96**, and **98** the reaction was run in the dark by covering the reaction vessel in foil.

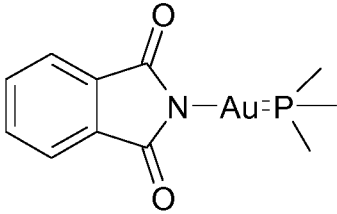
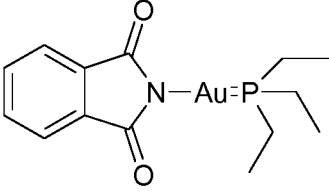
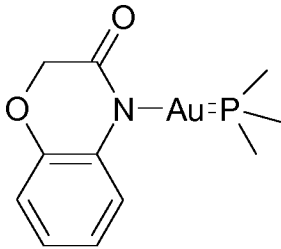
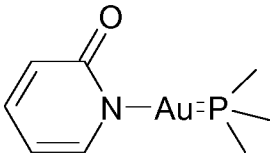
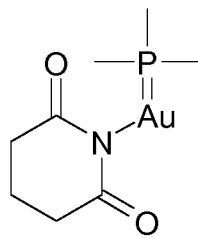
The solvent (or combination of solvents) used for trituration and isolation of target compounds **I** can be selected from the following: MeOH, EtOH, Et₂O, EtOAc, isohexane, pentane or DCM.

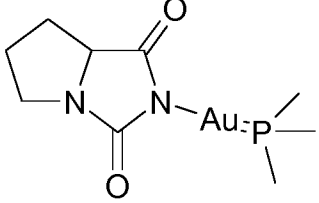
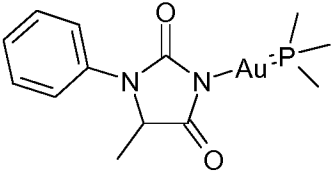
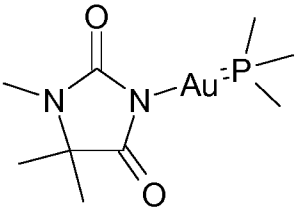
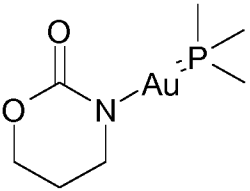
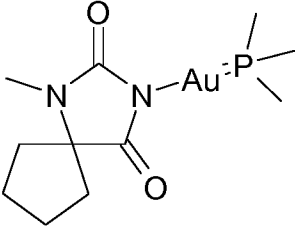
- 5 Some of the compounds were prepared using methods in which minor modifications to the general methods were made; specifically, these methods involved small changes to the stoichiometry of reagents (1 – 2.2 equivalents), duration of reaction (1 - 86 h) and volume of solvent (2 - 6 mL). In some cases reactions were purged with nitrogen.
- 10 The following compounds were made using these methods:

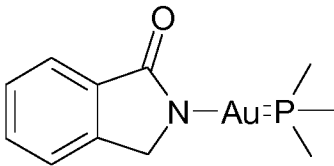
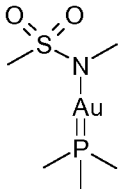
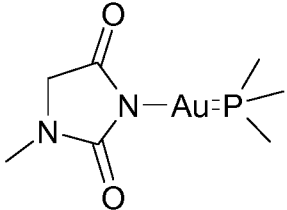
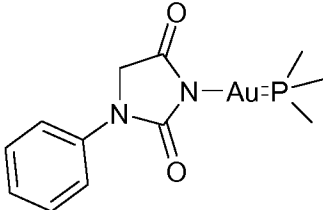
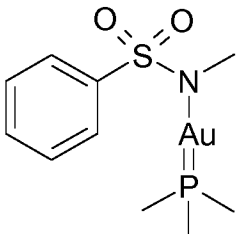
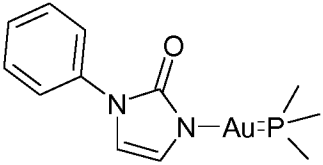
Table 1

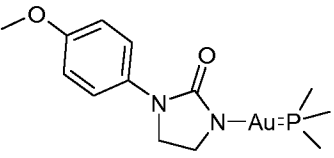
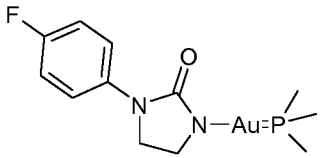
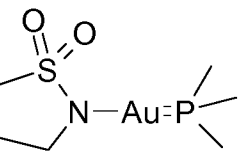
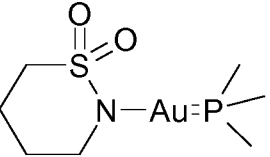
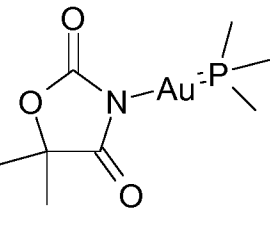
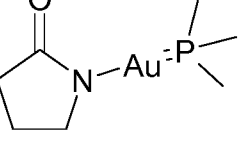
Structure	Compound Number	Method	Analytical Data
			Physical appearance/Yield
	1	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.84 (2H, s), 3.56 (2H, t, <i>J</i> = 4.7 Hz), 3.36 (2H, t, <i>J</i> = 4.7 Hz), 1.58 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.46 (s).
			Grey solid; 55 mg, 90%
	2	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.29 (2H, t, <i>J</i> = 5.6 Hz), 2.03 (2H, t, <i>J</i> = 6.8 Hz), 1.47-1.65 (m, 13H). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.57 (s).
			White solid; 91 mg, 71%
	3	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.84 (2H, s), 3.56 (2H, t, <i>J</i> = 4.5 Hz), 3.37 (2H, t, <i>J</i> = 4.5 Hz), 1.88 (6H, dq, <i>J</i> = 10.4, 7.6 Hz), 1.11 (9H, dt, <i>J</i> = 18.7, 7.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm 30.52 (s).

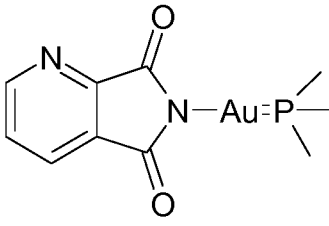
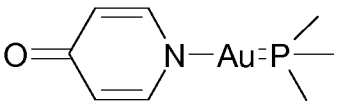
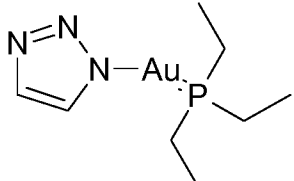
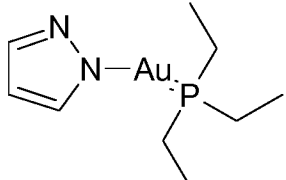
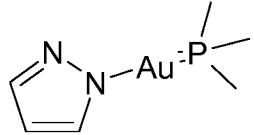
			Grey solid; 32 mg, 48%
	4	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.29 (2 H, dq <i>J</i> = 7.2, 3.6 Hz), 1.92 (3H, s), 1.59 (9H, d, <i>J</i> = 11.4 Hz), 1.04 (3H, t, <i>J</i> = 7.2 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.70 (s).
			Dark grey solid; 35 mg, 60%
	5	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.30 (2H, t, <i>J</i> = 7.6 Hz), 3.11 (2H, t, <i>J</i> = 7.6 Hz), 2.51 (3H, s), 1.57 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm - 10.08 (s)
			Grey solid; 51 mg, 85%
	6	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.53-7.48 (2H, m), 7.24-7.18 (2H, m), 6.82 (1H, tt, <i>J</i> = 7.3, 1.1 Hz), 3.70 (2H, t, <i>J</i> = 7.6 Hz), 3.51 (2H, t, <i>J</i> = 7.6 Hz), 1.60 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.11 (s)
			White solid; 62 mg, 88%
	7	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 2.43 (4H, s), 1.62 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.80 (s)
			Off-white solid; 51 mg, 85%
	8	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 4.11(4H, s), 1.63 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm - 10.24 (s)
			Brown solid; 36 mg, 57%
	9	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 4.09 (2H, t, <i>J</i> = 7.8 Hz), 3.49 (2H, t, <i>J</i> = 7.8 Hz), 1.59 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.21 (s).

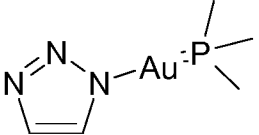
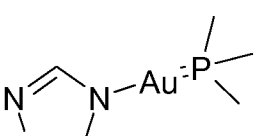
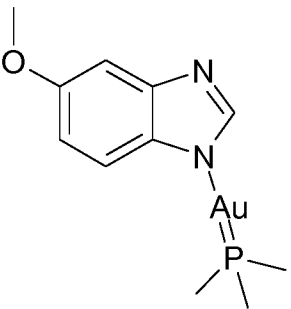
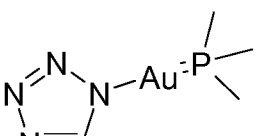
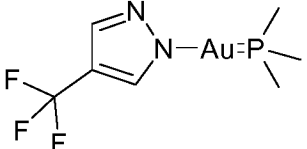
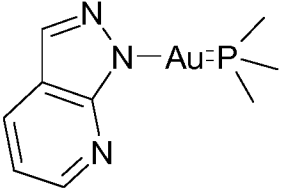
			White solid; 57 mg, 98%
	10	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.70-7.64 (4H, m), 1.67 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.61 (s)
			White solid; 53 mg, 74%
	11	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.71-7.62 (4H, m), 1.98 (6H, dq, <i>J</i> = 18.9, 7.6 Hz), 1.15 (9H, dt, <i>J</i> = 18.9, 7.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm 31.65 (s)
			Grey solid; 20 mg, 25%
	12	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.29 (1H, dd, <i>J</i> = 7.8, 1.8 Hz), 6.87-6.81 (2H, m), 6.74 (1H, m), 4.36 (2H, s), 1.66 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.47 (s)
			White solid; 58 mg, 84%
	13	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.31 (1H, m), 7.14 (1H, ddd, <i>J</i> = 8.8, 6.6, 2.3 Hz), 6.14 (1H, dm, <i>J</i> = 9.1 Hz), 6.01 (1H, tt, <i>J</i> = 6.3, 1.3 Hz), 1.63 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.29 (s).
			Brown solid; 43 mg, 72%
	14	A	¹ H-NMR (400 MHz, <i>CDC</i> ₃): δ ppm 2.51 (4H, t, <i>J</i> = 6.7 Hz), 1.92 (2H, quint, <i>J</i> = 6.6 Hz), 1.61 (9H, d, <i>J</i> = 11.1 Hz). ³¹ P-NMR (162 MHz, <i>CDC</i> ₃): δ ppm -11.40 (s)
			Brown solid; 47 mg, 76%

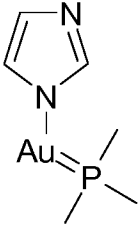
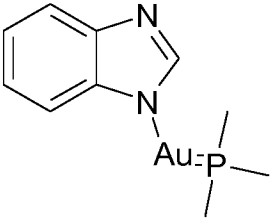
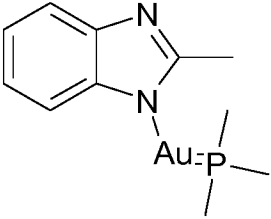
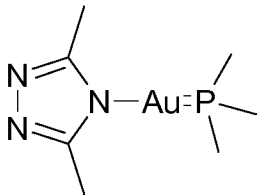
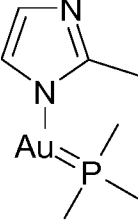
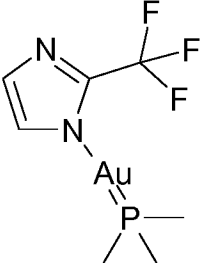
	15	B	¹H-NMR (400 MHz, <i>CDCl</i>₃): δ ppm 4.02 (1H, t, <i>J</i> = 8.1 Hz), 3.68 (1H, dt, <i>J</i> = 11.4, 7.1 Hz), 3.13 (1H, m), 2.14 (1H, m), 2.07-1.88 (2H, m), 1.76 (1H, m), 1.61 (9H, d, <i>J</i> = 11.1 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm -11.25 (s) Pink solid; 27 mg, 28%
	16	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.51 (2H, dd, <i>J</i> = 8.6, 1.0 Hz), 7.34 (2H, dd, <i>J</i> = 8.6, 7.6 Hz), 7.06 (1H, tt, <i>J</i> = 7.6, 1.0 Hz), 4.66 (1H, q, <i>J</i> = 6.8 Hz), 1.66 (9H, d, <i>J</i> = 11.6 Hz), 1.25 (3H, d, <i>J</i> = 6.8 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.10 (s) White solid; 73 mg, 97%
	17	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 2.68 (3H, s), 1.62 (9H, d, <i>J</i> = 11.6 Hz), 1.18 (6H, s). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.10 (s) Off-white solid; 62 mg, 93%
	18	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 3.98 (2H, t, <i>J</i> = 5.7 Hz), 3.32 (2H, t, <i>J</i> = 5.7 Hz), 1.70 (2H, quint, <i>J</i> = 5.7 Hz), 1.57 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -11.46 (s) Brown solid; 45 mg, 75%
	19	A	¹H-NMR (400MHz, <i>DMSO-d</i>₆): δ ppm 2.70 (3H, s), 1.81-1.67 (8H, m), 1.62 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.12 (s). White solid; 60 mg, 85%

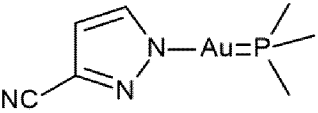
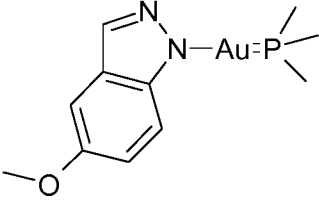
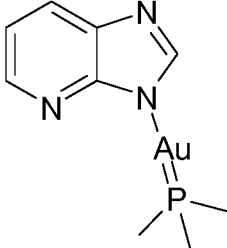
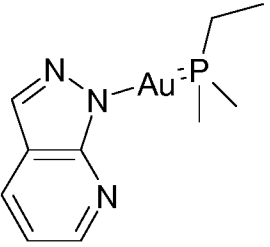
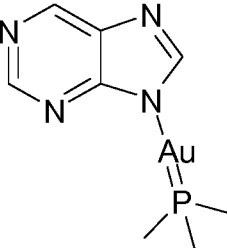
	20	E	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.53 (1H, dt, <i>J</i> = 7.3, 1.0 Hz), 7.45-7.42 (2H, m), 7.37 (1H, m), 4.35 (2H, s), 1.64 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.58 (s). Off-white solid; 45 mg, 69%
	21	A	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 2.82 (3H, d, <i>J</i> = 2.2 Hz), 2.62 (3H, s), 1.59 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -11.70 (s) Grey solid; 61 mg, 98%
	22	A	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 3.71 (2H, s), 2.75 (3H, s), 1.62 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.99 (s) White solid; 52 mg, 83%
	23	A	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 7.61-7.57 (2H, m), 7.34-7.28 (2H, m), 7.01 (1H, tt, <i>J</i> = 7.3, 1.0 Hz), 4.26 (2H, s), 1.65 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.93 (s) White solid; 53 mg, 73%
	24	A	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 7.77-7.72 (2H, m), 7.52-7.48 (3H, m), 2.66 (3H, d, <i>J</i> = 2.0 Hz), 1.62 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -11.61 (s) Grey solid; 19 mg, 26%
	25	A	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 7.77-7.73 (2H, m), 7.38-7.32 (2H, m), 7.09 (1H, tt, <i>J</i> = 7.6, 1.0 Hz), 6.77 (1H, dd, <i>J</i> = 2.8, 1.3 Hz), 6.29 (1H, dd, <i>J</i> = 2.8, 0.8 Hz), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.33 (s)

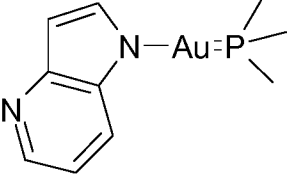
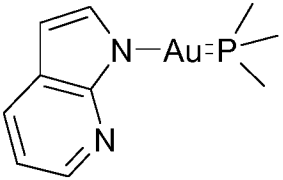
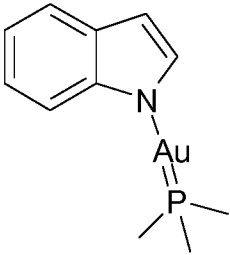
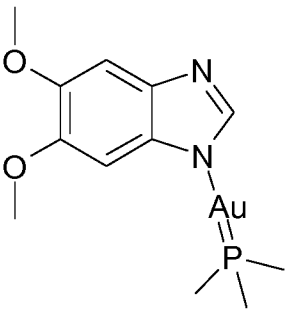
			White solid; 43 mg, 61%
	26	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.42-7.37 (2H, m), 6.83-6.78 (2H, m), 3.68 (3H, s), 3.68-3.62 (2H, m), 3.52-3.46 (2H, m), 1.59 (9H d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.80 (s)
			Brown solid; 54 mg, 71%
	27	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.53-7.47 (2H, m), 7.08-7.01 (2H, m), 3.70-3.65 (2H, m), 3.53-3.47 (2H, m), 1.59 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.91 (s)
			White solid; 51 mg, 68%
	28	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.32 (2H, t, <i>J</i> = 6.6 Hz), 2.76-2.70 (2H, m), 2.20-2.12 (2H, m), 1.59 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.73 (s)
			White solid; 47 mg, 73%
	29	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.39-3.33 (2H, m), 2.72-2.68 (2H, m), 1.98-1.91 (2H, m), 1.58 (9H, d, <i>J</i> = 11.6 Hz), 1.49-1.42 (2H, m). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.24 (s)
			Off-white solid; 48 mg, 73%
	30	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 1.65 (9H, d, <i>J</i> = 11.9 Hz), 1.37 (6H, s). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.01 (s)
			Grey solid; 59 mg, 91%
	31	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 3.29 (2H, t, <i>J</i> = 6.6 Hz), 1.96-1.84 (4H, m), 1.57 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.28 (s)

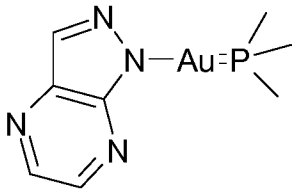
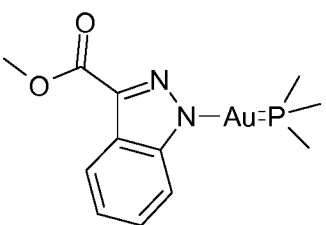
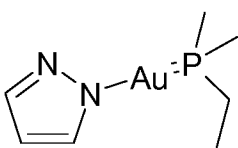
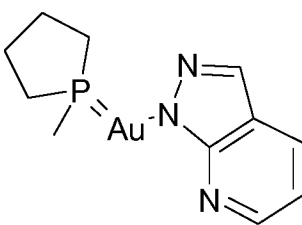
			White solid; 51 mg, 88%
	32	F	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.84 (1H, dd, <i>J</i> = 5.0, 1.5 Hz), 8.09 (1H, dd, <i>J</i> = 7.6, 1.5 Hz), 7.64 (1H, dd, <i>J</i> = 7.6, 5.0 Hz), 1.68 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.40 (s)
			White solid; 43 mg, 63%
	33	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.45 (1H, app d, <i>J</i> = 7.3 Hz), 5.97 (1H, app d, <i>J</i> = 7.3 Hz), 1.64 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.17 (s)
			Brown solid; 32 mg, 53%
	34*	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.76 (2H, br s), 1.89 (6H, dq, <i>J</i> = 10.1, 7.6 Hz), 1.23 (9H, dt, <i>J</i> = 18.7, 7.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm 27.19 (br s)
			Colourless oil; 120 mg, 100%
	35	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.65 (2H, br s), 6.39 (1H, t, <i>J</i> = 1.9 Hz), 1.86 (6H, dq, <i>J</i> = 10.1, 7.7 Hz), 1.23 (9H, dt, <i>J</i> = 18.7, 7.7 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm 30.41 (br s)
			Colourless oil; 122 mg, 100%
	36	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.45 (2H, br s), 6.19 (1H, t, <i>J</i> = 1.8 Hz), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.88 (s)
			White solid; 161 mg, 98%

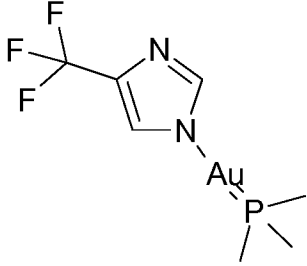
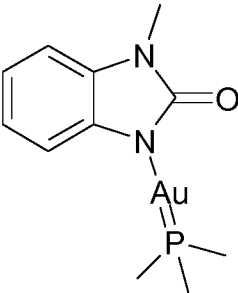
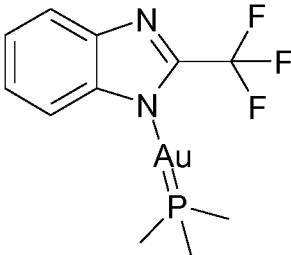
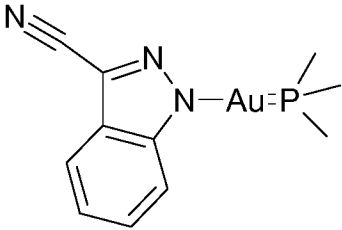
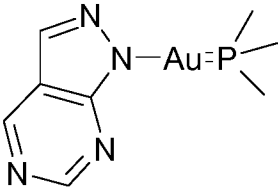
	37*	C	¹ H-NMR (400 MHz, <i>CDCl</i> ₃): δ ppm 7.75 (2H, br s), 1.61 (9H, d, <i>J</i> = 11.1 Hz). ³¹ P-NMR (162 MHz, <i>CDCl</i> ₃): δ ppm -12.29 (s) Beige solid; 101 mg, 97%
	38*	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.96 (2H, br s), 1.67 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.86 (s) White solid; 52 mg, 95%
	39*	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.70 (1H, br s), 7.42 (1H, d, <i>J</i> = 8.3 Hz), 7.08 (1H br s), 6.66 (1H, d, <i>J</i> = 8.3 Hz), 3.75 (3H, s), 1.71 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.20 (s) Yellow solid; 54 mg, 79%
	40*	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.74(1H, br s), 1.71 (9H, d, <i>J</i> = 12.1 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.71 (s) White solid; 51 mg, 92%
	41	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.83 (2H, s), 1.65 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.45 (s) Off-white solid; 36 mg, 55%
	42*	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.33 (1H, dd, <i>J</i> = 4.4, 2.8 Hz), 8.08 (1H, dd, <i>J</i> = 7.9, 1.5 Hz), 8.02 (1H, br s), 6.93 (1H, dd, <i>J</i> = 7.9, 4.4 Hz), 1.71 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.81 (s)

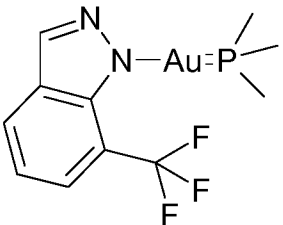
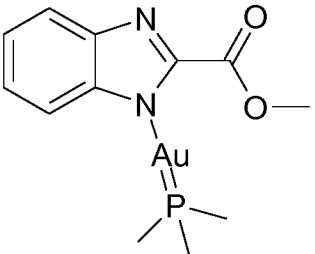
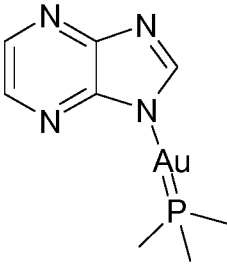
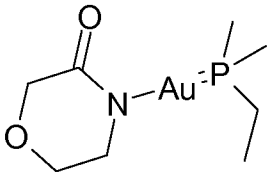
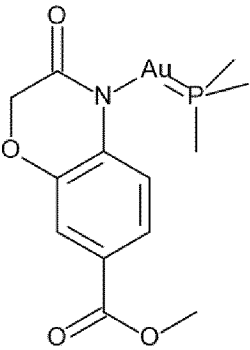
			Off-white solid; 46 mg, 73%
	43	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.22 (1H, br s), 6.87 (2H, br s), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.16 (s)
			White solid; 49 mg, 86%
	44	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.80 (1H, br s), 7.56 (2H, dd, <i>J</i> = 5.8, 3.1 Hz), 7.00 (2H, dd, <i>J</i> = 5.8, 3.1 Hz), 1.71 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.26 (s)
			White solid; 62 mg, 95%
	45	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.43 (2H, br s), 6.91 (2H, br s), 2.48 (3H, s), 1.71 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -8.71 (s)
			Pale pink solid; 66 mg, 97%
	46*	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 2.17 (6H, br s), 1.65 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.21 (s)
			White solid; 40 mg, 67%
	47	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 6.65 (2H, br s), 2.27 (3H, s), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -9.57 (s)
			White solid; 61 mg, 100%
	48	C	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.04 (2H, s), 1.68 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.69 (s)
			Grey solid; 61 mg, 92%

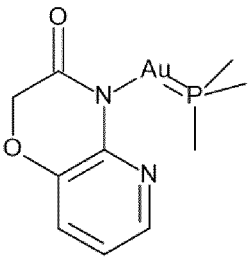
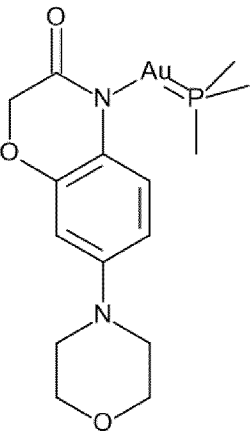
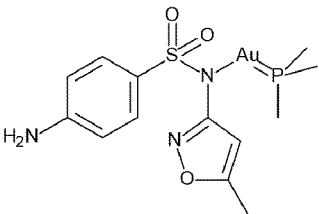
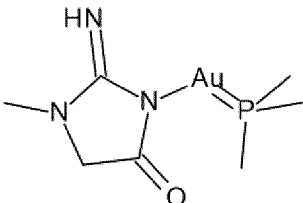
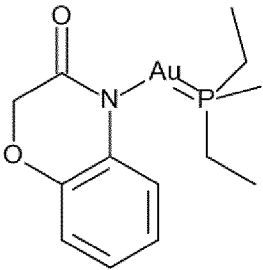
 Chemical structure of compound 49**: A pyridine ring with a nitrile group (NC) at the 2-position and a trimethylphosphino-gold complex (Au=P(CH₃)₃) at the 4-position.	49**	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.59 (1H, br s), 6.85 (1H, br s), 1.66 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -11.23 (s) White solid; 48 mg, 80%
 Chemical structure of compound 50*: A benzimidazole ring system with a methoxy group (OCH₃) at the 6-position and a trimethylphosphino-gold complex (Au=P(CH₃)₃) at the 2-position.	50*	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.86 (1H, d, <i>J</i> = 1.0 Hz), 7.50 (1H, d, <i>J</i> = 8.8 Hz), 7.03 (1H, d, <i>J</i> = 2.3 Hz), 6.78 (1H, dd, <i>J</i> = 8.8, 2.3 Hz), 3.73 (3H, s), 1.69 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.17 (s) White solid; 42 mg, 62%
 Chemical structure of compound 51*: A pyrimidine ring system with a trimethylphosphino-gold complex (Au=P(CH₃)₃) at the 2-position.	51*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.19 (1H, d, <i>J</i> = 4.5 Hz), 8.00 (1H, s), 7.92 (1H, dd, <i>J</i> = 7.8, 1.3 Hz), 7.04 (1H, dd, <i>J</i> = 7.8, 4.5 Hz), 1.72 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.00 (s) Yellow solid; 59 mg, 94%
 Chemical structure of compound 52*: A benzimidazole ring system with an ethylphosphino-gold complex (Au=P(CH₃)₂CH₂CH₃) at the 2-position.	52*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.34 (1H, dd, <i>J</i> = 4.5, 1.8 Hz), 8.08 (1H, ddd, <i>J</i> = 7.8, 1.8, 0.9 Hz), 8.03 (1H, d, <i>J</i> = 0.9 Hz), 6.94 (1H, dd, <i>J</i> = 7.8, 4.5 Hz), 2.01 (2H, dq, <i>J</i> = 11.4, 7.6 Hz), 1.70 (6H, d, <i>J</i> = 11.4 Hz), 1.91 (3H, dt, 20.2, 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 3.01 (s) Brown oil; 34 mg, 54%
 Chemical structure of compound 53*: A pyrimidine ring system with a trimethylphosphino-gold complex (Au=P(CH₃)₃) at the 2-position.	53*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 9.00 (1H, s), 8.73 (1H, s), 8.17 (1H, br s), 1.73 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.73 (s) Beige solid; 51 mg, 80%

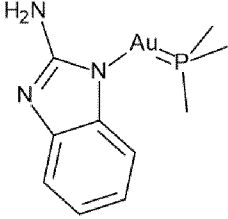
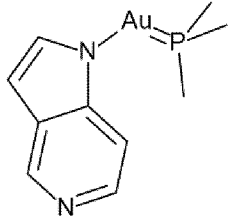
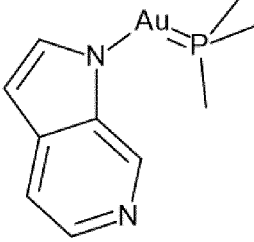
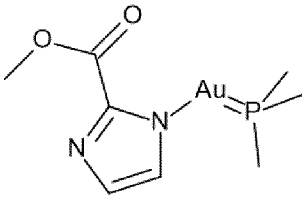
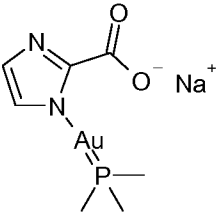
	54	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.13 (1H, dd, <i>J</i> = 4.5, 1.5 Hz), 7.79 (1H, app d, <i>J</i> = 8.1 Hz), 7.42 (1H, dd, <i>J</i> = 2.8, 0.8 Hz), 6.89 (1H, dd, <i>J</i> = 8.1, 4.5 Hz), 6.43 (1H, m), 1.69 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.17 (s) White solid; 45 mg, 71%
	55	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.05 (1H, dd, <i>J</i> = 4.7, 1.6 Hz), 7.81 (1H, ddd, <i>J</i> = 7.7, 1.6, 0.8 Hz), 7.28 (1H, d, <i>J</i> = 2.8 Hz), 6.83 (1H, dd, <i>J</i> = 7.7, 4.7 Hz), 6.29 (1H, dd, <i>J</i> = 2.8, 1.3 Hz), 1.69 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.01 (s) White solid; 40 mg, 63%
	56	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.74 (1H, m), 7.65 (1H, m), 7.36 (1H, dd, <i>J</i> = 2.5, 0.5 Hz), 7.09 (1H, ddd, <i>J</i> = 8.1, 6.8, 1.3 Hz), 7.00 (1H, ddd, <i>J</i> = 7.8, 6.8, 1.0 Hz), 6.51 (1H, m), 1.90 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.06 (s) Pale pink solid; 58 mg, 92%
	57	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.60 (1H, s), 7.09 (2H, s), 3.75 (6H, s), 1.71 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.08 (s) Off-white solid; 66 mg, 90%

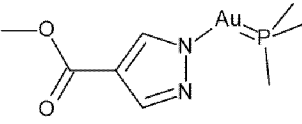
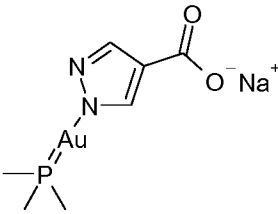
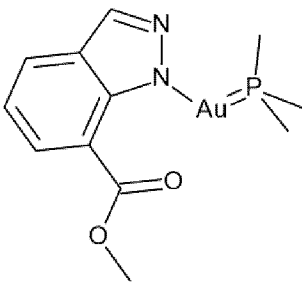
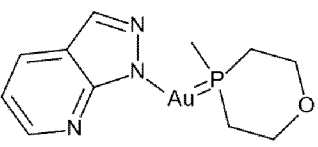
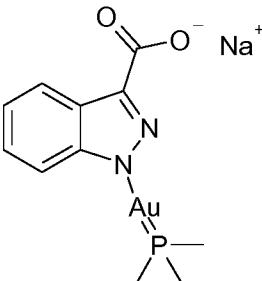
	58*	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.39 (2H, m), 8.32 (1H, s), 1.72 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.54 (s) Off-white solid; 39 mg, 61 %
	59*	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.98 (1H, app d, <i>J</i> = 8.1 Hz), 7.75 (1H, app d, <i>J</i> = 8.3 Hz), 7.24 (1H, m), 7.12 (1H, m), 3.85 (3H, s), 1.73 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.04 (s) White solid; 30 mg, 41%
	60	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.39 (2H, s), 6.10 (1H, s), 1.95-1.86 (2H, m), 1.57 (6H, d, <i>J</i> = 10.6 Hz), 1.11 (3H, dt, <i>J</i> = 19.7, 7.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm 2.32 (s) Light brown solid; 36 mg, 57%
	61*	A	¹ H-NMR (400 MHz, <i>CDCl</i> ₃): δ ppm 8.34 (1H, dd, <i>J</i> = 4.3, 1.5 Hz), 7.98 (1H, br s), 7.94 (1H, dd, <i>J</i> = 8.1, 1.5 Hz), 6.78 (1H, dd, <i>J</i> = 8.1, 1.5 Hz), 2.24-2.14 (2H, m), 1.84-1.74 (6H, m), 1.63 (3H, d, <i>J</i> = 10.9 Hz). ³¹ P-NMR (162 MHz, <i>CDCl</i> ₃): δ ppm 10.74 (s) Light brown solid; 28 mg, 67%

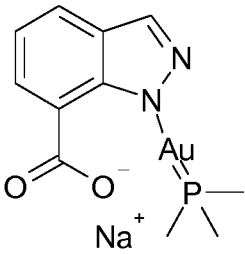
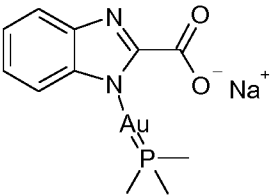
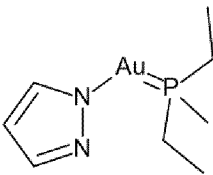
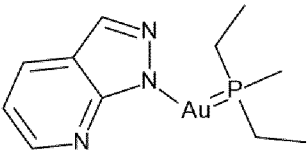
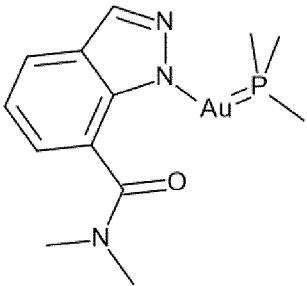
	62*	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.34 (1H, s), 7.31 (1H, m), 1.66 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.18 (s) White solid; 58 mg, 88%
	63	C	¹H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 7.04 (1H, ddd, <i>J</i> = 6.8, 1.5, 0.5 Hz), 6.89 (1H, ddd, <i>J</i> = 6.8, 1.5, 0.5 Hz), 6.83 (1H, td, <i>J</i> = 6.8, 1.5 Hz), 6.80 (1H, td, <i>J</i> = 6.8, 1.5 Hz), 3.23 (3H, s), 1.69 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.19 (s). Cream solid; 59 mg, 87%
	64	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.80 (1H, d, <i>J</i> = 7.6 Hz), 7.68 (1H, d, <i>J</i> = 7.8 Hz), 7.27-7.12 (2H, m), 1.75 (9H, d, <i>J</i> = 12.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.39 (s) Brown solid; 27 mg, 36%
	65*	A	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.85 (1H, d, <i>J</i> = 8.3 Hz), 7.74 (1H, d, <i>J</i> = 8.1 Hz), 7.33 (1H, m), 7.20 (1H, m), 1.73 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.27 (s) White solid; 44 mg, 65%
	66*	A	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 9.18 (1H, s), 8.76 (1H, s), 8.26 (1H, s), 1.72 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.07 (s) White solid; 42 mg, 66%

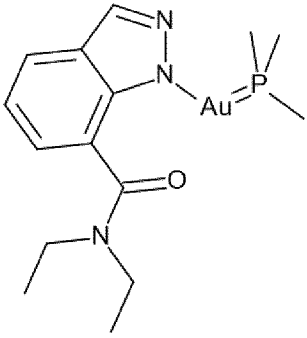
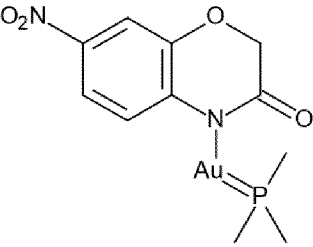
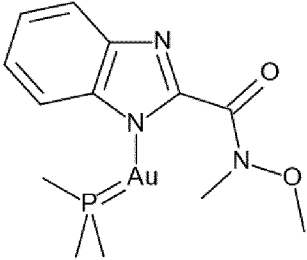
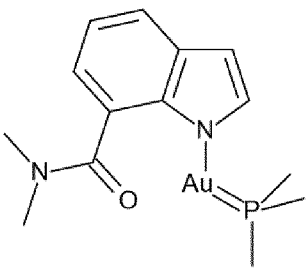
	67*	A	¹H-NMR (400MHz, <i>CDCl</i>₃): δ ppm 8.20 (1H, br s), 7.92 (1H, br s), 7.52 (1H, app d, <i>J</i> = 7.1 Hz), 7.00 (1H, app t, <i>J</i> = 7.6 Hz), 1.66 (9H, d, <i>J</i> = 11.1 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm -12.84 (s) Pale yellow solid; 39 mg, 52%
	68	A	¹H-NMR (400MHz, <i>DMSO-d</i>₆): δ ppm 7.73 (1H, d, <i>J</i> = 7.6 Hz), 7.65 (1H, d, <i>J</i> = 8.1 Hz), 7.19 (1H, dd, <i>J</i> = 7.6, 7.1 Hz), 7.13 (1H, dd, <i>J</i> = 8.1, 7.1 Hz), 3.88 (3H, s), 1.74 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.96 (s) White solid; 23 mg, 32%
	69	C	¹H-NMR (400MHz, <i>DMSO-d</i>₆): δ ppm 8.33 (1H, s), 8.24 (2H, br s), 1.72 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.04 (s) Brown solid; 58 mg, 91%
	70	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 3.83 (2H, s), 3.55 (2H, t, <i>J</i> = 4.8 Hz), 3.35 (2H, t, <i>J</i> = 4.8 Hz), 1.87 (2H, dq, <i>J</i> = 10.8, 7.6 Hz), 1.54 (6H, d, <i>J</i> = 10.6 Hz), 1.10 (3H, dt, <i>J</i> = 19.9, 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 3.1 (s) Brown oil; 42 mg, 74%
	71	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.49 (1H, dd, <i>J</i> = 8.3, 2.0 Hz), 7.36 (1H, d, <i>J</i> = 8.3 Hz), 7.34 (1H, d, <i>J</i> = 2.0 Hz), 4.46 (2H, s), 3.78 (3H, s), 1.68 (9H, d, <i>J</i> = 12.0 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.51 (s) White solid; 69 mg, 89%

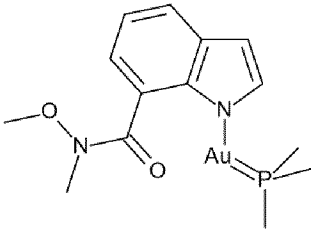
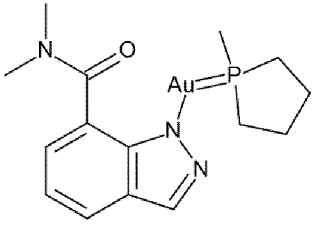
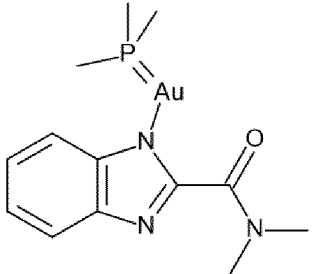
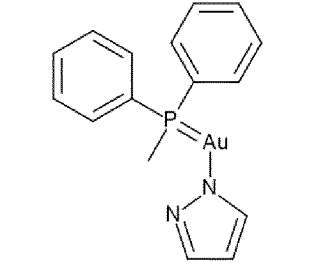
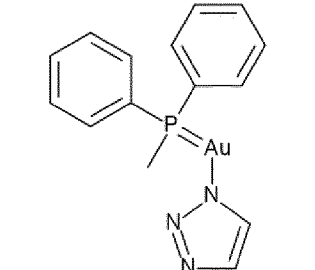
	72	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.83 (1H, dd, <i>J</i> = 5.1, 1.5 Hz), 7.17 (1H, ddd, <i>J</i> = 7.6, 1.5, 0.5 Hz), 6.76 (1H, dd, <i>J</i> = 7.6, 5.0 Hz), 4.46 (2H, s), 1.65 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.83 (s) Off-white solid; 40 mg, 59%
	73	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.14 (1H, m), 6.48 - 6.44 (2H, m), 4.31 (2H, s), 3.71 - 3.68 (4H, m), 2.97 - 2.94 (4H, m), 1.65 (9H, d, <i>J</i> = 11.2 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.46 (s) Off-white solid; 66 mg, 80%
	74	A	¹H-NMR (400 MHz, CD₃OD): δ ppm 7.57 (2H, app d, <i>J</i> = 8.8 Hz), 6.64 (2H, app d, <i>J</i> = 8.8 Hz), 6.06 (1H, s), 5.50 (2H, s), 2.25 (3H, s), 1.68 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, CD₃OD): δ ppm -11.50 (s) Beige solid; 82 mg, 96%
	75	C	¹H-NMR (400 MHz, CD₃CN): δ ppm 5.20 (1H, br s), 3.64 (2H, s), 2.86 (3H, s), 1.59 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, CD₃CN): δ ppm -9.61 (s) Cream solid; 56 mg, 90 %
	76	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.26 (1H, dd, <i>J</i> = 7.8, 1.5 Hz), 6.88-6.82 (2H, m), 6.78-6.72 (1H, m), 4.37 (2H, s), 2.05-1.90 (4H, m), 1.62 (3H, d, <i>J</i> = 10.9 Hz), 1.17 (6H, dt, <i>J</i> = 19.5, 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 18.03 (s)

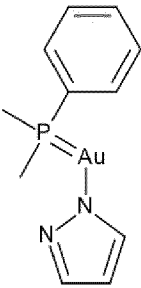
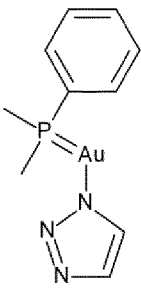
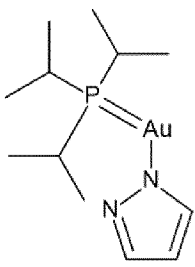
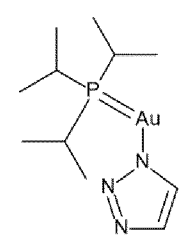
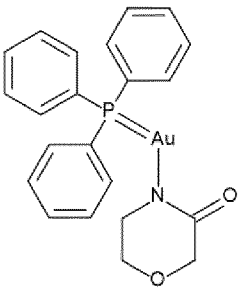
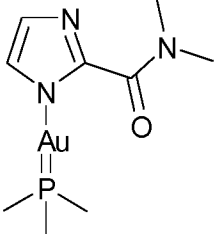
			Cream solid; 43 mg, 64%
	77	C	¹ H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.07 (2H, br s), 6.68 (2H, br s), 5.57 (2H, br s), 1.69 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -8.52 (s)
			White solid; 55 mg, 84%
	78	A	¹ H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 8.73 (1H, s), 7.94 (1H, d, <i>J</i> = 5.6 Hz), 7.43 (1H, d, <i>J</i> = 5.6 Hz), 7.23 (1H, d, <i>J</i> = 2.5 Hz), 6.46 (1H, m), 1.70 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.30 (s)
			White solid; 26 mg, 41%
	79	A	¹ H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 8.85 (1H, s), 7.85 (1H, d, <i>J</i> = 5.4 Hz), 7.40 (1H, d, <i>J</i> = 5.4 Hz), 7.38 (1H, d, <i>J</i> = 2.4 Hz), 6.38 (1H, m), 1.71 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.34 (s)
			Pale orange solid; 32 mg, 51 %
	80	A	¹ H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 7.08 (1H, s), 7.06 (1H, s), 3.75 (3H, s), 1.67 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -11.97 (s)
			Pale pink solid; 60 mg, 93%.
	81	I	¹ H-NMR (400 MHz, <i>DMSO-d6</i>): δ ppm 6.85 (2H, br s), 1.63 (9H, d, <i>J</i> = 11.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -13.17 (s)
			White solid; 67 mg, 89%

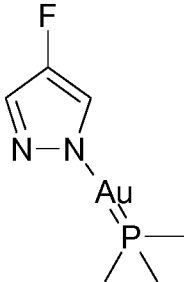
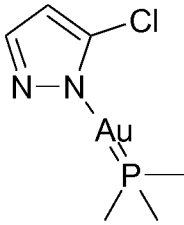
	82	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.90 (2H, br s), 3.67 (3H, s), 1.65 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.43 (s)
			White solid; 61 mg, 95%
	83	I	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 7.56 (1H, br s), 7.49 (1H, br s), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.53 (s)
			White solid; 67 mg, 89%
	84*	A	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.16 (1H, s), 7.95 (1H, d, <i>J</i> = 7.6 Hz), 7.74 (1H, dd, <i>J</i> = 7.6, 1.0 Hz), 6.98 (1H, t, <i>J</i> = 7.6 Hz), 3.90 (3H, s), 1.69 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -13.04 (s)
			Off-white solid; 79 mg, 57%
	85*	J	¹ H-NMR (400 MHz, <i>CDCl</i> ₃): δ ppm 8.44 (1H, dd, <i>J</i> = 4.4, 1.5 Hz), 8.01 (1H, br s), 7.99 (1H, dd, <i>J</i> = 7.8, 1.5 Hz), 6.88 (1H, dd, <i>J</i> = 7.8, 4.4 Hz), 4.06-4.01 (2H, m), 3.94-3.88 (2H, m), 2.31-2.21 (2H, m), 2.05-1.94 (2H, m), 1.72 (3H, d, <i>J</i> = 10.6 Hz). ³¹ P-NMR (162 MHz, <i>CDCl</i> ₃): δ ppm -9.66 (s)
			Cream solid; 22 mg, 50%
	86*	I	¹ H-NMR (400 MHz, <i>DMSO-d</i> ₆): δ ppm 8.19 (1H, d, <i>J</i> = 7.6 Hz), 7.57 (1H, d, <i>J</i> = 7.8 Hz), 7.10 (1H, br s), 6.92 (1H, br s), 1.54 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -10.90 (s)
			Cream solid; 72 mg, 86%

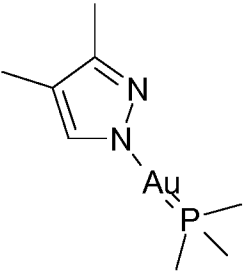
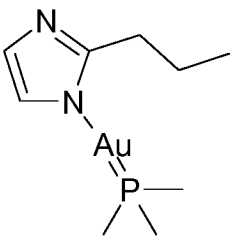
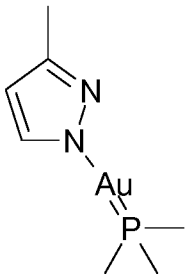
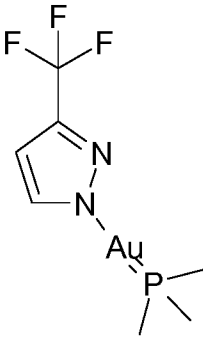
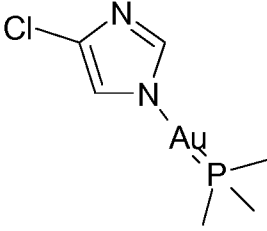
	87*	I	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.91 (1H, s), 7.58 (1H, d, <i>J</i> = 7.6 Hz), 7.55 (1H, d, <i>J</i> = 7.6 Hz), 6.77 (1H, t, <i>J</i> = 7.6 Hz), 1.62 (9H, d, <i>J</i> = 11.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -14.42. (s) Yellow solid; 74 mg, 89%
	88	I	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.60-7.45 (2H, m), 7.05-6.90 (2H, m), 1.69 (9H, d, <i>J</i> = 11.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -12.17 (s) Cream solid; 72 mg, 87%
	89	C.	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.70-7.20 (2H, m), 6.19 (1H, s), 2.04-1.88 (4H, m), 1.61 (3H, d, <i>J</i> = 10.9 Hz), 1.16 (6H, dt, <i>J</i> = 19.2, 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 16.12 (s) Brown gum; 17 mg, 31%
	90*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.35 (1H, dd, <i>J</i> = 4.5, 1.5 Hz), 8.09 (1H, dd, <i>J</i> = 7.8, 1.5 Hz), 8.02 (1H, s), 6.94 (1H, dd, <i>J</i> = 7.8, 4.5 Hz), 2.10-1.95 (4H, m), 1.67 (3H, d, <i>J</i> = 10.9 Hz), 1.20 (6H, dt, <i>J</i> = 19.5, 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 16.63 (s) Cream solid; 26 mg, 42%
	91*	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.07 (1H, s), 7.69 (1H, dd, <i>J</i> = 7.8, 1.0 Hz), 6.98 (1H, dd, <i>J</i> = 6.8, 1.0 Hz), 6.92 (1H, dd, <i>J</i> = 7.8, 6.8 Hz), 3.07 (3H, s), 2.78 (3H, s), 1.68 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -11.61 (s) White solid; 62 mg, 83%

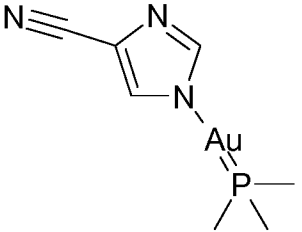
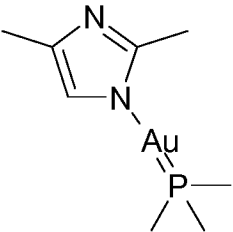
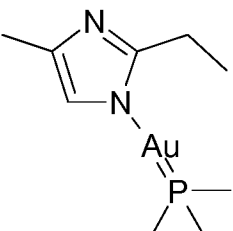
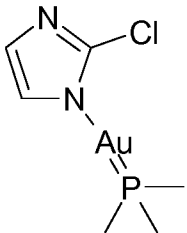
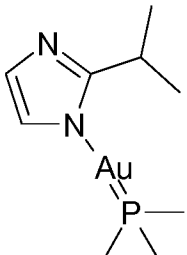
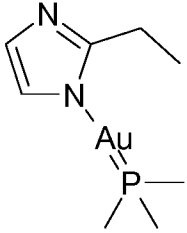
	92*	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.05 (1H, s), 7.67 (1H, dd, <i>J</i> = 6.1, 3.0 Hz), 6.95-6.88 (2H, m), 3.60 (2H, br s), 3.14 (2H, q, <i>J</i> = 7.1 Hz), 1.66 (9H, d, <i>J</i> = 11.6 Hz), 1.25 (3H, t, <i>J</i> = 7.1 Hz), 1.00 (3H, t, <i>J</i> = 7.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -11.89 (s) White solid; 68 mg, 86%
	93	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.81 (1H, dd, <i>J</i> = 8.8, 2.5 Hz), 7.64 (1H, d, <i>J</i> = 2.5 Hz), 7.43 (1H, d, <i>J</i> = 8.8 Hz), 4.55 (2H, s), 1.68 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.51 (s) Light brown solid; 24 mg, 32%
	94	G	¹H-NMR (400MHz, <i>DMSO-d</i>₆): δ ppm 7.72-7.60 (2H, m), 7.14-7.09 (2H, m), 3.86 (1.5H, s), 3.79 (1.5H, s), 3.62 (1.5H, s), 1.72 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.96 (s) Beige solid; 12 mg, 15%
	95	G	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.48 (1H, d, <i>J</i> = 7.8 Hz), 7.19 (1H, d, <i>J</i> = 2.8 Hz), 6.81 (1H, dd, <i>J</i> = 7.8, 7.1 Hz), 6.71 (1H, dd, <i>J</i> = 7.1, 1.3 Hz), 6.38 (1H, dd, <i>J</i> = 2.8, 1.3 Hz), 3.05 (3H, s), 2.75 (3H, s), 1.65 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.88 (s) White solid; 65 mg, 87%

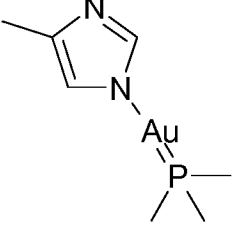
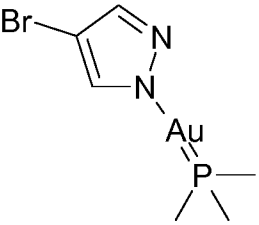
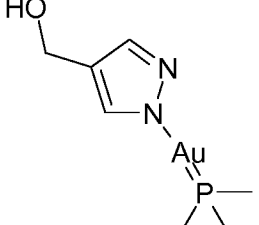
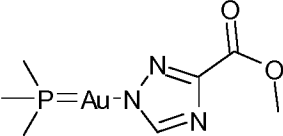
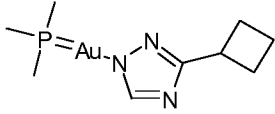
	96	G	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.50 (1H, br dd, <i>J</i> = 7.3, 1.0 Hz), 7.19 (1H, d, <i>J</i> = 2.5 Hz), 6.81 (1H, dd, <i>J</i> = 7.3, 7.1 Hz), 6.78 (1H, dd, <i>J</i> = 7.1, 1.8 Hz), 6.38 (1H, dd, <i>J</i> = 2.5, 1.5 Hz), 3.33 (3H, br s), 3.19 (3H, br s), 1.65 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.51 (s) Beige solid; 43 mg, 58%
	97*	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.07 (1H, s), 7.68 (1H, d, <i>J</i> = 7.8 Hz), 7.00-6.90 (2H, m), 3.04 (3H, s), 2.77 (3H, s), 2.10-2.00 (2H, m), 2.10-2.00 (2H, m), 1.95-1.85 (4H, m), 1.61 (3H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 10.04 (s) Dark pink gum; 52 mg, 86%
	98	G	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.66 (1H, d, <i>J</i> = 7.6 Hz), 7.60 (1H, d, <i>J</i> = 7.6 Hz), 7.13-7.05 (2H, m), 3.44 (3H, s), 3.04 (3H, s), 1.70 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -11.18 (s) Dark purple gummy solid; 25 mg, 34%
	99	C	¹H-NMR (400 MHz, <i>CDCl</i>₃): δ ppm 7.72-7.62 (6H, m), 7.53-6.44 (6H, m), 6.41 (1H, t, <i>J</i> = 2.0 Hz), 2.14 (3H, d, <i>J</i> = 10.1 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm 17.24 (s) White solid, 126 mg, 88%
	100*	C	¹H-NMR (400 MHz, <i>CDCl</i>₃): δ ppm 7.84-7.76 (2H, m), 7.70-7.63 (4H, m), 7.56-7.44 (6H, m), 2.17 (3H, d, <i>J</i> = 10.4 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm 15.16 (s) Beige solid, 111 mg, 87%

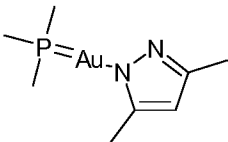
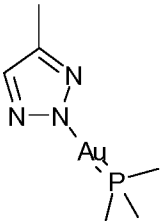
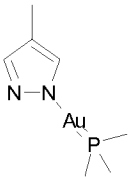
	101	K	¹H-NMR (400 MHz, <i>CDCl</i>₃): δ ppm 7.80-7.73 (2H, m), 7.69 (2H, d, <i>J</i> = 2.0 Hz), 7.55-7.47 (3H, m), 6.41 (1H, t, <i>J</i> = 2.0 Hz), 1.87 (6H, d, <i>J</i> = 10.4 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm -0.30 (s) White solid, 75 mg, 69%
	102*	K	¹H-NMR (400 MHz, <i>CDCl</i>₃): δ ppm 7.84-7.74 (4H, m), 7.58-7.49 (3H, m), 1.89 (6H, d, <i>J</i> = 10.9 Hz). ³¹P-NMR (162 MHz, <i>CDCl</i>₃): δ ppm 1.37 (s) White solid, 93 mg, 86%
	103	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.46 (2H, br s), 6.21 (1H, t, <i>J</i> = 1.8 Hz), 2.48-2.38 (3H, m), 1.28 (18H, dd, <i>J</i> = 16.2, 7.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 63.15 (s) White solid, 115 mg, 95%
	104*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.67 (2H, br s), 2.50-2.43 (3H, m), 1.30 (18H, dd, <i>J</i> = 16.2, 7.1 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 62.53 (s) Brown solid, 101 mg, 97%
	105	G	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.67-7.53 (15H, m), 3.92 (2H, br s), 3.64-3.61 (2H, m), 3.55-3.51 (2H, m). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm 31.60 (s) Grey solid, 80 mg, 89%
	106	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.05 (1H, s), 6.99 (1H, s), 3.57 (3H, br s), 3.02 (3H, br s), 1.70 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -12.68 (s)

			Brown oil; 33 mg, 90%
	107	C	¹ H-NMR (400MHz, <i>DMSO-d</i> ₆): δ ppm 7.40 (1H, br s), 7.35 (1H, br s), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.59 (s)
			White solid, 55 mg, 96%
	108*	C	¹ H-NMR (400MHz, <i>DMSO-d</i> ₆): δ ppm 7.39 (1H, s), 6.16 (1H, d, <i>J</i> = 1.8 Hz), 1.65 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d</i> ₆): δ ppm -11.48 (s)
			White solid, 41 mg, 64%

	109*	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.05 (1H, s), 2.10 (3H, br s), 1.89 (3H, s), 1.64 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.67 (s) White solid, 75 mg, 93%
	110	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 6.65 (2H, s), 2.60 (2H, t, <i>J</i> = 7.6 Hz), 1.71 (2H, sext, <i>J</i> = 7.6 Hz), 1.65 (9H, d, <i>J</i> = 11.6 Hz), 0.90 (3H, t, <i>J</i> = 7.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -9.54 (s) White solid, 59 mg, 64%
	111*	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.25 (1H, br s), 5.95 (1H, br s), 2.21 (3H, br s), 1.65 (9H, d, <i>J</i> = 11.4 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.63 (s) White solid, 105 mg, 96%
	112*	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.52 (1H, m), 6.57 (1H, d, <i>J</i> = 1.8 Hz), 1.67 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -11.43 (s) Off-white solid, 85 mg, 66%
	113*	C	¹H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.11 (1H, br s), 6.75 (1H, br s), 1.65 (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.40 (s) White solid, 85 mg, 76%

	114*	C	¹ H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 7.68 (1H, d, <i>J</i> = 0.8 Hz), 7.41 (1H, d, <i>J</i> = 0.8 Hz), 1.67 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.42 (s) Off-white solid, 92 mg, 79%
	115*	F	¹ H-NMR (400MHz, <i>DMSO-d6</i>): δ ppm 6.38 (1H, br.s), 2.25 (3H, s), 2.06 (3H, s), 1.65 (9H, d, <i>J</i> = 11.7 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm -10.75 (s) Pale brown gum, 124 mg, 100%
	116*	F	¹ H-NMR (400 MHz, <i>DMSO-D6</i>): δ ppm 6.35 (1H, s), 2.55 (2H, q, <i>J</i> = 7.4 Hz), 2.04 (3H, s), 1.61 (9H, d, <i>J</i> = 11.7 Hz), 1.18 (3H, t, <i>J</i> = 7.4 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm - 8.54 (s) Pale brown gum, 127 mg, 100%
	117	F	¹ H-NMR (400 MHz, <i>DMSO-D6</i>): δ ppm 6.78 (2H, br s), 1.66 (9H, d, <i>J</i> = 11.9 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm - 9.81 (s) Off-white solid, 117 mg, 95%
	118	F	¹ H-NMR (400 MHz, <i>DMSO-D6</i>): δ ppm 6.71 (2H, br s), 3.08 (1H, br s), 1.65 (9H, d, <i>J</i> = 11.9 Hz), 1.27 (6H, br s). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm - 8.08 (s) Pale orange gum, 130 mg, 100%
	119	F	¹ H-NMR (400 MHz, <i>DMSO-D6</i>): δ ppm 6.77 (2H, br s), 2.66 (2H, q, <i>J</i> = 7.5 Hz), 1.65 (9H, d, <i>J</i> = 11.4 Hz), 1.24 (3H, t, <i>J</i> = 7.5 Hz). ³¹ P-NMR (162 MHz, <i>DMSO-d6</i>): δ ppm - 8.65 (s) Pale yellow gum, 119 mg, 98%

	120*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.04 (1H, br s), 6.55 (1H, s), 2.11 (3H, s), 1.64 (9H, d, <i>J</i> = 11.9 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm - 9.00 (s) Pale yellow gum, 109 mg, 96%
	121	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.47 (1H, br s), 7.42 (1H, br s), 1.61 (9H, d, <i>J</i> = 11.5 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm - 10.94 (s) White solid, 122 mg, 93%
	122	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.33 (2H, br s), 4.44 (1H, br s), 4.32 (2H, s), 1.64 (9H, d, <i>J</i> = 11.5 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm - 10.48 (s) Yellow gum, 101 mg, 87%
	123*	C	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 8.12 (1H, br s), 3.79 (3H, br s), 1.68 (9H, d, <i>J</i> = 12.3 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.42 (s) White powder, 91 mg, 69%
	124*	A	¹H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 7.73 (0.5H, br s), 7.61 (0.5H, br s) [the signals at 7.73 ppm and 7.61 ppm coalesce to a br s at 7.69 ppm on warming to 75°C], 3.62 (0.5H br s), 3.43 (0.5H, br s) [the signals at 3.62 ppm and 3.43 ppm coalesce to a br s at 3.61 ppm on warming to 75°C], 2.24 (4H, br s), 1.96 (1H, m), 1.84 (1H, m), 1.67, (9H, d, <i>J</i> = 11.6 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.75, -10.26 (s) [the two signals at - 9.75 ppm and -10.26 ppm coalesce to a singlet at -9.86 ppm on warming to 75°C]. Pink powder, 109 mg, 83%

	125	C	1H-NMR (400 MHz, <i>DMSO-d</i>₆): δ ppm 5.64 (1H, s), 2.05 (6H, br s), 1.57, (9H, d, <i>J</i> = 11.2 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.69 (s) White powder, 108 mg, 88%
	126*	C	1H-NMR (400 MHz, <i>DMSO-d</i>₆): 7.30 (1H, br s), 2.25-2.06 (3H, m) [the signals at 2.25-2.06 ppm coalesce to a br s at 2.15 ppm on warming to 75°C]. ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -9.37, -10.26, -11.47 (s) [the three signals at -9.37 ppm, -10.26 ppm and -11.47 ppm coalesce to a br s at -10.11 ppm on warming to 75°C] Grey solid, 49 mg, 94%
	127	C	1H-NMR (400 MHz, <i>DMSO-d</i>₆): 7.39-7.08 (2H, m), 1.97-1.88 (3H, m), 1.58 (9H, d, <i>J</i> = 11.5 Hz). ³¹P-NMR (162 MHz, <i>DMSO-d</i>₆): δ ppm -10.59 (s)

*structural assignment to be confirmed: structure may be a regioisomer of this structure in which the Au is connected through a different N atom of the heterocyclic ring, or may represent a mixture of the possible regioisomers.

- 5 **assigned on basis of X-ray crystallography experiments, although may represent a mixture of the possible regioisomers

Example 2

Growth Media

10 Tryptic Soy Broth

Formula / Litre	
Pancreatic Digest of Casein	17.0 g
Enzymatic Digest of Soybean	3.0 g
Sodium Chloride	5.0 g
Di-potassium hydrogen Phosphate	2.5 g
Glucose	2.5 g

Directions for use: Dissolve 30 g of the medium in one litre of purified water, mix thoroughly, and then autoclave at 121°C for 15 minutes.

Luria Broth

Formula / Litre	
Tryptone	10.0 g
Yeast Extract	5.0 g
NaCl	5.0 g

- 5 Directions for use: Dissolve components in 1 litre of distilled or deionized water and sterilize by autoclaving at 121°C for 15 minutes.

Mueller Hinton II Broth (Cation-Adjusted)

Formula / Litre	
Beef Extract	3.0 g
Acid Hydrolysate of Casein	17.5 g
Starch	1.5 g
*Adjusted and/or supplemented as required with appropriate salts to provide 20–25 mg/L of calcium and 10–12.5 mg/L of magnesium and as additionally required to meet performance criteria.	

- 10 Directions for use: Dissolve components in 1 litre of distilled or deionized water and sterilize by autoclaving at 121°C for 15 minutes.

Brain Heart Infusion Broth

Formula / Litre	
Brain Heart Infusion solids	12.5 g
Beef heart infusion solids	5 g
Proteose peptone	10g
Glucose	2 g
Sodium Chloride	5 g
Di-sodium Phosphate	2.5 g

- 15 Directions for use: Dissolve components in 1 litre of purified water. Heat the mixture with frequent agitation to completely dissolve the medium, and sterilize by autoclaving at 121°C for 15 minutes.

Growth assay for S.aureus.

Stock solution of the test compounds (20mg/ml) in dimethyl sulfoxide (DMSO) were serially diluted in DMSO and each diluted compound added in duplicate to a 96-well plate to a final DMSO concentration of 2% (v/v). An overnight culture of *S. aureus* (Oxford strain) grown in tryptic soy broth (TSB) was diluted to approximately 5×10^7 cfu/ml and 150µl of this sample was added to each well of the 96-well plates. Control wells included an 'untreated' control with bacteria in TSB in the presence of 2% DMSO and a negative sample (containing 150µl TSB growth media in the presence of 2% DMSO). Plates were incubated in a shaking incubator at 37°C for 22-24 hours and bacterial growth assessed by absorbance at a wavelength of 595nm. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of compound that inhibited growth compared to the no-treatment control.

Variation of growth assays for:

Klebsiella pneumoniae, *Acinetobacter baumannii* or *E.coli* (ATCC 25922): use of 1/100 overnight dilution to set up assay, medium used: Luria broth (LB); incubation without shaking.

P.aeruginosa (ATCC 27853): use of 1/100 overnight dilution to set up assay, medium used: Cation adjusted Mueller Hinton broth (CaMHB); incubation without shaking.

Compound	<i>S. aureus</i> MIC (µg/mL)	<i>K.</i> <i>pneumoniae</i> MIC (µg/mL)	<i>E.coli</i> MIC (µg/mL)	<i>P.</i> <i>aeruginosa</i> MIC (µg/mL)
1	<0.8	3.1-6.3	3.1	12.5
2	<0.8	6.3	3.1-6.3	12.5
3	<0.8	12.5	12.5	25-50
4	<0.8	3.1	1.6	12.5
5	<0.8	3.1	6.3	12.5
6	<0.8	3.1-6.3	1.6	12.5
7	<0.8	3.1-6.3	6.3	6.3-12.5
8	<0.8	3.1-6.3	6.3	12.5
9	<0.8	6.3	3.1-6.3	12.5
10	≤0.8	1.6-3.1	1.6-3.1	

Compound	<i>S. aureus</i> MIC (µg/mL)	<i>K.</i> <i>pneumoniae</i> MIC (µg/mL)	<i>E.coli</i> MIC (µg/mL)	<i>P.</i> <i>aeruginosa</i> MIC (µg/mL)
11	≤0.8	12.5-25	12.5	
12		1.6-3.1	1.6-3.1	
13		3.1	1.6-3.1	
14	<0.8	3.1	1.6	
15	<0.8	3.1-6.3	1.6-3.1	
16	0.8	3.1-6.3	3.1-6.3	
17	<0.8	3.1-6.3	3.1	
18	0.8	3.1	1.6-3.1	
19	0.8	3.1-6.3	1.6-3.1	
20	<0.8	3.1	1.6	
21	0.8-1.6	3.1	1.6	
22	1.6	3.1	1.6	
23	0.8	1.6-3.1	1.6	
24	0.8-1.6	3.1	1.6-3.1	
25	<0.8	3.1	0.8-1.6	
26	0.8-1.6	3.1	1.6	
27	0.8	3.1	1.6	
28	<0.8	3.1	0.8-1.6	
29	0.8-1.6	3.1	1.6	
30	<0.8	3.1	1.6	
31	<0.8	3.1	0.8-1.6	
32	<0.8	3.1	0.8-1.6	
33	<0.8	3.1	1.6	
34	1.6	12.5	6.3	12.5-25
35	1	6.3	6.3	12.5
36	<0.8	3.1	3.1-6.3	6.3-12.5
37	0.8	3.1-6.3	1.6	
38	<0.8	3.1	3.1	6.3-12.5
39	<0.8	3.1-6.3	6.3	12.5
40	<0.8	3.1-6.3	3.1-6.3	12.5

Compound	<i>S. aureus</i> MIC (µg/mL)	<i>K.</i> <i>pneumoniae</i> MIC (µg/mL)	<i>E.coli</i> MIC (µg/mL)	<i>P.</i> <i>aeruginosa</i> MIC (µg/mL)
41	1.6	3.1	1.6-3.1	
42	≤0.8	1.6-3.1	1.6	
43	<0.8	3.1	0.8-1.6	
44	0.8	3.1	1.6	
45	0.8	3.1	1.6	
46	<0.8	3.1	0.8-1.6	
47	<0.8	3.1	1.6-3.1	
48	<0.8		1.6	
49	<0.8	1.6-3.1	0.8-1.6	
50	<0.8	3.1	1.6	
51	0.8-1.6	3.1	0.8-1.6	
52	<0.8	3.1	1.6	
53	<0.8	3.1	1.6	
54	<0.8	3.1	1.6	
55	<0.8	3.1	1.6	
56	<0.8	3.1-6.3	1.6-3.1	
57	<0.8	3.1	1.6-3.1	
58	<0.8	3.1	1.6	
59	<0.8	3.1	1.6	
60	<0.8	3.1-6.3	3.1	
61	<0.8	3.1-6.3	3.1	
62	<0.8	3.1	1.6	
63	<0.8	1.6-3.1	1.6	
64	<0.8	3.1	1.6	
65	<0.8	3.1	1.6	
66	<0.8	3.1	<0.8	
67	<0.8	3.1	1.6	
68	<0.8	3.1	1.6	
69	<0.8	3.1	1.6	
70	<0.8	3.1-6.3	1.6	

Compound	<i>S. aureus</i> MIC (µg/mL)	<i>K.</i> <i>pneumoniae</i> MIC (µg/mL)	<i>E.coli</i> MIC (µg/mL)	<i>P.</i> <i>aeruginosa</i> MIC (µg/mL)
71	≤0.8	1.6-3.1	3.1	25
72	≤0.8	1.6	3.1-6.3	12.5-25
73	≤0.8	1.6-3.1	3.1-6.3	25-50
74	≤0.8	1.6	3.1	25
75	≤0.8-1.6	≤0.8-3.1	1.6-3.1	25
76	≤0.8-1.6	1.6-25	3.1-25	12.5-25
77	≤0.8	≤0.8-1.6	1.6-3.1	12.5
78	≤0.8-1.6	≤0.8-3.1	1.6-3.1	25
79	≤0.8-12.5	≤0.8-1.6	1.6	25
80	≤0.8-12.5	≤0.8-1.6	1.6	25
81	≤0.8	1.6	1.6-3.1	12.5
82	≤0.8	1.6-3.1	3.1	12.5
83	≤0.8-1.6	1.6-3.1	3.1	12.5-25
84	≤0.8	≤0.8-3.1	1.6-3.1	12.5
85	1.6-3.1	1.6-6.3	6.3-12.5	25-50
86	≤0.8-3.1	≤0.8-3.1	3.1	6.3-25
87	≤0.8-3.1	≤0.8-3.1	3.1-6.3	12.5-25
88	≤0.8-3.1	≤0.8-3.1	1.6-3.1	6.3-12.5
89	≤0.8	3.1-6.3	6.3	12.5
90	≤0.8	3.1	6.3	12.5-25
91	≤0.8-1.6	≤0.8-1.6	3.1	12.5
92	≤0.8-1.6	1.6	3.1-6.3	6.3-12.5
93	≤0.8	0.8	<0.8-3.1	6.3-25
95	1.6-3.1	1.6-3.1	3.1-6.3	6.3-12.5
96	≤0.8-3.1	1.6-3.1	3.1-6.3	3.1-12.5
97	1.6-3.1	3.1	6.3	12.5
98	≤0.8-1.6	1.6-3.1	3.1	3.1-12.5
99	1.6	25-50	50-100	>100
100	1.6-3.1	37.5-50	100	>100
101	≤0.8-1.6	12.5-25	12.5-50	25

Compound	<i>S. aureus</i> MIC ($\mu\text{g/mL}$)	<i>K.</i> <i>pneumoniae</i> MIC ($\mu\text{g/mL}$)	<i>E.coli</i> MIC ($\mu\text{g/mL}$)	<i>P.</i> <i>aeruginosa</i> MIC ($\mu\text{g/mL}$)
102	$\leq 0.8-1.6$	12.5-25	12.5-25	25
103	$\leq 0.8-1.6$	25-50	25-75	25
104	$\leq 0.8-1.6$	25-50	50-75	50
105	1.6-3.1	>100	100	100
106	$\leq 0.8-3.1$	1.6-3.1	3.1	12.5-25
107	$\leq 0.8-1.6$	3.1-6.3	3.1-6.3	12.5
108	$\leq 0.8-1.6$	3.1	3.1-6.3	12.5
109	0.8	3.1-6.2	1.6-3.1	25
110	0.8	1.6-6.2	1.6-3.1	12.5-25
111	0.4-0.8	3.1	1.6-3.1	12.5-25
112	0.4-1.6	1.6-3.1	1.6-3.1	25
113	0.8-1.6	1.6-6.2	1.6-3.1	25
114	$\leq 0.2-0.8$	1.6-3.1	1.6-3.1	25
115	0.4-0.8	3.1	1.6-3.1	12.5-25
116	0.8-1.6	3.1	3.1	12.5-25
117	0.8	3.1	1.6-3.1	25
118	0.4-0.8	3.1	1.6-3.1	25
119	0.4-0.8	3.1	1.6-3.1	25
120	0.8	3.1	3.1	25

Inhibition of Neisseria gonorrhoeae (NCTC 8375) growth on solid media

N. gonorrhoeae was grown for 48 hours at 37°C on Chocolate agar plates (BD Diagnostics). A culture loop-full of bacterial culture was picked from the plate and re-suspended in 50 μL sterile phosphate buffered saline. The suspension was spread evenly onto the surface of a fresh chocolate agar plate and left to dry (approximately 5 minutes). Small discs of blotting paper were placed on the surface of the agar plate and 3 μL of test compounds (at 20mg/ml) were applied to the discs. The plates were incubated overnight at 37 °C and zones of clearance around the disc were measured.

HepG2 cell inhibition assay

Cell counting kit-8 (Sigma, CCK-8) assays were performed to assess the effect of compounds on cell viability. The assay is based on the reduction of a water-soluble tetrazolium salt (WST-8) by cellular dehydrogenases to a formazan dye which can be detected spectroscopically. 96-well plates were seeded with the human hepatocyte cell line (HepG2) at approximately 8×10^3 cells per well in Eagle's Minimum Essential Medium (EMEM) with Earle's salts and sodium bicarbonate supplemented with 10% heat-inactivated foetal bovine serum 2mM glutamine and 1% non-essential amino acids (NEAA). The following day serial dilutions of compounds (dissolved and diluted in DMSO) were added to the cells in duplicates. Control wells included an 'untreated' control where cells were grown in the presence of 1% DMSO and a 'medium only' control (plus 1% DMSO). After 24 hours CCK-8 reagent (10 μ l) was added to each well and cell viability was assessed by measuring the absorbance at a wavelength of 450nm after 2-3h hours. Only living cells can reduce the tetrazolium salts into coloured formazan products. Results were expressed as 50% growth inhibition (TD₅₀) values compared to 'untreated' control.

Compound	HepG2 cell TD ₅₀ (μ g/mL)
1	4
2	3
3	6
4	7
5	6
6	9
7	11
8	9
9	7
10	15
11	4
12	4
13	3
14	7
15	3
16	10
17	8

18	5
19	13
20	2
21	4
24	5
25	5
26	6
27	4
28	9
29	3
30	3
31	3
36	7.3
37	11.9
38	7
39	9
40	6
41	16
42	5
43	4
44	5
45	5
46	5
47	3.9
48	4
50	3
51	3

Efficacy studies in the Galleria mellonella model

- 5 *G. mellonella* larvae at 5th or 6th instar stage were purchased from a commercial supplier and used within 3 days. Prior to infection larvae were kept at room temperature. Larvae were infected with bacteria (various Gram positive and negative bacteria, including *S.aureus*, *K.pneumoniae*, *E.coli* and *P.aeruginosa*) using a sterile Hamilton syringe. Bacteria cultures were grown overnight, washed x3 in PBS and resuspended in PBS. Larvae were wiped with 70% ethanol and 10µl of bacteria solution (to cause 80%-100%

death within 3- 4 days) was injected into the bottom right proleg of the larvae. Larvae injected with 10µl of PBS were used as negative controls. Larvae were then placed in petri dishes (1 dish per condition) containing filter paper at the bottom of the dish at 37°C. After various time points post infection (1-6h), larvae were taken from the incubator wiped again with 70% ethanol and injected with 10µl of various concentrations of compound, dissolved in either 5% dimethyl sulfoxide, 5% ethanol or 5% 1-methyl-2-pyrrolidinone into a proleg on the left hand-side. Control larvae received 10µl of 5% solvent. Ten larvae were injected for each condition. To assess the toxicity of the compound, larvae were injected with various concentrations of compound alone. Larvae were returned to a 37°C incubator and checked daily. Larvae were considered dead when no movement occurred when touched with a blunt pair of forceps. Black or discoloured larvae which still showed movement were considered to be alive. Numbers of dead larvae were recorded each day.

15 *Primary cells viability assay*

Neutrophils and peripheral blood mononuclear cells (PBMCs) were isolated from venous blood obtained from healthy volunteers as previously described (Nauseef, Methods in Molecular Biology, 412 (2007), pp. 15–20). In brief, heparinised blood was diluted 1:1 with 3% Dextran-500 PBS solution (Sigma) to allow for erythrocyte sedimentation. Buffy coat was centrifuged over Hypaque-Ficoll (GE Lifescience) and PBMCs were carefully collected from the interface of the Hypaque-Ficoll and the upper liquid layer. Pelleted neutrophils were collected after hypotonic lysis of residing erythrocytes. Isolated cells were washed and suspended in culture media (RPMI+ 10% FBS) at 2×10^6 cells/ mL. Cell suspensions were transferred into 96-well plates containing compound in serially diluted (1% final volume). After 24 hours, the reaction was stopped and cells were stained with AnnexinV and 7-AAD. Results were determined by FACSCalibur and viability was defined for AnnexinV/ 7-AAD double negative cells population.

Biofilm prevention assay (S. aureus)

The effect of a test compound on the formation of a *S. aureus* biofilm was assessed using a biofilm prevention assay as described by Merritt *et al.* Current Protocols in Microbiology, 2011, 1B.1.1-1B1.18 with slight modifications. Briefly, *S. aureus* was grown overnight in tryptic soy broth (TSB) and diluted to 1/100 before 150 µL was added to the wells of a flat bottomed 96-well plate. Three microliters of compound at the appropriate dilution in DMSO was added to the wells in duplicate. Controls included a positive control with bacteria alone in TSB with 2% DMSO and a negative (no bacteria) control with 150 µL

- TSB containing 2% DMSO. Plates were sealed with AeraSeal™ and incubated at 37°C for 24 hours. Plates were then washed three times with PBS, dried at 60 °C for 1 hour and stained with crystal violet for 1 hour. The plates were again washed three times with water, then dried 33% acetic acid was added to re-solubilize the crystal violet stain bound to the adherent cells. Absorbance was then measured at 595 nm and expressed as a percentage of the bacteria only control. A biofilm inhibitory concentration (BIC₉₀) was determined as the concentration at which biofilm mass (measured by crystal violet staining) was reduced by at least 90% compared to untreated controls.
- 10 The effect of a test compound on preformed *S. aureus* biofilms can also be assessed. Briefly *S.aureus* was plated in 96-well plates as described in above and incubated at 37 °C for 24 hours. Biofilms were then washed 3 times with TSB and 150 µL of fresh TSB and 3 µL of compound at the appropriate dilution in DMSO was added to the wells in duplicate. Plates were again sealed with AeraSeal™ and reincubated at 37 °C for 24
- 15 hours. Biofilm was then detected as described above.

Compound	<i>S.aureus</i> BF dispersal BIC ₉₀ (µg/mL)
1	≤0.8
3	≤0.8
12	≤0.8
14	≤0.8
18	≤0.8
21	1.6
25	≤0.8
28	≤0.8
32	≤0.8
36	≤0.8
42	≤0.8
43	≤0.8
46	≤0.8
48	≤0.8
49	≤0.8
54	≤0.8

57	≤ 0.8
----	------------

Biofilm assay for A. baumannii

A.baumannii was grown overnight in LB broth and diluted 1/100-1/500 before 200 μ L was added to the wells of a flat bottomed 96-well plate with TSP 96 pins lid inserted. Plates with pins were incubated at 37 °C for 24 hours. Pins were washed with sterile phosphate buffered saline three times and exposed to compounds at pre-determined concentration in LB broth for 24 hours. Pins were washed again and either stained with crystal violet as described in the *S.aureus* biofilm assay, or incubated with LB media for 24 hours and the minimum biofilm eradication concentration (MBEC) was measured as the lowest concentration of compounds preventing further planktonic growth.

Compound	Minimum biofilm eradication conc. (MBEC) μ g/mL
1	2.5-5
3	5-10
42	10-20
36	20
52	10
53	10
57	10
58	20
59	20
60	10
61	10
62	10
63	20
66	20
70	10
105	40
84	10

Persister cell assay

To determine whether *S. aureus* persister cells were susceptible to treatment with a test compound, a persister cell (or SCV) isolate *hemB* mutant of NCTC 8325-4 was used (Von Eiff *et al.*, (1997) J Bacteriol 179:4706-4712). This persister cell variant displays varying

resistance to erythromycin and the aminoglycosides gentamicin and kanamycin. Growth assays were performed essentially as described above with the bacteria being grown in TSB. Disc assays were also performed by plating bacteria on TSB agar. Discs impregnated with an amount of test compound were placed on top of the agar. The plates were incubated overnight at 37 °C and any zone of bacterial inhibition was observed.

Sensitivity of multidrug resistant clinical isolates

The activity of test compounds against multi-drug resistant bacterial strains was assessed by the disk diffusion assay; a standardised method to assess for the antimicrobial susceptibility of microorganisms (adapted from EUCAST, Version 5, January 2015). In brief, bacterial cultures were suspended in phosphate buffer and spread evenly onto blood agar plates. Cellulose disks (5mm) were placed onto the agar plates and 3µl test compound (60µg/disk) were pipetted to the centre. A panel of standard antibiotics disks (Sigma) were used to control for the antimicrobial resistance profile of the individual strains (quantity as indicated in the table). The plates were then placed into a thermo-incubator and were cultured at 37°C over-night. Activity was recorded by measuring the zone of clearance (mm) around the disks.

Clinical isolate	CDC classification	Threat level	Size of clearance zone (mm) for 60 µg of Compound 35	Size of clearance zone (mm) for 60 µg of Compound 36
<i>E. faecalis</i> DSM13591	VRE	Serious	12	20
<i>A. baumannii</i> NC13421	MDRA	Serious	7	11
<i>K. pneumoniae</i> 13368	ESBL	Serious	8	15
<i>E. coli</i> 13400	ESBL	Serious	11	ND

Comparative data – size of clearance of zone (mm)

Antibiotic	Compound quantity (µg)	<i>E. faecalis</i> DSM13591	<i>A. baumannii</i> NC13421	<i>K. pneumoniae</i> 13368	<i>E. coli</i> 13400
Amoxycillin	2	17	R	R	R

Azetronam	30	R	R	11	23
Cefotaxime	30	R	R	R	18
Ceftriaxone	30	R	R	R	R
Colistin	10	N/A	11	9.5	12
Ertapenem	10	14	R	R	30
Imipenem	10	26	R	18	29
Linezolid	10	22	N/A	N/A	N/A
Meropenem	10	17	R	22	ND
Piperacillin/Tazo bactam	36	21	R	15	17
Vancomycin	30	R	N/A	N/A	N/A

R = resistant

N/A = strain not sensitive

ND = not done

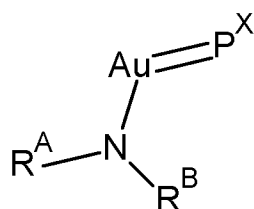
5

References

	doi
Aguinagalde, L., <i>et al.</i> , <i>J. Antimicrob. Chemother.</i> , 2015, 70(9), 2608-2617	10.1093/jac/dkv163
Glišić, BD & Djuran MI, <i>Dalton Trans.</i> , 2014, 43, 5950-5969	10.1039/c4dt00022f
Medeira, JM, <i>et al.</i> , <i>Inflammopharmacology</i> , 2012, 20(6), 297-306	10.1007/s10787-012-0149-1
Jackson-Rosario, S, <i>et al.</i> , <i>J. Biol. Inorg. Chem.</i> , 2009, 14(4), 507-519	10.1007/s00775-009-0466-z
Nomiya, K., <i>et al.</i> , <i>J. Chem. Soc., Dalton Trans.</i> , 1998, 4101–4108	10.1039/A806283H
Nomiya, K., <i>et al.</i> , <i>J. Inorganic Biochem.</i> , 2003, 95, 208-220	10.1016/S0162-0134(03)00125-9
Novelli, F, <i>et al.</i> , <i>Farmaco</i> , 1999, 54, 232–236	10.1016/S0014-827X(99)00019-1
Shaw, CF, <i>Chem Rev.</i> , 1999, 99(9), 2589-2600	10.1021/cr980431o
Rhodes, MD, <i>et al.</i> , <i>J. Inorg. Biochem.</i> , 1992, 46, 129-142	10.1016/0162-0134(92)80016-O
Fricker, SP, <i>Transition Met. Chem.</i> , 1996, 21, 377-383	10.1007/BF00139037

CLAIMS

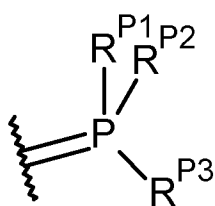
1. A compound of formula (I):



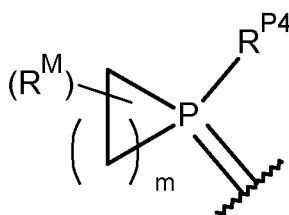
Formula (I)

for use in the prevention or treatment of a bacterial infection wherein:

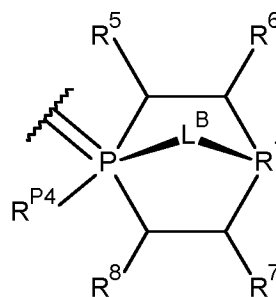
P^X is selected from the group consisting of (P1), (P2) and (P3);



(P1)



(P2)



(P3)

wherein

R^{P1} and R^{P2} are each independently selected from

methyl, ethyl, isopropyl and phenyl;

R^{P3} is selected from the group consisting of

methyl and ethyl,

isopropyl, t-butyl,

cyclopentyl,

phenyl,

4-membered or 5-membered heterocycloalkyl group linked to phosphorus via a carbon atom in the ring, including a single heteroatom independently selected from NR^Z, O and S,

-CF₃, -CH₂CF₃, -CH₂CF₂H, -CH₂CH₂OR^{PB},

-CH₂Q and -(CH₂)₂Q;

wherein Q is a C₅₋₆ heteroaryl group, optionally substituted with one or more groups R^{PA};

R^{P4} is selected from methyl and ethyl;

m is an integer selected from 1, 2 or 3;

R^M is one or more optional substituents on the ring independently selected from

R^{PC} when attached to a carbon atom adjacent the phosphorus atom, or
-OH, -OC₁₋₃alkyl and R^{PC}, when attached to other ring carbons;

5 -L^B- is methylene, ethylene or is absent;

when -L^B- is present, R^{P4} is absent and R¹ is selected from N, CH and CR^{PC};

when -L^B- is absent, R¹ is selected from the group consisting of

O,

NR^Z,

10 SO₂,

CH₂, CHF, CF₂ and CHR^{PC};

wherein R^Z is selected from the group consisting of

H, C₁₋₃alkyl, COC₁₋₃alkyl and SO₂C₁₋₃alkyl;

R⁵ and R⁸ are each independently selected from H and R^{PC};

15

R⁶ and R⁷ are each independently selected from H and R^{PC};

wherein R^{PC} is selected from the group consisting of

C₁₋₃alkyl, optionally substituted with one or more groups R^{PD};

wherein R^{PA} is selected from the group consisting of

20 linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with
one or more groups R^{AL},

-F, -Cl, -Br, -CN

-OH, -OR^{PE},

-CF₃, -CF₂H,

25 -COR^{PE},

-CH₂OH, -CH₂OR^{PE},

-COOH, -COOR^{PE}, -CONH₂, -CONHR^{PE}, -CONR^{PE}₂,

-OCOR^{PE}, -OCONH₂, -OCONHR^{PE}, -OCONR^{PE}₂,

-NH₂, -NHR^{PE}, -NR^{PE}₂,

30 -SO₂NH₂, -SO₂NHR^{PE}₂, -SO₂NR^{PE}₂,

-SO₂R^{PE},

-NHCOH, -NHCOR^{PE}, -NR^{PE}COH and -NR^{PE}COR^{PE};

and R^{PB} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with

35 one or more groups R^{AT},

C₃₋₆cycloalkyl, C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl or C₅₋₆heterocycloalkenyl
 optionally substituted with one or more groups R^{AT},
 phenyl optionally substituted with one or more groups R^{AR}, and
 C₅₋₆heteroaryl optionally substituted with one or more groups R^{AR};

5 R^{PE} is selected from

linear or branched C₁₋₄alkyl optionally substituted with one or more groups R^{PD};
 and R^{PD} is selected from the group consisting of

F,

OH and OC₁₋₃alkyl;

10 R^A is selected from the group consisting of

H;

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl,

C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl and C₅₋₆heterocycloalkenyl optionally
 substituted with one or more groups R^{AL},

15 C₅₋₆heteroaryl, optionally substituted with one or more groups R^{A1},

C₁₋₃alkyl substituted by phenyl or C₅₋₆heteroaryl, which groups may optionally
 substituted with one or more groups R^{A1},

R^B is selected from -COR^{A2} and -SO₂R^{A2};

or R^A and R^B together with the nitrogen atom to which they are attached form

20 a 5- or 6-membered heteroaryl, heterocycloalkyl or heterocycloalkenyl group
 optionally substituted with one or more groups selected from

oxo,

=NH;

phenyl optionally substituted with one or more groups R^{A1},

25 R^{A2}, and

R^{A1};

an 8- to 10-membered heterobicycyl group optionally substituted with one or more
 groups selected from

oxo,

30 -NO₂;

-C(=O)N(R^{N1})₂, wherein each R^{N1} is independently selected from

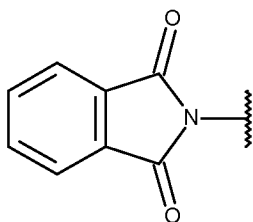
R^{N2} and -OR^{N3}, wherein R^{N2} and R^{N3} are each independently selected from
 linear unsubstituted C₁₋₆alkyl;

phenyl optionally substituted with one or more groups R^{A1},

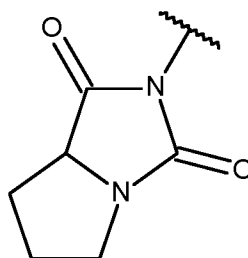
35 R^{A2} and

R^{A1};

with the proviso that when P^X is $P(C_2H_5)_3$, $-NR^A R^B$ is not selected from the groups (X1) or (X6)

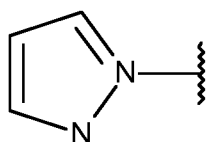


(X1)



(X6)

- 5 with the further proviso that when P^X is PPh_3 , $-NR^A R^B$ is not selected from the groups (X15):



(X15)

wherein

- 10 R^A is selected from the group consisting of
 linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with
 one or more groups R^{AL} ,
 $-F$, $-Cl$, $-Br$, $-CN$
 $-OH$, $-OR^{A2}$,
 15 $-CF_3$, $-CF_2H$,
 $-COR^{A2}$,
 $-CH_2OH$, $-CH_2OR^{A2}$, $-CHR^{A2}OH$, $CHR^{A2}OR^{A2}$
 $-COOH$, $-COOR^{A2}$, $-CONH_2$, $-CONHR^{A2}$, $-CONR^{A2}_2$,
 $-OCOR^{A2}$, $-OCONH_2$, $-OCONHR^{A2}$, $-OCONR^{A2}_2$,
 20 $-NH_2$, $-NHR^{A2}$, $-NR^{A2}_2$,
 $-SO_2NH_2$, $-SO_2NHR^{A2}_2$, $-SO_2NR^{A2}_2$,
 $-SO_2R^{A2}$,
 $-NHCOH$, $-NHCOR^{A2}$, $-NR^{A2}COH$ and $-NR^{A2}COR^{A2}$;

R^{A2} is selected from the group consisting of

- 25 linear or branched C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl optionally substituted with
 one or more groups R^{AT} ,

C₃₋₆cycloalkyl, C₄₋₆heterocycloalkyl, C₅₋₆cycloalkenyl or C₅₋₆heterocycloalkenyl
 optionally substituted with one or more groups R^{AT},
 phenyl optionally substituted with one or more groups R^{AR}, and
 C₅₋₁₀heteroaryl optionally substituted with one or more groups R^{AR};

5 where N is substituted by 2 R^{A2} groups, the N and the R^{A2} groups may together form a N-
 containing C₅₋₆ heterocycloalkyl group;

R^{AL} is selected from the group consisting of

linear or branched C₁₋₆alkyl optionally substituted with one or more groups R^{AT};

-F, -CN

10

-OH, -OR^{A2},

-CF₃, -CF₂H,

-COR^{A2},

-COOH, -COOR^{A2}, -CONH₂, -CONHR^{A2}, -CONR^{A2}₂,

-OCOR^{A2}, -OCONH₂, -OCONHR^{A2}, -OCONR^{A2}₂,

15

-NH₂, -NHR^{A2}, -NR^{A2}₂,

-SO₂NH₂, -SO₂NHR^{A2}₂, -SO₂NR^{A2}₂,

-SO₂R^{A2},

-NHCOH, -NHCOR^{A2}, -NR^{A2}COH and -NR^{A2}COR^{A2}; and

wherein R^{AR} is selected from the group consisting of

20

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with
 one or more groups R^{AL},

-F, -Cl, -Br, -CN

-OH, -OR^{1A1},

-CF₃, -CF₂H,

25

-COR^{1A1},

-CH₂OH, -CH₂OR^{1A1}, -CHR^{1A1}OH, CHR^{1A1}OR^{1A1}

-COOH, -COOR^{1A1}, -CONH₂, -CONHR^{1A1}, -CONR^{1A1}₂,

-OCOR^{1A1}, -OCONH₂, -OCONHR^{1A1}, -OCONR^{1A1}₂,

-NH₂, -NHR^{1A1}, -NR^{1A1}₂,

30

-SO₂NH₂, -SO₂NHR^{1A1}₂, -SO₂NR^{1A1}₂,

-SO₂R^{1A1},

-NHCOH, -NHCOR^{1A1}, -NR^{1A1}COH and -NR^{1A1}COR^{1A1};

R^{AT} is selected from the group consisting of

-F, -CN

35

-OH, -OC₁₋₃alkyl,

-CF₃, -CF₂H,

-COC₁₋₃alkyl,
 -COOH, -COOC₁₋₃alkyl, -CONH₂, -CONHC₁₋₃alkyl, -CON(C₁₋₃alkyl)₂,
 -OCOC₁₋₃alkyl, -OCONH₂, -OCONHC₁₋₃alkyl, -OCON(C₁₋₃alkyl)₂,
 -NH₂, -NHC₁₋₃alkyl, -N(C₁₋₃alkyl)₂,
 5 -SO₂NH₂, -SO₂NH(C₁₋₃alkyl)₂, -SO₂N(C₁₋₃alkyl)₂,
 -SO₂(C₁₋₃alkyl),
 -NHCOH, -NHCO(C₁₋₃alkyl), -N(C₁₋₃alkyl)COH and -N(C₁₋₃alkyl)CO(C₁₋₃alkyl);

and pharmaceutically acceptable salts and solvates thereof.

10 2. A compound for use according to claim 1, wherein P^X is P1, and both R^{P1} and R^{P2} are methyl.

3. A compound for use according to claim 1, wherein P^X is P1, and both R^{P1} and R^{P2} are ethyl.

15

4. A compound for use according to claim 1, wherein P^X is P1, R^{P1} is methyl and R^{P2} is ethyl.

5. A compound for use according to any one of claims 2 to 4, wherein R^{P3} is methyl.

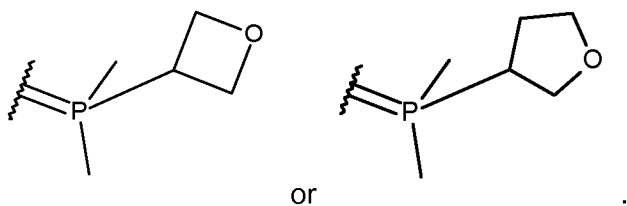
20

6. A compound for use according to any one of claims 2 to 4, wherein R^{P3} is ethyl.

7. A compound for use according to any one of claims 2 to 4, wherein R^{P3} is oxetanyl or tetrahydrofuranyl.

25

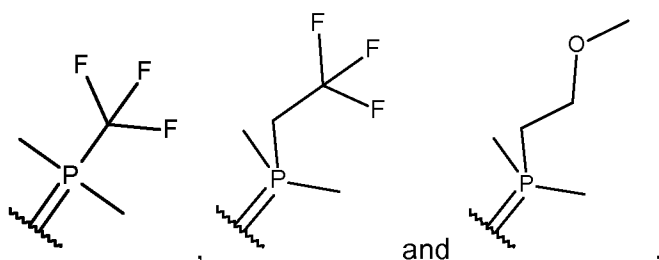
8. A compound for use according to claim 7, wherein P^X is:



9. A compound for use according to any one of claims 2 to 4, wherein R^{P3} is selected from the group consisting of -CF₃, -CH₂CF₃, -CH₂CF₂H and -CH₂CH₂OR^{PB}, where R^{PB} is a linear or branched C₁₋₆ alkyl.

30

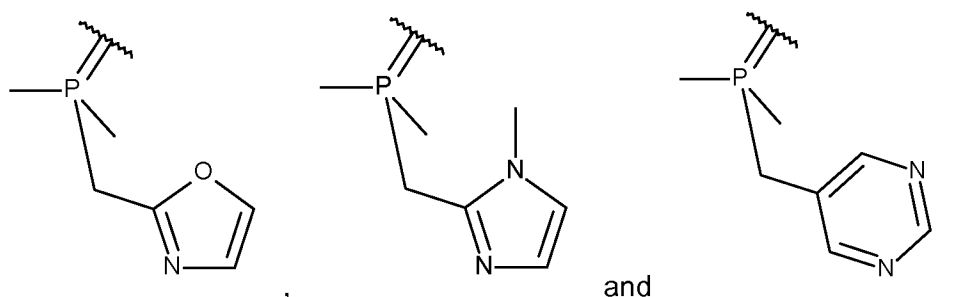
10. A compound for use according to claim 9, wherein P^X is selected from:



5

11. A compound for use according to any one of claims 2 to 4, wherein R^{P3} is $-CH_2Q$.

12. A compound for use according to claim 11, wherein P^X is selected from:



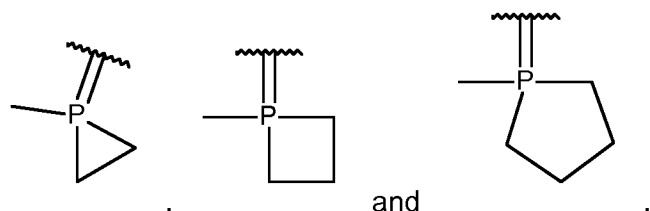
10

13. A compound for use according to claim 1, wherein P^X is $P2$, and R^{P4} is methyl.

14. A compound for use according to claim 1, wherein P^X is $P2$, and R^{P4} is ethyl.

15. A compound for use according to either claim 13 or claim 14, wherein the ring in $P2$ is not substituted.

16. A compound for use according to claim 15, wherein P^X is selected from:



20

17. A compound for use according to claim 1, wherein P^X is $P3$, and $-L^B-$ is methylene.

18. A compound for use according to claim 1, wherein P^X is P3, and $-L^B-$ is ethylene.

19. A compound for use according to either claim 17 or claim 18, wherein R^1 is N.

5

20. A compound for use according to either claim 17 or claim 18, wherein R^1 is CH.

21. A compound for use according to either claim 17 or claim 18, wherein R^1 is CR^{PC} , wherein R^{PC} is unsubstituted C_{1-3} alkyl.

10

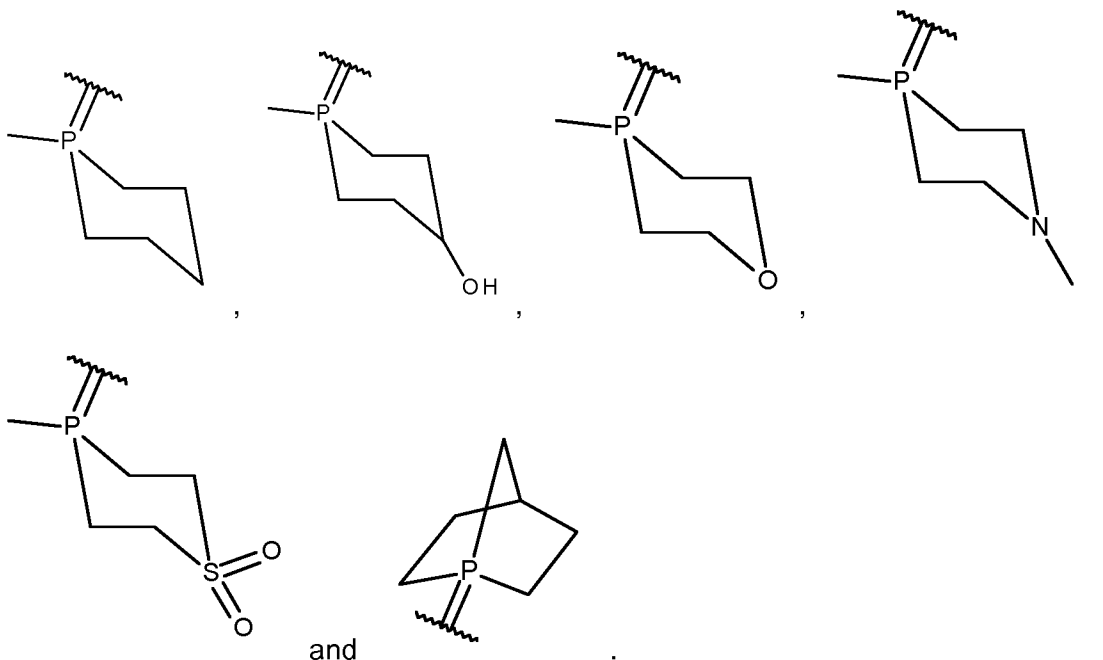
22. A compound for use according to claim 1, wherein P^X is P3, and $-L^B-$ is absent.

23. A compound for use according to claim 22, wherein R^1 is selected from the group consisting of O, NR^Z , and SO_2 , wherein R^Z is selected from H and C_{1-3} alkyl.

15

24. A compound for use according to claim 22, wherein R^1 is selected from the group consisting of CH_2 , CHF, CF_2 and CHR^{PC} , wherein R^{PC} is unsubstituted C_{1-3} alkyl.

25. A compound for use according to claim 1, wherein P^X is selected from:



26. A compound for use according to any one of claims 1 to 25, wherein R^A is linear or branched C_{1-6} alkyl optionally substituted with one or more groups R^{AL} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

5 27. A compound for use according to any one of claims 1 to 25, wherein R^A is unsubstituted linear or branched C_{1-6} alkyl; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

28. A compound for use according to either claim 26 or claim 27, wherein R^B is selected from $-CO(C_{1-6}alkyl)$ and $-SO_2R^{A2}$.

10

29. A compound for use according to any one of claims 26 to 28, wherein R^{AL} is selected from

-F, -CN

-OH, $-OR^{A2}$,

15

$-NH_2$, $-NHR^{A2}$, $-NR^{A2}_2$,

$-NHCOH$, $-NHCOR^{A2}$, $-NR^{A2}COH$ and $-NR^{A2}COR^{A2}$.

30. A compound for use according to claim 29, wherein R^{AL} is selected from

-F,

20

-OH, $-OR^{A2}$,

$-NH_2$, $-NHR^{A2}$ and $-NR^{A2}_2$.

31. A compound for use according to any one of claims 1 to 25, wherein R^A is C_{5-6} heteroaryl, optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

25

32. A compound for use according to claim 31, wherein R^A is C_5 heteroaryl, optionally substituted with one or more groups R^{A1} .

30

33. A compound for use according to claim 31, wherein R^A is C_6 heteroaryl, optionally substituted with one or more groups R^{A1} .

34. A compound for use according to any one of claims 1 to 25, wherein R^A is C_{1-3} alkyl substituted by phenyl or C_{5-6} heteroaryl, which groups may optionally be substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

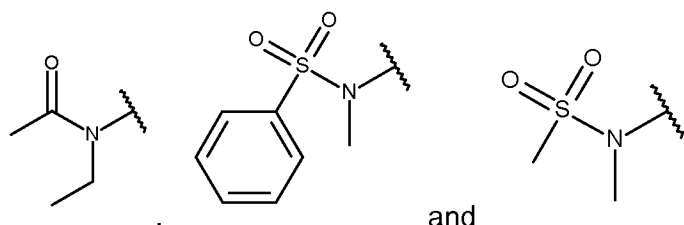
35

35. A compound for use according to claim 34 wherein R^A is C_{1-3} alkyl substituted by C_5 heteroaryl which is optionally substituted with one or more groups R^{A1} .

36. A compound for use according to claim 34 wherein R^A is C_{1-3} alkyl substituted by C_6 heteroaryl which is optionally substituted with one or more groups R^{A1} .

37. A compound for use according to any one of claims 1 to 25, wherein R^A is C_{1-3} alkyl substituted by phenyl which is optionally substituted with one or more groups R^{A1} ; and R^B is selected from $-COR^{A2}$ and $-SO_2R^{A2}$.

38. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is selected from:



39. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group optionally substituted with one or more groups selected from: oxo; phenyl optionally substituted with one or more groups R^{A1} ; R^{A2} , and R^{A1} .

40. A compound for use according to claim 39, wherein the 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group contains up to two heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$.

41. A compound for use according to claim 40, wherein the 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group is substituted with one or two oxo groups and optionally further substituted with one or more groups selected from: phenyl optionally substituted with one or more groups R^{A1} , and R^{A1} .

42. A compound for use according to claim 41, wherein $-NR^A R^B$ is a 5- or 6-membered heterocycloalkyl or heterocycloalkenyl group containing one heteroatom in the ring selected from N, O and S in addition to the N atom of $-NR^A R^B$.

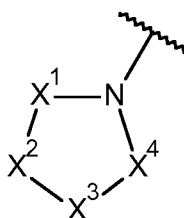
43. A compound for use according to claim 42, wherein the optional further substituents are selected from: linear or branched C₁₋₆alkyl; and phenyl optionally substituted with one or more groups selected from F, Cl, Br, CN, OH, O(C₁₋₆alkyl), COOH and COO(C₁₋₆alkyl).

5

44. A compound for use according to claim 42, wherein the optional further substituents are selected from: C₁₋₃alkyl; and phenyl optionally substituted with one or more groups selected from F, Cl, OH and O(C₁₋₆alkyl).

10

45. A compound for use according to any one of claims 1 to 25, wherein -NR^AR^B is the group (A1)



(A1)

15

wherein

X¹ is selected from C=O and CR^{4A}R^{4B};

X² is selected from O, CR^{4A}R^{4B} and NR^X; and

one of X³ and X⁴ is selected from C=O, CR^{4A}R^{4B} and SO₂, with the other group of X³ and X⁴ being selected from CR^{4A}R^{4B};

20

wherein R^X is selected from -H and -R^{A5};

each R^{4A} and R^{4B} is independently selected from

-H,

linear or branched C₁₋₄alkyl optionally substituted with one or more groups R^{AL},

phenyl, optionally substituted with one or more groups R^{A1},

25

C₅₋₆heteroaryl optionally substituted with one or more groups R^{A1},

independently geminal R^{4A} and R^{4B} groups may be joined to form a 5- or

6-membered alicyclic or 5- or 6- membered heteroalicyclic group optionally substituted with one or more groups R^{AL}, and

independently two vicinal R^{4A} groups may be joined to form a 5- or 6-membered

30

alicyclic, heteroalicyclic, aromatic or heteroaromatic group optionally

substituted with one or more groups R^{A1};

and R^{A5} is selected from the group consisting of

linear or branched C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl optionally substituted with one or more groups R^{AL},

C₃₋₆cycloalkyl or C₄₋₆heterocycloalkyl optionally substituted with one or more groups R^{AT},

5 phenyl, optionally substituted with one or more groups R^{A1},

C₅₋₆heteroaryl optionally substituted with one or more groups R^{A1}, or

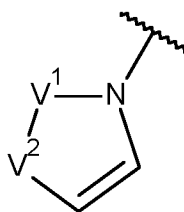
except when each of R^{P1} to R^{P3} is selected from ethyl, R^{A5} may be joined to a

vicinal R^{4A} or R^{4B} group to form a 5- or 6-membered heterocyclic or

heteroaromatic group optionally substituted with one or more groups R^{A1};

10

46. A compound for use according to any one of claims 1 to 25, wherein -NR^AR^B is the group (A2)



(A2)

15 wherein

V¹ is selected from C=O and SO₂;

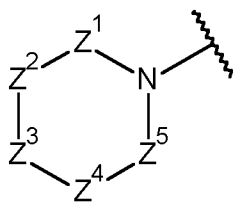
V² is selected from O, NR^X and CR^{4A}R^{4B};

with the proviso that when V¹ is SO₂, V² cannot be O;

wherein R^X, R^{4A} and R^{4B} are as defined in claim 44.

20

47. A compound for use according to any one of claims 1 to 25, wherein -NR^AR^B is the group (A4)



(A4)

25 wherein

Z¹ is selected from C=O and CR^{4A}R^{4B};

Z² and Z³ are each independently selected from the group consisting of

O,

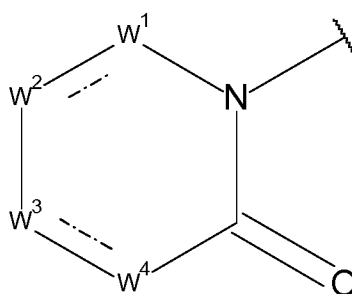
$CR^{4A}R^{4B}$, $C=O$ and

NR^X ,

with the proviso that any two adjacent groups of Z^1 to Z^4 cannot both be O, cannot both be $C=O$ and cannot both be NR^X ;

- 5 Z^4 is selected from $CR^{4A}R^{4B}$, and NR^X ;
and Z^5 is selected from $C=O$ and SO_2 ;
with R^{4A} , R^{4B} and R^X are as defined in claim 44.

48. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is the
10 group (A5)

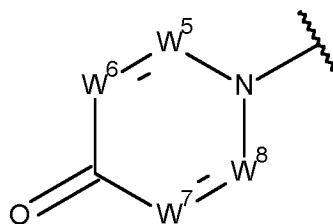


(A5)

wherein

- 15 a dotted line indicates that a bond may be present or absent; and
 W^1 to W^4 are each independently selected from CH and CR^{A1} .

49. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is the
group (A6)

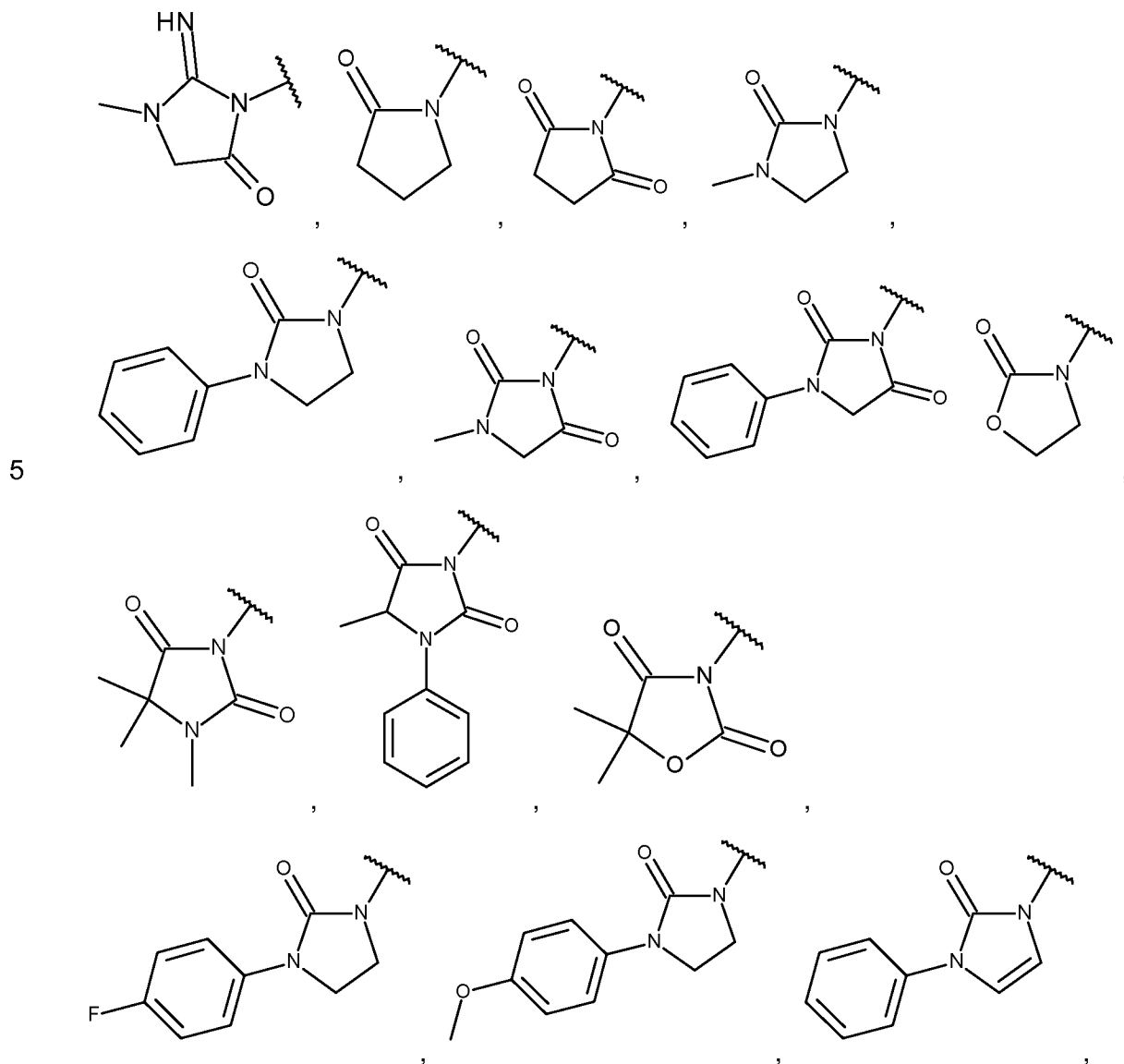


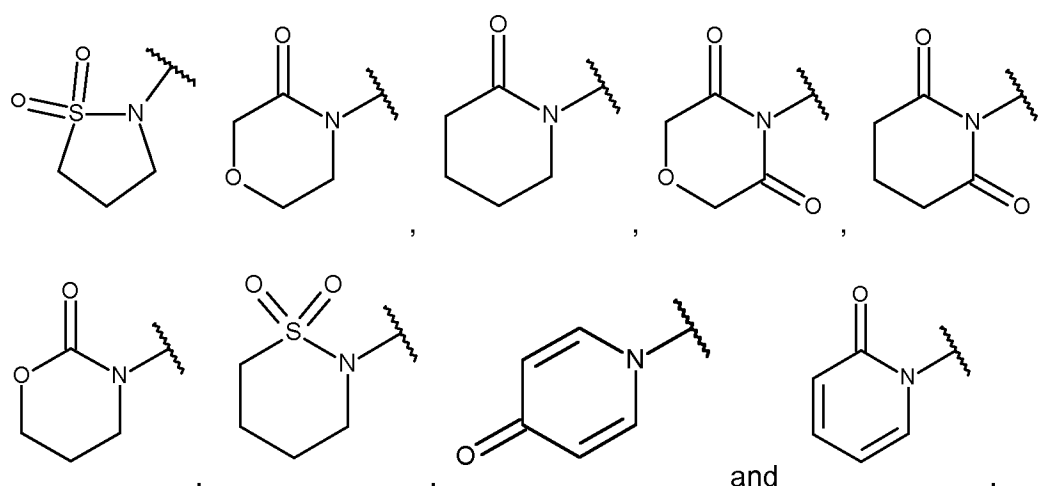
(A6)

wherein

W^5 to W^8 are each independently selected from CH and CR^{A1} .

50. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is selected from:





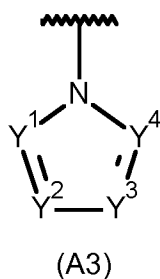
- 5 51. A compound for use according to any one of claims 1 to 25, wherein $-NR^{AB}$ is selected from a 5- or 6-membered heteroaryl group optionally substituted with one or more groups selected from: phenyl optionally substituted with one or more groups R^{A1} ; R^{A2} , and R^{A1} .
- 10 52. A compound for use according to claim 51, wherein the 5- or 6-membered heteroaryl group contains up to three heteroatoms in the ring selected from N, O and S in addition to the N atom of $-NR^{AB}$.
53. A compound for use according to claim 52, wherein the optional substituents are
15 selected from: phenyl optionally substituted with one or more groups R^{AL} ; R^{A2} , and R^{A1} .
54. A compound for use according to claim 51, wherein $-NR^{AB}$ is selected from a 5-membered heteroaryl group containing up to three N atoms in the ring in addition to the N atom of $-NR^{AB}$; optionally substituted with one or more groups R^{A1} .
- 20 55. A compound for use according to claim 54, wherein the optional substituents are selected from
- linear or branched C_{1-6} alkyl,
 - F, Cl, Br,
 - 25 -CN
 - CF_3 , - CF_2H , - CH_2F ,
 - OH, - $O(C_{1-6}alkyl)$,

-COOH and -COO(C₁₋₆alkyl).

56. A compound for use according to claim 56, wherein the optional substituents are selected from

- 5 linear or branched C₁₋₆alkyl,
 -CN
 -CF₃, -CF₂H and -CH₂F.

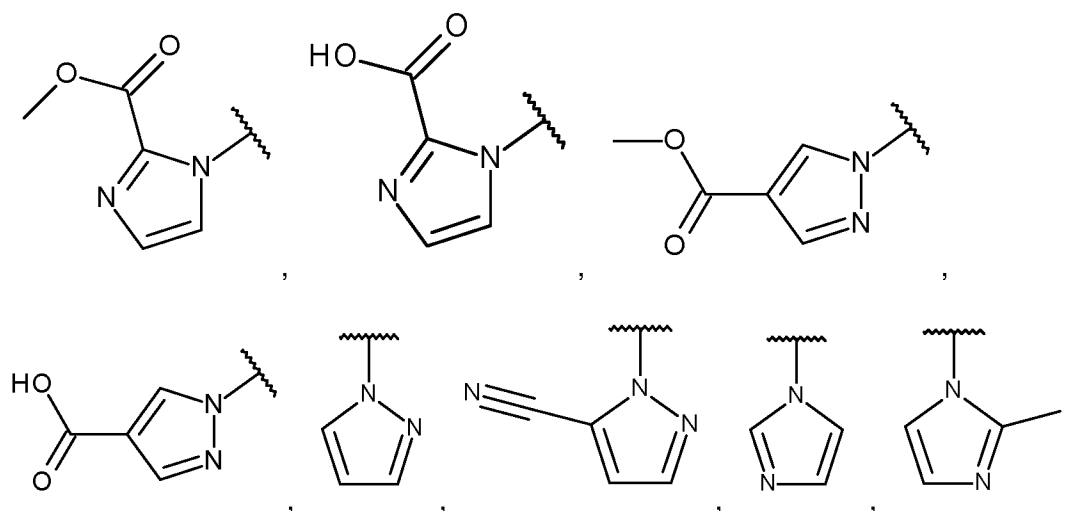
57. A compound for use according to any one of claims 1 to 25, wherein -NR^AR^B is the
 10 group (A3)

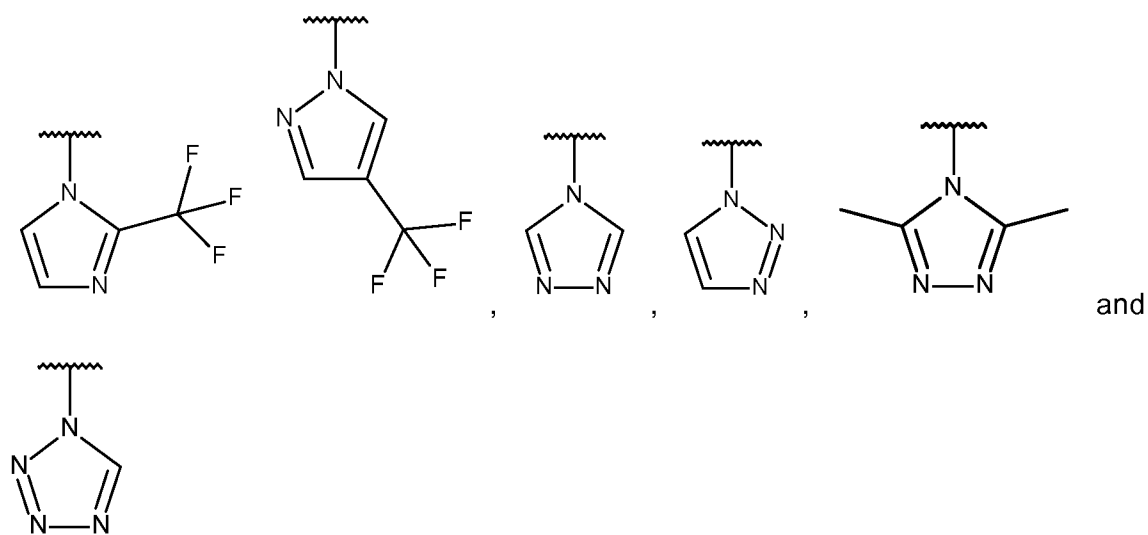


wherein

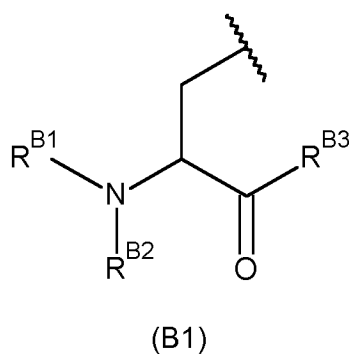
15 one group from Y¹ to Y⁴ is CR³, another is N and the remainder are independently selected from CR³ and N.

58. A compound for use according to any one of claims 1 to 25, wherein -NR^AR^B is
 20 selected from





- 5 59. A compound for use according to any one of claims 1 to 25, wherein $\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is an imidazolyl group, bearing a C substituent which is the group (B1)



10

wherein

R^{B1} is selected from the group consisting of

- H,
- COR^{A2} , - CONR^{A2} , $\text{CO}_2\text{R}^{\text{A2}}$, and
- $\text{SO}_2\text{R}^{\text{A2}}$;

15

R^{B2} is selected from -H, and linear or branched C_{1-4} alkyl; and

R^{B3} is selected from the group consisting of

- OH, - OR^{A2} ,
- NH_2 , - NHR^{A2} and - NR^{A2} .

20

60. A compound for use according to any one of claims 1 to 25, wherein $-NR^A R^B$ is selected from an 8- to 10-membered heterobicycyl group optionally substituted with one or more groups selected from: oxo; phenyl optionally substituted with one or more groups R^{A1} ; R^{A2} and R^{A1} .

5

61. A compound for use according to claim 60, wherein the 8- to 10-membered heterobicycyl group is a 9-membered heterobicycyl group.

62. A compound for use according to claim 61, wherein the 9-membered heterobicycyl group is a 9-membered 5,6 fused heterobicycyl group optionally substituted with one or more groups selected from: oxo; linear or branched C_{1-6} alkyl; -F; -Cl; -Br; -CN; -OH; $-O(C_{1-6}alkyl)$; -COOH and $-COO(C_{1-6}alkyl)$.

10

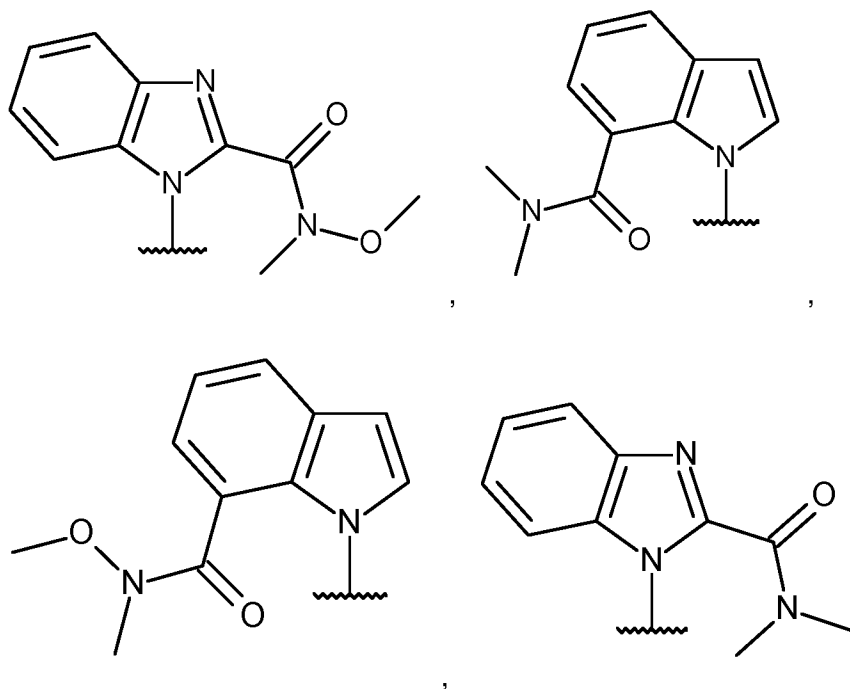
63. A compound for use according to claim 62, wherein the optional substituents are selected from: oxo; linear or branched C_{1-6} alkyl; -OH and $-O(C_{1-6}alkyl)$.

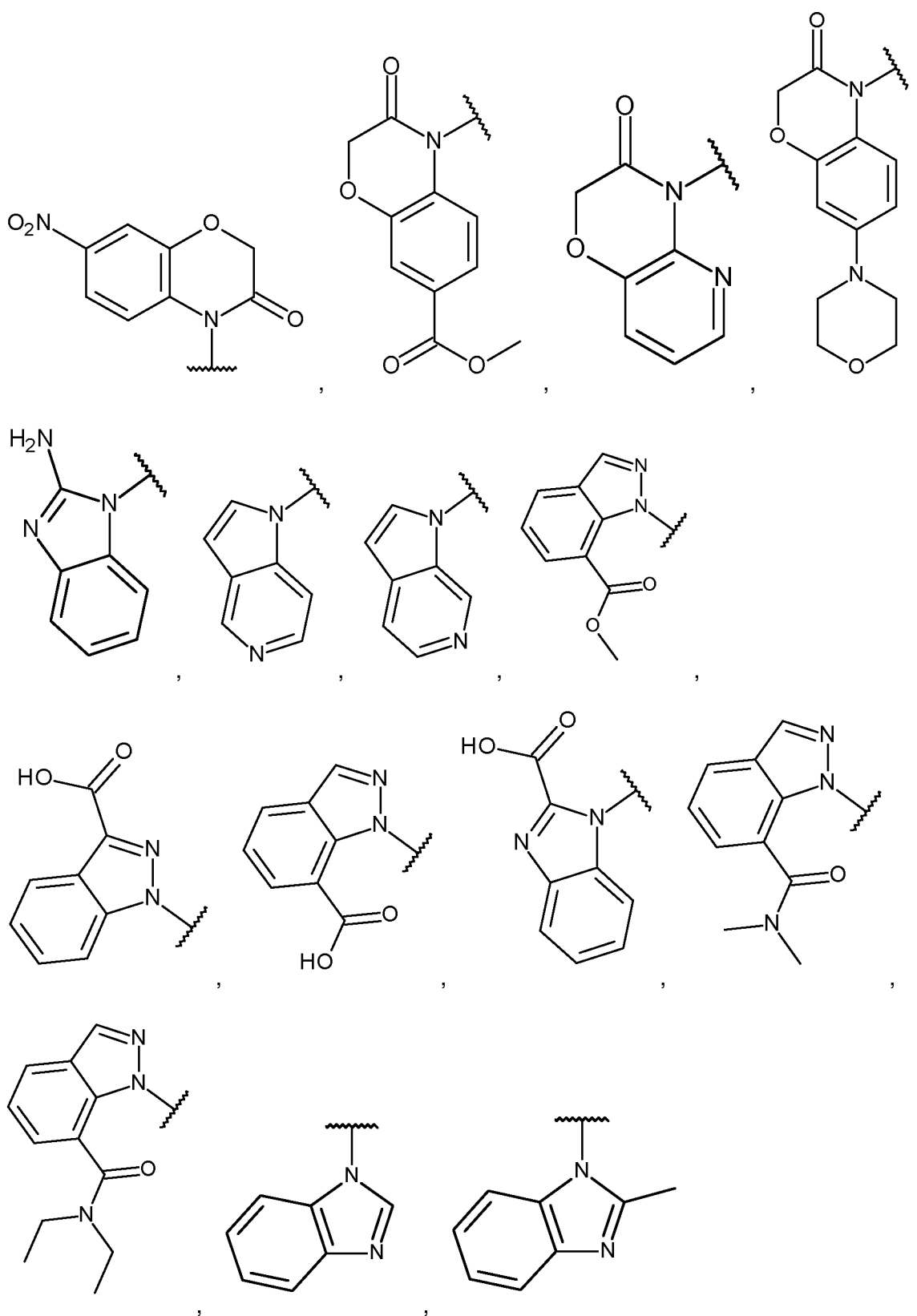
15

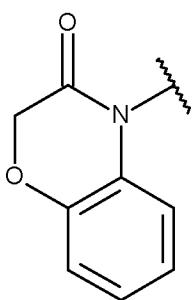
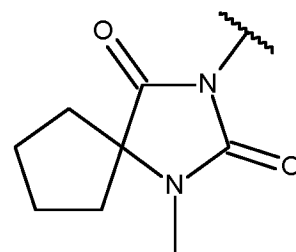
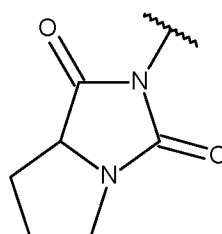
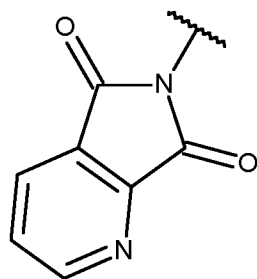
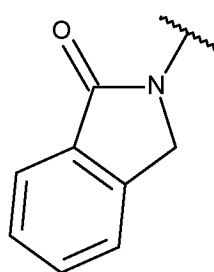
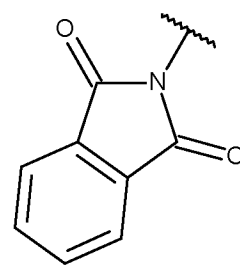
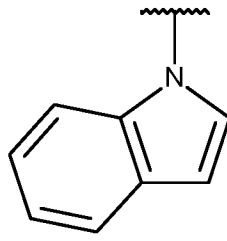
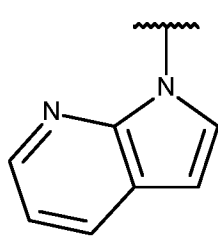
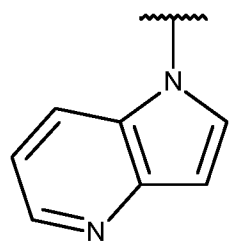
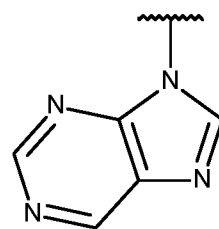
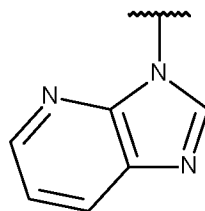
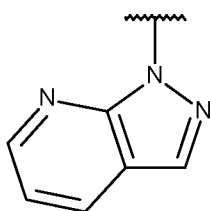
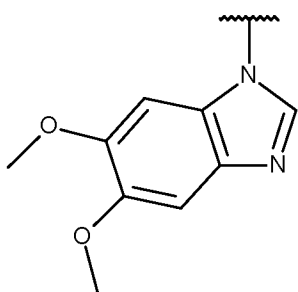
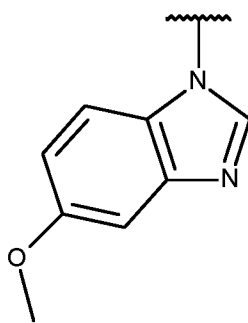
64. A compound for use according to claim 60, wherein the 8- to 10-membered heterobicycyl group is a 10-membered 6,6 fused heterobicycyl group optionally substituted with one or more groups selected from: oxo, and R^{A1} .

20

65. A compound for use according to claim 60, wherein $-NR^A R^B$ is selected from

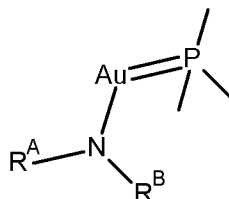






5 and

66. A compound for use according to claim 1, wherein the compound is a compound according to formula (Ia)

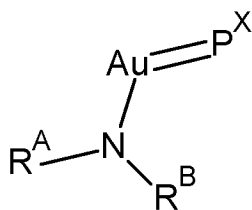


5

Formula (Ia)

wherein R^A and R^B are as defined in any one of claims 26 to 65.

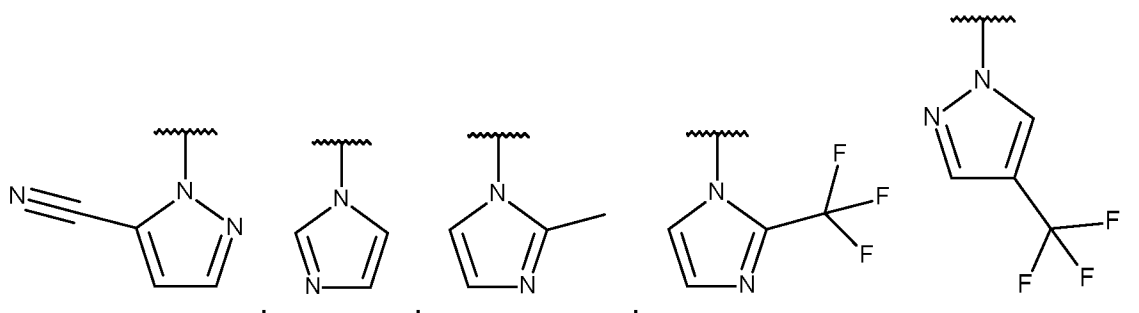
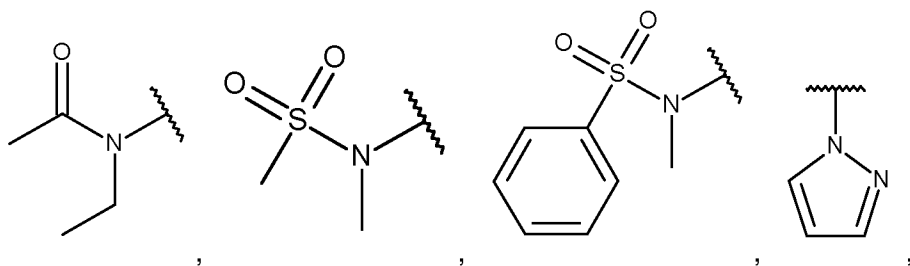
67. A compound for use according to claim 1, wherein the compound is a compound according to formula (Ib)



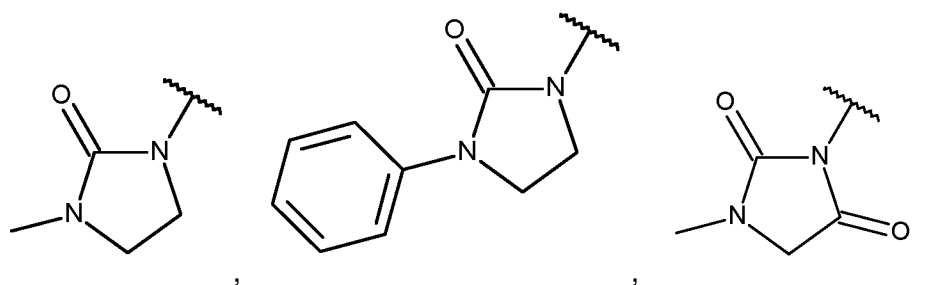
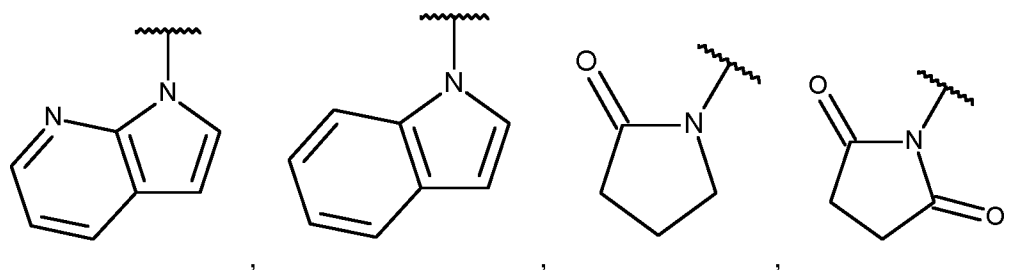
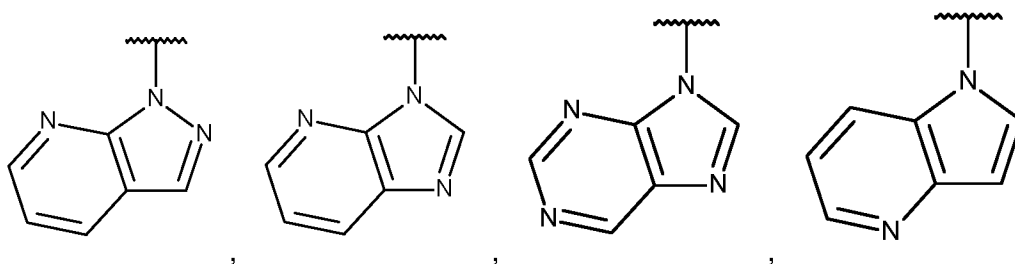
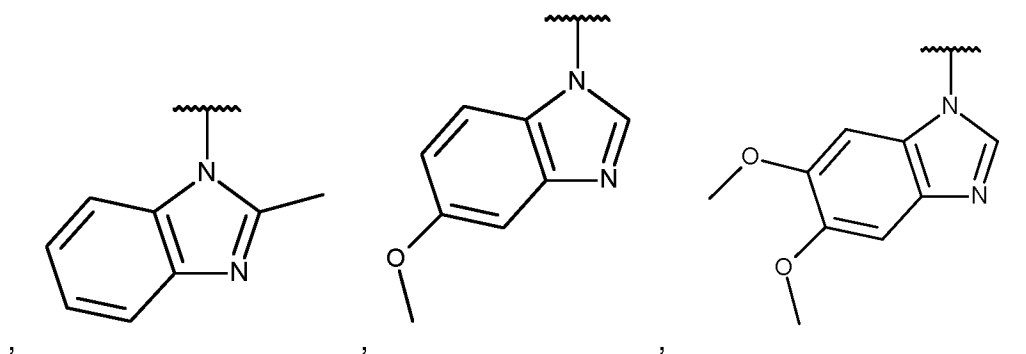
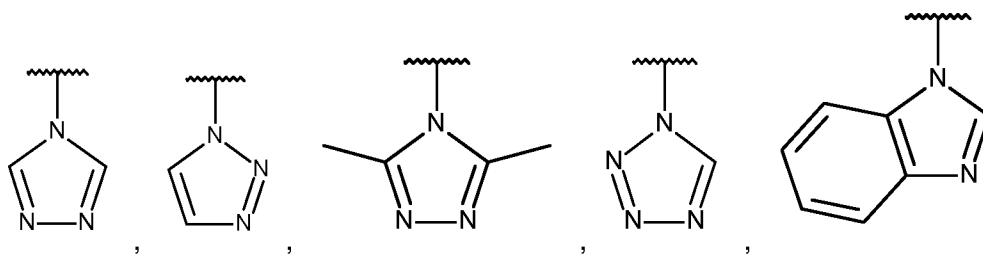
10

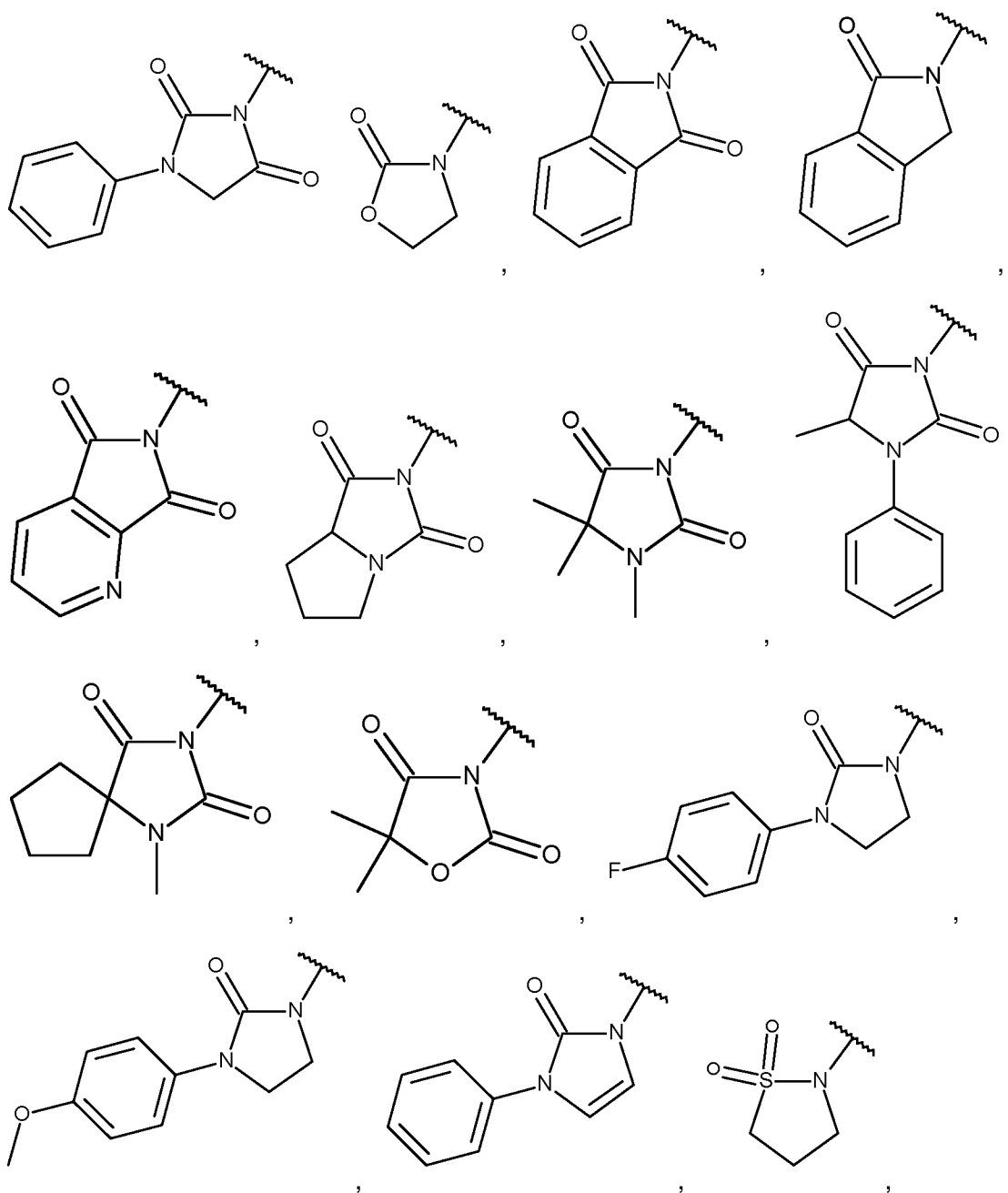
Formula (Ib)

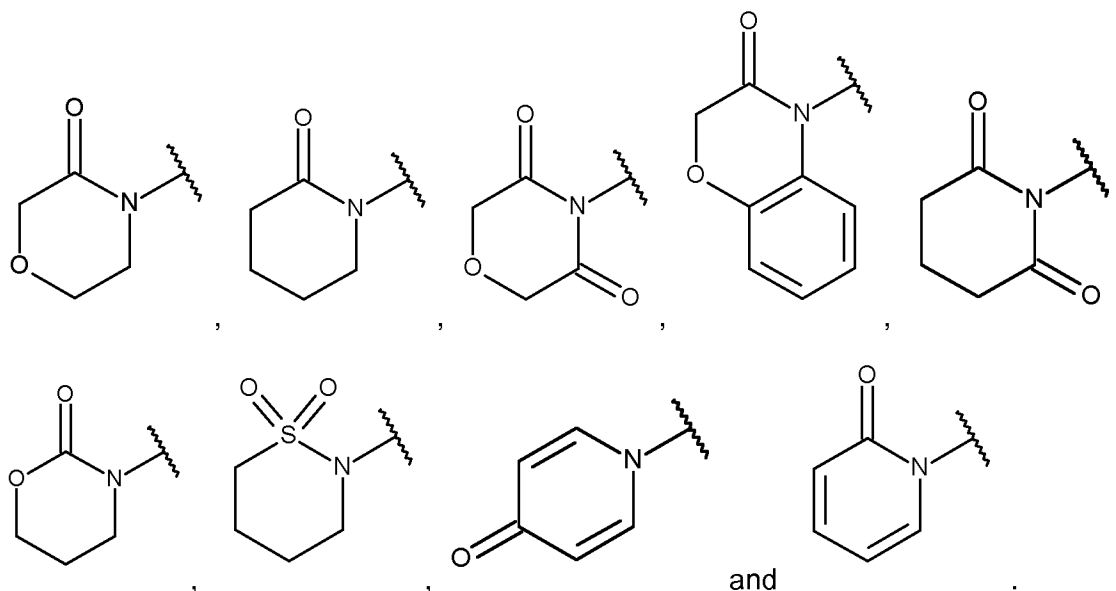
wherein P^X is as defined in any one of claims 1 to 25;
and $NR^A R^B$ is selected from:



15







68. A compound for use according to any one of claims 1 to 67, wherein the bacterial
5 infection prevented and/or treated is infection by one or more Gram-positive bacteria.

69. A compound for use according to any one of claims 1 to 67, wherein the bacterial
infection prevented and/or treated is infection by one or more Gram-negative bacteria.

70. A method for reducing the biomass of a biofilm, the method comprising exposing
10 the biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

71. A method for promoting the dispersal of microorganisms from a biofilm, the
15 method comprising exposing the biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

72. A method for killing a microorganism within a biofilm, comprising exposing the
biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

73. A method of sensitizing a microorganism in a biofilm to an antimicrobial agent by
20 exposing the biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

74. The method according to any one of claims 70 to 73, wherein the biofilm is an established biofilm.

75. A method for inhibiting the formation of a biofilm, the method comprising exposing the biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

76. The method according to claim 75 wherein the compound as described in any one of claims 1 to 67 is coated, impregnated or otherwise contacted with a surface or interface susceptible to biofilm formation.

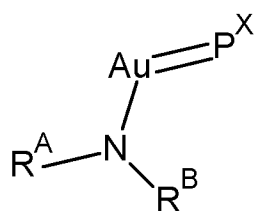
77. The method according to claim 76, wherein the surface is a surface of medical or surgical equipment, an implantable medical device, implant, or prosthesis

78. A method of removing or eliminating an existing biofilm, inhibiting biofilm formation, reducing the biomass of a biofilm, promoting the dispersal of microorganisms from a biofilm, sensitizing a microorganism in a biofilm to an antimicrobial agent, killing a microorganism within a biofilm, treating or preventing an infection, disease or disorder caused by a biofilm, inhibiting the growth of a microbial persister cell, killing a microbial persister cell, or treating or preventing an infection, disease or disorder caused by or associated with a microbial persister cell; the method comprising exposing the biofilm to an effective amount of a compound as described in any one of claims 1 to 67.

79. A method for killing microbial persister cells, or inhibiting the growth of microbial persister cells, comprising exposing the persister cell to an effective amount of a compound as described in any one of claims 1 to 67.

80. Use of a compound of a compound as described in any one of claims 1 to 67 to remove or eliminate an existing biofilm, inhibit biofilm formation, reduce the biomass of a biofilm, promote the dispersal of microorganisms from a biofilm, sensitize a microorganism in a biofilm to an antimicrobial agent, kill a microorganism within a biofilm, treat or prevent an infection, disease or disorder caused by a biofilm, inhibit the growth of a microbial persister cell, kill a microbial persister cell, or treat or prevent an infection, disease or disorder caused by or associated with a microbial persister cell.

81. A compound as described in any one of claims 1 to 67 for use in a method of removing or eliminating an existing biofilm, inhibiting biofilm formation, reducing the biomass of a biofilm, promoting the dispersal of microorganisms from a biofilm, sensitizing a microorganism in a biofilm to an antimicrobial agent, killing a microorganism within a biofilm, treating or preventing an infection, disease or disorder caused by a biofilm, inhibiting the growth of microbial persister cells, killing microbial persister cells, or treating or preventing an infection, disease or disorder caused by or associated with microbial persister cells.
82. The method according to any one of claims 70 to 79, the use according to claim 80, or the compound according to claim 81, wherein the biofilm comprises bacteria, or the microbial persister cells are bacteria.
83. The method according to any one of claims 64 to 73, the use according to claim 74, or the compound according to claim 75, wherein the bacteria are Gram positive bacteria.
84. The method according to any one of claims 70 to 79, the use according to claim 80, or the compound according to claim 81, wherein the bacteria are *Staphylococcus spp.*
85. The method according to any one of claims 70 to 79, the use according to claim 80, or the compound according to claim 81, wherein the bacteria are multi-drug resistant bacteria.
86. The method according to any one of claims 70 to 79, the use according to claim 80, or the compound according to claim 81 wherein the bacteria are small colony variants.
87. The method according to any one of claims 70 to 79, the use according to claim 80, or the compound according to claim 81, comprising further administering at least one additional antimicrobial agent.
88. A medical device coated or impregnated with a compound as described in any one of claims 1 to 67.
89. A compound of formula (I):

**Formula (I)**

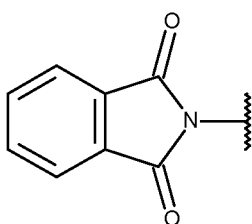
and pharmaceutically acceptable salts and solvates thereof wherein:

P^{X} , R^{A} and R^{B} are as defined in any one of claims 1 to 67,

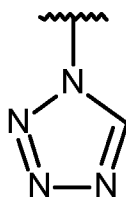
- 5 with the provisos that when P^{X} is $\text{P}(\text{CH}_3)_3$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is not selected from any of the groups (X1) to (X5), (X7) and (X12) to (X15);

and when P^{X} is $\text{P}(\text{C}_2\text{H}_5)_3$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is not selected from the groups (X1), (X6) to (X11), (X13) and (X14);

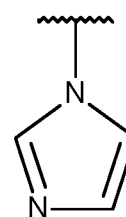
- 10 and when P^{X} is PPh_3 , $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is not selected from the groups (X2), (X12), (X14) and (X15):



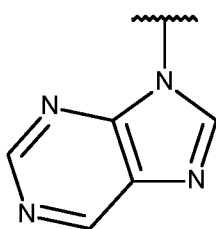
(X1)



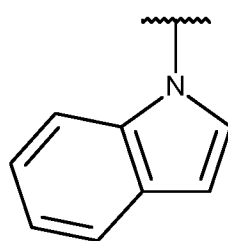
(X2)



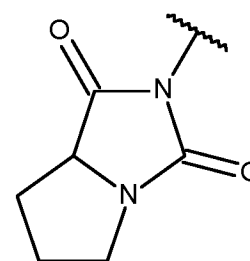
(X3)



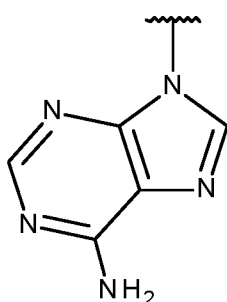
(X4)



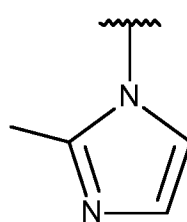
(X5)



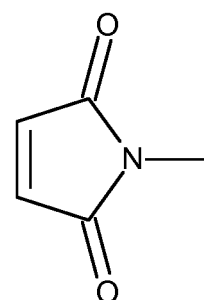
(X6)



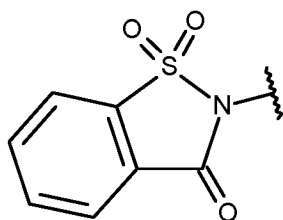
(X7)



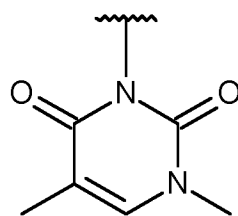
(X8)



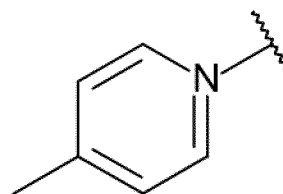
(X9)



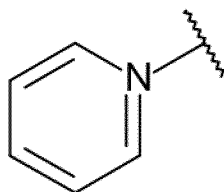
(X10)



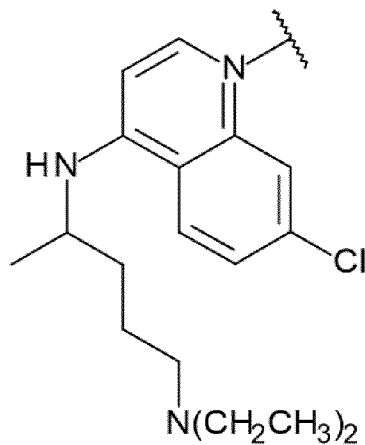
(X11)



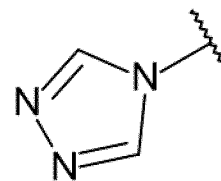
(X12)



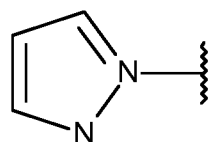
(X13)



(X14)



(X15)



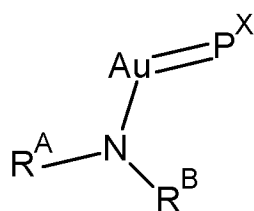
(X15)

90. A pharmaceutical composition comprising a compound according to claim 89.

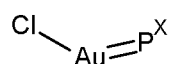
91. A pharmaceutical composition according to claim 90, which also comprises a
5 pharmaceutical acceptable diluent or excipient.

92. A compound according to claim 89 for use in a method of therapy.

93. A method of making a compound of formula (I):

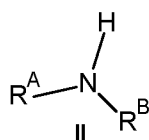
**Formula (I)**

wherein P^X , R^A and R^B are as defined in any one of claims 1 to 67, comprising reacting gold(I) complexes of formula **III**:

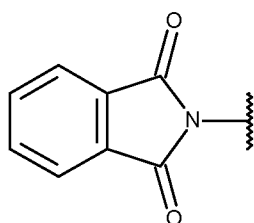
**III**

5

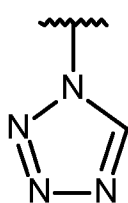
with a nitrogen containing derivative of general formula **II**:

**II**

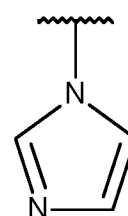
94. A method according to claim 93, wherein when P^X is $P(CH_3)_3$, $-NR^A R^B$ is not selected from any of the groups (X1) to (X5), (X7) and (X12) to (X15);
 10 and when P^X is $P(C_2H_5)_3$, $-NR^A R^B$ is not selected from the groups (X1), (X6) to (X11), (X13) and (X14):



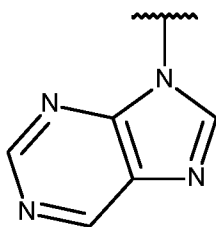
(X1)



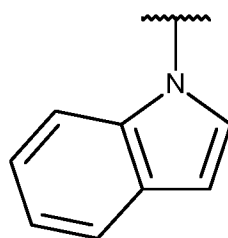
(X2)



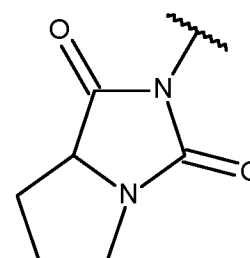
(X3)



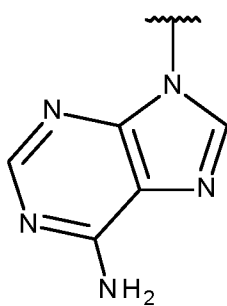
(X4)



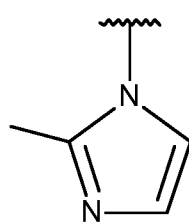
(X5)



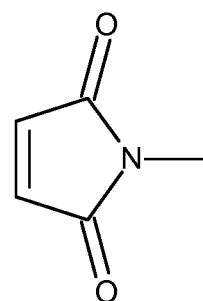
(X6)



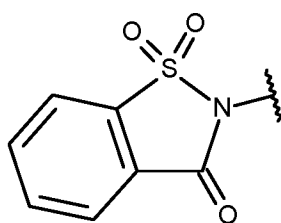
(X7)



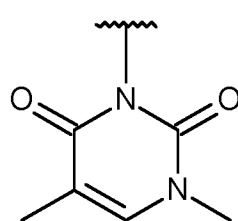
(X8)



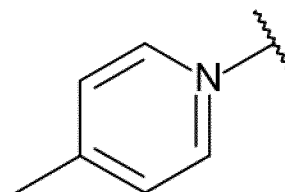
(X9)



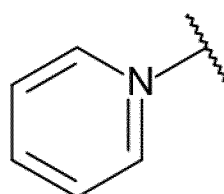
(X10)



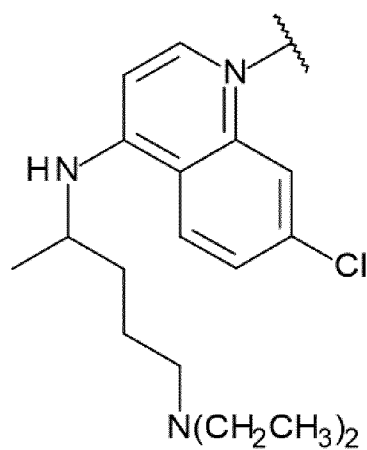
(X11)



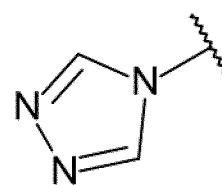
(X12)



(X13)



(X14)



(X15)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/079681

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F9/50 C07F9/572 C07F9/58 C07F9/59 C07F9/6503
C07F9/6506 C07F9/6518 C07F9/6524 C07F9/653 C07F9/6533
C07F9/6539 C07F9/6544 C07F9/6558 C07F9/6568 C07F9/6571

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BILJANA D. GLISIC ET AL: "Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of the gold ion and the ligand structure", DALTON TRANSACTIONS, vol. 43, no. 16, 4 February 2014 (2014-02-04), pages 5950-69, XP055202067, ISSN: 1477-9226, DOI: 10.1039/c4dt00022f Complexes 18, 19, 20, 21 and 22 in figure 3, on page 5954, and their use in treating bacterial infections (see title of figure 3) (Aqueous) pharmaceutical composition of complexes 18-22: Table 1 Complexes 73-76, figure 11, page 5961 and their use in treating malaria infections. Complex 106 in figure 16 on page 5965 and -/--	1-90,92

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 February 2017

Date of mailing of the international search report

03/03/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/079681

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	the use in treating E histolytica bacterial infections Complex 110 in figure 17 and the use in treating trypanosoma parasite infections: page 5966	
X	----- NOMIYA K ET AL: "Synthesis, crystal structure and antimicrobial activities of two isomeric gold(I) complexes with nitrogen-containing heterocycle and triphenylphosphine ligands, [Au(L)(PPh ₃)] (HL=pyrazole and imidazole)", JOURNAL OF INORGANIC BIOCHEMISTRY, ELSEVIER INC, US, vol. 78, no. 4, 31 March 2000 (2000-03-31) , pages 363-370, XP027300352, ISSN: 0162-0134 [retrieved on 2000-03-31] Complexes 1-5 and their use in treating bacterial infections: table 2	1-94
X	----- LEIRE AGUINAGALDE ET AL: "Auranofin efficacy against MDR Streptococcus pneumoniae and Staphylococcus aureus infections", JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY., vol. 70, no. 9, 4 July 2015 (2015-07-04), pages 2608-2617, XP055347684, GB ISSN: 0305-7453, DOI: 10.1093/jac/dkv163 Complexes 8 and 9 and their use in treating bacterial infections: figures 2 and 3	1-94
X	----- TAKASHI AMAGAI ET AL: "Preparation and Crystal Structure of New Gold(I) Complexes Linked to Pyrimidines", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 62, no. 4, 15 April 1989 (1989-04-15) , pages 1078-1080, XP055347798, JP ISSN: 0009-2673, DOI: 10.1246/bcsj.62.1078 complex 1 and 2 and their use in therapy of cancerous diseases: page 1080 Method of making the gold complexes by reaction of chloro(triphenylphosphine)gold with cyclic amines such as tegafur: page 1078, right column	89-94
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/079681

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUSAN J. BERNERS PRICE ET AL: "Tertiary phosphine complexes of gold(I) and gold(III) with imido ligands: ¹H, ³¹P, and ¹⁵N NMR spectroscopy, antiinflammatory activity, and x-ray crystal structure of (phthalimido)(triethylphosphine)gold(I)", INORGANIC CHEMISTRY, vol. 24, no. 21, October 1985 (1985-10), pages 3425-3434, XP055347796, EASTON, US ISSN: 0020-1669, DOI: 10.1021/ic00215a026 Imido-Au-PEt₃ complexes in table III, such as (ptm)AuPEt₃, (sac)AuPEt₃, (dph)AuPEt₃, and their use as antiinflammatory agents (page 3434, right column) Method of making (imidazol)AuPR₃ complexes by reacting Cl-AuPR₃ with imidazole-derivative: see page 3425, right column. -----	89-94
X	WILLIAM F. GABRIELLI ET AL: "Neutral mononuclear and dinuclear complexes of gold(I) featuring azole ligands: Synthesis, structure and cytotoxicity", POLYHEDRON., vol. 34, no. 1, 4 January 2012 (2012-01-04), pages 188-197, XP055347687, GB ISSN: 0277-5387, DOI: 10.1016/j.poly.2011.12.026 complexes VI and VII and their use in treating cancerous diseases: table 1 on page 193 Method of making the gold complexes by reaction of chloro(triphenylphosphine)gold with cyclic amines such as 1H-tetrazole: page 196, left column bottom -----	89-94