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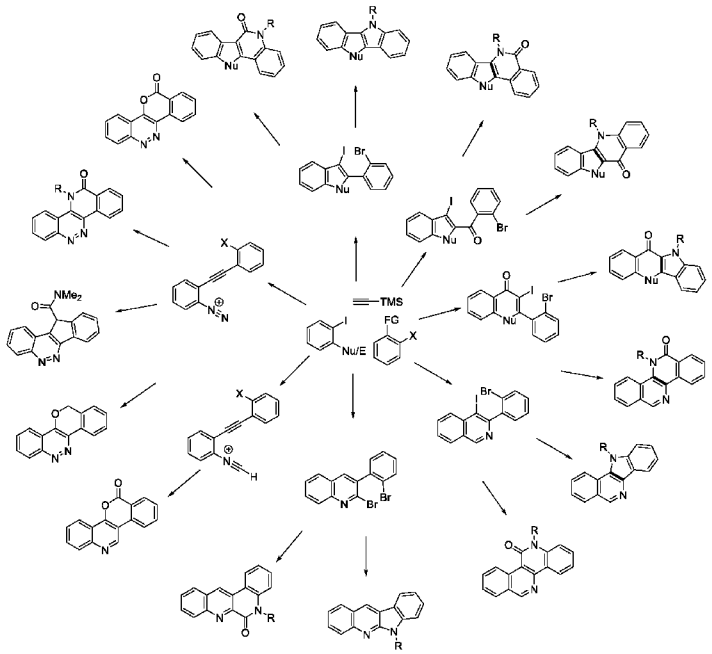

Figure 3

(57) Abstract: Provided herein are collections of compounds of formula a) to u), and salts thereof, which have polycyclic aromatic scaffolds and thus have structures targeted towards binding polynucleotide therapeutic targets, including polynucleotide-protein complexes. Also provided are compounds and salts themselves, methods of synthesizing such compounds, methods of identifying compounds having activity against a polynucleotide target, use of the compounds as reference compounds in assays, and phenotypic methods of identifying a new polynucleotide target using the compounds.

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COMPOUND COLLECTIONS, COMPOUNDS AND SYNTHESIS THEREOF

This patent application claims priority from Australian provisional patent application no. 2022902513 filed on 1 September 2022, the entire contents of which is incorporated herein by this reference.

Field

The present disclosure relates to collections of compounds of formula a) to u), and salts thereof, which have polycyclic aromatic scaffolds and thus have structures targeted towards binding polynucleotide therapeutic targets, including polynucleotide-protein complexes. The present disclosure also relates to compounds and salts themselves, methods of synthesizing such compounds, methods of identifying compounds having activity against a polynucleotide target, use of the compounds as reference compounds in assays, and phenotypic methods of identifying a new polynucleotide target using the compounds.

Background

Polynucleotides, DNA and RNA, play critical roles in protein expression and are involved in effectively all molecular pathways of disease. While most small-molecule drug discovery efforts are directed to the design of ligands for the encoded protein products of DNA and RNA, significant potential lies in the direct targeting of polynucleotides and the protein-polynucleotide complexes involved in the decoding process (transcription and translation) and/or in epigenetic modifications to the code.

Over the last twenty years, diversity-oriented synthesis (DOS) and fragment-based drug discovery (FBDD) have emerged as successful methods for accessing suitable screening sets for phenotypic and target-based drug discovery. The library design principles employed in these DOS and FBDD efforts, such as fraction-sp^3 (Fsp^3) and lead-likeness, have been principally developed with protein targets in mind.

In contrast to proteins, where π,π-interactions are weak, the binding of small molecules to polynucleotides often involves strong π,π-interactions, favouring sp^2-rich molecules. This is reflected in nature, where a diverse array of sp^2-rich bioactive secondary metabolites have been identified that make strong π,π-interactions with polynucleotides, for example DNA intercalators camptothecin **1** and berberine **2** (Figure 1). Natural products **1** and **2** and their synthetic analogues, such as ARC111 **3** and indenoisoquinoline LMP744 **4**, target DNA-topoisomerase I (TOP1) cleavage complexes (TOP1ccs), disrupting DNA replication and transcription. Transcriptional modification has also been achieved through the targeting of other DNA-protein complexes (e.g. DNA complexes with transcription factors, RNA polymerases and epigenetic modulators) or of functional DNA topologies (e.g. Z-DNA and G-quadraplexes). These DNA-small molecule binding events can lead to changes in the expression of

mRNAs and of non-coding RNAs (e.g. micro-RNAs), leading to down-stream changes in protein expression and cellular phenotype.

Direct targeting of RNAs with small molecules is also area of intense interest. A notable example is the recently approved drug for spinal muscular atrophy, risdiplam **5**, that binds to the mRNA encoding the dysfunctional survival motor neuron 2 (SMN2) protein and promotes read-through of a stop codon to give more functional SMN1 protein. Another example is the screening hit **6**, which selectively binds to a G-quadruplex within the mRNA encoding the oncogenic N-Ras protein, suppressing its translation. These and the many other examples of sp^2-rich compounds targeting polynucleotides indicate that DOS approaches directed to diverse sets of sp^2-rich scaffolds could prove useful in the discovery of new therapies based on targeting polynucleotides (DNA, mRNA, micro-RNA and other non-coding RNAs).

Summary

The present inventors have identified a scaffold-divergent approach to heteroacenes based on electrophilic cyclisation of alkynes (Figure 2). This provides access to a range of compounds having common structural features, being polycyclic and sp^2-rich, and whose structures are targeted towards binding of polynucleotide targets. A common synthetic methodology has been utilised to access these polycyclic systems, based on alkyne cyclisation and formation of a further heterocyclic ring to produce the polycyclic structures, for example by palladium- or copper-catalysed ring-closing amination and carboxyamination reactions. At the same time, the synthetic approach allows for incorporation of late-stage diversity, thereby providing compound collections which, when screened against polynucleotide targets, have a higher likelihood of generating hit and/or lead compounds.

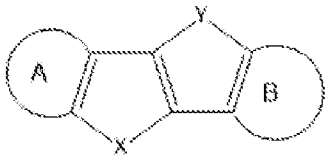
Accordingly, in a first aspect there is provided a collection of polycyclic compounds and/or salts thereof, for screening against a polynucleotide target, the collection comprising a plurality of polycyclic compounds which comprise at least 4 fused rings and have the formula

A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



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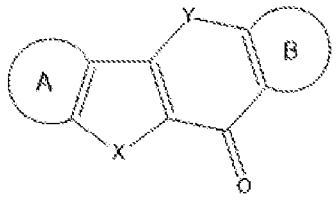

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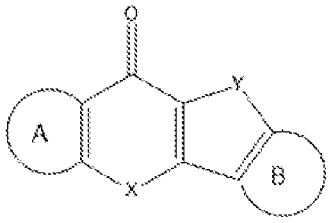
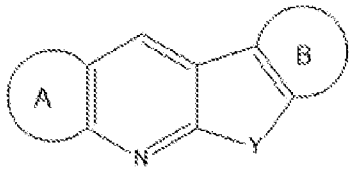
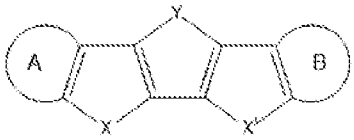


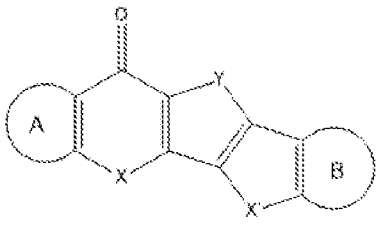


and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

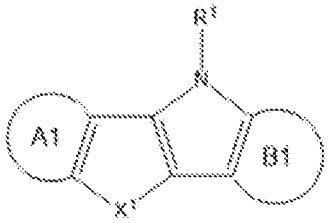


and


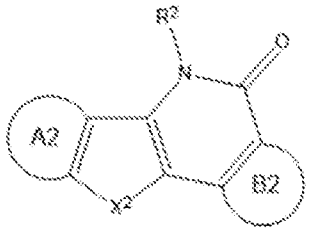
;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

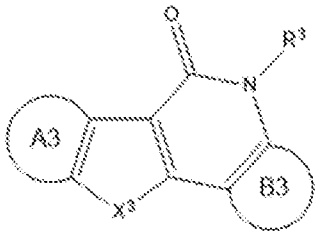
In some embodiments, the collection contains compounds from one or more of formulae a) to u), and/or salts thereof:

a) 

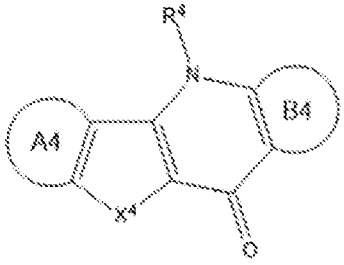
; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

b) 

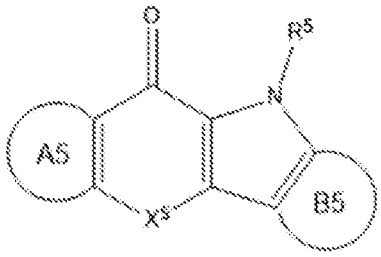
; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

c) 

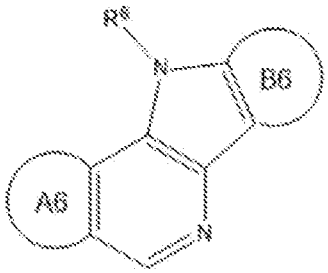
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

d) 

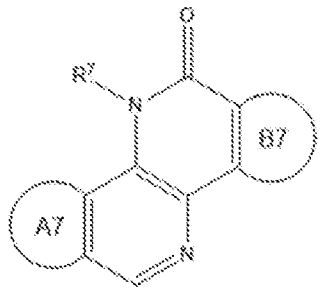
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

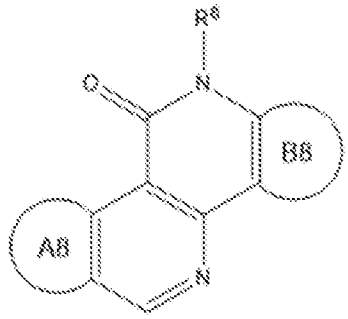
e) 

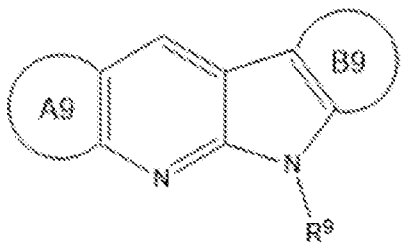
; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

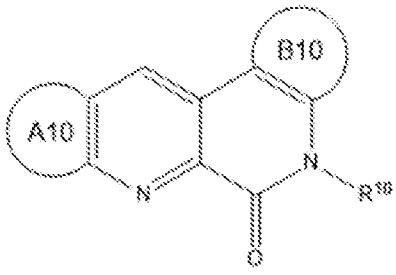
f) 

; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

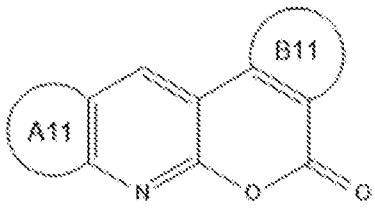
g)  ; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

h)  ; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

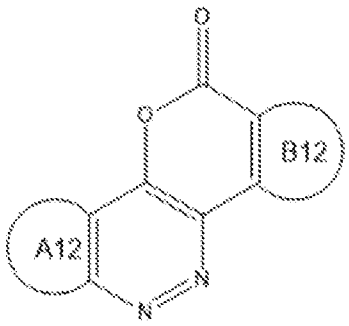
i)  ; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

j) 

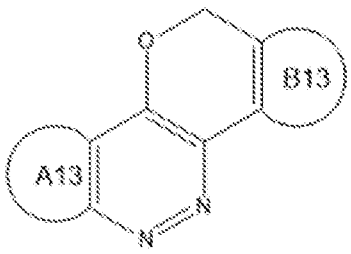
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

k) 

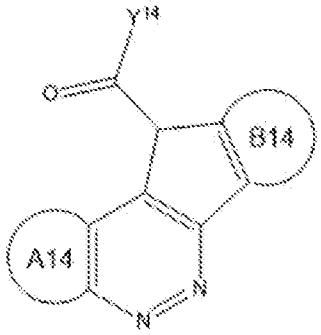
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

l) 

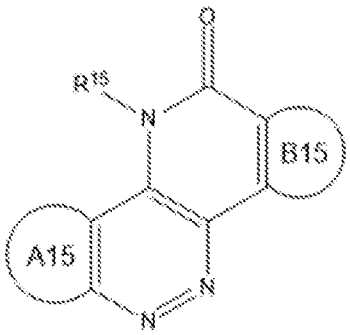
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

m) 

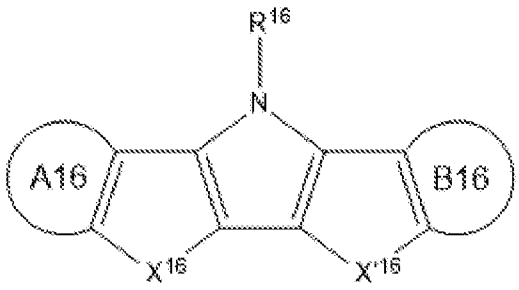
; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

n) 

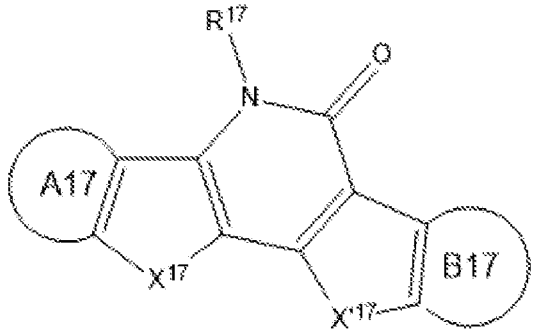
; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

o) 

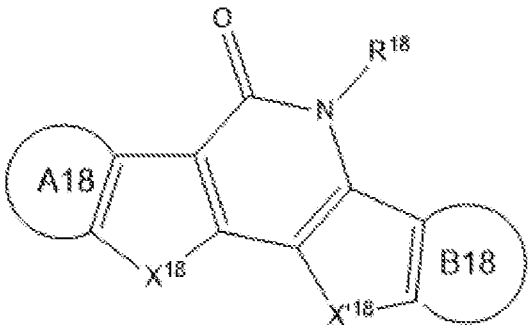
; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

p) 

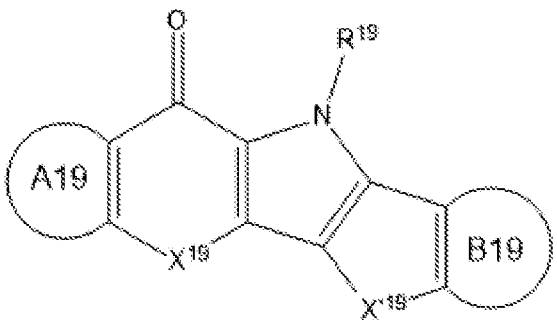
; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{16} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;



q) ; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

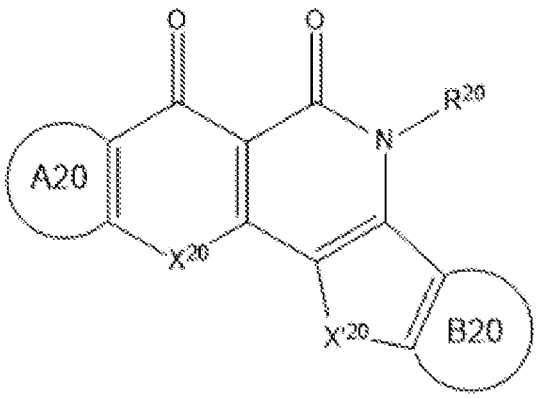


r) ; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

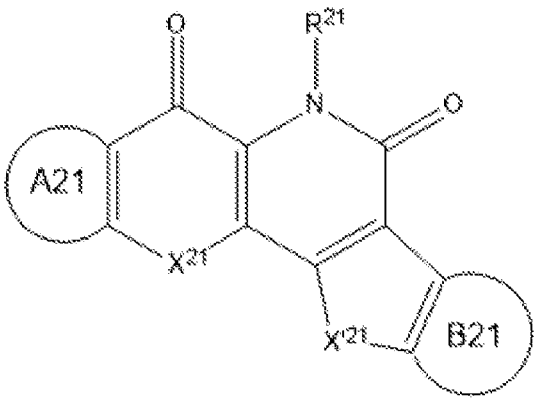


s) ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

-OC(O)-; and R^{19} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

t) 

; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3; or

u) 

; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{21} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

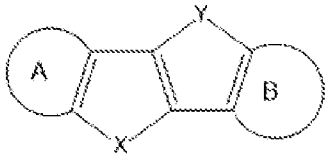
In another aspect, there is provided a polycyclic compound or salt thereof, wherein the polycyclic compound comprises at least 4 fused rings and has the formula

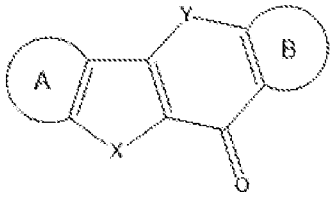
A-Het-Cyc-B

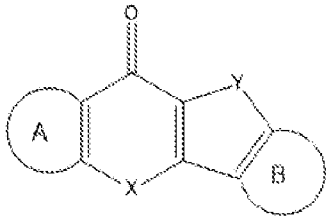
or

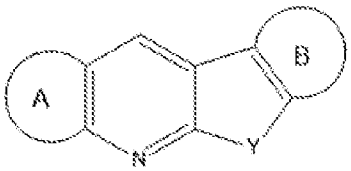
A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



,


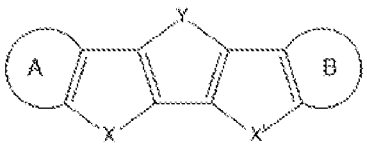
,


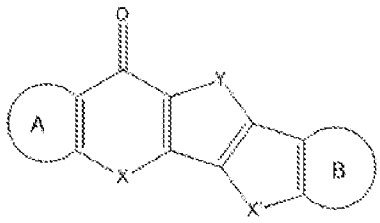


and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

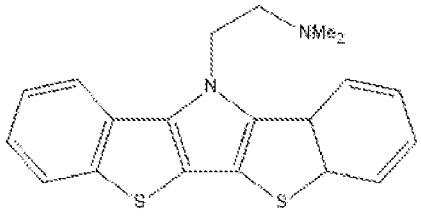
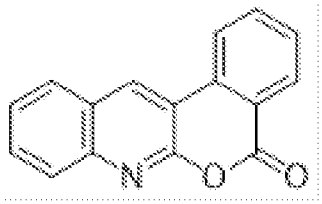
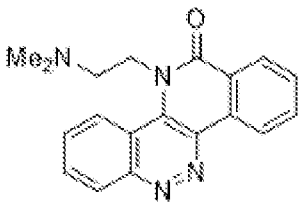
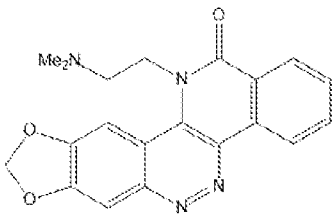
and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:



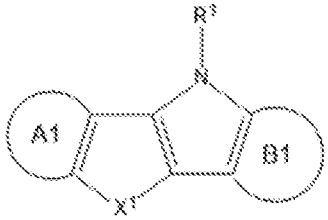
and


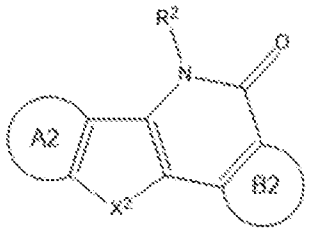
;

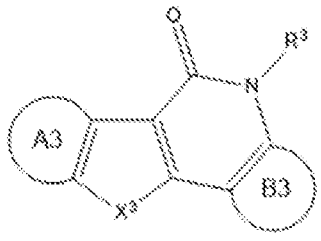
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein the compound is not  ,  ,  or  .

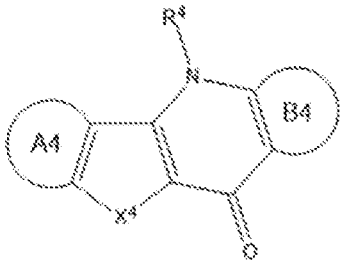
In some embodiments, the compound is selected from compounds having one of the following formulae:

a)  ; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

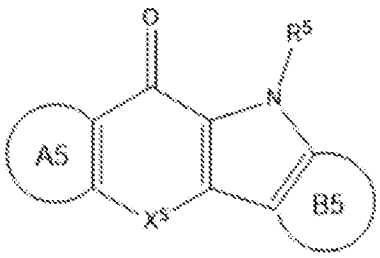
b)  ; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

c) 

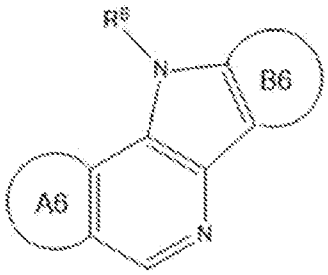
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

d) 

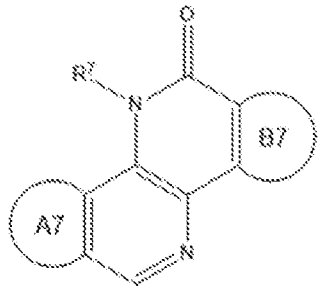
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

e) 

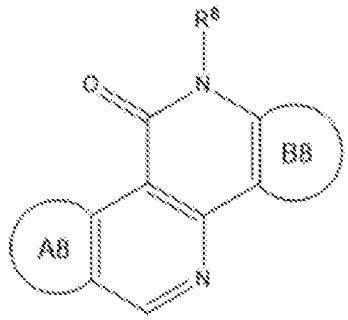
; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

f) 

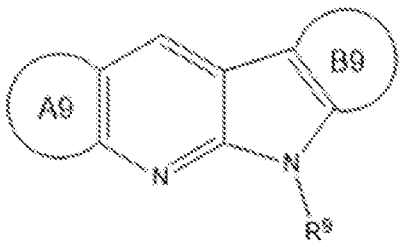
; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

g) 

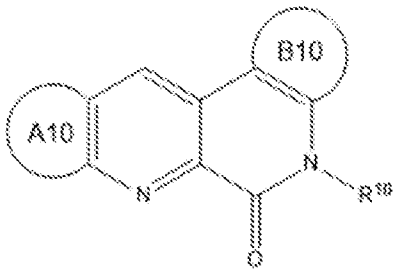
; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

h) 

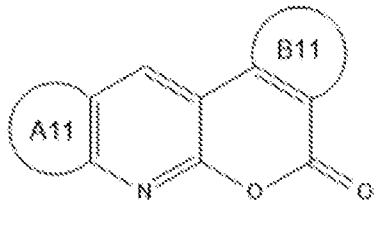
; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

i) 

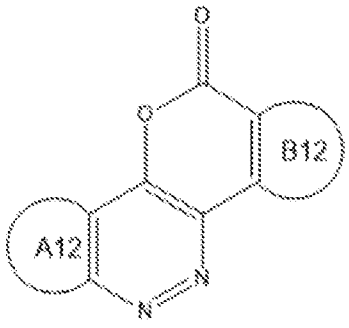
; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

j) 

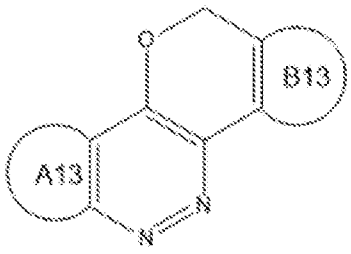
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

k) 

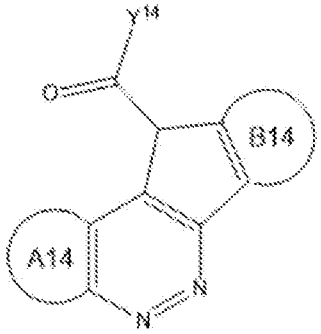
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

l) 

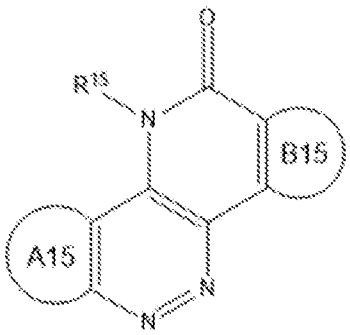
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

m) 

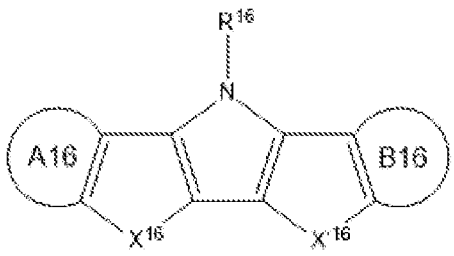
; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

n) 

; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; or

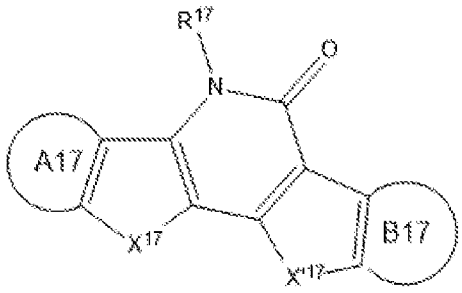
o) 

; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

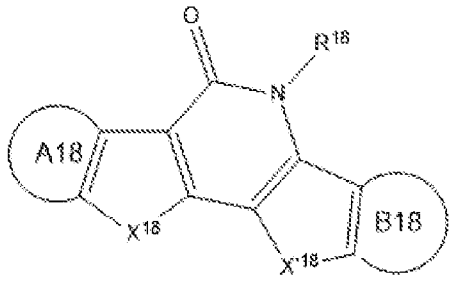
p) 

; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

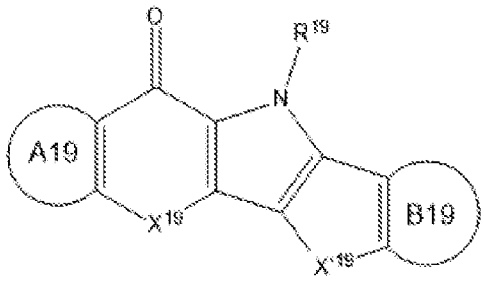
-OC(O)-; and R^{16} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

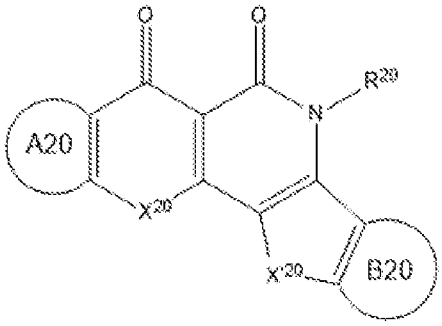
q) 

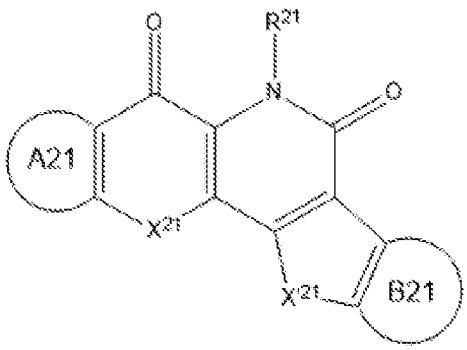
; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

r) 

; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

s)  ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{19} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

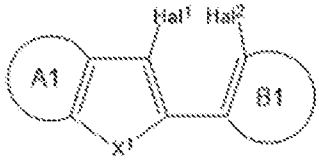
t)  ; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3; or

u)  ; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

-OC(O)-; and R^{21} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula a), as defined herein, comprising:

reacting a compound of formula

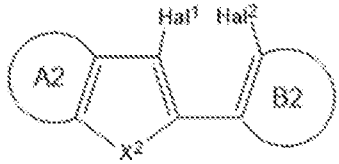


wherein A1, B1 and X^1 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^1-NH_2 in the presence of a palladium or copper catalyst, wherein R^1 is as defined herein; and optionally forming a salt of the compound.

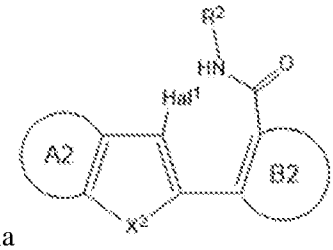
In another aspect, there is provided a method of synthesising a polycyclic compound of formula b), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A2, B2 and X^2 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^2-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^2 is as defined herein;

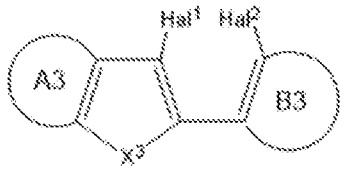
and if the product of step *i*) is a compound of formula 

rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

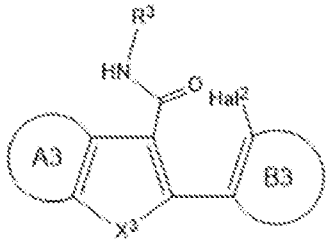
In another aspect, there is provided a method of synthesising a polycyclic compound of formula c), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A3, B3 and X^3 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^3-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^3 is as defined herein;

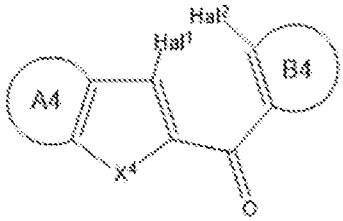


and if the product of step *i*) is a compound of formula rather than a compound of formula c),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula c); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula d), or salt thereof, as defined herein, comprising:

reacting a compound of formula

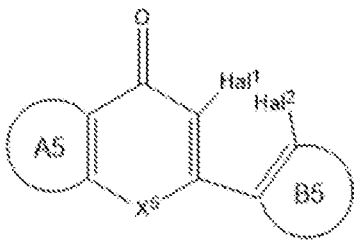


wherein A4, B4 and X^4 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^4-NH_2 in the presence of a copper catalyst, wherein R^4 is as defined herein; and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula e), or salt thereof, as defined herein, comprising:

reacting a compound of formula

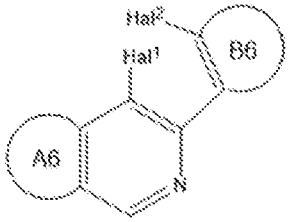


wherein A5, B5 and X^5 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^5NH_2 in the presence of a copper catalyst, wherein R^5 is as defined herein; and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula f), or salt thereof, as defined herein, comprising:

reacting a compound of formula

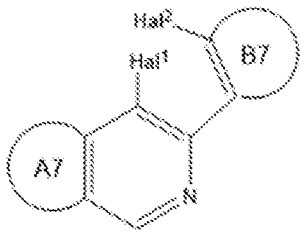


wherein A6, B6 and X^6 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^6NH_2 in the presence of a copper catalyst, wherein R^6 is as defined herein; and optionally forming a salt of the compound.

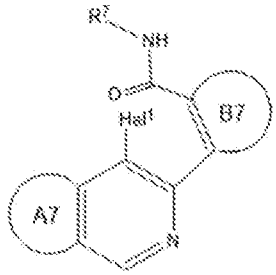
In another aspect, there is provided a method of synthesising a polycyclic compound of formula g), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A7 and B7 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^7-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^7 is as defined herein;

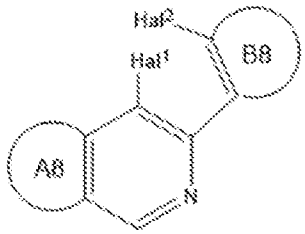
and if the product of step *i*) is a compound of formula 

rather than a compound of formula g),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula g); and optionally forming a salt of the compound.

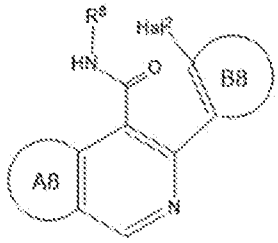
In another aspect, there is provided a method of synthesising a polycyclic compound of formula h), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A8 and B8 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^8-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^8 is as defined herein;

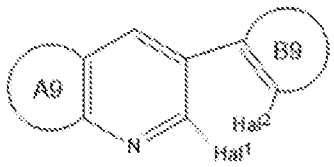


and if the product of step *i*) is a compound of formula rather than a compound of formula h),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula h); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula i) or salt thereof, as defined herein, comprising:

reacting a compound of formula

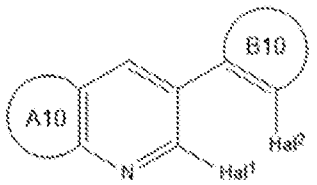


wherein A9 and B9 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^9NH_2 in the presence of a copper catalyst, wherein R^9 is as defined herein; and optionally forming a salt of the compound.

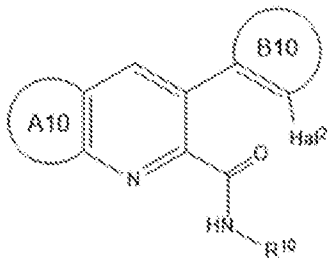
In another aspect, there is provided a method of synthesising a polycyclic compound of formula j), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A10 and B10 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

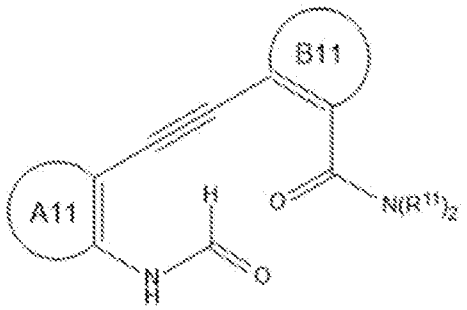
with a compound of formula R^{10}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{10} is as defined herein;

and if the product of step *i*) is a compound of formula  rather than a compound of formula j),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula j); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula k), or salt thereof, as defined herein, comprising:

reacting a compound of formula

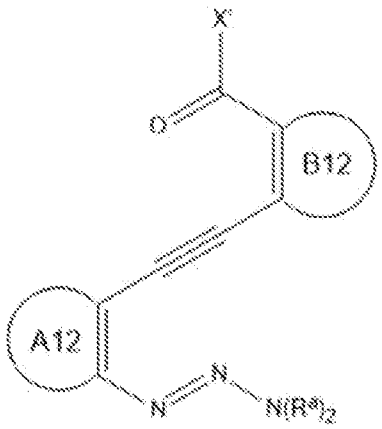


wherein A11 and B11 are as defined herein, and wherein each R^{11} is independently $C_{1\text{-}4}$alkyl;

with a dehydrating reagent, and then contacting the resulting product with an acid, thereby forming the compound of formula k); and optionally forming a salt of the compound.

In another aspect, there is provided, a method of synthesising a polycyclic compound or salt of formula l) as defined herein, comprising:

contacting a compound of formula

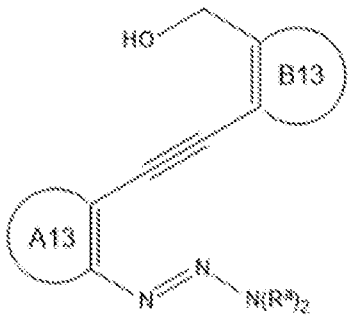


wherein A12 and B12 are as defined herein, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group, and X′ is OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

with an acid, thereby forming the compound of formula l); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula m), or salt thereof, as defined herein, comprising:

contacting a compound of formula

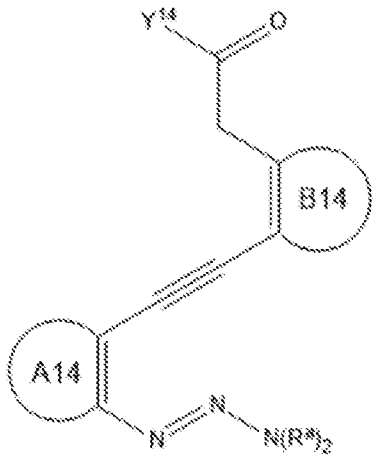


wherein A13 and B13 are as defined herein, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula m); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesizing a polycyclic compound of formula n), or salt thereof, as defined herein, comprising:

contacting a compound of formula

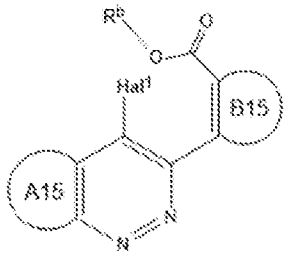


wherein A14, B14 and Y^{14} are as defined herein, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula n); and optionally forming a salt of the compound.

In another aspect, there is provided a method of synthesizing a compound of formula o), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A15 and B15 are as defined herein, Hal^1 is halogen, and R^b is C_{1-4}alkyl;

with $R^{15}NH_2$, wherein R^{15} is as defined herein, thereby forming the compound of formula o); and optionally forming a salt of the compound.

In another aspect, there is provided a method of identifying a compound having activity against a polynucleotide target or a polynucleotide-protein complex target, comprising:

testing a collection of compounds as defined herein or part thereof, or testing one or more compounds as defined herein for activity against a polynucleotide target; and

identifying whether the compound or compounds have activity against the polynucleotide target.

In another aspect, there is provided use of a compound as defined herein as a reference compound in a competition assay for determining activity of a test compound against a polynucleotide target.

In another aspect, there is provided a phenotypic method of identifying a new polynucleotide target for therapy of a disease or disorder, comprising

contacting a collection of compounds as defined herein or part thereof, or contacting one or more compounds as defined herein with a cell, tissue or animal disease model and monitoring for a change associated with a disease or disorder; and

if a change associated with the disease or disorder is identified, determining the biological target to which the compound binds.

Brief Description of the Drawings

Figure 1 shows examples of known polynucleotide targeting agents.

Figure 2 shows an embodiment of an sp^2-rich compound in accordance with the present disclosure and highlights molecular π-π-interactions that may be made with one or more nucleotide base groups.

Figure 3 shows a schematic of diversity-oriented synthetic approaches adopted in preparing compounds and collections according to the present disclosure.

Figure 4 shows a representative gel from a TOP1-mediated DNA cleavage assay conducted using compounds **77**, **56d** and **19a**. From left to right: Lane 1, DNA alone; lane 2, DNA and TOP1 without drug; lane 3, DNA and TOP1 with CPT (1 μM); lane 4, DNA and TOP1 with LMP744 (1 μM); lanes 5−16, DNA and TOP1 with the tested compounds at 0.1, 1.0, 10, and 100 μM concentrations, respectively. The arrows and numbers at left indicate the cleavage site positions. LMP744 is the positive non-camptothecin indenoisoquinoline control. B) Sequence of the 3'-[^{32}P]-labeled 117-bp DNA (labeled Guanine in red) with the indicated TOP1 cleavage site positions.

Figure 5 shows A-C) dose response curves for compounds **77**, **56d** and **19a**, respectively (% cell viability vs log[Drug](M)), using a PC3 prostate cancer cell line viability assay. Percentage inhibition of cell viability was determined using absorbance readings for each drug treatment expressed as a fraction of the vehicle control (0.1% DMSO) readings. For each drug concentration the mean (± SEM) was calculated and a sigmoidal curved was fitted to the data and used to calculate the IC_{50} of each compound.

Detailed Description

Definitions

Unless specifically defined otherwise, all technical and scientific terms used herein shall be taken to have the same meaning as commonly understood by one of ordinary skill in the art.

The present disclosure may refer to the contents of certain documents being incorporated herein by reference. In the event of any inconsistent teaching between the teaching of the present disclosure and the contents of those documents, the teaching of the present disclosure takes precedence.

It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art.

As used herein, the term “and/or”, e.g., “X and/or Y” shall be understood to mean either "X and Y" or "X or Y" and shall be taken to provide explicit support for both meanings or for either meaning.

As used herein, the term about, unless stated to the contrary, refers to +/- 10%, of the designated value.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or groups of compositions of matter. Thus, as used herein, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. For example, reference to "a" includes a single as well as two or more; reference to "an" includes a single as well as two or more; reference to "the" includes a single as well as two or more and so forth.

Unless otherwise indicated, terms such as "first," "second," etc. are used herein merely as labels, and are not intended to impose ordinal, positional, or hierarchical requirements on the items to which these terms refer. Moreover, reference to a "second" item does not require or preclude the existence of lower-numbered item (e.g., a "first" item) and/or a higher-numbered item (e.g., a "third" item).

As used herein, the phrase "at least one of", when used with a list of items, means different combinations of one or more of the listed items may be used and only one of the items in the list may be needed. The item may be a particular object, thing, or category. In other words, "at least one of" means any combination of items or number of items may be used from the list, but not all of the items in the list may be required. For example, "at least one of item A, item B, and item C" may mean item A; item A and item B; item B; item A, item B, and item C; or item B and item C. In some cases, "at least one of item A, item B, and item C" may mean, for example and without limitation, two of item A, one of item B, and ten of item C; four of item B and seven of item C; or some other suitable combination.

As used herein, the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

Each embodiment of the present disclosure described herein is to be applied *mutatis mutandis* to each and every other embodiment unless specifically stated otherwise or required otherwise by context.

As used herein, "C_a to C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl", or "C_{1-4}-alkyl" group includes alkyl groups having from 1 to 4 carbons, e.g. CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-.

As used herein, the term "alkyl" refers to a straight or branched hydrocarbon chain that is fully saturated (i.e., contains no double or triple bonds). Unless defined otherwise, the alkyl group may for example have from 1 to 12 carbon atoms (whenever it appears herein, a numerical range such as "1 to 12" refers to each integer in the given range; *e.g.*, "1 to 12 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 12 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 9 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as "C_{1-4}-alkyl" or similar designations. By way of example only, "C_{1-4}-alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like. Where specified, an alkyl group may be optionally substituted by one or more optional substituents as herein defined.

As used herein, the terms "halo" or "halogen," mean, in the context of the compounds defined herein, a fluorine, chlorine, bromine, or iodine atom, unless otherwise dictated by context. Additionally, terms such as "haloalkyl" may include monohaloalkyl and polyhaloalkyl. For example, the term "halo-C_1-C_4-alkyl" may include, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, 1-fluoro-2-bromoethyl, and the like.

As used herein, the term "alkylene" means a linear or branched saturated divalent hydrocarbon radical. For example, a C_{1-6}-alkylene includes methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

As used herein, the term "carbocyclyl" or "carbocyclic" means a cyclic ring or ring system containing only carbon atoms in the ring system backbone. When the carbocyclyl is a ring system, two or more rings may be joined together in a fused, bridged or spiro-connected fashion. Carbocyclyls may have any degree of saturation. Thus, carbocyclyls include cycloalkyls, cycloalkenyls, cycloalkynyls, and carbocyclic aromatic groups. The carbocyclyl group may have 3 to 20 carbon atoms, although the present definition also covers the occurrence of the term "carbocyclyl" where no numerical range is designated. The carbocyclyl group may also be a medium size carbocyclyl having 3 to 10 carbon atoms or 3 to 6 carbon atoms. The carbocyclyl group may be designated as "C_{5-10} carbocyclyl or 5-10-membered carbocyclic group" or similar designations. Examples of carbocyclyl rings include, but are not limited to, cyclohexyl, cyclohexenyl, 2,3-dihydro-indene, bicycle[2.2.2]octanyl, adamantyl, and spiro[4.4]nonanyl, phenyl and naphthyl.

As used herein, the term "aliphatic carbocyclic" or 'aliphatic carbocycle" means any of a non-aromatic monocyclic, bicyclic and polycyclic, (including fused, bridged or conjugated) hydrocarbon ring system, e.g. C_{3-20} (such as C_{3-10} or C_{3-8}). The ring or rings may be saturated, for example cycloalkyl, or may possess one or more double bonds (cycloalkenyl) and/or one or more triple bonds (cycloalkynyl). Examples of aliphatic carbocyclic groups are monocyclic 5-6-membered or bicyclic 9-10 membered ring systems. Suitable examples include cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopentenyl, cyclohexenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cyclooctatetraenyl and decalinyl. Where indicated, a carbocyclyl group may be optionally substituted by one or more optional substituents as herein defined.

As used herein, the term "aromatic carbocyclic", "aromatic carbocycle" or "aromatic" means an aromatic ring system containing only carbon atoms in the ring backbone. Typically, an aromatic group has from 5 to 18 carbon atoms, or from 5 to 10 carbon atoms. The aromatic group may for example be designated as "C_{5-10} aromatic". Examples of aromatic groups include, but are not limited to, phenyl and naphthyl.

As used herein, the term "heterocyclic" means an aromatic or non-aromatic ring system containing 3 or more ring atoms, that contain(s) one or more heteroatoms, that is, an element other than carbon, such as N, O and/or S, in the ring backbone. The remaining ring atoms are typically carbon atoms. In some embodiments, a heterocyclic group contains 1, 2, or 3 heteroatoms. A heterocyclic ring

can for example be a heterocycloalkyl ring or can for example be a heterocyclic aromatic (also known as heteroaryl) group, or if polycyclic, any combination thereof. In some embodiments, a heterocyclic group has from 5 to 20 ring atoms. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclic ring can also include one or more double bonds, e.g. it may be a heterocycloalkenyl group. The phrase "heterocyclic group" includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclic groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Heterocyclic groups include, but are not limited to, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homo piperazinyl, morpholinyl, homomorpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

As used herein, the term "heteroaryl", "heteroaromatic" or "aromatic heterocycle" means an aromatic ring system that contain(s) one or more heteroatoms, that is, an element other than carbon, such as N, O and/or S, in the ring backbone. The remaining ring atoms are typically carbon atoms. The heteroaromatic group may for example have 5-18 ring members (i.e. the number of atoms making up the ring backbone, including carbon atoms and heteroatoms). In some embodiments, the heteroaromatic group has from 5 to 10 ring atoms or from 5 to 7 ring atoms. A heteroaromatic group may for example be designated as "5-7 membered heteroaryl," "5-10 membered heterocycle," or similar designations. Examples of heteroaromatic rings include, but are not limited to, furyl, thienyl, phthalazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiophenyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, and benzothienyl.

As used herein, the term "optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 0, 1, 2, 3, 4, or 5 or more) substituents. In an embodiment, an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment, an optionally substituted group has 3 substituents. In another embodiment, an optionally substituted group has 4 substituents. In another embodiment, an optionally substituted group has 5 substituents.

It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as –

CH_2–, –CH_2CH_2–, –$CH_2CH(CH_3)CH_2$–, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene".

Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Other forms of isomerism include double bond isomerism in which compounds containing a carbon-carbon double bond may exist as Z or E isomers, conformational isomerism, and atropisomerism. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Separation of individual isomers or selective synthesis of individual isomers is accomplished by application of various methods which are known to practitioners in the art.

The skilled artisan will also recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures. For example, the term "tautomers" may refer to a set of compounds that have the same number and type of atoms but differ in bond connectivity and are in equilibrium with one another. A "tautomer" is a single member of this set of compounds. Typically, a single tautomer is drawn but it may be understood that this single structure may represent all possible tautomers that might exist. Examples may include enol-ketone tautomerism. When a ketone is drawn it may be understood that both the enol and ketone forms are part of the disclosure. Resonance forms and tautomers of compounds are within the scope of the present disclosure.

An isotope of an element other than the most commonly occurring isotope may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise. Such isotopically labeled compounds may for example be useful as research or diagnostic tools.

Those skilled in the art will appreciate that many organic compounds can form complexes in solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates, such as hydrates, exist when the compound incorporates solvent. It will be understood that the compounds of the present disclosure, as well as salts thereof, may be present in the form of solvates. Solvates of the compounds which are suitable are those where the associated solvent is pharmaceutically acceptable. Suitable solvates are pharmaceutically acceptable solvates including hydrates. It will be understood that the present disclosure encompasses unsolvated forms of the compounds, as well as solvated forms, such as hydrates.

Compounds disclosed herein may exist in one or more crystalline or amorphous forms. It will be understood that all such forms of the compounds are within the scope of the present disclosure.

As used herein, the term "therapy" includes curing a disease or disorder, as well as alleviation of or reduction of symptoms associated with a disease or disorder or condition. The term therapy also includes slowing the progression of a disease or disorder, as well as prophylaxis, and includes reducing the likelihood of contracting a disease or disorder or a symptom thereof.

Compound Collections for Screening against Polynucleotide Targets

The present disclosure provides collections of compounds (otherwise known as compound libraries) which have new polycyclic scaffolds, are sp^2-rich facilitating the possibility of establishing positive π-π-interactions with nucleoside bases.

As discussed above, most small-molecule drug discovery efforts are directed to the design of ligands for the encoded protein products. However, the present disclosure relates to compound collections which are targeted towards binding of polynucleotide targets, and the use of which is expected to provide an increased likelihood of identifying lead compounds for that class of target.

Identifying novel and strong chemical starting points remains a significant challenge in drug discovery. Thus, there is significant value to the field of pharmaceutical research and development in providing target-focused compound collections.

In the present disclosure, many example compounds in the collections have low molecular weight. During the process of lead optimisation, polynucleotide binding fragments such as the present compounds can be "grown" through SAR- and/or structure-guided approaches to make additional interactions with a protein binding partner (see Figure 2) to improve binding or other properties required for a pharmaceutical active agent. However, according to Lipinski's 'rule of 5', compounds with molecular weight >500 Da are less likely to be suitable for use as an orally active drug. Thus, the provision of low molecular weight compounds in the present collections provides compounds which, when found to be active against a polynucleotide target of interest, are amenable to further optimisation, including incorporation of additional functionality, without losing drug-like properties.

The compound collections of the present disclosure are based on a scaffold-divergent synthesis strategy. Providing a diverse series of scaffolds yet retaining a fused polycyclic structure with high sp^2 character, provides compound collections that, on screening against polynucleotide targets, have a high likelihood of allowing identification of lead compounds due to the range of structures encompassed by the scaffolds.

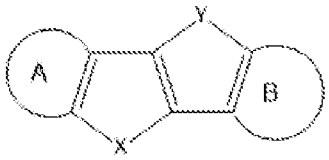
Thus, in one aspect, the present disclosure provides a collection of polycyclic compounds and/or salts thereof, for screening against a polynucleotide target, the collection comprising a plurality of polycyclic compounds which comprise at least 4 fused rings and have the formula

A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



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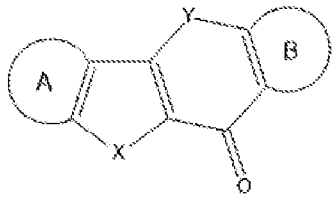

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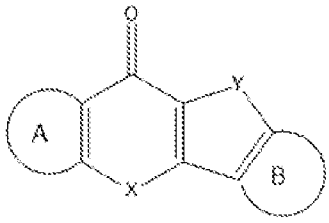
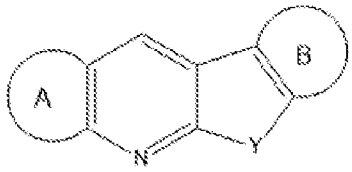
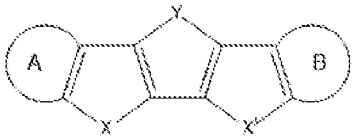


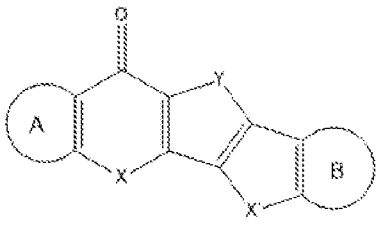


and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

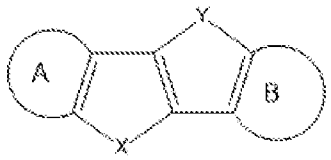
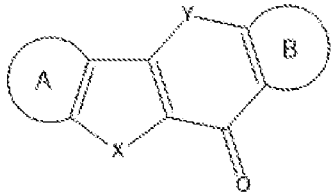
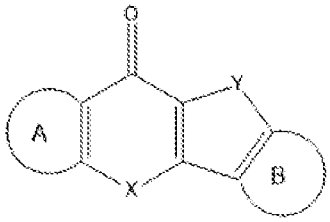
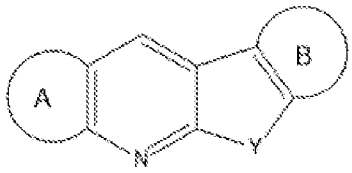
and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

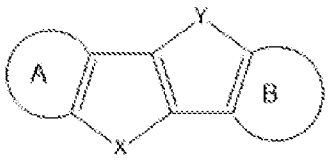
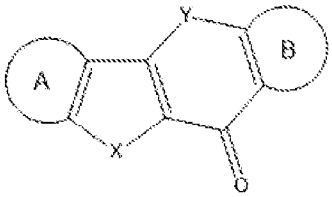
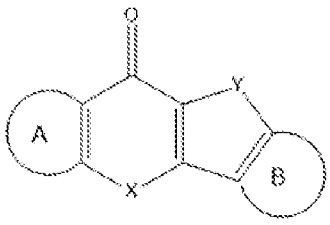
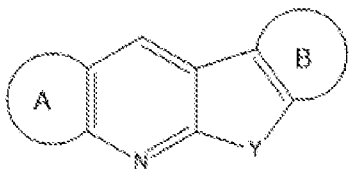


and


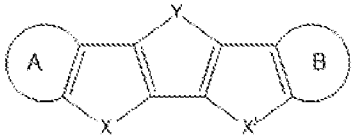
;

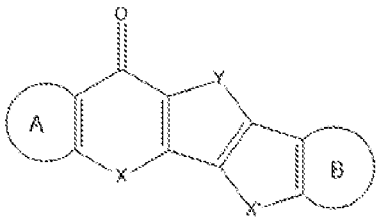
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the collection comprises or consists of compounds of the formula A-Het-Cyc-B, i.e.  ,  ,  and  ; or salts thereof.

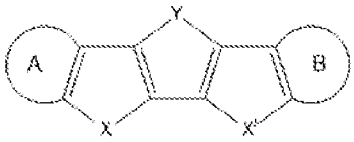
In some embodiments, the collection comprises or consists of compounds of the formula  , and/or salts thereof. In some embodiments, the collection comprises or consists of compounds of the formula  , and/or salts thereof. In some embodiments, the collection comprises or consists of compounds of the formula  , and/or salts thereof. In some embodiments, the collection comprises or consists of compounds of the formula  , and/or salts thereof.

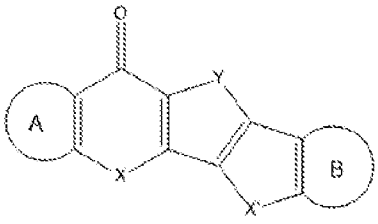
In some embodiments, the collection comprises or consists of compounds of the formula A-Het-Cyc-Het2-B, i.e.



and 

, and/or salts thereof. In some embodiments, the collection comprises or consists of compounds of the formula



, and/or salts thereof. In some embodiments, the collection comprises or consists of compounds of the formula 

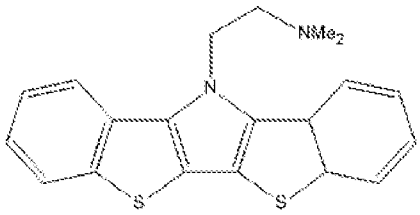
, and/or salts thereof.

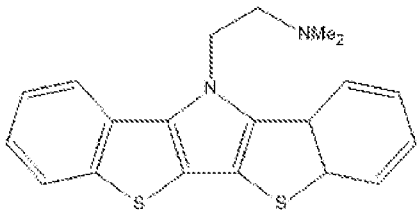
The compounds and/or salts which may be part of the collection are further defined in the section titled 'Compounds' below. Embodiments discussed in relation to the compounds and/or salts below, also apply equally in relation to the compounds and/or salts which are present in the collections of the present disclosure.

In some embodiments, the collection comprises compounds of formula a), or salts thereof. In some embodiments, the collection comprises compounds of formula b), or salts thereof. In some embodiments, the collection comprises compounds of formula c), or salts thereof. In some embodiments, the collection comprises compounds of formula d), or salts thereof. In some embodiments, the collection comprises compounds of formula e), or salts thereof. In some embodiments, the collection comprises compounds of formula f), or salts thereof. In some embodiments, the collection comprises compounds of formula g), or salts thereof. In some embodiments, the collection comprises compounds of formula h), or salts thereof. In some embodiments, the collection comprises compounds of formula i), or salts thereof. In some embodiments, the collection comprises compounds of formula j), or salts thereof. In some embodiments, the collection comprises compounds of formula k), or salts thereof. In some embodiments, the collection comprises compounds of formula l), or salts thereof. In some embodiments, the collection comprises compounds of formula m), or salts thereof. In some embodiments, the collection comprises compounds of formula n), or salts thereof. In some embodiments, the collection comprises compounds of formula o), or salts thereof. In some embodiments, the collection comprises compounds of formula p), or salts thereof. In some embodiments, the collection comprises compounds of formula q), or salts thereof. In some embodiments, the collection comprises compounds of formula r), or salts thereof. In some embodiments, the collection comprises compounds of formula s), or salts

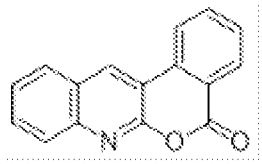
thereof. In some embodiments, the collection comprises compounds of formula t), or salts thereof. In some embodiments, the collection comprises compounds of formula u), or salts thereof.

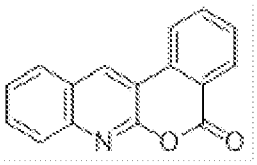
In some embodiments, the collection comprises two or more example compounds provided herein.

In some embodiments, the collection contains the compound  , or a salt thereof.

In some other embodiments, the collection does not contain the compound  , or a salt thereof.

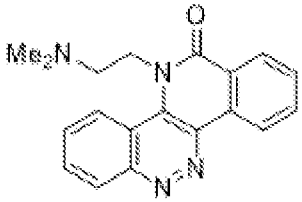
In some embodiments, the collection contains compounds of the formula p) or salts thereof, but only compounds wherein A16 is different from B16 and/or X^{16} is different from X'^{16}, or salts thereof. In some embodiments, the collection contains compounds of the formula p) or salts thereof, but only compounds wherein A16 is different from B16, or salts thereof. In some embodiments, the collection contains compounds of the formula p) or salts thereof, but only compounds wherein X^{16} is different from X'^{16}, salts thereof. In some embodiments, the collection does not contain compounds of formula p), or salts thereof.

In some embodiments, the collection contains the compound  , or a salt thereof.

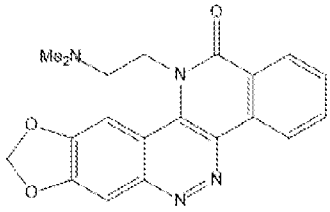
In some other embodiments, the collection does not contain the compound  , or a salt thereof.

In some embodiments, the collection does not contain compounds of formula k), or salts thereof.

In some embodiments, the collection contains one or both of the compounds

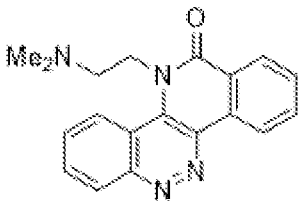


or

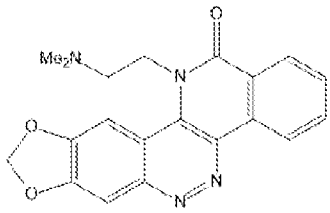


, or salts thereof.

In some other embodiments, the collection does not contain the compounds



or



, or salts thereof.

In some embodiments, the collection does not contain compounds of formula o), or salts thereof.

A 'collection of compounds' can also be referred to as a compound collection, library of compounds or compound library.

The collection of compounds may be provided in any suitable form. In its simplest form, a collection may be a plurality of compounds as defined herein, and/or salts thereof.

By way of example, a set of containers (e.g. a glass or plastic vial or bottle) each containing a different compound from the collection may be provided, optionally in a suitable solvent. Single compounds may be provided in containers, which may for example be stored together on the same site. As an alternative, multiple compounds may be provided in the same container (to facilitate rapid testing of a mixture, after which deconvolution can be carried out to identify the active compound or compounds if the mixture generates a positive result in an assay). Compounds may be provided in plates having wells, containing the compounds (e.g. dissolved in solvent), such as a 96-well plate. Thus in some embodiments, the collection of compounds comprises a plurality of compounds and/or salts, and or one or more containers. In some embodiments, the collection of compounds comprises a plurality of compounds and/or salts, and a container for each compound.

The collection of compounds is typically provided in a labelled or other form allowing identification of the individual compounds (e.g. a barcode that can be read by a barcode reader). In some embodiments, the collection of compounds comprises a plurality of compounds and/or salts, a container for each compound, and a label or other identifier for each container allowing identification of the compound.

In some embodiments, details of the individual compounds forming the collection may be input into a database and stored (for example details such as the compound name, structure, molecular weight, data of synthesis, purity information, date of accession to the collection, and/or amount remaining may be recorded). Information regarding compounds forming the collection may also be updated from time

to time if desired, for example as material is used and the amount remaining of a given compound decreases.

The collection comprises a plurality of compounds and/or salts as defined herein. In some embodiments, additional compounds and/or salts may also be incorporated into the collection. In some embodiments, at least 50% of the compounds in the collection are compounds as defined herein, or at least 60%, or at least 70%, or at least 80%, or at least 90%, or at least 95%. In some embodiments, the collection consists of compounds and/or salts as defined herein.

Collections as provided herein may be of differing sizes, depending on factors such as the availability of compounds and/or the resource available to synthesize compounds.

In some embodiments, the collection comprises at least 10 compounds and/or salts as defined herein, at least 100 compounds and/or salts as defined herein, at least 250 compounds and/or salts as defined herein, at least 500 compounds and/or salts as defined herein, or optionally at least 1000 compounds and/or salts as defined herein.

In some embodiments, the collection consists of compounds and/or salts as defined herein, and contains at least 10 compounds and/or salts, at least 100 compounds and/or salts, at least 250 compounds and/or salts, at least 500 compounds and/or salts, or optionally at least 1000 compounds and/or salts.

In some embodiments, the collection contains between 10 and 10000 compounds and/or salts as defined, or between 100 and 10000 compounds and/or salts as defined herein, or between 250 and/or 10000 compounds and/or salts as defined herein, or between 500 and/or 10000 compounds and/or salts as defined herein, or between 10 and 5000 compounds and/or salts as defined, or between 100 and 5000 compounds and/or salts as defined herein, or between 250 and/or 5000 compounds and/or salts as defined herein, or between 500 and/or 5000 compounds and/or salts as defined herein.

Compounds

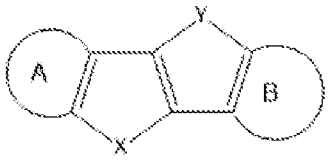
The present disclosure also provides a polycyclic compound or salt thereof, wherein the polycyclic compound comprises at least 4 fused rings and has the formula

A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



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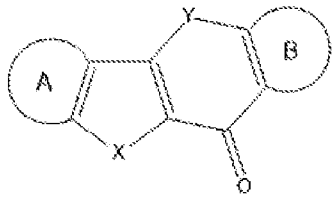

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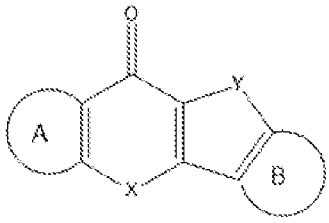
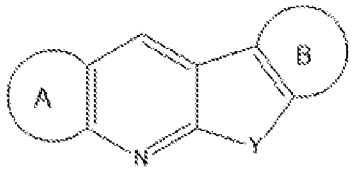
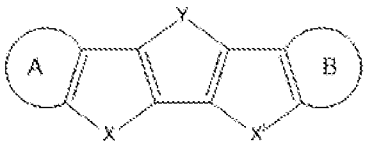




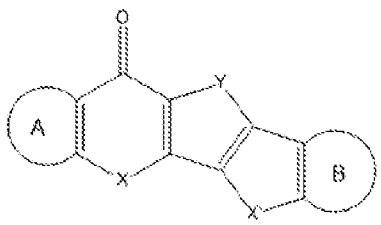
and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

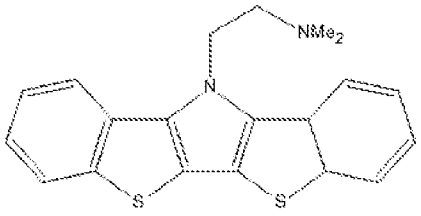
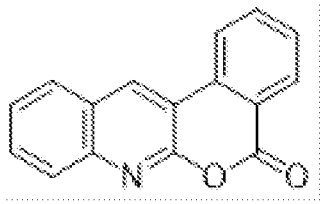
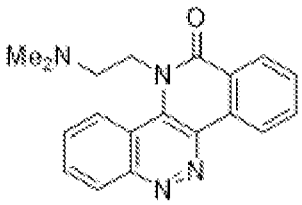
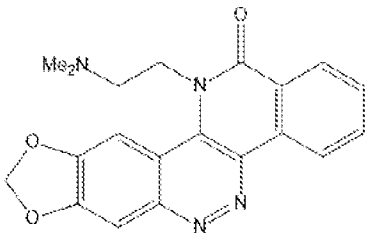


and

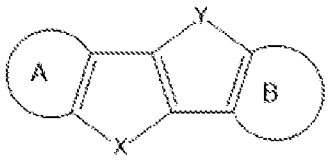
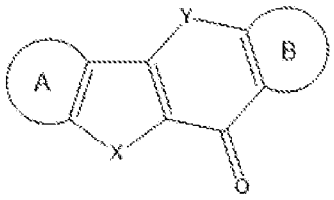
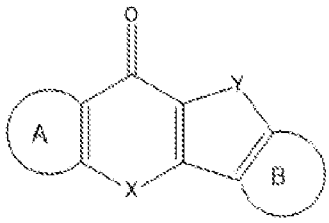
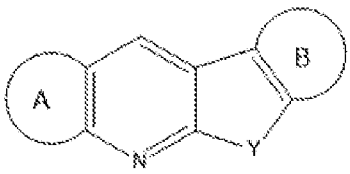
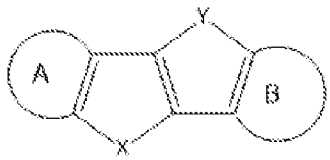


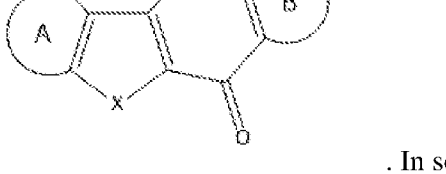
;

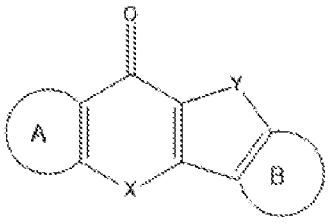
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

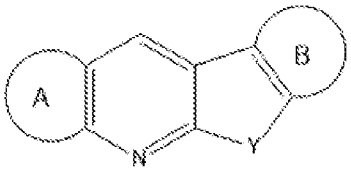
and wherein the compound is not  ,  ,  or  . In some embodiments, R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound is of the formula A-Het-Cyc-B, i.e.

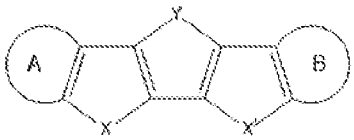
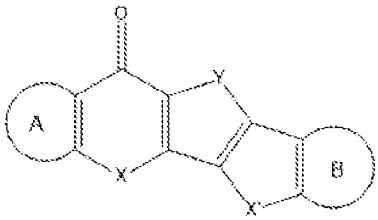
 ,  ,  ,  and  .

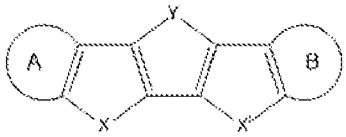
In some embodiments, the compound is of the formula  . In some embodiments, the compound is of the formula . In some

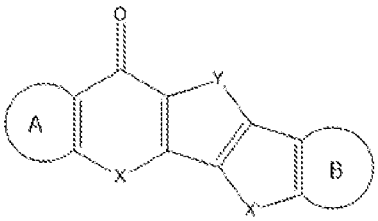
embodiments, the compound is of the formula  . In some embodiments,

the compound is of the formula  .

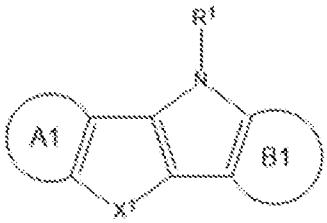
In some embodiments, the collection comprises or consists of compounds of the formula A-Het-Cyc-Het2-B, i.e.

 and  , and/or salts thereof. In some

embodiments, the collection compound is of the formula  . In some

embodiments, the compound is of the formula  .

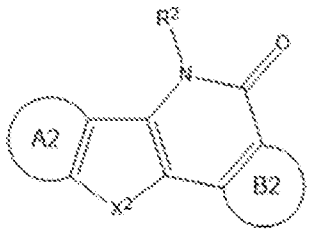
In some embodiments, the compound has the formula a)



a); wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents

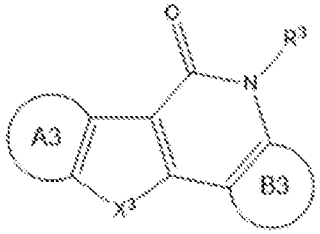
independently selected from methyl and CF_3. In some embodiments, R^1 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, A1 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A1 is phenyl or benzothiophene. In some embodiments, A1 is phenyl. In some embodiments, B1 is phenyl, thiophene or pyridine. In some embodiments, B1 is phenyl or thiophene. In some embodiments, B1 is phenyl. In some embodiments X^1 is O or S. In some embodiments, X^1 is S. In some embodiments, R^1 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^1 is phenyl optionally substituted by up to two substituents independently selected from the group consisting of methyl and CF_3. In some embodiments, R^1 is phenyl substituted by one CF_3.

In some embodiments, the compound has the formula b)



b); wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A2 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A2 is phenyl or benzothiophene. In some embodiments, A2 is phenyl. In some embodiments, B2 is phenyl, thiophene or pyridine. In some embodiments, B2 is phenyl or thiophene. In some embodiments, B2 is phenyl. In some embodiments X^2 is O or S. In some embodiments, X^2 is S. In some embodiments, R^2 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^2 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

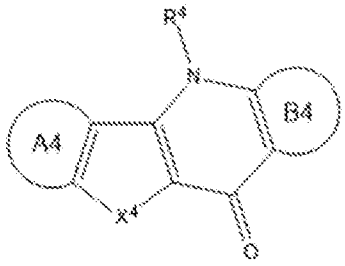
In some embodiments, the compound has the formula c)



c); wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}

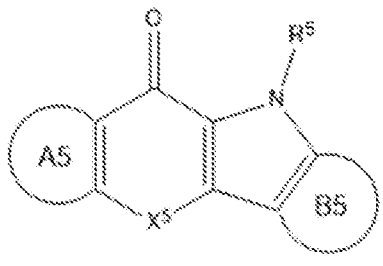
$_{4}$alkyl or N(C_{1-4}alkyl)$_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A3 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A3 is phenyl or benzothiophene. In some embodiments, A3 is phenyl. In some embodiments, B3 is phenyl, thiophene or pyridine. In some embodiments, B3 is phenyl or thiophene. In some embodiments, B3 is phenyl. In some embodiments X^3 is O or S. In some embodiments, X^3 is S. In some embodiments, R^3 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$. In some embodiments, R^3 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$.

In some embodiments, the compound has the formula d)



d); wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A4 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A4 is phenyl or benzothiophene. In some embodiments, A4 is phenyl. In some embodiments, B4 is phenyl, thiophene or pyridine. In some embodiments, B4 is phenyl or thiophene. In some embodiments, B4 is phenyl. In some embodiments X^4 is O or S. In some embodiments, X^4 is S. In some embodiments, R^4 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$. In some embodiments, R^4 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$.

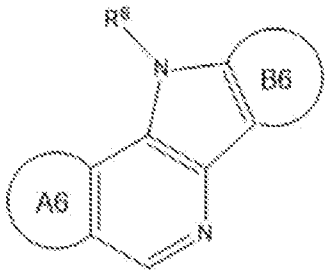
In some embodiments, the compound has the formula e)



e); wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or N(C_{1-4}alkyl)$_2$, said phenyl being optionally substituted by up to two substituents

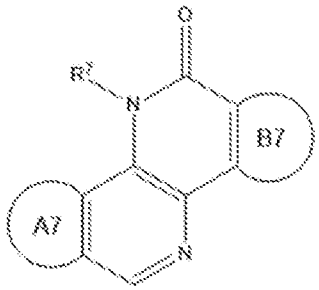
independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A5 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A5 is phenyl or benzothiophene. In some embodiments, A5 is phenyl. In some embodiments, B5 is phenyl, thiophene or pyridine. In some embodiments, B5 is phenyl or thiophene. In some embodiments, B5 is phenyl. In some embodiments X^5 is O or S. In some embodiments, X^5 is S. In some embodiments, R^5 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^5 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula f)



f); wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A6 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A6 is phenyl or benzothiophene. In some embodiments, A6 is phenyl. In some embodiments, B6 is phenyl, thiophene or pyridine. In some embodiments, B6 is phenyl or thiophene. In some embodiments, B6 is phenyl. In some embodiments, R^6 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^6 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

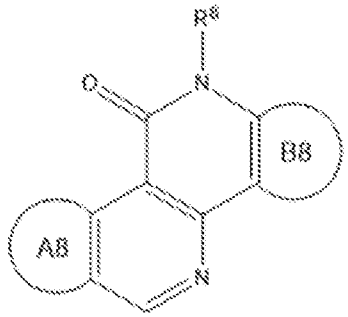
In some embodiments, the compound has the formula g)



g); wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl

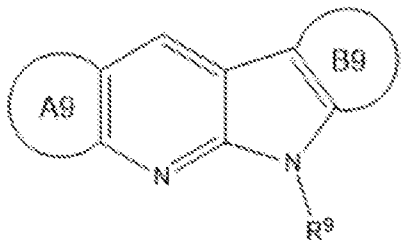
and CF_3. In some embodiments, A7 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A7 is phenyl or benzothiophene. In some embodiments, A7 is phenyl. In some embodiments, B7 is phenyl, thiophene or pyridine. In some embodiments, B7 is phenyl or thiophene. In some embodiments, B7 is phenyl. In some embodiments, R^7 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^7 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula h)



h); wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A8 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A8 is phenyl or benzothiophene. In some embodiments, A8 is phenyl. In some embodiments, B8 is phenyl, thiophene or pyridine. In some embodiments, B8 is phenyl or thiophene. In some embodiments, B8 is phenyl. In some embodiments, R^8 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^8 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

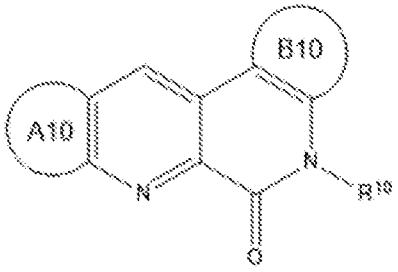
In some embodiments, the compound has the formula i)



i); wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A9 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A9 is phenyl or benzothiophene. In some embodiments, A9 is

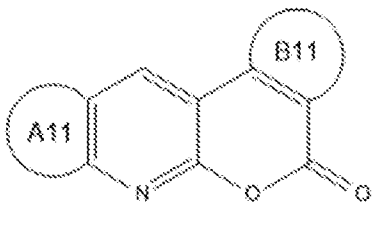
phenyl. In some embodiments, B9 is phenyl, thiophene or pyridine. In some embodiments, B9 is phenyl or thiophene. In some embodiments, B9 is phenyl. In some embodiments, R^9 is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^9 is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula j)



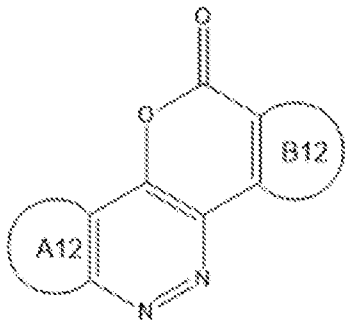
j); wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A10 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A10 is phenyl or benzothiophene. In some embodiments, A10 is phenyl. In some embodiments, B10 is phenyl, thiophene or pyridine. In some embodiments, B10 is phenyl or thiophene. In some embodiments, B10 is phenyl. In some embodiments, R^{10} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{10} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula k)

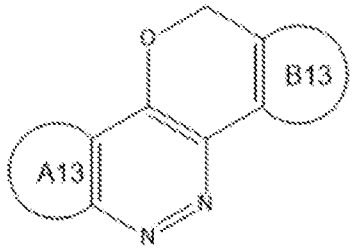


k); wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group. In some embodiments, A11 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A11 is phenyl or benzothiophene. In some embodiments, A11 is phenyl. In some embodiments, B11 is phenyl, thiophene or pyridine. In some embodiments, B11 is phenyl or thiophene. In some embodiments, B11 is phenyl.

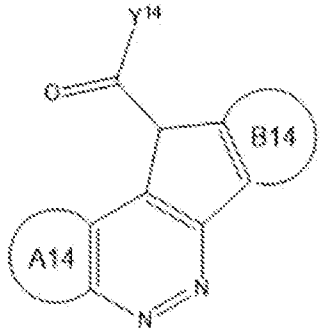
In some embodiments, the compound has the formula l)



l); wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group. In some embodiments, A12 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A12 is phenyl or benzothiophene. In some embodiments, A12 is phenyl. In some embodiments, B12 is phenyl, thiophene or pyridine. In some embodiments, B12 is phenyl or thiophene. In some embodiments, B12 is phenyl. In some embodiments, the compound has the formula m)

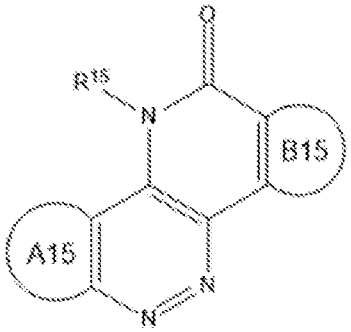


m); wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group. In some embodiments, A13 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A13 is phenyl or benzothiophene. In some embodiments, A13 is phenyl. In some embodiments, B13 is phenyl, thiophene or pyridine. In some embodiments, B13 is phenyl or thiophene. In some embodiments, B13 is phenyl. In some embodiments, the compound has the formula n)



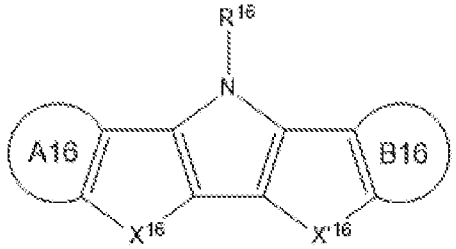
n); wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, A14 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A14 is phenyl or benzothiophene. In some embodiments, A14 is phenyl. In some embodiments, B14 is phenyl, thiophene or pyridine. In some embodiments, B14 is phenyl or thiophene. In some embodiments, B14 is phenyl.

In some embodiments, the compound has the formula o)



o); wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, A15 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A15 is phenyl or benzothiophene. In some embodiments, A15 is phenyl. In some embodiments, B15 is phenyl, thiophene or pyridine. In some embodiments, B15 is phenyl or thiophene. In some embodiments, B15 is phenyl. In some embodiments, R^{15} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

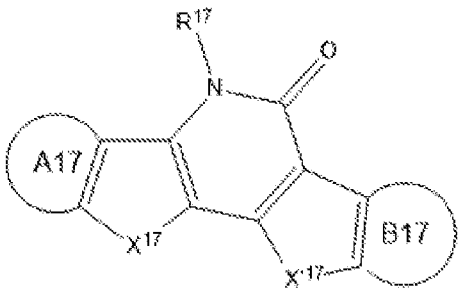
In some embodiments, the compound has the formula p)



p); wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{16} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A16 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A16 is phenyl or benzothiophene. In some embodiments, A16 is phenyl. In some embodiments, B16 is phenyl, thiophene or pyridine. In some embodiments, B16 is phenyl or thiophene. In some embodiments, B16 is phenyl. In some embodiments X^{16} is O or S. In some embodiments, X^{16} is S. In some embodiments X'^{16} is O or S. In some embodiments, X'^{16} is S. In some embodiments, R^{16} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{16} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

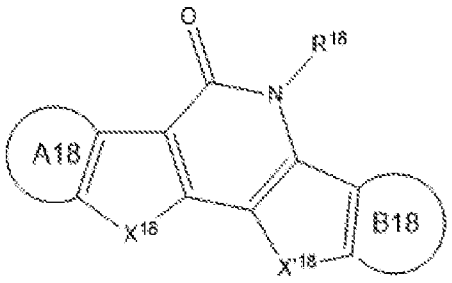
In some embodiments, the compound is of the formula p), and wherein A16 is different from B16 and/or X^{16} is different from X'^{16}. In some embodiments, A16 is different from B16. In some embodiments, X^{16} is different from X'^{16}.

In some embodiments, the compound has the formula q)



q); wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A17 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A17 is phenyl or benzothiophene. In some embodiments, A17 is phenyl. In some embodiments, B17 is phenyl, thiophene or pyridine. In some embodiments, B17 is phenyl or thiophene. In some embodiments, B17 is phenyl. In some embodiments X'^{17} is O or S. In some embodiments, X'^{17} is S. In some embodiments X^{17} is O or S. In some embodiments, X^{17} is S. In some embodiments, R^{17} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{17} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

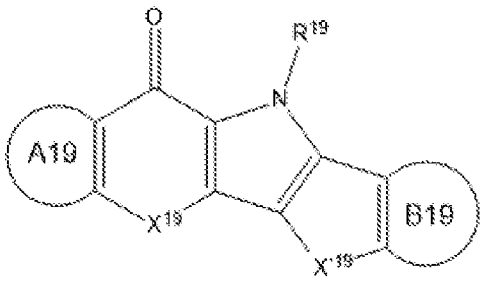
In some embodiments, the compound has the formula r)



r); wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents

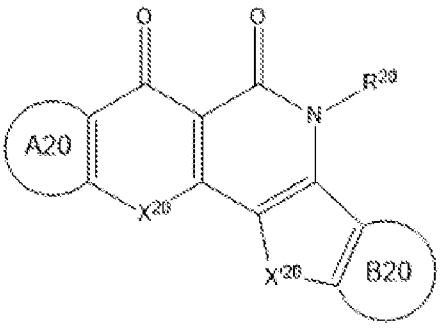
independently selected from methyl and CF_3. In some embodiments, A18 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A18 is phenyl or benzothiophene. In some embodiments, A18 is phenyl. In some embodiments, B18 is phenyl, thiophene or pyridine. In some embodiments, B18 is phenyl or thiophene. In some embodiments, B18 is phenyl. In some embodiments X^{18} is O or S. In some embodiments, X^{18} is S. In some embodiments X'^{18} is O or S. In some embodiments, X'^{18} is S. In some embodiments, R^{18} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{18} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula s)



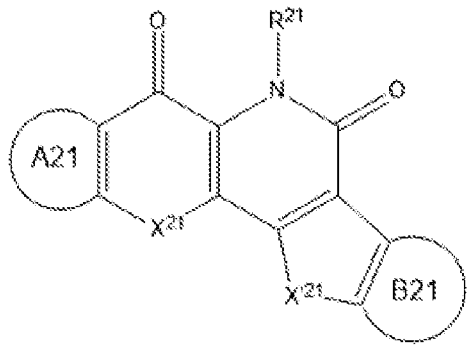
s); wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{19} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A19 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A19 is phenyl or benzothiophene. In some embodiments, A19 is phenyl. In some embodiments, B19 is phenyl, thiophene or pyridine. In some embodiments, B19 is phenyl or thiophene. In some embodiments, B19 is phenyl. In some embodiments X^{19} is O or S. In some embodiments, X^{19} is S. In some embodiments X'^{19} is O or S. In some embodiments, X'^{19} is S. In some embodiments, R^{19} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{19} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula t)



t); wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A20 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A20 is phenyl or benzothiophene. In some embodiments, A20 is phenyl. In some embodiments, B20 is phenyl, thiophene or pyridine. In some embodiments, B20 is phenyl or thiophene. In some embodiments, B20 is phenyl. In some embodiments X^{20} is O or S. In some embodiments, X^{20} is S. In some embodiments X'^{20} is O or S. In some embodiments, X'^{20} is S. In some embodiments, R^{20} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{20} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound has the formula u)



u); wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{21} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3. In some embodiments, A21 is phenyl, thiophene, pyridine or benzothiophene. In some embodiments, A21 is phenyl or benzothiophene. In some embodiments, A21 is phenyl. In some embodiments, B21 is phenyl, thiophene or pyridine. In

some embodiments, B21 is phenyl or thiophene. In some embodiments, B21 is phenyl. In some embodiments X^{21} is O or S. In some embodiments, X^{21} is S. In some embodiments X'^{21} is O or S. In some embodiments, X'^{21} is S. In some embodiments, R^{21} is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{21} is C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

In some embodiments, the compound is not a compound of formula k), or a salt thereof.

In some embodiments, the compound is not a compound of formula o), or a salt thereof.

In some embodiments, the compound is not a compound of formula p), or a salt thereof.

In some embodiments, the compound is not a salt. In other embodiments, the compound is provided in the form of a salt. Suitable salts include those formed with organic or inorganic acids or bases. Exemplary acid addition salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1′-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Exemplary base addition salts include, but are not limited to, ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine, N-methyl-D-glucomine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl -propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine.

Screening of Collections and Compounds

The collections and compounds/salts of the present disclosure find use in screening methods for identifying lead compounds for development of therapeutic agents having activity against polynucleotide targets, including polynucleotide-protein complex targets.

Thus, in another aspect, there is provided a method of identifying a compound having activity against a polynucleotide target or a polynucleotide-protein complex target, comprising:

testing a collection of compounds as defined herein or part thereof, or testing one or more compounds as defined herein for activity against a polynucleotide target; and

identifying whether the compound or compounds have activity against the polynucleotide target.

In some embodiments, the polynucleotide target is an RNA target.

In some embodiments, the RNA target is an mRNA target, micro-RNA or a non-coding RNA target.

In some embodiments, the polynucleotide target is a DNA target.

In some embodiments, the polynucleotide target is a polynucleotide-protein complex target.

In some embodiments, the polynucleotide target is a functional DNA topology.

In some embodiments, the polynucleotide target is a DNA complex with a transcription factor, an epigenetic modulator, an RNA-polymerase complex, Z-DNA, or a G-quadruplex.

In some embodiments, the polynucleotide target is selected from the group consisting of DNA-topoisomerase 1, mRNA encoding SMN2 protein, and G-quadruplex mRNA encoding oncogenic N-Ras protein.

Any suitable assay may be used for evaluating activity of a compound at a particular polynucleotide target. In some embodiments, the compound is tested for activity using an assay selected from the group consisting of a radiolabelled DNA-cleavage assay, a cell cytotoxicity assay, and an affinity assay for polynucleotides and their protein complexes by one or more of surface plasmon resonance assay, fluorometric assay, nuclear magnetic resonance assay and thermal shift assay.

In another aspect, there is provided use of a compound as defined herein as a reference compound in a competition assay for determining activity of a test compound against a polynucleotide target. For example, a radiolabelled form of the polycyclic compound as defined herein is used in the assay. Methods of introducing radioactive isotopes to compounds, such as ^{3}H, are known to persons of skill in the art.

In another aspect, there is provided a phenotypic method of identifying a new polynucleotide target for therapy of a disease or disorder, comprising

contacting a collection of compounds as defined herein or part thereof, or contacting one or more compounds as defined herein with a cell, tissue or animal disease model and monitoring for a change associated with a disease or disorder; and

if a change associated with the disease or disorder is identified, determining the biological target to which the compound binds.

In some embodiments, the compound is contacted with a cell.

In some embodiments, the compound is contacted with a tissue, for example an organoid, explant or *ex vivo* assay.

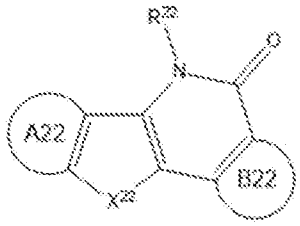
In some embodiments, the compound is contacted with an animal disease model.

Where a change associated with the disease or disorder is identified, any suitable means may be used to deconvolute the results and identify the biological target. Examples of suitable techniques include chemoproteomic approaches (e.g. resin-bound small molecules in target-drag down experiments), and experiments based on fluorescent and/or luminescent labelling (FRET, BRET), including photoactivated (covalent binding) ligands.

Topoisomerase inhibitors

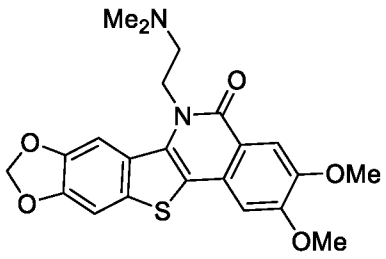
As discussed below, some scaffolds generated in the present disclosure are reminiscent of DNA intercalators that inhibit TOP1, and it has been demonstrated that certain compounds have activity in Top1-mediated DNA cleavage and PC3 cell viability assays. Such compounds thus have topoisomerase

activity, and find use in the therapy of cancers, such as colorectal cancer. Accordingly, the present disclosure also provides a compound of the formula v):



v)

or a salt thereof; wherein A22 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group which is optionally substituted by from 1 to 3 C_{1-4}alkoxy groups; X^{22} is O, S, NH or NC_{1-4}alkyl; and R^{22} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

In some embodiments, X^{22} is S. In some embodiments, A22 is a benzodioxole group. In some embodiments, B22 is phenyl which is optionally substituted by 1 or 2 methoxy groups, preferably substituted by 2 methoxy groups. In some embodiments, R^{22} is is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$. In some embodiments, R^{22} is C_{1-4} alkyl substituted by $N(C_{1-4}alkyl)_2$, preferably a $-CH_2CH_2N(Me)_2$ group. In some embodiments, the compound of formula v) is 

.

There is also provided a compound of formula v), b), or o) as defined herein, or a salt thereof, or a pharmaceutical composition comprising the compound or salt, for use in the treatment of a cancer, for example colorectal cancer. There is also provided a method of treating a cancer, such as colorectal cancer, in a subject, comprising administering an effective amount of a compound of formula v), b) or o) as defined herein, or a salt thereof, or a pharmaceutical composition comprising the compound or salt, to the subject. There is also provided use of a compound of formula v), b) or o) as defined herein, or a salt herein, for the manufacture of a medicament for the treatment of a cancer, such as colorectal cancer.

Diversity-Oriented Synthesis of Compounds

As discussed above, the compound collections and compounds of the present disclosure are based on a scaffold-divergent synthesis strategy. The scaffolds developed originate from a common approach based on cyclisation of alkynes, and conceptually originating from alkyne and aromatic

components (see Figure 3). Generation of a sp^2-rich polynucleotide-biased fragment library has been devised based on the electrophilic cyclisation of alkynes, with scaffold modifications including the use of intermolecular and intramolecular electrophiles and variations in the nature of a second ring closure. Iterative use of halocyclisation further extends the range of heteroacene scaffolds that can be accessed. These methods are yet further complemented by other heteroacene syntheses using electrophilic cyclisation. The methods are also applicable to the generation of more substituted systems for further library diversification and/or lead optimisation.

The compounds of formulae a) to u), or salts thereof, may for example be synthesized by methods described below, or by modification of these methods. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever.

Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include e.g. those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, **1989**, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **1995**, which are both hereby incorporated herein by reference in their entirety.

Starting materials are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

In some cases, it may be necessary and/or desirable to protect sensitive or reactive groups on intermediate compounds during synthesis of compounds. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. Examples of such groups include: OH (including dials), NH_2, CO_2H, SH and C=O. As used herein, the term "protecting group", means an introduced functionality which temporarily renders a particular functional group inactive under certain conditions. The protecting group may be removed at a convenient subsequent stage using methods known from the art. Exemplary forms of protected groups include: for amino (NH_2) - carbamates (such as Cbz, Boc, Fmoc), benzylamines, acetamides (e.g. acetamide, trifluoroacetamide); for carbonyl - acetals, ketals, dioxanes, dithianes, and hydrazones; for hydroxy - ethers (e.g. alkyl ethers, alkoxylalkyl ethers, allyl ethers, silyl ethers, benzyl ethers,

tetrahydropyranyl ethers), carboxylic acid esters, acetals (e.g. acetonide and benzylidene acetal); for thio (SH) -ethers (e.g. alkyl ethers, benzyl ethers), esters; and for CO_2H - esters (e.g. alkyl esters, benzyl esters).

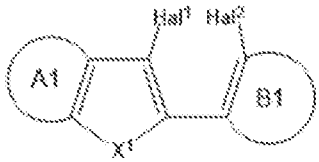
Compounds of the present disclosure may be separated from a reaction mixture and further purified, if desired, by any suitable method, such as column chromatography, high pressure liquid chromatography, or recrystallization.

Where the compounds of the present disclosure contain one or more chiral centers, as discussed above such compounds can be prepared or isolated as pure stereoisomers, e.g. as individual enantiomers, or stereoisomer-enriched mixtures, or racemic mixtures. All such stereoisomers (and enriched and racemic mixtures) are included within the scope of the present technology. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

A compound of formulae a) to u) or v), which is a free acid or free base may if desired be converted into a salt of the compound. Any suitable method of production of a salt form of the compound may be employed. For example, where the compound is a free base, it may be contacted with an acid (such as HCl in the case of forming a hydrochloride salt) to form the salt. Where the compound is a free acid, it may for example be contacted with a base (e.g. NaOH, in the case of forming a sodium salt). Such a salt formation step may for example be carried out in the presence of a diluent or solvent. Salt forms of organic compounds often have lower solubility in some organic solvents than the parent compounds, particularly in less polar organic solvents. Thus, in some embodiments, a compound of formulae a) to u) or v), which is a free acid or free base may be dissolved in a suitable solvent, and contacted with a base or acid as appropriate, with the resulting salt precipitating from solution, which can if desired by obtained by filtration or decanting, or conversely, if not precipitated from solution, can be extracted using an appropriate solvent.

In one aspect, there is provided a method of synthesising a polycyclic compound of formula a), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A1, B1 and X^1 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

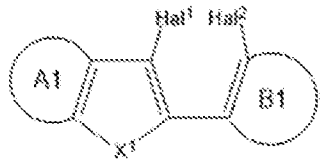
with a compound of formula R^1-NH_2 in the presence of a palladium or copper catalyst, wherein R^1 is as defined herein; and optionally forming a salt of the compound.

In some embodiments, Hal^1 is I and Hal^2 is Br.

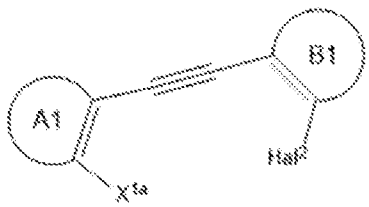
In some embodiments the catalyst is a copper catalyst. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the catalyst is a palladium catalyst. In some embodiments, the palladium catalyst is that produced from Pd_2dba_3 and Xantphos. The reaction may for example be carried out in the presence of a base, such as Cs_2CO_3. The reaction may for example be carried out in the presence of a solvent such as 1,4-dioxane. The reaction may for example be carried out at elevated temperature, for example at reflux.

In some embodiments, the compound of formula



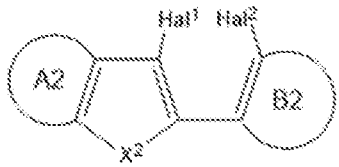
is produced by subjecting a compound of formula



, wherein A1, B1 and Hal^2 are as defined herein, and X^{1a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

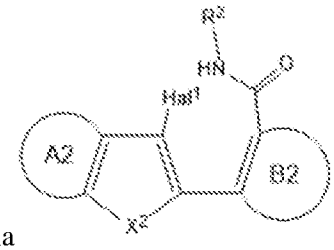
In another aspect, there is provided a method of synthesising a polycyclic compound of formula b), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A2, B2 and X^2 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^2-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^2 is as defined herein;

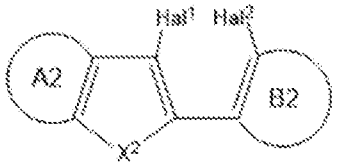
and if the product of step *i*) is a compound of formula  rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

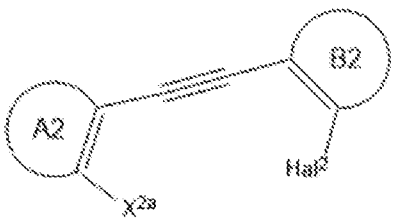
In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. In some embodiments Pd_2dba_3 is used, together with Xantphos. Typically a base is used, such as triethylamine or Cs_2CO_3. Typically the reaction is carried out under carbon monoxide atmosphere. In some embodiments, the reaction is carried out under a carbon monoxide atmosphere and then under an inert atmosphere such as a nitrogen atmosphere. Typically an organic solvent is used, such as NMP or 1,4-dioxane.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula



is produced by subjecting a compound of formula

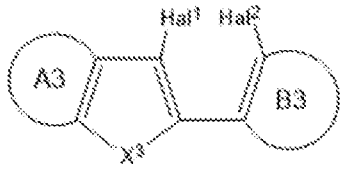


, wherein A2, B2 and Hal^2 are as defined herein, and X^{2a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-one

hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

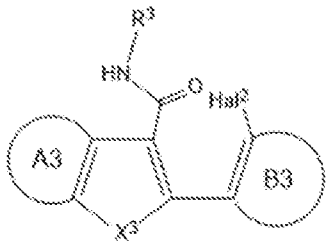
In another aspect, there is provided a method of synthesising a polycyclic compound of formula c), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A3, B3 and X^3 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^3-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^3 is as defined herein;



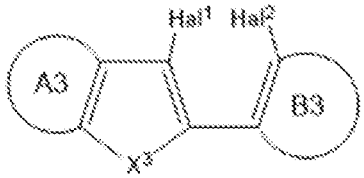
and if the product of step *i*) is a compound of formula rather than a compound of formula c),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula c); and optionally forming a salt of the compound.

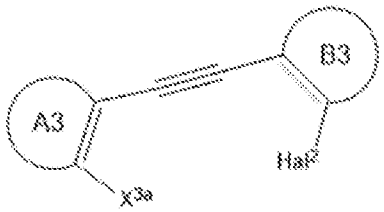
In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. In some embodiments, Pd_2dba_3 is used together with Xantphos. Typically a base is used, such as triethylamine or Cs_2CO_3. Typically the reaction is carried out under carbon monoxide atmosphere. In some embodiments, the reaction is carried out under carbon monoxide atmosphere, and then under an inert atmosphere, such as a nitrogen atmosphere, Typically an organic solvent is used, such as NMP or 1,4-dioxane.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula



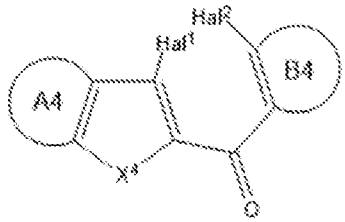
is produced by subjecting a compound of formula



, wherein A3, B3 and Hal^2 are as defined herein, and X^{3a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-one hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula d), or salt thereof, as defined herein, comprising:

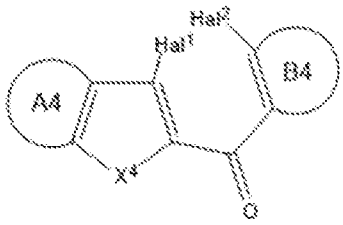
reacting a compound of formula



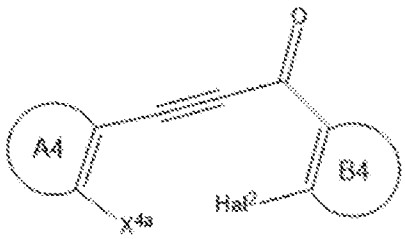
wherein A4, B4 and X^4 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^4-NH_2 in the presence of a copper catalyst, wherein R^4 is as defined herein; and optionally forming a salt of the compound.

In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.



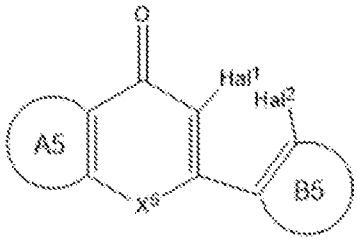
In some embodiments, the compound of formula is produced by



subjecting a compound of formula , wherein A4, B4, Hal^2 are as defined herein, and X^{4a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2. The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula e), or salt thereof, as defined herein, comprising:

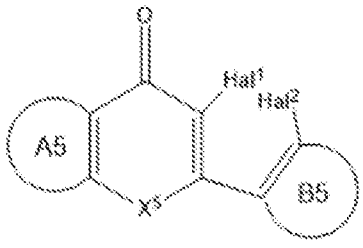
reacting a compound of formula

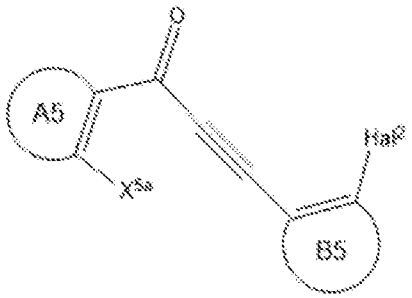


wherein A5, B5 and X^5 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^5NH_2 in the presence of a copper catalyst, wherein R^5 is as defined herein; and optionally forming a salt of the compound.

In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

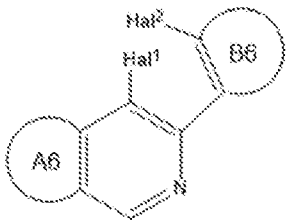
In some embodiments, the compound of formula  is produced by



subjecting a compound of formula , wherein A5, B5 and Hal^2 are as defined herein, and X^{5a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2. The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula f), or salt thereof, as defined herein, comprising:

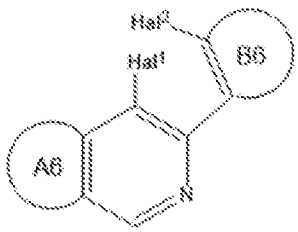
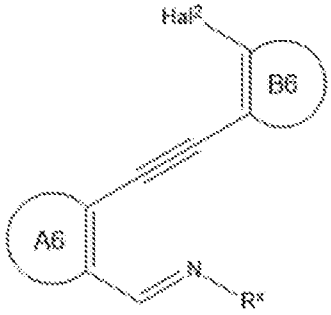
reacting a compound of formula



wherein A6, B6 and X^6 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

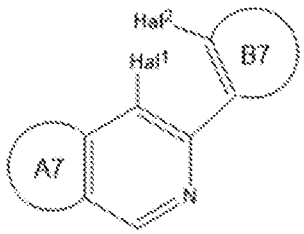
with a compound of formula R^6NH_2 in the presence of a copper catalyst, wherein R^6 is as defined herein; and optionally forming a salt of the compound.

In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula  is produced by subjecting a compound of formula  , wherein A6, B6 and Hal^2 are as defined herein, and R^X is OC_{1-4}alkyl or C_{1-4}alkyl; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with $CuBr_2$. The reaction may for example be carried out in the presence of a solvent such as dimethylacetamide.

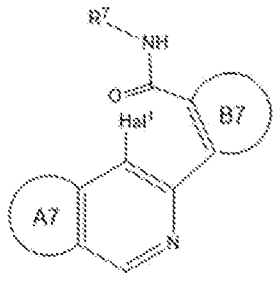
In another aspect, there is provided a method of synthesising a polycyclic compound of formula g), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A7 and B7 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

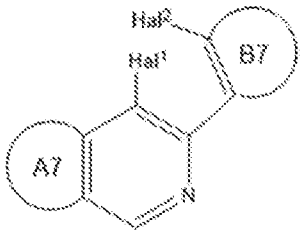
with a compound of formula R^7-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^7 is as defined herein;

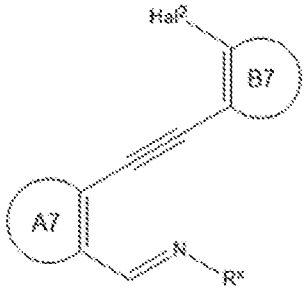
and if the product of step *i*) is a compound of formula  rather than a compound of formula g),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula g); and optionally forming a salt of the compound.

In some embodiments, Hal^1 and Hal^2 are each Br. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. In some embodiments Pd_2dba_3 is used, together with Xantphos. Typically a base is used, such as triethylamine or Cs_2CO_3. Typically the reaction is carried out under carbon monoxide atmosphere. In some embodiments, the reaction is carried out under a carbon monoxide atmosphere and then under an inert atmosphere such as a nitrogen atmosphere. Typically an organic solvent is used, such as NMP or 1,4-dioxane.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

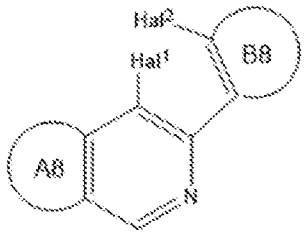
In some embodiments, the compound of formula 

is produced by subjecting a compound of formula 

, wherein A7, B7 and Hal^2 are as defined herein, and R^X is $OC_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkyl; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with $CuBr_2$. The reaction may for example be carried out in the presence of a solvent such as dimethylacetamide.

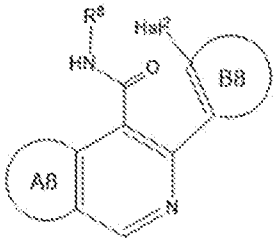
In another aspect, there is provided a method of synthesising a polycyclic compound of formula h), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A8 and B8 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^8-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^8 is as defined herein;

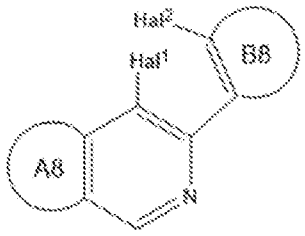
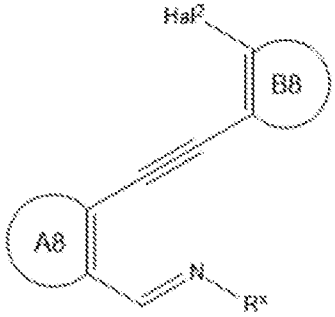


and if the product of step *i*) is a compound of formula rather than a compound of formula h),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula h); and optionally forming a salt of the compound.

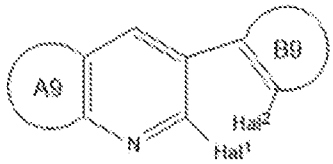
In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. In some embodiments Pd_2dba_3 is used, together with Xantphos. Typically a base is used, such as triethylamine or Cs_2CO_3. Typically the reaction is carried out under carbon monoxide atmosphere. In some embodiments, the reaction is carried out under a carbon monoxide atmosphere and then under an inert atmosphere such as a nitrogen atmosphere. Typically an organic solvent is used, such as NMP or 1,4-dioxane.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula  is produced by subjecting a compound of formula  , wherein A8, B8 and Hal^2 are as defined herein, and R^X is OC_{1-4}alkyl or C_{1-4}alkyl; to a halocyclization reaction. For example, the alkyne-containing compound may be treated with ICl. The reaction may for example be carried out in the presence of a solvent such as acetonitrile, in the presence of a base such as sodium acetate.

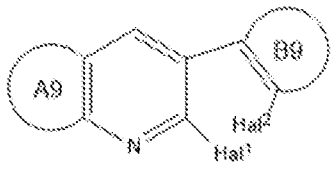
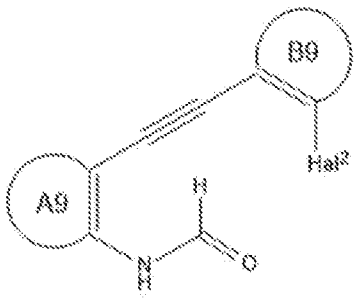
In another aspect, there is provided a method of synthesising a polycyclic compound of formula i) or salt thereof, as defined herein, comprising:

reacting a compound of formula



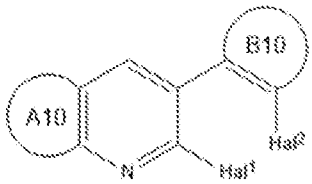
wherein A9 and B9 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^9NH_2 in the presence of a copper catalyst, wherein R^9 is as defined herein; and optionally forming a salt of the compound. In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula  is produced by reacting a compound of formula  , wherein A9, B9 and Hal^2 are as defined herein; with a dehydrating reagent, and then contacting the resulting product with a halide source. Examples of dehydrating reagents include Burgess' reagent and $POCl_3$. A base such as triethylamine may be used if desired. Typically the reaction is carried out in the presence of a solvent, such as dichloromethane. The halide source may for example be a tetraalkylammonium halide, such as tetraethylammonium bromide.

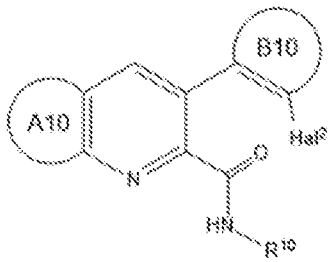
In another aspect, there is provided a method of synthesising a polycyclic compound of formula j), or salt thereof, as defined herein, comprising:

i) reacting a compound of formula



wherein A10 and B10 are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{10}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{10} is as defined herein;

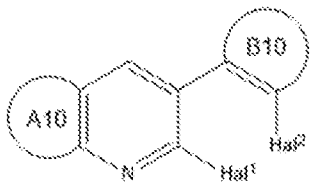
and if the product of step *i*) is a compound of formula  rather than a compound of formula j),

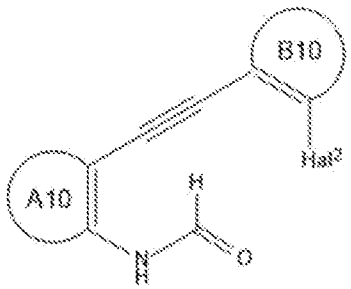
ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula j); and optionally forming a salt of the compound.

In some embodiments, Hal^1 and Hal^2 are each Br. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a

phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. In some embodiments Pd_2dba_3 is used, together with Xantphos. Typically a base is used, such as triethylamine or Cs_2CO_3. Typically the reaction is carried out under carbon monoxide atmosphere. In some embodiments, the reaction is carried out under a carbon monoxide atmosphere and then under an inert atmosphere such as a nitrogen atmosphere. Typically an organic solvent is used, such as NMP or 1,4-dioxane.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

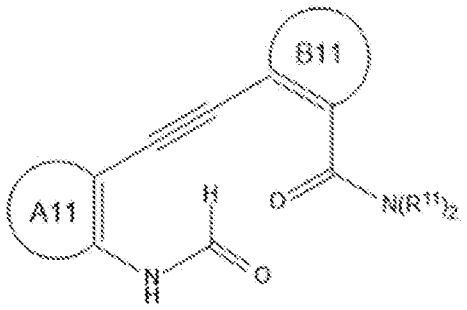
In some embodiments, the compound of formula 

is produced by reacting a compound of formula 

, wherein A10, B10 and Hal^2 are as defined herein; with a dehydrating reagent, and then contacting the resulting product with a halide source. Examples of dehydrating reagents include Burgess' reagent and $POCl_3$. A base such as triethylamine may be used if desired. Typically the reaction is carried out in the presence of a solvent, such as dichloromethane. The halide source may for example be a tetraalkylammonium halide, such as tetraethylammonium bromide

In another aspect, there is provided a method of synthesising a polycyclic compound of formula k), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A11 and B11 are as defined herein, and wherein each R^{11} is independently C_{1-4}alkyl;

with a dehydrating reagent, and then contacting the resulting product with an acid, thereby forming the compound of formula k); and optionally forming a salt of the compound.

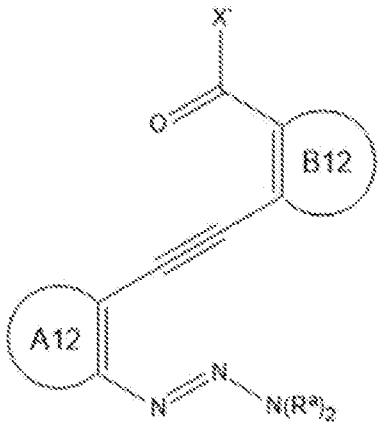
In some embodiments, the dehydrating reagent is Burgess' reagent or $POCl_3$.

In some embodiments, the acid is methanesulfonic acid.

Typically, the reaction is carried out in the presence of a solvent, such as dichloromethane.

In another aspect, there is provided a method of synthesising a polycyclic compound or salt of formula l) as defined herein, comprising:

contacting a compound of formula



wherein A12 and B12 are as defined herein, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group, and X′ is OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

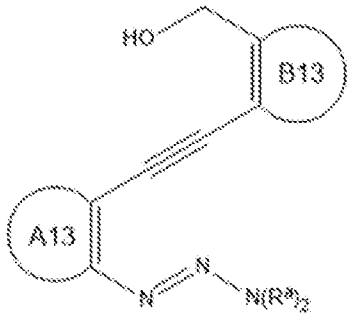
with an acid, thereby forming the compound of formula l); and optionally forming a salt of the compound.

In some embodiments, the acid is a sulfonic acid such as methanesulfonic acid.

Typically, the reaction is carried out in the presence of a solvent, such as dichloromethane.

In another aspect, there is provided a method of synthesising a polycyclic compound of formula m), or salt thereof, as defined herein, comprising:

contacting a compound of formula



wherein A13 and B13 are as defined herein, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

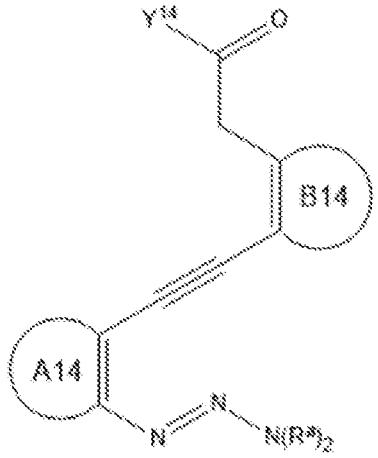
with an acid, thereby forming the compound of formula m); and optionally forming a salt of the compound.

In some embodiments, the acid is a sulfonic acid such as methanesulfonic acid.

Typically, the reaction is carried out in the presence of a solvent, such as dichloromethane.

In another aspect, there is provided a method of synthesizing a polycyclic compound of formula n), or salt thereof, as defined herein, comprising:

contacting a compound of formula



wherein A14, B14 and Y^{14} are as defined herein, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

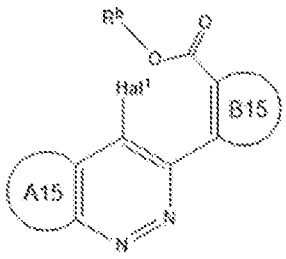
with an acid, thereby forming the compound of formula n); and optionally forming a salt of the compound.

In some embodiments, the acid is a sulfonic acid such as methanesulfonic acid.

Typically, the reaction is carried out in the presence of a solvent, such as dichloromethane.

In another aspect, there is provided a method of synthesizing a compound of formula o), or salt thereof, as defined herein, comprising:

reacting a compound of formula



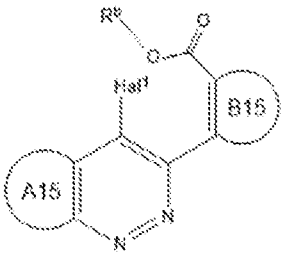
wherein A15 and B15 are as defined herein, Hal^1 is halogen, and R^b is C_{1-4}alkyl;

with $R^{15}NH_2$, wherein R^{15} is as defined herein, thereby forming the compound of formula o); and optionally forming a salt of the compound.

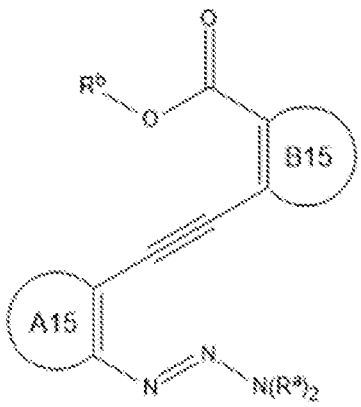
Typically, the reaction is carried out at elevated temperature. In some embodiments a microwave reactor is used.

Typically the reaction is carried out in the presence of a solvent, such as acetonitrile.

In some embodiments, the compound of formula



is produced by contacting a compound of formula



wherein A15, B15 and R^b are as defined herein, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid and a halide source.

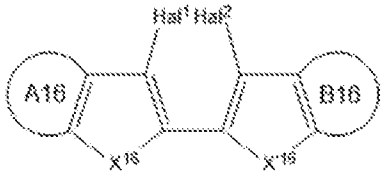
In some embodiments, the acid is a sulfonic acid such as methanesulfonic acid.

In some embodiments, the halide source is a tetraalkylammonium halide, such as tetraethylammonium chloride.

Typically, a solvent is used, such as dichloromethane.

In another aspect, there is provided a method of synthesizing a compound of formula p), or salt thereof, as defined herein, comprising:

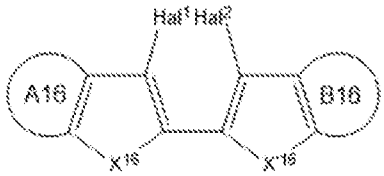
reacting a compound of formula



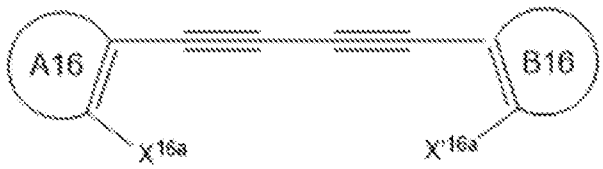
wherein A16, B16, X^{16} and X'^{16} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{16}-NH_2 in the presence of a copper catalyst, wherein R^{16} is as defined herein; thereby forming the compound of formula p); and optionally forming a salt of the compound.

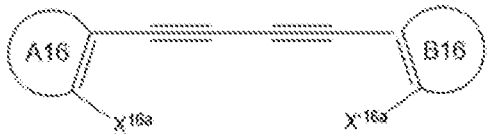
In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, Hal^1 is I and Hal^2 is I. In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula 

is produced by

reacting a compound of formula 

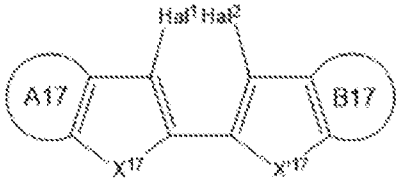
, wherein A16, and B16 are as defined herein, X^{16a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; and X'^{16a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

The compound of formula 

may for example be prepared by Sonogashira coupling of a suitable diyne with an aromatic or heteroaromatic halide. The diyne may for example be prepared by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

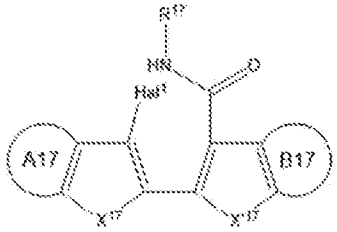
In another aspect, there is provided a method of synthesizing a compound of formula q), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A17, B17, X^{17} and X'^{17} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{17}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{17} is as defined herein;

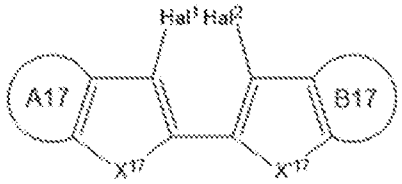
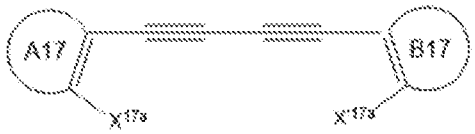
and if the product of step *i*) is a compound of formula 

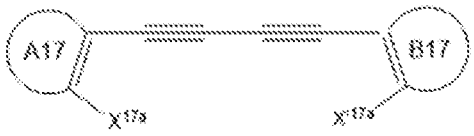
rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments, Hal^1 is I and Hal^2 is I. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. Typically a base is used, such as triethylamine. Typically the reaction is carried out under carbon monoxide atmosphere. Typically an organic solvent is used, such as NMP.

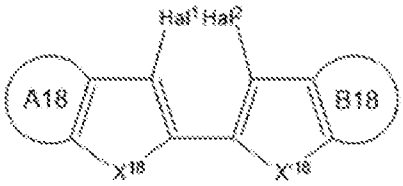
Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula  is produced by reacting a compound of formula  , wherein A17, and B17 are as defined herein, X^{17a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; and X'^{17a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

The compound of formula  may for example be prepared by Sonogashira coupling of a suitable diyne with an aromatic or heteroaromatic halide. The diyne may for example be prepared by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

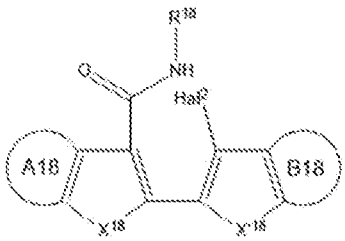
In another aspect, there is provided a method of synthesizing a compound of formula r), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A18, B18, X^{18} and X'^{18} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

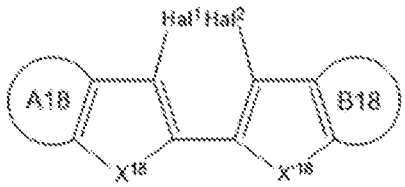
with a compound of formula R^{18}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{18}s as defined herein;

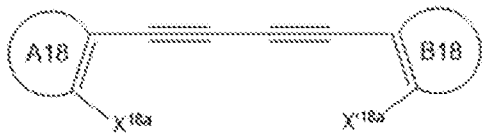
and if the product of step *i*) is a compound of formula  rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

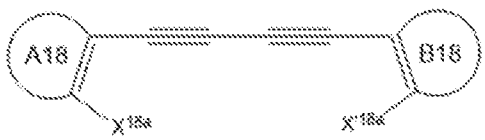
In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments, Hal^1 is I and Hal^2 is I. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. Typically a base is used, such as triethylamine. Typically the reaction is carried out under carbon monoxide atmosphere. Typically an organic solvent is used, such as NMP.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula 

is produced by reacting a compound of formula 

, wherein A18 and B18 are as defined herein, X^{18a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; and X'^{18a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.

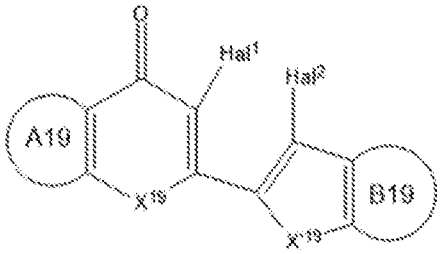
The compound of formula 

may for example be prepared by Sonogashira coupling of a suitable diyne with an aromatic or heteroaromatic halide. The

diyne may for example be prepared by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

In another aspect, there is provided a method of synthesizing a compound of formula s), or salt thereof, as defined herein, comprising:

reacting a compound of formula

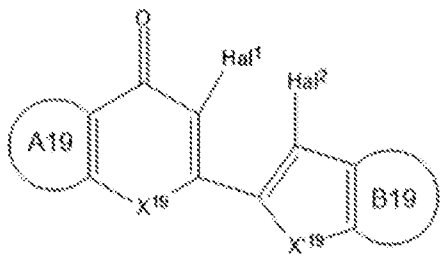


wherein A19, B19, X^{19} and X'^{19} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{19}-NH_2 in the presence of a copper catalyst, wherein R^{19} is as defined herein; thereby forming the compound of formula p); and optionally forming a salt of the compound.

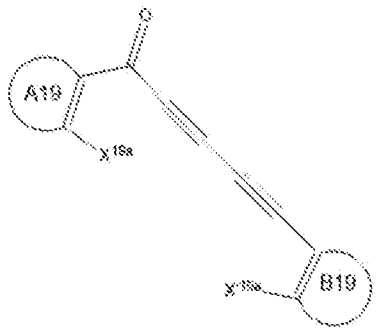
In some embodiments, Hal^1 is I and Hal^2 is Br. In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, Hal^1 is I and Hal^2 is I. In some embodiments, Hal^1 is Br and Hal^2 is Br. In some embodiments the copper catalyst is CuI. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula



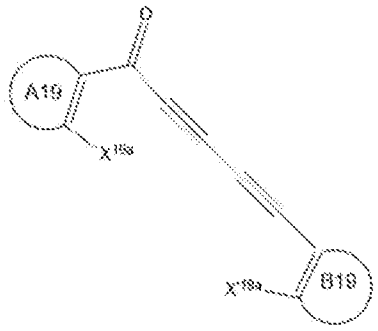
is produced by

reacting a compound of formula



, wherein A19, and B19 are as defined herein, X^{19a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; and X'^{19a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on

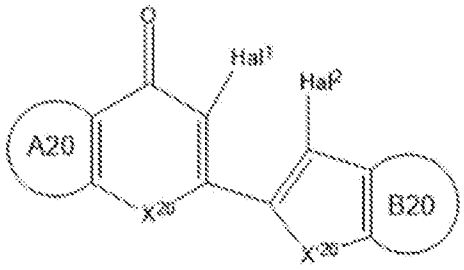
hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.



The compound of formula may for example be produced by deprotonation of a suitable aryl/heteroaryl diyne and reaction with an acyl species, such as an ester or acyl chloride. The aryl/heteroaryl diyne may itself be produced by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

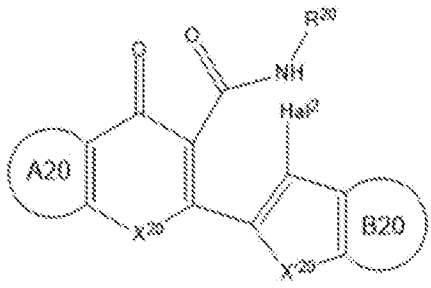
In another aspect, there is provided a method of synthesizing a compound of formula t), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A20, B20, X^{20} and X'^{20} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{20}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{20} is as defined herein;

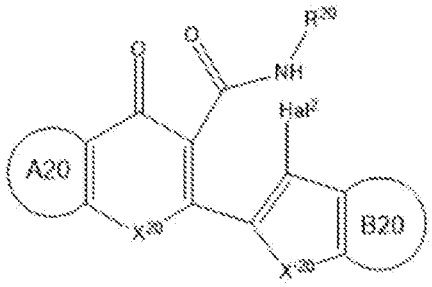


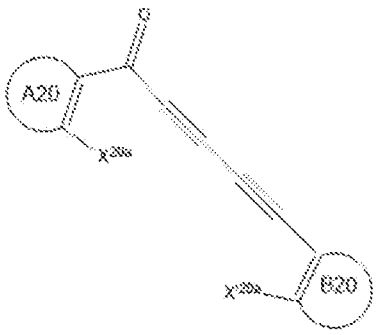
and if the product of step *i*) is a compound of formula rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

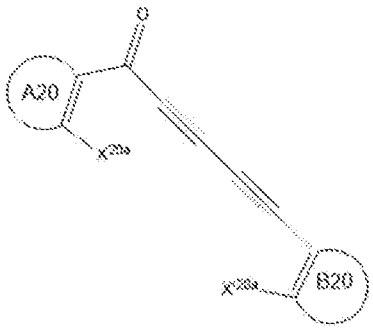
In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a

phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments, the reaction is carried out using palladium acetate and triphenylphosphine. Typically a base is used, such as triethylamine. Typically the reaction is carried out under carbon monoxide atmosphere. Typically an organic solvent is used, such as NMP.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.In some embodiments, the compound of formula 

is produced by reacting a compound of formula 

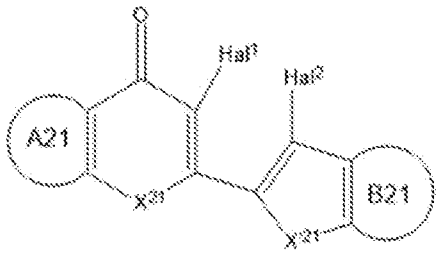
, wherein A20, and B20 are as defined herein, X^{20a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; and X'^{20a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.



The compound of formula may for example be produced by deprotonation of a suitable aryl/heteroaryl diyne and reaction with an acyl species, such as an ester or acyl chloride. The aryl/heteroaryl diyne may itself be produced by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

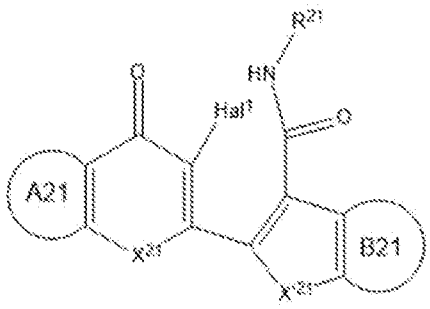
In another aspect, there is provided a method of synthesizing a compound of formula u), or salt thereof, as defined herein, comprising:

reacting a compound of formula



wherein A21, B21, X^{21} and X'^{21} are as defined herein, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{21}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{21} is as defined herein;



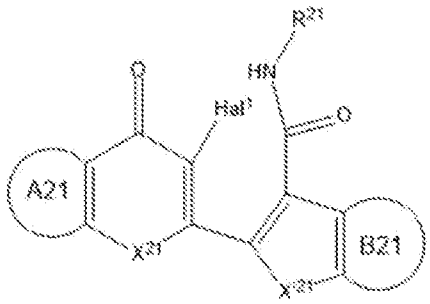
and if the product of step *i*) is a compound of formula rather than a compound of formula b),

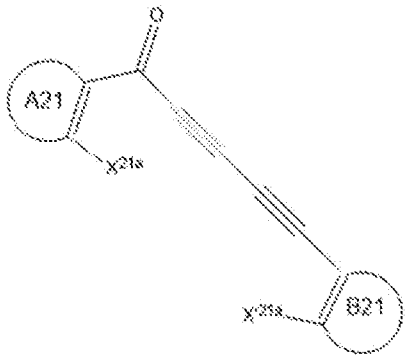
ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

In some embodiments, Hal^1 is Br and Hal^2 is I. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. In some embodiments,

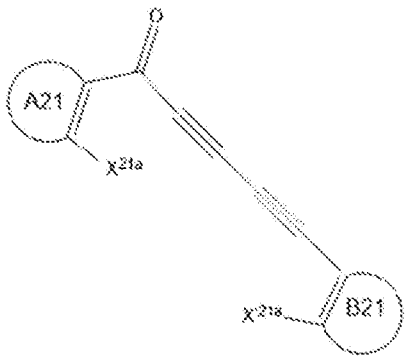
the reaction is carried out using palladium acetate and triphenylphosphine. Typically a base is used, such as triethylamine. Typically the reaction is carried out under carbon monoxide atmosphere. Typically an organic solvent is used, such as NMP.

Where step *ii*) is carried out, in some embodiments a copper catalyst is used. In some embodiments the copper catalyst is a copper(I) catalyst, for example a copper(I) salt, preferably CuI. Where step *ii)* is carried out, in some embodiments a palladium catalyst is used, for example additional palladium catalyst beyond that used in step *i)* may be used if needed. In some embodiments, the palladium catalyst is a palladium (II) catalyst. For example, palladium $(OAc)_2$ may be added, optionally together with a phosphine ligand, e.g. such as triphenylphosphine, RuPhos, xantphos or BINAP. The reaction may for example be carried out in the presence of a base, such as K_3PO_4. The reaction may for example be carried out in the presence of a solvent such as nBuOH, ethylene glycol, or a mixture thereof.

In some embodiments, the compound of formula 

is produced by reacting a compound of formula 

, wherein A21 and B21 are as defined herein, X^{21a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; and X'^{21a} is $OC_{1\text{-}4}$alkyl, $SC_{1\text{-}4}$alkyl, NH_2, $NHC_{1\text{-}4}$alkyl or $N(C_{1\text{-}4}alkyl)_2$; to halocyclization reaction. For example, the alkyne-containing compound may be treated with I_2 $CuBr_2$, or MPHT (N-methylpyrrolidin-2-on hydrotribromide). The reaction may for example be carried out in the presence of a solvent such as dichloromethane.



The compound of formula may for example be produced by deprotonation of a suitable aryl/heteroaryl diyne and reaction with an acyl species, such as an ester or acyl chloride. The aryl/heteroaryl diyne may itself be produced by Sonogashira coupling of suitable alkyne partners (optionally protected by e.g. a TMS group, followed by deprotection after the coupling step).

Those skilled in the art will appreciate that the disclosure herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the disclosure includes all such variations and modifications.

Examples

The present disclosure is further illustrated by the following non-limiting examples.

General Synthetic Methods for Preparation of Compounds

The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

All reactions in the present disclosure were performed under an inert atmosphere of anhydrous $N_2(g)$, unless otherwise stated. Solvents used for various reactions were dried using a commercial solvent purification system. DCE and THF were purchased in an anhydrous form and stored under $N_2(g)$. Solvents used in reaction extractions and chromatography and all other reagents were used as supplied by commercial vendors without further purifications or drying. All glassware used was dried by heating with a heat gun under high vacuum. Hexanes with a boiling point range of 40–60 °C was used in chromatography. Flash column chromatography was performed on either 40–60 or 20–40 micron silica

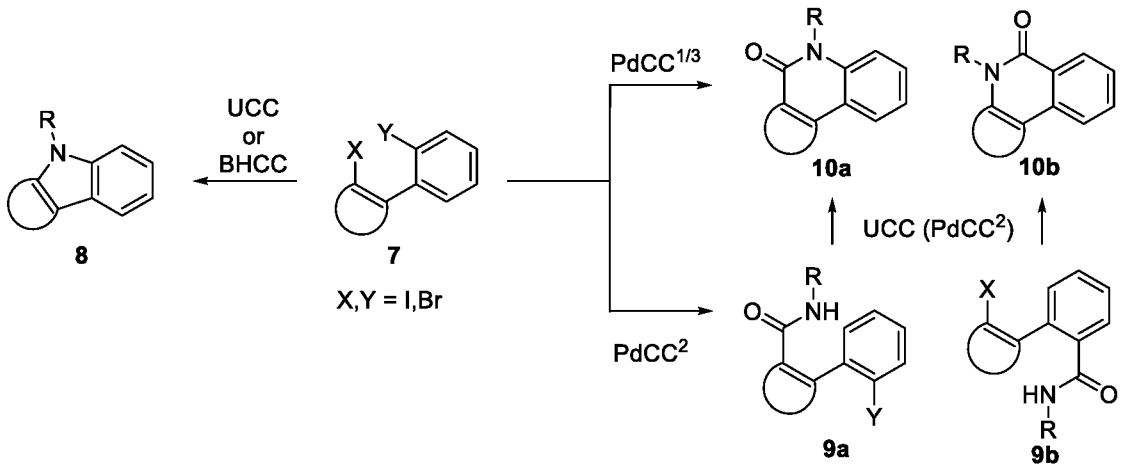
gel. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 101 MHz, for selected compounds the number of attached hydrogens to each carbon atom was determined using Distortionless Enhancement by Polarization Transfer with detection of quaternary carbons (DEPTQ-135), as indicated. All chemical shifts were calibrated using residual non-deuterated solvent (e.g. chloroform) as an internal reference and are reported in parts per million (δ) relative to trimethylsilane (δ = 0). Thin layer chromatography (TLC) was performed using 0.25 mm thick plates pre-coated with Merck Kieselgel 60 F254 silica gel, and visualised using UV light (254 nm and 365 nm). Liquid chromatography mass spectrometry (LCMS) was performed using either APCI or ESI LCMS. Each method used 254 nm detector and a reverse phase C8(2) 5 μ 50 × 4.6 mm 100A column. The column temperature was 30 °C and the injection volume, 2 μL. The eluent system used was solvent A (H_2O with 0.1% formic acid) and solvent B (MeCN with 0.1% formic acid). LCMS (ESI) method: the gradient starts from [95 % solvent A / 5 % solvent B] for 1 minute, reaches [100% solvent B] over 1.5 min, maintained for 1.3 min, and then changed to [95 % solvent A / 5 % solvent B] over 1.2 min. LCMS (APCI) method: the gradient starts from [95 % solvent A / 5 % solvent B] for 1 min, reaches [100% solvent B] over 1.9 min, maintained for 2 min, and then changed to [95 % solvent A / 5 % solvent B] over 1.0 min. Analytical HPLC was performed on an Agilent 1260 Infinity Analytical HPLC with a G1312B 1260 binary pump and G4212B 1260 DAD detector. The column used was a Zorbax Eclipse Plus C18 Rapid Resolution 4.6 x 100 mm, 3.5 micron. The eluent system used was [Solvent A: H_2O with 0.1% Formic Acid; Solvent B: MeCN with 0.1% Formic Acid]. All the samples were analyzed using a 'PP gradient method', in which the gradient increases from [95 % solvent A / 5 % solvent B] to [100 % solvent B] over 9 min and maintained at [100 % solvent B] for 1 min with flow rate of 1.0 mL/min. High resolution mass spectra (HRMS) were recorded on both a time-of-flight mass spectrometer fitted with either an electrospray (ESI) ion or atmospheric pressure chemical ionization (APCI) source, the capillary voltage was 4000 V or on an exactive mass spectrometer fitted with an ASAP ion source.

Results and Discussion

The electrophilic cyclisation of alkynes has emerged as a functional group tolerant method of synthesis for a range of aromatic heterocycles and carbocycles. In the present disclosure, the inventors have sought to achieve a diversification of a discrete set of substrates by modifying the nature of the nucleophile (Nu) or electrophile (E) and X (X = halide, amide, or ester) (see Figure 3).

For reactions proceeding through diazonium and nitrilium intermediates, one-step bicyclisation methods have been developed (Figure 3). For those proceeding through a dihalide intermediate (I/Br or Br/Br), secondary ring closure can potentially be achieved through various methods. In the present disclosure, the inventors have developed an Ullmann coupling cyclisation (UCC) and a Buchwald-Hartwig coupling cyclisation protocol for the conversion of **7** → **8** (Figure 3). and a Pd-mediated carboxyamidation cyclisation (PdCC) sequence **7** → **9a,b** → **10a,b** (Figure 3). The PdCC can be

achieved in a single operation using catalytic Pd-mediated carboxyamidation conditions involving $Pd(OAc)_2$ and $CO_{(g)}$ ($PdCC^1$). However, in cases where this stalls at the amide **9a,b**, Ullmann conditions (UCC) are employed to complete cyclisation to **10a,b** ($PdCC^2$). Alternatively, a more universal protocol for PDCC can be achieved using Buchwald-Hartwig conditions (Pd-Xantphos) in the presence of CO (g) ($PDCC^3$). In all cases, the regioselectivity of this process can be controlled based on the relative reactivity of I and Br to Pd-insertion, i.e. **7** (X = I, Y = Br) gives lactam **10a** and **7** (X = Br, Y = I) gives lactam **10b**. In the present disclosure, all UCC and PdCC reactions have been performed with 1,1-dimethylethylenedimine (DMD), to give **8-10** R = $(CH_2)_2NMe_2$, so as to bias the product towards TOP1 inhibition. This R-group can be further diversified in a broader screening set.



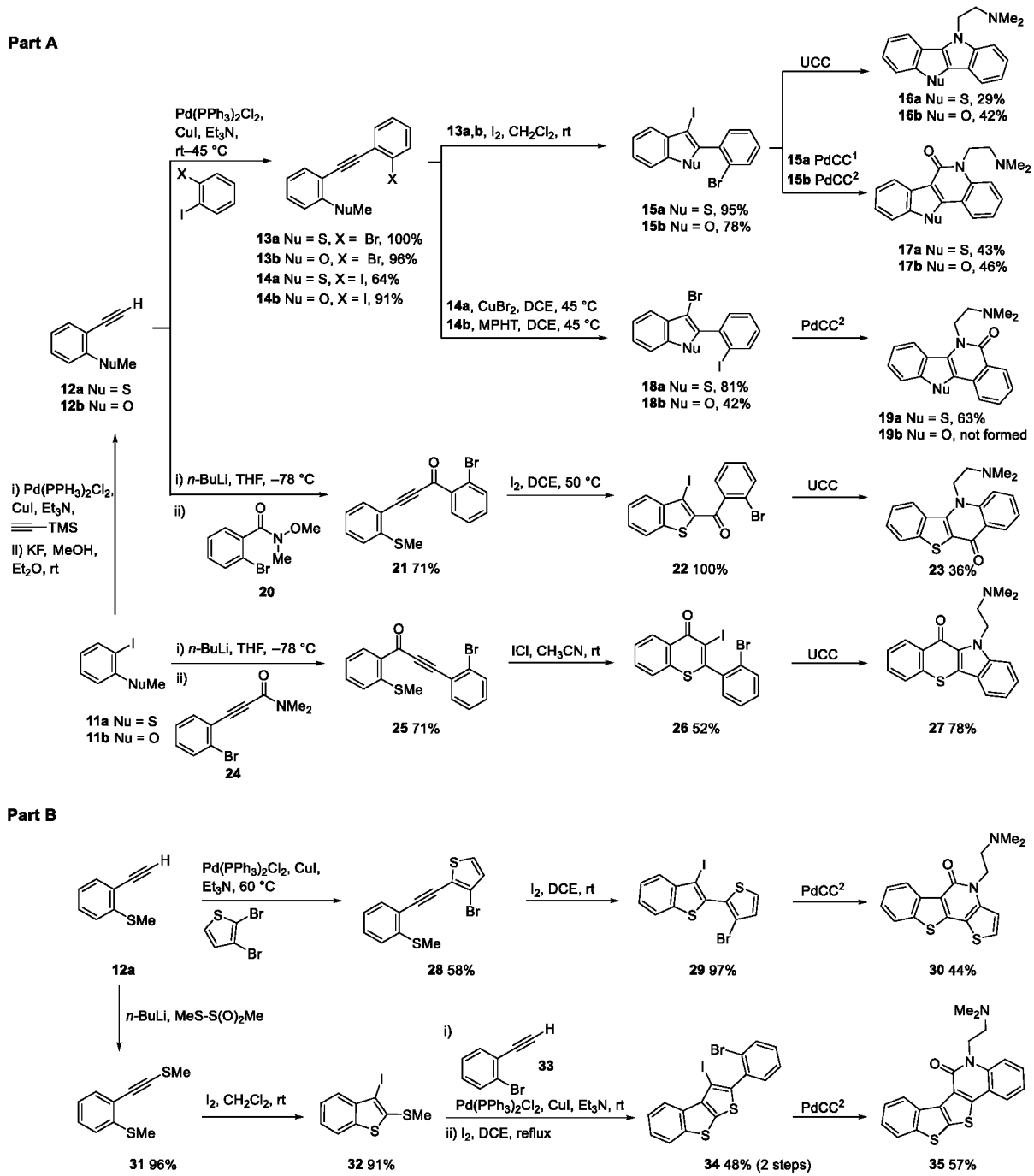
Scheme 1: Late-stage ring closure of dihalides **7.** Ullmann coupling cyclisation (UCC): R-NH_2, CuI 20-40 mol%, K_3PO_4, *n*-BuOH, ethylene glycol. Buckwald-Hartwig coupling cyclisation (BHCC): Pd_2dba_3, Xantphos, Cs_2CO_3 1,4-dioxane, reflux. Pd-mediated carboxyamidation cyclisation-1 ($PdCC^1$): R-NH_2, $Pd(OAc)_2$ 10 mol%, PPh_3, $CO_{(g)}$, Et_3N, NMP. Pd-mediated carboxyamidation cyclisation-2 ($PdCC^2$): as for $PdCC^1$ then UCC. Pd-mediated carboxyamidation cyclisation-3 ($PdCC^3$): Pd_2dba_3 (cat.), Xantphos (cat.), Cs_2CO_3 (3-5 equiv.), 1,4-dioxane, CO (g), 70 °C, 2-8 h under CO (g), followed by 120 °C under N_2 (g), 10-20 h.

The first series of heteroacenes incorporated a strategy to diversify the positioning of a carbonyl atom in related scaffolds **16a,b**, **17a,b**, **19a,b**, **23** and **27** (Scheme 2, Part A). Sequential Sonogashira coupling of terminal alkynes **12a,b** (accessed from **11a,b**) with either 1,2-diiodobenzene or 1-bromo-2-iodobenzene furnished substrates **13a,b** and **14a,b** in good to excellent yields (64%-100%). Iodocyclisation of bromides of **13a,b** with molecular iodine furnished iodo-bromo compounds **15a,b** (78-95%). The bromocyclisation of the iodides **14a,b** required greater experimentation, though the best yields were obtained using $CuBr_2$ for the methylsulfide **14a** and *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) for the methyl ether **14b** to give corresponding bromo-iodo compounds **18a,b** (42-81%). UCC and $PdCC^{1/2}$ of **15a,b** with DMD gave pyrroles **16a,b** (29-42%) and lactams **17a,b** (43-46%), respectively. Attempted formation of the regiosomeric lactams **19a,b** through $PdCC^2$ of **18a,b**

with DMD was successful for the thiopheno system **18a→19a** (63%) but stalled at the amide stage for furano system **18b** (amide not shown), which could not be ring closed to **19b**, reflecting a limitation in the method for scaffold **19** (Nu = O).

Further transposing of the carbonyl was achieved in the synthesis of scaffold analogues **23** and **27** (attempted for Nu = SMe only). For **23** this involved reaction of lithiated alkyne **12a** with Weinreb amide **20** to give propynone **21** (71%), which underwent efficient iodocyclisation to **22** (100%) and UCC with DMD to give **23** (36%) in modest yield.[2] For **27**, reaction of lithiated **11a** (Li for I exchange) with propynamide **24** afforded propynone **25** (71%), that underwent iodocyclisation to **26** (52%) and UCC with DMD to give **27** (78%). These syntheses required two recent innovations in iodocyclisation chemistry.[2] Firstly, the iodocyclisation of alkynes with unfavourable electronic bias **21→22**, using high iodine concentrations at elevated temperatures.[2] Secondly, endo/exo control in the iodocyclisation of **25**, where more polar iodonium sources (ICl in CH_3CN) favour 6-*endo* iodocyclisation and iodine in DCM favours 5-exo cyclisation.

In Scheme 2 Part B, there is exemplified two other modes of divergent heteroacene synthesis. Firstly, the 1,2-dihalobenzene used to access **13-14a,b** can be replaced with 2,3-dibromothiophene (and potentially other dihaloheterocycles) to progress through the Sonogashira coupling (**28**, 58%), iodocyclisation (**29**, 97%) and $PdCC_2$ sequence to give the thiophene analogue of **17a**, 30 (44%). In the second example, another latent nucleophile (SMe) is introduced onto the alkyne **12a** to give **31** (96%), which enables a sequence of iodocyclisation (**32**, 91%), Sonogashira coupling and iodocyclisation (**34**, 48%), followed by $PdCC_2$ to give **35** (57%).[1]

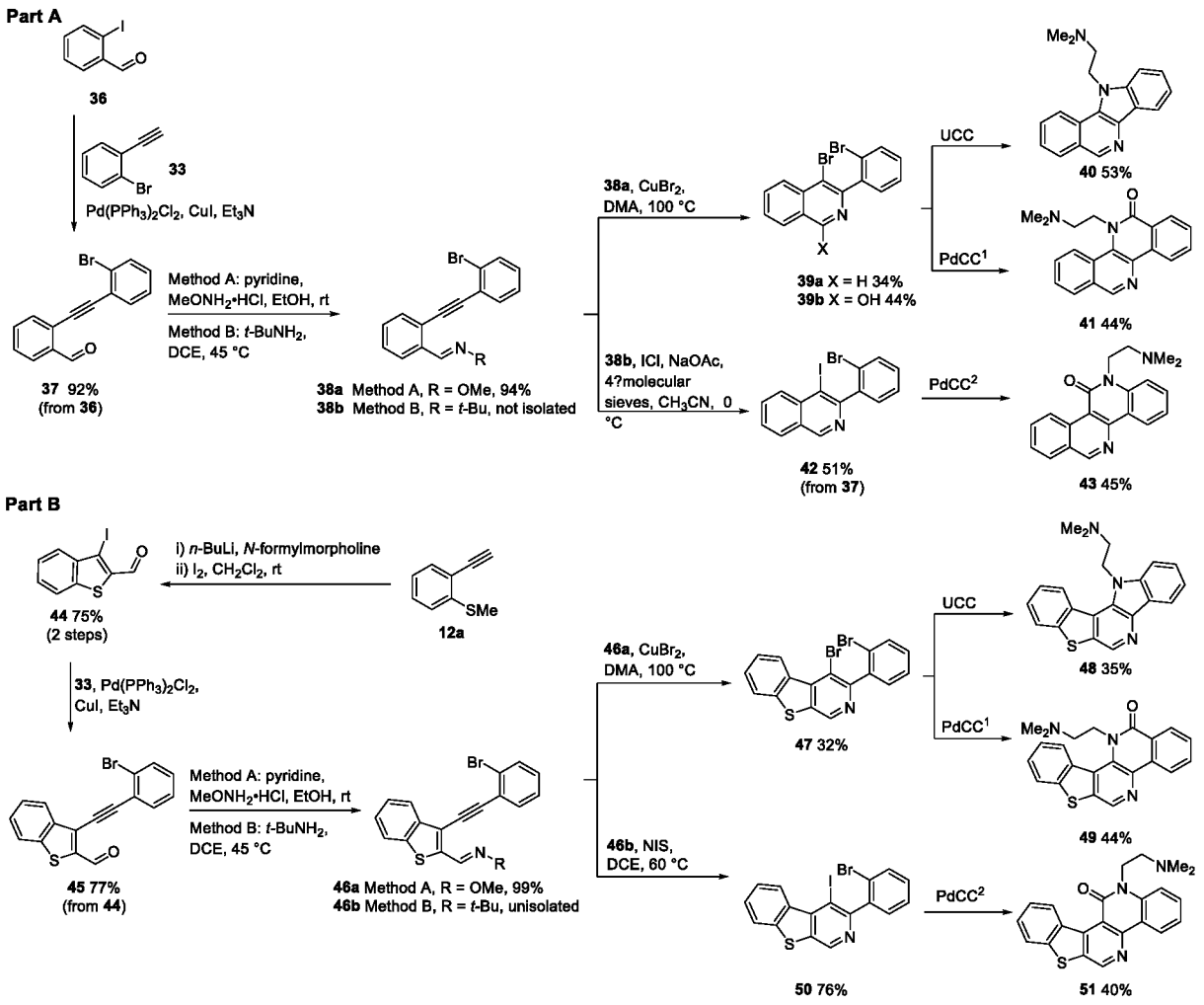


Scheme 2. Preparation of **16a,b, 17a,b, 19a,b, 23, 27, 30** and **35**

The construction of a series of equivalent pyridyl analogues **40**, **41**, and **43** was investigated next (Scheme 3, Part A). This approach centered on the halocyclisation of imines **38a,b**. The synthesis of **38a,b** involved Sonogashira coupling of 2-iodobenzaldehyde **36** with bromoethynylbenzene **33** to give **37** (92%) followed by Schiff base condensation with $MeONH_2$ (Method A) to give **38a** (94%) or *t*-$BuNH_2$ (Method B) to give **38b** (not isolated). Bromocyclisation of **38a** was achieved using the method previously described by Yu *et al.*[3] employing $CuBr_2$ in DMA at 100 °C, giving **39a** (34%). The yield of

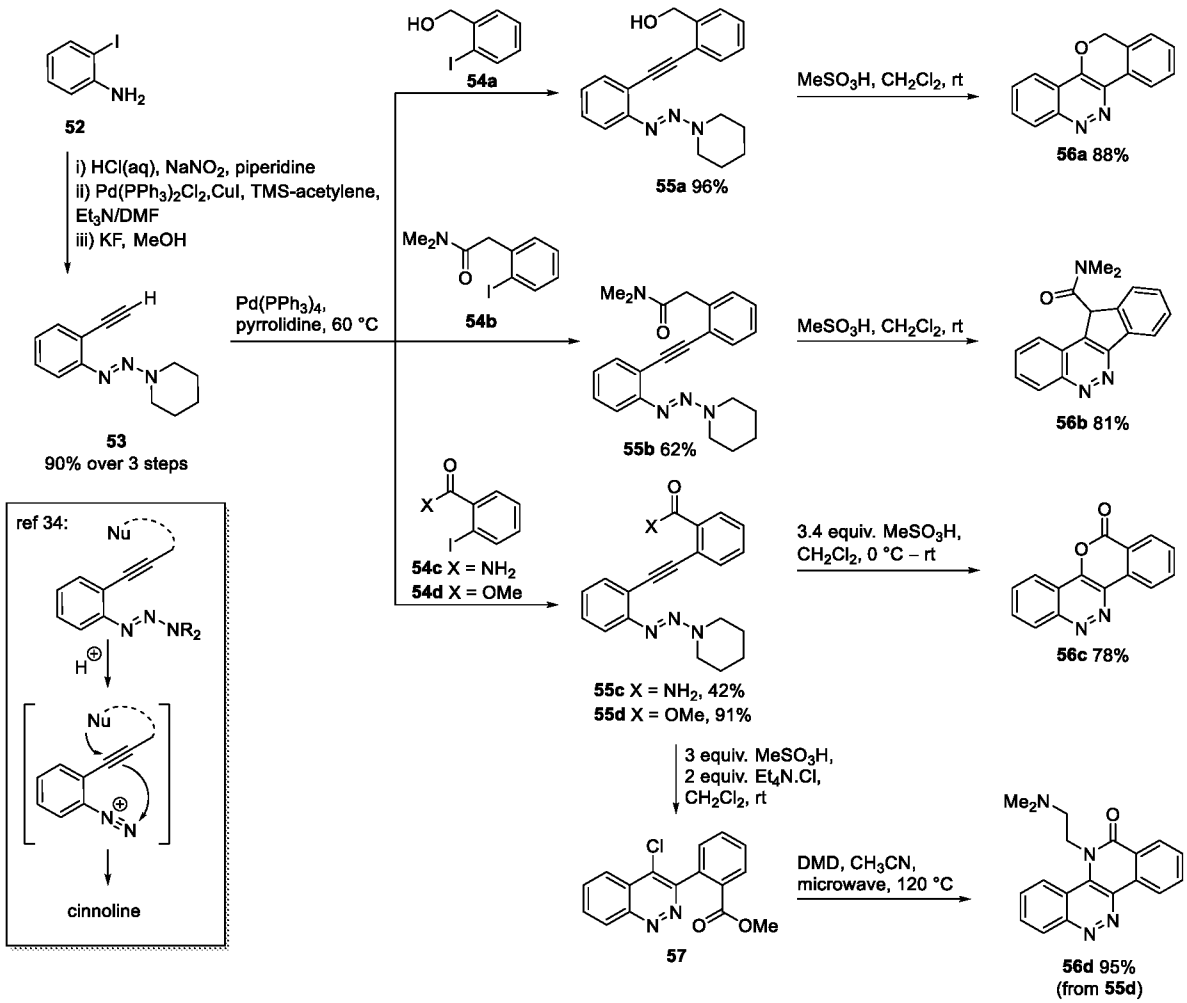
this reaction was limited by a competing oxidative-cyclisation to give lactam **39b** (44%) as the major by-product. Oxime **38a** could not be iodocyclised, though the corresponding *t*-Bu-aldimine **38b** could be by employing ICl in CH_3CN with a weak base (NaOAc) to give product **42** (51%). UCC of dibromide **39a** with DMD gave the heterotetracene **40** (53%). PdCC[1] of dibromide **39a** with DMD proved surprisingly regioselective, favoring lactam **41** (44%) as the major product (no regioisomeric lactam could be detected). A possible explanation for this regioselectivity is that under the thermal reaction conditions (80 °C in *N*-methyl-2-pyrrolidone) nucleophilic aromatic substitution of the bromo group on the isoquinoline precedes Pd-mediated carbonylative ring closure onto the bromophenyl ring. This regioselectivity is reversed in the PdCC[2] of the iodobromo substrate **42** with DMD, giving **43** (45%). In this case, Pd-mediated carboxyamidation with DMD precedes ring closure onto the bromophenyl, in a separate UCC step.

In Scheme 3 Part B, alkyne **12a** was converted into 3-iodobenzo[*b*]thiophene-2-carbaldehyde (**44**) by formylation and iodocyclisation. Iodoaldehyde **44** was then subject to an identical series of reactions to those used in Part A to generate a series of thiopheno-fused systems **48**, **49** and **51**.[2]



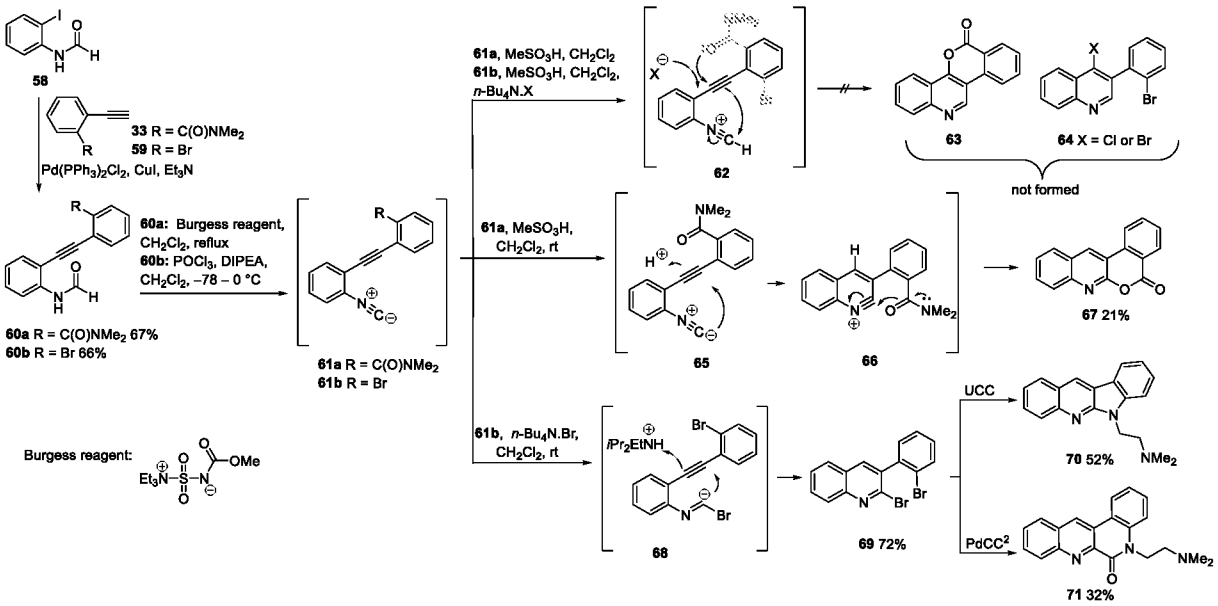
Scheme 3: Preparation of **40**, **41**, **43**, **48**, **49**, and **51**.

Triazenes can be used to operate as masked diazoniums that could be unmasked by acid in the presence of a nucleophile Nu (tethered or untethered) to give a cinnoline (Scheme 4 Box).[4] In the present disclosure, this chemistry was exploited toward the rapid assembly of a series cinnolines **56a-d** from 2-iodoaniline **52** (Scheme 4). Terminal alkyne **53** was prepared in three steps, involving diazotisation and triazene formation, followed by Sonogashira coupling with TMS-acetylene and deprotection. A Cu-free Sonogashira coupling was employed to couple alkyne **53** to iodobenzenes **54a-d**, giving tolans **55a-d** (42-96%). Treatment of tolans **55a-c** with $MeSO_3H$ unmasked the diazonium cation and induced electrophilic co-cyclisation to give **56a-c**. Treatment of the ester **55d** with $MeSO_3H$ in the presence of tetraethylammonium chloride gave a chlorocinnoline **57** (unpurified). Reaction of **57** with DMD at elevated temperature afforded **56d**[52] through a domino nucleophilic aromatic substitution lactamisation sequence in excellent yield (95%).



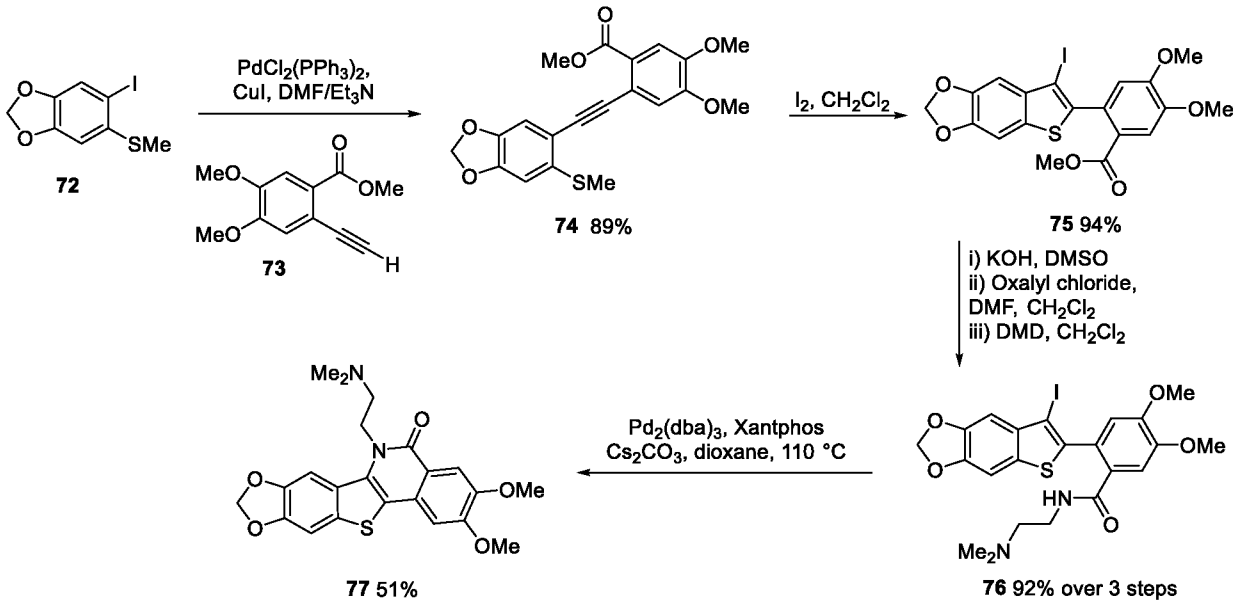
Scheme 4: Preparation of **56a-d**

Given the success of the diazonium cyclisations to give cinnolines, the inventors proposed to explore related cyclisation on nitrilium ion **62** to give **63** and **64** (Scheme 5). Sonogashira coupling of 2-iodophenylformamide **58** to alkynes **33** and **59** gave tolans **60a** and **60b**, respectively (66–67%). Reaction of **60a** with Burgess reagent and of **60b** with $POCl_3$ and diisopropylethylamine (DIPEA) gave rise to the isonitriles **61a** and **61b**, respectively. Both isocyanides **61a,b** were stable in solution (^{1}H NMR), but reverted to the formamides **60a,b** upon attempted extractive work up, consequently, they were not isolated but used directly in the next reaction. Attempted protonation and cyclisation of **61a** and **61b** to quinolines **63** and **64** respectively, via nitrilium ion **62** failed. Rather, **61a** gave the regioisomeric quinoline **67** (21% from **60a**) and **61b** reverted to the formamide **60b**. Bromocyclisation of **61b** to give **69** (72%) was achieved upon addition of $Et_4N.Br$ without acid, in a process previously described by Mitamura *et al.*[5] This involves nucleophilic cyclisation of a bromide adduct ion **68** with concomitant protonation by residual diisopropylethylammonium ion (from isonitrile formation). Ring closure of dibromide **69** under UCC and PDCC[2] conditions gave **70** (52%) and **71** (32%), respectively.



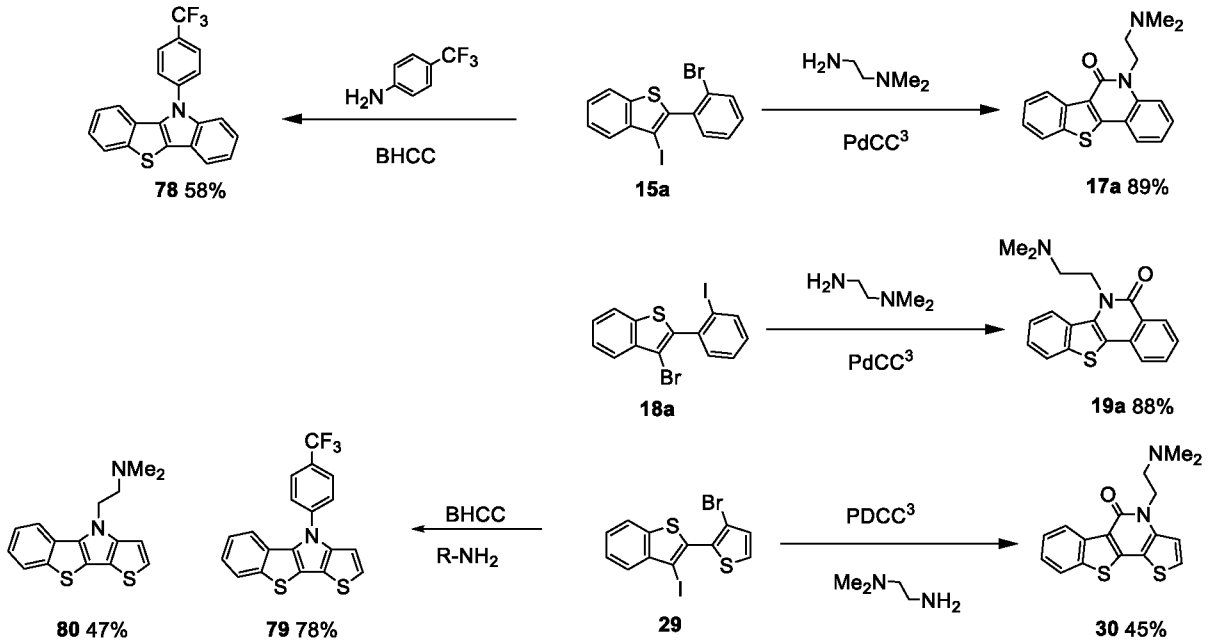
Scheme 5: Preparation of **67**, **70** and **71**

Finally, since **19a** (Scheme 2) proved to be active as a TOP1 inhibitor (see below), analogue **77** was also prepared (Scheme 6) that bears the additional TOP1 protein binding methoxy and methylenedioxy groups seen in **3** and **4** (Figure 1). Sonogashira coupling of the known aryliodide **72** and arylalkyne **73** afforded tolan **74** (89%). Iodocyclisation of **74** proceeded chemoselectively through the methylsulfide (and not the ester) to give benzo[*b*]thiophene **75** (94%). The ester was efficiently converted to the amide **76** (92% over 3 steps) and cyclised under Buchwald-Hartwig conditions to furnish the target compound **77** (51%).



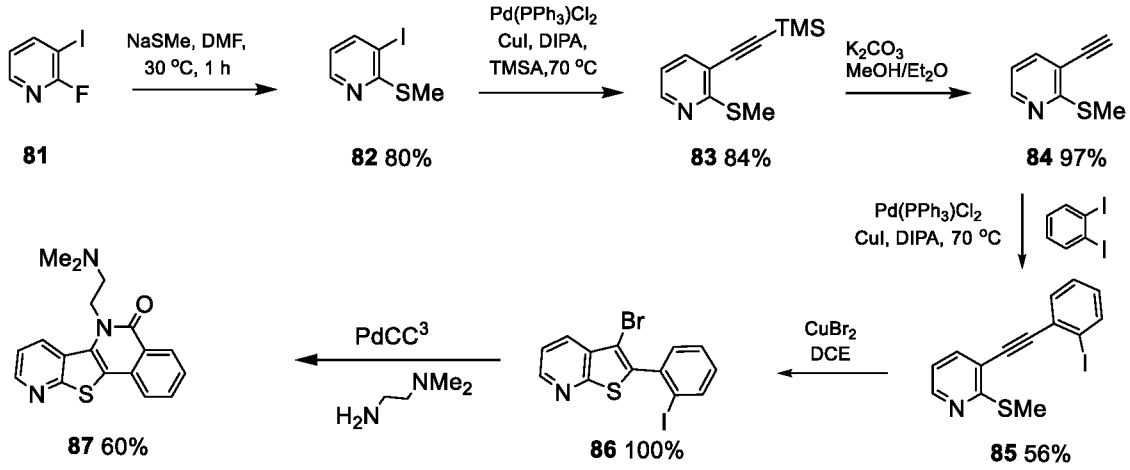
Scheme 6: Preparation of fully decorated compound **77**

Efficient coupling-cyclisation processes for the three benzo[*b*]thiophene substrates **15a**, **18a**, and **29** could also be achieved with improved efficiency using the PdCC^3 protocol to give lactams **17a** (89% from **15a**), **19a** (89% from **18a**), **30** (89% from **29**) (Scheme 7). Substrates **15a** and **29** were also reacted with amines to generate a pyrrole ring through BHCC, giving **78** (58% from **15a**), **79** (78% from **29**), and **80** (47% from **29**) (Scheme 7).



Scheme 7: Examples of efficient coupling-cyclisation processes using PdCC^3 and BHCC

The benzo[*b*]thiophene substrate can be replaced with other heterocycles, as exemplified for the pyridine **81** which, like other benzene substrates above, also bears ortho halo (iodo) and nucleophilic (NuMe = SMe) groups. Conversion of **81** to alkyne **84** (81% over 2 steps), followed by Sonogashira coupling (gives **85** 56%) and bromo-cyclisation bromo-iodo substrate thiophenofused pyridine **86** (100%). Reaction **86** with DMD under $PdCC^3$ conditions gave the polyfused heterocycle **87** (60%) (Scheme 8).



Scheme 8: Exemplification of ortho iodo/SMe pyridine **82** as alternative heterocyclic substrate to benzene furnishing polyfused hetereocycle **87** through a sequence of halocyclization and PdCC.

*General Procedure A (Sonogashira coupling) for the synthesis of alkynes **13a**, **13b**, **14a**, **14b**, **28**, **37**, **45**, **60a**, **60b**, and **74**.*

The respective 2-iodobenzene was dissolved in Et_3N (0.2 M) in a dry round-bottom flask (RBF), followed by addition of CuI (4–6 mol%) and $Pd(PPh_3)_2Cl_2$ (2–3 mol%). The RBF was then degassed and backfilled with N_2(g) three times. Finally, a solution of the terminal alkyne (1.2 equiv.) in Et_3N (1 M) was added dropwise under an N_2(g) atmosphere. The reaction mixture was stirred at rt–60 °C overnight. On completion, the suspension was filtered through Celite® and washed with Et_2O. Washed with H_2O twice and with brine twice, the organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography to yield the desired alkyne.

*General Procedure B (Cu-free Sonogashira coupling) for the synthesis of alkynes **55a-d**.*

54a-d was dissolved in pyrrolidine (0.5 M), followed by addition of $Pd(PPh_3)_4$ (5 mol%). The RBF was degassed and backfilled with N_2(g) for three times. Finally, a solution of **53** (1.5 equiv.) in pyrrolidine (3 M) was added dropwise under N_2(g) atmosphere. The reaction mixture was heated at 60°C for 4–16 h. On completion, the suspension was filtered through Celite® and washed with EtOAc. Washed with H_2O three times, the organic extract was dried over anhydrous $MgSO_4$, filtered and

concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) to yield the desired alkynes **55a-d**.

*General Procedure C (Sonogashira Coupling–Desilylation) for the synthesis of alkynes **53**, **59**, and **73**.*

The respective 2-iodobenzene was dissolved in Et3N (0.2 M) in a dry round-bottom flask (RBF), followed by addition of CuI (4–6 mol%) and Pd(PPh3)2Cl2 (2–3 mol%). The RBF was then degassed and backfilled with N2 three times. Finally, trimethylsilylacetylene (1.2 equiv.) was added dropwise under an N_2(g) atmosphere. The reaction mixture was stirred at room temperature (rt) overnight. On completion, the suspension was filtered through Celite® and extracted with Et_2O twice, and washed with H_2O twice and with brine twice. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by a silica plug (100% hexanes) to yield the TMS-protected terminal alkyne, which was then dissolved in MeOH/Et_2O (2 : 1, 0.2 M), followed by addition of K_2CO_3 (1−2 equiv.). The reaction mixture was stirred at rt overnight. On completion, the mixture was concentrated to a residue and taken up in Et_2O. Washed with H_2O twice and with brine twice, the organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the desired terminal alkynes, which were directly used in the next step without further purification.

*General Procedure D (Iodocyclisation) for the synthesis of iodides **15a,b**, **22**, **29**, **34**, **44**, **75**:*

I_2 (1.2 − 3 equiv.) was added to a stirred solution of the respective alkyne substrates in dry CH_2Cl_2 (0.2 M) under an N_2(g) atmosphere. The reaction mixture was stirred at rt for 1 – 18 h. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 twice. The combined organic extracts were washed with H_2O twice and with brine twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the desired iodocyclised product.

*General UCC Procedure for the final ring closure of **15a**, **15b**, **22**, **26**, **39a**, **47** and **69**.*

In a dry RBF, the respective dihalide was dissolved in dry *n*-butanol or DMF (0.1−0.2 M). K_3PO_4 (4 equiv.), ethylene glycol (12 equiv.), 1,1-dimethylethane-1,2-diamine (DMD) (15 equiv.) and CuI (10−40 mol%) were added sequentially into the flask. The RBF was degassed and backfilled with N_2(g) three times, and the reaction mixture was heated at 80−110 °C. On completion, the reaction mixture was cooled down to rt, quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic extracts were washed with H_2O three times and with brine twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography to yield the desired alkyne.

*General BHCC Procedure for the final ring closure of **15a**, **18a**,* and ***29***.

In a dry RBF, the respective dihalide was dissolved in dry 1,4-dioxane or toluene (0.1−0.2 M). Cs_3CO_3 (2-4 equiv.), Pd_2dba_3 (cat.), and Xantphos (cat.) and an amine (1-15 equiv.) coupling partner. The RBF was degassed and backfilled with N_2(g) three times, and the reaction mixture was heated to reflux. On completion, the reaction mixture was cooled down to rt, quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic extracts were washed with H_2O three times and with brine twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography to yield the desired alkyne.

*General PdCC[1] Procedure for the final ring closure of **15a**, **39b** and **47**.*

The respective dihalide, $Pd(OAc)_2$ (10 mol%), CuI (10 mol%), PPh_3 (1.5 equiv.), DMD (15 equiv.), Et_3N (2 equiv.) and dry NMP (0.1−0.15 M) was added to a dry RBF. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 80 °C for 15−49 h under CO(g) atmosphere. On completion, the reaction mixture was cooled down to rt, quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic extracts were washed with H_2O three times and with brine twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography to yield the desired final product.

*General PdCC[2] Procedure as a two-step sequence for the final ring closure of **15b**, **18a**, **18b**, **29**, **34**, **42**, **50** and **79**.*

Step 1: use General PdCC[1] Procedure to form the secondary amide; step 2: use a modified UCC Procedure to close the ring and form final products (use *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMD) in lieu of DMD).

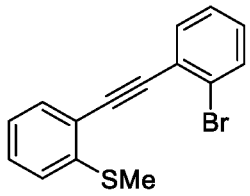
*General PdCC[3] Procedure for the final ring closure of **15a**, **18a**, **29**, and **86**.*

In a dry RBF, the respective dihalide was dissolved in dry 1,4-dioxane (0.1−0.2 M). Cs_3CO_3 (2-4 equiv.), Pd_2dba_3 (cat.), and Xantphos (cat.) and an amine (1-15 equiv.) coupling partner. The RBF was degassed and backfilled with CO (g) three times and the reaction mixture was heated to 70 °C. Upon complete consumption of the dihalo starting material, the CO atmosphere was replace with N_2 (g) and the reaction mixture heated 120 °C. Upon completion, the reaction was cooled down to rt, quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic extracts were washed with H_2O three times and with brine twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography to yield the desired alkyne.

The following materials were prepared according to literature procedures: **12a-b**,[7] **19**,[7] **20-22**,[2] **31-32**,[1] **33-34**,[2] **44-45**,[2] **46b**,[2] **50**,[2] **1-((2-iodophenyl)diazenyl) piperidine**,[4] **58**,[8] **59**[9].

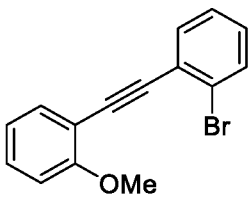
Synthetic Methods

(2-((2-Bromophenyl)ethynyl)phenyl)(methyl)sulfane (13a):



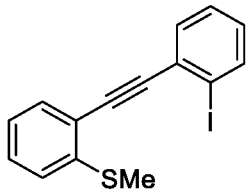
Compound **13a** was synthesised according to General Procedure A. The crude product obtained was purified by flash column chromatography (49:1 hexanes:EtOAc, R_f = 0.3) to yield **13a** (577 mg, 100%) as a yellow oil. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.62 (dt, *J* = 7.5, 1.2 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.36-7.28 (m, 2H), 7.22 – 7.16 (m, 2H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H), 2.52 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 133.7 (CH), 132.9 (CH), 132.6 (CH), 129.6 (CH), 129.3 (CH), 127.1 (CH), 125.6 (C), 125.5 (C), 124.43 (CH), 124.41 (CH), 121.2 (C), 94.3 (C), 91.5 (C), 15.4 (CH_3). LCMS (API-ES) *m/z* (%): 4.2 min, 304.9. HPLC: PP gradient method, t_R = 7.7 min, 97.9 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{12}BrS^+$ [M + H]$^+$ 302.9838, found 302.9831. The spectroscopic data are consistent with those previously reported in the literature.

1-Bromo-2-((2-methoxyphenyl)ethynyl)benzene (13b):



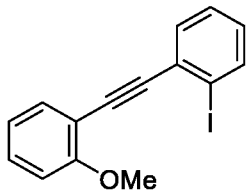
Compound **13b** was synthesised according to General Procedure A. The crude product (2.80 g) was purified by flash column chromatography (100% hexanes, R_f = 0 → 4:1 hexanes:EtOAc, R_f = 0.7) to yield the title compound (2.35 g, 96%) as a bright orange oil. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.60 (app td, *J* = 7.8, 1.4, 2H), 7.55 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), 7.30-7.26 (td, *J* = 7.6, 1.3 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H). HPLC: PP gradient method, t_R = 7.6 min, 90.8 % purity at 254 nm. HR-APCI calcd for $C_{15}H_{12}BrO$ [M + H]$^+$ 287.0066 and 289.0047, found 287.0065 and 289.0044. The spectroscopic data are consistent with those previously reported in the literature.

(2-((2-Iodophenyl)ethynyl)phenyl)(methyl)sulfane (14a):



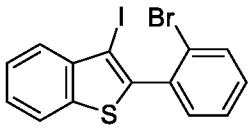
Compound **14a** was synthesised according to General Procedure A. The crude product obtained (brown oil, 1.38 g) was purified by flash column chromatography (50:1 hexanes:EtOAc, R_f = 0.25) to yield **14a** (227 mg, 64%) as a light purple oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 0.9 Hz, 1H), 7.58 (td, J = 7.5, 1.7 Hz, 2H), 7.34 (td, J = 7.6, 1.2 Hz, 1H), 7.33 (ddd, J = 8.0, 7.4, 1.5 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.13 (td, J = 7.5, 1.2 Hz, 1H), 7.04 – 6.99 (m, 1H), 2.53 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 138.9 (CH), 133.0 (CH), 132.9 (CH), 130.0 (C), 129.6 (CH), 129.3 (CH), 127.9 (CH), 124.5 (CH), 124.4 (CH), 121.2 (C), 100.7 (C), 97.6 (C), 90.6 (C), 15.4 (CH_3). LCMS (APCI) *m/z* (%): t = 4.8 min, 351.0 (100, M + H$^+$). HPLC: PP gradient method, t_R = 7.1 min, 95.7 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{12}IS^+$ [M + H]$^+$ 350.9699, found 350.9695. The spectroscopic data are consistent with those previously reported in the literature.

1-Iodo-2-((2-methoxyphenyl)ethynyl)benzene (14b):



Compound **14b** was synthesised according to General Procedure A. The crude product obtained (14.12 g, red oil) was purified by flash column chromatography (49:1 hexanes:EtOAc, R_f = 0.33) to yield the title product (3.89 g, 91%) as an orange oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.62 – 7.53 (m, 2H), 7.36 – 7.29 (m, 2H), 7.06 – 7.03 (m, 1H), 7.02 – 6.93 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H). LCMS (APCI) *m/z* (%): t = 4.4 min, 335.0 (100, M + H$^+$). HPLC: PP gradient method, t_R = 6.7 min, 92.8 % purity at 254 nm. The spectroscopic data are consistent with those previously reported in the literature.

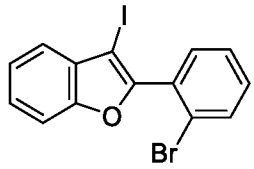
2-(2-Bromophenyl)-3-iodobenzo[*b*]thiophene (15a):



Compound **15a** was synthesised according to General Procedure D. **15a** (705 mg, 95%) was obtained as a yellow oil and directly used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.9, 1.1 Hz, 2H), 7.73 (dd, J = 8.2, 0.9 Hz, 1H), 7.50 (ddd, J = 7.2, 4.6, 1.1 Hz, 1H), 7.46-7.41 (m, 3H), 7.35 (ddd, J = 8.0, 6.0, 3.2 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 141.8 (C), 141.0 (C), 139.5 (C), 136.1 (C), 133.2 (CH), 132.7 (CH), 130.9 (CH), 127.4 (CH), 126.2

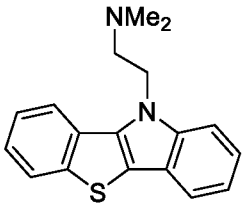
(CH), 125.9 (CH), 125.6 (CH), 124.7 (C), 122.4 (CH), 83.7 (C). HPLC: PP gradient method, t_R = 8.4 min, 92.6 % purity at 254 nm. HR-APCI (*m/z*) calcd for $C_{14}H_8BrIS^+$ $[M]^+$ 413.8569, found 413.8561. The spectroscopic data are consistent with those previously reported in the literature.

2-(2-Bromophenyl)-3-iodobenzofuran (15b):



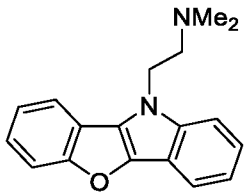
Compound **15b** was synthesised according to General Procedure D. The crude product obtained was purified by flash column chromatography (9:1 hexanes:CH_2Cl_2, R_f = 0.33) to yield **15b** (2.54 g, 78%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.52 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43-7.34 (m, 3H). LCMS (ESI) *m/z* (%): *t* = 4.6 min, 271.0 (100, M-I$^-$) and 272.9 (70, M-I$^-$). HPLC: PP gradient method, t_R = 8.2 min, 96.4 % purity at 254 nm. HR-APCI calcd for $C_{14}H_8BrIO$ $[M]^+$ 397.8798 and 399.8778, found 397.8791 and 399.8771. The spectroscopic data are consistent with those previously reported in the literature.

2-(10*H*-Benzo[4,5]thieno[3,2-*b*]indol-10-yl)-*N*,*N*-dimethylethan-1-amine (16a):



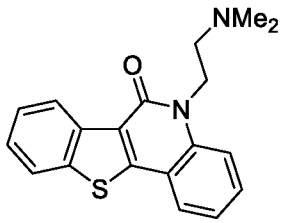
Compound **16a** was synthesised according to General UCC Procedure. The crude product (83 mg, yellow solid) obtained was purified by flash column chromatography (99:1 CH_2Cl_2:MeOH, R_f = 0.3) to yield **16a** (25 mg, 29%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.46 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 2H), 7.37 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 2H), 7.23 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 4.69 (app d, *J* = 8.0 Hz, 2H), 2.80 (app d, *J* = 8.0 Hz, 2H), 2.41 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 141.5 (C), 137.4 (C), 127.0 (C), 124.8 (CH), 124.5 (CH), 124.0 (CH), 123.2 (CH), 121.9 (C), 119.8 (CH), 119.7 (CH), 119.6 (CH), 115.7 (C), 109.9 (CH), 58.9 (CH_2), 46.2 (CH_3), 43.8 (CH_2). LCMS (ESI) *m/z* (%): *t* = 2.6 min, 295.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.2 min, 98.2 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{18}H_{19}N_2S^+$ $[M + H]^+$ 295.1263, found 295.1272.

2-(10*H*-Benzofuro[3,2-*b*]indol-10-yl)-*N*,*N*-dimethylethan-1-amine (16b):



Compound **16b** was synthesised according to General UCC Procedure. The crude product was purified by flash column chromatography (10:5:1 hexanes:CH_2Cl_2:Et_3N, R_f = 0.35) to yield **16b** (86 mg, 42%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (ddd, J = 7.9, 1.2, 0.8 Hz, 1H), 7.78-7.75 (m, 1H), 7.65-7.63 (m, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 3H), 7.22 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 4.54 (t, J = 7.6 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 2.37 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 159.3 (C), 142.5 (C), 139.7 (C), 126.8 (C), 123.9 (CH), 122.8 (CH), 122.6 (CH), 119.7 (CH), 118.9 (C), 117.6 (CH), 117.5 (CH), 113.8 (C), 112.9 (CH), 110.1 (CH), 59.0, 46.1, 44.0. LCMS (ESI) m/z (%): t = 3.1 min, 278.9 (100, M + H$^+$), 279.9 (20, M + H$^+$). HPLC: PP gradient method, t_R = 5.5 min, 98.0 % purity at 254 nm. HR-ESI calcd for $C_{18}H_{19}N_2O$ [M + H]$^+$ 279.1492, found 279.1487.

5-(2-(Dimethylamino)ethyl)benzo[4,5]thieno[3,2-*c*]quinolin-6(5*H*)-one (17a):

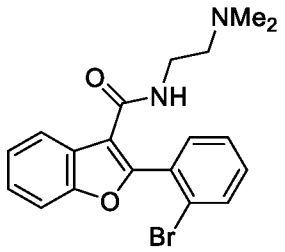


PdCC[1]: Compound **17a** was synthesised according to General PdCC[1] Procedure. The crude product (182 mg) was purified by flash column chromatography (3:1 Et_2O:MeOH, R_f = 0.35) to yield **17a** (25 mg, 43%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, J = 8.0, 1.3 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.60 – 7.42 (m, 4H), 7.30 – 7.24 (m, 1H), 4.60 – 4.52 (m, 2H), 2.72 – 2.64 (m, 2H), 2.42 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 158.7 (C), 147.7 (C), 137.9 (C), 137.3 (C), 137.2 (C), 130.5 (CH), 126.2 (CH), 125.8 (CH), 125.7 (CH), 125.4 (CH), 123.5 (C), 122.4 (CH), 122.0 (CH), 118.0 (C), 115.1 (CH), 56.3 (CH_2), 46.0 (CH_3), 40.7 (CH_2). LCMS (ESI) m/z (%): t = 4.7 min, 323.1. HPLC: PP gradient method, t_R = 5.5 min, 90.8 % purity at 254 nm. HR-ESI (m/z) calcd for $C_{19}H_{19}N_2OS^+$ [M + H]$^+$ 323.1213, found 323.1221.

PdCC[3]: To a dry RBF, 2-(2-bromophenyl)-3-iodobenzo[*b*]thiophene (100 mg, 0.241 mmol), Cs_2CO_3 (235 mg, 0.723 mmol), Pd_2dba_3 (22.0 mg, 0.0241 mmol), and Xantphos (27.9 mg, 0.0482 mmol) were added and dissolved in anhydrous 1,4-dioxane (1.20 mL). The vessel was subsequently degassed and backfilled with N_2(g) three times and allowed to stir at room temperature for 10 minutes. *N,N*-Dimethylethylenediamine (DMD) (0.0389 mL, 0.362 mmol) was then added to the flask before it was subsequently degassed and backfilled with CO (g) three times and allowed to stir under this atmosphere for 4.5 h at 70 °C. After the dehalogenated pyridine starting material had been consumed, the atmosphere of the vessel was reverted back to N_2(g) and the reaction mixture was allowed to stir at 120 °C for 20 h.

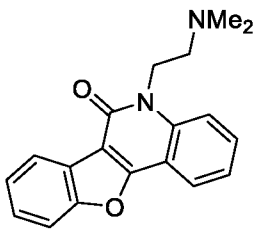
Upon completion, the mixture was extracted with EtOAc (3 x 20 mL) and filtered through Celite ®, before being washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was subsequently collected, dried over $MgSO_4$, and concentrated under vacuum. The crude product was then purified via flash column chromatography (95% EtOAc/ 5% Et_3N/ 1% MeOH, R_f = 0.30) to yield the desired compound (69.0 mg, 88%) as an amber wax. Data in accordance with that above.

2-(2-Bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzofuran-3-carboxamide:



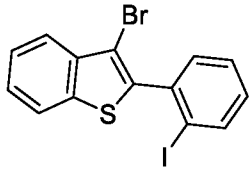
14b (100 mg, 251 µmol), $Pd(OAc)_2$ (5.6 mg, 25 µmol), PPh_3 (98.6 mg, 376 µmol), DMD (331 mg, 3.76 mmol, 0.41 mL), Et_3N (51 mg, 501 µmol, 47 µL), CuI (4.8 mg, 25 µmol) and dry NMP (2.5 mL) was added to a 10 mL dry RBF accordingly. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 80 °C for 18 h. After heating, the mixture was cooled down rt, diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with H_2O (2 x 20 mL), and brine (2 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product obtained (light yellow oil) was purified by flash column chromatography (100% EtOAc → 9:1 EtOAc:MeOH, R_f = 0.2) to yield **2-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzofuran-3-carboxamide** (62 mg, 64%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.13 (m, 1H), 7.75 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 – 7.34 (m, 3H), 6.40 (br s, 1H), 3.41 (td, *J* = 6.0, 4.8 Hz, 2H), 2.36 (t, *J* = 5.9 Hz, 2H), 2.07 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 163.1 (C), 154.6 (C), 154.4 (C), 133.5 (CH), 132.7 (CH), 131.8 (CH), 131.4 (C), 127.7 (CH), 126.8 (C), 125.5 (CH), 124.5 (C), 124.1 (CH), 122.4 (CH), 115.2 (C), 111.4 (CH), 57.1 (CH_2), 44.8 (CH_3), 36.6 (CH_2). LCMS (ESI) *m/z* (%): *t* = 2.3 min, 657.1 (100, M + H^+) and 389.1 (100, M + H^+). HPLC: PP gradient method, t_R = 5.2 min, 94.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{20}BrN_2O_2^+$ [M + H]$^+$ 387.0703, found 387.0711.

5-(2-(Dimethylamino)ethyl)benzofuro[3,2-*c*]quinolin-6(5*H*)-one (17b):



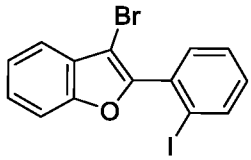
In a dry RBF, **2-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzofuran-3-carboxamide** (60 mg, 155 µmol) was dissolved in *n*-butanol (0.8 mL) and K_3PO_4 (132 mg, 620 µmol, 4.0 equiv.), ethylene glycol (104 µL, 1.86 mmol, 12 equiv.), TMD (288 mg, 2.48 mmol, 0.37 mL), and CuI (11.8 mg, 62 µmol), were added accordingly. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 90 °C for 15 h. After heating, the reaction mixture was cooled down to rt and diluted with EtOAc (20 mL). The combined organic layer was washed with H_2O (2 x 15 mL) and brine (2 x 15 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (44 mg) obtained was purified by flash column chromatography (10:1 EtOAc:MeOH, R_f = 0.1) to yield **16b** (34 mg, 72%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 6.0, 2.3 Hz, 1H), 8.20 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.38 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.59 (br t, *J* = 7.8 Hz, 2H), 2.69 (br t, *J* = 7.9 Hz, 2H), 2.43 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 157.6 (C), 155.6 (C), 138.8 (C), 131.0 (CH), 126.3 (CH), 124.7 (C), 124.6 (CH), 122.7 (CH), 122.5 (CH), 122.4 (CH), 115.2 (CH), 113.2 (C), 111.5 (CH), 110.3 (C), 56.5 (CH_2), 46.0 (CH_3), 40.7 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.06 min, 307.2 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.1 min, 99.2 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_2O_2^+$ [M + H]$^+$ 307.1441, found 307.1447.

3-Bromo-2-(2-iodophenyl)benzo[*b*]thiophene (18a):



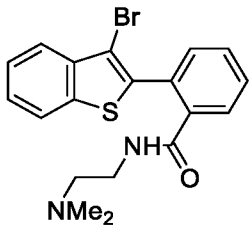
$CuBr_2$ (899 mg, 4.03 mmol, 3.0 equiv.) was added to a stirred solution of **14a** (470 mg, 1.34 mmol) in dry DCE (7 mL) under N_2(g) atmosphere. The reaction was heated at 45 °C for 15 h. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (35 mL), and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with H_2O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained (pale yellow solid, 550 mg) was purified by flash column chromatography (40:1 hexanes:CH_2Cl_2, R_f = 0.55) to yield **18a** (453 mg, 81%) as a white crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.16 (ddd, *J* = 8.0, 7.0, 2.1 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 140.6 (C), 139.5 (CH), 138.5 (C), 138.4 (C), 138.0 (C), 131.7 (CH), 130.8 (CH), 128.2 (CH), 125.9 (CH), 125.4 (CH), 123.9 (CH), 122.5 (CH), 108.6 (CH), 100.4 (C). LCMS (ESI) *m/z* (%): *t* = 4.9 min, 413.9 (100, M + H$^+$). HPLC: PP gradient method, t_R = 7.4 min, 97.0 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{14}H_9BrIS^+$ [M + H]$^+$ 414.8648, found 414.8634. mp 134–136 °C.

3-Bromo-2-(2-iodophenyl)benzofuran (18b):



14b (407 mg, 1.22 mmol) was dissolved in anhydrous DCE (6.5 mL), followed by addition of *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) (575 mg, 1.31 mmol). The orange solution was heated at 45 °C over a period of 69 h. On completion, the mixture was cooled down to rt, diluted with saturated $Na_2S_2O_3$ solution (30 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with H_2O (2 x 50 mL) and brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained (light yellow oil, 630 mg) was purified by flash column chromatography (25:1 hexanes:CH_2Cl_2, R_f = 0.6) to yield **18b** (202 mg, 42%) as a transparent oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.0, 1.2 Hz, 1H), 7.61 (dd, J = 7.7, 1.5 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.48 (td, J = 7.5, 1.2 Hz, 1H), 7.46 – 7.33 (m, 2H), 7.19 (ddd, J = 8.0, 7.3, 1.8 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 153.8 (C), 153.4 (C), 139.9 (CH), 134.8 (C), 132.4 (CH), 131.4 (CH), 128.4 (C), 128.0 (CH), 125.9 (CH), 123.7 (CH), 120.2 (CH), 111.8 (CH), 98.3 (C), 97.0 (C). LCMS (APCI) *m/z* (%): t = 4.7 min, 399.9 (100, M + H$^+$). HPLC: PP gradient method, t_R = 7.1 min, 99.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{14}H_9BrIO^+$ [M + H]$^+$ 398.8876, found 398.8882.

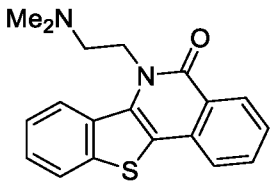
2-(3-Bromobenzo[*b*]thiophen-2-yl)-*N*-(2-(dimethylamino)ethyl)benzamide:



18a (250 mg, 602 µmol), $Pd(OAc)_2$ (20 mg, 90 µmol), PPh_3 (237 mg, 903 µmol), DMD (796 mg, 9.03 mmol, 0.97 mL), Et_3N (122 mg, 1.2 mmol, 0.11 mL), CuI (11 mg, 60 µmol) and dry NMP (4.5 mL) was added to a 25 mL dry RBF accordingly. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 90 °C for 19 h. After heating, the mixture was cooled down to rt, diluted with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with H_2O (2 x 25 mL), and brine (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (463 mg, orange oil) obtained was purified by flash column chromatography (9:1 EtOAc:MeOH, R_f = 0.2) to yield **2-(3-bromobenzo[*b*]thiophen-2-yl)-*N*-(2-(dimethylamino)ethyl)benzamide** (192 mg, 79%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 1H), 7.85 (dd, J = 8.0, 1.3 Hz, 1H), 7.82 (dd, J = 8.0, 1.0 Hz, 1H), 7.58 – 7.40 (m, 5H), 6.37 (br s, 1H), 3.23 (td, J = 5.9, 4.7 Hz, 2H), 2.03 (t, J = 5.9 Hz, 2H), 1.70 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 167.7 (C), 138.8 (C), 138.4 (C),

137.0 (C), 136.9 (C), 132.0 (CH), 130.4 (C), 130.3 (CH), 129.7 (CH), 129.6 (CH), 125.9 (CH), 125.5 (CH), 123.8 (CH), 122.4 (CH), 108.5 (C), 56.9 (CH_2), 44.5 (CH_3), 37.4 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.1 min, 403.0 (100, M + H^+). HPLC: PP gradient method, t_R = 5.0 min, 98.1 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{20}N_2BrOS^+$ [M + H]$^+$ 403.0474, found 403.0482.

6-(2-(Dimethylamino)ethyl)benzo[4,5]thieno[3,2-*c*]isoquinolin-5(6*H*)-one (19a):

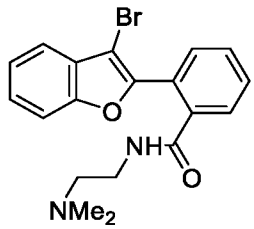


In a dry RBF, 2-(3-bromobenzo[*b*]thiophen-2-yl)-*N*-(2-(dimethylamino)ethyl) benzamide (73 mg, 181 µmol) was dissolved in *n*-butanol (0.9 mL) and K_3PO_4 (154 mg, 724 µmol), ethylene glycol (121 µL, 2.17 mmol), TMD(337 mg, 2.9 mmol, 0.43 mL), and CuI (14 mg, 72 µmol) were added accordingly. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 90 °C for 22 h. After heating, the reaction mixture was cooled down to rt and diluted with EtOAc (20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (2 x 15 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (47 mg) obtained was purified by flash column chromatography (94:5:1 EtOAc:Et_3N:MeOH, R_f = 0.15) to yield **19a** (61 mg, 80%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 4.5 Hz, 2H), 7.54-7.49 (m, 1H), 7.47 (ddd, *J* = 8.5, 7.1, 1.4 Hz, 1H), 7.41 (td, *J* = 7.6, 7.1, 1.1 Hz, 2H), 4.81 (t, *J* = 8.0 Hz, 2H), 2.81 (t, *J* = 8.1 Hz, 2H), 2.43 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 162.5 (C), 138.6 (C), 133.0 (C), 132.8 (CH), 132.4 (C), 130.8 (C), 129.1 (CH), 127.6 (CH), 125.8 (CH), 125.4 (CH), 124.0 (C), 123.9 (CH), 123.5 (CH), 123.2 (CH), 117.9 (C), 57.0 (CH_2), 46.1 (CH_3), 43.5 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.1 min, 323.1 (100, M + H^+). HPLC: PP gradient method, t_R = 4.9 min, 95.5 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_2OS^+$ [M + H]$^+$ 323.1213, found 323.1220.

PdCC^3: To a dry RBF, 3-bromo-2-(2-iodophenyl)benzo[b]thiophene (100 mg, 0.241 mmol), Cs_2CO_3 (235 mg, 0.723 mmol), Pd_2dba_3 (22.0 mg, 0.0241 mmol), and Xantphos (27.9 mg, 0.0482 mmol) were added and dissolved in anhydrous 1,4-dioxane (1.20 mL). The vessel was subsequently degassed and backfilled with N_2(g) three times and allowed to stir at room temperature for 10 minutes. *N,N*-Dimethylethylenediamine (0.0389 mL, 0.362 mmol) was then added to the flask before it was subsequently degassed and backfilled with CO (g) three times and allowed to stir under this atmosphere for 4.5 h at 70 °C. After the dehalogenated pyridine starting material has been consumed, the atmosphere of the vessel was reverted back to N_2(g) and the reaction mixture was allowed to stir at 120 °C for 20 h. Upon completion, the mixture was extracted with EtOAc (3 x 20 mL) and filtered through Celite ®, before being washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was subsequently

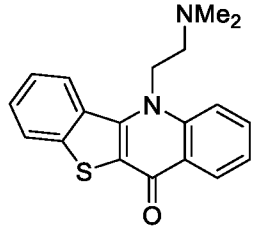
collected, dried over $MgSO_4$, and concentrated under vacuum. The crude product was then purified via flash column chromatography (95% EtOAc/ 5% Et_3N/ 1% MeOH, R_f = 0.30) to yield the desired compound (68.5 mg, 88%) as an amber wax. ^1H NMR (401 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.76 – 7.62 (m, 2H), 7.58 – 7.32 (m, 3H), 4.82 (t, *J* = 8.1 Hz, 2H), 2.82 (t, *J* = 8.2 Hz, 2H), 2.44 (s, 6H). LCMS (APCI) *m/z*: 323.2 [M+H$^+$].

2-(3-Bromobenzofuran-2-yl)-*N*-(2-(dimethylamino)ethyl)benzamide:



17b (125 mg, 313 µmol), $Pd(OAc)_2$ (11 mg, 47 µmol), PPh_3 (123 mg, 470 µmol), DMD (414 mg, 4.7 mmol, 0.51 mL), Et_3N (63 mg, 627 µmol, 57 µL) and dry NMP (2 mL) was added to a 25 mL dry RBF accordingly. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 90 °C for 20 h. After heating, the mixture was cooled down to rt, diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with H_2O (2 x 25 mL), and brine (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (270 mg, orange oil) obtained was purified by flash column chromatography (10:1 EtOAc:MeOH, R_f = 0.15) to yield the title product (91 mg, 75%) as a light yellow oil. ^1H NMR (401 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 1H), 7.79 – 7.71 (m, 1H), 7.61 – 7.51 (m, 3H), 7.49 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.36 (td, *J* = 7.3, 1.7 Hz, 1H), 7.33 (td, *J* = 7.3, 1.3 Hz, 1H), 6.36 (s, 1H), 3.32 (dd, *J* = 10.7, 5.9 Hz, 2H), 2.10 (t, *J* = 5.9 Hz, 3H), 1.85 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 168.5 (C), 154.0 (C), 150.7 (C), 137.0 (C), 130.9 (CH), 130.12 (CH), 130.11 (CH), 129.3 (CH), 128.8 (C), 126.7 (C), 125.9 (CH), 123.8 (CH), 120.2 (CH), 111.7 (CH), 96.7 (C), 57.2 (CH_2), 44.6 (CH_3), 37.3 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.2 min, 389.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 4.84 min, 95.1 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{20}BrN_2O_2$ [M + H]$^+$ 387.0703, found 387.0712.

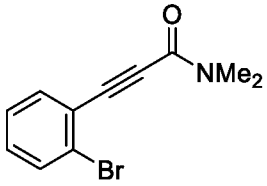
5-(2-(Dimethylamino)ethyl)benzo[4,5]thieno[3,2-*b*]quinolin-11(5*H*)-one (23):



Compound **23** was synthesised according to General UCC Procedure. The crude product (91 mg, bright yellow oil) obtained was purified by flash column chromatography (24:1 EtOAc:Et_3N, R_f =

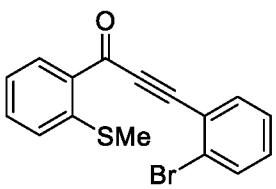
0.35) to yield **23** (23 mg, 36%) as a pale orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.00 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.63 – 7.50 (m, 2H), 7.45 (ddd, *J* = 7.9, 6.6, 1.2 Hz, 1H), 4.92 (t, *J* = 8.2 Hz, 2H), 3.05 (br t, *J* = 7.9 Hz, 2H), 2.50 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 142.5 (C), 142.0 (C), 141.4 (C), 132.8 (CH), 130.6 (C), 127.9 (CH), 126.8 (CH), 125.3 (CH), 125.1 (CH), 124.8 (CH), 123.5 (C), 123.1 (C), 123.0 (CH), 115.1 (CH), 57.37 (CH_2), 48.0 (CH_2), 46.2 (CH_3). LCMS (ESI) *m/z* (%): *t* = 2.7 min, 323.1 (100, M + H^+). HPLC: PP gradient method, t_R = 4.3 min, 96.2 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_2OS^+$ $[M + H]^+$ 323.1213, found 323.1216. mp 177–179 °C.

3-(2-Bromophenyl)-*N*,*N*-dimethylpropiolamide (24):



n-BuLi (3.15 mL, 7.88 mmol) was added dropwise to a stirred solution of **33**[3] (1.09 mL, 8.73 mmol) in dry THF (44 mL) at –78 °C under N_2(g) atmosphere. The solution was left to stir at –78 °C for 30 min, followed by dropwise addition of dimethylcarbamoyl chloride (0.88 mL, 9.60 mmol). The reaction mixture was then left at stirring at –78 °C for 5 min, then raised to rt. The dark brown suspension was quenched with saturated NH_4Cl solution and extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (2.01 g) was obtained as a brown oil and purified by flash column chromatography (2:1 hexanes:EtOAc , R_f = 0.3) to yield **24** (1.47 g, 74%) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.26 (td, *J* = 7.8, 1.8 Hz, 1H), 3.36 (s, 3H), 3.04 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 154.1 (C), 134.5 (CH), 132.5 (CH), 131.1 (CH), 127.2 (CH), 125.9 (C), 122.9 (C), 87.7 (C), 85.4 (C), 38.3 (CH_3), 34.1 (CH_3). LCMS (ESI) *m/z* (%): *t* = 3.6 min, 253.9 (100, M + H^+), 255.9 (80, M + H^+). HPLC: PP gradient method, t_R = 5.6 min, 98.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{11}H_{11}BrNO^+$ $[M + H]^+$ 252.0019, found 252.0022. mp 70–74 °C.

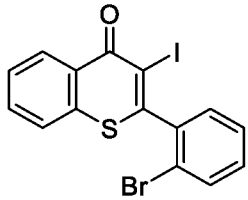
3-(2-Bromophenyl)-1-(2-(methylthio)phenyl)prop-2-yn-1-one (25):



n-BuLi (0.64 mL, 1.6 mmol, 2.5 M in hexanes) was added dropwise to a stirred solution of **11a** (400 mg, 1.6 mmol) in dry THF (8 mL) at –78 °C under N_2(g) atmosphere. The solution was left to stir at –78 °C for 15 min, followed by addition of a solution of **24** (353 mg, 1.4 mmol) in dry THF (2 mL).

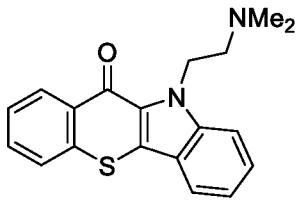
The reaction was left to stir at −78 °C for 1 h, then raised to rt and quenched with saturated NH_4Cl solution (40 mL) and extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with H_2O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (544 mg, brown oil) obtained was purified by flash column chromatography (19:1 hexanes:EtOAc, R_f = 0.25) to yield **25** (330 mg, 71%) as a bright yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.9, 1.5 Hz, 1H), 7.66 (dd, J = 7.7, 1.8 Hz, 1H), 7.62 (dd, J = 7.9, 1.3 Hz, 1H), 7.52 (ddd, J = 8.2, 7.2, 1.6 Hz, 1H), 7.37 – 7.20 (m, 4H), 2.44 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 177.4 (C), 145.0 (C), 135.3 (CH), 135.2 (CH), 133.5 (CH), 132.9 (C), 132.8 (CH), 131.8 (CH), 127.4 (CH), 126.7 (C), 124.2 (CH), 123.4 (CH), 122.9 (C), 90.6 (C), 90.3 (C), 15.5 (CH_3). LCMS (APCI) *m/z* (%): t = 3.4 min, 331.0 (25, M + H$^+$), 354.9 (100, M+Na$^+$). HPLC: PP gradient method, t_R = 7.2 min, 90.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{16}H_{12}BrOS^+$ [M + H]$^+$ 330.9787, found 330.9780. mp 96–100 °C.

2-(2-Bromophenyl)-3-iodo-4*H*-thiochromen-4-one (26):



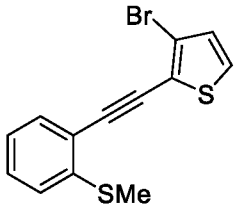
25 (140 mg, 423 µmol) was dissolved in anhydrous CH_3CN (4 mL) in a dry RBF, followed by slow addition of a solution of ICl (103 mg, 634 µmol) in anhydrous CH_3CN (0.9 mL) to the stirred solution. The reaction was left to stir at rt for 26 h in the dark. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (30 mL) and extracted with EtOAc (2 x 20 mL). Washed with H_2O (2 x 30 mL) and brine (2 x 30 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (185 mg) obtained was purified by flash column chromatography (2:1 hexanes:toluene, R_f = 0.2) to yield **26** (97 mg, 52%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, J = 8.7, 1.5 Hz, 1H), 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.71 – 7.57 (m, 3H), 7.48 (td, J = 7.5, 1.2 Hz, 1H), 7.39 (ddd, J = 8.1, 7.5, 1.8 Hz, 1H), 7.32 (dd, J = 7.6, 1.7 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 176.2 (C), 153.2 (C), 141.2 (C), 137.5 (C), 133.6 (CH), 132.2 (CH), 131.5 (CH), 130.24 (CH), 130.16 (CH), 128.7 (CH), 128.1 (CH), 127.5 (C), 125.6 (CH), 122.3 (C), 105.1 (C). LCMS (APCI) *m/z* (%): t = 3.4 min, 443.9 (25, M + H$^+$), 466.9 (100, M+Na$^+$). HPLC: PP gradient method, t_R = 7.0 min, 95.0 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_9BrIOS^+$ [M + H]$^+$ 442.8597, found 442.8597. mp 200–202 °C.

10-(2-(Dimethylamino)ethyl)thiochromeno[3,2-*b*]indol-11(10*H*)-one (27):



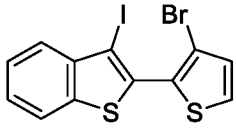
Compound **27** was synthesised according to General UCC Procedure. The crude product (51 mg) was purified by flash column chromatography (97:3 EtOAc:Et_3N, R_f = 0.25) to yield **27** (38 mg, 78%) as a bright yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 8.1, 1.6 Hz, 1H), 7.86 (dt, J = 8.1, 1.0 Hz, 1H), 7.76 (dd, J = 8.1, 1.3 Hz, 1H), 7.66 – 7.50 (m, 4H), 7.28 (td, J = 8.1, 1.4 Hz, 1H), 5.04 (br t, J = 7.6 Hz, 2H), 2.79 (br t, J = 7.6 Hz, 2H), 2.41 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 173.3 (C), 139.6 (C), 136.0 (C), 132.7 (C), 130.7 (CH), 129.0 (CH), 128.1 (CH), 127.7 (C), 126.9 (CH), 126.0 (CH), 123.0 (C), 120.9 (CH), 120.7 (C), 119.4 (C), 110.9 (CH), 59.6 (CH_2), 46.1 (CH_3), 44.0 (CH_2). LCMS (ESI) *m/z* (%): t = 2.5 min, 323.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.5 min, 97.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_2OS^+$ [M + H]$^+$ 323.1213, found 323.1221.

3-Bromo-2-((2-(methylthio)phenyl)ethynyl)thiophene (28):



Compound **28** was synthesised according to General Procedure A. The crude product (2.83 g) obtained was purified by flash column chromatography (100% hexanes → 17:3 hexanes:EtOAc, R_f = 0.45) to yield **28** (1.23 g, 58%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (ddd, J = 7.7, 1.5, 0.4 Hz, 1H), 7.33 (ddd, J = 8.0, 7.4, 1.5 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 7.20 (dd, J = 8.0, 0.9 Hz, 1H), 7.12 (td, J = 7.5, 1.2 Hz, 1H), 7.01 (d, J = 5.4 Hz, 1H), 2.53 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 141.8 (C), 132.5 (CH), 130.3 (CH), 129.3 (CH), 127.5 (CH), 124.5 (CH), 124.4 (CH), 120.8 (C), 120.8 (C), 116.3 (C), 94.5 (C), 87.2 (C), 15.3 (CH_3). HPLC: PP gradient method, t_R = 7.8 min, 97.1 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{13}H_{10}BrS_2^+$ [M + H]$^+$ 308.9402, found 308.9398.

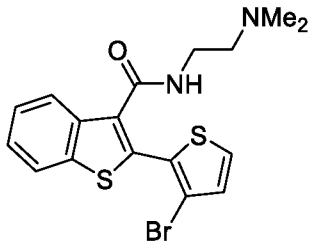
2-(3-Bromothiophen-2-yl)-3-iodobenzo[*b*]thiophene (29):



Compound **29** was synthesised according to General Procedure D. **29** (1.44 g, 97%) was obtained as a grey amorphous solid and directly used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (app tdd, J = 7.9, 1.4, 0.7, 2H), 7.51-7.47 (m, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.44 (ddd, J = 7.8, 7.2, 1.4, 1H), 7.13 (d, J = 5.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1

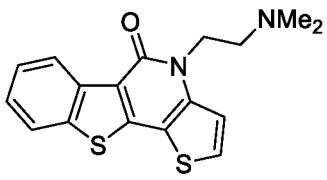
(C), 140.1 (C), 133.4 (C), 131.0 (CH), 128.4 (CH), 126.6 (CH), 126.3 (CH), 125.7 (CH), 122.3 (CH), 113.5 (C), 86.3 (C). One quaternary carbon is overlapping at 113.5 ppm. HPLC: PP gradient method, t_R = 8.5 min, 99.3 % purity at 254 nm. HR-APCI calcd for $C_{12}H_6BrIS_2$ $[M]^+$ 419.8133, found 419.8129.

2-(3-Bromothiophen-2-yl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*]thiophene-3-carboxamide:



Compound **29** (100 mg, 0.24 mmol), $Pd(OAc)_2$ (5.3 mg, 0.024 mmol), PPh_3 (94 mg, 0.36 mmol), DMD (80 µL, 0.71 mmol), Et_3N (70 µL, 0.47 mmol) and dry DMF (2.5 mL) was added to a Schlenk tube. The tube was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 80 °C for 17 h. On completion, the reaction mixture was cooled down to rt and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with H_2O (3 x 40 mL), saturated NH_4Cl solution (40 mL) and brine (2 x 40 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (165 mg) obtained was purified by flash column chromatography (4:1 MeOH:EtOAc, R_f = 0.17). **2-(3-Bromothiophen-2-yl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*]thiophene-3-carboxamide** (51 mg, 52%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.6, 1.7 Hz, 1H), 7.80 (dd, J = 8.2, 1.0 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.46-7.38 (m, 2H), 7.09 (d, J = 5.4, 1H), 6.41 (s, 1H), 3.39 (dd, J = 10.8, 5.9 Hz, 2H), 2.28 (t, J = 6.0 Hz, 2H), 2.05 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 163.7 (C), 139.8 (C), 138.2 (C), 133.4 (C), 132.5 (C), 131.3 (CH), 129.5 (C), 128.4 (CH), 125.8 (CH), 125.3 (CH), 125.0 (CH), 121.7 (CH), 113.4 (C), 57.1 (CH_2), 44.9 (CH_3), 37.0 (CH_2). LCMS (ESI) *m/z* (%): t = 3.9 min, 408.8 (100, M + H^+), 410.9 (80, M + H^+). HPLC: PP gradient method, t_R = 5.42 min, 97.0 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{17}H_{18}BrN_2OS_2^+$ $[M + H]^+$ 409.0038, found 409.0044.

4-(2-(Dimethylamino)ethyl)benzo[4,5]thieno[2,3-*d*]thieno[3,2-*b*]pyridin-5(4*H*)-one (30):

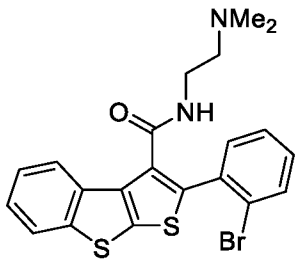


In a dry RBF, **2-(3-bromothiophen-2-yl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*] thiophene-3-carboxamide** (50 mg, 0.12 mmol) was dissolved in *n*-butanol (0.6 mL) and CuI (9.3 mg, 50 µmol), K_3PO_4 (104 mg, 0.49 mmol), ethylene glycol (80 µL, 1.47 mmol), and TMD (40 µL, 0.24 mmol) were added sequentially. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 90 °C for 17 h. After heating, the reaction mixture was cooled down to rt

and diluted with EtOAc (15 mL). The organic extract was washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (40 mg) obtained was then purified by flash column chromatography (3:1 EtOAc:MeOH, R_f = 0.33). **30** (33 mg, 83%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 5.5 Hz, 1H), 4.49 (t, J = 7.7 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.40 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 158.5 (C), 143.7 (C), 141.7 (C), 137.0 (C), 128.2 (CH), 125.87 (CH), 125.86 (CH), 125.3 (CH), 122.2 (CH), 120.9 (C), 117.2 (CH), 114.5 (C), 57.0 (CH_2), 45.9 (CH_3), 43.3 (CH_2). One quaternary carbon is overlapping at 137.0 ppm. LCMS (ESI) m/z (%): t = 4.0 min, 328.9 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.5 min, 95.3 % at 254 nm. HR-ESI (m/z) calcd for $C_{17}H_{17}N_2OS_2^+$ $[M + H]^+$ 329.0777, found 329.0788.

PdCC^3: To a dry RBF, 2-(3-bromothiophen-2-yl)-3-iodobenzo[b]thiophene (100 mg, 0.237 mmol), Cs_2CO_3 (232 mg, 0.712 mmol), Pd_2dba_3 (21.8 mg, 0.0238 mmol), and Xantphos (27.5 mg, 0.0475 mmol) were added and dissolved in anhydrous 1,4-dioxane (1.20 mL). The vessel was subsequently degassed and backfilled with N_2(g) three times and allowed to stir at room temperature for 10 minutes. *N,N*-Dimethylethylenediamine (0.0383 mL, 0.356 mmol) was then added to the flask before it was subsequently degassed and backfilled with CO (g) three times and allowed to stir under this atmosphere for 4.5 h at 70 °C. After the dehalogenated pyridine starting material has been consumed, the atmosphere of the vessel was reverted back to N_2(g) and the reaction mixture was allowed to stir at 120 °C for 20 h. Upon completion, the mixture was extracted with EtOAc (3 x 20 mL) and filtered through Celite ®, before being washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was subsequently collected, dried over $MgSO_4$, and concentrated under vacuum. The crude product was then purified via flash column chromatography (95% EtOAc/ 5% Et_3N/ 1% MeOH, R_f = 0.25) to yield the desired compound (69.0 mg, 45%) as a dark orange wax. Data in accordance with that recorded above.

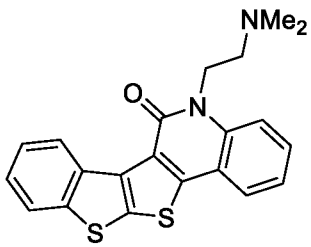
2-(2-Bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*]thieno[3,2-*d*]thiophene-3-carboxamide:



34[46] (95 mg, 0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 20 µmol), PPh_3 (79 mg, 0.30 mmol), DMD (0.34 mL, 3.2 mmol), Et_3N (60 µL, 0.40 mmol) and dry DMF (2.0 mL) were added to a 25 mL dry RBF. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 80 °C for 17 h. On completion, the reaction mixture was cooled down to rt, diluted with H_2O (25 mL)

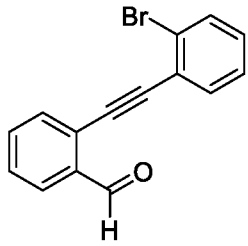
and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with saturated NH_4Cl solution (25 mL), H_2O (3 x 40 mL) and brine (2 x 30 mL). The organic extract was then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (142 mg) obtained was then purified by flash column chromatography (100% EtOAc → 7:3 EtOAc:MeOH, R_f = 0.45) to yield **2-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*]thieno[3,2-*d*]thiophene-3-carboxamide** (56 mg, 60%) as a pale brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 7.8, 1.5 Hz, 1H), 7.80 (dd, J = 7.8, 1.3 Hz, 1H), 7.69 (dd, J = 8.0, 1.2 Hz, 1H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.43-7.33 (m, 3H), 7.30 (td, J = 7.7, 1.8 Hz, 1H), 6.39 (s, 1H), 3.35 (dd, J = 11.0, 5.8 Hz, 2H), 2.18 (t, J = 6.0 Hz, 2H), 2.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (C), 143.6 (C), 143.2 (C), 139.2 (C), 138.4 (C), 134.3 (C), 133.1 (CH), 133.0 (CH), 132.7 (C), 130.7 (CH), 130.5 (C), 127.6 (CH), 125.2 (C), 124.8 (C), 124.8 (CH), 123.7 (CH), 122.9 (CH), 57.0 (CH_2), 44.8 (CH_3), 37.1 (CH_2). LCMS (ESI) *m/z* (%): t = 4.0 min, 460.8 (100, M + H$^+$), 462.8 (20, M + H$^+$). HPLC: PP gradient method, t_R = 6.0 min, 99.3 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{21}H_{20}BrN_2OS_2^+$ [M + H]$^+$ 459.0195, found 459.0205.

5-(2-(Dimethylamino)ethyl)benzo[4',5']thieno[3',2':4,5]thieno[3,2-*c*]quinolin-6(5*H*)-one (35):



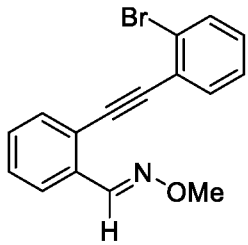
In a dry RBF, **2-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzo[*b*]thieno[3,2-*d*]thiophene-3-carboxamide** (50 mg, 0.11 mmol) was dissolved in *n*-butanol (0.55 mL) and CuI (8.3 mg, 40 µmol), K_3PO_4 (92 mg, 0.44 mmol), ethylene glycol (70 µL, 1.31 mmol), and TMD(30 µL, 0.22 mmol) were added sequentially. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 90 °C for 20 h. The reaction mixture was cooled down to rt and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (43 mg) obtained was purified by flash column chromatography (100 % EtOAc → 3:1 EtOAc:MeOH, R_f = 0.33) to yield **35** (39 mg, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (ddd, J = 8.2, 1.2, 0.6 Hz, 1H), 7.81 (app t, J = 7.3 Hz, 2H), 7.54-7.49 (m, 3H), 7.39 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.29-7.25 (m, 1H), 4.59 (app t, J = 7.8 Hz, 2H), 2.75-2.71 (app t, J = 7.9 Hz, 2H), 2.45 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 158.4 (C), 149.3 (C), 143.6 (C), 139.7 (C), 137.5 (C), 136.6 (C), 133.4 (C), 129.7 (CH), 126.6 (CH), 125.1 (CH), 124.9 (CH), 124.85 (C), 124.0 (CH), 122.6 (CH), 122.6 (CH), 118.7 (C), 115.2 (CH), 56.2 (CH_2), 46.0 (CH_3), 41.2 (CH_2). LCMS (API-ES) *m/z* (%): t = 4.2 min, 378.9 (100, M + H$^+$). HPLC: PP gradient method, t_R = 6.5 min, 99.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{21}H_{19}N_2OS_2^+$ [M + H]$^+$ 379.0933, found 379.0945.

2-((2-Bromophenyl)ethynyl)benzaldehyde (37):



Compound **37** was synthesised according to General Procedure A. The crude product (839 mg) obtained was purified by flash column chromatography (3:1 hexanes:CH_2Cl_2, R_f = 0.25) to yield **37** (678 mg, 92%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (d, *J* = 0.8 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.51 – 7.46 (td, *J* = 7.6, 1.1 Hz, 1H), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H), 7.23 (td, *J* = 7.5, 1.7 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 192.1 (CH), 136.3 (C), 133.9 (CH), 133.6 (CH), 133.5 (CH), 132.8 (CH), 130.3 (CH), 129.2 (CH), 127.33 (CH), 127.31 (CH), 126.6 (C), 125.9 (C), 124.8 (C), 94.8 (C), 89.5 (C). LCMS (ESI) *m/z* (%): *t* = 3.6 min, 285.0 (100, M + H$^+$). HPLC: PP gradient method, t_R = 7.04 min, 95.3 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{10}BrO^+$ [M + H]$^+$ 284.9910, found 284.9907. mp 66–68 °C. The spectroscopic data are consistent with those previously reported in the literature.

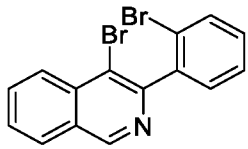
(*E*)-2-((2-Bromophenyl)ethynyl)benzaldehyde *O*-methyl oxime (38a):



O-Methylhydroxylamine hydrochloride (776 mg, 9.29 mmol) was slowly added to a stirred solution of **37** (530 mg, 1.86 mmol) in pyridine (3 mL) and EtOH (6 mL). The reaction mixture was left to stir at rt overnight. On completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). Washed with H_2O (2 x 30 mL) and brine (2 x 30 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (824 mg) obtained was purified by flash column chromatography (2:1 hexanes:CH_2Cl_2, R_f = 0.45) to yield **38a** (546 mg, 94%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.98 – 7.90 (m, 1H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.38 – 7.34 (m, 2H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H), 4.01 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 147.5 (CH), 133.7 (C), 133.4 (CH), 132.73 (CH), 132.66 (CH), 129.8 (CH), 129.5 (CH), 129.0 (CH), 127.2 (CH), 125.9 (C), 125.3 (CH), 125.2 (C), 122.7 (C), 93.4 (C), 91.0 (C), 62.3 (CH_3). LCMS (ESI)

m/z (%): *t* = 5.0 min, 314.0 (100, M + H^+). HPLC: PP gradient method, t_R = 8.0 min, 96.4 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{16}H_{13}BrNO^+$ [M + H]$^+$ 314.0175, found 314.0170.

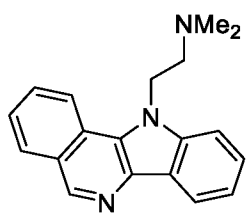
4-Bromo-3-(2-bromophenyl)isoquinoline (39a) and **4-bromo-3-(2-bromophenyl) isoquinolin-1-ol (39b):**



$CuBr_2$ (448 mg, 2.01 mmol, 2 equiv.) was added slowly to a stirred solution of **38a** (315 mg, 1.0 mmol) in dry dimethylacetamide (5 mL) under N_2(g) atmosphere. The reaction was heated at 100 °C for 17 h. After heating, the mixture was quenched with saturated NH_4Cl solution (35 mL) and extracted with EtOAc (3 x 30 mL). Washed with H_2O (2 x 80 mL) and brine (2 x 80 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (327 mg, brown oil) obtained was purified by flash column chromatography (3:1 hexanes:CH_2Cl_2, R_f = 0.1 → 1:1 hexanes:CH_2Cl_2, R_f = 0.2, → 2:3 hexanes:CH_2Cl_2, R_f = 0.7) to yield **39a** (122 mg, 34%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.32 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.06 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.88 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.50 – 7.38 (m, 2H), 7.32 (ddd, *J* = 8.1, 7.0, 2.2 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 152.4 (C), 151.2 (CH), 142.0 (C), 135.7 (C), 132.9 (CH), 132.2 (CH), 130.9 (CH), 130.0 (CH), 129.0 (C), 128.5 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 123.1 (C), 121.3 (C), 120.0 (C). LCMS (ESI) *m/z* (%): *t* = 5.6 min, 363.8 (100, M + H^+). HPLC: PP gradient method, t_R = 6.6 min, 96.6 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{10}Br_2N^+$ [M + H]$^+$ 361.9175, found 361.9176.

Byproduct **4-bromo-3-(2-bromophenyl)isoquinolin-1-ol 39b** (167 mg, 44%) was also obtained as an off-white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 8.88 (br s, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 2H). LCMS (ESI) *m/z* (%): *t* = 3.5 min, 377.8 (100, M+H^+). HPLC: PP gradient method, t_R = 5.8 min, 98.3 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{10}Br_2NO^+$ [M + H]$^+$ 377.9124, found 377.9123.

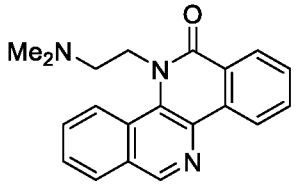
2-(11*H*-indolo[3,2-*c*]isoquinolin-11-yl)-*N*,*N*-dimethylethan-1-amine (40):



Compound **40** was synthesised according to General UCC Procedure. The crude product (68 mg, brown oil) obtained was purified by flash column chromatography (99:1 EtOAc:Et_3N, R_f = 0.2) to

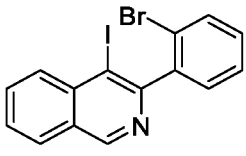
yield **40** (23 mg, 53%) as a light green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.83 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.63 – 7.51 (m, 2H), 7.39 (ddd, *J* = 7.9, 6.4, 1.6 Hz, 1H), 4.86 (br t, *J* = 8.1 Hz, 2H), 2.87 (br t, *J* = 8.1 Hz, 2H), 2.44 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 145.9 (CH), 140.0 (C), 135.1 (C), 130.1 (CH), 129.7 (CH), 127.7 (C), 127.0 (C), 126.2 (CH), 125.6 (CH), 124.5 (C), 122.9 (C), 120.8 (CH), 120.6 (CH), 120.2 (CH), 109.0 (CH), 58.3 (CH_2), 46.2 (CH_3), 44.4 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.3 min, 290.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 3.5 min, 96.7 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{20}N_3^+$ [M + H]$^+$ 290.1652, found 290.1659.

5-(2-(Dimethylamino)ethyl)dibenzo[*c*,*h*][1,5]naphthyridin-6(5*H*)-one (41):



Compound **41** was synthesised according to General PdCC[1] Procedure. The crude product (111 mg) was purified by flash column chromatography (9:1 EtOAc:MeOH, R_f = 0.2) to yield **41** (23 mg, 44%) as a beige oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.91 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.85 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 7.80 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 2H), 7.66 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 2H), 4.73 (t, *J* = 7.3 Hz, 2H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.33 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 164.3 (C), 148.0 (CH), 135.7 (C), 133.1 (CH), 132.3 (C), 130.2 (CH), 130.1 (C), 129.5 (C), 129.2 (CH), 128.9 (CH), 127.9 (CH), 127.5 (CH), 127.1 (C), 126.0 (C), 124.2 (CH), 124.1 (CH), 57.6 (CH_2), 48.8 (CH_2), 45.8 (CH_3). LCMS (ESI) *m/z* (%): *t* = 2.6 min, 318.2 (100, M + H$^+$). HPLC: PP gradient method, t_R = 4.9 min, 95.4 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{20}H_{20}N_3O^+$ [M + H]$^+$ 318.1601, found 318.1604.

3-(2-Bromophenyl)-4-iodoisoquinoline (42):

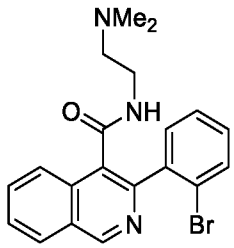


In a dry RBF, **37** (350 mg, 1.23 mmol) was dissolved in anhydrous DCE (6 mL), followed by addition of anhydrous $MgSO_4$ (443 mg, 3.68 mmol) and *tert*-butylamine (898 mg, 12.27 mmol, 1.29 mL). The reaction mixture was left to stir at 45 °C for 1 d. After heating, the reaction mixture was cooled down to rt, diluted with CH_2Cl_2 (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield **38b** (417 mg) as an orange oil. **38b** was unstable and used in situ in the next step. Rapid analysis of **38b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.14 – 8.09 (m, 1H), 7.64

(dd, J = 8.0, 1.3 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.42 – 7.36 (m, 2H), 7.32 (td, J = 7.6, 1.2 Hz, 1H), 7.21 (ddd, J = 8.1, 7.5, 1.7 Hz, 1H), 1.34 (s, 9H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 154.3 (CH), 138.2 (C), 133.5 (CH), 132.8 (CH), 132.6 (CH), 129.9 (CH), 129.8 (CH), 129.2 (CH), 127.3 (CH), 126.2 (CH), 125.5 (C), 125.4 (C), 123.6 (C), 93.1 (C), 91.5 (C), 30.1 (CH_3).

Oven-dried 4Å powdered molecular sieves was added to **38b** (265 mg, 779 µmol) and NaOAc (192 mg, 2.34 mmol) in a dry RBF, followed by addition of dry CH_2Cl_2 (15 mL) under N_2(g) atmosphere. A solution of ICl (253 mg, 1.56 mmol) and in dry CH_2Cl_2 (7.5 mL) was added slowly over 10 min to the stirred suspension, and reaction was left to stir at 0 °C for 4 h in the dark. The reaction mixture was filtered through Celite®. Washed with saturated $Na_2S_2O_3$ solution (2 x 30 mL), H_2O (2 x 30 mL) and brine (20 mL), the organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained (406 mg, brown oil) was purified by flash column chromatography (19:1 toluene:EtOAc, R_f = 0.2) to yield **42** (164 mg, 51% from **37**) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 0.7 Hz, 1H), 8.20 (dd, J = 8.5, 0.9 Hz, 1H), 8.00 (dt, J = 8.1, 1.0 Hz, 1H), 7.85 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.46 (td, J = 7.5, 1.2 Hz, 1H), 7.38 (dd, J = 7.6, 1.9 Hz, 1H), 7.33 (ddd, J = 8.0, 7.3, 1.8 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 157.0 (C), 152.2 (CH), 144.8 (C), 138.3 (C), 132.8 (CH), 132.5 (CH), 132.1 (CH), 130.9 (CH), 130.0 (CH), 128.6 (CH), 128.4 (C), 128.2 (CH), 127.5 (CH), 123.1 (C), 100.0 (C). LCMS (ESI) *m/z* (%): t = 5.6 min, 411.7 (100, M + H$^+$). HPLC: PP gradient method, t_R = 6.48 min, 82.6 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{10}BrIN^+$ [M + H]$^+$ 409.9036 and 411.9016, found 409.9043 and 411.9023. mp 164–166 °C.

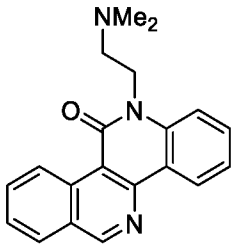
3-(2-Bromophenyl)-*N*-(2-(dimethylamino)ethyl)isoquinoline-4-carboxamide:



42 (75 mg, 183 µmol), $Pd(OAc)_2$ (4.1 mg, 18 µmol), PPh_3 (72 mg, 274 µmol), DMD (242 mg, 2.74 mmol, 0.30 mL), Et_3N (37 mg, 366 µmol, 33 µL) and dry NMP (1.8 mL) was added to a 10 mL dry RBF accordingly. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 90 °C for 47 h. After heating, the mixture was cooled down to rt, diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with H_2O (2 x 20 mL), and brine (2 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (138 mg) was purified by flash column chromatography (49:1 EtOAc:Et_3N, R_f = 0.15) to yield **3-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)isoquinoline-4-carboxamide** (53 mg, 73%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$ δ 9.34 (d, J = 0.9 Hz, 1H), 8.12 (dq, J = 8.5, 0.9 Hz, 1H), 8.05 (dt, J = 8.2, 1.1 Hz, 1H),

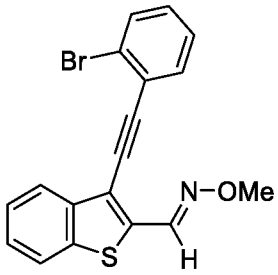
7.79 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.69 (dtd, J = 8.1, 3.5, 1.1 Hz, 2H), 7.46 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (td, J = 7.5, 1.2 Hz, 1H), 7.29 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H), 6.48 (br s, 1H), 3.37 (t, J = 7.0 Hz, 1H), 3.25 (br q, J = 5.3, 4.7 Hz, 2H), 2.36 (t, J = 8.1 Hz, 1H), 2.06 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 167.0 (C), 153.0 (CH), 149.3 (C), 140.7 (C), 133.5 (C), 132.9 (CH), 131.7 (CH), 131.3 (CH), 130.0 (CH), 128.1 (CH), 127.99 (C), 127.96 (CH), 127.62 (C), 127.59 (CH), 125.1 (CH), 123.2 (C), 57.1 (CH_2), 45.0 (CH_3), 37.1 (CH_2). LCMS (ESI) m/z (%): t = 2.0 min, 398.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 3.3 min, 79.2 % purity at 254 nm. HR-ESI (m/z) calcd for $C_{20}H_{21}BrN_3O^+$ [M + H]$^+$ 398.0863, found 398.0869.

12-(2-(Dimethylamino)ethyl)dibenzo[*c*,*h*][1,6]naphthyridin-11(12*H*)-one (43):



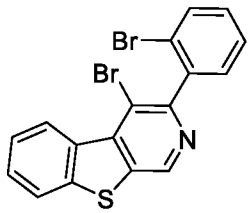
In a dry RBF, **3-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)isoquinoline-4-carboxamide** (34 mg, 85 µmol) was dissolved in *n*-butanol (0.8 mL) and K_3PO_4 (72 mg, 341 µmol), ethylene glycol (57 µL, 1.02 mmol), TMD(159 mg, 1.37 mmol, 0.2 mL), and CuI (6.5 mg, 34 µmol), were added accordingly. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 80 °C for 18 h. After heating, the reaction mixture was cooled down to rt, diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). Washed with H_2O (2 x 15 mL) and brine (2 x 15 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (29 mg) obtained was purified by flash column chromatography (19:1 EtOAc:MeOH, R_f = 0.1) to yield **43** (16.4 mg, 61%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (d, J = 9.0 Hz, 1H), 9.50 (d, J = 0.8 Hz, 1H), 9.09 (dd, J = 8.1, 1.6 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.94 (ddd, J = 8.6, 7.0, 1.5 Hz, 1H), 7.73 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.67 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.41 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 4.64 (br t, J = 7.9 Hz, 2H), 2.76 (br t, J = 7.9 Hz, 2H), 2.47 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 162.4 (C), 157.7 (CH), 147.7 (C), 138.1 (C), 134.5 (C), 132.9 (CH), 131.3 (CH), 128.7 (CH), 128.2 (C), 127.8 (CH), 127.3 (CH), 126.6 (CH), 122.6 (CH), 121.1 (C), 114.1 (CH), 113.2 (C), 56.1 (CH_2), 46.0 (CH_3), 41.3 (CH_2). LCMS (ESI) m/z (%): t = 2.3 min, 318.2 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.1 min, 95.8 % purity at 254 nm. HR-ESI (m/z) calcd for $C_{20}H_{20}N_3O^+$ [M + H]$^+$ 318.1601, found 318.1613.

3-((2-Bromophenyl)ethynyl)benzo[*b*]thiophene-2-carbaldehyde *O*-methyl oxime (46a):



O-Methylhydroxylamine hydrochloride (284 mg, 3.4 mmol) was slowly added to a stirred solution of **45** (232 mg, 680 µmol) in pyridine (3 mL) and EtOH (6 mL). The reaction mixture was left to stir at rt overnight. On completion, the reaction mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2 x 25 mL). Washed with H_2O (2 x 25 mL) and brine (2 x 25 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (500 mg) obtained was purified by flash column chromatography (10:1 hexanes: EtOAc, R_f = 0.45) to yield **46a** (247 mg, 99%) as a yellow solid. **46a** appears as a pair of E/Z isomers in ^{1}H NMR, ^{13}C NMR, LCMS and analytical HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.37 (s, 1H), 8.19 – 8.12 (m, 1H), 8.12 – 8.03 (m, 1H), 7.89 – 7.81 (m, 1H), 7.83 – 7.75 (m, 1H), 7.71 – 7.60 (m, 4H), 7.51 – 7.41 (m, 4H), 7.38 – 7.34 (m, 2H), 7.26 – 7.21 (m, 2H), 4.17 (s, 3H), 4.04 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 143.7 (CH), 141.2 (C), 140.2(CH), 139.32 (C), 139.29 (C), 138.5 (C), 137.7 (C), 133.7 (C), 133.54 (CH), 133.50 (CH), 132.8 (CH), 132.7 (CH), 130.04 (CH), 130.00 (CH), 127.4 (CH), 127.3(CH), 127.0 (CH), 126.8 (CH), 125.64 (C), 125.63 (C), 125.34 (CH), 125.30 (CH), 125.08 (C), 125.06 (C), 124.1 (CH), 123.7 (CH), 122.6 (CH), 122.4 (CH), 121.0 (C), 119.9 (C), 96.1 (C), 95.8 (C), 86.5 (C), 86.0 (C), 63.0 (CH_3), 62.8 (CH_3). LCMS (ESI) *m/z* (%): *t* = 7.8 min, 371.8 (40, M + H^+). HPLC: PP gradient method, t_R = 8.8 and 8.9 min, 95.1 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{18}H_{13}BrNOS^+$ $[M + H]^+$ 369.9896, found 369.9896.

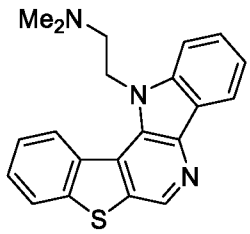
4-Bromo-3-(2-bromophenyl)benzo[4,5]thieno[2,3-*c*]pyridine (47):



$CuBr_2$ (205 mg, 918 µmol) was added slowly to a stirred solution **46a** (170 mg, 392 µmol) in DMA (3 mL) under N_2(g) atmosphere. The reaction was heated at 100 °C for 7 h. After heating, the mixture was quenched with saturated NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). Washed with H_2O (2 x 25 mL) and brine (2 x 25 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (163 mg) obtained was purified by flash column chromatography (100 % CH_2Cl_2, R_f = 0.4) to **47** (62 mg, 32%) as a brown foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (dd, *J* = 8.3, 1.3 Hz, 1H), 9.15 (s, 1H), 7.99 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.3,

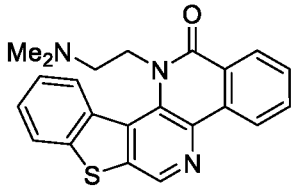
7.2, 1.2 Hz, 1H), 7.47 (ddd, *J* = 7.6, 7.2, 1.1 Hz, 1H), 7.42 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.34 (ddd, *J* = 8.1, 7.2, 2.0 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 154.4 (C), 142.7 (CH), 142.0 (C), 141.6 (C), 140.1 (C), 136.8 (C), 134.2 (C), 132.9 (CH), 130.9 (CH), 130.1 (CH), 129.5 (CH), 127.6 (CH), 127.1 (CH), 124.8 (CH), 123.4 (CH), 123.3 (C), 116.2 (C). LCMS (ESI) *m/z* (%): *t* = 4.3 min, 417.9 (50, M + H^+) and 419.9 (100, M + H^+). HPLC: PP gradient method, t_R = 7.6 min, 97.1 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{17}H_{10}Br_2NS^+$ $[M + H]^+$ 417.8895, found 417.8903.

2-(12*H*-Benzo[4',5']thieno[3',2':4,5]pyrido[3,2-*b*]indol-12-yl)-*N*,*N*-dimethylethan-1-amine (48):



Compound **48** was synthesised according to General UCC Procedure. The crude product (44 mg) obtained was purified by flash column chromatography (100% EtOAc, R_f = 0.2) to yield **48** (13 mg, 35%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.74 – 8.66 (m, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.67 – 7.55 (m, 4H), 7.41 (ddd, *J* = 7.9, 6.7, 1.3 Hz, 1H), 4.93 (br t, *J* = 7.9 Hz, 2H), 2.84 (br t, *J* = 7.9 Hz, 2H), 2.32 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 140.9 (C), 139.4 (C), 137.4 (CH), 134.1 (C), 133.1 (C), 131.1 (C), 127.6 (CH), 127.3 (CH), 126.6 (C), 126.2 (CH), 125.0 (CH), 123.9 (C), 123.8 (CH), 121.2 (CH), 120.5 (CH), 110.4 (CH), 58.4 (CH_2), 46.0 (CH_3), 45.9 (CH_2). LCMS (ESI) *m/z* (%): *t* = 2.6 min, 346.1 (60, M + H^+). HPLC: PP gradient method, t_R = 4.5 min, 94.2 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{21}H_{20}N_3S^+$ $[M + H]^+$ 346.1372, found 346.1379.

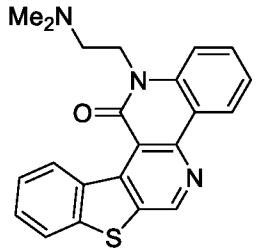
12-(2-(Dimethylamino)ethyl)benzo[*c*]benzo[4,5]thieno[2,3-*h*][1,5]naphthyridin-13(12*H*)-one (49):



Compound **49** was synthesised according to General PdCC[1] Procedure. The crude product (121 mg) was purified by two flash column chromatography (4:1 EtOAc:CH_2Cl_2, R_f = 0.25; 3:1 EtOAc:CH_2Cl_2, R_f = 0.2) to yield **49** (20 mg, 44%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.82 (dd, , *J* = 8.1, 1.1 Hz, 1H), 8.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.97 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.84 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.61 – 7.54 (m, 2H), 4.68 (br s, 2H), 2.25 (t, *J* = 6.5 Hz, 2H), 1.88 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (C), 141.1 (C), 139.3 (CH), 136. 8 (C), 135.4 (C), 135.1 (C), 133.3 (CH), 132.8 (C), 131.0 (C), 130.4 (C), 129.2 (CH), 128.4 (CH), 128.3 (CH), 127.0 (CH), 126.7 (C), 125.0 (CH), 123.8 (CH), 123.5

(CH), 57.2 (CH_2), 49.1 (CH_2), 45.3 (CH_3). LCMS (ESI) *m/z* (%): *t* = 3.9 min, 374.0 (100, M + H^+). HPLC: PP gradient method, t_R = 5.6 min, 95.5 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{22}H_{20}N_3OS^+$ $[M + H]^+$ 374.1322, found 374.1322.

13-(2-(Dimethylamino)ethyl)benzo[*h*]benzo[4,5]thieno[2,3-*c*][1,6]naphthyridin-12(13*H*)-one (51):

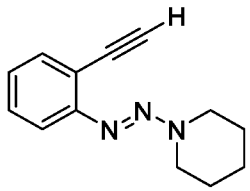


50[3] (42 mg, 90 µmol), $Pd(OAc)_2$ (2.0 mg, 9 µmol), PPh_3 (35 mg, 135 µmol), DMD (119 mg, 1.35 mmol, 0.15 mL), Et_3N (18 mg, 180 µmol, 16 µL) and dry NMP (1 mL) was added to a 10 mL dry RBF. The RBF was degassed and backfilled with CO(g) for three times, the reaction mixture was then heated at 90 °C for 28 h. On completion, the reaction mixture was cooled down to rt, diluted with H_2O (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (30 mL), H_2O (2 x 30 mL) and brine (2 x 30 mL). Dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, the crude product (85 mg) was purified by flash column chromatography (49:1 EtOAc:Et_3N, R_f = 0.15) to yield the **3-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzo[4,5]thieno [2,3-*c*]pyridine-4-carboxamide** (27 mg) as a cloudy white oil containing impurity but was directly used in the next step without further purification. LCMS (ESI) *m/z* (%): *t* = 2.3 min, 454.1 (100, M + H^+). HPLC: PP gradient method, t_R = 4.41 min, 81 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{22}H_{21}BrN_3OS^+$ $[M + H]^+$ 454.0583, found 454.0585.

In a dry RBF, **3-(2-bromophenyl)-*N*-(2-(dimethylamino)ethyl)benzo[4,5] thieno[2,3-*c*]pyridine-4-carboxamide** (20 mg, 44 µmol) was dissolved in *n*-butanol (0.4 mL) and K_3PO_4 (37 mg, 176 µmol), ethylene glycol (30 µL, 528 µmol, 12 equiv.), TMD (0.1 mL), and CuI (3.3 mg, 18 µmol), were added accordingly. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was then heated at 80 °C for 15 h. After heating, the reaction mixture was cooled down rt, diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with H_2O (2 x 30 mL) and brine (2 x 30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (32 mg) obtained was purified by flash column chromatography (19:1 EtOAc:MeOH, R_f = 0.2) to yield **51**(10 mg, 40% from **50**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 – 9.88 (m, 1H), 9.42 (s, 1H), 9.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.68 – 7.57 (m, 3H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.6 (br t, *J* = 7.8 Hz, 2H), 2.84 – 2.72 (br t, *J* = 7.8 Hz, 2H), 2.48 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 161.5 (C), 148.7 (CH), 148.1 (C), 142.3 (C), 141.0 (C), 137.7 (C), 136.7 (C), 134.6 (C), 132.1 (CH), 131.1 (CH), 129.1 (CH), 126.5 (CH), 124.8 (CH), 122.8 (CH), 121.5 (C), 117.6 (C), 114.1 (CH), 56.0

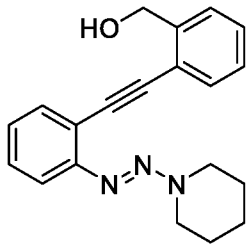
(CH_2), 46.0 (CH_3), 41.6 (CH_2). LCMS (ESI) *m/z* (%): *t* = 2.5 min, 374.1 (100, M + H^+). HPLC: PP gradient method, t_R = 5.8 min, 98.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{22}H_{20}N_3OS^+$ $[M + H]^+$ 374.1322, found 374.1336. mp 186–188 °C.

(*E*)-1-((2-Ethynylphenyl)diazenyl)piperidine (53):



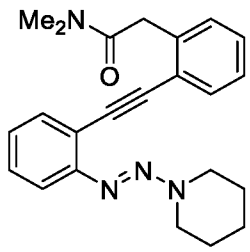
Compound **53** was synthesised according to General Procedure C from **(*E*)-1-((2-iodophenyl)diazenyl) piperidine**, the synthesis of which has been reported in our previous work.[51] Intermediate **1-((2-((trimethylsilyl)ethynyl)phenyl)diazenyl)piperidine** (2.3 g, quant.) was obtained as an orange oil after purified by flash column chromatography (49:1 hexanes:EtOAc, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddd, *J* = 0.4, 1.5, 7.6 Hz, 1H), 7.42 (dd, *J* = 0.8, 8.2 Hz, 1H), 7.25 (ddd, *J* = 1.5, 7.3, 8.2 Hz, 1H), 7.06 (dt, *J* = 1.2, 7.6 Hz, 1H), 3.85 (br s, 4H), 1.72 (br s, 6H), 0.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 133.0, 129.0, 124.9, 118.0, 116.7, 103.2, 98.2 24.3, 0.0. HR-ESI (*m/z*) calcd for $C_{16}H_{24}N_3Si^+$ $[M + H]^+$ 286.1734, found 286.1725. **53** (1.6 g, 90% from **52**) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.43 (dd, *J* = 0.8, 8.2 Hz, 1H), 7.29 (ddd, *J* = 1.5, 7.4, 8.2 Hz, 1H), 7.08 (dt, *J* = 1.2, 7.5 Hz, 1H), 3.84 (br s, 4H), 3.27 (s, 1H), 1.72 (br s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 133.6, 129.4, 125.0, 117.1, 116.9, 81.9, 81.0, 24.4.). LCMS (ESI) *m/z*: 214.2 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{13}H_{16}N_3^+$ $[M + H]^+$ 214.1339, found 214.1337.

(*E*)-(2-((2-(Piperidin-1-yldiazenyl)phenyl)ethynyl)phenyl)methanol (55a):



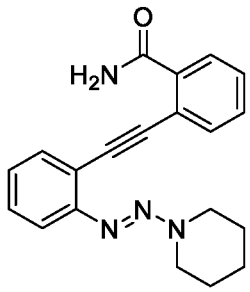
Compound **55a** was synthesised according to General Procedure B. The crude product obtained was purified by flash column chromatography (2:1 hexanes:EtOAc, R_f = 0.45) to yield **55a** (789 mg, 96%) as a pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.56 (m, 2H), 7.48 (dd, *J* = 0.8, 8.2 Hz, 1H), 7.36 – 7.39 (m, 1H), 7.28 – 7.33 (m, 3H), 7.13 (dt, *J* = 1.2, 7.6 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 2H), 3.88 (brs, 2H), 3.12 (t, *J* = 7.0 Hz, 1H), 1.72 (br s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 143.0, 132.9, 131.9, 129.3, 128.3, 127.6, 127.5, 125.1, 122.3, 117.5, 117.3, 93.0, 91.1, 64.5, 25.4, 24.2. LCMS (ESI) *m/z*: 320.1 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{20}H_{22}N_3O$ $[M + H]^+$ 320.1757, found 320.1757.

(*E*)-*N*,*N*-Dimethyl-2-(2-((2-(piperidin-1-yldiazenyl)phenyl)ethynyl)phenyl)acetamide (55b):



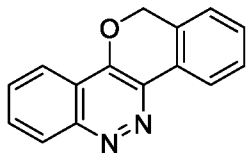
Compound **55b** was synthesised according to General Procedure B. The crude product obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) to yield **55b** (464 mg, 62%) as a brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.30 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.09 (s, 2H), 3.85 (br s, 4H), 2.95 (s, 3H), 2.94 (s, 3H), 1.71 (br s, 6H). HR-ESI (*m/z*) calcd for $C_{23}H_{26}N_4ONa^+$ [M + Na]$^+$ 397.1999, found 397.1980.

(*E*)-2-((2-(Piperidin-1-yldiazenyl)phenyl)ethynyl)benzamide (55c):



Compound **55c** was synthesised according to General Procedure B. The crude product obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) to yield **55c** (1.03 g, 42%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.25 (m, 1H), 7.62 (m, 1H), 7.55 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.42 – 7.50 (m, 3H), 7.34 (ddd, *J* = 1.5, 7.3, 8.2 Hz, 1H), 7.15 (dt, *J* = 1.2, 7.6 Hz, 1H), 5.85 (br s, 1H), 3.84 (br s, 4H), 1.72 (br s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 152.4, 133.43, 133.38, 132.8, 131.1, 130.9, 130.0, 128.5, 125.3, 120.9, 117.3, 116.8, 95.1, 92.0, 24.2. HR-ESI (*m/z*) calcd for $C_{20}H_{21}N_4O^+$ [M + H]$^+$ 333.1710, found 333.1711.

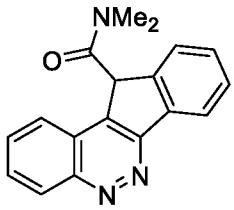
12*H*-Isochromeno[4,3-*c*]cinnoline (56a):



55a (350 mg, 1.09 mmol) was dissolved in CH_2Cl_2 (10 mL), followed by addition of HCl (2.74 mL, 1 M in Et_2O) solution. The reaction mixture was left to stir at rt for 1 h. On completion, the reaction was quenched by saturated $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The

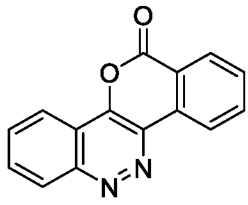
combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (4:1 hexanes:EtOAc, , R_f = 0.25) to yield **56a** (226 mg, 88%) as a pale orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 5.2 Hz, 1H), 8.42 (d, J = 5.7 Hz, 1H), 8.12 (d, J = 5.6 Hz, 1H), 7.76 (t, J = 5.5 Hz, 1H), 7.66 (t, J = 5.3 Hz, 1H), 7.51 (t, J = 5.0 Hz, 1H), 7.41 (t, J = 5.0 Hz, 1H), 7.17 (d, J = 5.0 Hz, 1H), 5.52 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 148.0, 137.5, 130.4, 129.9, 129.61, 129.57, 129.4, 129.2, 128.5, 124.2, 123.0, 120.8, 117.9, 69.1. LCMS (ESI) *m/z*: 235.1 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{15}H_{11}N_2O^+$ $[M + H]^+$ 235.0866, found 235.0851. mp 165–167 °C.

***N,N*-Dimethyl-11*H*-indeno[1,2-*c*]cinnoline-11-carboxamide (56b):**



55b (374 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C, followed by addition of $MeSO_3H$ (5 mmol). The reaction mixture was left to stir at rt for 72 h. On completion, the mixture was quenched by saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (3:1 hexanes:EtOAc) to yield **56b** (234 mg, 81%) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.52 (d, J = 8.5 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.76 – 7.79 (m, 2H), 7.68 – 7.74 (m, 2H), 7.50 (dd, J = 7.2, 8.2 Hz, 1H), 7.37 (s, 1H), 3.16 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.3, 149.6, 146.4, 132.6, 129.5, 129.2, 128.2, 127.4, 125.84, 125.79, 125.5, 125.4, 124.5, 111.4, 43.4. HR-ESI (*m/z*) calcd for $C_{18}H_{15}N_3ONa^+$ $[M + Na]^+$ 312.1107, found 312.1094.

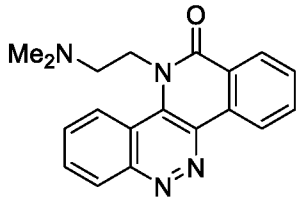
Isoquinolino[4,3-*c*]cinnolin-12(11*H*)-one (56c):



55c (900 mg, 2.71 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C, followed by addition of $MeSO_3H$ (906 mg, 9.22 mmol). The reaction mixture was allowed to warm to rt and left to stir for 72 h. After this time, saturated $NaHCO_3$ solution (15 mL) was added, followed by another 0.5 h stirring and extraction with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to afford the title compound as a bright yellow solid (524 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.53 (m, 1H), 8.32 – 8.34 (m, 1H), 8.25 – 8.28 (m, 1H),

7.85 – 7.94 (m, 3H), 7.43 – 7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 157.8, 151.3, 135.5, 134.5, 133.6, 131.5, 130.7, 130.4, 129.9, 128.6, 127.2, 123.8, 122.2, 120.6. LCMS (ESI) *m/z*: 249.1 [M + H]$^+$. HR-ESI (*m/z*) calcd for $C_{15}H_9N_2O_2^+$ [M + H]$^+$ 249.0659, found 249.0660. mp 273–274 °C.

11-(2-(Dimethylamino)ethyl)isoquinolino[4,3-*c*]cinnolin-12(11*H*)-one (56d):

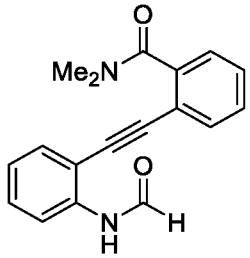


Compound **55d** was synthesised according to General Procedure B. The crude product obtained was purified by flash column chromatography (19:1 hexanes:EtOAc → 9:1 hexanes:EtOAc) to yield **55d** (1.08 g, 91%) which was directly used in the next step without characterisation.

55d (235 mg, 680 μmol) and tetraethylammonium chloride (224 mg, 1.35 mmol) were dissolved in CH_2Cl_2 (5 mL) at rt, followed by addition of $MeSO_3H$ (1 M in CH_2Cl_2, 2.03 mL). The reaction mixture was left to stir at rt for 2 h, then quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **57**.

57 (100 mg, 0.33 mmol) was dissolved in CH_3CN (2 mL), followed by addition of DMD (148 mg, 1.67 mmol). The reaction mixture was heated at 120 °C in the microwave for 1 h. After heating, the mixture was cooled down to rt, concentrated and purified by flash column chromatography (9:1 $CHCl_3$:MeOH, R_f = 0.25) to yield **56d** (101 mg, 95% from **55d**) as a beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 0.6, 8.2 Hz, 1H), 8.56 – 8.62 (m, 2H), 8.42 (ddd, *J* = 0.5, 1.3, 8.0 Hz, 1H), 7.76 – 7.91 (m, 3H), 7.69 (ddd, *J* = 1.2, 7.2, 8.1 Hz, 1H), 4.68 (t, *J* = 7.2 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.1, 133.6, 131.2, 130.4, 129.92, 129.88, 127.8, 123.9, 123.6, 115.8, 57.2, 47.4, 45.9. LCMS (ESI) *m/z*: 319.1 [M + H]$^+$. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_4O^+$ [M + H]$^+$ 319.1553, found 319.1556. mp 179–183 °C. The spectroscopic data are consistent with those previously reported in the literature.

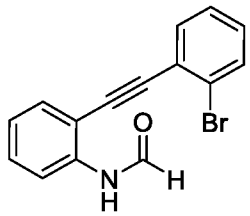
2-((2-Formamidophenyl)ethynyl)-*N*,*N*-dimethylbenzamide (60a):



Compound **60a** was synthesised according to General Procedure A. The crude product (466 mg, brown oil) obtained was purified by flash column chromatography (10:1 CH_2Cl_2:EtOAc, R_f = 0.2) to

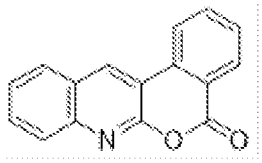
yield **60a** (337 mg, 67%) an orange oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.62 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.46 – 7.34 (m, 4H), 7.37 – 7.27 (m, 2H), 7.06 (td, *J* = 7.6, 1.2 Hz, 1H), 3.13 (s, 3H), 2.92 (s, 3H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 171.1 (C), 160.7 (CH), 140.3 (C), 138.4 (C), 132.2 (CH), 131.1 (CH), 130.1 (CH), 129.5 (CH), 128.4 (CH), 126.3 (CH), 123.4 (CH), 120.9 (C) 119.9 (CH), 111.4 (C), 93.9 (C), 89.2 (C), 39.4 (CH_3), 35.4 (CH_3). LCMS (ESI) *m/z* (%): *t* = 2.8 min, 293.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.0 min, 97.8 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{18}H_{17}N_2O_2^+$ [M + H]$^+$ 293.1285, found 293.1294.

***N*-(2-((2-Bromophenyl)ethynyl)phenyl)formamide (60b):**



Compound **60b** was synthesised according to General Procedure A. The crude product (1.86 g) obtained was purified by flash column chromatography twice (4:1 hexanes:EtOAc, R_f = 0.2; 1:1 hexanes:CH_2Cl_2) to yield **60b** (711 mg, 66%) as a grey amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 11.2 Hz, 1H), 8.51 (d, *J* = 1.7 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.43 (br s, 1H), 8.32 (br s, 1H), 7.66-7.63 (m, 2H), 7.61-7.56 (app td, *J* = 8.4, 1.6 Hz, 3H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.41-7.27 (m, 5H), 7.26-7.20 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.12 (td, *J* = 7.6, 1.1 Hz, 1H). This compound appears as a pair of rotamers (ratio = 0.36 : 1) in the ^{1}H NMR spectrum. LCMS (ESI) *m/z* (%): *t* = 3.6 min, 299.8 (60, M + H$^+$), 301.8 (50, M + H$^+$). HPLC: PP gradient method, t_R = 6.9 min, 97.9 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{11}BrNO^+$ [M + H]$^+$ 300.0019, found 300.0008.

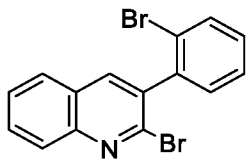
5*H*-Isochromeno[3,4-*b*]quinolin-5-one (67):



60a (100 mg, 342 µmol) was dissolved in dry CH_2Cl_2 (5 mL) in a dry RBF. The RBF was degassed and backfilled with N_2(g) for three times. Burgess reagent (122.3 mg, 513 µmol) was added under N_2(g) atmosphere, the reaction mixture was left to stir at rt for 22 h. After this time, the reaction was heated at reflux for 3 h, then cooled down to rt and diluted with CH_2Cl_2 (20 mL). Washed with H_2O (2 x 20 mL), the organic extract was dried over $MgSO_4$, filtered concentrated to about 5 mL in volume. **61a** obtained in the organic phase was directly used without isolation as *o*-alkynylaryl isocyanides are usually quite unstable.

$MeSO_3H$ (32.9 mg, 0.22 mL, 342 μmol) was added slowly to a stirred solution of **61a** in CH_2Cl_2 (5 mL) under N_2(g) atmosphere. The reaction mixture was left to stir at rt for 14 h. On completion, the reaction mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (brown oil) was purified by flash column chromatography (7:3 hexanes:EtOAc) to yield **63** (18 mg, 21% from **60a**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.44 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.89 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 7.58 (ddd, *J* = 7.9, 6.8, 0.9 Hz, 1H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 160.6 (C), 155.0 (C), 146.8 (C), 135.3 (CH), 133.5 (C), 132.9 (CH), 131.6 (CH), 131.2 (CH), 130.0 (CH), 128.6 (CH), 128.1 (CH), 126.7 (CH), 126.6 (C), 122.3 (CH), 121.8 (C), 113.9 (C). LCMS (ESI) m/z (%): *t* = 3.6 min, 248.1 (100, M + H$^+$). HPLC: PP gradient method, t_R = 5.0 min, 96.1% purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{16}H_{10}NO_2^+$ [M + H]$^+$ 248.0706, found 248.0705. The spectroscopic data are consistent with those previously reported in the literature.

2-Bromo-3-(2-bromophenyl)quinoline (69):

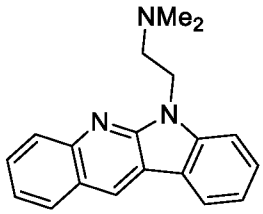


60b (200 mg, 0.67 mmol) and DIPEA (0.75 mL, 5.33 mmol,) were dissolved in CH_2Cl_2 (4.5 mL), followed by dropwise addition of $POCl_3$ (96 μL) under N_2(g) atmosphere at –78 °C. The reaction mixture was left to stir at 0 °C for 2 h. On completion, reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$(aq) solution (2 x 15 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated to about 5 mL in volume. **61b** obtained in the organic phase was directly used without isolation as *o*-alkynylaryl isocyanides are usually quite unstable.[53]

TBAB (644 mg, 2.00 mmol) was added slowly to a stirred solution of **61b** in CH_2Cl_2 (12 mL) under N_2(g) atmosphere. The reaction mixture was left to stir at rt for 17 h. On completion, the reaction mixture was concentrated under reduced pressure, diluted with H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with H_2O (2 x 75 mL) and brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (415 mg) was purified by flash column chromatography (2:1 CH_2Cl_2:hexanes, R_f= 0.4) to yield **69** (173 mg, 72% from **60b**) as an off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 1H), 8.02 (s, 1H), 7.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.78 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.44 (ddd, *J* = 7.5, 7.0, 1.4 Hz, 1H), 7.36-7.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (C), 143.0 (C), 140.0 (C), 138.4 (CH), 136.5 (C), 132.9 (CH), 131.4 (CH), 130.8 (CH), 130.2 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.0 (C), 124.1

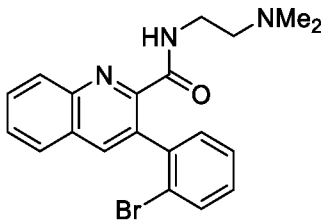
(C). LCMS (ESI) *m/z* (%): *t* = 3.7 min, 363.8 (100, M + H^+), 365.8 (50, M + H^+). HPLC: PP gradient method, t_R = 7.3 min, 90.4 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{15}H_{10}Br_2N^+$ [M + H]$^+$ 363.9155; found 363.9167.

2-(6*H*-Indolo[2,3-*b*]quinolin-6-yl)-*N*,*N*-dimethylethan-1-amine (70):



Compound **70** was synthesised according to General UCC Procedure.. The crude product (76 mg) obtained was purified by flash column chromatography (4:1 EtOAc:MeOH, R_f = 0.33) to yield **70** (31 mg, 52%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.61-7.52 (m, 2H), 7.46 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 4.72 (t, *J* = 7.2 Hz, 2H), 2.94 (app br s, 2H), 2.47 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 152.6 (C), 147.0 (C), 142.3 (C), 128.9 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 124.4 (C), 123.1 (CH), 121.7 (CH), 120.8 (C), 120.1 (CH), 118.3 (CH), 109.1 (C), 57.2 (CH_2), 45.9 (CH_3), 39.9 (CH_2). LCMS (ESI) *m/z* (%): *t* = 3.0 min, 290.1 (100, M + H^+), 291.1 (20, M + H^+). HPLC: PP gradient method, t_R = 5.3 min, 96.6 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{19}H_{19}N_3^+$ [M + H]$^+$ 290.1652, found 290.1656.

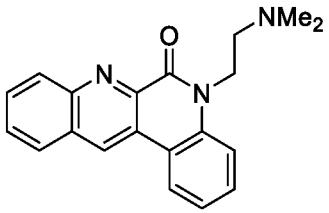
3-(2-Bromophenyl)-*N*-(2-(dimethylamino)ethyl)quinoline-2-carboxamide:



68 (99 mg, 0.27 mmol), $Pd(OAc)_2$ (6.1 mg, 27 μmmol), PPh_3 (107 mg, 0.41 mmol), DMD (0.45 mL, 4.1 mmol), Et_3N (50 μL, 0.55 mmol) and dry NMP (2 mL) were added to a 25 mL dry RBF. The RBF was degassed and backfilled with CO(g) for three times, and then heated at 80 °C for 40 h. On completion, the reaction mixture was cooled down to rt and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), saturated NH_4Cl solution (2 x 50 mL), and brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (182 mg) obtained was purified by flash column chromatography (100 % EtOAc, R_f = 0 → 2:1 EtOAc:MeOH, R_f = 0.4). The title compound (63 mg, 58%) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.67-7.63 (m, 2H), 7.42 (td, *J* = 7.5, 1.2 Hz, 1H), 7.36

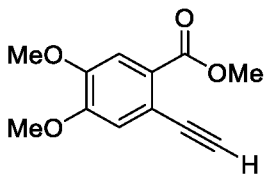
(dd, J = 7.6, 1.9 Hz, 1H), 7.29 – 7.23 (m, 1H), 3.59-3.51 (m, 2H), 2.60 (t, J = 6.1 Hz, 2H), 2.34 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 164.9 (C), 148.8 (C), 146.0 (C), 141.3 (C), 139.2, 134.2 (C), 132.2 (CH), 130.4 (CH), 130.1 (CH), 129.8 (CH), 129.0 (CH), 128.6 (C), 128.4 (CH), 127.7 (CH), 127.3 (CH), 123.5 (C), 58.4 (CH_2), 45.5 (CH_3), 37.3 (CH_2). LCMS (ESI) *m/z* (%): t = 3.2 min, 399.9 (100, M + H^+), 400.9 (20, M + H^+). HPLC: PP gradient method, t_R = 5.3 min, 92.5 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{20}H_{21}BrN_3O^+$ [M + H]$^+$ 398.0863, found 398.0871.

5-(2-(Dimethylamino)ethyl)dibenzo[*b,f*][1,7]naphthyridin-6(5*H*)-one (71):



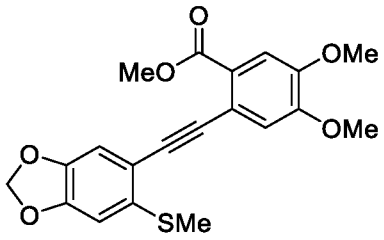
3-(2-Bromophenyl)-*N*-(2-(dimethylamino)ethyl)quinoline-2-carboxamide (34 mg, 85 µmol) was dissolved in *n*-butanol (0.85 mL) in a dry RBF, and CuI (6.5 mg, 34 µmol), K_3PO_4 (72 mg, 0.34 mmol), ethylene glycol (57 µL, 1.02 mmol), and TMD(30 µL, 0.17 mmol) were added sequentially. The RBF was degassed and backfilled with N_2(g) for three times, the reaction mixture was heated at 80 °C for 22 h. After heating, the reaction mixture was cooled down to rt, diluted with H_2O (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (29 mg) obtained was purified by flash column chromatography (100 % EtOAc → 100 % MeOH, R_f = 0.5) to yield **69** (15 mg, 56%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.37 (dd, J = 8.0, 1.4 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.80 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.67 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.58 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 4.60 (app t, J = 7.6 Hz, 2H), 2.75 (app t, J = 7.8 Hz, 2H), 2.42 (s, 6H). ^{13}C DEPT-Q NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 148.6 (C), 142.0 (C), 136.9 (C), 131.2 (CH), 130.7 (CH), 130.4 (CH), 130.2 (CH), 129.3 (C), 128.8 (CH), 127.8 (CH), 126.5 (C), 123.9 (CH), 123.0 (CH), 118.5 (C), 115.4 (CH), 56.1 (CH_2), 46.1 (CH_3), 41.7 (CH_2). LCMS (ESI) *m/z* (%): t = 3.1 min, 318.0 (100, M + H^+), 319.0 (20, M + H^+). HPLC: PP gradient method, t_R = 4.7 min, 94.6 % purity at 254 nm. HR-ESI (*m/z*) calcd for $C_{20}H_{20}N_3O^+$ [M + H]$^+$ 318.1601, found 318.1610.

Methyl 2-ethynyl-4,5-dimethoxybenzoate (73):



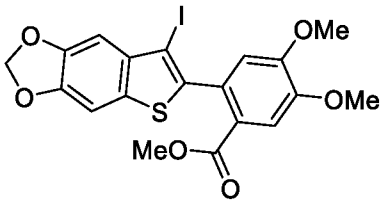
Compound **73** was synthesised according to General Procedure C. **73** (1.05 g, 93%) was obtained as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.00 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 151.5, 148.9, 125.1, 116.6, 116.3, 112.6, 82.3, 80.9, 56.1, 56.0, 52.0. LCMS (ESI) *m/z* : 221.1 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{12}H_{13}O_4^+$ $[M + H]^+$ 221.0808, found 221.0808.

Methyl 4,5-dimethoxy-2-((6-(methylthio)benzo[*d*][1,3]dioxol-5-yl)ethynyl)benzoate (74):



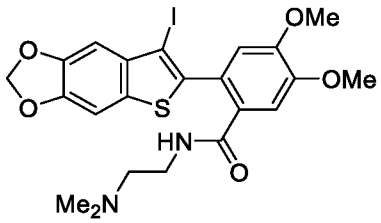
72 (250 mg, 850 µmol) was dissolved in Et_3N (2 mL) and DMF (2 mL) in a dry RBF, followed by addition of $Pd(PPh_3)_2Cl_2$ (18 mg, 26 µmol) and CuI (13 mg, 68 µmol). The RBF was then degassed and backfilled with N_2(g) for three times. Finally, **73** (225 mg, 1.02 mmol) was slowly added under N_2(g) atmosphere over a period of 2 h. The reaction was left to stir at rt for 16 h. On completion, the reaction mixture was filtered through Celite®, washed with EtOAc (40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (4:1 hexanes:EtOAc) to yield **74** (291 mg, 89%) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.10 (s, 1H), 7.01 (s, 1H), 6.75 (s, 1H), 5.98 (s, 2H), 3.95 (s, 3H), 3.94 (s, 6H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 139.1, 128.7, 127.0, 117.6, 96.7, 52.6, 45.6, 24.4. LCMS (ESI) *m/z*: 387.0 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{20}H_{19}O_6S^+$ $[M + H]^+$ 387.0897, found 387.0901. mp 184.2 – 184.9 °C.

Methyl 2-(7-iodothieno[2',3':4,5]benzo[1,2-*d*][1,3]dioxol-6-yl)-4,5-dimethoxybenzoate (75):



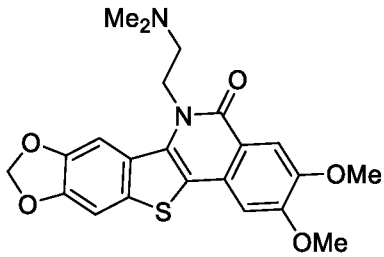
Compound **75** was synthesised according to General Procedure D. The crude product obtained was purified by flash column chromatography (3:1 hexanes:EtOAc) to yield **75** (414 mg, 94%) as a pale brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.18 (s, 1H), 7.16 (s, 1H), 6.04 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.3, 149.0, 147.5, 147.3, 140.6, 135.9, 132.6, 129.6, 123.6, 114.8, 113.0, 105.0, 101.6, 101.2, 81.4, 56.22, 56.16, 52.2. LCMS (ESI) *m/z*: 498.9 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{19}H_{16}O_6SI^+$ $[M + H]^+$ 498.9707, found 498.9699.

***N*-(2-(Dimethylamino)ethyl)-2-(7-iodothieno[2',3':4,5]benzo[1,2-*d*][1,3]dioxol-6-yl)-4,5-dimethoxybenzamide (76):**



75 (200 mg, 0.40 mmol) was dissolved in DMSO (8 mL), followed by addition of KOH (2 M, 4 mL). The reaction mixture was left to stir at rt for 16 h. After stirring, the solution was acidified to pH 3 (using 1M HCl) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the carboxylic acid. The acid was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C, followed by addition of DMF (2 drops) and oxalyl chloride (102 mg, 0.80 mmol). The solution was left to stir at rt for 3 h. After this time the reaction mixture was concentrated under reduced pressure, then redissolved in dry CH_2Cl_2 (10 mL) followed by addition of *N,N*-dimethylethylenediamine (106 mg, 1.2 mmol). The reaction mixture was left to stir at rt for 2 h. On completion, the mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford **76** as a pale brown amorphous solid (205 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 6.77 (s, 1H), 6.29 (br s, 1H), 6.04 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.15 – 3.19 (m, 2H), 1.98 (t, *J* = 5.9 Hz, 2H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 148.9, 148.5, 146.7, 146.7, 138.3, 135.2, 132.3, 128.0, 127.2, 123.9, 113.3, 111.3, 104.1, 100.7, 100.2, 82.1, 55.6, 55.2, 55.1, 43.4, 36.3. LCMS (ESI) *m/z*: 555.1 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{22}H_{24}N_2O_5SI^+$ $[M + H]^+$ 555.0445, found 555.0448.

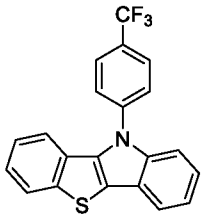
6-(2-(Dimethylamino)ethyl)-2,3-dimethoxy-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5] thieno[3,2-*c*]isoquinolin-5(6*H*)-one (77):



A sealed tube containing **76** (200 mg, 360 µmol), $Pd_2(dba)_3$ (8 mg, 8.7 µmol), Xantphos (10 mg, 17 µmol) and Cs_2CO_3 (353 mg, 1.1 mmol) in 1,4-dioxane (3 mL) was heated to 120 °C for 16 h. After heating, the reaction mixture was cooled to rt, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (1:9 MeOH:$CHCl_3$) to yield **77** as a pale brown solid (78 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.75 (s, 1H), 7.17 (s, 1H), 6.85

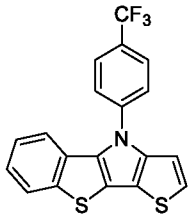
(s, 1H), 6.07 (s, 2H), 4.47 (t, J = 8.0 Hz, 2H), 4.03 (s, 3H), 4.00 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 2.42 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 153.7, 149.3, 147.6, 147.0, 132.1, 132.0, 127.7, 124.8, 117.1, 116.3, 108.9, 102.8, 102.6, 102.4, 101.9, 57.1, 56.23, 56.17, 45.9, 43.2. LCMS (ESI) *m/z*: 427.0 $[M + H]^+$. HR-ESI (*m/z*) calcd for $C_{22}H_{23}N_2O_5S^+$ $[M + H]^+$ 427.1322, found 427.1328. mp 263.8 – 266.9 °C.

10-(4-(Trifluoromethyl)phenyl)-10H-benzo[4,5]thieno[3,2-b]indole (78)



To a dry RBF, 2-(2-bromophenyl)-3-iodobenzo[*b*]thiophene (100 mg, 0.241 mmol) was added along with caesium carbonate (314 mg, 0.964 mmol), Pd_2dba_3 (44.1 mg, 0.0482 mmol), and Xantphos (55.8 mg, 0.0964 mmol) under nitrogen, and subsequently dissolved in anhydrous toluene or dioxane (8 mL). Following addition of 4-trifluoromethylaniline (0.0432 mL, 0.344 mmol), the vessel was degassed and backfilled with N_2(g) three times before being stirred at reflux for 40 h. Upon completion, the reaction mixture was extracted with DCM (3 x 20 mL) and filtered through Celite ® before being washed with water (3 x 20 mL) and brine (2 x 20 mL). The organic layer was collected, dried over $MgSO_4$, and concentrated under vacuum. The crude material was then purified via column chromatography (95% PET spirits / 5% DCM, R_f = 0.30) to yield the desired compound (51.2 mg, 58%) as a powdery white solid. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 3H), 7.88 – 7.83 (m, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.45 – 7.39 (m, 1H), 7.38 – 7.27 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.34, 142.28, 141.30, 136.98, 130.14 (q, J = 32.9 Hz), 127.81, 127.09 (q, J = 3.7 Hz), 126.63, 124.66, 124.39, 124.27, 124.08, 124.045 (q, J = 1,080 Hz), 122.65, 121.25, 120.53, 119.74, 118.36, 110.83. LCMS (APCI) *m/z*: 367.1 $[M^+]$.

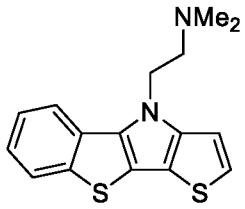
4-(4-(Trifluoromethyl)phenyl)-4H-benzo[4,5]thieno[3,2-b]thieno[2,3-d]pyrrole (79)



To a dry microwave tube, 2-(3-bromothiophen-2-yl)-3-iodobenzo[b]thiophene (100 mg, 0.237 mmol) was added along with caesium carbonate (232 mg, 0.712 mmol), Pd_2dba_3 (21.8 mg, 0.0238 mmol), and Xantphos (27.5 mg, 0.0475 mmol) under nitrogen, and subsequently dissolved in anhydrous

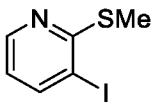
1,4-dioxane (1.19 mL). Following addition of 4-trifluoromethylaniline (0.0257 mL, 0.356 mmol), the vessel was degassed and backfilled with N_2(g) three times before being stirred in the microwave at 140 degrees Celsius for 3 h (200 W). Upon completion, the reaction mixture was extracted with EtOAc (3 x 30 mL) and filtered through Celite ® before being washed with water (3 x 20 mL) and brine (2 x 20 mL). The organic layer was collected, dried over $MgSO_4$, and concentrated under vacuum. The crude material was then purified via column chromatography (95% PET spirits/ 5% DCM, R_f = 0.30) to yield the desired compound (62.4 mg, 70%) as a powdery white solid. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 3H), 7.78 – 7.64 (m, 2H), 7.43 – 7.35 (m, 1H), 7.30 – 7.15 (m, 3H), 7.01 (d, *J* = 5.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.41, 141.82, 141.32, 135.80, 129.20 (qd, *J* = 33.0, 0.0 Hz), 126.99, 126.75 (q, *J* = 3.8 Hz), 125.35, 125.03, 124.19, 123.97, 123.71 (q, *J* = 272.1 Hz), 123.21, 119.28, 117.49, 117.20, 111.37. LCMS (APCI) *m/z*: 374.1 [M+H$^+$].

2-(4H-Benzo[4,5]thieno[3,2-b]thieno[2,3-d]pyrrol-4-yl)-N,N-dimethylethan-1-amine (80)



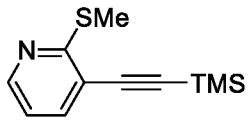
To a dry microwave tube, 2-(3-bromothiophen-2-yl)-3-iodobenzo[b]thiophene (100 mg, 0.237 mmol) was added along with caesium carbonate (232 mg, 0.712 mmol), Pd_2dba_3 (21.8 mg, 0.0238 mmol), and Xantphos (27.5 mg, 0.0475 mmol) under nitrogen, and subsequently dissolved in anhydrous 1,4-dioxane (1.19 mL). Following addition of N,N-dimethylethylenediamine (0.0383 mL, 0.356 mmol), the vessel was degassed and backfilled with N_2(g) three times before being stirred in the microwave at 140 degrees Celsius for 3 h (200 W). Upon completion, the reaction mixture was extracted with EtOAc (3 x 30 mL) and filtered through Celite ® before being washed with water (3 x 20 mL) and brine (2 x 20 mL). The organic layer was collected, dried over $MgSO_4$, and concentrated under vacuum. The crude material was then purified via column chromatography (95% EtOAc/ 5% Et_3N/ 1% MeOH, R_f = 0.25) to yield the desired compound (33.60 mg, 47%) as an amber wax. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.88 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.85 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.28 (td, *J* = 7.6, 1.1 Hz, 2H), 7.21 (d, *J* = 5.3 Hz, 1H), 7.08 (d, *J* = 5.3 Hz, 1H), 4.61 (a pp. t, *J* = 7.6 Hz, 2H), 2.81 (app. t, *J* = 7.8 Hz, 2H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.80, 141.54, 136.79, 127.69, 124.58, 124.53, 124.33, 122.98, 118.64, 115.52, 114.64, 110.83, 59.48, 46.25, 46.10.

3-Iodo-2-(methylthio)pyridine (82):



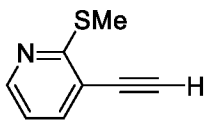
In a dry RBF, 2-fluoro-3-iodopyridine (3.57 g, 16.0 mmol) was dissolved in DMF to form a 0.2 M solution (80 mL), proceeded by addition of three equivalents of NaSMe (3.36 g, 48.0 mmol). The solution was degassed and backfilled with N_2(g) three times and stirred at 30 degrees Celsius for 1 h. Upon completion, the product was extracted with 120 mL of EtOAc, and washed with water (3 x 80 mL) and brine (2 x 80 mL). The organic layer was collected, dried over $MgSO_4$, and concentrated under vacuum to yield the crude product (3.20 g, 80 %) as a pale-yellow crystal. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.73 (dd, *J* = 7.7, 4.7 Hz, 1H), 2.53 (s, 3H). LCMS (APCI) *m/z*: 252.0 [M+H$^+$]. Data in accordance with that previously reported.

2-(Methylthio)-3-((trimethylsilyl)ethynyl)pyridine (83):



In a dry RBF under N_2(g) atmosphere, 3-iodo-2-(methylthio)pyridine (3.00 g, 12.0 mmol) was added and dissolved in DIPA to make a 0.2 M solution (60 mL). The vessel was placed in an ice bath and subsequently purged and backfilled with N_2(g) three times. $Pd_2(PPh_3)_2Cl_2$ (168 mg, 0.239 mmol) and CuI (137 mg, 0.717 mmol) were then added to the mixture before the vessel was again purged and backfilled with N_2(g) three times. The flask was then taken out of the ice bath and stirred at room temperature; TMS-acetylene (2.35 g, 23.9 mmol) was slowly added to the flask over 1h, and the reaction mixture was allowed to stir overnight. The resulting solution was extracted with Et_2O (2 x 50 mL) and filtered through Celite® before being washed with water (3 x 30 mL) and brine (2 x 30 mL); the organic layer was subsequently dried over $MgSO_4$ and concentrated to give the desired compound (2.23 g, 84%) as a dark brown oil. The crude mixture was used in subsequent reactions without further purification. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.92 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.56 (s, 3H), 0.29 (s, 9H). LCMS (APCI) *m/z*: 222.2 [M+H$^+$]. Data in accordance with that previously reported.

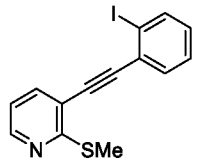
3-Ethynyl-2-(methylthio)pyridine



In a clean RBF, 2-(methylthio)-3-((trimethylsilyl)ethynyl)pyridine (2.03 g, 9.18 mmol) was dissolved in a 1:1 solution of MeOH/Et_2O to a concentration of 0.2 M. K_2CO_3 (2.54 g, 18.36 mmol) was then added, with the resulting mixture stirred at room temperature overnight. Upon completion the reaction mixture was concentrated under vacuum, extracted three times with 50 mL of Et_2O and filtered through Celite. The extract was washed with water (3 x 30 mL) and brine (2 x 30 mL), with the aqueous

layer collected and dried over $MgSO_4$, before being filtered and concentrated under vacuum to give the final product (1.33 g, 97%) as a dark brown oil. The product was used in subsequent reactions without further purification. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.62 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.96 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.58 (s, 1H), 2.58 (s, 4H). LCMS (APCI) *m/z*: 150.1 [M+H$^+$]. Data in accordance with that previously reported.

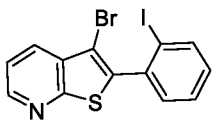
3-((2-Iodophenyl)ethynyl)-2-(methylthio)pyridine (85):



To a small dry RBF, 3-ethynyl-2-(methylthio)pyridine (1.33 g, 8.94 mmol) was dissolved in DIPA to make a 0.5 M solution. The vessel was kept in an ice bath and degassed and backfilled with nitrogen three times before being put aside.

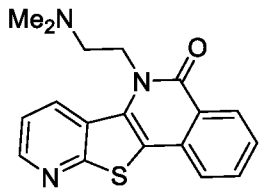
To another double-necked RBF, 1,2-diiodobenzene (5.90 g, 17.9 mmol) was dissolved in DIPA to make a 0.7 M solution, which was subsequently cooled down in an ice bath before being degassed and backfilled with N_2(g) three times. CuI (102 mg, 0.536 mmol) and $Pd(PPh_3)_2Cl_2$ (125 mg, 0.179 mmol) were then added to the RBF and the vessel was once again degassed and backfilled with N_2(g) three times. The mixture was then brought to a stir at 60 degrees Celsius before the previously prepared solution containing the respective alkyne was added drop-wise over a period of 5 hours; the reaction was then stirred overnight. Upon completion, the mixture was extracted with Et_2O (3 x 50 mL) and filtered through Celite ® before being washed with water (3 x 40 mL) and brine (2 x 40 mL). The organic layer was collected and dried over $MgSO_4$, and then filtered and concentrated under vacuum. The crude product obtained was then purified via flash column chromatography (100% petroleum spirit → 95% petroleum spirit/5% EtOAc) to yield the desired compound (1.77 g, 56%) as light-yellow crystals. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.72 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H), 6.99 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.01, 148.36, 138.90, 138.86, 132.99, 129.86, 129.40, 127.85, 118.27, 117.41, 100.49, 99.79, 88.12, 77.24, 13.21. LCMS (APCI) *m/z*: 352.0 [M+H$^+$].

3-Bromo-2-(2-iodophenyl)thieno[2,3-b]pyridine (86):



To a small RBF, 3-((2-iodophenyl)ethynyl)-2-(methylthio)pyridine (500 mg, 1.42 mmol) was added along with $CuBr_2$ (636 mg, 2.85 mmol) before being dissolved in dry DCE (7 mL) to make a 0.2 M solution. The vessel was subsequently degassed and backfilled with N_2(g) three times, and the reaction was stirred at 60 degrees Celsius overnight. Upon completion, the reaction was quenched with 5 mL of $Na_2S_2O_3$, extracted with DCM (3 x 30 mL), and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organic layer was collected, dried over $MgSO_4$ and filtered before being concentrated under vacuum to generate the desired compound (604 mg, quant.) as a pale-yellow crystal. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.45 (dtd, *J* = 14.2, 7.6, 1.6 Hz, 3H), 7.17 (ddd, *J* = 8.0, 7.1, 2.0 Hz, 1H). LCMS (APCI) *m/z*: 415.9 [M+H$^+$].

6-(2-(Dimethylamino)ethyl)pyrido[3',2':4,5]thieno[3,2-c]isoquinolin-5(6H)-one (87):



To a dry RBF, 3-bromo-2-(2-iodophenyl)thieno[3,2-b]pyridine (100 mg, 0.240 mmol), Cs_2CO_3 (235 mg, 0.721 mmol), Pd_2dba_3 (22.0 mg, 0.0240 mmol), and Xantphos (27.8 mg, 0.0481 mmol) were added and dissolved in anhydrous 1,4-dioxane (1.20 mL). The vessel was subsequently degassed and backfilled with N_2(g) three times and allowed to stir at room temperature for 10 minutes. *N,N*-Dimethylethylenediamine (0.0388 mL, 0.361 mmol) was then added to the flask before it was subsequently degassed and backfilled with CO (g) three times and allowed to stir under this atmosphere for 4.5 h at 70 °C. After the dehalogenated pyridine starting material has been consumed, the atmosphere of the vessel was reverted back to N_2(g) and the reaction mixture was allowed to stir at 120 °C for 20 h. Upon completion, the mixture was extracted with EtOAc (3 x 20 mL) and filtered through Celite ®, before being washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was subsequently collected, dried over $MgSO_4$, and concentrated under vacuum. The crude product was then purified via flash column chromatography (95% EtOAc/ 5% Et_3N/ 1% MeOH, R_f = 0.30) to yield the desired compound (47.0 mg, 60%) as an dark amber wax. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.70 – 8.55 (m, 2H), 8.50 (d, *J* = 7.9 Hz, 1H), 7.83 – 7.67 (m, 2H), 7.57 (ddd, *J* = 8.2, 6.5, 1.8 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.6 Hz, 1H), 4.84 – 4.70 (t, *J* = 8 Hz, 2H), 2.85 – 2.73 (t, *J* = 8 Hz, 2H), 2.42 (s, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.48, 160.46, 147.95, 133.45, 132.54, 131.53, 130.97, 129.54, 128.56, 125.38, 124.84, 123.90, 120.46, 117.77, 57.15, 46.38, 43.85. LCMS (APCI) *m/z*: 324.2 [M+H$^+$].

Topoisomerase I inhibitory activity

TOP1 plays a key role modifying and maintaining DNA topology during cellular replication and transcription. TOP1 inhibitors, such as **1-4** (Figure 1), exert their cytotoxic effect on cancer cells by binding to TOP1/DNA cleavage complexes (TOP1cc), forming stable ternary complexes that collide with replication forks leading to DNA damage and apoptosis. TOP1 inhibitors also influence transcription, for example, in hypoxic cancer cells compounds **1** and **2** selectively suppress the expression of hypoxia inducible factor HIF-1α, which is a driver of tumour progression. In this scenario, inhibition of TOP1 increases in the transcription of micro-RNAs, miR-17-5p and miR-155, that promote selective degradation of HIF-1α mRNA.

Many of the scaffolds generated in the present disclosure are reminiscent of DNA intercalators that inhibit TOP1, such as **2-4** (Figure 1). To further bias these scaffolds to interact with TOP1cc the inventors have included the *N,N*-dimethylaminoethylene group in ARC111 (compound **3**, Figure 1) to many of the synthesised compounds.

Top1-mediated DNA cleavage assay

Selected scaffolds were tested for TOP1 inhibition at 100, 10, 1, and 0.1 μM in a TOP1-mediated DNA cleavage assay, which was performed as previously reported.[6] This assay uses 3'-radiolabeled DNA substrates to identify compounds that stabilise TOP1ccs. A representative polyacrylamide gel of the TOP1-mediated DNA cleavage assay conducted on compounds **77**, **56d** and **19a** can be seen in Figures 3A-B. From these data it can be seen that **19a** and **56d** showed significant TOP1 inhibition in a dose-dependent manner.

PC3 cell viability determination

TOP1 inhibitors **77**, **56d** and **19a** were also tested for cytotoxicity towards prostate cancer PC3 cells. Dose response curves for representative compounds **77** (IC_{50} = 0.23 μM), **56d** (IC_{50} = 4.44 μM) and **19a** (IC_{50} = 1.99 μM) can be seen in Figures 4A-C.

PC3 cell viability assay

Routine cell culture: PC3 prostate cancer cell lines were cultured in DMEM (containing 10% fetal calf serum and penicillin-streptomycin). Cells were grown at 37 °C with 5 % CO_2 and passaged when 80-90% confluent 4 times before use. Cells were harvested by trypsin treatment (5 min) then quenched with an equal volume of serum containing media and the cell suspension then centrifuged at 200 xg for 5 min and the pellet resuspended in 5 mL of media. Cells were exposed to Trypan blue (excludes dead cells) and counted with a haemocytometer. Before treatment with drug compounds, cells were plated at 2,500 cells/well in 96 well plates and incubated at 37 °C with 5 % CO_2 in a humidified incubator for 24 h. Drug stock solutions (50 or 10 mM) were diluted x 1000 in media to a final concentration of either 50 μM or 10 μM with a DMSO vehicle concentration of 0.1%. Compounds were then serially diluted in media (containing 0.1% DMSO) to give 8 final concentrations, all at 0.1%

DMSO. Cell culture supernatants were aspirated and replaced with drug containing media. Drug treatments were performed in duplicate wells, while potential plate layout-specific variation in cell growth was accounted for by addition of a vehicle control (0.1% DMSO). An untreated control (media only) was included in each assay. Cells were then incubated with drug compounds at 37 °C with 5 % CO_2 in a humidified incubator for 72 h prior to assay. Cell media were diluted with CellTitre AQueous One Solution to produce a final concentration of 317 µg/mL. Cell culture supernatants were then aspirated from wells and replaced with 100 µL of CellTitre solution. Triplicate cell-free control wells containing only CellTitre solution were also included in each assay. Cells were then incubated at 37 °C with 5 % CO_2 in a humidified incubator for 1 h at which time absorbance was read at 490 nm with a microplate reader. When analysing data, background absorbance (taken from cell-free control wells) was subtracted from each reading. To determine percentage inhibition of cell viability, absorbance readings for each drug treatment were expressed as a fraction of the vehicle control (0.1% DMSO) readings. For each drug concentration the mean (± SEM) is calculated and a sigmoidal curved is fitted to the data and used to calculate the IC_{50} of each compound.

Observations from Top1-mediated DNA cleavage and PC3 cell viability assays

The results from the above-mentioned Top1-mediated DNA cleavage and PC3 cell viability assays demonstrate that introduction of the methylenedioxy and methoxy groups seen in **3** to scaffold **19a** gives **77**, which is approximately 10-fold more potent than **19a** in terms of TOP1 inhibitory activity and PC3 cytotoxicity.

Conclusion

A scaffold-divergent synthesis strategy for the generation of a sp^2-rich polynucleotide-biased fragment library has been devised based on the electrophilic cyclisation of alkynes.[10] Scaffold modifications include the use of intermolecular and intramolecular electrophiles and variations in the nature of the second (dihalide) ring closure. The iterative use of halocyclisation further extends the range heteroacene scaffolds that can be accessed. The methods are also applicable to the generation of more substituted systems for further library diversification and/or lead optimisation.

The polynucleotide-biased fragment library of scaffolds generated in the present disclosure has proven useful in identifying novel TOP1 inhibitors that target the TOP1cc and may be further useful for additional target and phenotypic screening.

The present disclosure also includes the following numbered items:

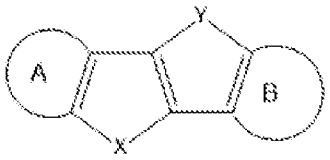
1. A collection of polycyclic compounds and/or salts thereof, for screening against a polynucleotide target, the collection comprising a plurality of polycyclic compounds which comprise at least 4 fused rings and have the formula

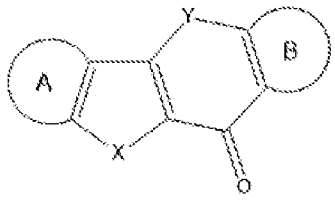
A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



,


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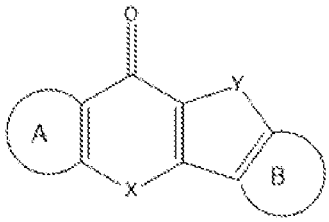
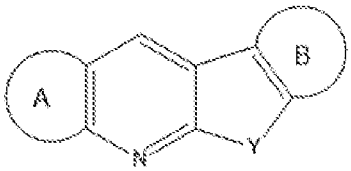
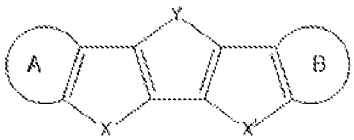


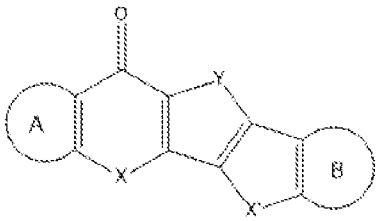


and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

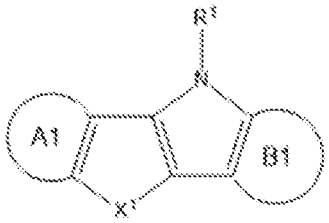


and


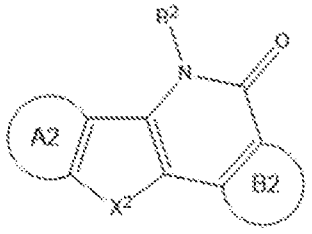
;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

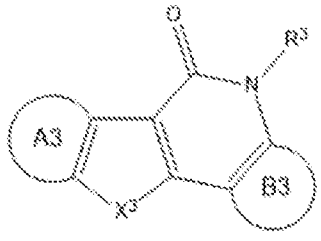
2. The collection of polycyclic compounds and/or salts according to item 1, wherein the collection contains compounds from one or more of formulae a) to u), and/or salts thereof:

a) 

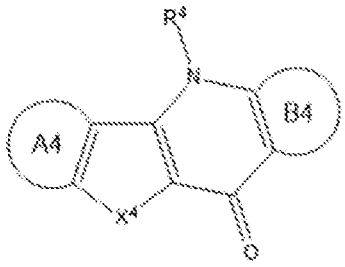
; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

b) 

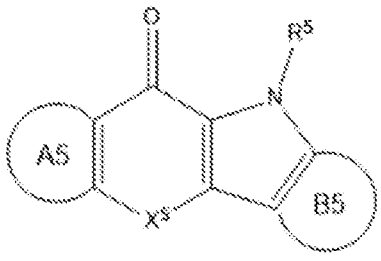
; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

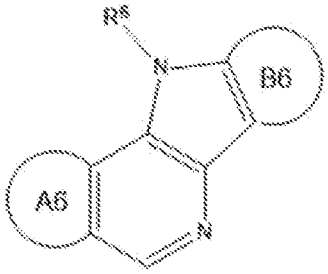
c) 

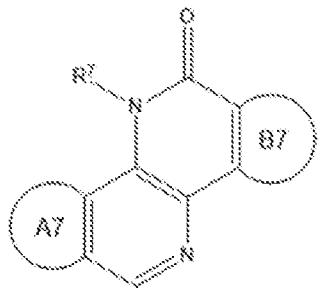
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

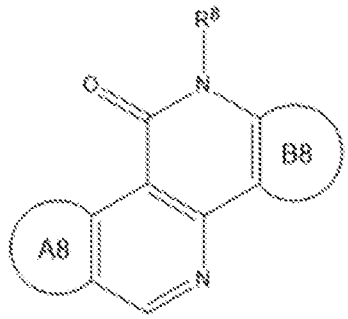
d) 

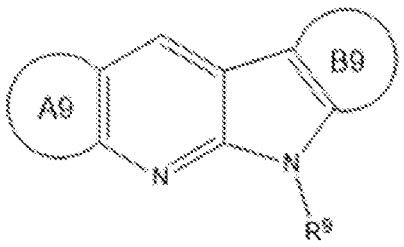
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

e)  ; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

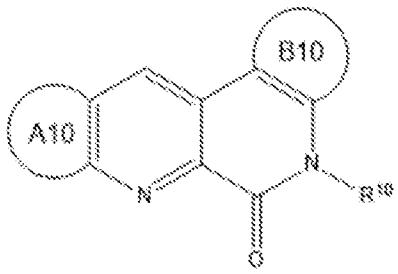
f)  ; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

g)  ; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

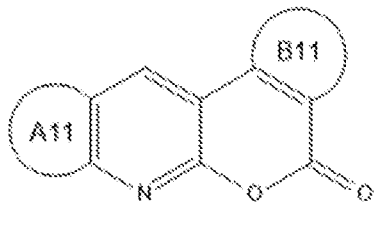
h)  ; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

i) 

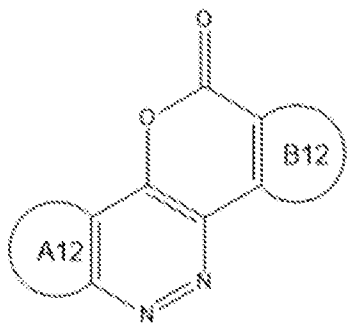
; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

j) 

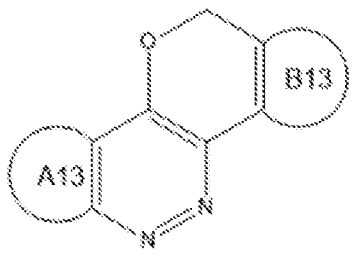
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

k) 

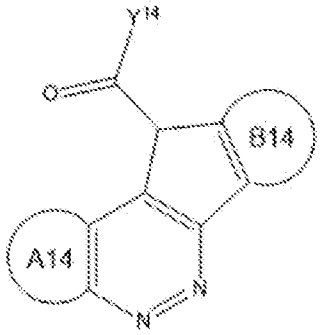
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

l) 

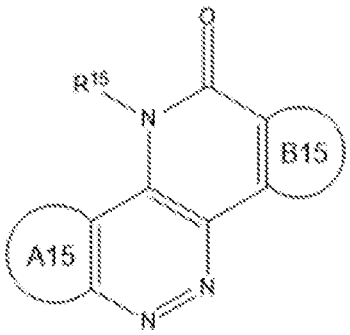
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

m) 

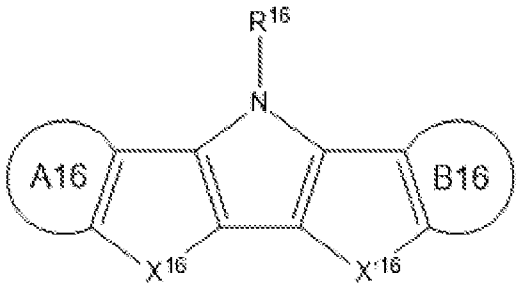
; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

n) 

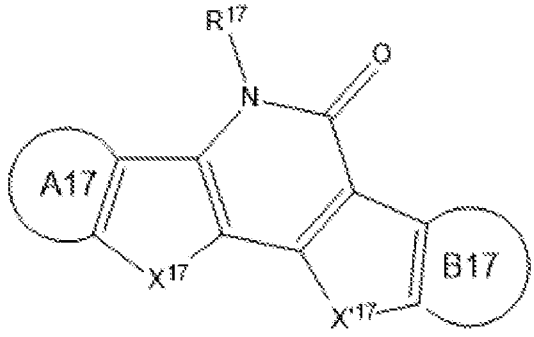
; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

o) 

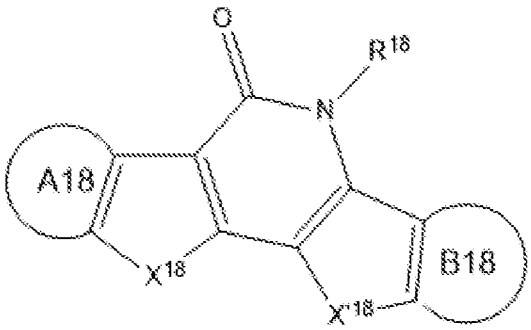
; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

p) 

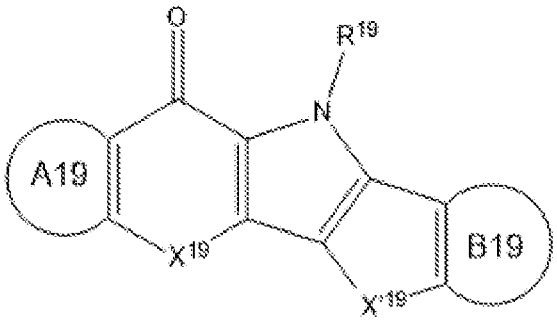
; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{16} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;



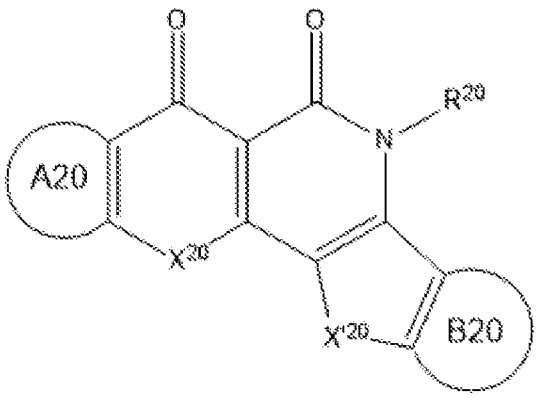
q) ; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;



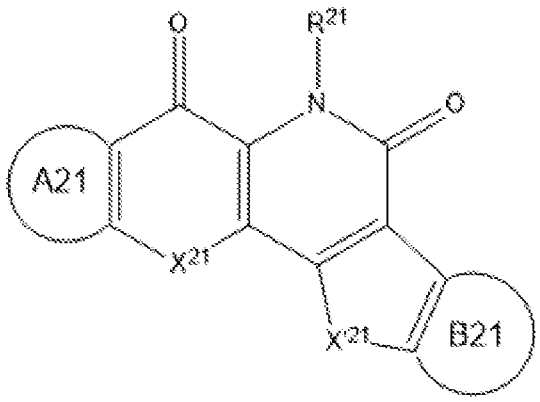
r) ; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;



s) ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{19} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

t) 

; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; or

u) 

; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{21} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

3. The collection of polycyclic compounds and/or salts according to item 2, wherein A1-A21 are each independently selected from the group consisting of phenyl, thiophene, pyridine and benzothiophene.

4. The collection of polycyclic compounds and/or salts according to item 3, wherein A1-A21 are each independently selected from the group consisting of phenyl and benzothiophene.

5. The collection of polycyclic compounds and/or salts according to any of items 2 to 4, wherein B1-B21 are each independently selected from the group consisting of phenyl, thiophene and pyridine.

6. The collection of polycyclic compounds and/or salts according to item 5, wherein B1-B21 are each independently selected from the group consisting of phenyl and thiophene.

7. The collection of polycyclic compounds and/or salts according to any of items 2 to 6, wherein X^1-X^5 and X^{16}-X^{21} are each independently selected from O and S.

8. The collection of polycyclic compounds and/or salts according to any of items 2 to 7, wherein R^1-R^{21} are each C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

9. The collection of polycyclic compounds and/or salts according to any of items 2 to 8, wherein R^1-R^{21} are each C_{1-4}alkyl substituted by $N(C_{1-4}alkyl)_2$.

10. The collection of polycyclic compounds and/or salts according to any of items 2 to 9, wherein the collection contains one or more compounds of the formula p) and/or salts thereof, and wherein A16 is different from B16 and/or X^{16} is different from X'^{16}.

11. The collection as claimed according to any of items 1 to 10, wherein the collection comprises: at least 10 compounds and/or salts as defined in any of items 1 to 10, optionally at least 100 compounds and/or salts as defined in any of items 1 to 10, optionally at least 250 compounds and/or salts as defined in any of claims 1 to 10, optionally at least 500 compounds and/or salts as defined in any of items 1 to 10, or optionally at least 1000 compounds and/or salts as defined in any of items 1 to 10.

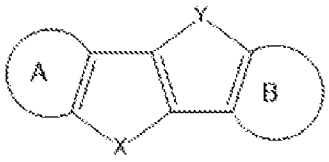
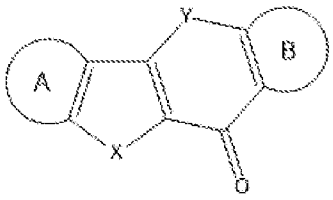
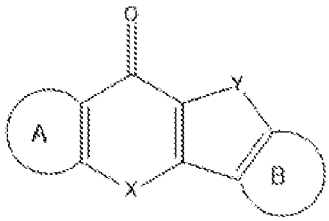
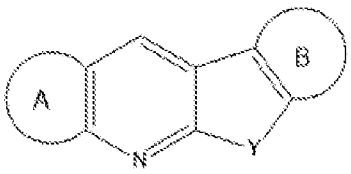
12. A polycyclic compound or salt thereof, wherein the polycyclic compound comprises at least 4 fused rings and has the formula

A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

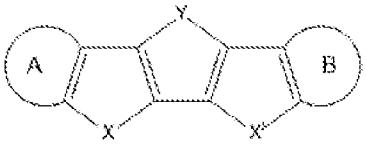
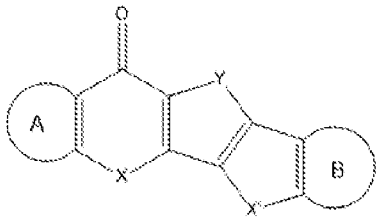
wherein A-Het-Cyc-B is selected from the group consisting of:

and ;

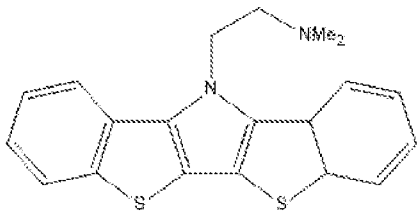
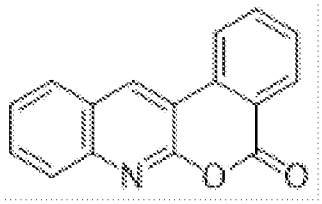
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

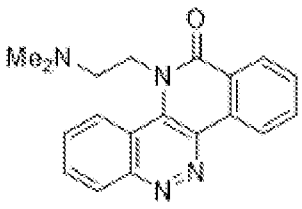
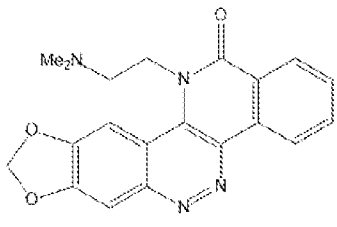
and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

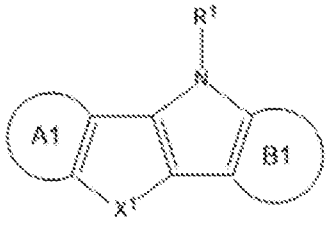
and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

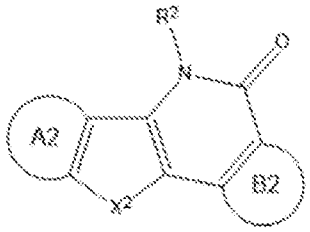
and wherein the compound is not  ,  ,


or  .

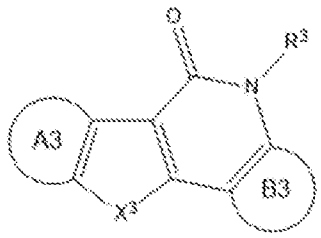
13. The polycyclic compound or salt according to item 12, wherein the compound is selected from compounds having one of the following formulae:

a) 

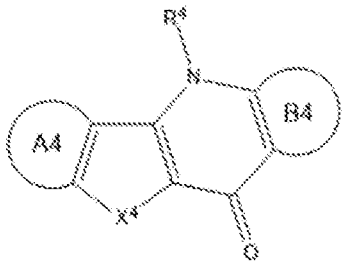
; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

b) 

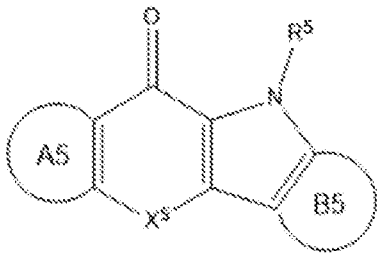
; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

c) 

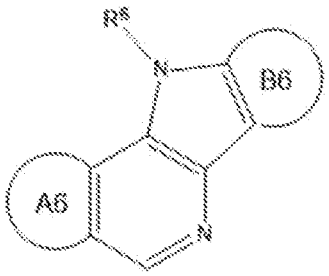
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

d) 

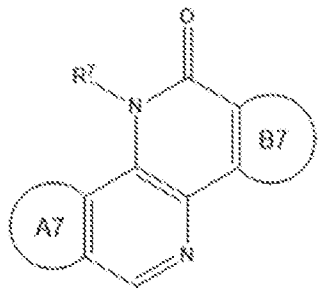
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

e) 

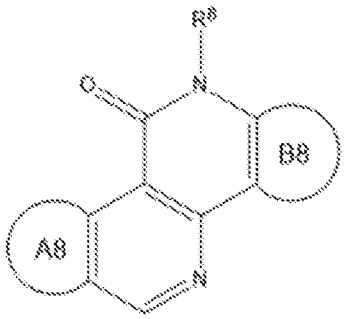
; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

f) 

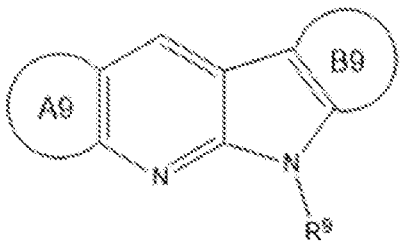
; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

g) 

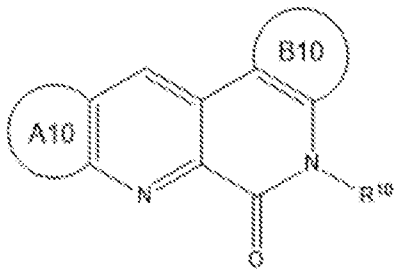
; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

h) 

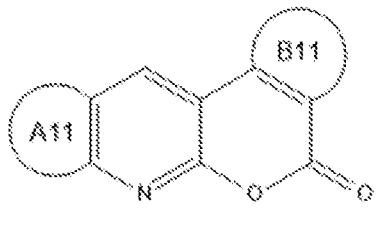
; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

i) 

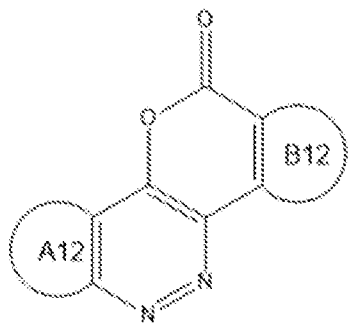
; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

j) 

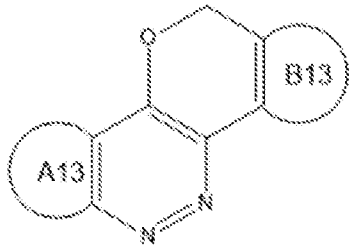
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

k) 

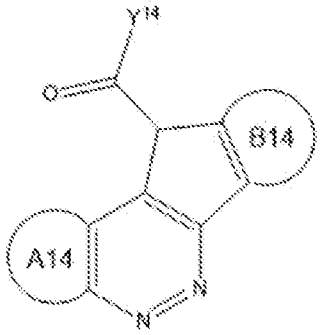
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

l) 

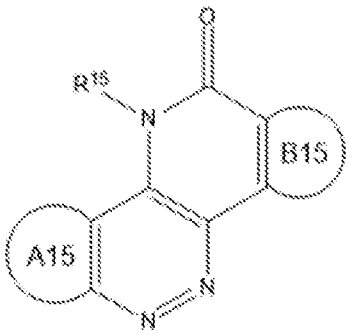
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

m) 

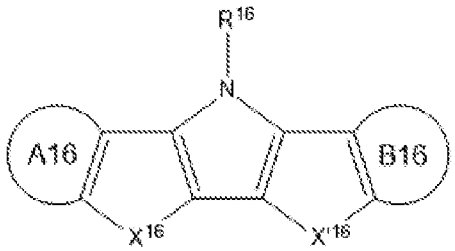
; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

n) 

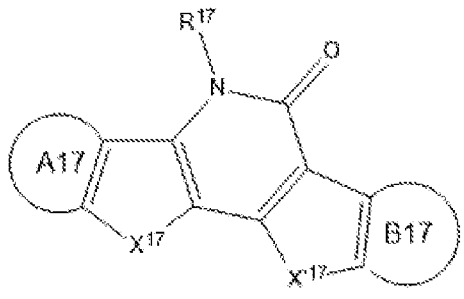
; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; or

o) 

; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

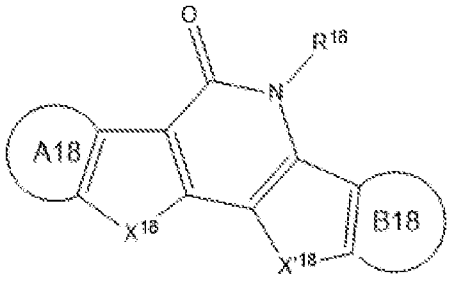
p) 

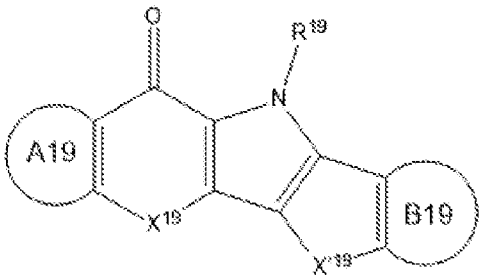
; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{16} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

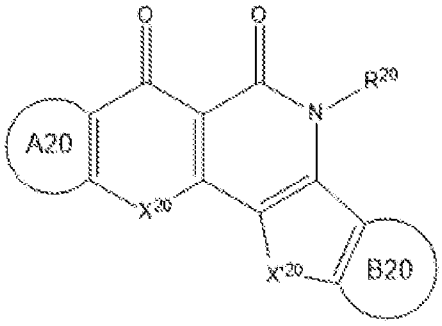
q) 

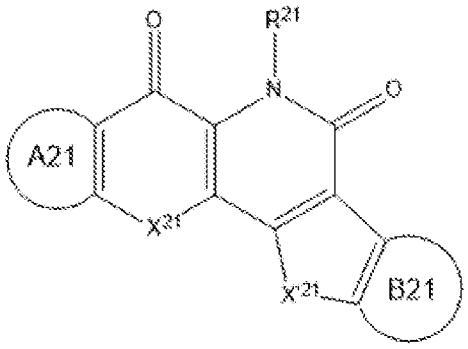
; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17}

is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

r)  ; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

s)  ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{19} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

t)  ; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; or

u) 

; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{21} is hydrogen or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

14. The polycyclic compound or salt according to item 13, wherein A1-A21 are each independently selected from the group consisting of phenyl, thiophene, pyridine and benzothiophene.

15. The polycyclic compound or salt according to item 14, wherein A1-A21 are each independently selected from the group consisting of phenyl and benzothiophene.

16. The polycyclic compound or salt according to any of items 13 to 15, wherein B1-B21 are each independently selected from the group consisting of phenyl, thiophene and pyridine.

17. The polycyclic compound or salt according to item 16, wherein B1-B21 are each independently selected from the group consisting of phenyl and thiophene.

18. The polycyclic compound or salt according to any of items 13 to 17, wherein X^1-X^5 and X^{16}-X^{21} are each independently selected from O and S.

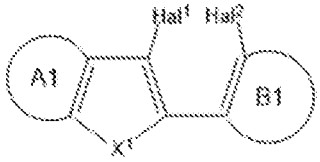
19. The polycyclic compound or salt according to any of items 13 to 18, wherein R^1-R^{21} are each C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$.

20. The polycyclic compound or salt according to item 19, wherein R^1-R^{21} are each C_{1-4}alkyl substituted by $N(C_{1-4}alkyl)_2$.

21. The polycyclic compound or salt according to any of items 13 to 20, wherein the compound is of the formula p), and wherein A16 is different from B16 and/or X^{16} is different from X'^{16}.

22. A method of synthesising a polycyclic compound of formula a), as defined in any of items 13 to 20, comprising:

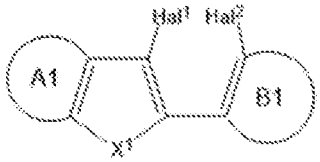
reacting a compound of formula



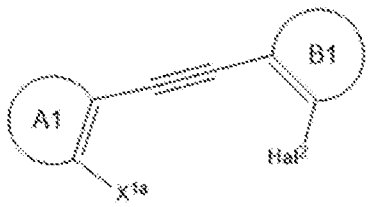
wherein A1, B1 and X^1 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^1-NH_2 in the presence of a copper catalyst, wherein R^1 is as defined in any of items 13 to 20; and optionally forming a salt of the compound.

23. The method according to item 22, wherein the compound of formula



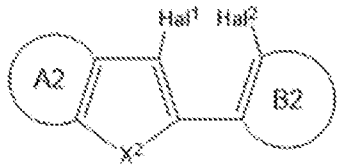
is produced by subjecting a compound of formula



, wherein A1, B1 and Hal^2 are as defined in item 22, and X^{1a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

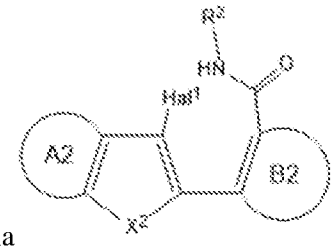
24. A method of synthesising a polycyclic compound of formula b), or salt thereof, as defined in any of items 13 to 20, comprising:

i) reacting a compound of formula



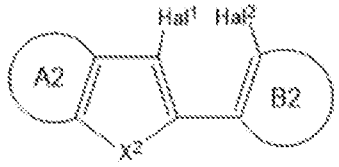
wherein A2, B2 and X^2 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^2-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^2 is as defined in any of items 13 to 20;

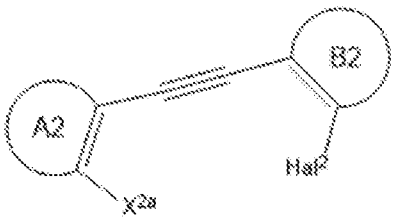
and if the product of step *i*) is a compound of formula  rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

25. The method according to item 24, wherein the compound of formula



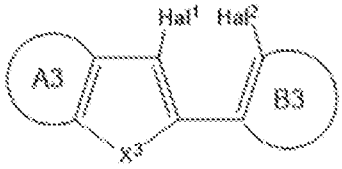
is produced by subjecting a compound of formula



, wherein A2, B2 and Hal^2 are as defined in item 24, and X^{2a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

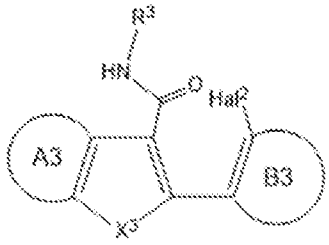
26. A method of synthesising a polycyclic compound of formula c), or salt thereof, as defined in any of items 13 to 20, comprising:

i) reacting a compound of formula



wherein A3, B3 and X^3 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

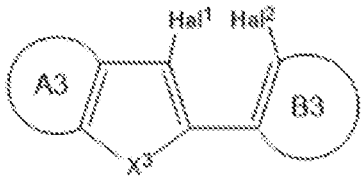
with a compound of formula R^3-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^3 is as defined in any of items 13 to 20;



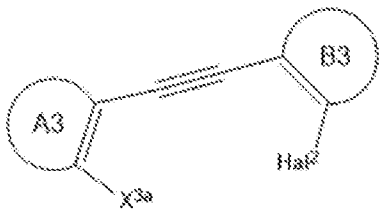
and if the product of step *i*) is a compound of formula rather than a compound of formula c),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula c); and optionally forming a salt of the compound.

27. The method according to item 26, wherein the compound of formula



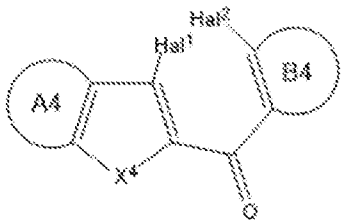
is produced by subjecting a compound of formula



, wherein A3, B3 and Hal^2 are as defined in item 26, and X^{3a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

28. A method of synthesising a polycyclic compound of formula d), or salt thereof, as defined in any of items 13 to 20, comprising:

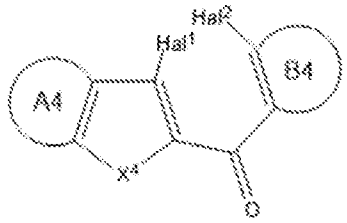
reacting a compound of formula



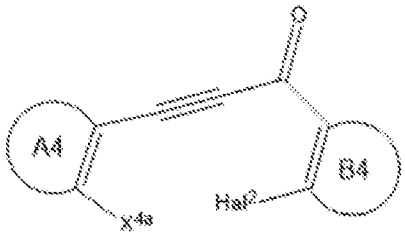
wherein A4, B4 and X^4 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^4-NH_2 in the presence of a copper catalyst, wherein R^4 is as defined in any of items 13 to 20; and optionally forming a salt of the compound.

29. The method according to item 28, wherein the compound of formula



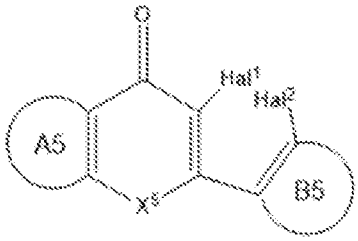
is produced by subjecting a compound of formula



, wherein A4, B4, Hal^2 are as defined in item 28, and X^{4a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

30. A method of synthesising a polycyclic compound of formula e), or salt thereof, as defined in any of items 13 to 20, comprising:

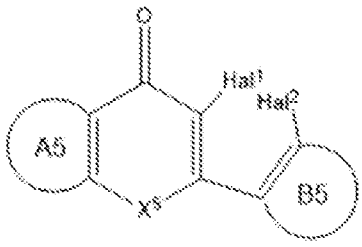
reacting a compound of formula



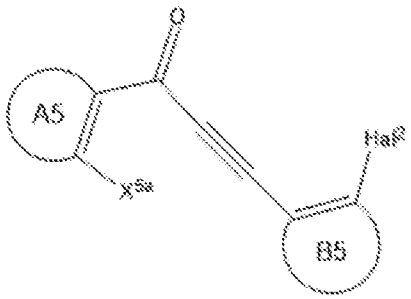
wherein A5, B5 and X^5 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^5NH_2 in the presence of a copper catalyst, wherein R^5 is as defined in any of items 13 to 20; and optionally forming a salt of the compound.

31. The method according to item 30, wherein the compound of formula



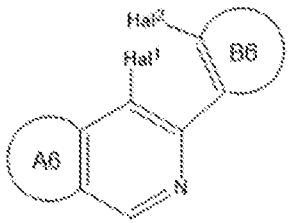
is produced by subjecting a compound of formula



, wherein A5, B5 and Hal^2 are as defined in item 30, and X^{5a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

32. A method of synthesising a polycyclic compound of formula f), or salt thereof, as defined in any of items 13 to 20, comprising:

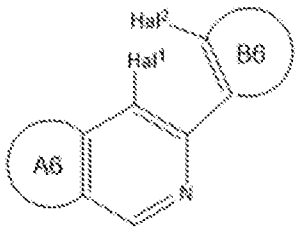
reacting a compound of formula



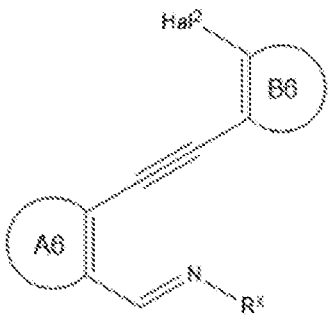
wherein A6, B6 and X^6 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^6NH_2 in the presence of a copper catalyst, wherein R^6 is as defined in any of items 13 to 20; and optionally forming a salt of the compound.

33. The method according to item 32, wherein the compound of formula



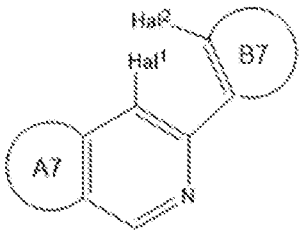
is produced by subjecting a compound of formula



, wherein A6, B6 and Hal^2 are as defined in item 32, and R^X is OC_{1-4}alkyl or C_{1-4}alkyl; to a halocyclization reaction.

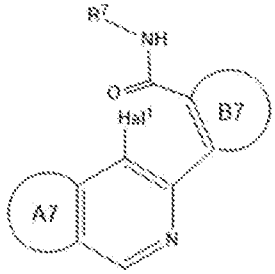
34. A method of synthesising a polycyclic compound of formula g), or salt thereof, as defined in any of items 13 to 20, comprising:

i) reacting a compound of formula



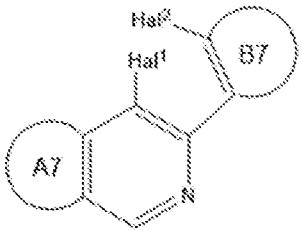
wherein A7 and B7 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

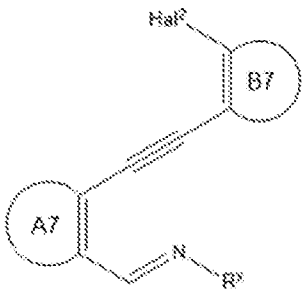
with a compound of formula R^7-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^7 is as defined in any of items 13 to 20;

and if the product of step *i*) is a compound of formula 

rather than a compound of formula g),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula g); and optionally forming a salt of the compound.

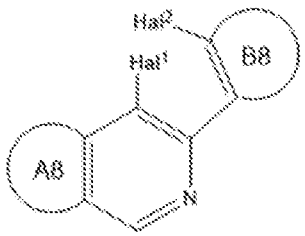
35. The method according to item 34, wherein the compound of formula 

is produced by subjecting a compound of formula 

, wherein A7, B7 and Hal^2 are as defined in item 34, and R^X is $OC_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkyl; to a halocyclization reaction.

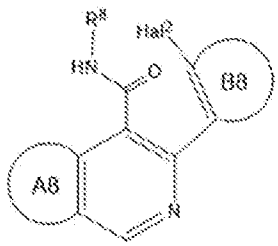
36. A method of synthesising a polycyclic compound of formula h), or salt thereof, as defined in any of items 13 to 20, comprising:

i) reacting a compound of formula



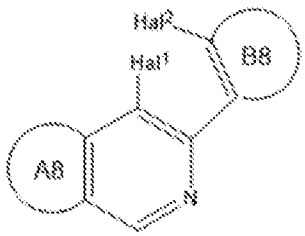
wherein A8 and B8 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

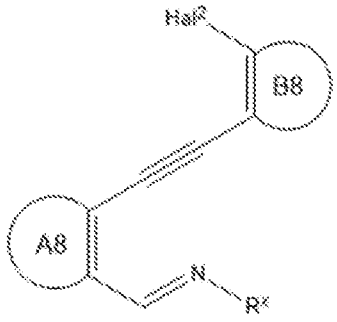
with a compound of formula R^8-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^8 is as defined in any of items 13 to 20;

and if the product of step *i*) is a compound of formula 

rather than a compound of formula h),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula h); and optionally forming a salt of the compound.

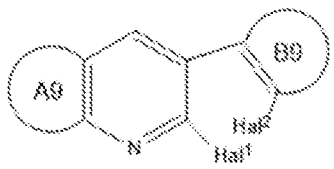
37. The method according to item 36, wherein the compound of formula 

is produced by subjecting a compound of formula 

, wherein A8, B8 and Hal^2 are as defined in item 36, and R^X is $OC_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkyl; to a halocyclization reaction.

38. A method of synthesising a polycyclic compound of formula i) or salt thereof, as defined in any of items 13 to 20, comprising:

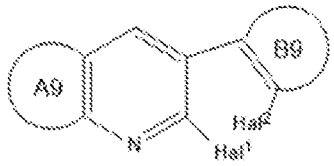
reacting a compound of formula



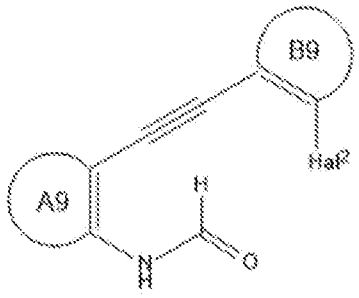
wherein A9 and B9 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^9NH_2 in the presence of a copper catalyst, wherein R^9 is as defined in any of items 13 to 20; and optionally forming a salt of the compound.

39. The method according to item 38, wherein the compound of formula



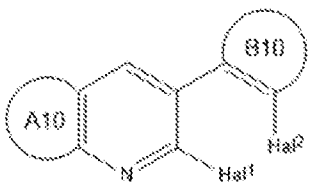
is produced by reacting a compound of formula



, wherein A9, B9 and Hal^2 are as defined in item 38; with a dehydrating reagent, and then contacting the resulting product with a halide source.

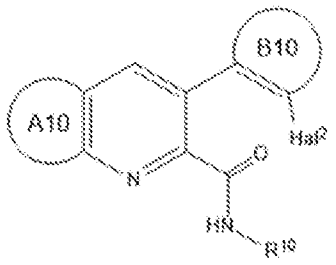
40. A method of synthesising a polycyclic compound of formula j), or salt thereof, as defined in any of items 13 to 20, comprising:

i) reacting a compound of formula

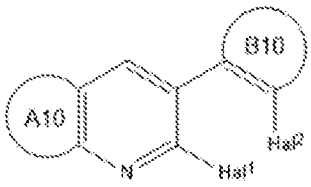
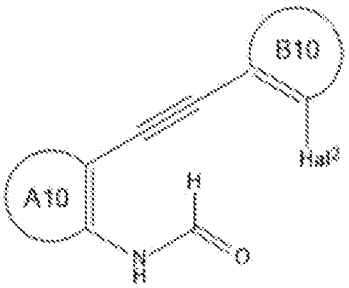


wherein A10 and B10 are as defined in any of items 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{10}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{10} is as defined in any of items 13 to 20;

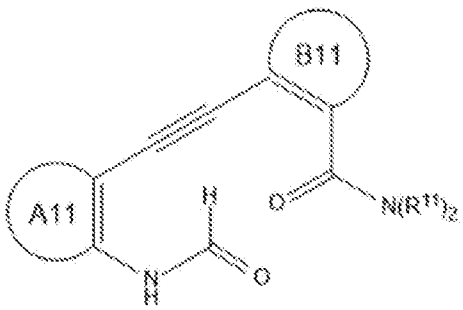
and if the product of step *i*) is a compound of formula  rather than a compound of formula j),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula j); and optionally forming a salt of the compound.

41. The method according to item 40, wherein the compound of formula  is produced by reacting a compound of formula  , wherein A10, B10 and Hal^2 are as defined in item 40; with a dehydrating reagent, and then contacting the resulting product with a halide source.

42. A method of synthesising a polycyclic compound of formula k), or salt thereof, as defined in any of items 13 to 20, comprising:

reacting a compound of formula

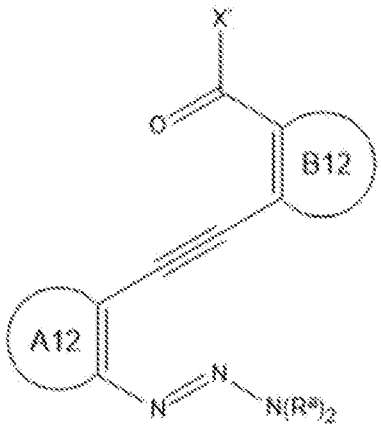


wherein A11 and B11 are as defined in any of items 13 to 20, and wherein each R^{11} is independently $C_{1\text{-}4}$alkyl;

with a dehydrating reagent, and then contacting the resulting product with an acid, thereby forming the compound of formula k); and optionally forming a salt of the compound.

43. A method of synthesising a polycyclic compound or salt of formula l) as defined in any of items 13 to 20, comprising:

contacting a compound of formula

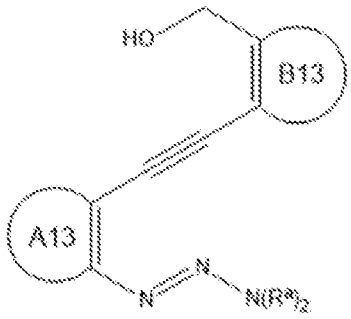


wherein A12 and B12 are as defined in any of items 13 to 20, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group, and X′ is OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

with an acid, thereby forming the compound of formula l); and optionally forming a salt of the compound.

44. A method of synthesising a polycyclic compound of formula m), or salt thereof, as defined in any of items 13 to 20, comprising:

contacting a compound of formula

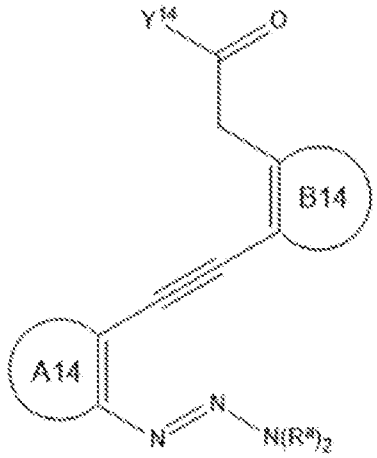


wherein A13 and B13 are as defined in any of items 13 to 20, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula m); and optionally forming a salt of the compound.

45. A method of synthesizing a polycyclic compound of formula n), or salt thereof, as defined in any of items 13 to 20, comprising:

contacting a compound of formula

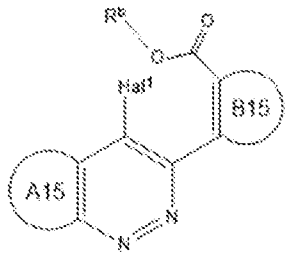


wherein A14, B14 and Y^{14} are as defined in any of items 13 to 20, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula n); and optionally forming a salt of the compound.

46. A method of synthesizing a compound of formula o), or salt thereof, as defined in any of items 13 to 20, comprising:

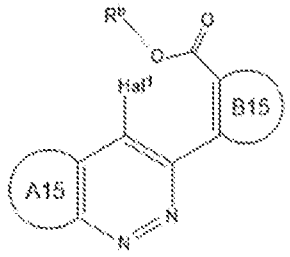
reacting a compound of formula



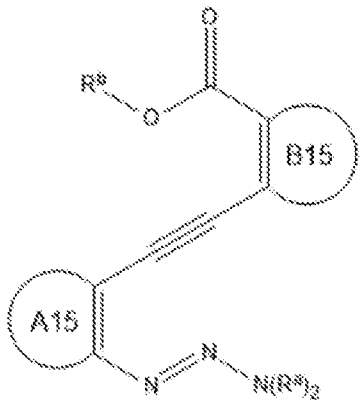
wherein A15 and B15 are as defined in any of items 13 to 20, Hal^1 is halogen, and R^b is C_{1-4}alkyl;

with $R^{15}NH_2$, wherein R^{15} is as defined in any of items 13 to 20, thereby forming the compound of formula o); and optionally forming a salt of the compound.

47. The method according to item 46, wherein the compound of formula



is produced by contacting a compound of formula



wherein A15, B15 and R^b are as defined in any of items 13 to 20, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid and a halide source.

48. A method of identifying a compound having activity against a polynucleotide target or a polynucleotide-protein complex target, comprising:

testing a collection of compounds as defined in any of items 1 to 11 or part thereof, or testing one or more compounds as defined in any of items 12 to 21 for activity against a polynucleotide target; and

identifying whether the compound or compounds have activity against the polynucleotide target.

49. The method as according to item 48, wherein the polynucleotide target is an RNA target, optionally an mRNA target, micro-RNA or a non-coding RNA target.

50. The method according to item 49, wherein the polynucleotide target is a DNA target.

51. The method according to any of items 48 to 50, wherein the polynucleotide target is a polynucleotide-protein complex or a functional DNA topology.

52. The method according to any of items 48 to 51, wherein the polynucleotide target is a DNA complex with a transcription factor, an epigenetic modulator, an RNA-polymerase complex, Z-DNA, or a G-quadruplex.

53. The method according to any of items 48 to 52, wherein the polynucleotide target is selected from the group consisting of DNA-topoisomerase 1, mRNA encoding SMN2 protein, and G-quadruplex mRNA encoding oncogenic N-Ras protein.

54. The method according to any of items 48 to 53, wherein the compound is tested for activity using an assay selected from the group consisting of a radiolabelled DNA-cleavage assay, a cell cytoxicity assay, and an affinity assay for polynucleotides and their protein complexes by one or more of surface plasmon resonance assay, fluorometric assay, nuclear magnetic resonance assay and thermal shift assay.

55. Use of a compound as defined in any of items 13 to 21 as a reference compound in a competition assay for determining activity of a test compound against a polynucleotide target.

56. Use of a compound according to item 55, wherein a radiolabelled form of the compound as defined in any of items 13 to 21 is used in the assay.

57. A phenotypic method of identifying a new polynucleotide target for therapy of a disease or disorder, comprising

contacting a collection of compounds as defined in any of items 1 to 11 or part thereof, or contacting one or more compounds as defined in any of items 13 to 21 with a cell, tissue or animal disease model and monitoring for a change associated with a disease or disorder; and

if a change associated with the disease or disorder is identified, determining the biological target to which the compound binds.

58. The phenotypic method according to item 57, wherein the compound is contacted with a cell.

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Claims

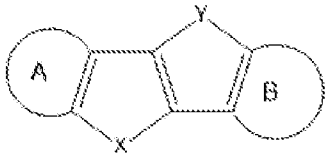
1. A collection of polycyclic compounds and/or salts thereof, for screening against a polynucleotide target, the collection comprising a plurality of polycyclic compounds which comprise at least 4 fused rings and have the formula

A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



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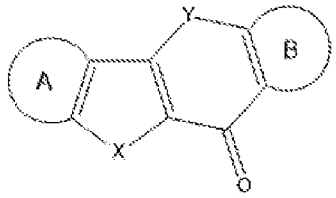

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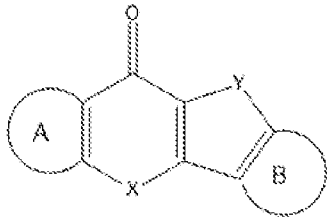
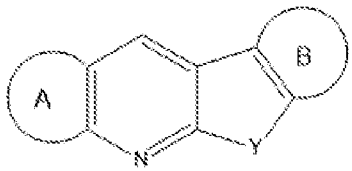
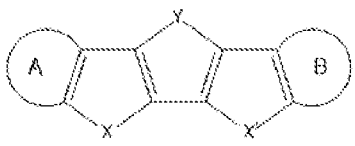


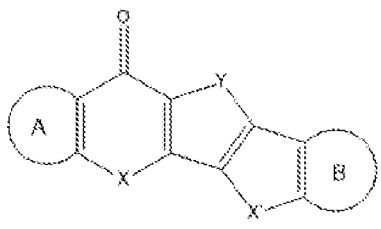
and


;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2-$, $-C(C(O)OC_{1-4}alkyl)-$, $-C(C(O)N(C_{1-4}alkyl)_2)-$ or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:



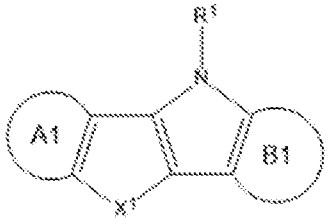
and


;

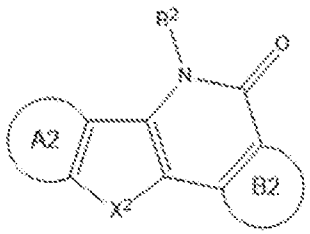
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}$

$_4$alkyl)$_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

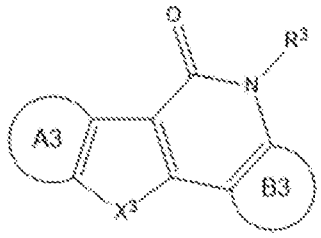
2. The collection of polycyclic compounds and/or salts as claimed in claim 1, wherein the collection contains compounds from one or more of formulae a) to u), and/or salts thereof:

a) 

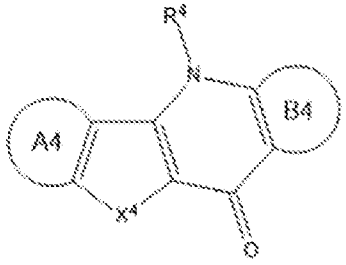
; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

b) 

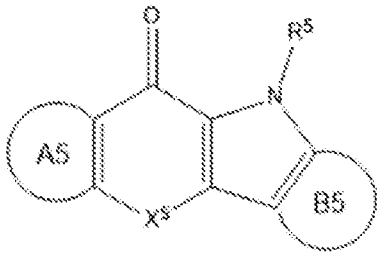
; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

c) 

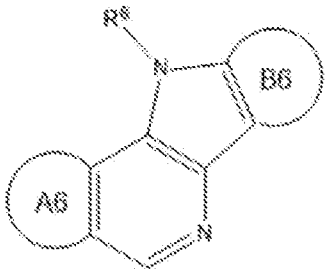
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

d) 

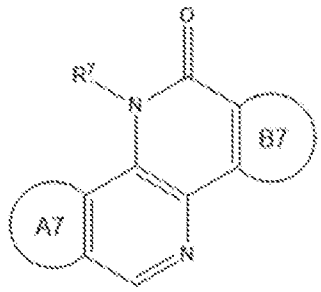
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

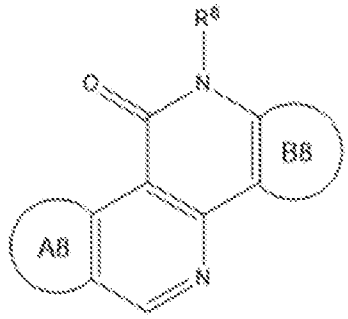
e) 

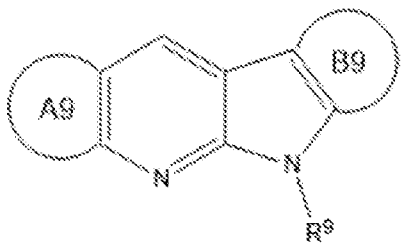
; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

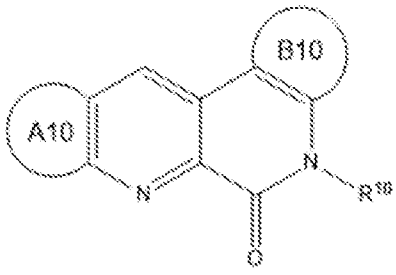
f) 

; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

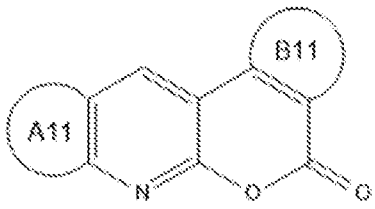
g)  ; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

h)  ; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

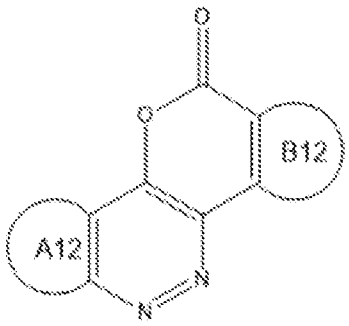
i)  ; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

j) 

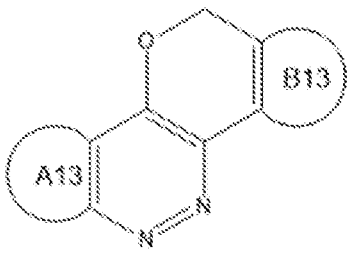
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

k) 

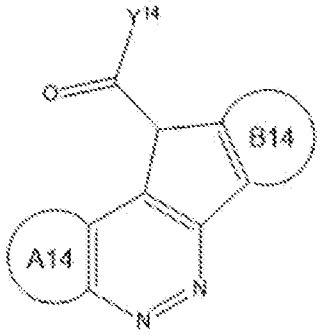
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

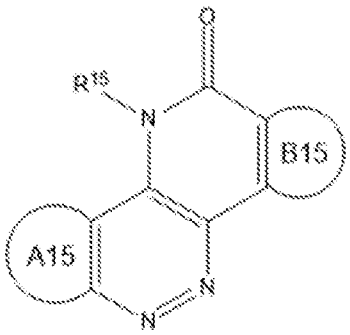
l) 

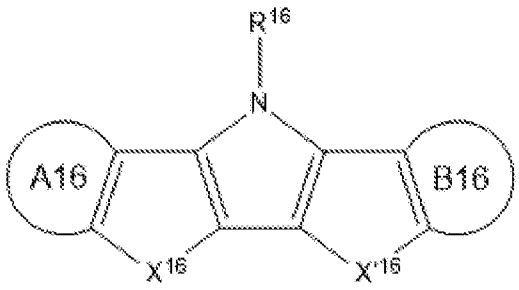
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

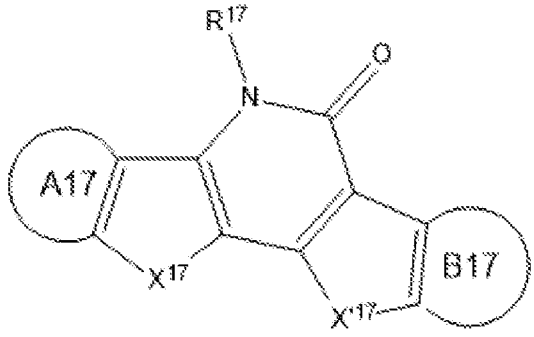
m) 

; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

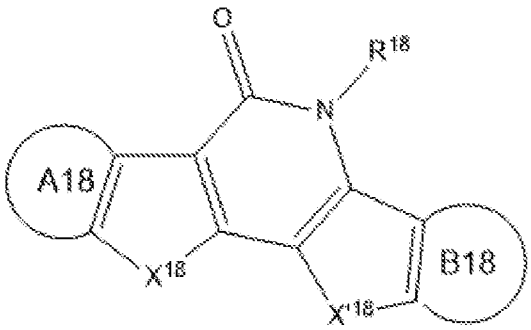
n)  ; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

o)  ; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

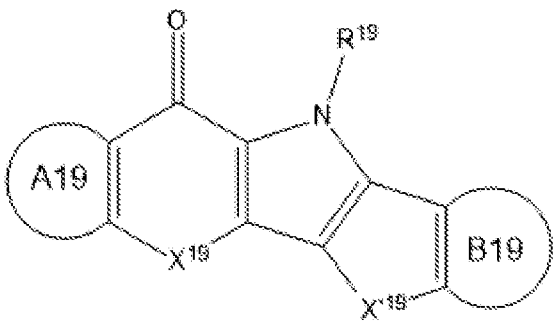
p)  ; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{16} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;



q) ; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

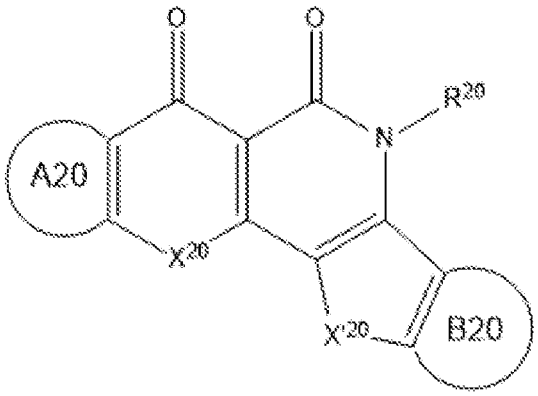


r) ; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

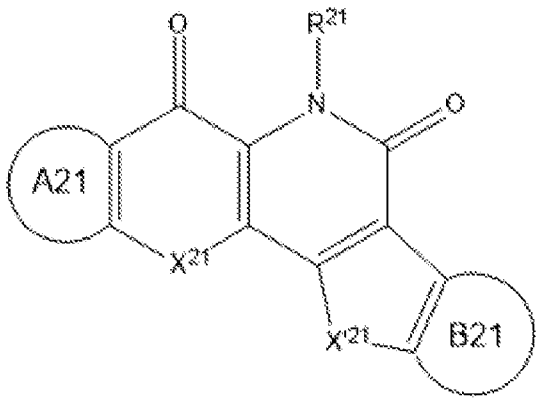


s) ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

-OC(O)-; and R^{19} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;



t) ; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3; or



u) ; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{21} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

3. The collection of polycyclic compounds and/or salts as claimed in claim 2, wherein A1-A21 are each independently selected from the group consisting of phenyl, thiophene, pyridine and benzothiophene.

4. The collection of polycyclic compounds and/or salts as claimed as claimed in claim 3, wherein A1-A21 are each independently selected from the group consisting of phenyl and benzothiophene.

5. The collection of polycyclic compounds and/or salts as claimed in any of claims 2 to 4, wherein B1-B21 are each independently selected from the group consisting of phenyl, thiophene and pyridine.

6. The collection of polycyclic compounds and/or salts as claimed in claim 5, wherein B1-B21 are each independently selected from the group consisting of phenyl and thiophene.

7. The collection of polycyclic compounds and/or salts as claimed in any of claims 2 to 6, wherein X^1-X^5 and X^{16}-X^{21} are each independently selected from O and S.

8. The collection of polycyclic compounds and/or salts as claimed in any of claims 2 to 7, wherein R^1-R^{21} are each H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, optionally wherein R^1-R^{21} are each C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, optionally wherein R^1-R^{21} are each C_{1-4}alkyl substituted by $N(C_{1-4}alkyl)_2$.

9. The collection of polycyclic compounds and/or salts as claimed in any of claims 2 to 8, wherein R^1-R^{21} are each phenyl optionally substituted by up to two substituents independently selected from methyl and CF_3, optionally wherein R^1-R^{21} are each phenyl substituted by one CF_3.

10. The collection of polycyclic compounds and/or salts as claimed in any of claims 2 to 9, wherein the collection contains one or more compounds of the formula p) and/or salts thereof, and wherein A16 is different from B16 and/or X^{16} is different from X'^{16}.

11. The collection as claimed in any of claims 1 to 10, wherein the collection comprises:

at least 10 compounds and/or salts as defined in any of claims 1 to 10, optionally at least 100 compounds and/or salts as defined in any of claims 1 to 10, optionally at least 250 compounds and/or salts as defined in any of claims 1 to 10, optionally at least 500 compounds and/or salts as defined in any of claims 1 to 10, or optionally at least 1000 compounds and/or salts as defined in any of claims 1 to 10.

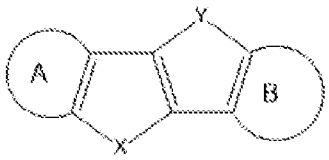
12. A polycyclic compound or salt thereof, wherein the polycyclic compound comprises at least 4 fused rings and has the formula

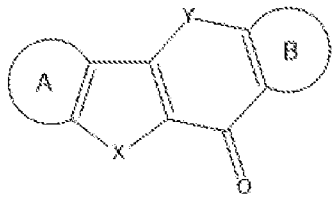
A-Het-Cyc-B

or

A-Het1-Cyc-Het2-B

wherein A-Het-Cyc-B is selected from the group consisting of:



,


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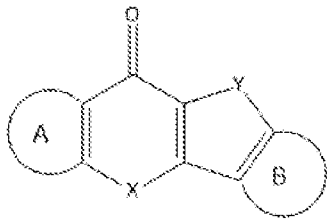
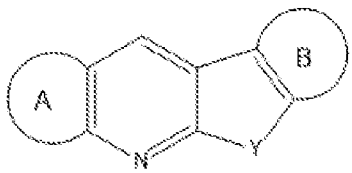
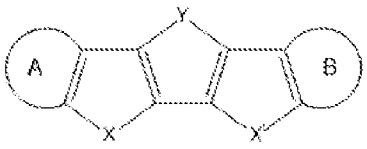




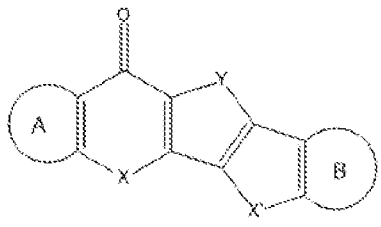
and ;

wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; Y is NR, -C(O)NR-, -NRC(O)-, $-OCH_2$-, $-C(C(O)OC_{1-4}alkyl)$-, $-C(C(O)N(C_{1-4}alkyl)_2)$- or -OC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein A-Het1-Cyc-Het2-B is selected from the group consisting of:

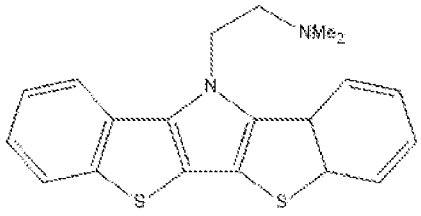
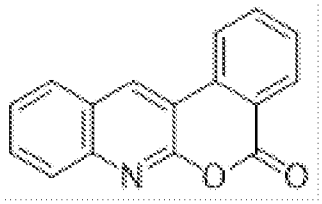
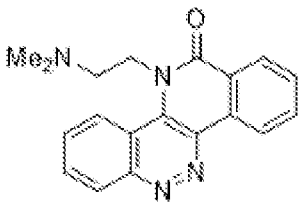
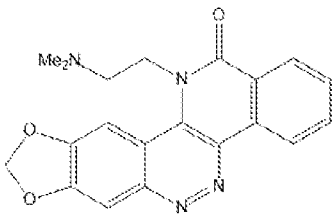


and

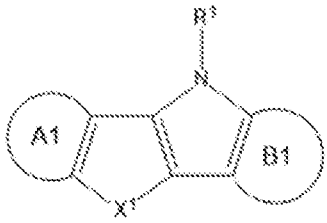


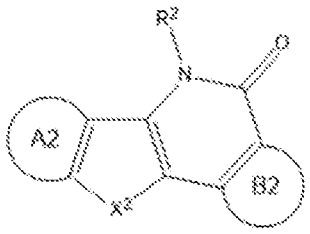
;

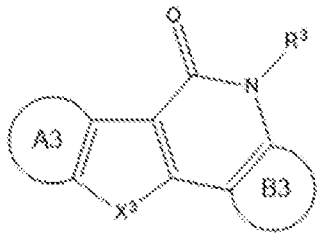
wherein A is a 5-10-membered carbocyclic or heterocyclic aromatic group; B is a 5-10-membered carbocycle or heterocyclic aromatic group; X is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X′ is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; Y is NR, -C(O)NR-, -NRC(O)-; and R is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

and wherein the compound is not  ,  ,  or  .

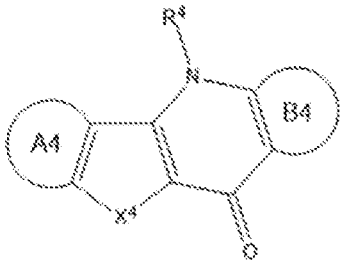
13. The polycyclic compound or salt as claimed in claim 12, wherein the compound is selected from compounds having one of the following formulae:

a)  ; wherein A1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B1 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^1 is O, S, NH or NC_{1-4}alkyl; and R^1 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

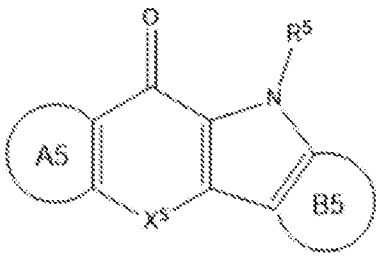
b)  ; wherein A2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B2 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^2 is O, S, NH or NC_{1-4}alkyl; and R^2 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

c) 

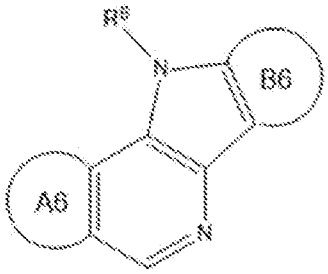
; wherein A3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B3 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^3 is O, S, NH or NC_{1-4}alkyl; and R^3 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

d) 

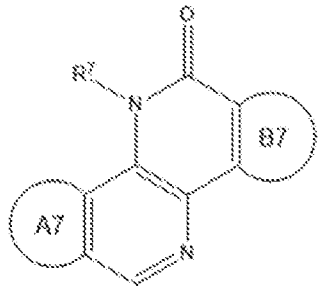
; wherein A4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B4 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^4 is O, S, NH or NC_{1-4}alkyl; and R^4 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

e) 

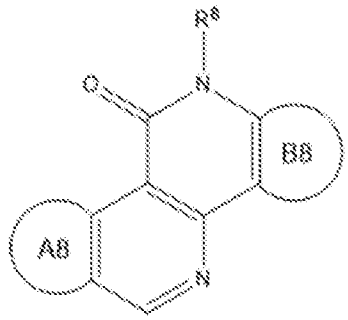
; wherein A5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B5 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^5 is O, S, NH or NC_{1-4}alkyl; and R^5 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

f) 

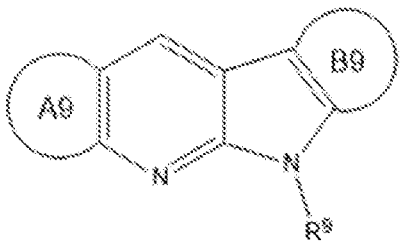
; wherein A6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B6 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^6 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

g) 

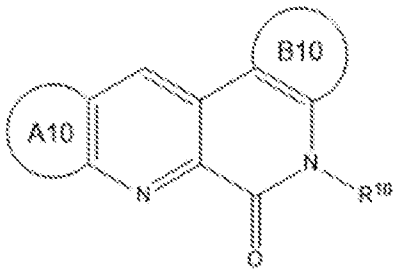
; wherein A7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B7 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^7 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

h) 

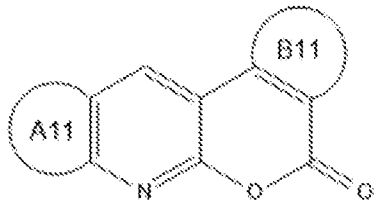
; wherein A8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B8 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^8 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

i) 

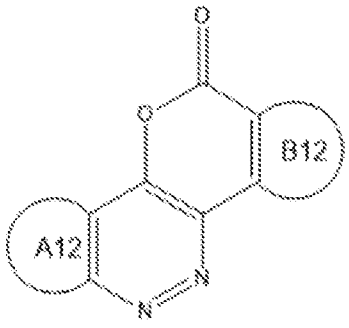
; wherein A9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B9 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^9 is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

j) 

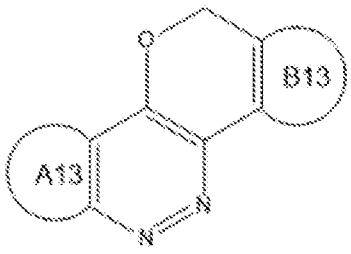
; wherein A10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B10 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{10} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

k) 

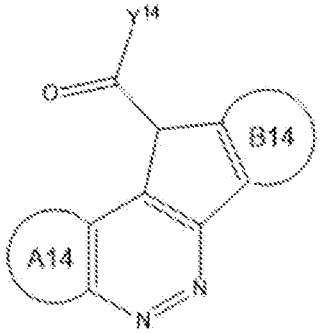
; wherein A11 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B11 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

l) 

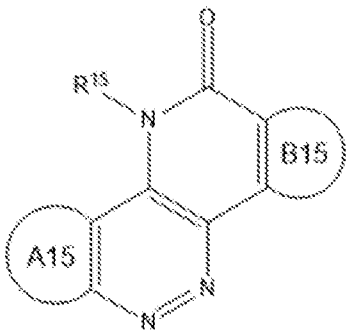
; wherein A12 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B12 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

m) 

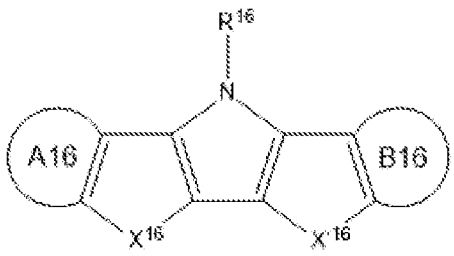
; wherein A13 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and B13 is a 5-10 membered carbocyclic or heterocyclic aromatic group;

n) 

; wherein A14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B14 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and Y^{14} is OC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; or

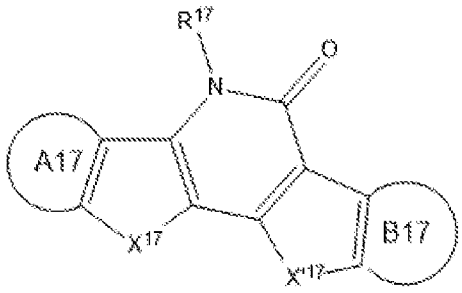
o) 

; wherein A15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B15 is a 5-10 membered carbocyclic or heterocyclic aromatic group; and R^{15} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

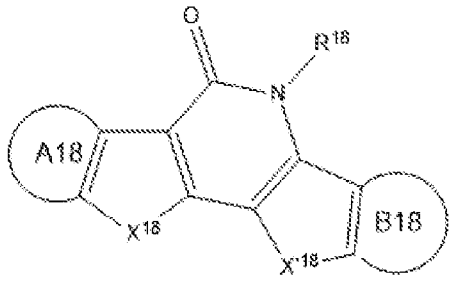
p) 

; wherein A16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B16 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{16} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{16} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

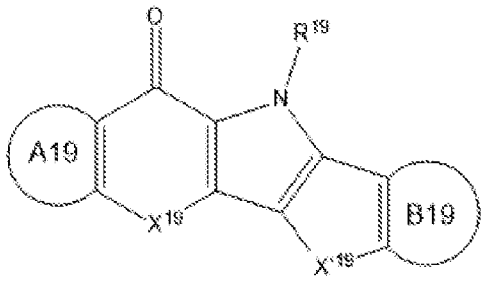
-OC(O)-; and R^{16} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

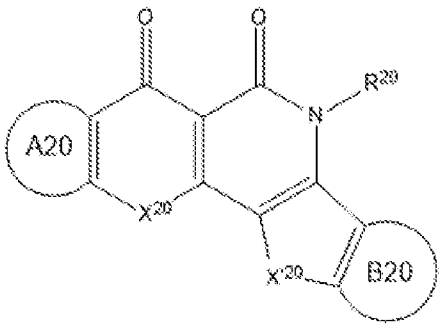
q) 

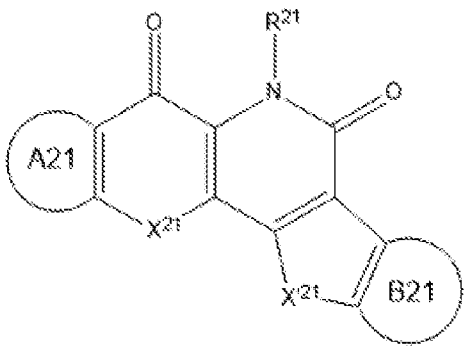
; wherein A17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B17 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{17} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{17} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{17} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

r) 

; wherein A18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B18 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{18} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{18} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{18} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

s)  ; wherein A19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B19 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{19} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{19} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{19} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3;

t)  ; wherein A20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B20 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{20} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{20} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or -OC(O)-; and R^{20} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3; or

u)  ; wherein A21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; B21 is a 5-10 membered carbocyclic or heterocyclic aromatic group; X^{21} is O, S, NH, NC_{1-4}alkyl, -CH=N-, -N=N- or -C(O)O-; X'^{21} is O, S, NH, NC_{1-4}alkyl, -N=CH-, -N=N- or

-OC(O)-; and R^{21} is H, C_{1-4}alkyl, phenyl or benzyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, said phenyl being optionally substituted by up to two substituents independently selected from methyl and CF_3, and said benzyl being optionally substituted by up to two substituents independently selected from methyl and CF_3.

14. The polycyclic compound or salt as claimed in claim 13, wherein A1-A21 are each independently selected from the group consisting of phenyl, thiophene, pyridine and benzothiophene.

15. The polycyclic compound or salt as claimed in claim 14, wherein A1-A21 are each independently selected from the group consisting of phenyl and benzothiophene.

16. The polycyclic compound or salt as claimed in any of claims 13 to 15, wherein B1-B21 are each independently selected from the group consisting of phenyl, thiophene and pyridine.

17. The polycyclic compound or salt as claimed in claim 16, wherein B1-B21 are each independently selected from the group consisting of phenyl and thiophene.

18. The polycyclic compound or salt as claimed in any of claims 13 to 17, wherein X^1-X^5 and X^{16}-X^{21} are each independently selected from O and S.

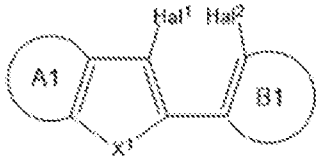
19. The polycyclic compound or salt as claimed in any of claims 13 to 18, wherein R^1-R^{21} are each H or C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, optionally wherein R^1-R^{21} are each C_{1-4}alkyl, said C_{1-4} alkyl being optionally substituted by NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$, optionally wherein R^1-R^{21} are each C_{1-4}alkyl substituted by $N(C_{1-4}alkyl)_2$.

20. The polycyclic compound or salt as claimed in claim 19, wherein R^1-R^{21} are each phenyl optionally substituted by up to two substituents independently selected from methyl and CF_3, optionally wherein R^1-R^{21} are each phenyl substituted by one CF_3.

21. The polycyclic compound or salt as claimed in any of claims 13 to 20, wherein the compound is of the formula p), and wherein A16 is different from B16 and/or X^{16} is different from X'^{16}.

22. A method of synthesising a polycyclic compound of formula a), as defined in any of claims 13 to 20, comprising:

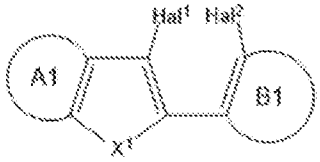
reacting a compound of formula



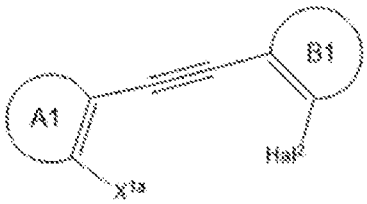
wherein A1, B1 and X^1 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^1-NH_2 in the presence of a palladium or copper catalyst, wherein R^1 is as defined in any of claims 13 to 20; and optionally forming a salt of the compound.

23. The method as claimed in claim 22, wherein the compound of formula



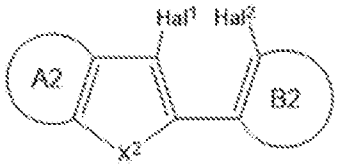
is produced by subjecting a compound of formula



, wherein A1, B1 and Hal^2 are as defined in claim 22, and X^{1a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

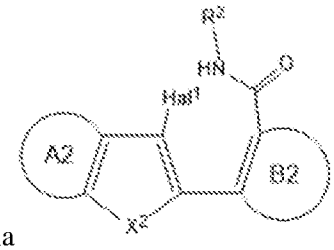
24. A method of synthesising a polycyclic compound of formula b), or salt thereof, as defined in any of claims 13 to 20, comprising:

i) reacting a compound of formula



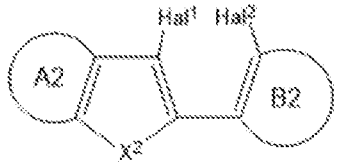
wherein A2, B2 and X^2 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

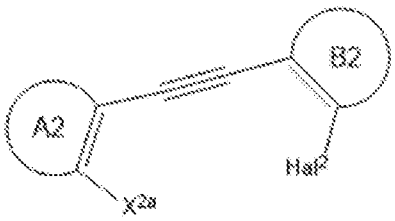
with a compound of formula R^2-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^2 is as defined in any of claims 13 to 20;

and if the product of step *i*) is a compound of formula  rather than a compound of formula b),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula b); and optionally forming a salt of the compound.

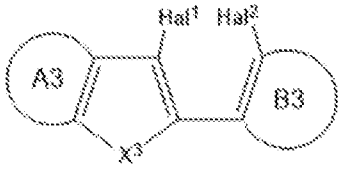
25. The method as claimed in claim 24, wherein the compound of formula

 is produced by subjecting a compound of formula

 , wherein A2, B2 and Hal^2 are as defined in claim 24, and X^{2a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

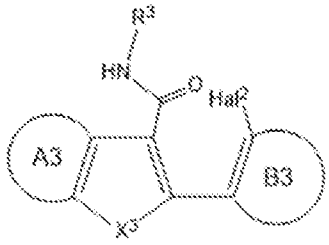
26. A method of synthesising a polycyclic compound of formula c), or salt thereof, as defined in any of claims 13 to 20, comprising:

i) reacting a compound of formula



wherein A3, B3 and X^3 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

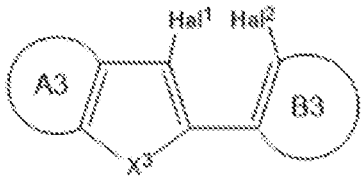
with a compound of formula R^3-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^3 is as defined in any of claims 13 to 20;



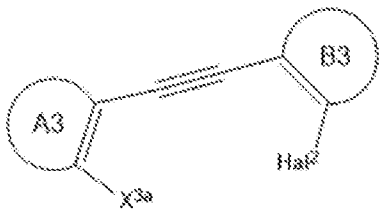
and if the product of step *i*) is a compound of formula rather than a compound of formula c),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula c); and optionally forming a salt of the compound.

27. The method as claimed in claim 26, wherein the compound of formula



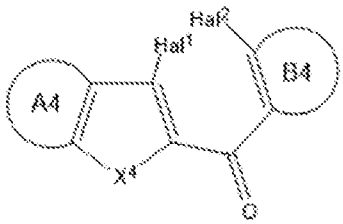
is produced by subjecting a compound of formula



, wherein A3, B3 and Hal^2 are as defined in claim 26, and X^{3a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

28. A method of synthesising a polycyclic compound of formula d), or salt thereof, as defined in any of claims 13 to 20, comprising:

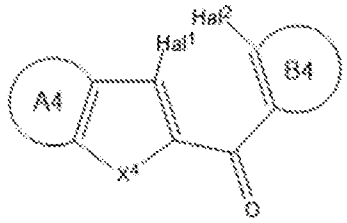
reacting a compound of formula



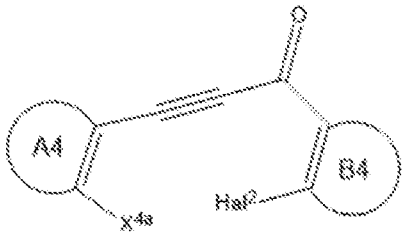
wherein A4, B4 and X^4 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^4-NH_2 in the presence of a copper catalyst, wherein R^4 is as defined in any of claims 13 to 20; and optionally forming a salt of the compound.

29. The method as claimed in claim 28, wherein the compound of formula



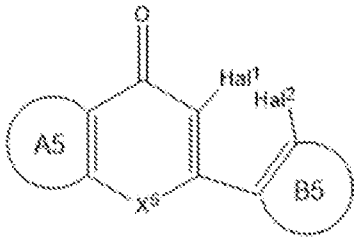
is produced by subjecting a compound of formula



, wherein A4, B4, Hal^2 are as defined in claim 28, and X^{4a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

30. A method of synthesising a polycyclic compound of formula e), or salt thereof, as defined in any of claims 13 to 20, comprising:

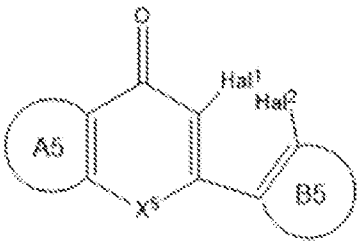
reacting a compound of formula



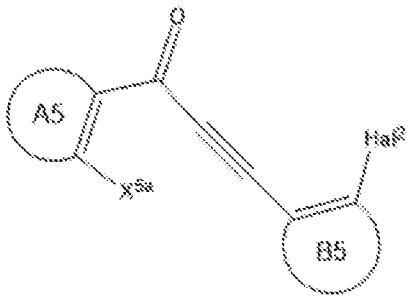
wherein A5, B5 and X^5 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^5NH_2 in the presence of a copper catalyst, wherein R^5 is as defined in any of claims 13 to 20; and optionally forming a salt of the compound.

31. The method as claimed in claim 30, wherein the compound of formula



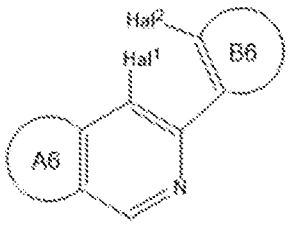
is produced by subjecting a compound of formula



, wherein A5, B5 and Hal^2 are as defined in claim 30, and X^{5a} is OC_{1-4}alkyl, SC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$; to a halocyclization reaction.

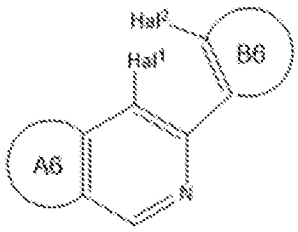
32. A method of synthesising a polycyclic compound of formula f), or salt thereof, as defined in any of claims 13 to 20, comprising:

reacting a compound of formula

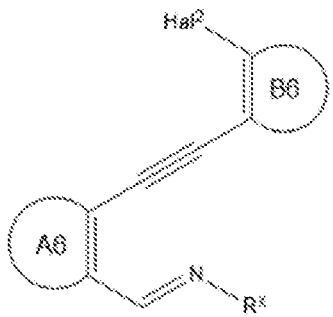


wherein A6, B6 and X^6 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^6NH_2 in the presence of a copper catalyst, wherein R^6 is as defined in any of claims 13 to 20; and optionally forming a salt of the compound.



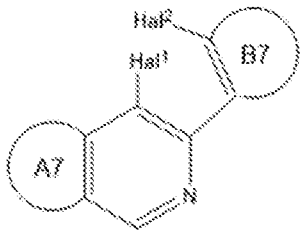
33. The method as claimed in claim 32, wherein the compound of formula



is produced by subjecting a compound of formula , wherein A6, B6 and Hal^2 are as defined in claim 32, and R^X is OC_{1-4}alkyl or C_{1-4}alkyl; to a halocyclization reaction.

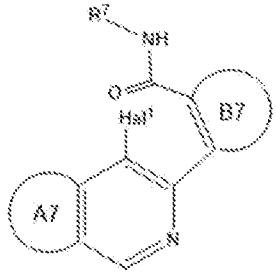
34. A method of synthesising a polycyclic compound of formula g), or salt thereof, as defined in any of claims 13 to 20, comprising:

i) reacting a compound of formula



wherein A7 and B7 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

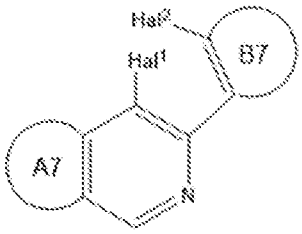
with a compound of formula R^7-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^7 is as defined in any of claims 13 to 20;

and if the product of step *i*) is a compound of formula 

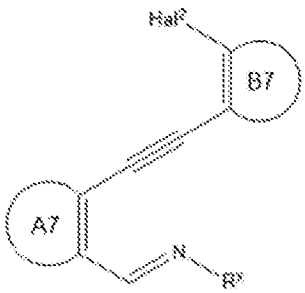
rather than a compound of formula g),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula g); and optionally forming a salt of the compound.

35. The method as claimed in claim 34, wherein the compound of formula



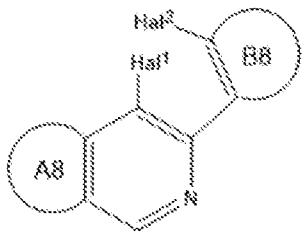
is produced by subjecting a compound of formula



, wherein A7, B7 and Hal^2 are as defined in claim 34, and R^X is $OC_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkyl; to a halocyclization reaction.

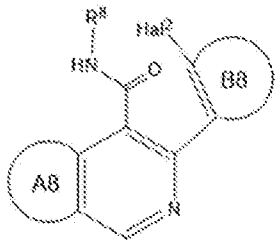
36. A method of synthesising a polycyclic compound of formula h), or salt thereof, as defined in any of claims 13 to 20, comprising:

i) reacting a compound of formula



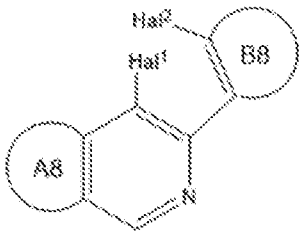
wherein A8 and B8 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

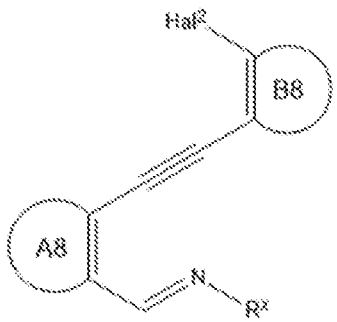
with a compound of formula R^8-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^8 is as defined in any of claims 13 to 20;

and if the product of step *i*) is a compound of formula 

rather than a compound of formula h),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula h); and optionally forming a salt of the compound.

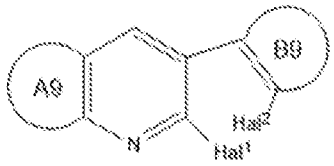
37. The method as claimed in claim 36, wherein the compound of formula 

is produced by subjecting a compound of formula 

, wherein A8, B8 and Hal^2 are as defined in claim 36, and R^X is $OC_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkyl; to a halocyclization reaction.

38. A method of synthesising a polycyclic compound of formula i) or salt thereof, as defined in any of claims 13 to 20, comprising:

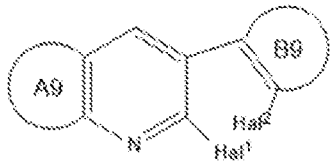
reacting a compound of formula



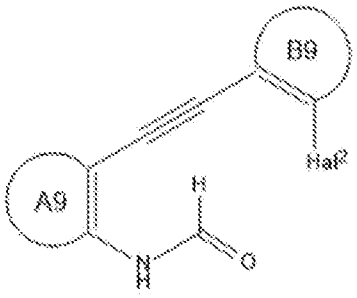
wherein A9 and B9 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^9NH_2 in the presence of a copper catalyst, wherein R^9 is as defined in any of claims 13 to 20; and optionally forming a salt of the compound.

39. The method as claimed in claim 38, wherein the compound of formula



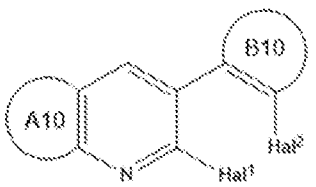
is produced by reacting a compound of formula



, wherein A9, B9 and Hal^2 are as defined in claim 38; with a dehydrating reagent, and then contacting the resulting product with a halide source.

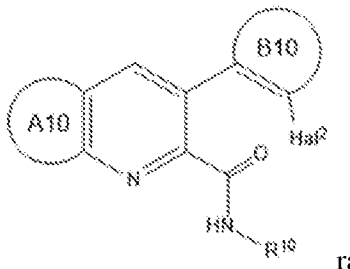
40. A method of synthesising a polycyclic compound of formula j), or salt thereof, as defined in any of claims 13 to 20, comprising:

i) reacting a compound of formula

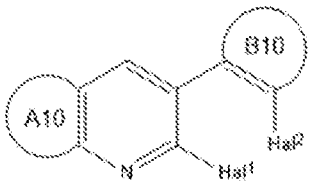
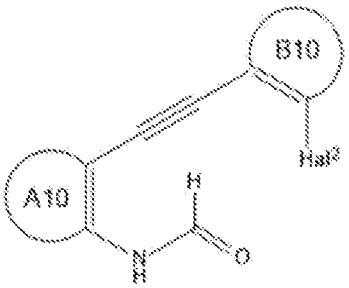


wherein A10 and B10 are as defined in any of claims 13 to 20, Hal^1 is halogen; and Hal^2 is halogen;

with a compound of formula R^{10}-NH_2 in the presence of a palladium catalyst and carbon monoxide, wherein R^{10} is as defined in any of claims 13 to 20;

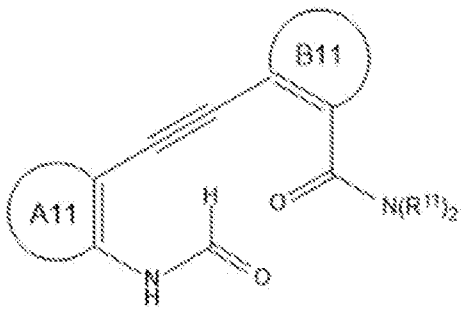
and if the product of step *i*) is a compound of formula  rather than a compound of formula j),

ii) contacting the product of step *i*) with a copper or palladium catalyst to form the compound of formula j); and optionally forming a salt of the compound.

41. The method as claimed in claim 40, wherein the compound of formula  is produced by reacting a compound of formula  , wherein A10, B10 and Hal^2 are as defined in claim 40; with a dehydrating reagent, and then contacting the resulting product with a halide source.

42. A method of synthesising a polycyclic compound of formula k), or salt thereof, as defined in any of claims 13 to 20, comprising:

reacting a compound of formula

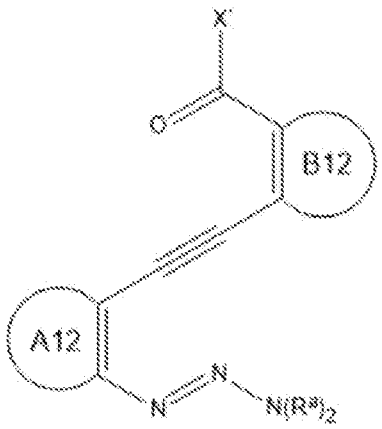


wherein A11 and B11 are as defined in any of claims 13 to 20, and wherein each R^{11} is independently C_{1-4}alkyl;

with a dehydrating reagent, and then contacting the resulting product with an acid, thereby forming the compound of formula k); and optionally forming a salt of the compound.

43. A method of synthesising a polycyclic compound or salt of formula l) as defined in any of claims 13 to 20, comprising:

contacting a compound of formula

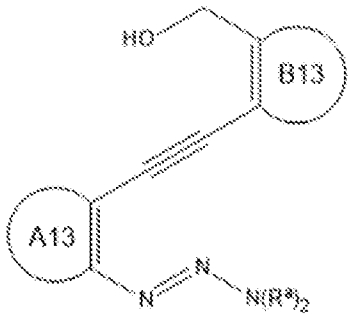


wherein A12 and B12 are as defined in any of claims 13 to 20, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group, and X′ is OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

with an acid, thereby forming the compound of formula l); and optionally forming a salt of the compound.

44. A method of synthesising a polycyclic compound of formula m), or salt thereof, as defined in any of claims 13 to 20, comprising:

contacting a compound of formula

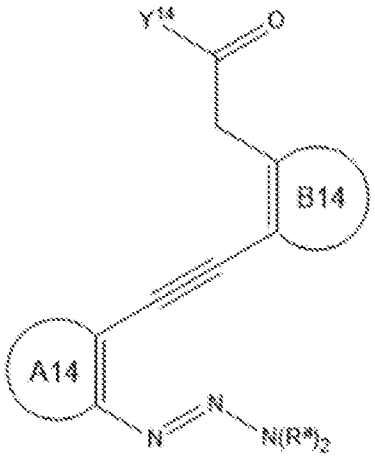


wherein A13 and B13 are as defined in any of claims 13 to 20, each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula m); and optionally forming a salt of the compound.

45. A method of synthesizing a polycyclic compound of formula n), or salt thereof, as defined in any of claims 13 to 20, comprising:

contacting a compound of formula

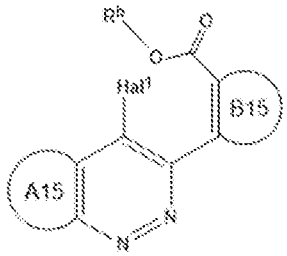


wherein A14, B14 and Y^{14} are as defined in any of claims 13 to 20, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid, thereby forming the compound of formula n); and optionally forming a salt of the compound.

46. A method of synthesizing a compound of formula o), or salt thereof, as defined in any of claims 13 to 20, comprising:

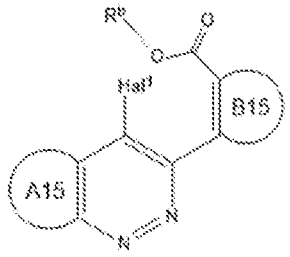
reacting a compound of formula



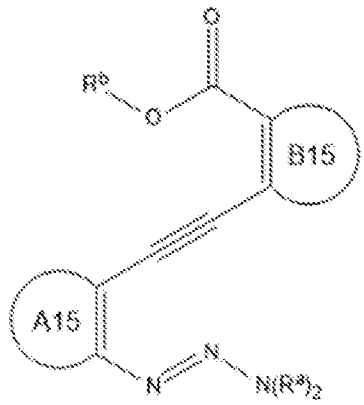
wherein A15 and B15 are as defined in any of claims 13 to 20, Hal^1 is halogen, and R^b is C_{1-4}alkyl;

with $R^{15}NH_2$, wherein R^{15} is as defined in any of claims 13 to 20, thereby forming the compound of formula o); and optionally forming a salt of the compound.

47. The method as claimed in claim 46, wherein the compound of formula



is produced by contacting a compound of formula



wherein A15, B15 and R^b are as defined in any of claims 13 to 20, and each R^a is independently C_{1-4}alkyl, or both R^a groups together with their connecting nitrogen form a pyrrolidine, piperidine or homopiperidine group;

with an acid and a halide source.

48. A method of identifying a compound having activity against a polynucleotide target or a polynucleotide-protein complex target, comprising:

testing a collection of compounds as defined in any of claims 1 to 11 or part thereof, or testing one or more compounds as defined in any of claims 12 to 21 for activity against a polynucleotide target; and

identifying whether the compound or compounds have activity against the polynucleotide target.

49. The method as claimed in claim 48, wherein the polynucleotide target is an RNA target, optionally an mRNA target, micro-RNA or a non-coding RNA target.

50. The method as claimed in claim 49, wherein the polynucleotide target is a DNA target.

51. The method as claimed in any of claims 48 to 50, wherein the polynucleotide target is a polynucleotide-protein complex or a functional DNA topology.

52. The method as claimed in any of claims 48 to 51, wherein the polynucleotide target is a DNA complex with a transcription factor, an epigenetic modulator, an RNA-polymerase complex, Z-DNA, or a G-quadruplex.

53. The method as claimed in any of claims 48 to 52, wherein the polynucleotide target is selected from the group consisting of DNA-topoisomerase 1, mRNA encoding SMN2 protein, and G-quadruplex mRNA encoding oncogenic N-Ras protein.

54. The method as claimed in any of claims 48 to 53, wherein the compound is tested for activity using an assay selected from the group consisting of a radiolabelled DNA-cleavage assay, a cell cytoxicity assay, and an affinity assay for polynucleotides and their protein complexes by one or more of surface plasmon resonance assay, fluorometric assay, nuclear magnetic resonance assay and thermal shift assay.

55. Use of a compound as defined in any of claims 13 to 21 as a reference compound in a competition assay for determining activity of a test compound against a polynucleotide target.

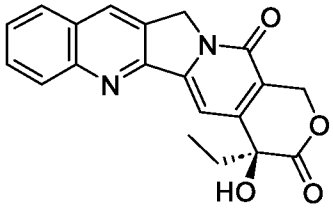
56. Use of a compound as claimed in claim 55, wherein a radiolabelled form of the compound as defined in any of claims 13 to 21 is used in the assay.

57. A phenotypic method of identifying a new polynucleotide target for therapy of a disease or disorder, comprising

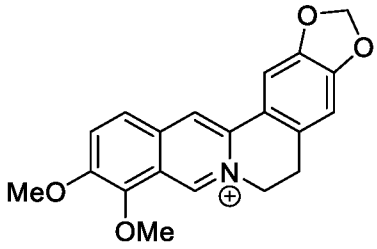
contacting a collection of compounds as defined in any of claims 1 to 11 or part thereof, or contacting one or more compounds as defined in any of claims 13 to 21 with a cell, tissue or animal disease model and monitoring for a change associated with a disease or disorder; and

if a change associated with the disease or disorder is identified, determining the biological target to which the compound binds.

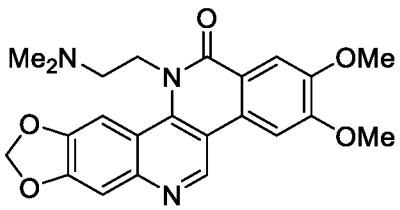
58. The phenotypic method as claimed in claim 57, wherein the compound is contacted with a cell.



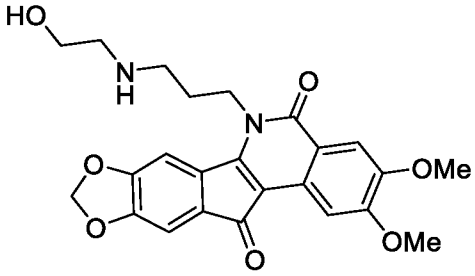
1 camptothecin



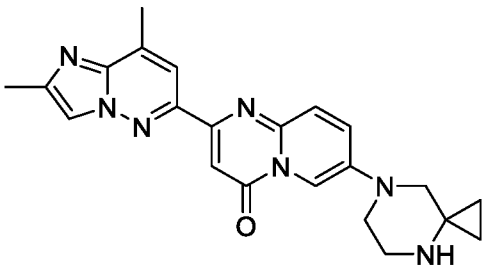
2 berberine



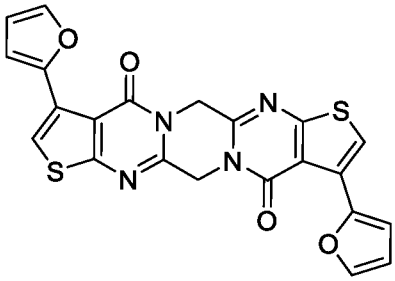
3 ARC111



4 LMP744



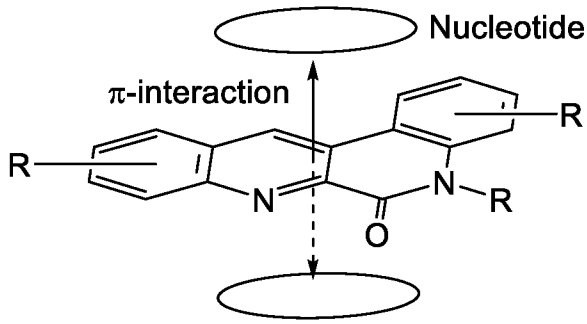
5 risdiplam



6 G4 mRNA binder

Figure 1

π-Interactions with one or more nucleotide base groups



R-groups, N and C=O make addtional D/RNA and/or protein interactions

Figure 2

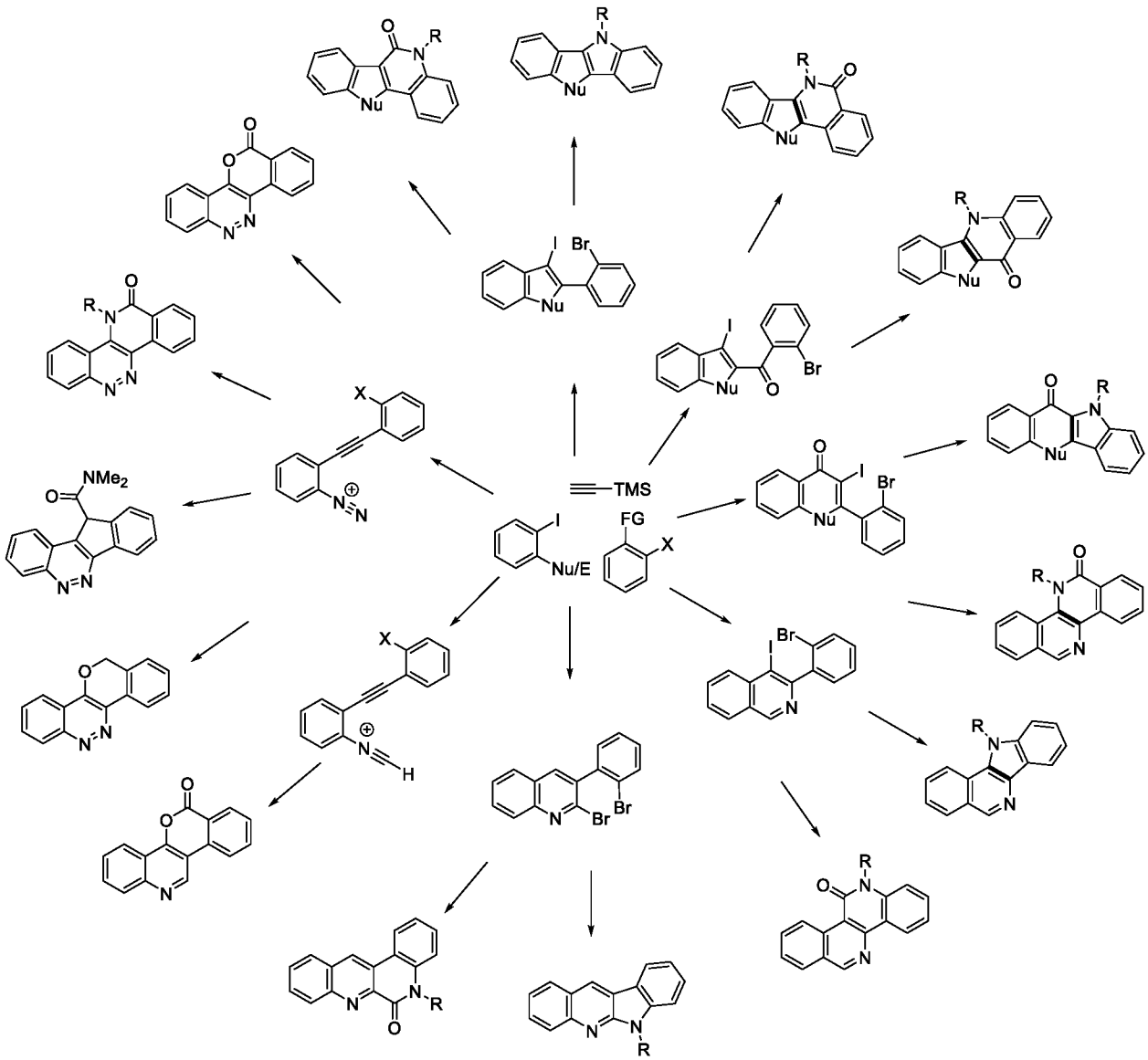


Figure 3

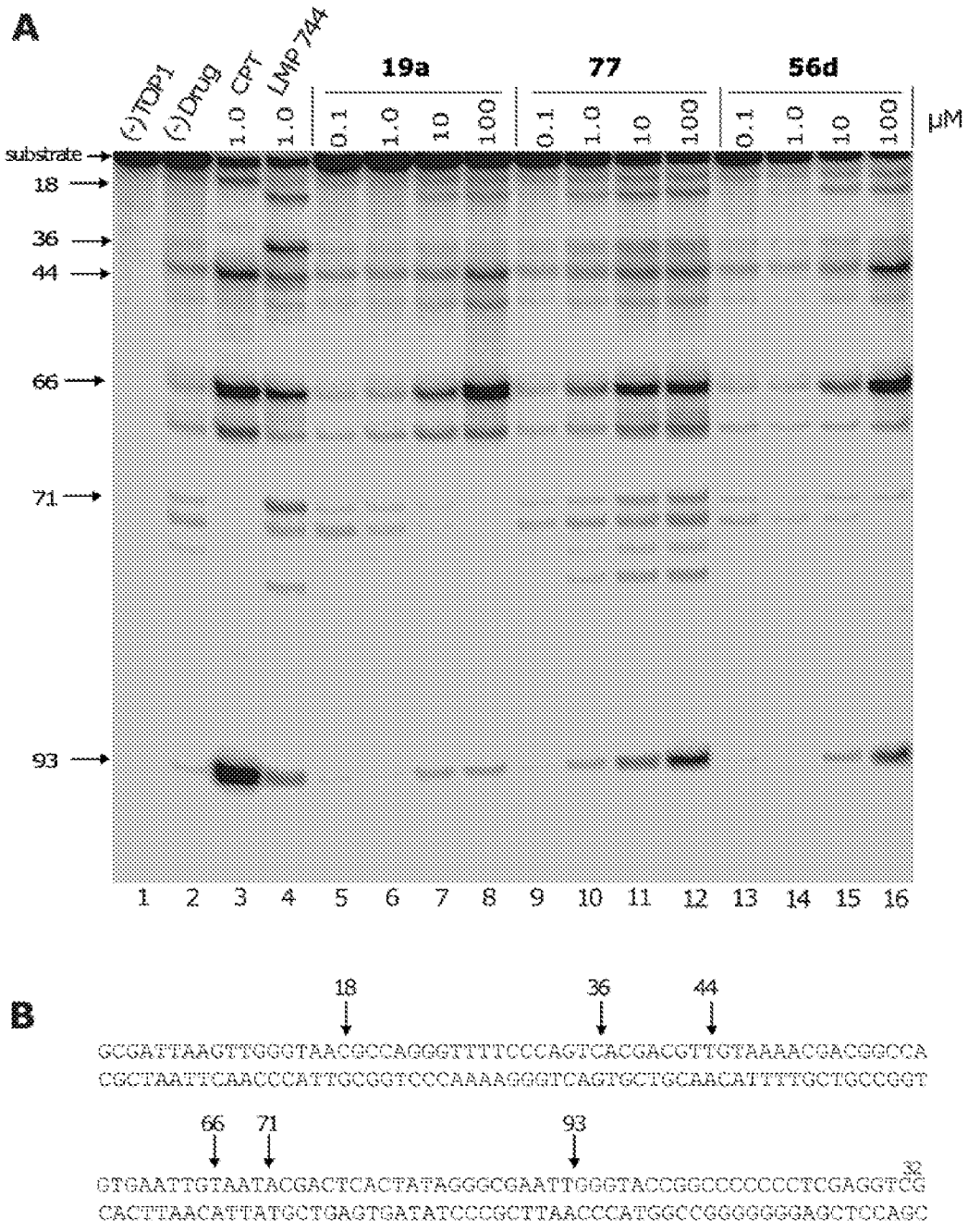

A
(-)TOP1
(-)Drug
1.0 CPT
1.0 LMP744
19a
77
56d
0.1
1.0
10
100
μM
substrate
18
36
44
66
71
93
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
B
18
36
44
GCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCA
CGCTAATTCAACCCATTGCGGTCCCAAAAGGGTCAGTGCTGCAACATTTTGCTGCCGGT
66
71
93
32
GTGAATTGTAATACGACTCACTATAGGGCGAATTGGGTACCGGCCCCCCCTCGAGGTCG
CACTTAACATTATGCTGAGTGATATCCCGCTTAACCCATGGCCGGGGGGGAGCTCCAGC

Figure 4

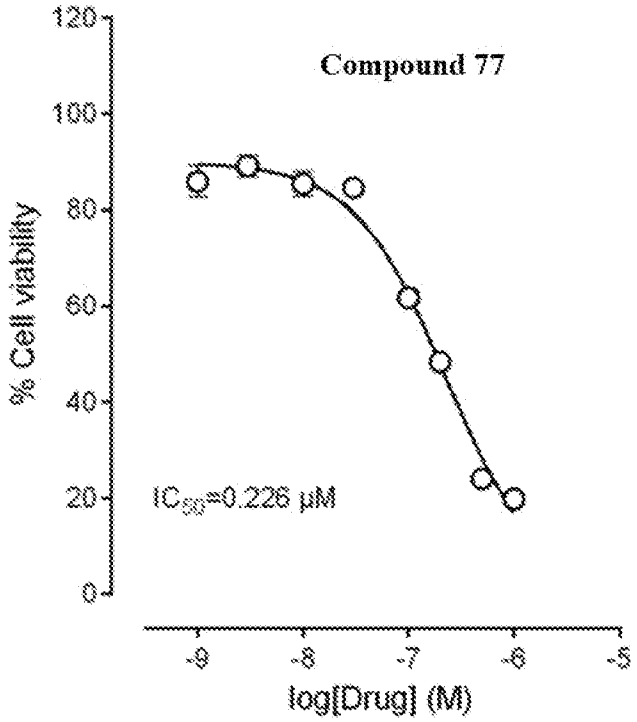


Figure 5A

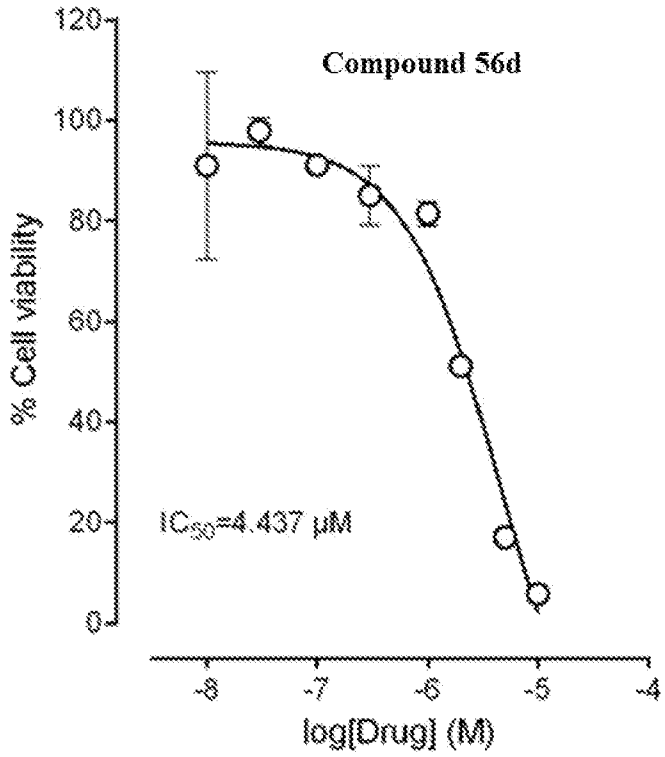


Figure 5B

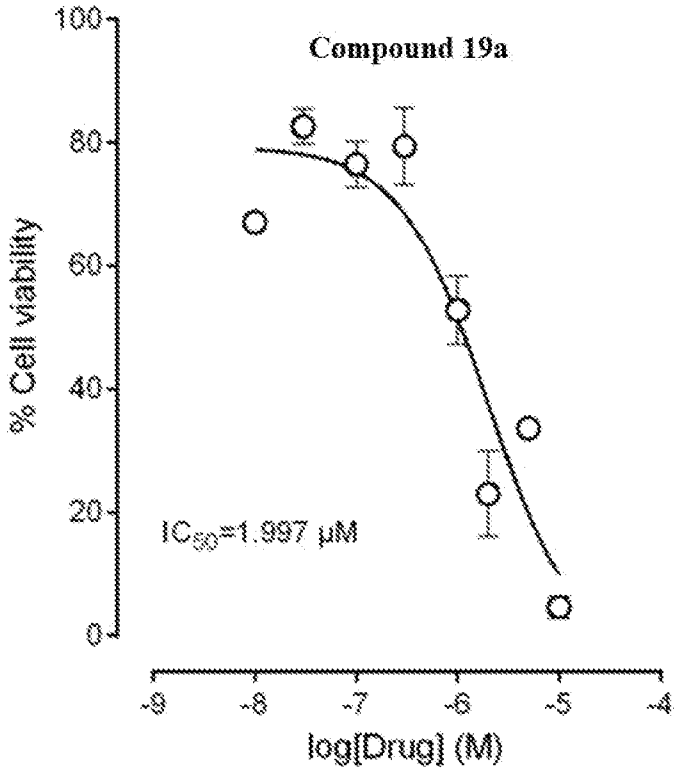

Compound 19a
% Cell viability
100
80
60
40
20
0
IC50=1.997 µM
-9
-8
-7
-6
-5
-4
log[Drug] (M)

Figure 5C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2023/050856

A. CLASSIFICATION OF SUBJECT MATTER

C07D 495/04 (2006.01) ***A61P 35/00 (2006.01)*** ***C07D 471/04 (2006.01)*** ***C07D 493/04 (2006.01)*** ***C07D 495/14 (2006.01)***

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)

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)

Databases REGISTRY and CAPLUS: structure search based on claims 1 and 12

Applicant and inventor names searched in Espacenet and internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] 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

"D" document cited by the applicant in the international application

"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	Date of mailing of the international search report
18 December 2023	18 December 2023

Name and mailing address of the ISA/AU

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Authorised officer

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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2023/050856**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 447703 A1 (THE WELLCOME FOUNDATION LIMITED) 25 September 1991 See 1B on page 11, compound 10H-benzofuro[3,2-b]indole	12-19
X	EP 2629345 B1 (NIPPON STEEL & SUMIKIN CHEMICAL CO., LTD.) 06 December 2017 See page 21, synthesis example 1, compound A-1 and the starting material	12-20
X	CN 113121542 A (CHANGZHOU UNIVERSITY) 16 July 2021 See compounds 4b and 4o on pages 9 and 26, respectively	12-17, 19
X	US 2022/0216424 A1 (MERCK PATENT GMBH) 07 July 2022 See compound 5a on page 173	12-17, 19
X	CN 111057062 A (JIANGSU YINUOFEI BIOLOGICAL TECHNOLOGY CO., LTD.) 24 April 2020 See the second product in the reaction scheme of claim 1	12-17, 19
X	CN 110396094 A (EAST CHINA NORMAL UNIVERSITY) 01 November 2019 See compounds 2a, 2r, 2u, 2v and 2z from page 9 onwards	12-18
X	CN 104370930 A (SICHUAN UNIVERSITY) 25 February 2015 See the product of example 1 in paragraph 0013	12-18
X	US 2014/0163219 A1 (SUOMING ZHANG) 12 June 2014 See compounds 22B and 23B on page 34	12-19
X	JP 2009-054809 A (MITSUI CHEMICALS INC.) 12 March 2009 See compounds 2, 3, 5, 41, 42, 53, 57, 69, 73, 77, 85 and 89 from page 7 onwards	12-17
X	JP 5055689 B2 (KONICA MINOLTA HOLDINGS, INC.) 24 October 2012 See the starting material of the reaction scheme on page 30	12-17, 19
X	Werner, L. H. *et al*, "Thianaphtheno[3,2-b]indoles", *Journal of the American Chemical Society*, 1957, **79**(7), 1675-80 See table 1 and compound numbers 2 to 5	12-19
A	Ruchelman, A. L. *et al*, "11H-Isoquino[4,3-c]cinnolin-12-ones: novel anticancer agents with potent topoisomerase I-targeting activity and cytotoxicity", *Bioorganic & Medicinal Chemistry*, 2004, **12**(4), 795-806 (DOI: 10.1016/j.bmc.2003.10.061) See title, abstract, page 797	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2023/050856

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9, 11-20, 22-27, 32-37 and 43-58

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

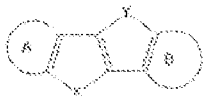
☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of: **Box III**
This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

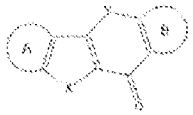
This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

Invention 1: Claims 1-9, 11-20, 48-58 (in part) and 22-27, 32-37, 43-37 (in full) are directed to compounds of general formula



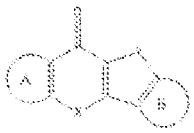
and. The feature of compounds of this general formula is specific to this group of claims.

Invention 2: Claims 1-9, 11-20, 48-58 (in part) and 28, 29 (in full) are directed to compounds of general formula



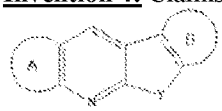
. The feature of compounds of this general formula is specific to this group of claims.

Invention 3: Claims 1-9, 11-20, 48-58 (in part) and 30, 31 (in full) are directed to compounds of general formulae



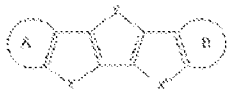
and. The feature of compounds of this general formula is specific to this group of claims.

Invention 4: Claims 1-9, 11-20, 48-58 (in part) and 38-42 (in full) are directed to compounds of general formula

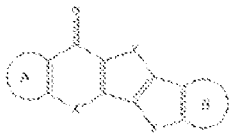


. The feature of compounds of this general formula is specific to this group of claims.

Invention 5: Claims 1-9, 11-20, 48-58 (in part) and 10, 21 (in full) are directed to compounds of general formula



. The feature of compounds of this general formula is specific to this group of claims.

Invention 6 Claims 1-9, 11-20, 48-58 (in part) are directed to compounds of general formula  . The feature of compounds of this general formula is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all the claimed inventions and which provides a technical relationship among them is compounds with a polycyclic ring system where the compounds are active against TOP1. However this feature does not make a contribution over the prior art because it is disclosed in:

Supplemental Box

Ruchelman, A. L. et al, "11H-Isoquino[4,3-c]cinnolin-12-ones: novel anticancer agents with potent topoisomerase I-targeting activity and cytotoxicity", *Bioorganic & Medicinal Chemistry*, 2004, **12**(4), 795-806. See the example compounds, especially compound 2 on page 797 and table 1 on page 798.

Therefore, in the light of this document this common feature cannot be a special technical feature. As a result, there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2023/050856**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
EP 447703 A1	25 September 1991	EP 0447703 A1	25 Sep 1991
		FI 924171 A	17 Sep 1992
		JP H06503549 A	21 Apr 1994
		MC 2251 A1	25 Mar 1993
		WO 9114688 A1	03 Oct 1991
EP 2629345 B1	06 December 2017	EP 2629345 A1	21 Aug 2013
		EP 2629345 B1	06 Dec 2017
		CN 103155200 A	12 Jun 2013
		CN 103155200 B	23 Mar 2016
		JP WO2012050003 A1	24 Feb 2014
		JP 5834015 B2	16 Dec 2015
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		TW 201231615 A	01 Aug 2012
		TW I488942 B	21 Jun 2015
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		WO 2012050003 A1	19 Apr 2012
CN 113121542 A	16 July 2021	CN 113121542 A	16 Jul 2021
		CN 113121542 B	30 Sep 2022
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		CN 113614082 A	05 Nov 2021
		EP 3947372 A1	09 Feb 2022
		KR 20210143247 A	26 Nov 2021
		WO 2020193447 A1	01 Oct 2020
CN 111057062 A	24 April 2020	CN 111057062 A	24 Apr 2020
CN 110396094 A	01 November 2019	CN 110396094 A	01 Nov 2019
		CN 110396094 B	12 Oct 2021
CN 104370930 A	25 February 2015	CN 104370930 A	25 Feb 2015
		CN 104370930 B	17 Aug 2016
US 2014/0163219 A1	12 June 2014	US 2014163219 A1	12 Jun 2014
		US 8969373 B2	03 Mar 2015
		CN 102911254 A	06 Feb 2013
		CN 103703006 A	02 Apr 2014

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2023/050856**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		CN 103703006 B	10 Aug 2016
		EP 2740734 A1	11 Jun 2014
		EP 2740734 B1	06 Sep 2017
		JP 2014533237 A	11 Dec 2014
		JP 5945837 B2	05 Jul 2016
		KR 20140076547 A	20 Jun 2014
		KR 101768985 B1	17 Aug 2017
		WO 2013017026 A1	07 Feb 2013
JP 2009-054809 A	12 March 2009	JP 2009054809 A	12 Mar 2009
JP 5055689 B2	24 October 2012	JP 2006066580 A	09 Mar 2006
		JP 5055689 B2	24 Oct 2012

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.