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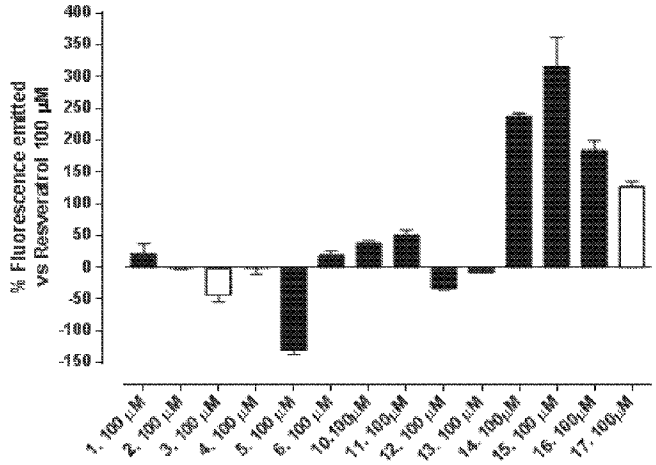
Fig. 1



(57) Abstract: This invention describes a class of compounds able to activate the human SIRT1 enzyme and regulate many metabolic functions. This invention relates to compounds that can be employed in medical applications, specifically for the treatment or prevention of cardiometabolic diseases, such as diabetes, and of cardiovascular disorders, such as coronaropathy, heart failure and atherosclerosis.

[Continued on next page]

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DESCRIPTION

FNEW ACTIVATORS OF SIRT1 ENZYME FOR THE TREATMENT OF CARDIOVASCULAR AND CARDIOMETABOLIC PATHOLOGIES

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FIELD OF THE INVENTION

This invention describes a class of compounds able to activate the human SIRT1 enzyme and regulate many metabolic functions. This invention relates to compounds that can be employed in medical applications, specifically for the treatment or prevention of cardiometabolic diseases, such as diabetes, and of cardiovascular disorders, such as coronaropathy, heart failure and atherosclerosis.

BACKGROUND OF THE INVENTION

Sirtuins are a conserved family of deacetylase enzymes deeply involved in cellular physiological processes. To date, seven types of enzymes have been described, classified from SIRT1 to SIRT7 on the basis of their different cellular localization. SIRT1 is biosynthesized in the nucleus and – on the basis of cellular needs – transferred into the cytosol through a shuttling system. In the cytosol SIRT1, influences mitochondrial activity and the metabolism of the whole cell through the modulation of different transcription cofactors which are essential for the maintenance of cellular homeostasis.

SIRT1 was first described in the yeast Saccharomyces cerevisiae and then in worms and flies, where it modulates the lifespan. The reduction of SIRT1 expression / activity, due to physiological aging and also observed in mammals, may explain the worsening of age-related cellular functions and may be linked to cardiovascular and non-cardiovascular pathologies. Recent studies have shown that SIRT1 is less effective in patients with heart failure and coronary heart disease; furthermore, pre-clinical studies have demonstrated that SIRT1 activity is reduced after ischemia-reperfusion injury. SIRT1 is also involved in insulin resistance, suggesting that it may

represent a novel and interesting target in the management of type II diabetes mellitus.

Cardiovascular diseases are still today the main cause of morbidity and mortality in Western countries and aging represents one of the main risk factors.

At present, resveratrol represents the reference activator of SIRT1. Many pharmacological effects exhibited by resveratrol in the cardiovascular system, such as vascular and myocardial protection, increased bioavailability of NO and positive effects on lipid parameters, are probably mediated through the activation of SIRT1. In spite of the numerous preclinical and clinical findings, there are great limitations on the therapeutic use of resveratrol because of its low bioavailability and metabolic issues. Although many attempts have been made to overcome problems related to its absorption by using polyphenol microemulsion formulations (SRT501), no significant improvements have been achieved. Therefore, research on and the development of new molecules activators of SIRT1 are currently considered as truly innovative strategies for the treatment of age-related diseases.

In 2007 Sinclair et al. were the first to develop synthetic derivatives starting from the resveratrol structure; other non-stilbene compounds have since been developed and are currently in advanced experimental phases. The compound SRT1720 is one of the most studied compounds: it has shown to be able to prolong life expectancy, control glucose homeostasis in different animal models of diabetes and protect the myocardium from ischemia / reperfusion injury. Furthermore, SRT2104 is a very promising SIRT1 activator, as it showed high tolerability when administered for 28 days to elderly volunteers; moreover, an assessment of its pharmacodynamic profile in humans gave promising results in respect of lipid parameters. Very recently, the results of a clinical trial in type II diabetes mellitus patients were published: the compound SRT2104 is well tolerated by diabetic patients and promotes a reduction in body weight; however, it

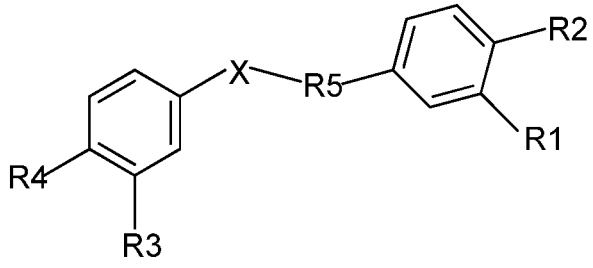
exerts no significant cardiometabolic and vascular effect. The compound SRT3025, another SIRT1 activator, has also been included in a phase I clinical trial; however, the prolongation of the QT interval (time of depolarization and repolarization of the ventricular cells) that was observed discouraged the researchers and no further study was conducted.

Since SIRT1 plays a key role in the regulation of cellular physiological processes, there is a great interest in identifying and developing novel SIRT1 activators to be employed in the treatment/prevention of cardiovascular diseases. Such compounds may provide novel ways to treat age-related diseases.

The compounds covered by this patent have been developed with the aim of improving the activity, selectivity and bioavailability of the SIRT1 activators discovered so far, and our preliminary data confirm their potential usefulness as SIRT1 activators. Indeed, novel molecules have been synthetized and they have shown SIRT1 activating properties; some of these compounds have been found to be more potent than resveratrol. Furthermore, they have shown interesting cardioprotective properties in an experimental model of acute myocardial infarction.

SUMMARY OF THE INVENTION

This invention relates to a compound having the structural formula (I):



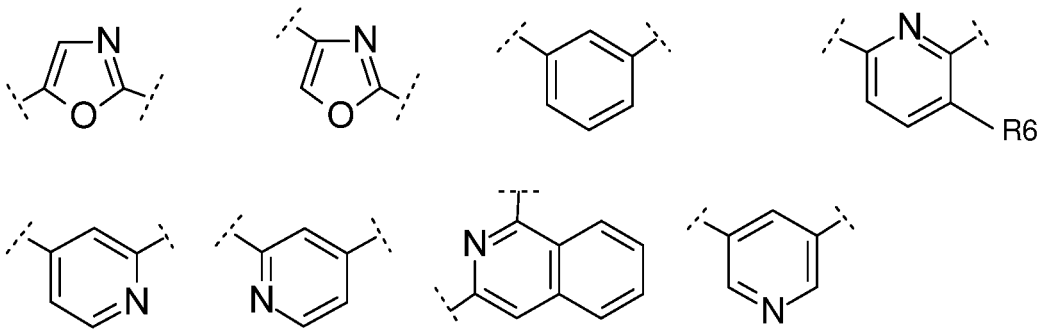
(I)

wherein

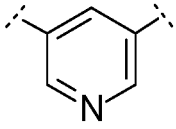
R1, R2, R3 e R4 are independently selected from –OH and -H;

X is selected from: -NH, O, S;

R5 is selected from among the following groups:



R6 is selected from –H or a non-substituted phenyl group,



with the condition that when R5 is

R2 and R3 are never simultaneously –OH.

The compound of this invention, or a pharmaceutical composition comprising said compound, is used as a medicament for the treatment or prevention of ischemic pathologies, cardio-metabolic pathologies, including diabetes, and cardiovascular pathologies, including coronary pathologies, heart failure, acute myocardial infarction and atherosclerosis.

BRIEF DESCRIPTION OF THE FIGURES

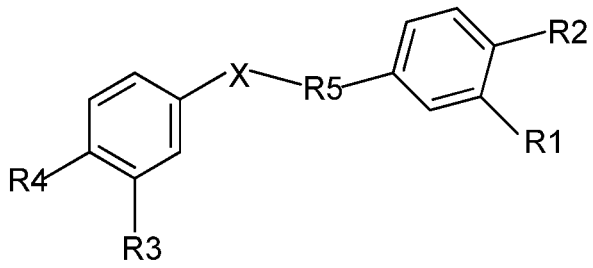
Figure 1 shows the effects of compounds 1-36 on SIRT1; data are expressed as a % vs resveratrol.

Figure 2 shows the effects of different concentrations of compounds 14-17 on SIRT1; data are expressed as a % vs resveratrol.

Figure 3 shows the effects of compounds 14 and 15 in reducing the ischemic area after an ischemia/reperfusion injury. Ischemic areas are expressed as a % of the whole left ventricle area.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a compound having the structural formula (I):



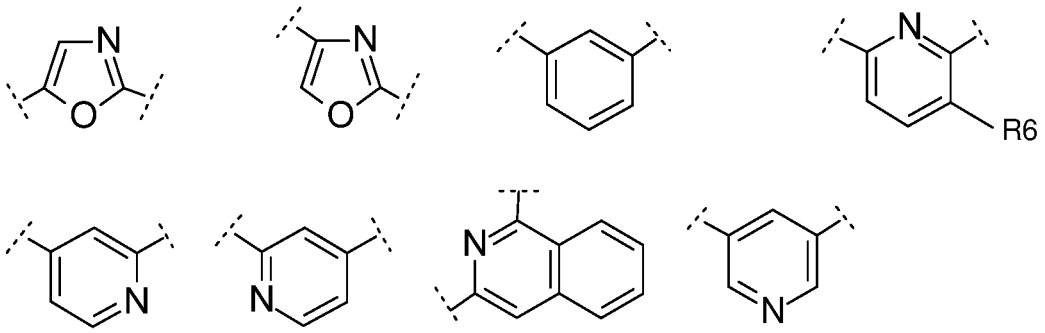
(I)

wherein

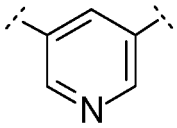
R1, R2, R3 e R4 are independently selected from –OH and -H;

X is selected from: -NH, O, S;

R5 is selected from among the following groups:



R6 is selected from –H or a non-substituted phenyl group,



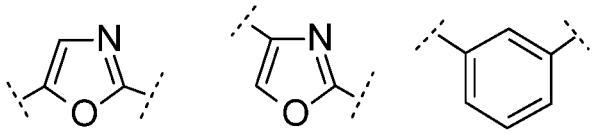
with the condition that when R5 is

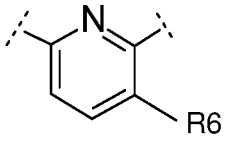
R2 and R3 are never simultaneously –OH.

In one embodiment of the invention, X is selected from –NH and -O.

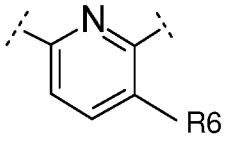
In one embodiment of the invention, X is –NH.

In one embodiment of the invention, R1, R2, R3 and R4 are independently selected from –OH and –H, X is selected from –NH and –O and R5 is

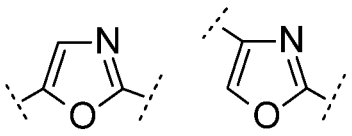
selected from the groups 

 and R6 is –H.

In a preferred embodiment of the invention, R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is

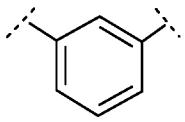
 and R6 is –H.

In one embodiment of the invention, R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is selected from the groups:



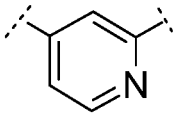
.

In one embodiment of the invention, R1, R2, R3 and R4 are independently selected from –OH and –H, X is selected from –O and -NH and R5 is



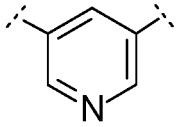
.

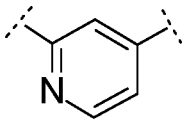
In one embodiment of the invention, R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is

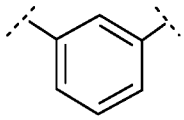


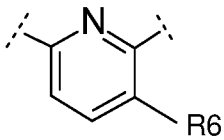
.

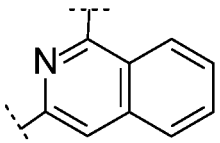
In one embodiment of the invention R1, R3 = H and R2, R4 = OH; or R2, R3 = H and R1, R4 = OH; or R2, R4 = H and R1, R3 = OH, X is –NH and

R5 is  .

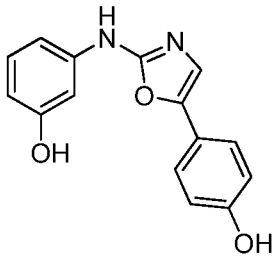
In one embodiment of the invention R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is  .

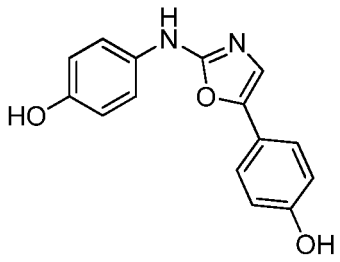
In one embodiment of the invention R1, R2, R3 and R4 are independently selected from –OH and –H, X is –S and R5 is  .

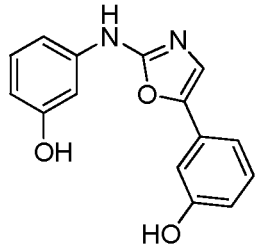
In one embodiment of the invention R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is  and R6 is a non-substituted phenyl group.

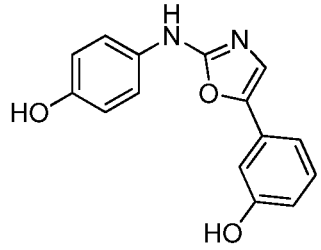
In one embodiment of the invention R1, R2, R3 and R4 are independently selected from –OH and –H, X is –NH and R5 is  .

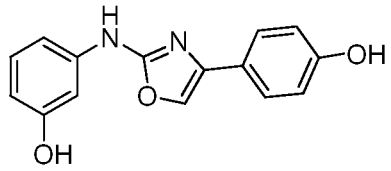
The compound according to this invention is selected from:

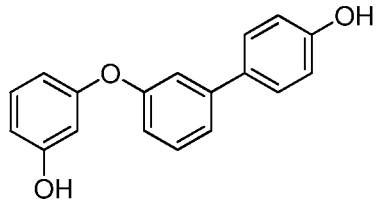
(1) 

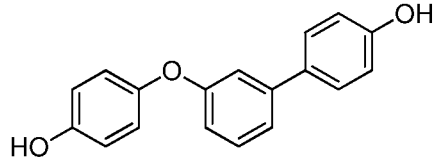
(2) 

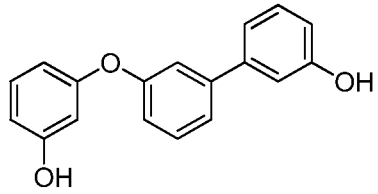
(3) 

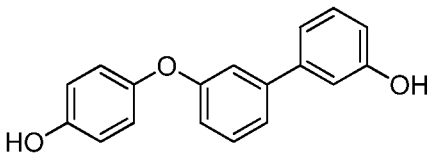
(4) 

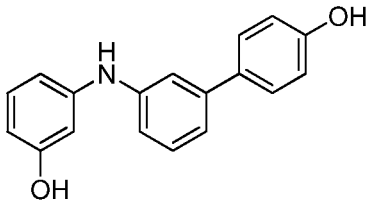
(5) 

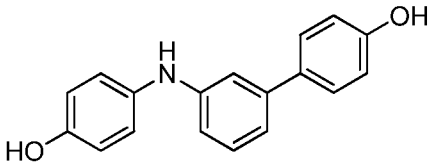
(6) 

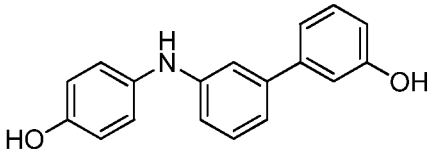
(7) 

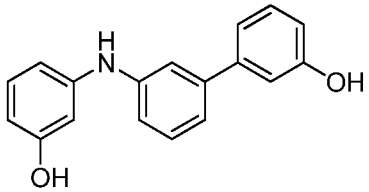
(8) 

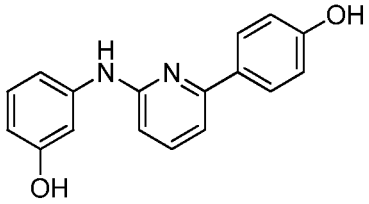
(9) 

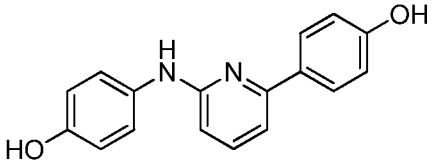
(10) 

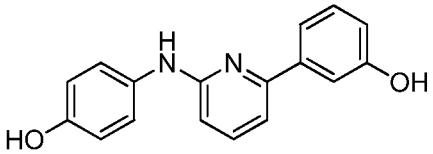
(11) 

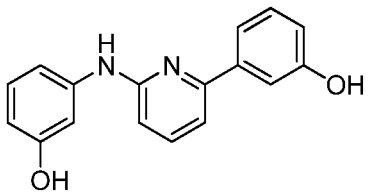
(12) 

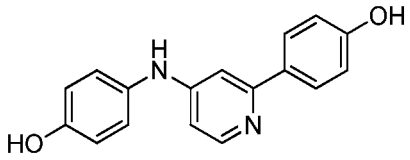
(13) 

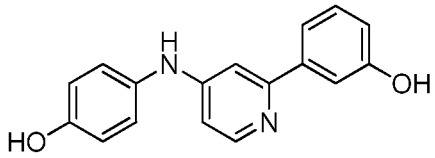
(14) 

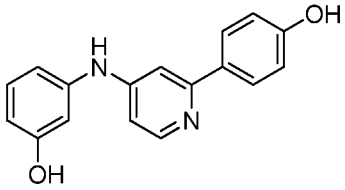
(15) 

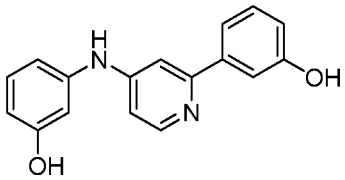
(16) 

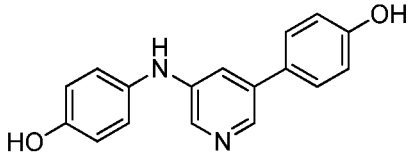
(17) 

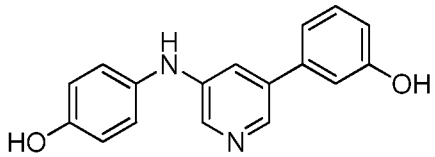
(18) 

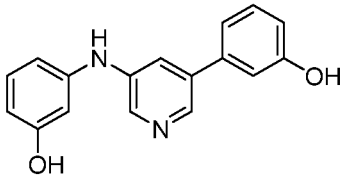
(19) 

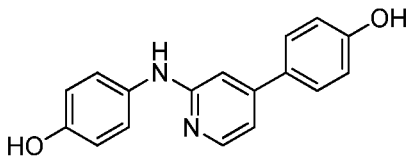
(20) 

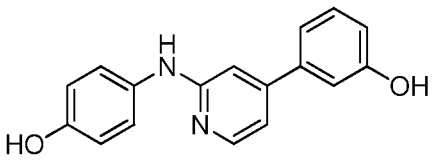
(21) 

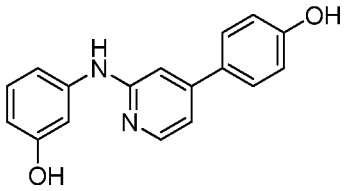
(22) 

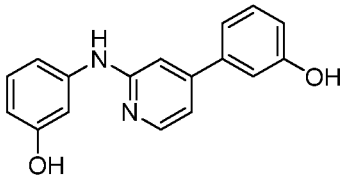
(23) 

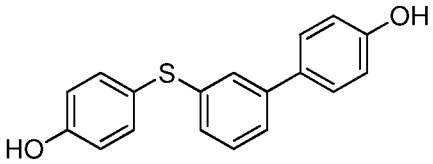
(24) 

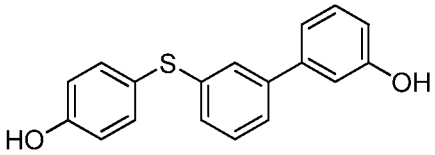
(25) 

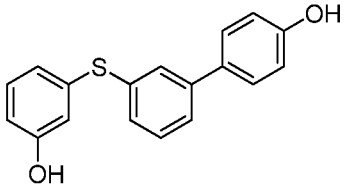
(26) 

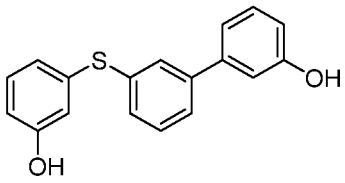
(27) 

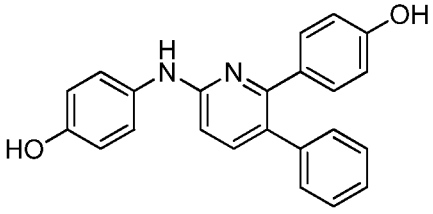
(28) 

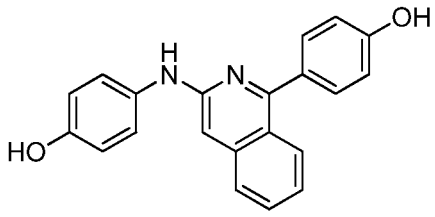
(29) 

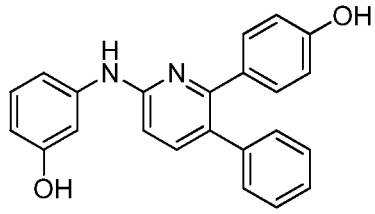
(30) 

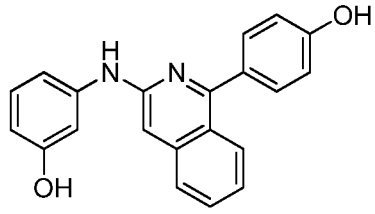
(31) 

(32) 

(33) 

(34) 

(35) 

(36) 

The compounds of the invention activate the SIRT1 enzyme and regulate cell metabolism and the transcription of numerous factors that are important for cell survival. In particular, the compounds are capable of activating the SIRT1 enzyme and favoring cell survival following an insult, for example following an ischemic insult.

A further aspect of this invention relates to a pharmaceutical composition comprising the compound according to the invention and pharmaceutically acceptable excipients, adjuvants and/or carriers.

In one embodiment of this invention, the pharmaceutical composition is formulated for enteral use, preferably oral or sublingual; for example, the composition is prepared in the form of pills, capsules, tablets, granular powder, hard-shelled capsules, orally dissolving granules, sachets or lozenges.

In one embodiment of this invention, the pharmaceutical composition is formulated for parenteral use, for example intravenous, subcutaneous or intramuscular, preferably intravenous.

A further aspect of this invention relates to the compound as described above or the pharmaceutical composition comprising the compound for use as a medicament, preferably for use in the treatment or in the prevention of cardiovascular pathologies, including coronary pathologies, heart failure, acute myocardial infarction and atherosclerosis.

A further aspect of this invention relates to the compound as described above or the pharmaceutical composition comprising the compound used in association or in combination with other molecules. Said molecules are selected from: ACE inhibitors, statins, sartans, calcium channel blockers, beta-blockers, vasodilators, digitalin, antianginal, anti-ischemic, antiarrhythmic, antihypertensive and hypocholesterolemic drugs and combinations thereof.

A further aspect of this invention relates to a method for the treatment or prevention of cardio-metabolic pathologies, including diabetes, and cardiovascular pathologies, including coronary pathologies, heart failure, acute myocardial infarction and atherosclerosis.

Said method comprises at least a step of administering an effective dose of the compound of this invention or of the pharmaceutical composition comprising said compound to a patient who has a need for said compound.

The process for preparing the compound according to this invention is exemplified in the experimental part.

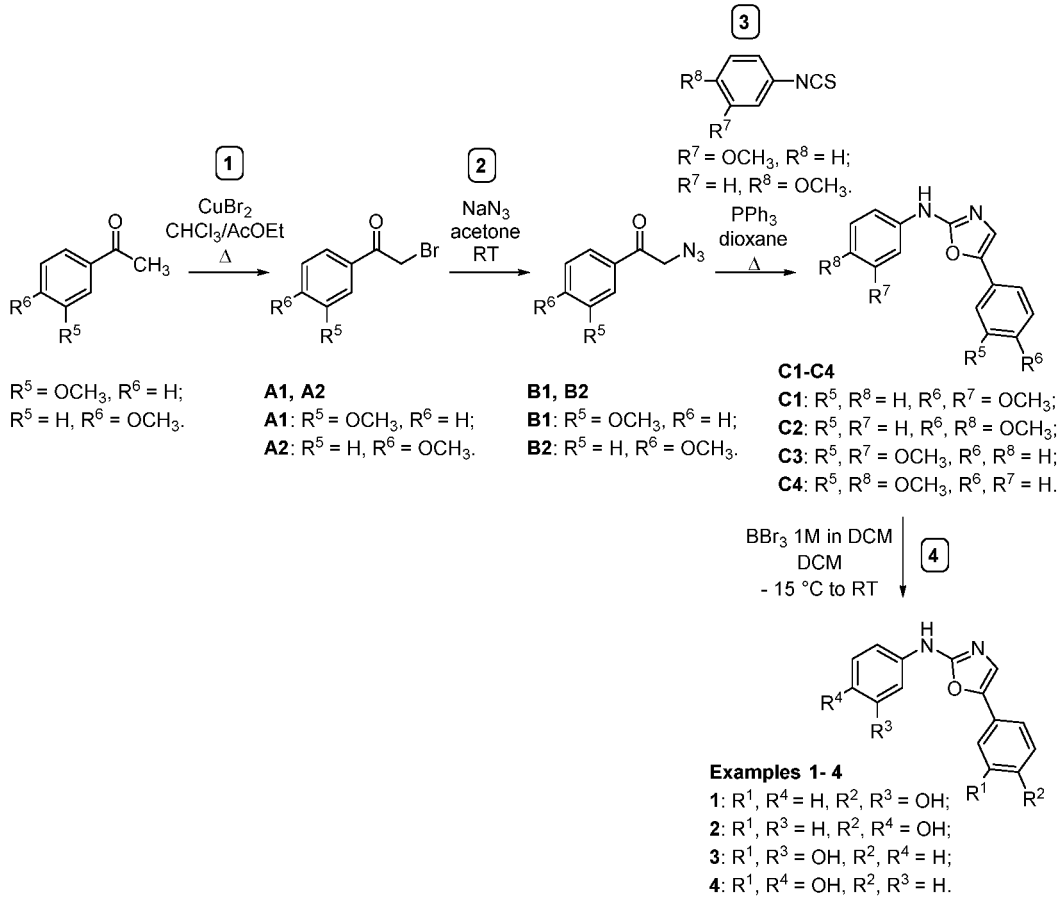
Examples

Synthesis of compounds

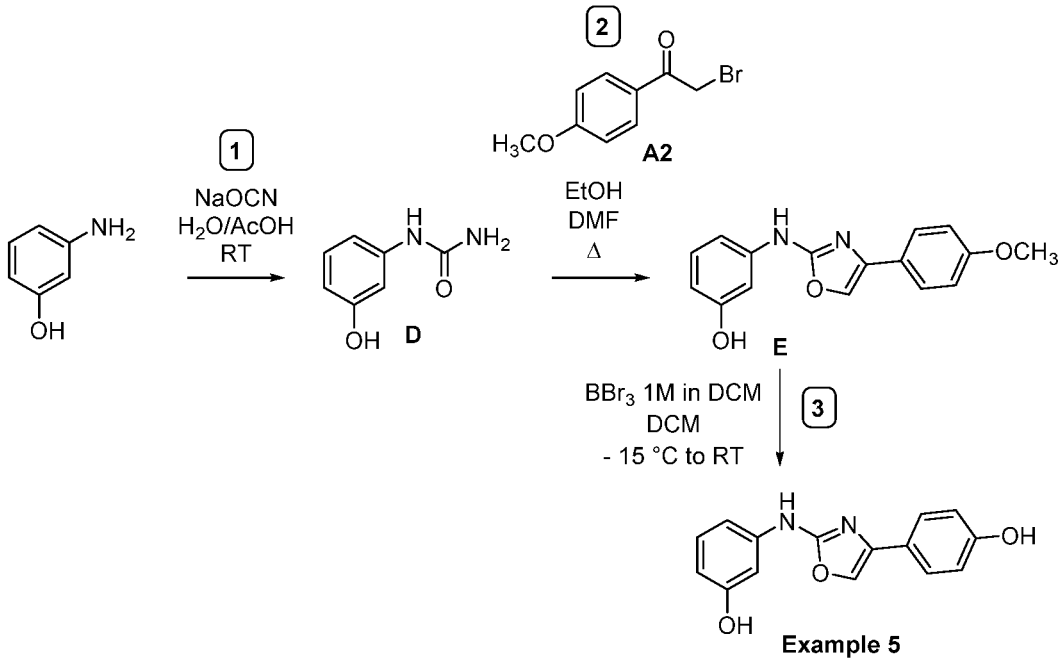
The compounds of this invention (examples 1-36) can be prepared according to the procedures described in the following schemes (schemes 1-8), specific for each series of examples.

In the procedures described below all temperatures are expressed in degrees Celsius. The following abbreviations or reagents are explained as follows: room temperature, 20-25 °C (rt), hours (h), minutes (min.), aqueous solution (aq.), potassium carbonate (K_2CO_3), sodium bicarbonate

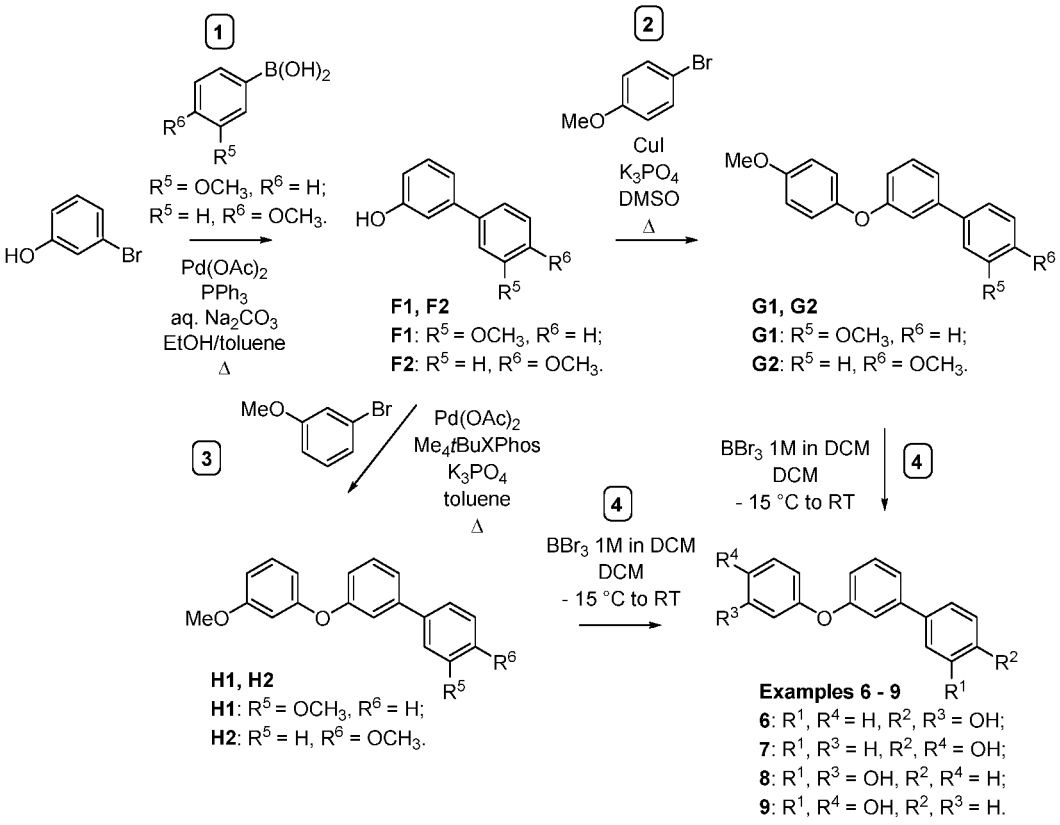
($NaHCO_3$), sodium carbonate (Na_2CO_3), potassium phosphate (K_3PO_4), dichloromethane (DCM), chloroform ($CHCl_3$), methanol (MeOH), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), ethanol (EtOH), tetrahydrofuran (THF), triethylamine (Et_3N), trifluoroacetic acid (TFA), di-tert-butyl dicarbonate ($(Boc)_2O$) isopropanol (*i*PrOH), *N*,*N*-dimethylformamide (DMF), molar concentration (M), volume/volume ratio (v/v), millimoles (mmol), millilitres (mL), thin layer chromatography (TLC), nuclear magnetic resonance (NMR), palladium acetate ($Pd(OAc)_2$), ris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), (2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1-biphenyl) (Me_4*t*BuXPhos), triphenylphosphine (PPh_3), cupric bromide ($CuBr_2$), sodium azide (NaN_3), cuprous iodide (CuI), boron tribromide (BBr_3), sodium cyanate (NaOCN), acetic acid (AcOH).



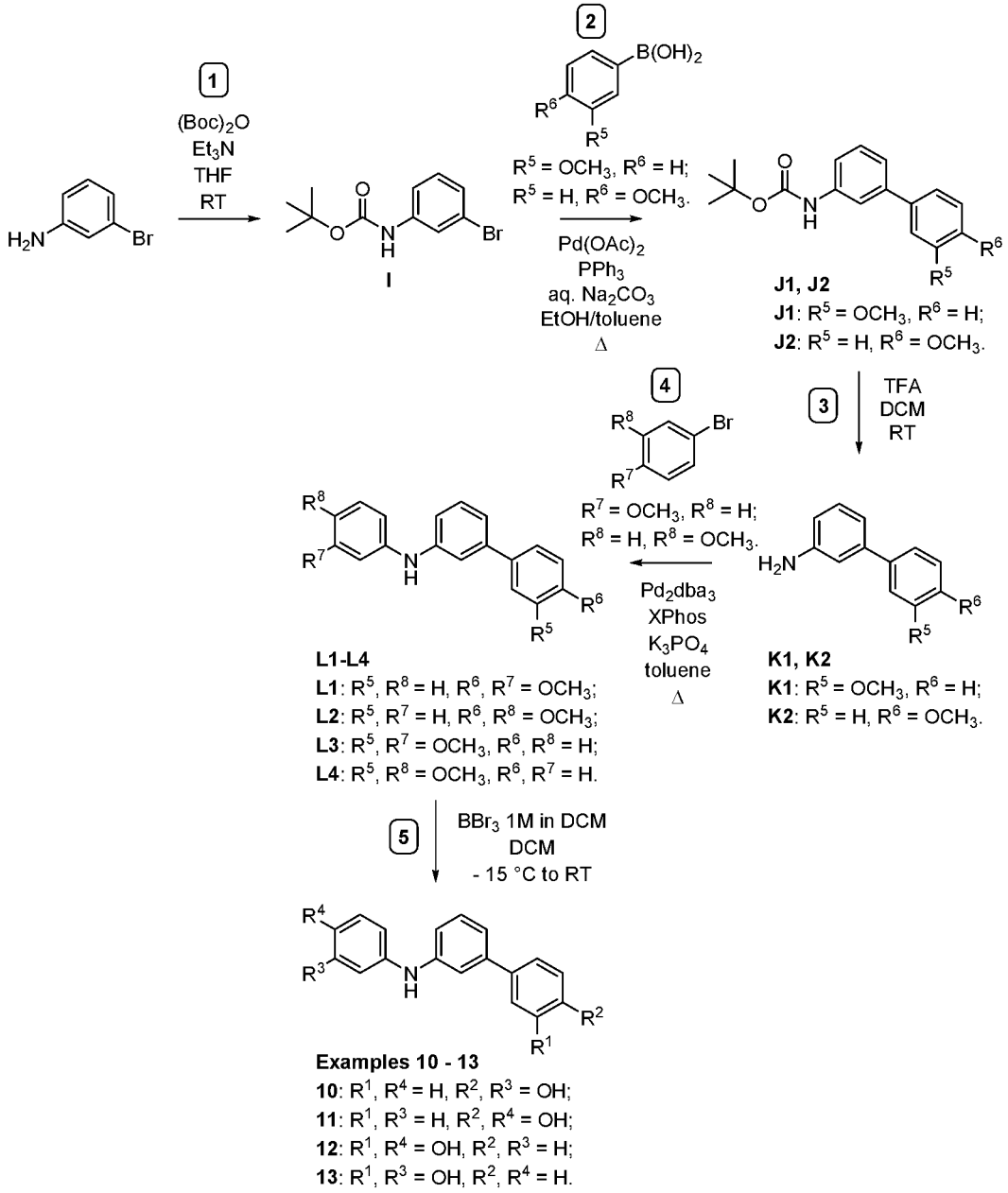
Scheme 1. Synthesis of oxazole derivatives: examples 1-4.



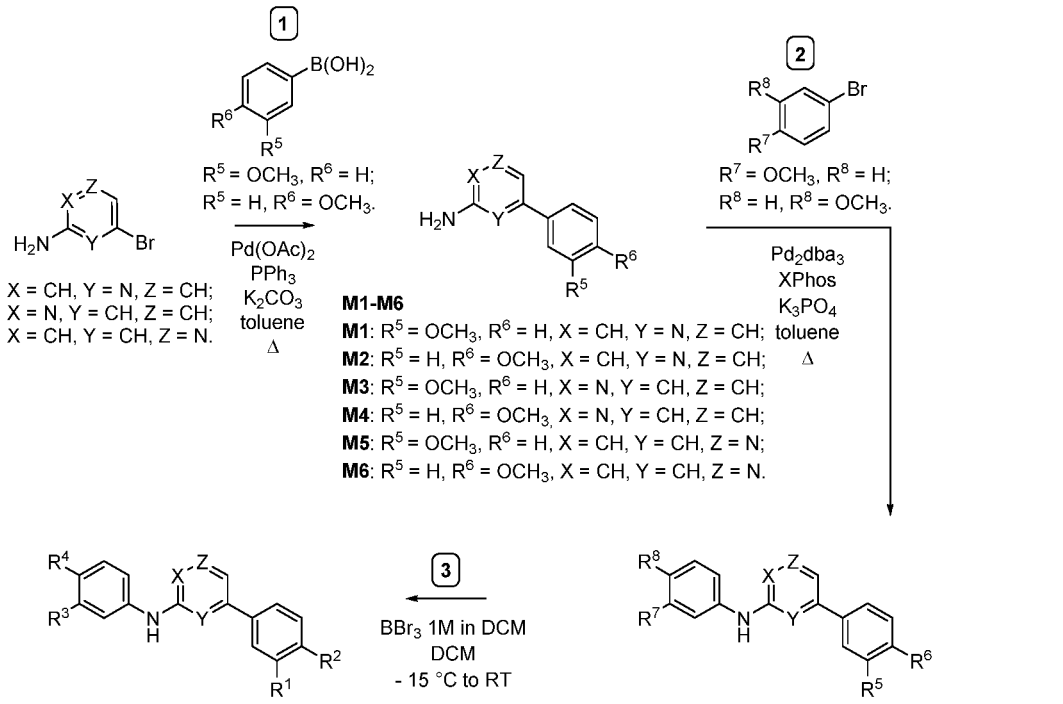
Scheme 2. Synthesis of oxazole derivative: example 5.



Scheme 3. Synthesis of diaryl ether derivatives: examples 6-9.



Scheme 4. Synthesis of aniline derivatives: examples 10-13.



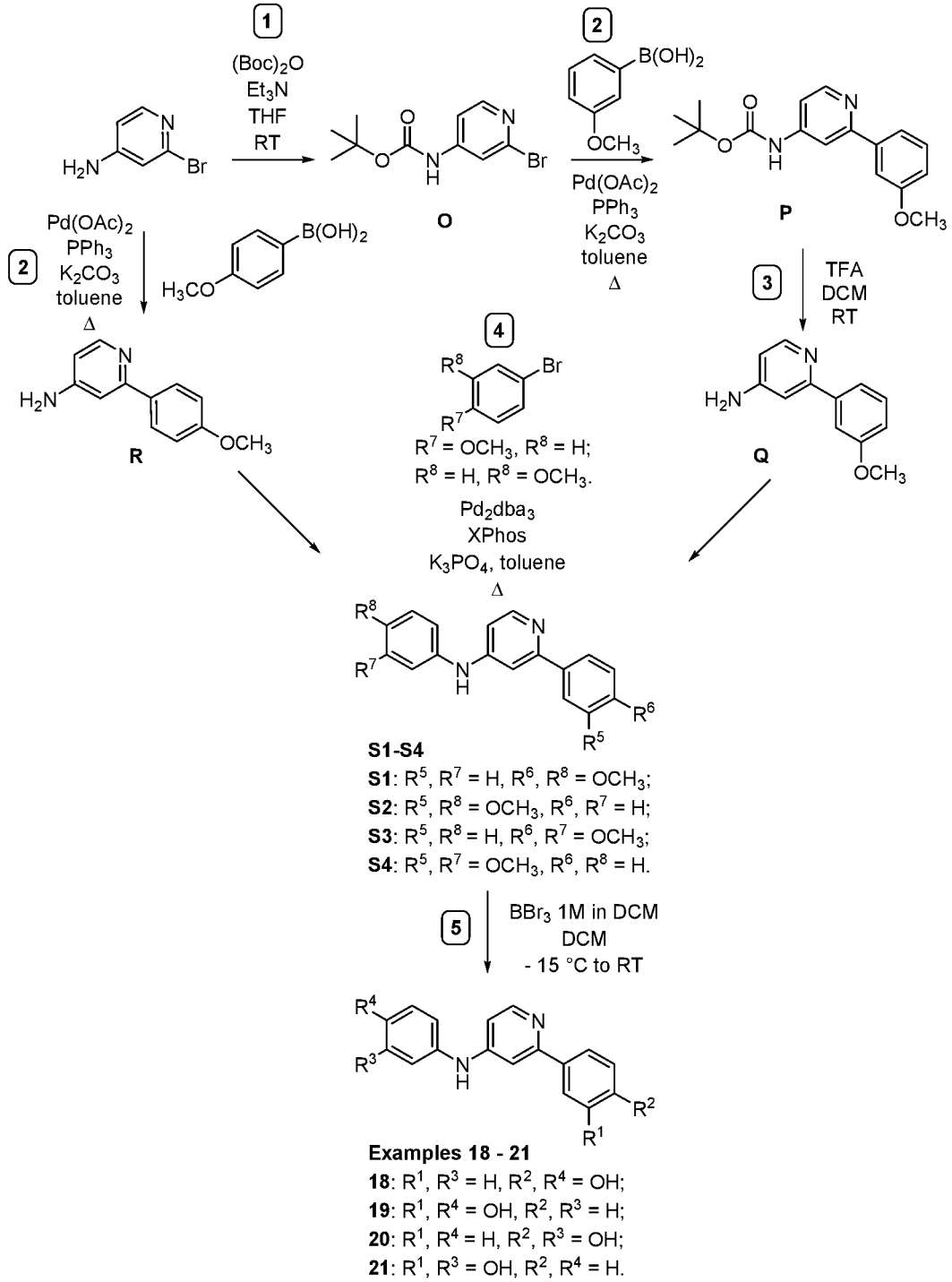
Examples 14 - 17, 22 - 28

14: R^1, R^4 = H, R^2, R^3 = OH, X = CH, Y = N, Z = CH;
15: R^1, R^3 = H, R^2, R^4 = OH, X = CH, Y = N, Z = CH;
16: R^1, R^4 = OH, R^2, R^3 = H, X = CH, Y = N, Z = CH;
17: R^1, R^3 = OH, R^2, R^4 = H, X = CH, Y = N, Z = CH;
22: R^1, R^3 = H, R^2, R^4 = OH, X = CH, Y = CH, Z = N;
23: R^1, R^4 = OH, R^2, R^3 = H, X = CH, Y = CH, Z = N;
24: R^1, R^3 = OH, R^2, R^4 = H, X = CH, Y = CH, Z = N;
25: R^1, R^3 = H, R^2, R^4 = OH, X = N, Y = CH, Z = CH;
26: R^1, R^4 = OH, R^2, R^3 = H, X = N, Y = CH, Z = CH;
27: R^1, R^4 = H, R^2, R^3 = OH, X = N, Y = CH, Z = CH;
28: R^1, R^3 = OH, R^2, R^4 = H, X = N, Y = CH, Z = CH.

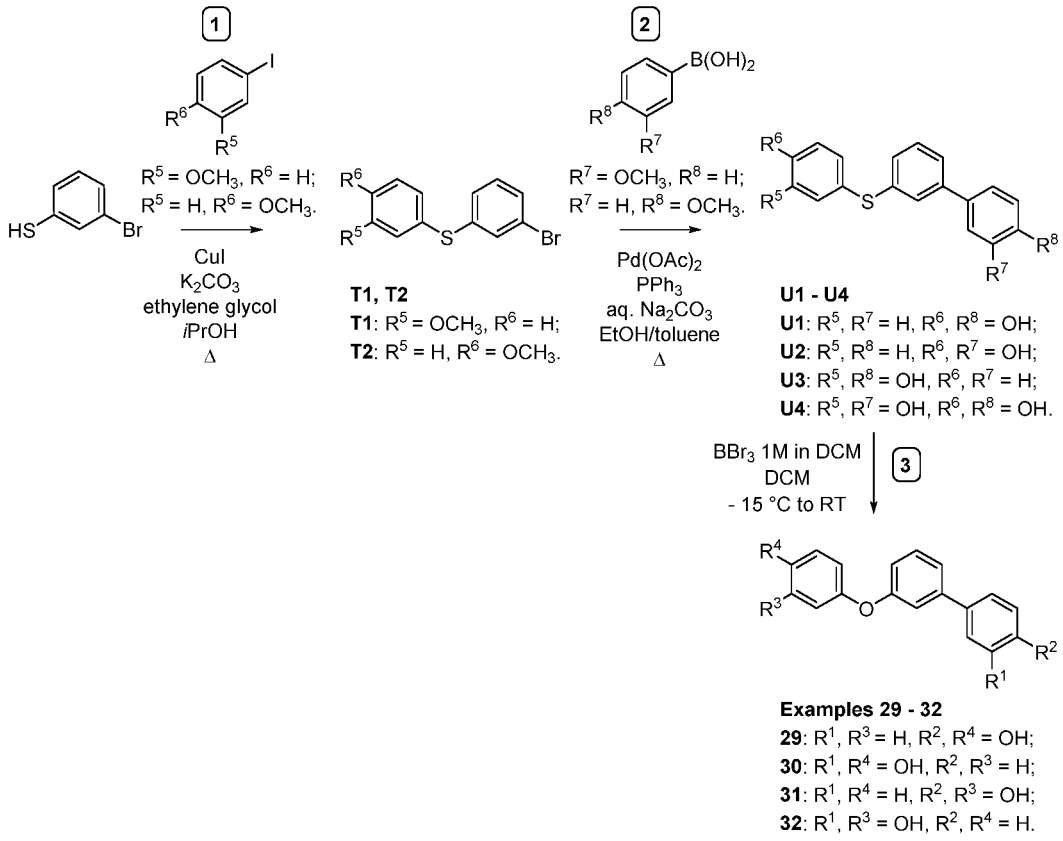
N1-N11

N1: R^5, R^7 = OCH_3, R^6, R^8 = H, X = CH, Y = N, Z = CH;
N2: R^5, R^8 = OCH_3, R^6, R^7 = H, X = CH, Y = N, Z = CH;
N3: R^5, R^8 = H, R^6, R^7 = OCH_3, X = CH, Y = N, Z = CH;
N4: R^5, R^7 = H, R^6, R^8 = OCH_3, X = CH, Y = N, Z = CH;
N5: R^5, R^7 = OCH_3, R^6, R^8 = H, X = N, Y = CH, Z = CH;
N6: R^5, R^8 = OCH_3, R^6, R^7 = H, X = N, Y = CH, Z = CH;
N7: R^5, R^8 = H, R^6, R^7 = OCH_3, X = N, Y = CH, Z = CH;
N8: R^5, R^7 = H, R^6, R^8 = OCH_3, X = N, Y = CH, Z = CH;
N9: R^5, R^7 = H, R^6, R^8 = OCH_3, X = CH, Y = CH, Z = N;
N10: R^5, R^8 = OCH_3, R^6, R^7 = H, X = CH, Y = CH, Z = N;
N11: R^5, R^7 = OCH_3, R^6, R^8 = H, X = CH, Y = CH, Z = N.

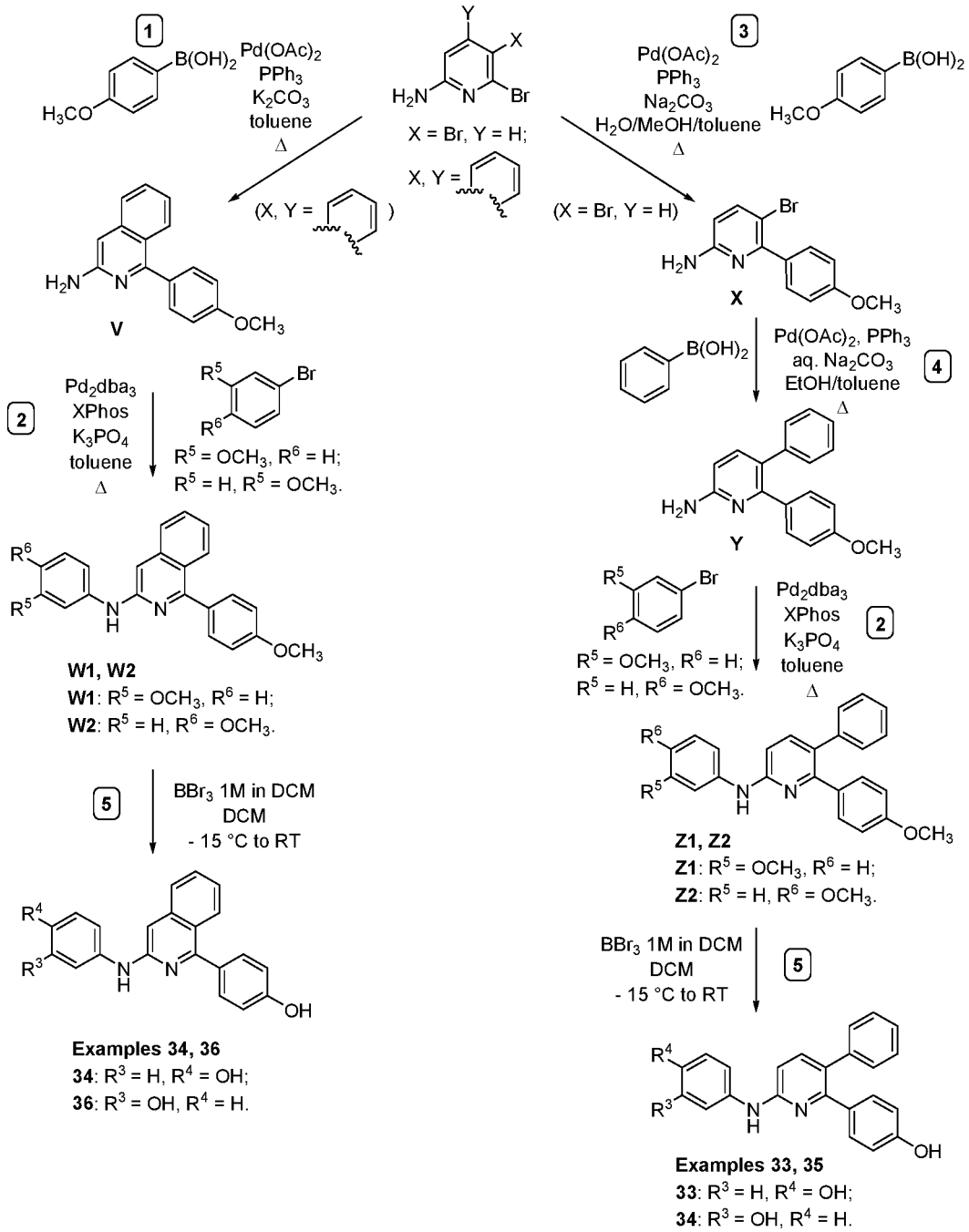
Scheme 5. Synthesis of pyridine derivatives: examples 14-17 and 22-28.



Scheme 6. Synthesis of pyridine derivatives: examples 18-21.



Scheme 7. Synthesis of diaryl thioether derivatives: examples 29-32.



Scheme 8. Synthesis of isoquinoline derivatives: examples 34 and 36; and triaryl-substituted pyridine derivatives: examples 33 and 35.

5

Procedures for the preparation of compounds 1-36

Scheme 1.

Step 1.

In a round-bottomed flask, commercially available 3- or 4-methoxy-substituted acetophenone (3.33 mmol, 500 mg) was dissolved in chloroform (7.6 mL) and ethyl acetate (7.6 mL) (1:1 v/v) to give a clear solution. Then copper (II) bromide (6.66 mmol) was added and the reaction was stirred at 85 °C for 3 h. The reaction mass was then filtered through a Celite bed, which was washed repeatedly with EtOAc. The filtrate was concentrated under vacuum. The resulting crude product was purified by column chromatography over silica gel, using *n*-hexane/EtOAc mixtures as the eluent, in order to get pure substituted phenacyl bromides A1 (72% yield) or A2 (78% yield). [A1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.87 (s, 3H), 4.45 (s, 2H), 7.16 (ddd, 1H, J = 8.3, 2.7, 0.9 Hz), 7.40 (t, 1H, J = 7.9 Hz), 7.51 (t, 1H, J = 2.1 Hz), 7.56 (dt, 1H, J = 7.9, 1.2 Hz). A2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (s, 3H), 4.40 (s, 2H), 6.96 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.97 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.5 Hz).]

Step 2.

Intermediate A1 or A2 (1.20 mmol, 275 mg) was dissolved in acetone (19.7 mL) and a single portion of sodium azide (2.40 mmol) was added to the stirred mixture, which was allowed to stir at rt overnight. The mixture was concentrated and then the residue was partitioned between EtOAc and H_2O and the aqueous layer extracted several times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to yield pure

intermediate azides B1 (92% yield) or B2 (95% yield). [B1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 4.55 (s, 2H), 7.17 (ddd, 1H, J = 8.0, 2.4, 1.2 Hz), 7.37-7.47 (m, 3H). B2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (s, 3H), 4.51 (s, 2H), 6.93-6.99 (m, 2H), 7.86-7.92 (m, 2H).]

Step 3.

Azide B1 or B2 (0.523 mmol, 100 mg) was dissolved in anhydrous 1,4-dioxane (2 mL) and commercially available 3- or 4-methoxyphenyl isothiocyanate (0.436 mmol) was added, followed by PPh_3 (0.523 mmol). The mixture was stirred at 100 °C for 30 min. The cooled solution was concentrated and the resulting crude product was purified by column chromatography over silica gel using *n*-hexane/EtOAc mixtures as the eluent, to yield intermediate C1 (83% yield); C2 (57% yield); C3 (35% yield) or C4 (74% yield). [C1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 6H), 6.63 (dd, 1H, J = 8.1, 2.0 Hz), 6.94 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.00-7.05 (m, 2H), 7.17 (t, 1H, J = 2.3 Hz), 7.26 (t, 1H, J = 8.2 Hz), 7.47 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz). C2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.81 (s, 3H), 3.84 (s, 3H), 6.88-6.95 (m, 4H), 6.99 (s, 1H), 7.40 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.45 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.4 Hz). C3: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 3.85 (s, 3H), 6.63 (ddd, 1H, J = 8.3, 2.3, 0.6 Hz), 6.83 (ddd, 1H, J = 8.2, 2.5, 0.8 Hz), 7.03 (ddd, 1H, J = 8.1, 2.1, 0.7 Hz), 7.07 (t, 1H, J = 2.0 Hz), 7.11-7.20 (m, 3H), 7.26 (t, 1H, J = 8.2 Hz), 7.31 (t, 1H, J = 8.0 Hz). C4: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.81 (s, 3H), 3.85 (s, 3H), 6.81 (ddd, 1H, J = 8.3, 2.5, 0.7 Hz), 6.92 (AA'XX', 2H, J_{AX} = 9.0 Hz,

$J_{AA'/XX'}$ = 2.9 Hz), 7.05 (t, 1H, J = 1.0 Hz), 7.10-7.15 (m, 2H), 7.23 (t, 1H, J = 8.0 Hz), 7.41 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz).]

Step 4.

A solution of methoxylated intermediate C1, C2, C3 or C4 (0.337 mmol, 100 mg) in anhydrous DCM (5.5 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (3.4 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate mixtures) to yield pure phenolic compounds examples 1-4 (example 1: yield 92%, example 2: yield 20%, example 3: yield 21%, example 4: yield 98%).

Scheme 2.

Step 1.

A solution of sodium cyanate (6.05 mmol) in H_2O (2.7 mL) was added slowly to the mixture of commercially available 3-aminophenol (5.50 mmol, 600 mg) in glacial acetic acid (0.6 mL) and H_2O (5.4 mL) at room temperature. Upon the completion of the addition, the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with H_2O, and extracted several times with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The resulting crude product was purified by column chromatography over silica gel using

DCM/MeOH mixture 8:2 as the eluent in order to obtain pure phenylurea D (yield 85%). [D: ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.76 (bs, 2H), 6.28 (ddd, 1H, J = 8.0, 2.4, 0.9 Hz), 6.69 (ddd, 1H, J = 8.1, 2.0, 0.9 Hz), 6.96 (t, 1H, J = 8.0 Hz), 7.01 (t, 1H, J = 2.2 Hz), 8.37 (bs, 1H), 9.18 (s, 1H).]

Step 2.

In a sealed vial, an equimolar mixture of compound D (1.45 mmol, 220 mg) and compound A2 (Scheme 1, 1.45 mmol) in ethanol (2.9 mL) was refluxed in the presence of DMF (0.22 mL) for about 7 h. The progress of the reaction was monitored by TLC. Upon the disappearance of the starting materials, the reaction mixture was cooled and concentrated under vacuum. The crude residue was purified by column chromatography over silica gel (*n*-hexane/EtOAc 3:7) to afford intermediate E (yield 26%). [E: ^{1}H-NMR (acetone-d_6) δ (ppm): 3.83 (s, 3H), 6.68-6.72 (m, 1H), 6.98 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.20-7.26 (m, 3H), 7.46-7.49 (m, 1H), 7.62 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.50 (s, 1H), 9.83 (bs, 1H).]

Step 3.

A solution of methoxylated intermediate E (0.365 mmol, 103 mg) in anhydrous DCM (6 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (1.8 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude

product was purified by flash chromatography (*n*-hexane/ethyl acetate 3:7) to yield the pure phenolic compound, example 5 (yield 33%).

Scheme 3.

Step 1.

A solution of $Pd(OAc)_2$ (0.0435 mmol) and triphenylphosphine (0.218 mmol) in ethanol (3.3 mL) and toluene (3.3 mL) was stirred at rt under inert atmosphere for 10 min. After that period, commercially available 3-bromophenol (1.45 mmol, 250 mg), a 2 M aqueous solution of Na_2CO_3 (3.3 mL), and commercially available 3- or 4-methoxybenzeneboronic acid (2.32 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by flash column chromatography; eluting with *n*-hexane/EtOAc mixtures as eluents afforded the biaryl intermediates F1 (99% yield) or F2 (99% yield). [F1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.87 (s, 3H), 6.83 (ddd, 1H, J = 8.0, 2.6, 1.0 Hz), 6.90 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 7.06 (t, 1H, J = 2.0 Hz), 7.11 (t, 1H, J = 2.1 Hz), 7.14-7.16 (m, 1H), 7.16-7.18 (m, 1H), 7.31 (t, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 8.0 Hz). F2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.85 (s, 3H), 4.73-4.93 (bs, 1H), 6.78 (ddd, 1H, J = 8.1, 2.5, 0.9 Hz), 6.97 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.02 (dd, 1H, J = 2.2, 1.7 Hz), 7.13 (ddd, 1H, J = 7.7, 1.7, 1.0 Hz), 7.29 (t, 1H, J = 8.0 Hz), 7.51 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz).]

Step 2.

A vial was loaded with K_3PO_4 (1.62 mmol) and intermediate F1 or F2 (1.62 mmol, 324 mg). Then, in an inert atmosphere, copper (I) iodide (0.081 mmol) in DMSO (0.6 mL) and commercially available 4-bromoanisole (0.81 mmol) were added. The vial was sealed, and the reaction mixture was stirred at 130 °C. After the reaction mixture was heated for 24 h, it was cooled to rt and the workup consisted of filtration of the reaction mixture through a Celite pad and washing with EtOAc. The filtrate was concentrated under vacuum to give a crude residue, which was then purified by flash chromatography, using mixtures of *n*-hexane/EtOAc as the eluent to give intermediates G1 (28% yield) or G2 (46% yield). [G1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.81 (s, 3H), 3.85 (s, 3H), 6.87-6.94 (m, 4H), 7.03 (AA'XX', 2H, J_{AX} = 9.1 Hz, $J_{AA'/XX'}$ = 3.0 Hz), 7.08 (t, 1H, J = 2.1 Hz), 7.13 (ddd, 1H, J = 7.6, 1.6, 0.9 Hz), 7.18 (t, 1H, J = 2.0 Hz), 7.28 (t, 1H, J = 1.3 Hz), 7.30-7.38 (m, 2H). F2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.81 (s, 3H), 3.84 (s, 3H), 6.85-6.88 (m, 1H), 6.89 (AA'XX', 2H, J_{AX} = 9.1 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.95 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.02 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 3.0 Hz), 7.14 (t, 1H, J = 2.1 Hz), 7.23 (dt, 1H, J = 8.2, 1.3 Hz), 7.33 (t, 1H, J = 7.9 Hz), 7.48 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz).]

Step 3.

A sealed vial was charged with Me_4*t*BuXPhos (0.0125 mmol), $Pd(OAc)_2$ (0.00832 mmol), K_3PO_4 (0.832 mmol), intermediate F1 or F2 (0.499 mmol, 100 mg), commercially available 3-bromoanisole (0.416 mmol) and toluene

(0.8 mL) under a positive pressure of argon. The resulting mixture was heated at 100 °C overnight. The mixture was allowed to cool to room temperature and then filtered through a small pad of Celite and washed several times with ethyl acetate; the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (*n*-hexane/EtOAc mixtures) to afford diaryl ether derivatives H1 (58% yield) or H2 (71% yield). [H1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.85 (s, 3H), 6.60-6.70 (m, 3H), 6.90 (dd, 1H, J = 8.2, 1.8 Hz), 6.97-7.03 (m, 1H), 7.09 (t, 1H, J = 1.9 Hz), 7.12-7.18 (m, 1H), 7.19-7.28 (m, 2H), 7.30-7.43 (m, 3H). H2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.85 (s, 3H), 6.60-6.69 (m, 3H), 6.93-6.99 (m, 3H), 7.20-7.27 (m, 2H), 7.30 (ddd, 1H, J = 7.6, 1.6, 1.2 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.50 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz).]

Step 4.

A solution of methoxylated intermediate G1, G2, H1 or H2 (0.349 mmol, 107 mg) in anhydrous DCM (4.1 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (2.2 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude product was purified by chromatography over silica gel (*n*-hexane/ethyl acetate mixtures) to yield pure phenolic compounds, examples 6-9

(example 6: yield 76%, example 7: yield 77%, example 8: yield 71%, example 9: yield 95%).

Scheme 4.

Step 1.

Et_3N (2.4 mL) and di-*tert*-butyl dicarbonate (10.5 mmol) were added to a solution of commercially available 3-bromoaniline (8.72 mmol, 1.50 g) in anhydrous THF (22.2 mL) at 0 °C, and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure; then the residue was diluted with EtOAc and sequentially washed with a saturated solution of sodium bicarbonate, water and brine. The organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography with a mixture of *n*-hexane/EtOAc 95:5 as the eluent to afford intermediate I (62% yield). [I: ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (s, 9H), 6.47 (bs, 1H), 7.10-7.18 (m, 2H), 7.20 (dt, 1H, J = 7.2, 2.0 Hz), 7.67 (s, 1H).]

Step 2.

A solution of $Pd(OAc)_2$ (0.0495 mmol) and triphenylphosphine (0.248 mmol) in ethanol (3.7 mL) and toluene (3.7 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, intermediate I (1.65 mmol, 450 mg), a 2 M aqueous solution of Na_2CO_3 (3.7 mL), and commercially available 3- or 4-methoxybenzeneboronic acid (2.64 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under an inert atmosphere overnight. After being cooled to rt, the

mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude residue was purified by flash column chromatography, eluting with *n*-hexane/EtOAc mixtures as eluents to afford intermediates J1 (89% yield) or J2 (89% yield). [J1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.53 (s, 9H), 3.86 (s, 3H), 6.53 (bs, 1H), 6.89 (ddd, 1H, *J* = 8.2, 2.6, 0.9 Hz), 7.11 (t, 1H, *J* = 2.1 Hz), 7.17 (ddd, 1H, *J* = 7.7, 1.6, 1.0 Hz), 7.23-7.28 (m, 1H), 7.31-7.28 (m, 3H), 7.59 (s, 1H). J2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.53 (s, 9H), 3.85 (s, 3H), 6.51 (bs, 1H), 6.96 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.22 (dt, 1H, *J* = 7.4, 1.5 Hz), 7.27-7.35 (m, 2H), 7.52 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.59 (s, 1H).]

Step 3.

Compounds J1-J2 (2.18 mmol, 653 mg) were dissolved in DCM (9.8 mL), cooled to 0 °C, treated with trifluoroacetic acid (3.0 mL), and stirred at rt until complete consumption of the starting material (as verified by TLC). The mixture was concentrated to dryness under reduced pressure, diluted with EtOAc, and washed with a 1 M $NaHCO_3$ aqueous solution. The organic layer was dried over Na_2SO_4 and concentrated to give the title compounds K1 (85% yield) or K2 (94% yield). [K1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 6.70 (ddd, 1H, *J* = 7.9, 2.3, 0.9 Hz), 6.89 (ddd, 1H, *J* = 8.2, 2.6, 0.9 Hz), 6.92 (t, 1H, *J* = 1.9 Hz), 7.00 (ddd, 1H, *J* = 7.6, 1.6, 1.0 Hz), 7.10 (t, 1H, *J* = 2.0 Hz), 7.15 (ddd, 1H, *J* = 7.6, 1.6, 1.0 Hz), 7.23 (t, 1H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.9 Hz). K2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 6.64 (ddd, 1H,

J = 7.9, 2.3, 0.9 Hz), 6.87 (t, 1H, J = 1.9 Hz), 6.93-6.98 (m, 3H), 7.20 (t, 1H, J = 7.8 Hz), 7.50 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz).]

Step 4.

A solution of Pd_2dba_3 (0.0125 mmol), XPhos (0.0502 mmol), K_3PO_4 (0.878 mmol), commercially available 3- or 4-bromoanisole (0.627 mmol) and aniline intermediate K1 or K2 (0.753 mmol, 150 mg) in toluene (1.3 mL) was stirred at 100 °C under an inert atmosphere in a sealed vial for 20 h. The reaction mixture was allowed to cool to room temperature, then filtered through a small Celite pad, washed with ethyl acetate and concentrated under vacuum. The crude residue obtained was purified by flash column chromatography (eluent mixtures of *n*-hexane/EtOAc) to give intermediates L1 (86% yield); L2 (91% yield); L3 (54% yield) or L4 (39% yield). [L1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.85 (s, 3H), 6.50 (ddd, 1H, J = 8.2, 2.4, 0.8 Hz), 6.67-6.73 (m, 2H), 6.96 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.05 (ddd, 1H, J = 8.0, 2.3, 1.0 Hz), 7.14 (ddd, 1H, J = 7.7, 1.7, 1.0 Hz), 7.18 (t, 1H, J = 8.1 Hz), 7.28 (t, 1H, J = 1.9 Hz), 7.31 (t, 1H, J = 7.9 Hz), 7.50 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz). L2: ^{1}H-NMR (acetone-d_6) δ (ppm): 3.77 (s, 3H), 3.82 (s, 3H), 6.85-7.03 (m, 6H), 7.08-7.27 (m, 5H), 7.48-7.56 (m, 2H). L3: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.86 (s, 3H), 6.51 (ddd, 1H, J = 8.2, 2.4, 0.8 Hz), 6.67-6.74 (m, 2H), 6.90 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 7.07-7.13 (m, 2H), 7.13-7.21 (m, 3H), 7.29-7.37 (m, 3H). L4: ^{1}H-NMR (acetone-d_6) δ (ppm): 3.77 (s, 3H), 3.85 (s, 3H), 6.87-6.93 (m, 3H), 6.96 (ddd, 1H, J = 8.1, 2.4, 0.9 Hz), 7.02 (ddd, 1H, J = 7.6, 1.7, 1.0 Hz),

7.10-7.13 (m, 1H), 7.13-7.18 (m, 3H), 7.19 (bs, 1H), 7.21-7.24 (m, 1H), 7.25 (t, 1H, *J* = 7.9 Hz), 7.34 (t, 1H, *J* = 7.9 Hz).]

Step 5.

A solution of methoxylated intermediate L1, L2, L3 or L4 (0.426 mmol, 130 mg) in anhydrous DCM (5.0 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (2.7 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of starting material as verified by TLC analysis). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude product was purified by chromatography over silica gel (*n*-hexane/ethyl acetate mixtures) to yield pure phenolic compounds, examples 10-13 (example 10: yield 72%, example 11: yield 83%, example 12: yield 98%, example 13: yield 86%).

Scheme 5.

Step 1.

A solution of $Pd(OAc)_2$ (0.0607 mmol) and triphenylphosphine (0.303 mmol) in toluene (19.6 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, commercially available 2-amino-6-bromopyridine (X = CH, Y = N, Scheme 5) or 2-amino-4-bromopyirdine (X = N, Y = CH, Scheme 5) or 3-amino-5-bromopyridine (X = CH, Y = CH, Z = N, Scheme 5)(2.02 mmol, 350 mg), anhydrous K_2CO_3 (3.03 mmol), and commercially available 3- or 4-methoxybenzeneboronic acid (4.04 mmol) were sequentially added. The

resulting mixture was heated at 100 °C in a sealed vial under an inert atmosphere overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude residue was purified by flash column chromatography, eluting with *n*-hexane/EtOAc mixtures as eluents to afford the biaryl intermediates M1 (99% yield); M2 (91% yield); M3 (97% yield), M4 (98% yield), M5 (99% yield) or M6 (94% yield). [M1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (s, 3H), 4.67 (bs, 2H), 6.48 (dd, 1H, J = 8.1, 0.6 Hz), 6.93 (ddd, 1H, J = 8.2, 2.6, 1.0 Hz), 7.08 (dd, 1H, J = 7.5, 0.7 Hz), 7.34 (t, 1H, J = 7.9 Hz), 7.46-7.55 (m, 3H). M2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.85 (s, 3H), 4.67 (bs, 2H), 6.42 (dd, 1H, J = 8.1, 0.7 Hz), 6.97 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.03 (dd, 1H, J = 7.6, 0.7 Hz), 7.49 (dd, 1H, J = 8.1, 7.6 Hz), 7.90 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz). M3: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 4.64 (bs, 2H), 6.70 (dd, 1H, J = 1.5, 0.7 Hz), 6.88 (dd, 1H, J = 5.5, 1.6 Hz), 6.96 (ddd, 1H, J = 8.3, 2.6, 0.9 Hz), 7.10 (t, 1H, J = 2.1 Hz), 7.17 (ddd, 1H, J = 7.7, 1.6, 0.9 Hz), 7.37 (t, 1H, J = 7.9 Hz), 8.14 (dd, 1H, J = 5.4, 0.5 Hz). M4: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 4.45-4.55 (bs, 2H), 6.68 (dd, 1H, J = 1.5, 0.7 Hz), 6.86 (dd, 1H, J = 5.4, 1.6 Hz), 6.98 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.54 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.08 (dd, 1H, J = 5.4, 0.6 Hz). M5: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 6.93 (ddd, 1H, J = 8.2, 2.6, 0.8 Hz), 7.07 (t, 1H, J = 2.0 Hz), 7.10-7.15 (m, 1H), 7.16 (t, 1H, J = 2.3 Hz), 7.37 (t, 1H, J = 8.0 Hz), 8.09 (d, 1H, J = 2.5 Hz), 8.25 (d, 1H, J =

1.5 Hz). M6: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.50-3.90 (bs, 2H), 3.85 (s, 3H), 6.98 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.12 (dd, 1H, J = 2.5, 2.0 Hz), 7.48 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.04 (d, 1H, J = 2.6 Hz), 8.23 (d, 1H, J = 1.9 Hz).]

Step 2.

A solution of Pd_2dba_3 (0.0108 mmol), XPhos (0.0433 mmol), K_3PO_4 (0.757 mmol), commercially available 3- or 4-bromoanisole (0.541 mmol) and aniline intermediate M1, M2, M3, M4, M5 or M6 (0.649 mmol, 130 mg) in toluene (1.1 mL) was stirred at 100 °C under an inert atmosphere in a sealed vial for 20 h. The reaction mixture was allowed to cool to room temperature, then filtered through a small Celite pad and washed with ethyl acetate; the filtrate was concentrated under vacuum. The crude residue obtained was purified by flash column chromatography (eluent mixtures of *n*-hexane/EtOAc) to give intermediates N1 (64% yield), N2 (48% yield), N3 (99% yield), N4 (83% yield), N5 (42% yield), N6 (23% yield), N7 (40% yield), N8 (22% yield), N9 (2% yield), N10 (57% yield) or N11 (63% yield). [N1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.91 (s, 3H), 6.62 (ddd, 1H, J = 8.3, 2.5, 0.7 Hz), 6.83 (d, 1H, J = 7.8 Hz), 6.91-6.98 (m, 2H), 7.18-7.25 (m, 3H), 7.37 (t, 1H, J = 7.9 Hz), 7.53-7.62 (m, 2H), 7.64 (t, 1H, J = 2.1 Hz). N2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.90 (s, 3H), 6.64 (dd, 1H, J = 8.3, 0.6 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 6.95 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 7.13 (dd, 1H, J = 7.5, 0.7 Hz), 7.32 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.49-7.56 (m, 2H), 7.58-7.61 (m, 1H). N3:

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.87 (s, 3H), 6.60 (ddd, 1H, J = 8.1, 2.5, 0.8 Hz), 6.60-6.67 (bs, 1H), 6.78 (d, 1H, J = 8.2 Hz), 6.92 (ddd, 1H, J = 8.0, 2.0, 0.7 Hz), 7.98 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.13-7.18 (m, 2H), 7.24 (t, 1H, J = 8.1 Hz), 7.55 (t, 1H, J = 7.9 Hz), 7.97 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.5 Hz). N4: ^{1}H-NMR (acetone-d_6) δ (ppm): 3.78 (s, 3H), 3.86 (s, 3H), 6.65 (dd, 1H, J = 8.3, 0.6 Hz), 6.91 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.01 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.19 (dd, 1H, J = 7.5, 0.6 Hz), 7.54 (dd, 1H, J = 8.2, 7.6 Hz), 7.66 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 8.01 (bs, 1H), 8.05 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz). N5: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.86 (s, 3H), 6.62 (ddd, 1H, J = 8.4, 2.4, 0.8 Hz), 6.73 (bs, 1H), 6.91-6.99 (m, 3H), 7.00 (t, 1H, J = 2.2 Hz), 7.07-7.12 (m, 2H), 7.16 (ddd, 1H, J = 7.6, 1.6, 1.0 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.37 (t, 1H, J = 7.9 Hz), 8.25 (d, 1H, J = 5.6 Hz). N6: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.85 (s, 3H), 6.57 (bs, 1H), 6.84-6.96 (m, 5H), 7.07 (t, 1H, J = 2.0 Hz), 7.13 (ddd, 1H, J = 7.6, 1.7, 1.0 Hz), 7.24-7.30 (m, 2H), 7.35 (t, 1H, J = 7.9 Hz), 8.18 (dd, 1H, J = 5.3, 0.6 Hz). N7: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.85 (s, 3H), 6.62 (ddd, 1H, J = 8.2, 2.4, 0.8 Hz), 6.90-7.01 (m, 5H), 7.06-7.10 (m, 1H), 7.25 (t, 1H, J = 8.1 Hz), 7.54 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.21 (dd, 1H, J = 5.4, 0.5 Hz). N8: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.84 (s, 3H), 6.51 (bs, 1H), 6.83-6.85 (m, 1H), 6.88 (dd, 1H, J = 5.4, 1.6 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 6.95 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.24-7.30 (m, 2H), 7.50 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz),

8.16 (d, 1H, J = 5.3 Hz). N9: ^{1}H-NMR (acetone-d_6) δ (ppm): 3.79 (s, 3H), 3.84 (s, 3H), 6.91-6.96 (m, 2H), 7.00-7.06 (m, 2H), 7.16-7.22 (m, 2H), 7.34 (s, 1H), 7.45 (s, 1H), 7.53-7.58 (m, 2H), 8.21 (bs, 1H). N10: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.85 (s, 3H), 5.69 (bs, 1H), 6.90 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 6.93 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 7.05 (t, 1H, J = 2.1 Hz), 7.09-7.16 (m, 3H), 7.33-7.39 (m, 2H), 8.23 (d, 1H, J = 2.6 Hz), 8.28 (d, 1H, J = 1.8 Hz). N11: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.80 (s, 3H), 3.86 (s, 3H), 5.88 (bs, 1H), 6.57 (dd, 1H, J = 8.0, 2.1 Hz), 6.67 (t, 1H, J = 2.2 Hz), 6.72 (dd, 1H, J = 8.0, 1.5 Hz), 6.94 (ddd, 1H, J = 8.2, 2.5, 0.7 Hz), 7.08 (t, 1H, J = 2.1 Hz), 7.10-7.16 (m, 1H), 7.22 (t, 1H, J = 8.1 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.60 (t, 1H, J = 2.3 Hz), 8.37 (d, 1H, J = 2.5 Hz), 8.39 (d, 1H, J = 1.8 Hz).]

Step 3.

A solution of methoxylated intermediate N1, N2, N3, N4, N5, N6, N7, N8, N9, N10 or N11 (0.653 mmol, 200 mg) in anhydrous DCM (7.6 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (4.2 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was diluted with water, treated with a 1 M aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude product was purified by chromatography over silica gel (*n*-hexane/ethyl acetate mixtures) to yield pure phenolic compounds,

examples 14-17 and 22-28 (example 14: 92% yield, example 15: 78% yield, example 16: 81% yield, example 17: 99% yield, example 22: 6% yield, example 23: 31% yield, example 24: 32% yield, example 25: 74% yield, example 26: 63% yield, example 27: 44% yield, example 28: 63% yield).

Scheme 6.

Step 1.

Et_3N (0.64 mL) and di-*tert*-butyl dicarbonate (4.62 mmol) at 0 °C were added to a solution of commercially available 4-amino-2-bromopyirdine (2.31 mmol, 400 mg) in anhydrous THF (5.9 mL), and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure; then the residue was diluted with EtOAc and sequentially washed with a saturated solution of sodium bicarbonate, water and brine. The organic phase was dried with Na_2SO_4 and concentrated. The crude reaction product was purified by column chromatography over silica gel with a mixture of *n*-hexane/EtOAc 8:2 as the eluent to afford intermediate O (72% yield). [^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (s, 9H), 6.68 (bs, 1H), 7.18 (dd, 1H, J = 5.6, 2.0 Hz), 7.64 (d, 1H, J = 1.9 Hz), 8.17 (d, 1H, J = 5.7 Hz).]

Step 2.

A solution of $Pd(OAc)_2$ (0.0520 mmol) and triphenylphosphine (0.260 mmol) in toluene (16.8 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, commercially available 4-amino-2-bromopyirdine (for the synthesis of intermediate R, Scheme 6) or intermediate O (for the synthesis of intermediate P, Scheme 6)(1.73 mmol, 300 mg), anhydrous K_2CO_3 (2.60

mmol), and commercially available 3- or 4-methoxybenzeneboronic acid (3.47 mmol, 3-methoxybenzeneboronic acid for the synthesis of intermediate P and 4-methoxybenzeneboronic acid for the synthesis of intermediate R, Scheme 6) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under an inert atmosphere overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude residue was purified by flash column chromatography, eluting with n-hexane/EtOAc mixtures (for intermediate P) or EtOAc/MeOH (for intermediate R) as eluents to afford the biaryl intermediates P (96% yield) or R (84% yield). [P: ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 3.89 (s, 3H), 6.77 (bs, 1H), 6.96 (ddd, 1H, J = 8.2, 2.6, 0.8 Hz), 7.24 (dd, 1H, J = 5.6, 2.1 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.49-7.54 (m, 1H), 7.57 (t, 1H, J = 2.0 Hz), 7.77 (d, 1H, J = 1.8 Hz), 8.51 (d, 1H, J = 5.5 Hz). R: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.85 (s, 3H), 4.20 (bs, 2H), 6.46 (dd, 1H, J = 5.6, 2.3 Hz), 6.90 (d, 1H, J = 2.2 Hz), 6.96 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.87 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.28 (d, 1H, J = 5.6 Hz).]

Step 3.

Compound P (1.77 mmol, 532 mg) was dissolved in DCM (8 mL), cooled to 0 °C, treated with trifluoroacetic acid (2.4 mL), and stirred at rt until complete consumption of the starting material (TLC). The mixture was concentrated to dryness under reduced pressure, diluted with EtOAc, and washed with a

1 M solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated to give the pure compound P which was used in the next step without further purification (99% yield). [^{1}H-NMR ($CDCl_3$) δ (ppm): 3.88 (s, 3H), 4.25 (bs, 2H), 6.50 (dd, 1H, J = 5.6, 2.3 Hz), 6.91-6.98 (m, 2H), 7.90 (t, 1H, J = 7.9 Hz), 7.46 (ddd, 1H, J = 7.7, 1.5, 1.0 Hz), 7.48-7.53 (m, 1H), 8.31 (d, 1H, J = 5.6 Hz).]

Step 4.

A solution of Pd_2dba_3 (0.0120 mmol), XPhos (0.0483 mmol), K_3PO_4 (0.844 mmol), commercially available 3- or 4-bromoanisole (0.603 mmol) and aniline intermediate R or Q (0.724 mmol, 145 mg) in toluene (1.2 mL) was stirred at 100 °C under an inert atmosphere in a sealed vial for 20 h. If the starting material with a stoichiometric defect (bromoanisole) was still visible by TLC, further aliquots of Pd_2dba_3 and XPhos were added and the reaction was heated for a further 6 h. The reaction mixture was allowed to cool to room temperature, then filtered through a small Celite pad, washed with ethyl acetate and concentrated under vacuum. The crude residue obtained was purified by flash column chromatography (eluent mixtures of *n*-hexane/EtOAc) to give intermediates S1 (57% yield), S2 (51% yield), S3 (83% yield), S4 (33% yield). [S1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.84 (s, 3H), 6.09 (bs, 1H), 6.59 (dd, 1H, J = 5.8, 2.2 Hz), 6.89-6.99 (m, 4H), 7.03 (d, 1H, J = 2.0 Hz), 7.17 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 7.84 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.28 (d, 1H, J = 5.8 Hz). S2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 3.87 (s, 3H), 5.99 (bs, 1H), 6.63

(dd, 1H, J = 5.7, 2.3 Hz), 6.90-6.97 (m, 3H), 7.07 (d, 1H, J = 2.2 Hz), 7.17 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.33 (t, 1H, J = 7.9 Hz), 7.42 (dt, 1H, J = 7.7, 1.3 Hz), 7.49 (t, 1H, J = 2.0 Hz), 8.32 (d, 1H, J = 5.7 Hz). S3: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.85 (s, 3H), 6.24 (bs, 1H), 6.69 (dd, 1H, J = 7.8, 2.2 Hz), 6.75-6.85 (m, 3H), 6.97 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.22 (d, 1H, J = 2.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.87 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.35 (d, 1H, J = 5.7 Hz). S4: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.88 (s, 3H), 6.21 (bs, 1H), 6.69 (dd, 1H, J = 8.1, 2.4 Hz), 6.77 (t, 1H, J = 2.2 Hz), 6.79-6.85 (m, 2H), 6.95 (ddd, 1H, J = 8.1, 2.6, 0.9 Hz), 7.25 (d, 1H, J = 2.2 Hz), 7.28 (t, 1H, J = 8.1 Hz), 7.34 (t, 1H, J = 7.9 Hz), 7.42-7.46 (m, 1H), 7.51 (t, 1H, J = 2.1 Hz), 8.38 (d, 1H, J = 5.7 Hz).]

Step 5.

A solution of methoxylated intermediate S1, S2, S3 or S4 (0.421 mmol, 129 mg) in anhydrous DCM (4.9 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (2.7 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was diluted with water, treated with a 1 M aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The residue was purified by flash chromatography (ethyl acetate or EtOAc/MeOH mixtures) to yield pure phenolic compounds, examples 18-21 (example 18: 45% yield, example 19:

78% yield, example 20: 62% yield, example 21: 76% yield).

Scheme 7.

Step 1.

Cu(I) iodide (0.0795 mmol), potassium carbonate (3.18 mmol), commercially available 3- or 4-iodoanisoloe (1.59 mmol) and 3-bromothiophenol (1.59 mmol, 300 mg) were dissolved in a mixture of *i*-propanol (1.1 mL) and ethylene glycol (0.2 mL) in a screw-capped test tube under an inert atmosphere. The reaction was heated to 80 °C and stirred for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted several times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by flash column chromatography over silica gel using petroleum ether as the eluent to afford the desired thioether derivatives T1 (83% yield) or T2 (46% yield). [T1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.78 (s, 3H), 6.84 (ddd, 1H, J = 8.3, 2.5, 0.8 Hz), 6.92 (t, 1H, J = 2.1 Hz), 6.97 (ddd, 1H, J = 7.7, 1.5, 0.9 Hz), 7.15 (t, 1H, J = 7.9 Hz), 7.20-7.28 (m, 2H), 7.34 (ddd, 1H, J = 7.9, 1.8, 1.1 Hz), 7.44 (t, 1H, J = 1.8 Hz). T2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 6.93 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.02-7.11 (m, 2H), 7.21-7.26 (m, 2H), 7.43 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz).]

Step 2.

A solution of $Pd(OAc)_2$ (0.0204 mmol) and triphenylphosphine (0.102 mmol) in ethanol (1.5 mL) and toluene (1.5 mL) was stirred at rt under an inert

atmosphere for 10 min. After that period, intermediate T1 or T2 (0.676 mmol, 200 mg), a 2 M aqueous solution of Na_2CO_3 (1.5 mL), and commercially available 3- or 4-methoxybenzeneboronic acid (1.08 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under an inert atmosphere overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulphate and concentrated under vacuum. The crude residue was purified by flash column chromatography, eluting with petroleum ether/EtOAc mixtures as eluents to afford intermediates U1 (91% yield), U2 (67% yield), U3 (71% yield) or U4 (61% yield). [U1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.84 (s, 3H), 6.91 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 6.95 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.09 (ddd, 1H, *J* = 7.6, 1.8, 1.3 Hz), 7.27 (t, 1H, *J* = 7.6 Hz), 7.32 (dt, 1H, *J* = 7.8, 1.5 Hz), 7.39 (t, 1H, *J* = 1.6 Hz), 7.42-7.48 (m, 4H). U2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.84 (s, 3H), 6.88 (ddd, 1H, *J* = 8.3, 2.6, 0.9 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.03 (t, 1H, *J* = 2.1 Hz), 7.09 (ddd, 1H, *J* = 7.6, 1.6, 1.0 Hz), 7.13 (ddd, 1H, *J* = 7.7, 1.8, 1.2 Hz), 7.26-7.33 (m, 2H), 7.35 (dt, 1H, *J* = 8.2, 1.7 Hz), 7.41 (t, 1H, *J* = 1.8 Hz), 7.45 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz). U3: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (s, 3H), 3.84 (s, 3H), 6.79 (ddd, 1H, *J* = 8.3, 2.5, 0.9 Hz), 6.91 (t, 1H, *J* = 2.1 Hz), 6.93-6.98 (m, 3H), 7.21 (t, 1H, *J* = 8.0 Hz), 7.29 (dt, 1H, *J* = 8.0, 1.5 Hz), 7.35 (t, 1H, *J* = 7.7 Hz), 7.44 (dt, 1H, *J* = 8.0, 1.5 Hz), 7.48 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ =

2.6 Hz), 7.58 (t, 1H, J = 1.6 Hz). U4: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.77 (s, 3H), 3.85 (s, 3H), 6.79 (ddd, 1H, *J* = 8.3, 2.5, 0.9 Hz), 6.88-6.93 (m, 2H), 6.96 (ddd, 1H, *J* = 7.7, 1.7, 1.0 Hz), 7.07 (t, 1H, *J* = 2.1 Hz), 7.13 (ddd, 1H, *J* = 7.6, 1.6, 1.0 Hz), 7.22 (t, 1H, *J* = 8.0 Hz), 7.31-7.36 (m, 2H), 7.37 (t, 1H, *J* = 7.6 Hz), 7.47 (dt, 1H, *J* = 7.4 Hz), 7.61 (t, 1H, *J* = 1.6 Hz).]

Step 3.

A solution of methoxylated intermediate U1, U2, U3 or U4 (0.372 mmol, 120 mg) in anhydrous DCM (4.3 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (2.4 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The crude residue was purified by chromatography over silica gel (*n*-hexane/ethyl acetate mixtures) to yield pure phenolic compounds, examples 29-32 (example 29: yield 78%, example 30: yield 92%, example 31: yield 99%, example 32: yield 99%).

Scheme 8.

Step 1.

A solution of $Pd(OAc)_2$ (0.0403 mmol) and triphenylphosphine (0.201 mmol) in toluene (13.0 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, commercially available 3-amino-1-bromoisoquinoline (1.34 mmol, 300 mg), anhydrous K_2CO_3 (2.02 mmol), and commercially

available 4-methoxybenzeneboronic acid (2.69 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under an inert atmosphere overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude residue was purified by flash column chromatography over silica gel, eluting with a 7:3 petroleum ether/EtOAc mixture as the eluent to afford intermediate V (97% yield). [^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (s, 3H), 4.48 (bs, 2H), 6.72 (s, 1H), 7.04 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.17 (ddd, 1H, J = 8.6, 6.7, 1.2 Hz), 7.47 (ddd, 1H, J = 8.4, 6.7, 1.2 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.62 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.90 (dd, 1H, J = 8.5, 0.8 Hz).]

Step 2.

1) Synthesis of W1 and W2. A solution of Pd_2dba_3 (0.0162 mmol), XPhos (0.0650 mmol), K_3PO_4 (1.29 mmol), commercially available 3- or 4-bromoanisole (0.812 mmol) and intermediate V (0.975 mmol, 244 mg) in toluene (1.6 mL) was stirred at 100 °C under argon in a sealed vial for 20 h. The reaction mixture was allowed to cool to room temperature, then filtered through a small Celite pad and washed with ethyl acetate; the filtrate was concentrated under vacuum. The crude residue obtained was purified by column chromatography over silica gel (eluent mixtures of petroleum ether/EtOAc) to give intermediates W1 (96% yield) or W2 (63% yield). [W1: ^{1}H-NMR

($CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.90 (s, 3H), 6.61 (ddd, 1H, J = 8.2, 2.4, 0.7 Hz), 6.72 (bs, 1H), 6.91 (dd, 1H, J = 7.9, 1.4 Hz), 6.96 (t, 1H, J = 2.2 Hz), 7.06 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.20-7.30 (m, 3H), 7.51 (ddd, 1H, J = 8.3, 6.8, 1.2 Hz), 7.60-7.69 (m, 3H), 7.95 (dd, 1H, J = 8.5, 0.8 Hz). W2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 3.90 (s, 3H), 6.52 (bs, 1H), 6.92 (s, 1H), 6.95 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.06 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.17 (ddd, 1H, J = 8.5, 6.7, 1.3 Hz), 7.28 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.46 (ddd, 1H, J = 8.3, 6.7, 1.2 Hz), 7.54 (d, 1H, J = 8.4 Hz), 7.64 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.91 (dd, 1H, J = 8.4, 0.8 Hz).]

2) Synthesis of Z1 and Z2. A solution of Pd_2dba_3 (0.0186 mmol), XPhos (0.0744 mmol), K_3PO_4 (0.930 mmol), commercially available 3- or 4-bromoanisole (0.990 mmol) and intermediate Y (0.619 mmol, 171 mg) in toluene (1.1 mL) was stirred at 100 °C under argon in a sealed vial for 20 h. As the starting material with a stoichiometric defect (aniline derivative) was still visible by TLC, further aliquots of Pd_2dba_3 and XPhos were added and the reaction was heated for a further 20 h. The reaction mixture was allowed to cool to room temperature, then filtered through a small Celite pad and washed with ethyl acetate; the filtrate was concentrated under vacuum. The crude residue obtained was purified by column chromatography over silica gel (eluent mixtures of petroleum ether/EtOAc) to give intermediates

Z1 (64% yield) or Z2 (65% yield). [Z1: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.78 (s, 3H), 3.82 (s, 3H), 6.60 (dd, 1H, J = 8.3, 2.4 Hz), 6.70 (bs, 1H), 6.76 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 6.89 (dd, 1H, J = 8.1, 1.4 Hz), 6.94 (d, 1H, J = 8.4 Hz), 7.12-7.20 (m, 3H), 7.20-7.29 (m, 4H), 7.33 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.55 (d, 1H, J = 8.4 Hz). Z2: ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.78 (s, 3H), 3.82 (s, 3H), 6.52 (bs, 1H), 6.71 (d, 1H, J = 8.4 Hz), 6.76 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 6.92 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.11-7.18 (m, 2H), 7.19-7.33 (m, 7H), 7.49 (d, 1H, J = 8.5 Hz).]

Step 3.

A solution of $Pd(OAc)_2$ (0.0360 mmol) and triphenylphosphine (0.180 mmol) in toluene (5.7 mL) and MeOH (0.57 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, commercially available 5,6-dibromopyridin-2-amine (1.20 mmol, 300 mg), Na_2CO_3 (2.40 mmol), water (1.4 mL) and commercially available 4-methoxybenzeneboronic acid (1.20 mmol) were sequentially added. The resulting mixture was heated at 110 °C in a sealed vial overnight. After being cooled to rt, the mixture was diluted with water and extracted several times with EtOAc. The combined organic phases were dried and concentrated. The crude product was purified by flash column chromatography over silica gel. Elution with a 75:25 petroleum ether/EtOAc mixture as the eluent afforded intermediate X (73% yield). [^{1}H-NMR ($CDCl_3$) δ (ppm): 3.85 (s, 3H), 4.50 (bs, 2H), 6.34 (d, 1H, J = 8.6 Hz),

6.96 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.61 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.64 (d, 1H, J = 8.6 Hz).]

Step 4.

A solution of $Pd(OAc)_2$ (0.0234 mmol) and triphenylphosphine (0.117 mmol) in ethanol (1.8 mL) and toluene (1.8 mL) was stirred at rt under an inert atmosphere for 10 min. After that period, intermediate X (0.780 mmol, 217 mg), a 2 M aqueous solution of Na_2CO_3 (1.8 mL), and commercially available benzeneboronic acid (1.24 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial overnight. After being cooled to rt, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried and concentrated. The crude product was purified by flash column chromatography over silica gel. Elution with a 7:3 petroleum ether/EtOAc mixture as the eluent afforded the intermediates Y (98% yield). [^{1}H-NMR ($CDCl_3$) δ (ppm): 3.77 (s, 3H), 4.52 (bs, 2H), 6.52 (d, 1H, J = 8.3 Hz), 6.75 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.10-7.15 (m, 2H), 7.16-7.29 (m, 5H), 7.48 (d, 1H, J = 8.3 Hz).]

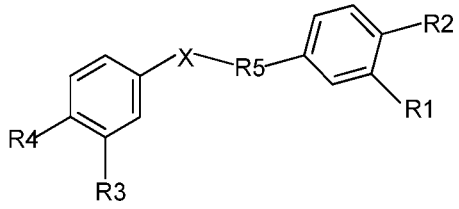
Step 5.

A solution of methoxylated intermediate W1, W2, Z1 or Z2 (0.370 mmol, 132 mg) in anhydrous DCM (4.3 mL) was cooled to -15 °C and treated dropwise with a 1 M solution of BBr_3 in dichloromethane (2.3 mL), and the resulting solution was stirred at 0 °C for 1 h and at rt until the reaction was complete (disappearance of the starting material as verified by TLC analysis). The

mixture was diluted with water, treated with a 1 M aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The residue was purified by chromatography over silica gel ($CHCl_3$/MeOH mixtures) to yield pure phenolic compounds, examples 34 and 36 (from W1 and W2) and examples 33 and 35 (from Z1 and Z2) (example 33: 46% yield, example 34: 82% yield, example 35: 64% yield, example 36: 48% yield).

The obtained compounds 1-36 are exemplified in table 1.

Table 1



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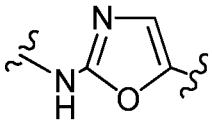
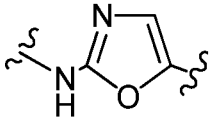
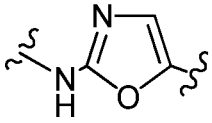
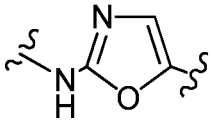
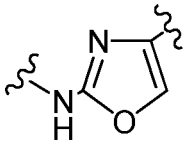
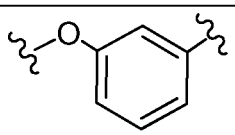
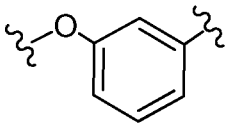
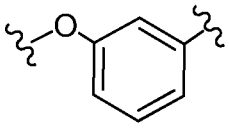
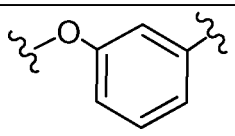
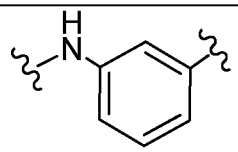
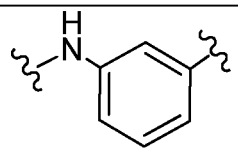
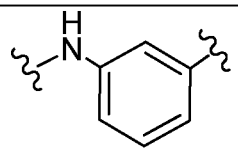
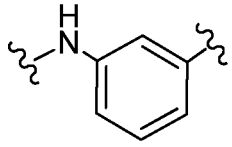
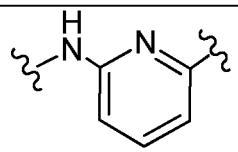
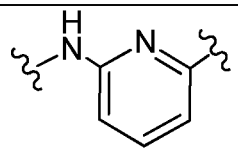
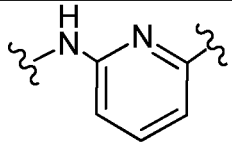
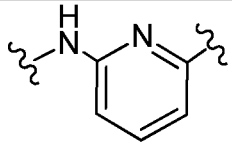
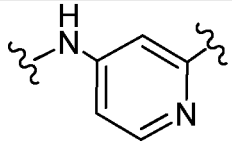
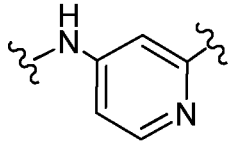
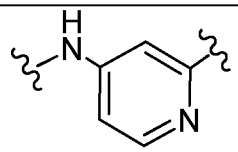
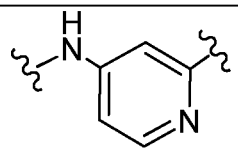
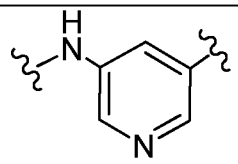
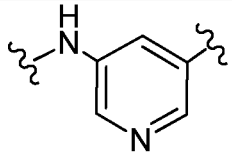
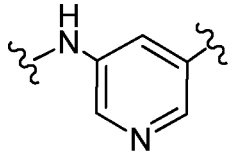
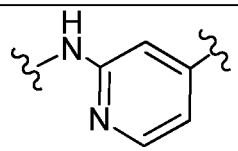
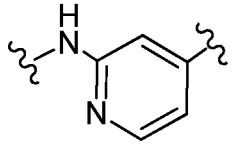
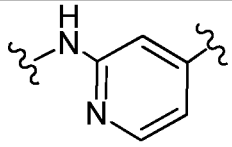
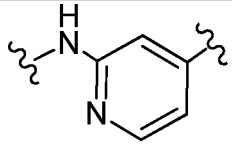
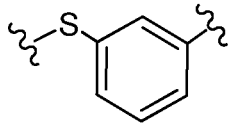
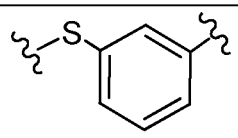
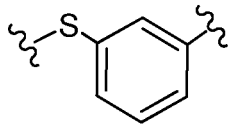
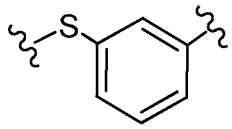
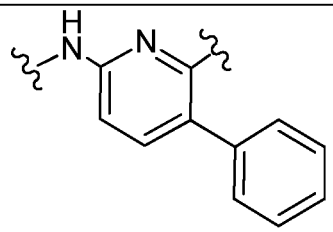
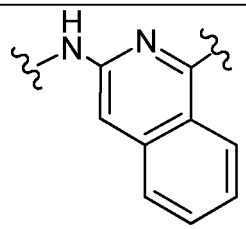
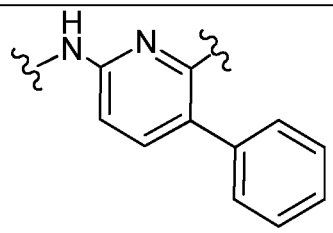
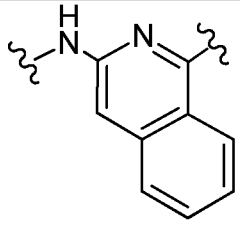
1	H	OH	OH	H	
2	H	OH	H	OH	
3	OH	H	OH	H	
4	OH	H	H	OH	
5	H	OH	OH	H	
6	H	OH	OH	H	
7	H	OH	H	OH	
8	OH	H	OH	H	
9	OH	H	H	OH	

10	H	OH	OH	H	
11	H	OH	H	OH	
12	OH	H	H	OH	
13	OH	H	OH	H	
14	H	OH	OH	H	
15	H	OH	H	OH	
16	OH	H	H	OH	
17	OH	H	OH	H	
18	H	OH	H	OH	
19	OH	H	H	OH	

20	H	OH	OH	H	
21	OH	H	OH	H	
22	H	OH	H	OH	
23	OH	H	H	OH	
24	OH	H	OH	H	
25	H	OH	H	OH	
26	OH	H	H	OH	
27	H	OH	OH	H	
28	OH	H	OH	H	
29	H	OH	H	OH	

30	OH	H	H	OH	
31	H	OH	OH	H	
32	OH	H	OH	H	
33	H	OH	H	OH	
34	H	OH	H	OH	
35	H	OH	OH	H	
36	H	OH	OH	H	

Characterization of compounds 1-36

Compound 1. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.43-6.48 (m, 1H), 6.89 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.07-7.14 (m, 3H), 7.40-7.47

(m, 3H), 8.29 (s, 1H), 8.51 (s, 1H), 9.04 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 104.83, 109.07, 109.34, 116.64, 120.65, 121.31, 125.42 (2C), 130.47 (2C), 141.85, 145.79, 156.86, 157.77, 159.03.

Compound 2. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.81 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.88 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.07 (s, 1H), 7.42 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.56 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.97 (s, 1H), 8.48 (s, 1H), 8.81 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 116.28 (2C), 116.61 (2C), 119.37 (2C), 120.65, 121.49, 125.26 (2C), 133.11, 145.49, 153.13, 157.57, 157.63.

Compound 3. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.48 (dt, 1H, J = 6.4, 2.4 Hz), 6.75 (ddd, 1H, J = 8.1, 2.4, 0.8 Hz), 7.02-7.16 (m, 4H), 7.22 (t, 1H, J = 7.9 Hz), 7.28 (s, 1H), 7.41-7.45 (m, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 104.98, 109.20, 109.55, 110.48, 115.11, 115.13, 123.15, 130.52, 130.75, 130.90, 141.67, 145.43, 157.46, 158.73, 159.06.

Compound 4. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.73 (ddd, 1H, J = 8.1, 2.5, 0.9 Hz), 6.82 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.03 (t, 1H, J = 1.9 Hz), 7.06 (ddd, 1H, J = 7.7, 1.5, 1.0 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.23 (s, 1H), 7.56 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 8.01 (bs, 1H), 8.42 (bs, 1H), 8.90 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 110.28, 114.90, 114.96, 116.32 (3C), 119.66 (2C), 123.11, 130.84, 132.81, 145.13, 153.31, 158.20, 158.66.

Compound 5. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.67-6.71 (m, 1H), 6.89 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.18 (d, 1H, J = 2.4 Hz), 7.21-7.25 (m, 2H), 7.46-7.50 (m, 1H), 7.54 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.51 (bs, 1H), 9.82 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 105.29, 108.75, 112.14, 112.80, 116.61, 121.85, 124.02, 126.05 (2C), 130.57 (2C), 139.89, 153.99, 157.92, 158.89.

Compound 6. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.50-6.54 (m, 2H), 6.62 (ddd, 1H, J = 8.1, 2.3, 0.9 Hz), 6.90-6.95 (m, 3H), 7.16-7.22 (m, 1H), 7.23 (t, 1H, J = 1.9 Hz), 7.37 (dt, 1H, J = 8.2, 1.5 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.50

(AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.49 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 106.64, 110.45, 111.26, 116.58 (2C), 117.67, 117.78, 122.18, 128.90 (2C), 130.98, 131.19, 132.32, 143.74, 158.31, 158.45, 159.51, 159.74.

Compound 7. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.82 (ddd, 1H, J = 8.1, 2.5, 1.0 Hz), 6.88 (AA'XX', 2H, J_{AX} = 9.1 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 6.95 (AA'XX', 2H, J_{AX} = 9.1 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.12 (t, 1H, J = 2.0 Hz), 7.26 (ddd, 1H, J = 7.7, 1.7, 1.1 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.46 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.28 (s, 1H), 8.47 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 115.90, 115.99, 116.57, 117.13, 121.91 (4C), 128.83 (2C), 130.83 (2C), 132.60, 143.60, 149.92, 154.79, 158.25, 160.32.

Compound 8. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.51-6.55 (m, 2H), 6.63 (ddd, 1H, J = 8.1, 2.3, 0.9 Hz), 6.85 (ddd, 1H, J = 8.1, 2.4, 1.0 Hz), 7.01 (ddd, 1H, J = 8.0, 2.4, 1.1 Hz), 7.07-7.12 (m, 2H), 7.20 (t, 1H, J = 8.4 Hz), 7.24 (t, 1H, J = 2.0 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.39 (dt, 1H, J = 8.2, 1.4 Hz), 7.46 (t, 1H, J = 7.9 Hz), 8.42-8.56 (bm, 2H). ^{13}C-NMR (acetone-d_6) δ (ppm): 106.81, 110.61, 111.43, 114.58, 115.57, 118.10, 118.67, 118.98, 122.71, 130.84, 131.10, 131.26, 142.60, 143.82, 158.54, 158.78, 159.39, 159.79.

Compound 9. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.83 (ddd, 1H, J = 8.1, 2.5, 0.9 Hz), 6.86-6.91 (m, 3H), 6.97 (AA'XX', 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 7.03-7.08 (m, 2H), 7.13 (t, 1H, J = 2.0 Hz), 7.23-7.31 (m, 2H), 7.39 (t, 1H, J = 7.9 Hz), 8.30 (s, 1H), 8.43 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 114.56, 115.49, 116.28, 116.89, 117.17 (2C), 118.97 (2C), 121.60, 122.03, 130.80, 130.93, 142.83, 143.66, 149.77, 154.89, 158.75, 160.36.

Compound 10. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.36 (ddd, 1H, J = 8.0, 2.3, 0.8 Hz), 6.61-6.66 (m, 1H), 6.71 (t, 1H, J = 2.2 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.03-7.09 (m, 3H), 7.28 (t, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 1.9 Hz), 7.37 (bs, 1H), 7.47 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.15 (s, 1H), 8.42 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 104.83,

108.26, 109.64, 116.40, 116.49 (2C), 116.60, 119.22, 128.75 (2C), 130.34, 130.79, 133.44, 142.86, 145.04, 146.04, 158.02, 159.28.

Compound 11. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.81 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.85 (ddd, 1H, J = 8.1, 2.3, 0.9 Hz), 6.89 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 6.93 (ddd, 1H, J = 7.6, 1.7, 1.0 Hz), 7.02 (bs, 1H), 7.07 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.13 (t, 1H, J = 2.0 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.42 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.38 (s, 1H), 8.01 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 113.69, 113.91, 116.43 (2C), 116.71 (2C), 117.50, 123.17 (2C), 128.72 (2C), 130.30, 133.77, 136.04, 142.83, 147.57, 153.58, 157.91.

Compound 12. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.77-6.85 (m, 3H), 6.87-6.93 (m, 1H), 6.93-6.98 (m, 1H), 7.01-7.10 (m, 5H), 7.16 (t, 1H, J = 1.9 Hz), 7.18-7.26 (m, 2H), 8.04 (s, 1H), 8.36 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 113.95, 114.53, 114.66, 115.01, 116.71 (2C), 117.83, 118.92, 123.33, 130.33 (2C), 130.58, 135.86, 142.88, 143.97, 147.64, 153.67, 158.62.

Compound 13. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.37 (ddd, 1H, J = 8.1, 2.3, 0.9 Hz), 6.64 (ddd, 1H, J = 8.1, 2.1, 0.8 Hz), 6.72 (t, 1H, J = 2.2 Hz), 6.82 (ddd, 1H, J = 8.1, 2.4, 1.0 Hz), 7.04-7.12 (m, 5H), 7.26 (t, 1H, J = 8.1 Hz), 7.31 (t, 1H, J = 7.9 Hz), 7.37 (t, 1H, J = 1.8 Hz), 7.42 (bs, 1H), 8.18 (s, 1H), 8.40 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 104.97, 108.43, 109.79, 114.61, 115.20, 116.70, 117.38, 118.98, 119.62, 130.44, 130.70, 130.87, 142.96, 143.70, 145.15, 145.91, 158.73, 159.31.

Compound 14. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.44 (ddd, 1H, J = 7.9, 2.4, 1.0 Hz), 6.73 (d, 1H, J = 8.1 Hz), 6.93 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.10 (t, 1H, J = 8.0 Hz), 7.15-7.19 (m, 1H), 7.21 (d, 1H, J = 7.5 Hz), 7.46 (t, 1H, J = 2.2 Hz), 7.56 (t, 1H, J = 7.9 Hz), 8.00 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.15 (bs, 1H), 8.18 (s, 1H), 8.54 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 106.49, 108.82, 108.89, 110.46, 110.83, 116.17 (2C), 128.90 (2C), 130.19, 132.15, 138.75, 144.09, 155.99, 156.72, 158.78, 159.12.

Compound 15. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.60 (dd, 1H, J = 8.2, 0.5 Hz), 6.82 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.91 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.14 (dd, 1H, J = 7.5, 0.5 Hz), 7.46-7.56 (m, 3H), 7.86 (bs, 1H), 7.93-8.01 (m, 3H), 8.53 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 107.42, 109.60, 116.10 (2C), 116.15 (2C), 122.48 (2C), 128.77 (2C), 132.25, 134.80, 138.64, 153.27, 155.88, 157.54, 159.03.

Compound 16. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.68 (dd, 1H, J = 8.4, 0.6 Hz), 6.82 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.86 (ddd, 1H, J = 8.0, 2.5, 0.9 Hz), 7.18 (dd, 1H, J = 7.5, 0.6 Hz), 7.27 (t, 1H, J = 7.9 Hz), 7.50-7.58 (m, 4H), 7.62 (t, 1H, J = 2.0 Hz), 7.94 (bs, 1H), 7.99 (s, 1H), 8.40 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 108.64, 110.70, 114.38, 116.18 (2C), 116.38, 118.64, 122.39 (2C), 130.28, 134.71, 138.68, 142.27, 153.27, 155.77, 157.55, 158.54.

Compound 17. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.44 (ddd, 1H, J = 8.0, 2.4, 1.0 Hz), 6.81 (dd, 1H, J = 8.3, 0.6 Hz), 6.88 (ddd, 1H, J = 8.0, 2.5, 0.9 Hz), 7.10 (t, 1H, J = 8.1 Hz), 7.21-7.31 (m, 3H), 7.40 (t, 1H, J = 2.2 Hz), 7.54-7.64 (m, 3H), 8.18 (s, 1H), 8.20 (bs, 1H), 8.41 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 106.46, 108.99, 109.96, 110.85, 111.60, 114.47, 116.49, 118.75, 130.25, 130.36, 138.80, 142.19, 143.98, 155.93, 156.80, 158.61, 158.77.

Compound 18. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.58 (dd, 1H, J = 5.7, 2.2 Hz), 6.74-6.84 (m, 4H), 7.01-7.07 (m, 3H), 7.72 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 8.12 (d, 1H, J = 5.7 Hz), 8.39 (s, 1H), 9.31 (bs, 1H), 9.58 (bs, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 103.15, 106.21, 115.27 (2C), 115.91 (2C), 124.01 (2C), 127.60 (2C), 130.43, 131.45, 149.53, 152.64, 153.84, 156.62, 158.10.

Compound 19. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.64 (dd, 1H, J = 5.7, 2.2 Hz), 6.74-6.82 (m, 3H), 7.05 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 7.09 (d, 1H, J = 2.0 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.29 (dt, 1H, J = 7.8, 1.4 Hz), 7.33 (t, 1H, J = 2.0 Hz), 8.16 (d, 1H, J = 5.6 Hz), 8.46 (s, 1H), 9.32 (s, 1H), 9.46

(s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 104.23, 106.91, 113.17, 115.57 115.93 (2C), 116.98, 124.15 (2C), 129.50, 131.33, 140.99, 149.76, 152.71, 153.95, 156.60, 157.53.

Compound 20. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.43 (ddd, 1H, J = 8.1, 2.1, 1.0 Hz), 6.62-6.68 (m, 2H), 6.80 (dd, 1H, J = 5.6, 2.2 Hz), 6.83 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.26 (d, 1H, J = 2.1 Hz), 7.77 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.21 (d, 1H, J = 5.7 Hz), 8.72 (s, 1H), 9.43 (s, 1H), 9.65 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 104.53, 106.55, 107.52, 109.57, 110.59, 115.30 (2C), 127.65 (2C), 129.37, 130.06, 130.31, 141.77, 149.78, 150.82, 156.86, 158.19.

Compound 21. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.42-6.48 (m, 1H), 6.62-6.69 (m, 2H), 6.77-6.82 (m, 1H), 6.86 (dd, 1H, J = 5.6, 2.2 Hz), 7.14 (t, 1H, J = 8.3 Hz), 7.25 (t, 1H, J = 7.8 Hz), 7.29-7.35 (m, 2H), 7.37 (t, 1H, J = 1.9 Hz), 8.26 (d, 1H, J = 5.6 Hz), 8.76 (s, 1H), 9.46 (s, 1H), 9.50 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 105.62, 106.72, 108.22, 109.76, 110.73, 113.23, 115.71, 117.03, 129.57, 130.12, 140.83, 141.65, 149.98, 150.94, 156.81, 157.59, 158.25.

Compound 22. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.95 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.03 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.26 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.65 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.13 (dd, 1H, J = 2.4, 1.7 Hz), 8.18 (d, 1H, J = 2.4 Hz), 8.30 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 117.13, 117.26, 117.30, 123.44, 124.94, 125.86 (2C), 126.80, 129.19, 129.33, 129.47, 129.59, 131.39, 147.44, 154.19, 156.19, 160.10.

Compound 23. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.75 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.9 Hz), 6.78 (ddd, 1H, J = 8.1, 2.4, 0.8 Hz), 6.93 (t, 1H, J = 2.0 Hz), 6.98-7.03 (m, 3H), 7.25 (t, 1H, J = 7.9 Hz), 7.29 (t, 1H, J = 2.2 Hz), 8.01 (s, 1H), 8.05 (d, 1H, J = 1.2 Hz), 8.14 (d, 1H, J = 2.3 Hz), 9.16 (s, 1H), 9.57 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 113.42, 114.96, 115.70, 115.96 (2C), 117.01, 117.45, 122.35 (2C), 130.12, 132.91, 135.95, 136.68, 139.09,

142.45, 152.95, 157.85.

Compound 24. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.51 (ddd, 1H, J = 8.0, 2.2, 0.8 Hz), 6.73-6.81 (m, 2H), 7.00 (ddd, 1H, J = 8.1, 2.4, 0.9 Hz), 7.19 (t, 1H, J = 3.0 Hz), 7.22-7.29 (m, 2H), 7.48 (t, 1H, J = 7.9 Hz), 7.76 (t, 1H, J = 2.2 Hz), 8.43 (d, 1H, J = 1.9 Hz), 8.48 (d, 1H, J = 2.5 Hz), 8.56 (s, 1H), 9.52 (s, 1H), 9.81 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 104.03, 108.11, 108.38, 113.53, 115.09, 117.55, 119.94, 130.12, 130.17, 135.93, 138.06, 138.35, 138.82, 140.16, 143.45, 157.92, 158.31.

Compound 25. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.69 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.84-6.90 (m, 4H), 7.40 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 7.50 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 8.03-8.07 (m, 1H), 8.62 (s, 1H), 8.96 (s, 1H), 9.75 (bs, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 105.43, 110.89, 115.17 (2C), 115.86 (2C), 120.85 (2C), 127.66 (2C), 128.64, 133.35, 147.89, 147.98, 151.84, 157.28, 158.33.

Compound 26. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.70 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 6.80-6.90 (m, 3H), 7.01 (t, 1H, J = 2.0 Hz), 7.03-7.09 (m, 1H), 7.28 (t, 1H, J = 7.9 Hz), 7.40 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 8.09 (d, 1H, J = 5.5 Hz), 8.68 (s, 1H), 8.98 (bs, 1H), 9.63 (bs, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 106.31, 111.34, 113.15, 115.20 (2C), 115.82, 117.17, 121.03 (2C), 130.13, 133.17, 139.61, 148.03, 148.29, 151.98, 157.29, 157.90.

Compound 27. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.25-6.33 (m, 1H), 6.84-6.92 (m, 2H), 6.93-7.05 (m, 4H), 7.28 (s, 1H), 7.49-7.57 (m, 2H), 8.13 (d, 1H, J = 5.4 Hz), 8.90 (s, 1H), 9.19 (bs, 1H), 9.79 (bs, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm): 105.11, 106.78, 107.67, 109.17, 111.75, 115.93 (2C), 127.74 (2C), 128.47, 129.21, 142.92, 147.82, 148.12, 156.64, 157.68, 158.45.

Compound 28. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.27-6.34 (m, 1H), 6.85 (ddd, 1H, J = 8.0, 2.4, 0.9 Hz), 6.95 (dd, 1H, J = 5.4, 1.5 Hz), 6.99-7.06 (m, 4H), 7.10 (ddd, 1H, J = 7.7, 1.7, 1.0 Hz), 7.27-7.33 (m, 2H), 8.18 (d, 1H, J = 5.3 Hz), 8.96 (s, 1H), 9.20 (s, 1H), 9.66 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ (ppm):

105.18, 107.70, 107.79, 109.21, 112.20, 113.22, 115.94, 117.22, 129.21, 130.18, 139.43, 142.77, 147.94, 148.40, 156.62, 157.68, 157.95.

Compound 29. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.90 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 6.93 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.04 (ddd, 1H, J = 7.7, 1.8, 1.3 Hz), 7.30 (td, 1H, J = 7.6, 0.7 Hz), 7.34-7.38 (m, 2H), 7.38-7.44 (m, 4H), 8.48 (bs, 1H), 8.69 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 116.61, 117.56 (2C), 123.02, 124.64, 126.23, 126.47, 128.83 (4C), 130.23, 132.51, 136.88, 140.55, 142.69, 158.29, 159.15.

Compound 30. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.83 (ddd, 1H, J = 8.1, 2.4, 1.0 Hz), 6.93 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.00-7.04 (m, 2H), 7.11 (ddd, 1H, J = 7.6, 1.9, 1.3 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.31-7.40 (m, 3H), 7.42 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 8.58 (bs, 2H). ^{13}C-NMR (acetone-d_6) δ (ppm): 114.61, 115.52, 117.62 (2C), 118.96, 122.77, 125.14, 126.62, 127.24, 130.28, 130.81, 137.01 (2C), 140.76, 142.78, 142.82, 158.78, 159.25.

Compound 31. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.76 (ddd, 1H, J = 8.1, 2.4, 0.9 Hz), 6.83 (t, 1H, J = 1.8 Hz), 6.86 (ddd, 1H, J = 7.7, 1.7, 0.9 Hz), 6.92 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.28 (ddd, 1H, J = 7.7, 1.8, 1.1 Hz), 7.42 (td, 1H, J = 7.7, 0.4 Hz), 7.48 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.6 Hz), 7.53 (ddd, 1H, J = 7.8, 1.8, 1.1 Hz), 7.59 (td, 1H, J = 1.8, 0.4 Hz), 8.49 (bs, 2H). ^{13}C-NMR (acetone-d_6) δ (ppm): 115.28, 116.60 (2C), 118.11, 122.54, 126.27, 128.91 (2C), 129.91, 130.12, 130.62, 131.11, 132.21, 136.73, 137.72, 143.07, 158.43, 159.05.

Compound 32. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.77 (ddd, 1H, J = 8.1, 2.4, 0.9 Hz), 6.82-6.90 (m, 3H), 7.05-7.11 (m, 2H), 7.20 (t, 1H, J = 7.8 Hz), 7.27 (t, 1H, J = 8.1 Hz), 7.34 (ddd, 1H, J = 7.7, 1.7, 1.1 Hz), 7.44 (t, 1H, J = 7.7 Hz), 7.55 (ddd, 1H, J = 7.7, 1.7, 1.1 Hz), 7.59 (t, 1H, J = 1.6 Hz), 8.49 (bs, 2H). ^{13}C-NMR (acetone-d_6) δ (ppm): 114.62, 115.40, 115.65, 118.26, 119.00, 122.70, 126.76, 130.27, 130.66, 130.86, 130.89, 131.41, 136.97, 137.45, 142.45, 143.13, 158.82, 159.05.

Compound 33. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.69 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 6.74 (d, 1H, J = 8.5 Hz), 6.80 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.14-7.29 (m, 7H), 7.49 (d, 1H, J = 8.4 Hz), 7.54 (AA'XX', 2H, J_{AX} = 8.9 Hz, $J_{AA'/XX'}$ = 2.7 Hz), 7.94 (s, 1H), 7.98 (bs, 1H), 8.36 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 107.57, 115.26 (2C), 116.22 (2C), 122.45 (2C), 126.24, 126.92, 129.02 (2C), 130.37 (2C), 132.19 (2C), 133.26, 134.78, 140.93, 142.28, 153.38, 155.32, 156.58, 157.89.

Compound 34. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.85 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 6.95 (s, 1H), 7.02 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.18 (ddd, 1H, J = 8.3, 6.7, 1.2 Hz), 7.37 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.8 Hz), 7.47 (ddd, 1H, J = 8.4, 6.7, 1.2 Hz), 7.58 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.67 (bs, 1H), 7.93 (dd, 1H, J = 8.6, 0.9 Hz), 8.11 (bs, 1H), 8.66 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 97.41, 115.77 (2C), 116.50 (2C), 116.56, 122.36, 123.37, 123.56 (2C), 126.39, 128.24, 130.55, 131.90, 132.17 (2C), 134.56, 141.11, 153.89, 153.95, 158.84, 160.43.

Compound 35. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.43 (ddd, 1H, J = 8.0, 2.4, 1.0 Hz), 6.70 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz), 6.87 (d, 1H, J = 8.4 Hz), 7.08 (t, 1H, J = 8.0 Hz), 7.16-7.25 (m, 4H), 7.25-7.30 (m, 4H), 7.43 (t, 1H, J = 2.2 Hz), 7.55 (d, 1H, J = 8.4 Hz), 8.17 (bs, 1H), 8.24 (s, 1H), 8.39 (bs, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 106.52, 108.94, 108.99, 110.84, 115.32 (2C), 126.99, 127.05, 129.05 (2C), 130.22, 130.36 (2C), 132.25 (2C), 133.08, 140.98, 142.10, 144.03, 155.30, 155.68, 157.93, 158.79.

Compound 36. ^{1}H-NMR (acetone-d_6) δ (ppm): 6.46 (ddd, 1H, J = 7.9, 2.4, 1.1 Hz), 7.00-7.08 (m, 3H), 7.12 (t, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 2.2 Hz), 7.21 (s, 1H), 7.25 (ddd, 1H, J = 8.5, 6.8, 1.2 Hz), 7.53 (ddd, 1H, J = 9.5, 6.7, 1.2 Hz), 7.61 (AA'XX', 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.98 (dd, 1H, J = 8.6, 0.9 Hz), 8.01 (s, 1H), 8.23 (s, 1H), 8.67 (s, 1H). ^{13}C-NMR (acetone-d_6) δ (ppm): 99.86, 106.49, 109.16, 110.93, 115.84 (2C), 122.76, 124.06, 126.65, 128.24, 130.53, 130.68, 131.91, 132.29 (2C), 140.92, 144.28, 152.17, 158.85, 159.01, 160.38.

In vitro screening for the evaluation of SIRT1 enzyme activity.

A commercially available enzyme kit was used to perform a preliminary screening of the original compounds developed and synthetized as SIRT1 activators. The enzyme activity was monitored through a spectrofluorimetric approach.

In particular, the enzyme substrate (comprising a polypeptide conjugated with a fluorophore through an acetyl bond (Arg-His-Lys-Lys (e-acetyl)-AMC)) is incubated with the SIRT1 enzyme and NAD+ as a cofactor. The deacetylation of the polypeptide leads to the formation of the acetylated fluorophore (acetyl-AMC), which releases the fluorophore and emits fluorescence, after the addition of a developer.

The fluorescence, which is directly proportional to the enzyme's activity, was analyzed using a spectrofluorimetric plate (λex 350-360 nm, λem 450-465 nm) and the data obtained were expressed as a % of the fluorescence evoked by 100 μM resveratrol, used as the reference activator of SIRT1.

Many of the tested compounds showed higher activity when compared with the reference compound. In particular, at a concentration of 100 μM, compounds 14, 15, 16 and 17 (pyridine derivatives) showed a markedly higher effectiveness in activating the purified enzyme than resveratrol 100 μM (Figures 1 and 2, table 2). Moreover, all the pyridine derivatives showed concentration-dependent SIRT1 activation. The incubation of compounds 1, 2, 3, 4, 5 (oxazolidine derivatives), 6 (diaryl-ether derivative), 10, 11, 12 and 13 (aniline derivatives) at 100 μM resulted in a clearly lower SIRT1 activation than was induced by resveratrol 100 μM.

Table 2 - the table shows the effects of the synthetized compounds on SIRT1 (expressed as a % *vs* the reference compound resveratrol 100 μM). Negative values indicate that the compound reduced the activity of the enzyme.

Compound	3µM	10µM	30µM	100µM
1				21 ± 16.0
2				-1 ± 2.0
3				-44 ± 10.6
4				-1 ± 10.3
5				-130 ± 7.6
6				19 ± 6.2
10				37.80 ± 3.1
11				50.35 ± 8.29
12				-33.79 ± 1.92
13				-8.43 ± 0.52
14	156.41 ± 1.45	156.74 ± 34.68	202.14 ± 16.52	238.12 ± 4.86
15	94.54 ± 6.54	216.47 ± 9.01	289.21 ± 14.14	316.36 ± 45.61
16	84.02 ± 13.91	110.36 ± 14.71	134.25 ± 8.36	184.21 ± 15.91
17	28.41 ± 21.01	66.25 ± 11.84	86.65 ± 9.58	127.52 ± 7.7
Resveratrol				100 ± 2.1

Evaluation of the cardioprotection properties in an in vivo model of ischemia / reperfusion injury.

The most active SIRT1 activators were selected for the purpose of evaluating their cardioprotection properties in an in vivo rat model of ischemia / reperfusion injury. Wistar albino rats (males, 300-350 g) were treated i.p. with the compounds 120 min before proceeding with the experimental model of acute myocardial infarct.

The rats were anesthetized with pentobarbital sodium (70mg / kg i.p.) and connected to an electrocardiograph to monitor cardiac activity. Following tracheotomy, respiratory activity was kept constant by means of an artificial respirator (70 breaths / min, 1ml of air blown / 100g) for the whole duration of the experimental procedure.

After partial thoracotomy, the heart was exposed and reversible occlusion of the left coronary artery was performed for 30 minutes by means of a ligature with a surgical needle (13mm, C1, 3/8 circular, 6-0). After the removal of the occlusion, reperfusion was maintained for 120 min. The animals were then sacrificed by administration of an anesthetic overdose and a morphometric evaluation of the heart was performed.

The left ventricle was transversally cut into slices about 2 mm thick and each slice was incubated for 20 min at 37 ° C in triphenyl-tetrazolium chloride in order to distinguish the ischemic areas, which appeared pale pink or white, from the vital areas, which appeared red in colour.

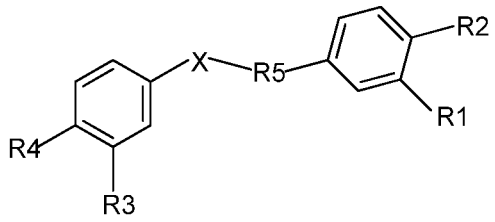
On the basis of the in vitro results obtained for the purified enzyme, compounds 14 and 15 were selected in order to evaluate their cardioprotective activity in an in vivo model of acute myocardial infarction, since at all tested concentrations (from 3 to 100 µM) they showed an activation equivalent to or higher than resveratrol 100 µM. Both compounds significantly reduced the ischemic area *vs* the vehicle (DMSO 1% p/v), and thus showed a significant protective effect against myocardial injury. In particular, compound 14 at 1 mg/kg (i.p.) proved to be even more effective than diazoxide 40mg/kg (i.p.), selected as a reference cardioprotective drug. Compound 15, at a dose of 1mg/kg, was less effective than compound 14. However, it significantly reduced the ischemic area (Figure 3, Table 3). The cardioprotective effect was dose-dependent, since at a dose of 10 mg/Kg compound 15 showed a significant improvement in effectiveness.

Table 3 – Percentage of ischemic area (Ai) *vs* left ventricle area (Alv).

	Ai/Alv %
Vehicle	45.8 ± 2.42
Diazoxide 40 mg/Kg	20.8 ± 2.45
Comp. 14. 1 mg/Kg	11.95 ± 2.04
Comp. 15. 1 mg/Kg	31.05 ± 0.25
Comp. 15. 10 mg/Kg	6.40 ± 3.40
	Ai/Alv %
Vehicle	45.8 ± 2.42
Diazoxide 40 mg/Kg	20.8 ± 2.45
Comp. 14. 1 mg/Kg	11.95 ± 2.04
Comp. 15. 1 mg/Kg	31.05 ± 0.25
Comp. 15. 10 mg/Kg	6.40 ± 3.40

CLAIMS

1. A compound of formula (I):



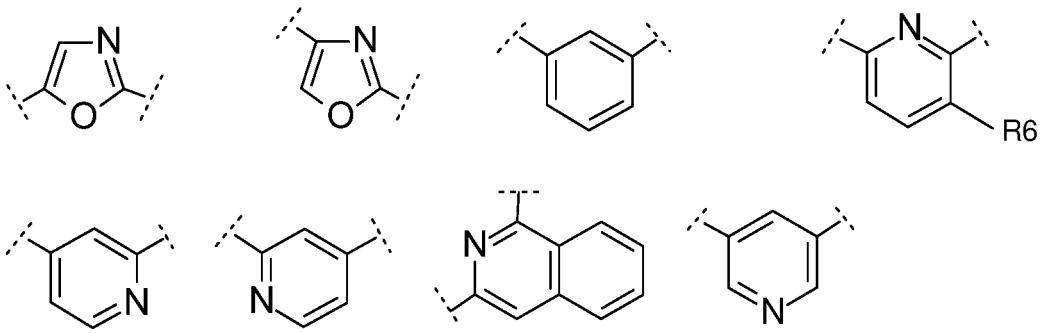
(I)

wherein

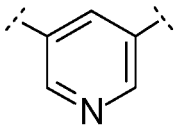
R1, R2, R3 and R4 are independently selected from –OH and -H;

X is selected from: -NH, -O, -S,

R5 is selected from among the following groups:



R6 is selected from –H or a non-substituted phenyl group,



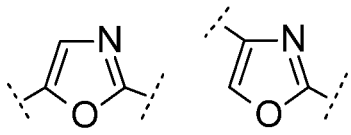
with the condition that when R5 is

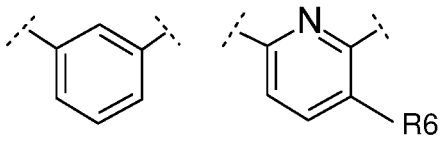
R2 and R3 are never –OH.

2. The compound according to claim 1, wherein X is selected from: –NH and -O.

3. The compound according to claim 1 or 2, wherein X is –NH.

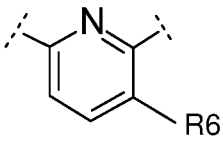
4. The compound according to any one of claims 1-3, wherein R5 is selected from among the following groups:





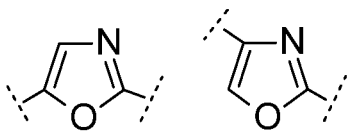
and R6 is –H .

5. The compound according to claim 4, wherein R5 is



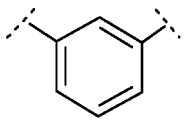
and R6 is –H.

6. The compound according to any one of claims 1 to 3, wherein R5 is selected from among the following groups:



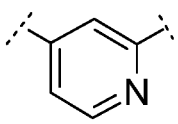
.

7. The compound according to any one of claims 1 to 3, wherein R5 is



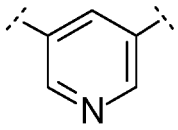
.

8. The compound according to any one of claims 1 to 3, wherein R5 is



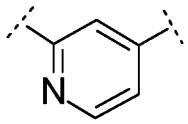
.

9. The compound according to any one of claims 1 to 3, wherein R5 is



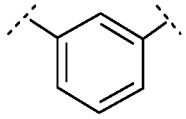
.

10. The compound according to any one of claims 1 to 3, wherein R5 is



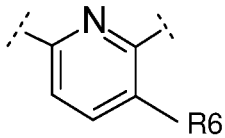
.

11. The compound according to claim 1, wherein X is S and R5 is



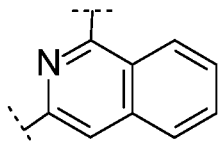
.

12. The compound according to any one of claims 1 to 3, wherein R5 is



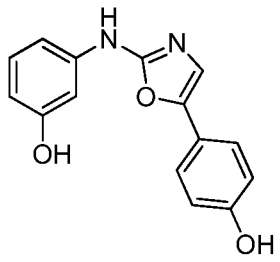
and R6 is a non-substituted phenyl group.

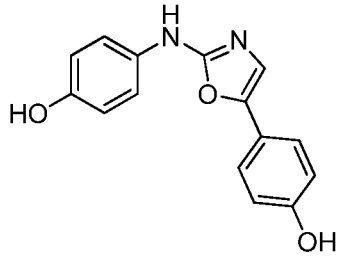
13. The compound according to any one of claims 1 to 3, wherein R5 is

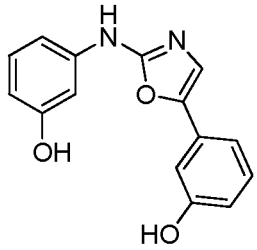


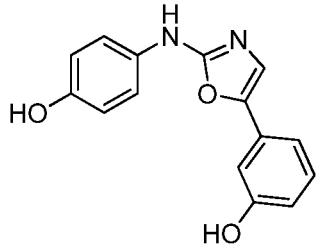
.

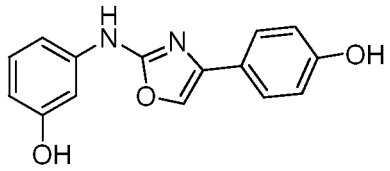
14. The compound according to any one of the preceding claims selected from:

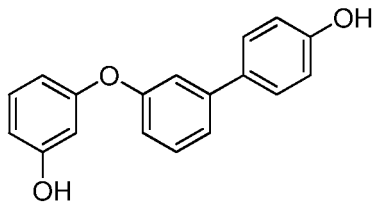


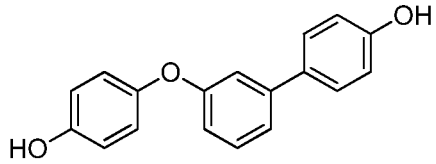


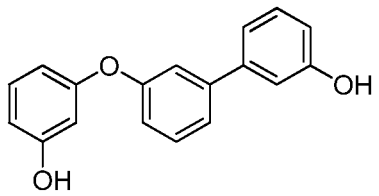


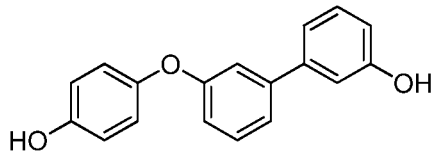


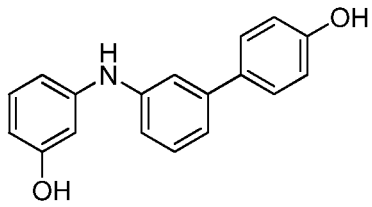


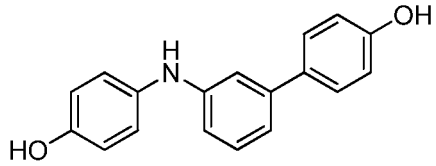


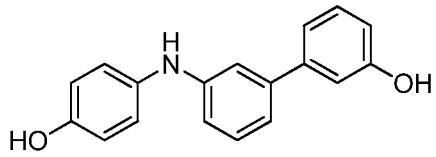


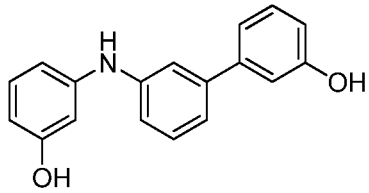


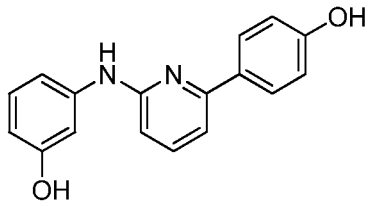


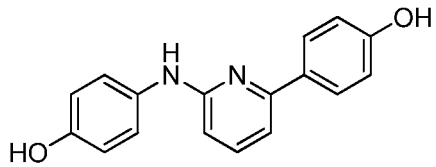


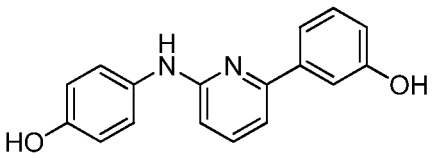


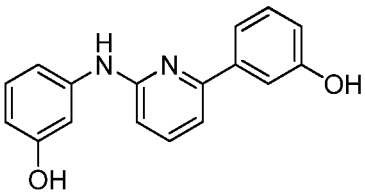


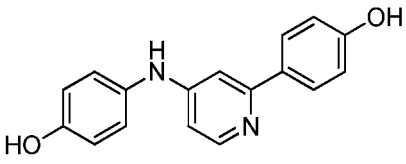


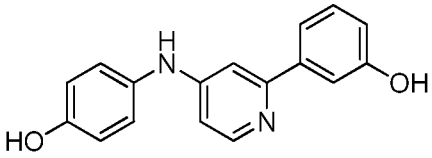


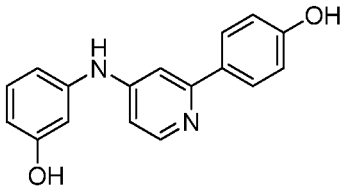


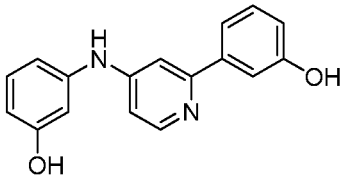


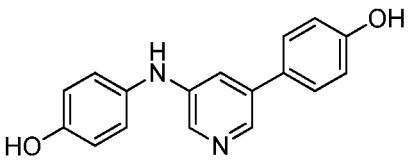


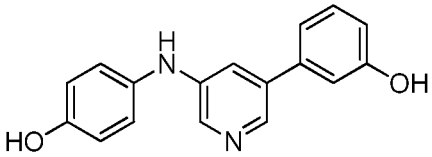


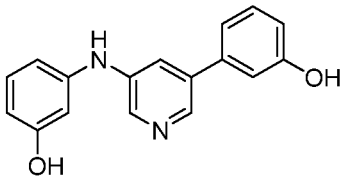


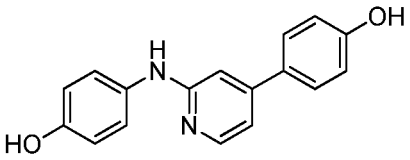


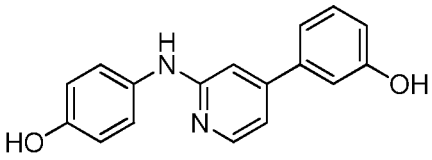


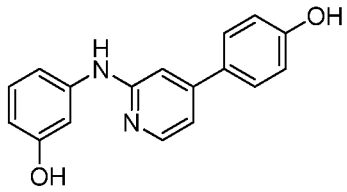


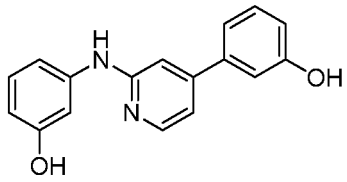












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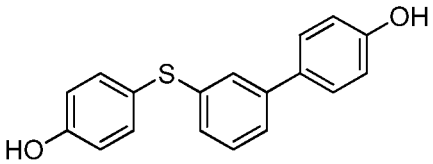
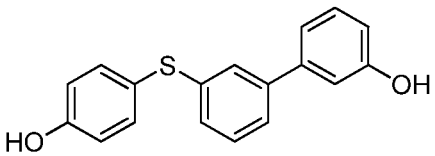
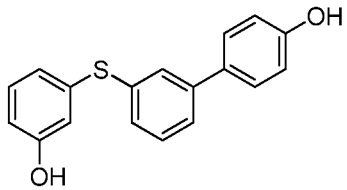
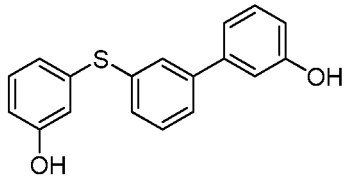
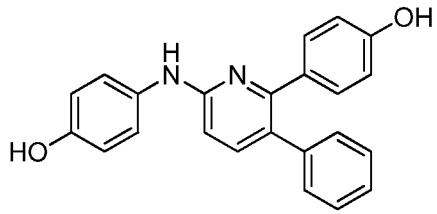
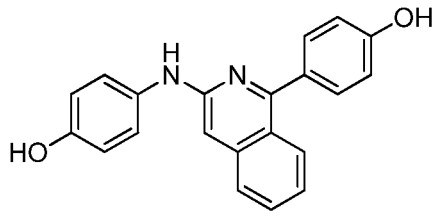
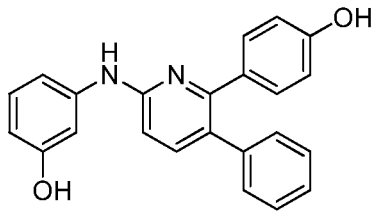
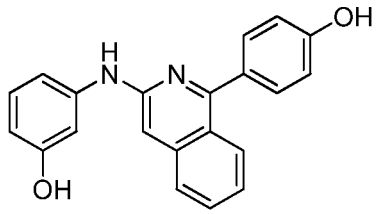








15. A pharmaceutical composition comprising the compound according to any one of the preceding claims and pharmaceutically acceptable excipients, adjuvants and/or carriers.

16. The pharmaceutical composition according to claim 15 or the compound according to any one of claims 1 to 14 for use as a medicament.

17. The pharmaceutical composition according to claim 15 or the compound according to any one of claims 1 to 14, for use in the treatment or in the prevention of cardio-metabolic pathologies, preferably diabetes, and cardiovascular pathologies, preferably coronary pathologies, heart failure, acute myocardial infarction and atherosclerosis.

18. The pharmaceutical composition according to claim 15 or the compound according to any one of claims 1 to 14 for use in association or in combination with other molecules selected from: ACE inhibitors, statins, sartans, calcium channel blockers, beta-blockers, vasodilators, digitalin, antianginal, anti-ischemic, antiarrhythmic, antihypertensive and hypocholesterolemic drugs and combinations thereof.

Fig. 1

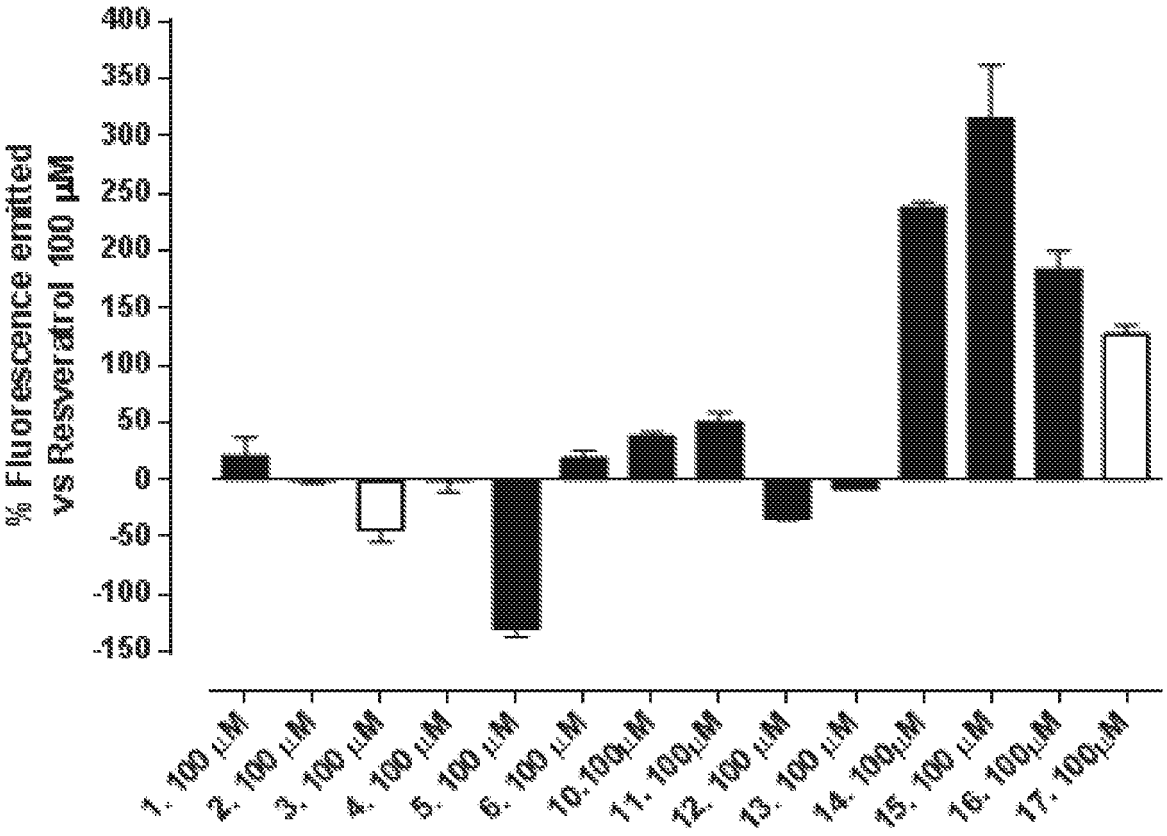

% Fluorescence emitted
vs Resveratrol 100 µM
400
350
300
250
200
150
100
50
0
-50
-100
-150
1. 100 µM
2. 100 µM
3. 100 µM
4. 100 µM
5. 100 µM
6. 100 µM
10. 100µM
11. 100µM
12. 100 µM
13. 100 µM
14. 100µM
15. 100 µM
16. 100µM
17. 100µM

Fig. 2

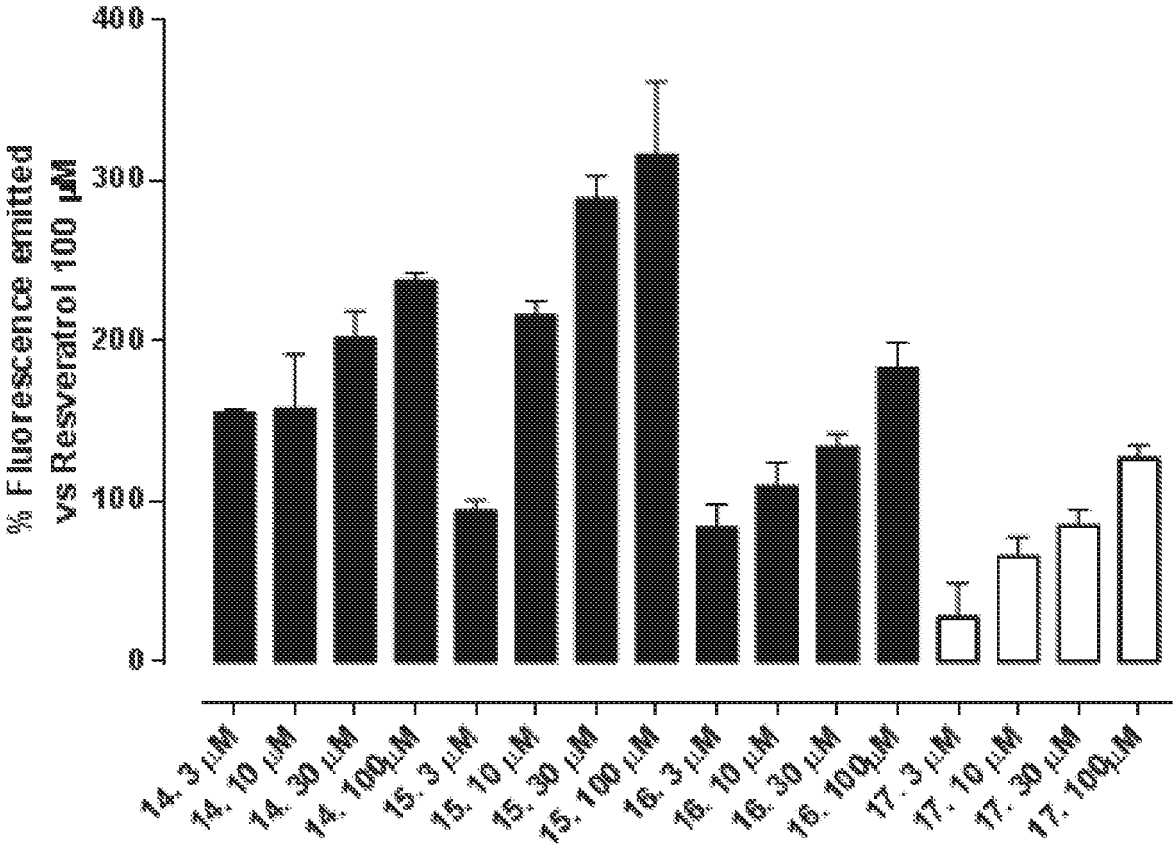
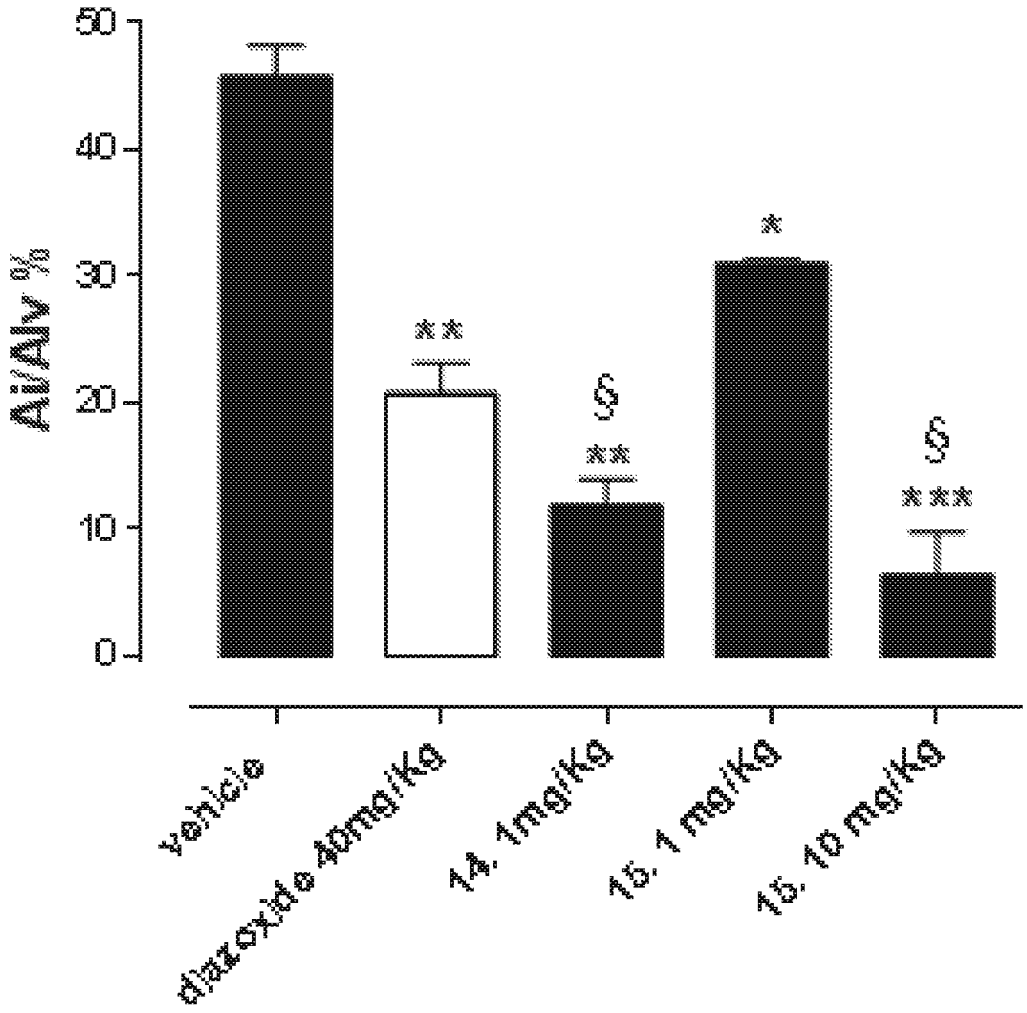

% Fluorescence emitted vs Resveratrol 100 µM
400
300
200
100
0
14. 3 µM
14. 10 µM
14. 30 µM
14. 100µM
15. 3 µM
15. 10 µM
15. 30 µM
15. 100 µM
16. 3 µM
16. 10 µM
16. 30 µM
16. 100µM
17. 3 µM
17. 10 µM
17. 30 µM
17. 100µM

Fig. 3


Ai/Alv %
0
10
20
30
40
50
**
§
**
*
§
***
vehicle
diazoxide 40mg/kg
14. 1mg/kg
15. 1 mg/kg
15. 10 mg/kg

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051489

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 C07D217/22 C07C39/00 C07C323/09 C07D263/48
A61K31/421 A61K31/44 A61K31/4418 A61K31/472 A61P9/10
A61P9/04 A61P3/10

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)
C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN TAIJIE ET AL: "Cu-mediated selective O-arylation on C-6 substituted pyridin-2-ones", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 54, no. 11, 10 January 2013 (2013-01-10), pages 1401-1404, XP028577991, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2012.12.126 page 1402; example 2; table 2 ----- -/--	1,2,4,5

[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

"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
9 April 2019	13/05/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIREN ET AL.: "A benzannulation protocol to prepare substituted aryl amines using a Michael-Aldol reaction of beta-keto sulfones", J. ORG. CHEM., vol. 74, 24 September 2009 (2009-09-24), pages 7781-7789, XP002782525, page 7784; example 32	1,4,7,11
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X	SUN T AL.: "Synthesis of N-heterocyclic carbene-Pd(II)-2-methyl-4,5-dihydrooxazole complexes and their application toward highly chemoselective mono-Suzuki-Miyaura coupling of dichlorobenzenes", ASIAN J. ORG. CHEM., vol. 7, 10 February 2018 (2018-02-10), pages 781-787, XP002782528, page 784; example 14b	1-4,7
X	JEANNE L. BOLLIGER ET AL: "Access to 2-Aminopyridines - Compounds of Great Biological and Chemical Significance", ADVANCED SYNTHESIS & CATALYSIS, vol. 353, no. 6, 18 April 2011 (2011-04-18), pages 945-954, XP055422594, DE ISSN: 1615-4150, DOI: 10.1002/adsc.201000942 table 2	1-5,9

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOR M ET AL: "Cyclohexylcarbamic acid 3'- or 4'-substituted biphenyl-3-yl esters as fatty acid amide hydrolase inhibitors: Synthesis, quantitative structure-activity relationships, and molecular modeling studies", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 47, no. 21, 2 September 2004 (2004-09-02), pages 4998-5008, XP002386388, ISSN: 0022-2623, DOI: 10.1021/JM031140X page 4998; example 3m	1
X	TONSON ABRAHAM: "Metalation of 2-methyl-N-phenylbenzamide with n-butyllithium. Formation of N,3-diphenyl-1-isoquinolin-amine by subsequent reaction with benzonitrile", MONATSHEFTE FÜR CHEMIE, vol. 113, 1982, pages 371-374, XP002782529, page 372; example 8	1-3,13
X	LIANG ET AL.: "Palladium-catalyzed C(sp2)-H pyridocarbonylation of N-aryl-2-aminopyridines: dual function of the pyridyl moiety", ORGANIC LETTERS, vol. 16, 7 May 2014 (2014-05-07), pages 2748-2751, XP002782530, page 2749	1-3,10
X	BUTLER D E ET AL: "Novel Pharmacological Activity of a Series of Substituted Pyridines", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 14, no. 7, 1971, pages 575-579, XP002321162, ISSN: 0022-2623, DOI: 10.1021/JM00289A005 table I	8
X	DAHLGREN ET AL.: "Virtual screening and optimization yield low-nanomolar inhibitors of the tautomerase activity of Plasmodium falciparum macrophage migration inhibitory factor", J. MED. CHEM., vol. 55, 15 October 2012 (2012-10-15), pages 10148-10159, XP002782531, page 10150	8

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051489

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/010637 A2 (GPC BIOTECH AG [DE]; EICKHOFF JAN EIKE [DE]; HAFENBRADL DORIS [DE]; SC) 2 February 2006 (2006-02-02) examples ----	1-18
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X	WO 98/24794 A1 (LILLY CO ELI [US]; GOODSON THEODORE JR [US]; HARPER RICHARD W [US]; HE) 11 June 1998 (1998-06-11) page 23; example 8 ----	1,2,4,7
A	WO 2009/146358 A1 (SIRTRIS PHARMACEUTICALS INC [US]; VU CHI B [US]; NG PUI YEE [US]; BLUM) 3 December 2009 (2009-12-03) examples ----	1-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/051489

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