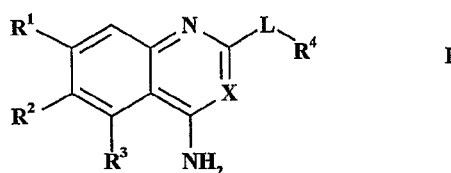


PROCESS FOR THE PRODUCTION OF 4-AMINO-2,5-BISHETEROCYCLYLQUINAZOLINES

This invention relates to a novel process for producing quinazoline compounds which are useful in therapy. More specifically, the compounds are useful in the treatment of benign prostatic hyperplasia.

International Patent Application WO 98/30560 discloses a number of substituted quinoline and quinazoline compounds of formula (I) which find use in the treatment of benign prostatic hyperplasia,



10

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

15 R^3 represents a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen, C_{1-4} alkoxy, C_{1-4} alkyl and CF_3 ;

R^4 represents a 4-, 5-, 6-, or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^8R^9$, $SO_2NR^8R^9$, $(CH_2)_bNR^8R^9$ and $NHSO_2(C_{1-4} \text{ alkyl})$, and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;

25 R^8 and R^9 independently represent H or C_{1-4} alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S;

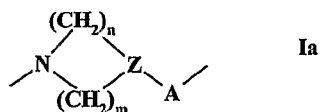
b represents 0, 1, 2 or 3;

30 X represents CH or N; and

L is absent,

2

or represents a cyclic group of formula Ia,



in which N is attached to the 2-position of the quinoline or quinazoline ring;

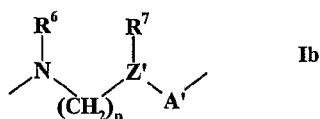
5 A is absent or represents CO or SO₂;

Z represents CH or N;

m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and

n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

10 or represents a chain of formula Ib,



in which N is attached to the 2-position of the quinoline or quinazoline ring;

15 A' and Z' have the same significance as A and Z above, respectively;

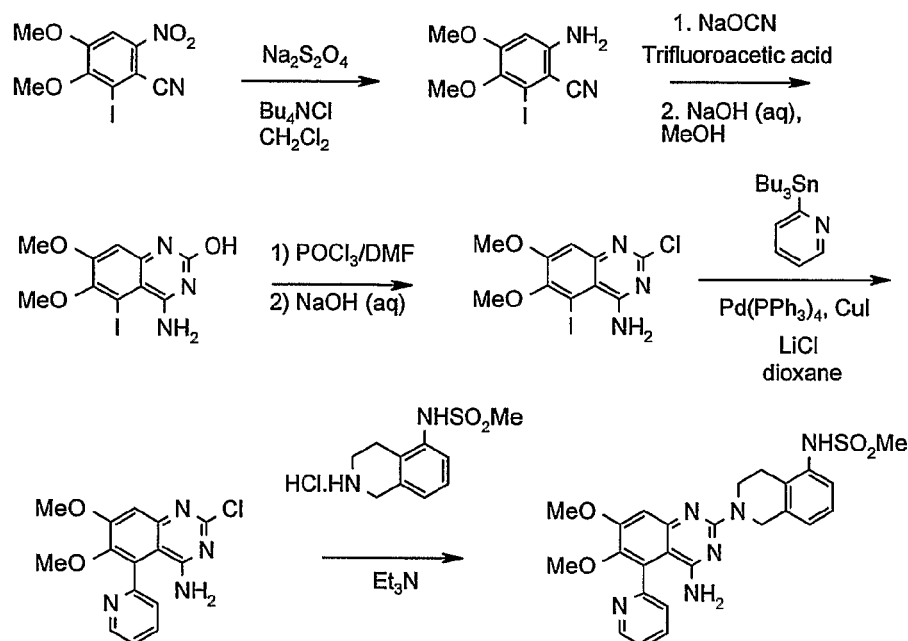
R⁶ and R⁷ independently represent H or C₁₋₄ alkyl; and

p represents 1, 2 or 3, and in addition, when Z' represents CH, it may represent 0.

20 The compounds of formula (I) in which X represents N, and L is absent are of particular interest. Of these compounds, 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline is of special interest.

25 According to WO 98/30560, the compounds of formula (I) can be produced by a number of processes. However, none of these processes involves the condensation of the two main parts of the molecule in a convergent synthesis in which the quinazoline ring is formed and each process suffers disadvantages. For example, 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-

yl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline (the compound of Example 19 in WO 98/30560) is prepared according to the following scheme:



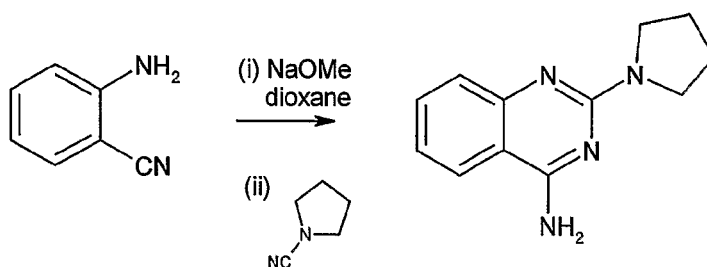
The routes described in WO 98/30560 suffer the disadvantage that they involve the use of tributyl stannyl pyridine in combination with copper iodide and tetrakis (triphenylphosphine) palladium. One problem of this route is that the tributyl stannyl pyridine is expensive to purchase. The compound is toxic and there are issues of worker safety and concerning the environment. After use, spent reactants are difficult and expensive to dispose of because of the adverse effects organotin compounds have on their surroundings. A further problem with the prior art process is its lack of convergency. A number of synthetic steps are required to produce the quinazoline compounds in the disclosed processes, with each synthetic step leading both to a reduction in yield and increasing the possibility of competing side reactions. Thus the conventional sequence requires effort to purify the product and may not give an optimal yield.

A further problem with the prior art process of WO 98/30560 is that large pebble-like aggregates are formed in the reactor during the reaction. The identity of these aggregates is not clear but they are believed to be formed of inorganic material derived from the various inorganic additives used during the reaction such as lithium chloride and copper iodide. In this process, there is the risk that the pebble-like aggregates could crack the reactor causing leakage of the

reaction medium and the hazard of fire or poisoning. At the very least there is the problem that the reaction leads to scratching of the interior of the reaction vessel thus causing premature wearing of the vessel, poor heat dissipation in the mixture or blocking.

5

The use of sodium methoxide in dioxane has been reported recently for the synthesis of 2-aminoquinazolines (see van Muijlwijk-Koezen *et al*, J Med Chem, 2000, vol 43 (11), p2227-2238, in particular the preparation of compound 4k):



10 However, the reaction was carried out at reflux, and the yield obtained was only 34%.

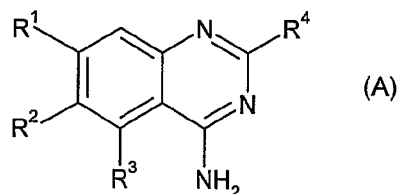
It is an aim of the present invention to provide a synthetically efficient process for the production of quinazoline derivatives which avoids the problems of the prior art process. It is also an aim to provide a process in which the convergency (ie the bringing together of synthetic fragments) is maximised. It is thus an aim to provide a route to the compounds of formula (I) of greatest interest which offers an improved yield relative to the existing routes. It is a further aim of the process of the present invention to avoid the use of organotin compounds on account of their hazardous nature. It is a further aim of the present invention to provide a process which minimizes the number of synthetic steps required and which avoids the problem of competing reactions and/or the disposal of hazardous materials. It is also desirable to avoid heating of reaction mixtures where possible.

25

We have found an improved route to the quinazoline derivatives of formula (I) above of greatest interest which satisfies some or all of the above aims.

5

According to the present invention, there is provided a process for the production of a compound of formula (A), or a pharmaceutically acceptable salt or solvate thereof,



5 wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

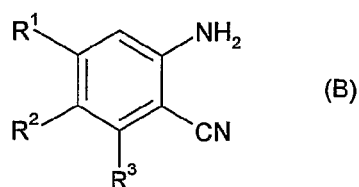
R^3 represents a 5- or 6-membered heterocyclic ring containing at least one
10 heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen, C_{1-4} alkoxy, C_{1-4} alkyl and CF_3 ;

R^4 is a 4-, 5-, 6- or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one
15 heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^7R^8$, $SO_2NR^7R^8$, $(CH_2)_bNR^7R^8$ and $NHSO_2(C_{1-4} \text{ alkyl})$, and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;

20 R^7 and R^8 independently represent H or C_{1-4} alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S; and

b represents 0, 1, 2 or 3;

the process comprising condensing a compound of formula (B),



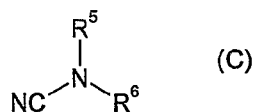
25

wherein

R^1 to R^3 are as defined above;

6

with a compound of formula (C),



wherein

- R⁵ and R⁶ taken together with the N atom to which they are attached represent a
- 5 4-, 5-, 6-, or 7-membered N-containing heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH,
- 10 C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, CONR⁷R⁸, SO₂NR⁷R⁸, (CH₂)_bNR⁷R⁸ and NHSO₂(C₁₋₄ alkyl), and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;
- R⁷, R⁸ and b are as defined above; and
- where necessary or desired, converting the resulting compound of formula (A)
- 15 into a pharmaceutically acceptable salt or solvate, or converting the resulting salt or solvate into a compound of formula (A).

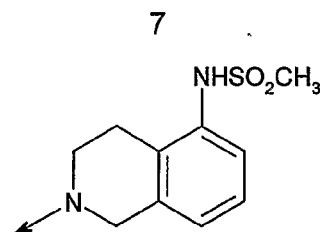
Preferably R¹ represents methoxy.

- 20 Preferably R² represents methoxy.

Preferably R³ represents an aromatic ring. More preferably, R³ represents pyridyl, pyrimidyl, thienyl, furanyl or oxazolyl. More preferably R³ represents 2-pyridyl or 2-pyrimidyl, 2-pyridyl being most preferred.

25

- Preferably, R⁵ and R⁶ together with the N atom to which they are attached represent a saturated 6-membered N-containing ring which is fused to an optionally substituted benzene or pyridine ring. More preferably, R⁵ and R⁶ together with the N atom to which they are attached represent an optionally
- 30 substituted tetrahydroisoquinoline ring system. Most preferably, R⁵ and R⁶ together with the N atom to which they are attached represent a group of formula



Thus, the process is most preferably used to prepare 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline.

5

Preferably the reaction is carried out in a polar aprotic solvent, for example dimethylsulfoxide.

10 Preferably, the reaction is carried out at a temperature in the range 10-30°C.

Preferably the reaction is carried out in the presence of a base. More preferably, the base is an alkali metal alkoxide or an alkaline earth metal alkoxide. More preferably, the base is sodium *t*-butoxide or sodium *t*-pentoxide, the latter being

15

In a further aspect of the present invention, there is provided a process for the production of a compound of formula (C), as defined above, which comprises reaction of a compound of formula (E),

20



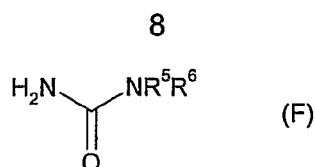
or an acid addition salt thereof,

wherein R^5 and R^6 are as defined above, with BrCN in the presence of an amine base.

25 Preferably, the base is a tri- C_{1-8} alkyl, C_{3-8} cycloalkyl or a heterocyclic amine. Most preferably the base is *N,N*-diisopropylethylamine.

The invention also provides an alternative process for the production of a compound of formula (C), as defined above, which comprises reaction of a

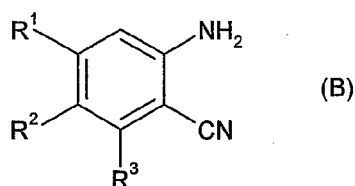
30 compound of formula (F),



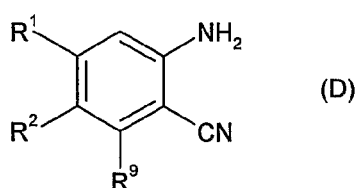
wherein R^5 and R^6 are as defined in claim 1, with methanesulphonyl chloride in the presence of pyridine. Compounds of formula (F) may be prepared from compounds of formula (E) by reaction with sodium cyanate in water, as illustrated
 5 by Example 3A(a). Compounds of formula (E) are either known or may be prepared by known techniques.

Preferably, the above two processes for preparing compounds of formula (C) are used to prepare *N*-(2-cyano-1,2,3,4-tetrahydro-5-
 10 isoquinolyl)methanesulfonamide.

In another aspect of the invention, there is provided a process for the production of a compound of formula (B),



15 wherein
 R^1 to R^3 are as defined above;
 which comprises reaction of a compound of formula (D),



wherein;

20 R^1 and R^2 are as defined above; and
 R^9 is a leaving group;
 with a pyridyl boronate.

Preferably R^9 is iodine.

25

Preferably the pyridine derivative is a 2-pyridyl boronate.

Most preferably, the process is used to prepare 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile.

- 5 Preferably, the reaction is carried out in a polar aprotic solvent. More preferably, the polar aprotic solvent is tetrahydrofuran or isopropyl acetate.

Preferably, the coupling reaction to form the 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile is carried out above room temperature. Preferably, this
10 reaction is carried out in the presence of a catalyst. More preferably, the catalyst is a palladium (0) catalyst. Most preferably, the catalyst is derived from palladium (II) acetate by reduction *in situ*. Preferably, this coupling reaction is carried out in the presence of a base. The base is preferably an alkali metal carbonate, and more preferably it is potassium carbonate.

15

The pyridyl boronate may be prepared by reaction of a bromopyridine with triisopropylborate at or below room temperature. Preferably, this reaction is carried out in the presence of a base. The base is preferably an alkyl lithium reagent. n-Butyl lithium is a preferred alkyl lithium reagent.

20

Compounds of formula (D) may be prepared from known compounds, or compounds that are readily prepared, using known techniques, as illustrated by Example 1.

- 25 The invention further provides compounds of formula (B), as defined above, and compounds of formula (C), as defined above.

The invention is illustrated by the following examples in which the following abbreviations may be used:

30

DMSO = dimethylsulfoxide
DCM = dichloromethane
Et = ethyl
EtOAc = ethyl acetate

K₂EDTA = ethylenediaminetetraacetic acid, dipotassium salt

nBuLi = n-butyllithium

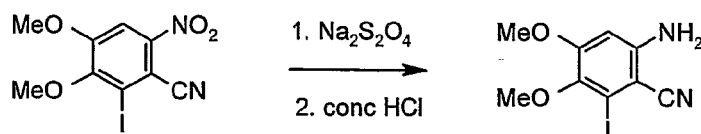
OAc = acetate

THF = tetrahydrofuran

5

Example 1

Preparation of 6-amino-2-iodo-3,4-dimethoxybenzonitrile



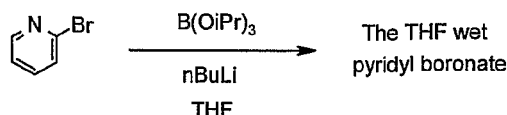
In a reactor vessel, a suspension of 6-nitro-2-iodo-3,4-dimethoxybenzonitrile [see
 10 Example 1(d) of WO 98/30560, 10kg) in ethanol (60 l) at room temperature was
 charged with a solution of sodium dithionite (15.6 kg of technical grade material)
 in water (67.5 l) over 45 mins maintaining the temperature below 35°C. The
 addition vessel was washed with water (10 l). The resulting mixture was warmed
 to reflux (ca. 85°C) for ca. 90 mins and then the temperature adjusted to 65°C. A
 15 solution of 6M aqueous hydrochloric acid (12.5 l) was added over ca. 10 mins
 and the resulting mixture stirred at 65°C for ca. 5 hours before being cooled to
 room temperature. The pH was adjusted to the range 7–8 using 40% sodium
 hydroxide (2 l), the resulting mixture left to stir for 3 hours, filtered and washed
 with water (50 l). The damp cake was slurried in water (90 l) overnight at room
 20 temperature, filtered, washed with water (100 l) and dried *in vacuo* to give 8.35kg
 (92%) of the title compound.

Example 2

Preparation of 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile

25

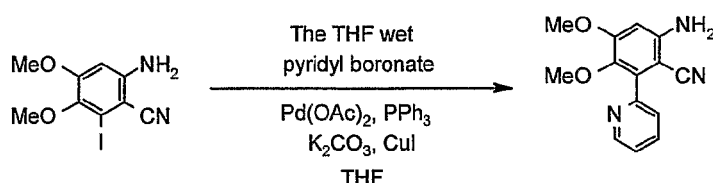
(a) Preparation of the 2-pyridyl boronate



Under nitrogen, a stirred solution of 2-bromopyridine (150g, 0.95 mol) and
 triisopropylborate (218ml, 0.95 mol) in THF was cooled to -25°C. A 2.5M solution
 30 of n-BuLi in hexanes (378ml, 0.95 mol) was added at such a rate that the

temperature did not exceed -24°C . After completion of the addition, the reaction was allowed to warm to room temperature and stirred at this temperature for 18 hours. After this time, the reaction mixture was filtered, washed with THF and the procedure deemed complete before the filter pad had completely dried. A portion of the THF wet boronate was used in the subsequent reaction. Analysis of the THF wet boronate by ^1H NMR, showed a pyridine H : isopropyl methine H ratio of 1:3.75 and that the material contained 54% w/w solvent.

(b) Preparation of 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile



10

Under nitrogen, to anhydrous THF (1000ml) was added 6-amino-2-iodo-3,4-dimethoxybenzonitrile (see Example 1, 50.0g, 164 mmol), $\text{Pd}(\text{OAc})_2$ (1.85g, 8.22 mmol), PPh_3 (triphenylphosphine, 4.31g, 16.4 mmol), THF wet boronate [from step (a), 286g, 493 mmol], CuI (12.5g, 65 mmol) and K_2CO_3 (45.5g, 328 mmol). The reaction mixture was then stirred at reflux for 16 hours. After this time, the reaction mixture was cooled to room temperature and water (1000ml) added. The mixture was then filtered through an Arbocel™ filter aid pad and the pad washed with THF (500ml). The filtrate was then extracted with CH_2Cl_2 (1000ml). The aqueous phase was back extracted with CH_2Cl_2 (500ml) and the combined CH_2Cl_2 extracts were evaporated *in vacuo* to yield the crude product as a dark brown solid. Recrystallisation from EtOAc (250ml) afforded 37.6g (87%) of the title compound as a beige solid.

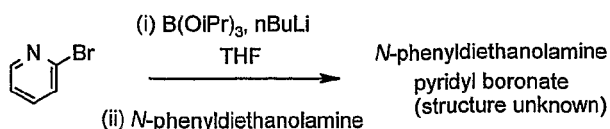
15

20

Example 2A

25 **Alternative route to 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile**

(a) Preparation of the *N*-phenyldiethanolamine pyridyl boronate



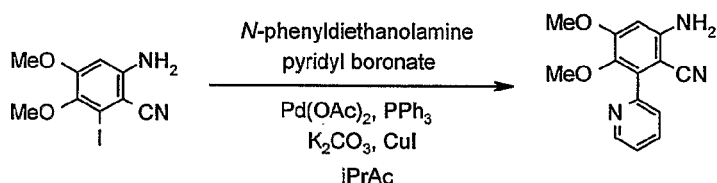
Under nitrogen, a stirred solution of 2-bromopyridine (843g, 5.33 mol) and triisopropylborate (1.20kg, 6.40 mol) in THF (6.74l) was cooled to -75°C. A 1.6M solution of n-BuLi in hexanes (4.00l, 6.40 mol) was added at such a rate that the temperature did not exceed -67°C. After completion of the addition, the reaction

5 was allowed to warm to room temperature and stirred at this temperature for 16 hours. After this time, a solution of *N*-phenyldiethanolamine (966g, 5.33 mol) in THF (966ml) was added and the resulting mixture heated at reflux for 4 hours. The solvent was distilled and replaced with isopropanol until the head temperature was 76°C (distilling 11.3l and adding in 8.4l of isopropanol during

10 the process). The mixture was cooled to room temperature and stirred at this temperature for 12 hours. The mixture was filtered, the solid washed with isopropanol (1.7 l) and dried *in vacuo* overnight at 40°C to give 1605g of the subtitle compound. Analysis by ¹H NMR showed a ratio of pyridine : *N*-phenyldiethanolamine (or lithium alkoxide) : isopropyl of 1 : 1.25 : 1.55.

15

(b) Preparation of 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile



Under nitrogen, 6-amino-2-iodo-3,4-dimethoxybenzonitrile (see Example 1, 100g, 0.33 mol) was suspended in isopropyl acetate (1.4L) at 20°C. To the suspension

20 was charged palladium acetate (3.69g, 16 mmol), followed by triphenylphosphine (17.25g, 66 mmol), *N*-phenyldiethanolamine pyridyl boronate (263.4g of the batch prepared as described above), copper iodide (25.05g, 0.13 mol), then potassium carbonate (90.9g, 0.66 mol) and the suspension heated to reflux for 8 hours. The suspension was cooled to 70°C and maintained at this temperature

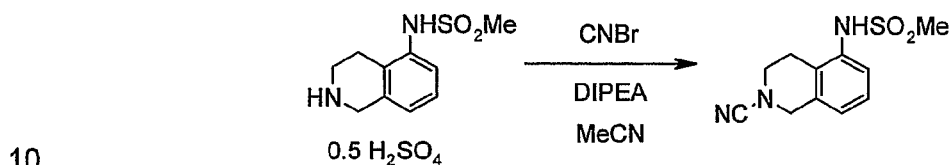
25 overnight. The suspension was cooled to 45°C, tetrahydrofuran (1 l) was added and the suspension stirred at 45°C for 1 hour. After this time, Arbocel™ filter aid was added and the mixture was filtered through Arbocel™ filter aid. The pad was washed with tetrahydrofuran (2 x 200ml) and isopropyl acetate (200ml). The resulting solution was washed twice with a 1:1 mixture of 5% aqueous K₂EDTA

30 and saturated brine (800ml), then washed with a 1:1 mixture of water and

saturated brine (800ml). The organic phase was distilled and replaced with isopropyl acetate to leave a final volume of isopropyl acetate of 500ml that was left to cool to room temperature overnight. The resulting suspension was filtered to give a light brown solid that was dried *in vacuo* overnight at 45°C to yield 59.6g (71%) of the title compound.

Example 3

Preparation of *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide

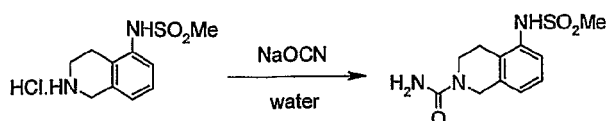


To a stirred slurry of *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide hemisulfate (prepared analogously to the compound of Example 19(b) in WO 98/30560, but using sulphuric acid in the final step in place of hydrochloric acid; 240g, 0.88 mol) in acetonitrile (2400ml) at 0°C was added *N,N*-diisopropylethylamine (326ml, 1.88 mmol). Cyanogen bromide (99.2g, 0.94 mol) was added over a period of 20 minutes keeping the temperature below 10°C. The resulting slurry was allowed to warm to 20°C and stirred at this temperature for 18hrs. After this time, water (2400ml) was added and the resulting mixture extracted with CH₂Cl₂ (2 × 2500ml). The combined organic phases were washed with water (2000ml) and evaporated to dryness. The resulting solid was reslurried in CH₂Cl₂ (360ml) and the solid collected by filtration to yield 158g (72%) of the title compound.

Example 3A

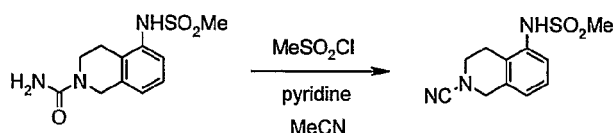
Alternative route to *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide

(a) Preparation of *N*-(2-carboxamide-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide



Under nitrogen, *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide hydrochloride (see Example 19(b), WO 98/30560, 50g, 190 mmol) was suspended in water (250ml) at 20°C. A solution of sodium cyanate (16.1g, 247 mmol) in water (250ml) was added slowly over a period of 5 minutes and the mixture then stirred at room temperature for 18 hours. The resulting suspension was filtered to give a white solid that was dried *in vacuo* overnight at 45°C to yield 45.0g (88%) of the subtitle compound.

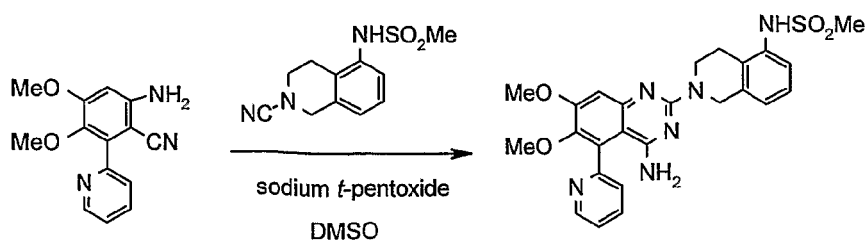
(b) Preparation of *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide



Under nitrogen, *N*-(2-carboxamide-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide [from step (a), 10.0g, 37.1 mol] was suspended in acetonitrile (100ml) at 20°C. Methanesulfonyl chloride (6.38g, 55.6 mmol) and pyridine (7.34g, 92.8 mmol) were added to the suspension. The reaction was stirred to form a solution then heated to 50°C and maintained at this temperature for 4 hours. The solution was cooled to room temperature and stirred overnight. The solvent was removed *in vacuo* and replaced with water (60ml). The resulting suspension was stirred for 3 hours then filtered to give a white solid. The solid was suspended in acetonitrile (50ml) and stirred at 20°C for 3 hours. The suspension was filtered to give a white solid that was dried *in vacuo* overnight at 45°C to yield 7.4g (79%) of the title compound.

Example 4

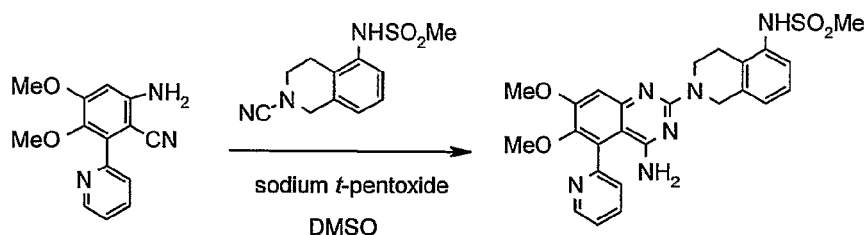
4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline



To a stirred solution of 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile (see Example 2 or 2A, 7g, 27 mmol) and *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide (see Example 3 or 3A, 9g, 36 mmol) in DMSO (21 ml) at room temperature, was added sodium-*t*-pentoxide (9.5g, 92 mmol) portionwise over 20 minutes keeping the temperature below 30°C. The resulting slurry was then stirred for 2 hours. After this time, iced water (35 ml) was added over 1 minute followed by ethyl acetate (35 ml) before reducing the pH of the biphasic mixture to 8.0 with 2M aqueous HCl (20ml). The aqueous phase was extracted with ethyl acetate (50 ml). The combined organics were washed with saturated NaCl solution (2 x 30ml), reduced in volume and stirred for 3 hours. After this time, the resulting slurry was filtered to yield 10.2g (74%) of the title compound.

Example 4A

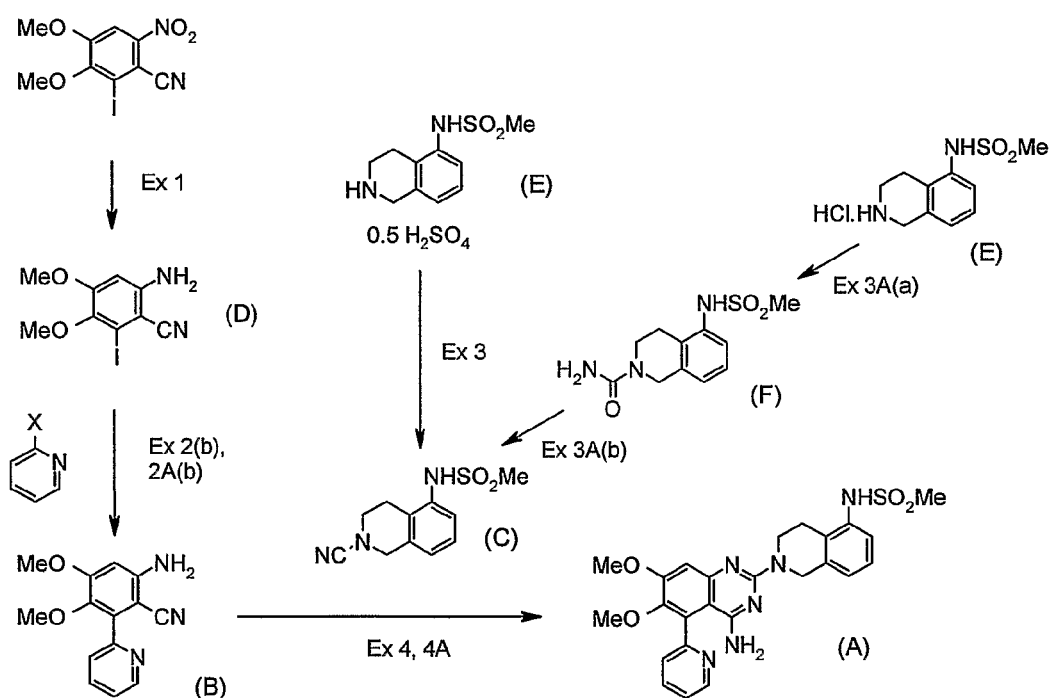
Alternative preparation of 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline



To a stirred solution of 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile (see Example 2 or 2A, 50g, 196 mmol) and *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide (see Example 3 or 3A, 63g, 251 mmol) in DMSO (300 ml) at room temperature, was added sodium-*t*-pentoxide (64.2g, 582 mmol) portionwise over 120 minutes keeping the temperature below 30°C. The resulting slurry was then stirred for 2 hours. After this time, water (500 ml) was added over 5 minutes followed by isopropyl acetate (150 ml). The aqueous phase was collected and partitioned with ethyl acetate (500 ml) before reducing the pH of the biphasic mixture to a range of 7.0-8.0 with 12M aqueous HCl (22ml). The aqueous phase was extracted with ethyl acetate (250 ml). The combined organics were reduced in volume and replaced with acetonitrile to give a final volume of 500ml and stirred for 13 hours. After this time, the resulting slurry was filtered to yield 105g of the crude product. This was then suspended

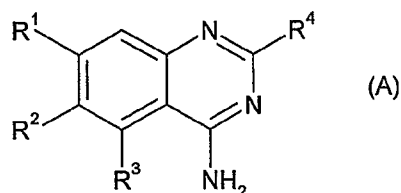
in acetonitrile (525ml), heated to reflux for one hour, cooled to room temperature and stirred for 13 hours. The resulting slurry was filtered to yield 87g (87%) of the title compound.

- 5 The preparation of 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline according to the above examples is illustrated in the following scheme, which also indicates the Example number of each step and the general formula that covers the relevant compound:



Claims:

1. A process for the production of a compound of formula (A), or a pharmaceutically acceptable salt or solvate thereof,



5

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

10 R^3 represents a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen, C_{1-4} alkoxy, C_{1-4} alkyl and CF_3 ;

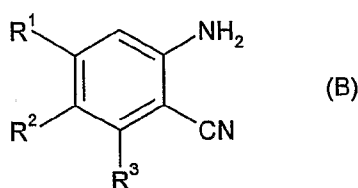
R^4 is a 4-, 5-, 6- or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a
15 benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^7R^8$, $SO_2NR^7R^8$, $(CH_2)_bNR^7R^8$ and $NHSO_2(C_{1-4} \text{ alkyl})$, and when S is a member of the ring system, it may be

20 substituted by 1 or 2 oxygen atoms;

R^7 and R^8 independently represent H or C_{1-4} alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S; and

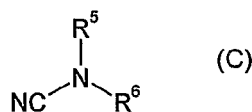
b represents 0, 1, 2 or 3;

25 the process comprising condensing a compound of formula (B),



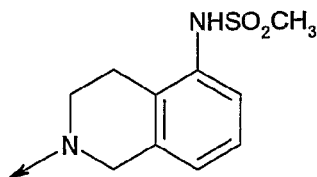
wherein

R¹ to R³ are as defined above;
with a compound of formula (C),



wherein

- 5 R⁵ and R⁶ taken together with the N atom to which they are attached represent a 4-, 5-, 6-, or 7-membered N-containing heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being
- 10 optionally substituted by one or more groups independently selected from OH, C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, CONR⁷R⁸, SO₂NR⁷R⁸, (CH₂)_bNR⁷R⁸ and NHSO₂(C₁₋₄ alkyl), and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;
R⁷, R⁸ and b are as defined above; and
- 15 where necessary or desired, converting the resulting compound of formula (A) into a pharmaceutically acceptable salt or solvate, or converting the resulting salt or solvate into a compound of formula (A).
2. A process as claimed in claim 1, wherein R¹ represents methoxy.
3. A process as claimed in claim 1 or 2, wherein R² represents methoxy.
- 20 4. A process as claimed in any one of claims 1, 2 or 3, wherein R³ represents an aromatic ring.
5. A process as claimed in claim 4, wherein R³ represents 2-pyridyl.
6. A process as claimed in any preceding claim, wherein R⁵ and R⁶ together with the nitrogen to which they are attached, represent a saturated 6-membered
- 25 N-containing ring which is fused to an optionally substituted benzene or pyridine ring.
7. A process as claimed in claim 6, wherein R⁵ and R⁶ together with the nitrogen to which they are attached represent a group of formula



8. A process as claimed in any one of the preceding claims, wherein the reaction is carried out in a polar aprotic solvent.

9. A process as claimed in any one of the preceding claims, wherein the reaction is carried out at a temperature in the range 10-30°C.

5 10. A process as claimed in any one of the preceding claims, wherein the reaction is carried out in the presence of a base.

11. A process as claimed in claim 10, wherein the base is an alkali metal alkoxide or an alkaline earth metal alkoxide.

12. A process as claimed in claim 11, wherein the base is sodium *t*-pentoxide.

10 13. A process for the production of a compound of formula (C), as defined in claim 1, which comprises reaction of a compound of formula (E),



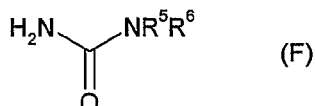
or an acid addition salt thereof,

wherein R^5 and R^6 are as defined in claim 1, with BrCN in the presence of an amine base.

15

14. A process as claimed in claim 13, wherein the amine is *N,N*-diisopropylethyl amine.

15. A process for the production of a compound of formula (C), as defined in claim 1, which comprises reaction of a compound of formula (F),

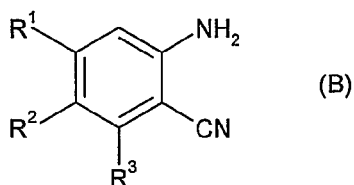


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wherein R^5 and R^6 are as defined in claim 1, with methanesulphonyl chloride in the presence of pyridine.

16. A process as claimed in any one of claims 13 to 15, wherein the product is *N*-(2-cyano-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide.

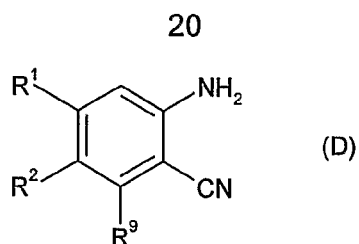
25 17. A process for the production of a compound of formula (B),



wherein

R^1 to R^3 are as defined in claim 1;

which comprises reaction of a compound of formula (D),



wherein;

R¹ and R² are as defined in claim 1; and

R⁹ is a leaving group;

- 5 with a pyridyl boronate.
18. A process as claimed in claim 17, wherein R⁹ is iodine.
19. A process as claimed in claim 17 or claim 18, wherein the pyridine derivative is a 2-pyridyl boronate.
20. A process as claimed in any one of claims 17 to 19, wherein the reaction is
- 10 carried out in a polar aprotic solvent.
21. A process as claimed in claim 20, wherein the polar aprotic solvent is tetrahydrofuran.
22. A process as claimed in any one of claims 17-21, wherein the reaction is carried out in the presence of a palladium (0) catalyst.
- 15 23. A process as claimed in any one of claims 17 to 22, wherein the product is 6-amino-3,4-dimethoxy-2-(2-pyridyl)benzonitrile.
24. A compound of formula (B), as defined in claim 1.
25. A compound of formula (C), as defined in claim 1.

fused to a benzene ring or a 5- or 6-membered heterocyclic ring, the ring system as a whole being optionally substituted.