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Effective Lab-Scale Preparation of Axitinib by Two CuI-Catalyzed Coupling Reactions

Li-Hai Zhai,[a,b] Li-Hong Guo[b], Yang-Hui Luo[a], Yang Ling[a] and Bai-Wang Sun[*a]

[a] School of Chemistry and Chemical Engineering, Southeast University, Nanjing, 211189, China.

[b] Lunan Pharmaceutical Co. LTD, Linyi,276000, Shandong, China.

*Corresponding Author E-mail: chmsunbw@seu.edu.cn; Fax: +86-025-52090614; Tel: +86-025-52090614.

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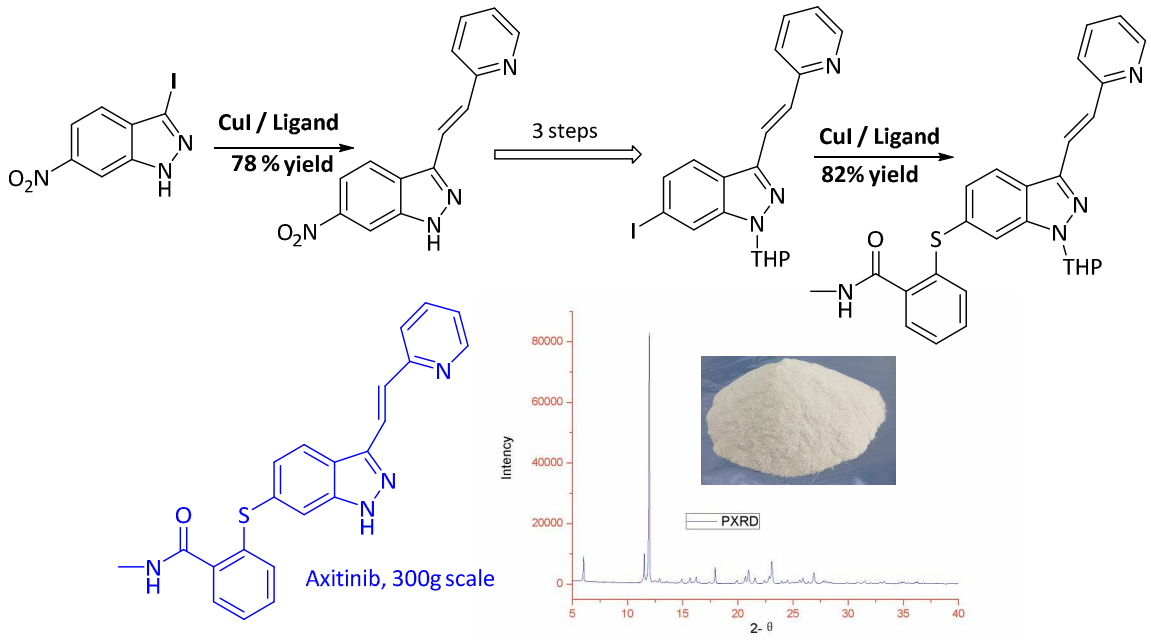
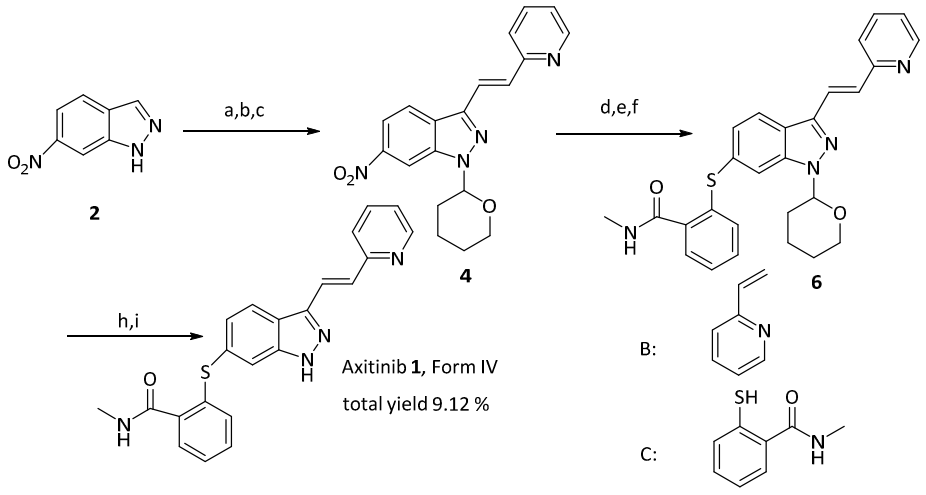


Abstract: The discovery and development of an efficient synthesis route to axinitib is reported. The first-generation route researched by Pfizer, implemented two Pd-catalyzed coupling reactions as key steps. In this work, the development of Heck-type and C-S coupling reactions catalyzed by CuI is briefly described, using an economic and practical protocol. Aspects of route, such as selecting ligands, solvent and other conditions are discussed in detail to obtain the optimal conditions. The scale up experiment was carried out to provide more than 300 g active pharmaceutical ingredients (API) of axitinib in Form XLI which was produced with 99.9 % purity in 39 % yield. In short, we provide a new choice of axitinib synthesis route, through two copper-catalyzed coupling reactions with good yield.

Key words: Axinitib, Synthesis, CuI-catalyzed, C-S coupling, Heck-type reaction.

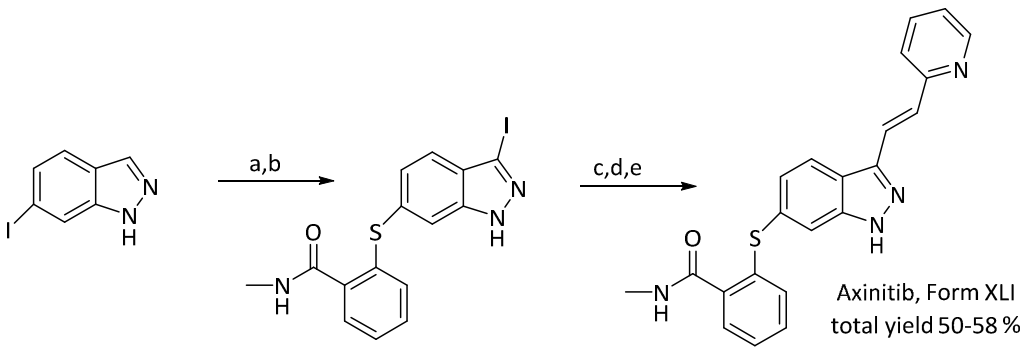
Introduction

Axitinib, a small molecule indazole derivative chemically known as (E)-N-Methyl-2-(3-(2-(pyridine-2-yl)-vinyl)-1H-indazol-6-ylthio) benzamide developed by Pfizer was approved in January 2012 by the U.S. FDA with the trade name Inlyta. It selectively inhibits vascular endothelial growth factor receptors (VEGFR) for the treatment of renal cell carcinoma.[1-3] There are two generations of synthetic routes of axinitib developed by Pfizer.[4] The key steps are the palladium catalyzed cross-coupling reactions, which purpose is through the building of C-C and C-S bonds, to complete the synthesis axitinib . (Scheme1 and Scheme2)



Regants and conditions: (a) I_2, K_2CO_3, DMF, ; (b)CH_2Cl_2, CH_3SO_3H, Dihydrofuran; (c) **compound B, i-Pr_2EtN,Pd(OAc)$_2$, (o-Tol)$_3$P, DMF;** (d) Iron, EtOH, NH_4Cl; (e)AcOH, $NaNO_2$, CH_2Cl_2, I_2 / KI; **(f) compound C, Pd(dppf)Cl_2, Cs_2CO_3,DMF;** (h) 1: p-TsOH, MeOH; 2: $NaHCO_3$; (i) AcOH, MeOH, Pd-removing, recrystalization.

Scheme 1 The first-generation synthesis route



Regants and conditions: **(a) Compound C, $Pd_2(dba)_3$, Xantphos, sodium bicarbonate, NMP** ; (b) I_2, KOH, NMP **(c) Compound B, $Pd(OAc)_2$, Xantphos, DIPEA, NMP;** (d) Pd-removing (e) NMP/THF, EtOH , seed crystals recrystalization.

Scheme 2 The second-generation synthesis route

Palladium was used to catalysis the Heck-type and C-S bond coupling reaction to provide the product of axitinib. Palladium is a very effective catalyst for these cross-coupling reactions. These reactions have been applied to the synthesis of many organic compounds, especially those of complex natural products, supermolecule chemistry, and engineering materials such as conducting polymers, molecular wires, and liquid crystals.[5-10] However, the high cost and residual of Pd (>25ppm after removing residual palladium by adsorption and crystallization), may not meet the demand for heavy metals content in the first-generation synthesis of axitinib, which demand for below 10ppm.[11,12] For the commercial route, a recrystallization was employed to ensure Pd levels were below 10 ppm and the formation of the desired solid form (Form XLI).

A considerable body of literatures describing C-S cross-coupling and Heck- type reactions with the application of other metals such as copper-, nickel-, cobalt-, and iron-based catalytic systems has been reported.[6,13-20] CuI has been used to catalyze the

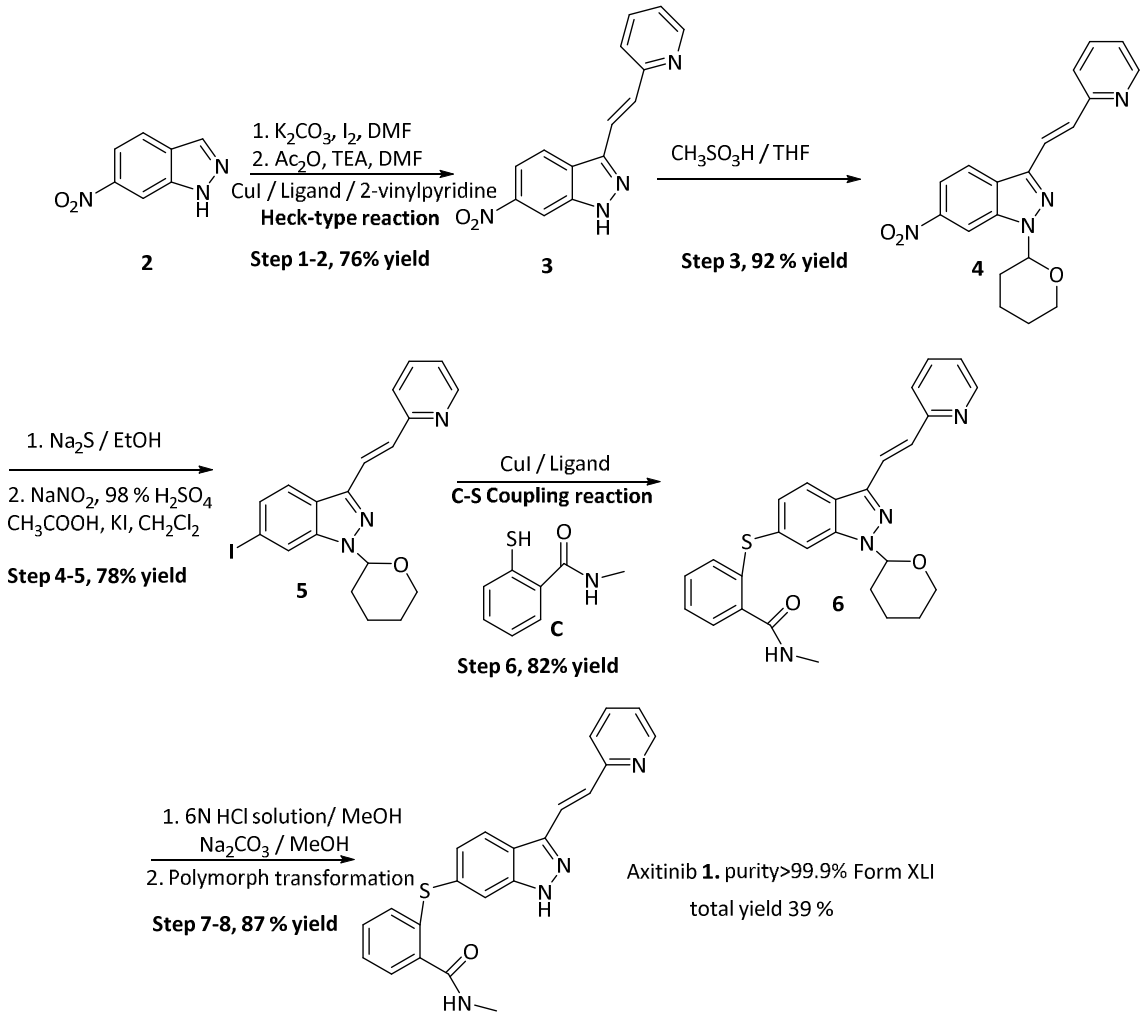
C-S cross-coupling reaction because of its stability to air and good activity with or without the assistance of supporting ligands.[21-26] Compared with the above C-S cross-coupling reaction, the application of CuI in the Heck-type reaction is reported less frequently, but there are some successful examples.[27-30] A copper catalytic systems are cheaper, and easier to remove the heavy metal residues relative to palladium. In fact, the heavy metal residual limit of copper is higher than palladium in the API. Considering the advantages of CuI catalyst in cross-coupling reactions, we wanted to reduce costs and avoid excessive heavy metal residues in the API. These issues are a great challenge for palladium catalysts.

As part of our drive to explore and develop a process for the preparation of axitinib, we recently initiated a systematic investigation to improve the existing chemical schemes to enhance the yield and quality of the API. In this report, we discuss our attempts to develop an efficient process for the preparation of axitinib. The purpose is to offer an alternative process on the basis of the literatures, and to find a cheaper and effective transition metal catalysis system.

RESULTS AND DISCUSSION

Our focus is to develop an efficient process for the preparation of axitinib. It focused on the following two aspects: improving the removal of heavy metals to avoid exceeding limits in API and improving the yield and quality of intermediates and product.

At first, we compared the two synthetic routes. The most noteworthy difference between the two processes is the order of C-S and C-C bond building. In the first-generation route，6-nitro indazole is the starting material. The iodination reaction, palladium-catalyzed Heck-type reaction, nitro reduction, Sandmeyer reaction



Scheme 3 The synthesis route in this work

and palladium-catalyzed C-S cross-coupling reaction have been performed in turn to construct the molecular skeleton of axitinib. Finally the target crystal form of API was

produced by removing THP protection groups and re-crystallization. In the second-generation route, 6-iodoindazole is the starting material. The C-S bond was constructed firstly, followed by iodination reaction and Heck-type reaction to complete coupling of 2-vinylpyridine. Introduction of 2-vinylpyridine late avoids opportunity for isomerization of the olefin. Heavy metals were not properly controlled in the initial version of this route. But, the commercial route managed control of Pd efficiently during isolation of crude aixitnib and a subsequent re-crystallization to lower Pd below 10 ppm and to obtain the desired crystal form. Compared with the first-generation process, this route is shorter by avoiding the Sandmeyer reaction in the main synthetic process, but this can lead to a higher cost of 6-iodoindazole relative to the 6-nitro indazole.

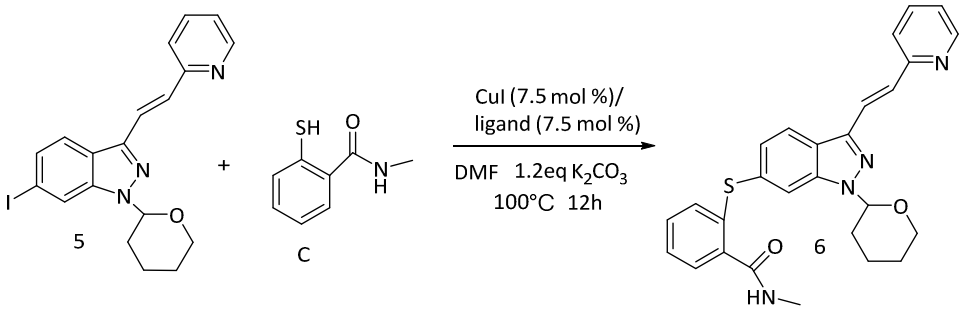
At the same time, early formation of C-S bond may lead to the formation of sulfoxide impurities. In the second-generation route, the indazole moiety has been acylated to avoid side reaction with 2-vinylpyridine and other electrophiles. A THP protecting group has been used in the first-generation route to achieve this goal. Both routes relied heavily upon removal of residual Pd.

Our purpose is seeking cheaper and more effective catalytic conditions to replace the expensive palladium catalyst. We choose the first-generation route as the improving base because of its cheaper raw materials and easier control of impurities. The final synthetic route is shown in Scheme 3.

Preparation of (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)-vinyl)-1-(tetrahydropyra-2-yl) -1H-indazol-6-ylthio) benzamide (compound 6)

Although palladium showed good activity in the C-S coupling reaction, application of other transition metals as catalyst has a lot of reports. In particular, CuI has been extensively researched for use in the reaction because of its low price, low toxicity and stability to air.[31-36] Because there are many successful examples of Cu-catalyzed C-S coupling reactions, CuI has been applied firstly to replace palladium as the C-S coupling reaction catalyst in this work.

Catalytic tests performed with freshly prepared CuCl and CuBr gave a lower yield (40-60 %) than commercially available CuI salt. At the same time, catalytic tests of Cu_2O showed that there is almost no desired product generated. The reaction conditions such as ligands, solvent, alkali selectivity and CuI amount were considered to optimize the synthetic process. The optimal reaction conditions are shown in Scheme 4.



Scheme 4 Synthesis route of compound **6**

Initially, reactions were performed with no ligand involved. N-methylpyrrolidinone (NMP) and potassium carbonate were found to be preferred in previous studies of copper-catalyzed C-N and C-O coupling reactions, [37] so we chose these conditions firstly.

The results showed that the conversion rate is low without ligands involved. The ligand was added to promote the reaction and improve the conversion rate. O, O-type, N, N-type and N, O-type ligands are most commonly used. These ligands have been selected to evaluate the results.

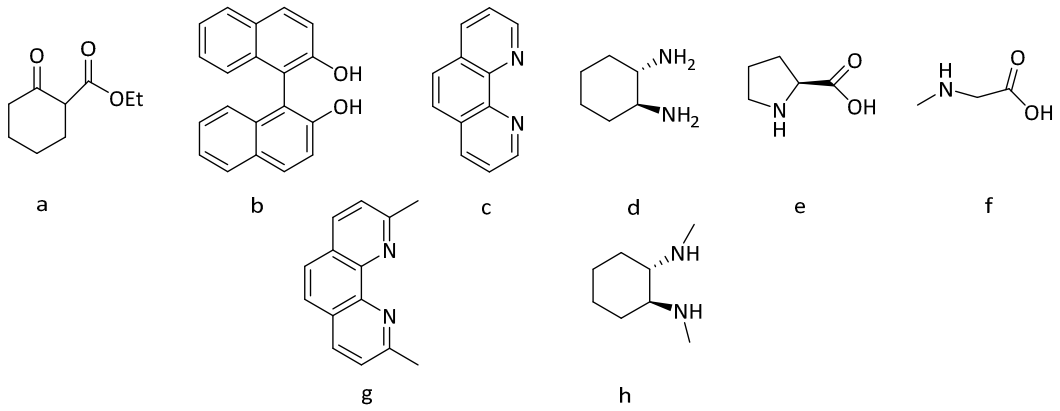


Figure 1 Molecular structure of the ligand

Table 1 Screening of Ligands for the synthesis of compound **6**

Entry	Ligand	Base	Isolated Yield(%)
1	a	K_2CO_3	67
2	b	K_2CO_3	63
3	c	K_2CO_3	84
4	c	No base	70 [i]
5	d	K_2CO_3	74
6	d	No base	72 [ii]
7	e	K_2CO_3	77
8	f	K_2CO_3	68
9	g	K_2CO_3	81
10	h	K_2CO_3	77
11	No ligand	K_2CO_3	10

Reaction conditions: compound 5 (0.01 mol), compound **C** (0.015 mol), K_2CO_3 (0.012 mol), CuI (40 mol % to compound **5**), ligand (40 mol % to compound **5**), solvent NMP (30 mL), 100 °C, 12 h. i: reaction time is over 24 h . ii: reaction time is 18 h, conversion of compound **5** is 100 %.

N, N-type ligands have a number of advantages in copper-catalyzed coupling reaction when compared with other ligands. These ligands showed good activity, wide applicability to the substrate and mild reaction conditions, etc. Test results prove this conclusion (Table 1). Entry 3 and entry 5 were significantly higher than that of other groups, in addition to the entry 7. Entry 9 provides a moderate yield just below entry 3. N, N'-Dimethyl-1, 2-cyclohexanediamine gave a higher yield than 1, 2-cyclohexanediamine (entry 11). It is interesting to note that in the absence of adding potassium carbonate, although the reaction time increases, N, N - type ligands (entry 4 and entry 6) also achieved moderate yield, this might be because of the basic role of ligand itself. Depending on the results we chose 1, 10-phenanthroline for further research.

NMP is the most commonly used and effective solvent for C-S coupling reaction, as verified by the experimental results (Table 2, entry 1). It appeared that by applying NMP and potassium carbonate, compound **6** was produced in 84 % yield. This yield is higher than other solvents. The need to use a polar solvent which contains the amide functional group is highlighted by the screening results presented in Table 2, which show that, DMF and NMP are excellent solvents for this coupling reaction (entries 1 and 4). The solvents which contain oxygen atoms such as DMSO, Dimethoxy ethane and Dioxane obtain similar yield, but below that of NMP and DMF. The findings may be because the coordination ability of N-Cu^{+} is stronger than that of O-Cu^{+}. The result of entry 7 suggests that water is not a suitable solvent for this reaction. Therefore water content should be controlled. Although NMP as solvent obtained the highest yield, considering its

high boiling point, and relatively poor water solubility, we still chose DMF as reaction solvent which obtains a comparable yield (83 %) to NMP.

Table 2 Screening of solvents for the synthesis of compound **6**

Entry	Solvent	Isolated Yield (%)
1	NMP	84
2	DMSO	79
3	Dimethoxy ethane	66[i]
4	DMF	83
5	Dioxane	78[i]
6	Toluene	70[i]
7	H_2O	Trace[ii]
8	MeCN	53[i]

Reaction conditions: compound **5** (0.01 mol), compound **C** (0.015 mol), K_2CO_3 (0.012 mol), CuI (40 mol % to compound **5**), 1,10-phenanthroline (40 mol % to compound **5**), 100 °C, 12 h. i: refluxing for 23 h. ii: at 80 °C for 18 h.

Table 3 Screening of bases for the synthesis of compound **6**

Entry	Base	Isolated Yield (%)
1	K_2CO_3	82
2	Cs_2CO_3	76
3	Na_2CO_3	57
4	TEA (triethylamine)	75
5	DIPEA (diisopropylethylamine)	80
6	NaOH	45

Reaction conditions: compound **5** (0.01 mol), compound C (0.015mol), K_2CO_3 (0.012mol), CuI (40 mol % to compound **5**), 1, 10-phenanthroline (40 mol % to compound **5**), DMF, 100°C, 12h.

A series of bases were screened. Of the four inorganic bases, potassium carbonate (82 %) gave similar results to organic base DIPEA (80 %), while cesium carbonate (76 %)

gave comparable results to triethylamine (75 %). Poorer results were obtained with sodium carbonate and sodium hydroxide (Table2). Considering economy and safety, we chose potassium carbonate as base in the reaction system.

Finally, the amount of CuI catalyst was changed to evaluate the influence to the isolated yield (Table 4). As showed in the results, lowering the amount of CuI to7.5 mol % has no impact on the efficiency of the reaction. A 5 % decrease in yield was noticed when the amount of CuI further reduced to 5 mol %. While the amount of CuI reduced to 2.5 mol %, the yield decreases to 58 %. When the amount of catalyst was reduced to 1.5 mol %, the yield was only 30 % after refluxing for 18 hours. Take into account these results, the appropriate amount of catalyst is 7.5 mol %.

Table 4 Screening of CuI amount in synthesis of compound **6**

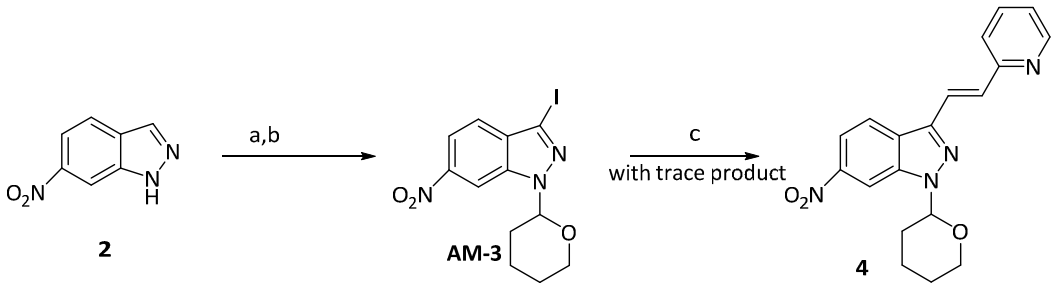
Entry	CuI (mol %)	Isolated Yield (%)
1	20	84
2	15	84
3	12.5	84
4	10	84
5	7.5	83
6	5	78
7	2.5	58
8	1.5	30[i]

Reaction conditions: compound **5** (0.01 mol), compound **C** (0.015mol), K_2CO_3 (0.012mol), 1, 10-phenanthroline (1.0 eq to CuI), DMF, 100°C, 12h. i: refluxing for 18 h

Preparation of (E)-6-nitro-3-(2-pyridin-2-yl-vinyl)-1H-indazole (Compound 3) by CuI catalyzed Heck reaction

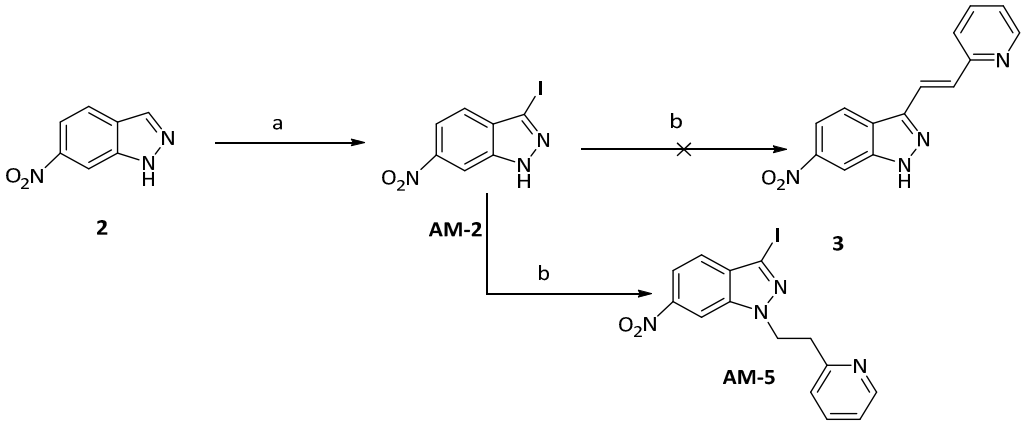
In addition to palladium, other metals especially copper salts have been reported to

catalyze Heck reaction.[27,38-40] After application of CuI / 1, 10-phenanthroline/ K_2CO_3 catalyst system on the C-S coupling reaction, we tried to catalyze Heck-type reaction using this catalyst in the synthesis process of axinitib.



Regants and conditions: (a) I_2, K_2CO_3, DMF, ; (b) CH_2Cl_2, CH_3SO_3H, Dihydrofuran; (c) **2**-vinylpyidine, CuI / 1,10-phenanthroline / K_2CO_3, DMF, 100°C

Scheme 5 Attempted synthesis of compound **4**



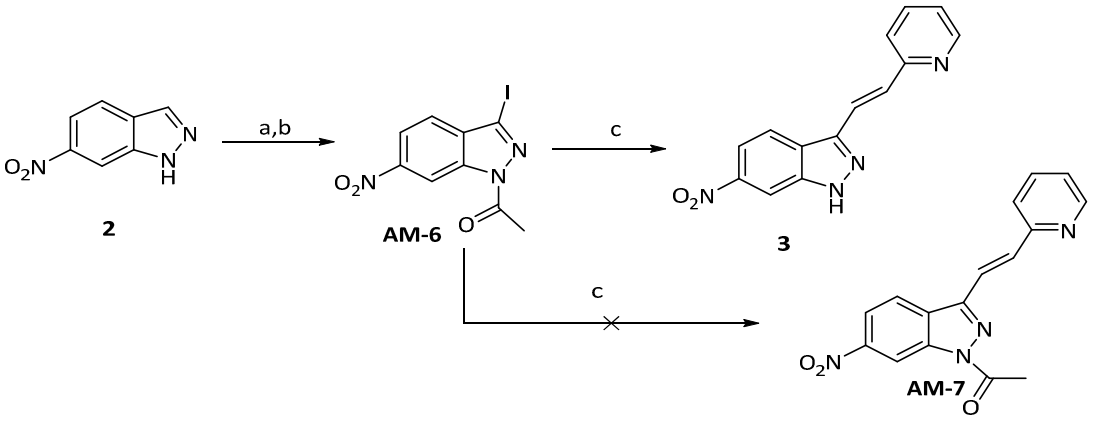
Regants and conditions: (a) I_2, K_2CO_3, DMF, ; (b) **2**-vinylpyidine, CuI / 1,10-phenanthroline / K_2CO_3, DMF, 100°C; **AM-5** characterization: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.52 (d, J = 1.9 Hz, 1H), 8.44 (d, J = 4.9 Hz, 1H), 7.90 (d, J = 8.9, 1.9 Hz, 1H), 7.66 - 7.54 (m, 2H), 7.21 - 7.11 (m, 2H), 4.96 (t, J = 6.9 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 158.15 , 149.46 , 146.98 , 139.20 , 136.93 , 130.84 , 124.01 , 122.61 , 122.26 , 115.93 , 107.83 , 93.66 , 49.26 , 38.18 .

Scheme 6 Attempted synthesis of compound **3**

At first, we used the method of the first-generation route to protect the imidogen in indazole with the THP group. Palladium is replaced by CuI as a catalyst used for the preparation of compound **4** (Scheme5). The result is disappointing. Even if the reaction is

performed more than 48 hours at 100 °C, only a trace of compound **4** is detected by HPLC (Method B). We assumed that the electronics of the THP group affect the activity of the reactants. So we tried to synthesis compound **3** without the protection of the indazole (Scheme 6). It is noteworthy that the conversion of compound **2** is 100 %, but the product is not the target compound **3**. Rather it is the adduct **AM-5**.

Heck reaction is facilitated by an electron deficient group. We designed a new synthetic route (Scheme7). Analogous to the Pfizer commercial route, the 1-position nitrogen atom in indazole was protected by an acetyl group in the process of AM-**6** synthesis. Then complete Heck reactions catalyzed by CuI to synthesis AM-**7**. The result showed that it is difficult to obtain a single intermediate AM-6 because the acetyl is very labile. Consequently, Heck-type coupling and removal of the acetyl group complete in one-pot to provide the intermediate compound **3** in 78 % yield.



Regants and conditions: (a) I_2,K_2CO_3,DMF, ; (b)Ac_2O, K_2CO_3, DMF; (c) **2**-vinylpyidine,CuI / 1,10-phenanthroline / K_2CO_3, DMF, 100 °C; **AM-6** charactarization: ^{13}C NMR (100 MHz, DMSO-d_6)δ 170.44 , 148.81 , 137.26 , 133.84 , 123.64 , 120.02 , 110.64 , 105.31 , 23.14 .

Scheme 7 Attempted synthesis of **AM-7**

Although the CuI/1, 10-phenanthroline/ K_2CO_3 catalytic system has shown excellent reactivity in the synthesis of compounds **3**, high load catalyst (40 %) need to be improved. The influence of the amount of CuI and the choice of ligands were evaluated (Table 5). As showed in Table 5, 1, 10-phenanthroline is acceptable ligand in a 77 % yield when the CuI amount was reduced to 13 mol % (entry 3). It is noteworthy that N, O-type ligand-----N-methylglycine provides a 76 % yield when the amount of CuI is 15 mol % (entry 8).

Other improvements in the synthetic process of axitinib were verified by the experiments. Such as , iron powder was replaced with sodium sulfide in the nitro reduction reaction, the post-processing methods were improved in Sandmeyer reaction, such as acetic acid as solvent, sulfuric acid instead of hydrochloric acid and sodium nitrite is added in solid form to reduce the using of water, these improvements promote the diazotization reaction. The products directly precipitate in the reaction system. These improvements have made reaction process with a better operability, and increased the product yield. In the process of preparation axitinib, p-toluenesulfonic acid is replaced by hydrochloric acid to de-protect THP group. As the liquid inorganic acid, hydrochloric acid is more effective.

Table 5 Screening of ligand and CuI amount in synthesis of compound **3**

Entry	Ligand	CuI (mol %)	Isolated yield (%)	Entry	Ligand	CuI (mol %)	Isolated yield (%)
1	c[i]	20[ii]	78	10	f	10	68
2	c	15	77	11	f	7	47
3	c	13	77	12	f	5	26
4	c	10	70	13	h	20	67
5	c	7	58	14	h	15	67
6	c	5	32	15	h	12.5	65
7	f	20	76	16	h	10	65
8	f	15	76	17	h	7.5	60
9	f	13	70	18	h	5	31

i: Ligand label is consistent with Figure 1. ii: Ligand is equivalent to CuI; K_2CO_3, DMF, 100 ℃.

CONCLUSION

In summary, an alternative synthesis of axitinib has been accomplished in total 39% yield overall on lab-scale through two coupling reactions---Heck-type reaction and C-S coupling reaction by using CuI-1, 10-phenanthroline-K_2CO_3 as the catalyst system. The axitinib produced is free from impurities and meets regulatory requirements with 4-fold overall yield in comparison with the first-generation procedure (9% in Form IV) but falls short of the second generation yield (50-58% in Form XLI).[4] This route avoids the use of Pd and only requires removal of the heavy metal Cu. The efficiency of this catalytic system has been tested in scale-up experiment. 326.4 g of axitinib API in Form XLI was produced with 99.9% purity in 39% yield. Residual Cu content was detected to be 2.2 ppm by atomic absorption spectroscopy.

Palladium is still better than copper in catalytic efficiency. There are more researches needed to make CuI-catalyzed synthesis routes more competitive. Considering the lower price, toxicity and appropriate yield, the modified processes evaluated have been shown to be acceptable from both a product quality and yield standpoint. We provide a choice of using non-precious metal catalysis-CuI for the production of axinitib.

EXPERIMENTAL SECTION

General

All of the starting materials, reagents, solvents and 2-vinylpyridine (compound B) are commercially available and used without further purification, unless otherwise specified. Two coupling reactions were carried out in dry reaction vessels under an atmosphere of dry nitrogen, other reactions on common conditions without nitrogen protection. Melting point was measured by WRD-1B Digital Melting Point Apparatus. ^{1}HNMR and ^{13}CNMR spectra were recorded in DMSO-d_6 or $CDCl_3$ using AVANCE AV-300 to 500MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (Hz), and integration. Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm), DMSO-d6 (39.5 ppm) on the δ scale.

The purity of the key intermediate and final APIs was determined by HPLC**.** The immediate purity was assessed by HPLC, using an Agilent 1100 series instrument.

Table 6 Gradient program for method A

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	40	60
15	10	90
20	0	100
24	0	100
25	40	60
30	40	60

Method A: HPLC method for compound **3** is a standard method using gradient on an Aglient SB-C18 column (5μm; 250mm × 4.6mm). Mobile phase solution A was 0.05 % trifluoroacetic acid in water (v/v), and mobile phase solution B was 0.05 trifluoroacetic acid in acetonitrile (v/v). Gradient elution was performed as showed in Table **6** with a run time of 25 min and a re-equilibration time of approximately 5 min. The flow rate was 1.0 mL / min and the column temperature was 25 °C. The injection volume was 5 μ L, and UV detection was performed at 254nm. Sample and standard solutions were prepared in acetonitrile at a nominal concentration of 0.5mg / mL.

Method B: For compound **4** and **5**, the HPLC column and mobile phases were identical to the compound **3.** Gradient elution was performed as showed in Table **7** with a run time of 51 min and a 4 min re-equilibration time. The flow rate was 1.0 mL / min, and the column temperature was 30 °C. The injection volume was 5 μ L, and UV detection was performed respectively at 220nm for intermediate 4 and 310nm for compound **5**. Sample and standard solutions were prepared in methanol at a nominal concentration of 0.5mg / mL.

Table **7** Gradient program for method B

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	60	40
25	50	50
45	0	100
50	0	100
51	60	40
55	60	40

Method C: HPLC method of N-methyl-2-sulfanyl benzamide (compound **C**), compound **6** and final product Axitinib is the same gradient elution method. The column is an Aglient SB-C18 column (5μm; 150mm × 4.6mm). Mobile phase solution A was 0.05 % monopotassium phosphate in water (m/v), and mobile phase solution B was acetonitrile. Gradient elution was performed as showed in Table **8**, with a run time of 39 min and a re-equilibration time of approximately 6 min.

Table **8** Gradient program for method C

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	80	20
5	80	20
25	40	60
32	10	90
38	10	90
39	80	20
45	80	20

The UV detection was performed respectively at 220nm for compound **6**, compound **C** and 233nm for axitinib. Sample and standard solutions were prepared

in methanol at a nominal concentration of 0.25mg / mL.

Preparation of (E)-6-nitro-3-(2-pyridin-2-yl-vinyl)-1H-indazole (Compound 3)

In a 10 L glass reactor vessel, 6-nitro-1H-indazole (350.0 g, 2.15 mol, 1.0 equiv) and potassium carbonate (594 g, 4.3 mol, 2.0 equiv) is added in DMF (1.5 L) at the room temperature (25 °C). Iodine solution (821.9 g dissolved in1 L DMF, 3.23 mol, 1.5 equiv) was added to reaction solution dropwise over 1-1.5 hours, while the reaction temperature could rise to 60 °C. The mixture is agitated for 6 hours until the reaction complete detected by HPLC. The reaction was quenched with 10 % sodium bisulfite aqueous solution 6 L (600 g, 5.77 mol, 2.7 equiv). The mixture is agitated for 2 hours to precipitate solids .Then the slurry is agitated for 2 hours at 10 °C. The solids was filtered, washed with water (1 L) and dried at 60 °C for 48 hours to provide 3-iodo-6-nitro-1H-indazole as yellow solids (613 g, 97.7 % yield with 96 % purity by HPLC using the Method A). Mp 245- 246 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 14.12 (s, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.9, 2.0 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d6) δ 146.88, 139.79, 30.29, 122.16, 115.76, 108.09, 94.22.

In the 10 L glass reactor vessel, 3-iodo-6-nitro-1H-indazole (600 g, 2.08 mol, 1.0 equiv) is added to a suspend solution of potassium carbonate (400 g, 3.12 mol, 1.5 equiv) in N, N-dimethyl formamide (DMF, 4L). The mixture is heated to 60 °C and acetic anhydride (425 g, 4.16 mol, 2 equiv) is added dropwise for 30 min, then react for 2 hours until the reaction complete detected by HPLC to obtain 1-acetyl-3-iodine- 6-nitro

indazole, which need not separate from the mixture and applied directly to the Heck-type reaction. 1, 10-phenanthroline (48.7 g, 0.27mol, 0.13 equiv) is added to the mixture at 60 °C. The solution is bubbling with N2 for 2 hours to remove dissolved oxygen and the vessel was charged with nitrogen. CuI (34.7 g, 0.27 mol, 0.13 equiv) and 2-vinyl pyridine (240g, 2.3 mol, 1.1 equiv) are added and the mixture is agitated for 8 hours at 100 °C until the reaction is complete detected by HPLC. The reaction mixture is stirring for 1 hour after ethanol (2 L) addition at 60 °C, then water (2 L) is slowly charged while maintaining the temperature at 60 °C. After that, the mixture is stirring for 4 hours at 60 °C to complete deacetylation reaction. The mixture further cooled to 15 °C to crystallize for 2 hours and then filtered. The solid was added to water(5 L), stirred for 2 hours to dissolve the inorganic salts, then filtered , recrystallized in isopropanol, isolated, dried in vacuum to afford (E)-6-nitro-3-(2-pyridin-2-yl- vinyl)-1H- indazole as faint yellow to green yellow solid (431.7 g，78 % yield with 95 % purity by HPLC using Method A). The product applied directly to the next reaction without further purification. Mp 308 °C (decomposed). Residual Cu content was determined to be 17.3 ppm by atomic absorption spectroscopy. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.99 (s, 1H), 8.66-8.55 (m, 1H), 8.51-8.41 (m, 1H), 8.06-7.96 (m, 1H), 7.92-7.76 (m, 1H), 7.79-7.66 (m, 1H), 7.43 (d, J = 16.4, 8.0 Hz, 1H), 7.35-7.20 (m, 1H), 6.53 (d, J = 1.7 Hz, 1H), 6.09 (s, 1H), 5.47 (d, J = 15.3 Hz, 1H), 5.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 155.40, 150.42, 149.96, 145.79, 143.55, 137.26, 129.27, 124.66, 122.95, 122.79, 114.46, 113.89, 93.47

Preparation of (E)-6-iodo-3-[2-(pyridin-2-yl)-vinyl]-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Compound 5)

Compound **3** (426 g, 1.6 mol, 1.0 equiv) react with 2,3-dihydropyran (DHP, 672 g, 8.0 mol, 5equiv) in tetrahydrofuran (4.5 L) in the presence of methanesulfonic acid (24 g, 0.24 mol, 0.15 equiv), the mixture refluxing for 6 hours to complete the reaction detected by HPLC. The mixture is concentrated, neutralized using Na_2CO_3 aqueous solution (100 g in 1L water) and filtered to obtain (E)-6-nitro-3- [2-(pyridin-2-yl) -vinyl]-1-(tetrahydro-2H-pyran-2-yl)1H-indazoe as yellow-green solid (507.6 g, 92 % yield with 96 % purity by HPLC using Method B). Mp 185 °C; MS m/z 351 $[M + H]^+$; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.85-8.39 (m, 2H), 8.12 (q, J = 9.0 Hz, 2H), 7.93 (d, J = 16.2 Hz, 1H), 7.83-7.52 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.08 (s, 1H), 5.84 (dd, J = 9.2, 2.8 Hz, 1H), 4.06 (d, J = 11.8 Hz, 1H), 3.82 (t, J = 10.9 Hz, 1H), 2.57 (t, J = 11.3 Hz, 1H), 2.35-2.09 (m, 2H), 1.98-1.35 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d6) δ 168.31, 155.32, 150.01, 142.45, 142.30, 137.34, 136.08, 132.98, 130.76, 130.45, 129.71, 128.24, 126.61, 124.08, 123.12, 122.24, 120.73, 115.18, 26.56.

(E)-6-nitro-3-[2-(pyridin-2-yl)-vinyl]-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (505 g, 1.44 mol, 1.0 equiv) is dissolved in methanol (3 L) and the aqueous solution of sodium sulphide (867 g, 3.6 mol, 2.5 equiv, $Na_2S·9H_2O$ in 2 L H2O) and THF (l L) is added. The reaction mixture is agitated for 3-4 hours at 60 °C (until the reaction is complete detected by HPLC). The insoluble salts are removed by filtering. Water (2 L) is added to the filtrate under vigorous stirring. Then the mixture is cooled to 0 °C stirring

for 2 hours. The mixture is filtered , rinsed with a mixture of methanol and water solution 1 L (methanol : water=1:3), the solids dried in vacuum for 24 hours at 45 °C to provide 6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1- (tetrahydropyran-2-yl) -1H-indazole (455 g, 90 % yield with a purity of 97 % by HPLC using Method B). Mp 115-117 °C; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.73-8.40 (m, 2H), 8.12 (q, J = 9.0 Hz, 2H), 7.93 (d, J = 16.2 Hz, 1H), 7.72 (t, J = 8.0 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 5.9 Hz, 1H), 5.84 (d, J = 9.2, 2.8 Hz, 1H), 4.06 (d, J = 11.8 Hz, 1H), 3.82 (t, J = 10.9 Hz, 1H), 2.57 (t, J = 11.4 Hz, 1H), 2.36-1.96 (m, 3H), 1.92-1.39 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d6) δ 168.31 , 155.32 , 150.01 , 142.38 (d, J = 15.4 Hz), 137.34 , 136.08 , 132.98 , 130.76 , 130.45 , 129.71 , 128.24 , 126.61 , 126.01 , 124.08 , 123.12 , 122.24 , 115.18 , 26.56 .

6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (450 g, 1.4 mol, 1 equiv) dissolved in acetic acid (1.2L) and sulphuric acid (275 g, 2.8 mol, 2 equiv, 98 % diluted sulphuric acid with 1 L water). The sodium nitrite (140 g, 2.03 mol, 1.45 equiv) is added in batches over 2 hours at -5 °C, the mixture is stirred for 2 hours at 0 °C to provide the diazonium salt solution, reaction is monitored by HPLC. A solution of potassium iodide (675 g, 4.06 mol, 2.9 equiv) dissolved in water (1.5 L) is added at 0 °C over 1.5 hour. The reaction mixture is agitated for 4 hours at 0 °C until complete detected by HPLC. Then the mixture is poured into a solution of 50 % aqueous sodium bisulfite (900 g sodium bisulfite in 1 L water) agitated for 2 hours. The mixture is filtered , rinsed with water (3×200 mL), the filter cake dried in a vacuum oven for 48 hours at 65 °C to provide (E)-6-iodo-3-[2-(pyridin-2-yl)-vinyl]-1-(tetrahydro-2H-pyran-

2-yl) -1H-indazole (525.7g , 87 % yield with a purity of 95 % by HPLC using Method B). The raw product can be refined by slurring with water and filtering through a short silica gel column to provide a product with purity above 99 % by HPLC. Mp 168-169 °C; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.69-8.57 (m, 1H), 8.01 (d, J = 1.4 Hz, 1H), 7.86 (d, J = 16.4 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.58-7.49 (m, 2H), 7.47 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.6, 4.8, 1.1 Hz, 1H), 5.68 (d, J = 9.1, 2.8 Hz, 1H), 4.04 (d, J = 11.4, 4.4, 2.5 Hz, 1H), 3.94 - 3.58 (m, 1H), 2.56 (t, J = 17.7, 10.4, 9.8, 4.2 Hz, 1H), 2.18 (t, J = 9.9, 3.6 Hz, 1H), 2.08 (d, J = 13.6, 3.5 Hz, 1H), 1.96-1.71 (m, 2H), 1.68 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d6) δ 155.04, 150.03, 142.25, 142.20, 137.36, 130.91, 130.81, 130.24, 123.73, 123.25, 123.18, 123.11, 121.76, 121.34, 119.87, 84.56, 84.26, 67.08, 29.31, 25.21, 22.60.

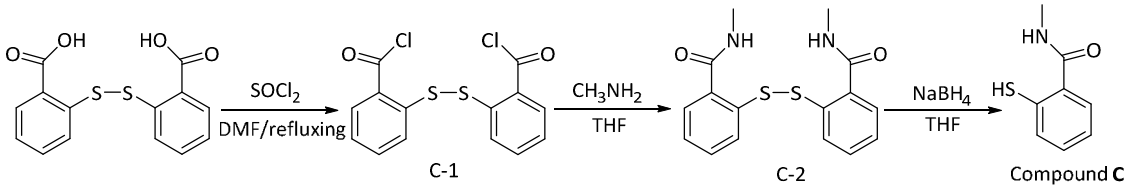
Preparation of (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)vinyl)-1H-indazol-6-ylthio) benzamide (Compound 1, Axitinib).

Preparation of N-methyl-2-sulfanyl benzamide (compound **C**) (Scheme 8)

2,2`-dithiosalicylic acid (800 g, 2.63 mol, 1 equiv) is dissolved in thionyl chloride (1000 g, 8.4 mol, 3.2 equiv) and N, N-dimethyl formamide (DMF, 10 mL) is added. The mixture refluxing for 4 hours, concentrated in vacuum, recrystallize in n-hexane. The solids are filtered, dried in vacuum to provide 2, 2`-dithiosalicylic acid dichloride (**C-1**, 850 g in 95 % yield).

The intermediates **C-1** (800 g, 2.33 mol, 1 equiv) dissolved in THF (2 L) is bubbled

with methyl amine gas under agitating at 0°C for over 1 hour until the PH is stable between 9 and 10, and stirring at room temperature for another 10 hours. The mixture is poured into water (5 L) and the slurry is filtered. The white solids are washed with water (3×800 mL), dried in vacuum oven to provide 2,2`-dithio-N-methylbenzamide (**C-2**, 513 g in 75% yield.).



Scheme 8 The synthesis of compound **C**

The intermediates C-2 (480 g, 1.44 mol, 1 equiv) is dissolved in THF (2.5 L). The solution is cooled to 0 °C, and sodium borohydride (225 g, 5.95mol, 4 equiv) is added in potions over 4 hours, while controlling the temperature is not higher than 30 °C. After the reaction complete, water (1 L) and acetic acid (450 mL) are added to the mixture to quench reaction, then ethyl acetate (4×800 mL) is added to extract the product. Under nitrogen protection, the organic phase is separated, dried, concentrated to provide N-methyl- 2-sulfanyl benzamide (compound **C)** as gray solids. (427.5 g in 89 % yield with purity of 94.3 % by HPLC using Method C. Mp 91-93°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 7.63 (d, J = 7.4, 2.1 Hz, 1H), 7.43(t, J = 7.6, 2.2 Hz, 1H), 7.30 (t, J = 7.3, 1.9 Hz, 1H), 2.82 (s, 3H).

Preparation of (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)-vinyl)-1H-indazol-6-ylthio) benzamide (axitinib)

Preparation of (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)-vinyl)-1-(tetrahydropy-ran-2-yl)-1H-indazol- 6-ylthio) benzamide (compound **6**)

Under nitrogen protection, compound **5** (520 g, 1.2 mol, 1 equiv) dissolved in DMF (2.5 L), is added to copper iodide (CuI, 17. 3g, 0.09 mol, 0.075 equiv), 1, 10-phenanthroline (16.3 g, 0.09 mol, 0.075 equiv), K_2CO_3 (200 g, 1.45 mol, 1.2 equiv) and compound **C** (301.5 g, 1.8 mol, 2.5 equiv) in turn. The mixture is agitated for 12 hours at 100 °C until the reaction is complete by HPLC. The mixture is cooled to 40 °C and ethyl acetate (2.5 L) is added and cooled to 20 °C to agitate for 1 hour. Water (5 L) is added and the mixture is agitated for another 1 hour at 20 °C to provide the slurry of the product which is filtered and washed with ethyl acetate (1 L), water (800 mL x 3) and ethyl acetate (500 mL x2) in turn. Brown solids were collected to dry in vacuum for 48 hours at 50 °C to provide compound **6.** (463 g in 82 % yield with a purity of 96.8 % by HPLC using Method C). Residual Cu content was determined to be 13.5 ppm by atomic absorption spectroscopy. Mp 240 °C, ^{1}H NMR (500 MHz, Chloroform-d) δ 8.67-8.58 (m, 1H), 8.13-7.78 (m, 3H), 7.78-7.29 (m, 7H), 7.32-7.11 (m, 2H), 5.64 (d, J = 25.8, 9.0, 2.8 Hz, 1H), 4.01 (d, J = 13.1 Hz, 0H), 3.92 (d, J = 12.0 Hz, 1H), 3.73 - 3.58 (m, 1H), 2.98 2.90 (m, 2H), 2.18 - 2.11 (m, 2H), 2.10 - 1.97 (m, 2H), 1.62 (q, J = 13.0, 11.9, 6.4 Hz, 1H), 1.23 (d, J = 20.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d6) δ 155.49, 149.98,

148.84, 143.32, 141.65, 137.27, 129.46, 124.62, 122.90, 122.80, 121.58, 114.67, 113.77, 91.58, 84.59, 67.00, 29.22, 25.3, 22.71.

Preparation of (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)-vinyl)-1H-indazol-6-yl -thiol) benzamide (axitinib)

Compound 6 (460 g, 0.975mol, 1equiv) and 6N hydrochloric acid (812.5 mL, 4.875 mol, 5 equiv) were added to methanol (2 L) and water (500 mL). The mixture stirred for 6 hours at 60 °C to complete the reaction detected by HPLC. The mixture is cooled to 10 °C, and methanol (1 L) and potassium carbonate aqueous solution (1000 g in 1 L water) are added, the mixture is agitated for 8 hours at 30 °C while the color changed from yellow to white. The mixture is filtered, washed with water (800 mL), ethanol (800 mL) and ethyl acetate (2×300 mL) in turn, dried in vacuum at 65 °C for 8 hours to provide (E)-N-Methyl-2-(3-(2-(pyridin-2-yl)-vinyl)-1H-indazol-6-ylthio) benzamide (axitinib) as white solids (342 g in 91 % yield and a purity of 99.65 % by HPLC using Method C). Mp 222.35 °C. This form is the axitinib monohydrate.

The axitinib monohydrate (340 g) and glacial acetic acid (1.8 L) were added to a three-necked flask (3L). The mixture was stirred and heated to 80 °C until the solids completely dissolved. Then, the reaction solution was slowly added of activated carbon (10 g) and stirred for 1 hour. The reaction mixture was filtered to remove the activated carbon, cooled to 20 °C (about 1 °C / min) and stirred to crystallize for 4 hours. The solids were filtered off and reprocessed using the above method. The solid was then

suspended in anhydrous ethanol (2 L), and stirred at 85°C for 18 hours. The reaction mixture was cooled (0.5 ° C / min) with stirring (60 rpm) to 20 ° C. The solids was filtered off, washed with ethanol, and dried in vacuo at 60 ° C. The product is axitinib anhydrous crystalline Form XLI (326.4 g in 96 % yield with purity 99.91 %). Residual Cu content was determined to be 2.2 ppm by atomic absorption spectroscopy. Mp 227.7 °C; 1H NMR (300 MHz, DMSO-d6) δ 13.27 (s, 1H), 8.60 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 5.4 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 16.4 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.63 - 7.44 (m, 3H), 7.29 (p, J = 7.4, 6.6 Hz, 3H), 7.19 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 2.78 (d, J = 4.6 Hz, 3H); 13C NMR (75 MHz, DMSO-d6) δ 167.89, 154.86, 149.54, 142.01, 141.86, 136.92, 136.88, 135.67, 132.52, 130.32, 129.99, 129.25, 127.80, 126.15, 125.59, 123.66, 122.68, 122.50, 121.79, 120.29, 114.76, 26.13.

AUTHOR INFORMATION

The authors declare no competing financial interest.

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