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The synthesis of Bcr-Abl inhibiting anticancer pharmaceutical agents imatinib, nilotinib and dasatinib

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Imatinib (**1**), nilotinib (**2**) and dasatinib (**3**) are Bcr-Abl tyrosine kinase inhibitors approved for the treatment of chronic myelogenous leukemia (CML). This review collates information from the journal and patent literature to provide a comprehensive reference source of the different synthetic methods used to prepare the aforementioned active pharmaceutical ingredients (API's).

1. Introduction

Imatinib (**1**), nilotinib (**2**) and dasatinib (**3**) are members of the 'tinib' stem of pharmaceutical agents which target tyrosine kinases.[1] Kinase inhibitors have found application in the treatment of a number of cancers including chronic myelogenous leukemia (CML), gastrointestinal tumours (GIST), dermatofibroma sarcoma protuberans (DFSP) and solid tumours such as non-small-cell lung cancer (NSCLC).[2]

Tyrosine kinases perform the function of transferring a phosphate functional group from ATP to a tyrosine residue in another protein. The Abelson (Abl) group of non-receptor tyrosine kinases are involved in signalling pathways for a number of cell functions.[3] These non-receptor kinases are normally deactivated by self-regulation and are only able to perform their function when the signalling pathway is activated.[3] A chromosomal translocation known as Philadelphia chromosome[4] is present in 95% of people with CML.[5,6] This chromosome causes the production of Bcr-Abl tyrosine kinase[7] which has been shown to induce leukaemia in mice[8] and hence implicates the protein as the cause of CML. The Bcr-Abl kinase is unable to self-regulate as a result of the fusion of the Bcr domain to the protein resulting in the permanent activation of the active site and causing the signalling pathway to be permanently turned 'on'. This results in CML, one of several myeloprolific disorders of pluripotential hematopetic stem cells in bone marrow.[9–11] It has been reported that CML frequency in Western countries is as high as 1 in 100 000 with its prevalence exponentially increasing with age.[12] It has also been identified as being more common in the male population (3 : 2).[13]

In 2001 Novartis launched the Bcr-Abl tyrosine kinase inhibitor imatinib (**1**). This was the first in family of 'tinib' drugs to be launched and has since proven to be a popular target drug for synthesis chemists. The following decade saw a number of kinase inhibitors being brought to the marketplace. Among these are the second generation Bcr-Abl tyrosine kinase inhibitors, nilotinib (**2**) from Novartis and dasatinib (**3**) from Bristol-Myers-Squibb (BMS).

Our group set itself the goal of producing imatinib (**1**) by a flow chemistry process and reported this in 2010.[14] A survey of the literature revealed that while there had been extensive progress on the preparation of imatinib (**1**), much of this knowledge was only available in the patent literature.[15] While the biochemistry and clinical application of imatinib and related kinase inhibitors[2] had been thoroughly reviewed, the methods used to make these important compounds had only been briefly reviewed previously.[16,17] This review therefore covers the synthesis of the three Bcr-Abl tyrosine kinase inhibitors on the market today; imatinib, the highest selling of the 'tinib' drugs; nilotinib (**2**), the second generation successor to imatinib (**1**); and dasatinib (**3**), a structurally distinct second generation Bcr-Abl inhibitor.

2. Synthesis of imatinib

Imatinib (**1**), 4-[(4-methylpiperazin-1-yl)methyl]-*N*-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]phenyl] benzamide [STI571, CAS: 152459-95-5], is a tyrosine kinase inhibitor developed by Novartis AG and is used for the treatment of CML and gastrointestinal stromal tumours (Fig. 1). It is currently produced by Novartis under the brand name Gleevec in the USA and Glivec (Europe, Australia and Latin America) in both cases being formulated as its mesylate salt.

The discovered link between Bcr-Abl and CML provided medicinal chemists with a specific target for a possible treatment of CML. High-throughput screening against a number of protein kinases identified the 2-phenylaminopyrimidine **4** as an inhibitor of protein kinase C (a family of serine and

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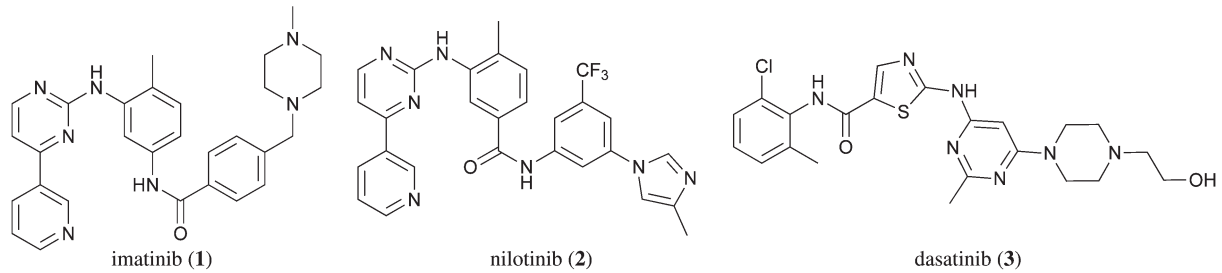


Fig. 1 Structure of imatinib (**1**), nilotinib (**2**) and dasatinib (**3**).

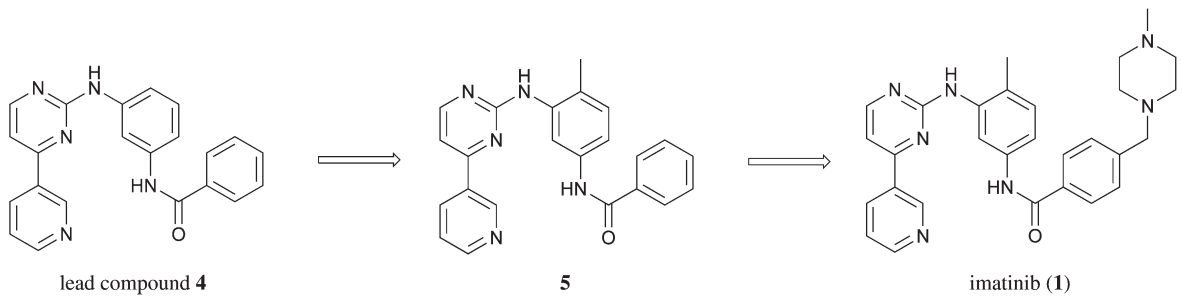


Fig. 2 Basic lead optimisation sequence resulting in imatinib (**1**).

threonine kinases)[10] and hence this structure underwent a programme of lead optimisation (Fig. 2).[18] Screening was conducted against v-Abl (a tyrosinekinase encoded by the ABL1 gene) and a number of other protein kinases in order to find an Abl specific compound. The benzamide unit at the 3 position of the central phenyl group was essential for high activity against v-Abl and the addition of a methyl group in the 6 position of the phenyl ring eliminated the undesired activity against protein kinase C, whilst maintaining activity against v-Abl. The resulting compound **5** had poor aqueous solubility in neutral conditions (acidic conditions being required for good aqueous solubility) and as such had poor oral bioavailability.[11] The addition of an *N*-methylpiperazine substituent increased the aqueous solubility and oral bioavailability.[18] The resulting compound, imatinib (**1**), is an Abl specific tyrosine kinase inhibitor that reduces proliferation and induces apoptosis in Bcr-Abl dependent cells, thus providing an effective treatment against CML. Interestingly, the remarkable selectivity of imatinib (**1**) comes from its preference for binding to the inactive conformation of Abl (Fig. 3).[19,20]

Imatinib (**1**) has also been approved for the treatment of gastrointestinal stromal tumours (GISTs) since it also inhibits c-kit, a membrane-bound tyrosine kinase receptor involved in cell signalling.[21] A total of 77% of GISTs contain a mutation in the c-kit receptor thus affecting the tyrosine kinase signalling pathway.[22] Imatinib (**1**) binds to the active site of c-kit thus switching off the signalling pathway. Imatinib (**1**) has also been shown to inhibit platelet derived growth factor (PDGF) and experimental studies into treatments based on this mode of action are ongoing.[21]

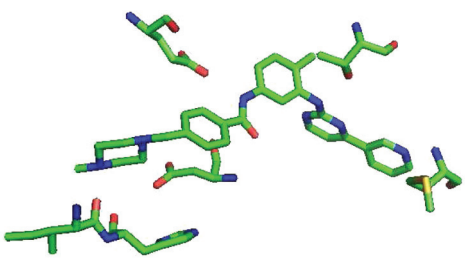
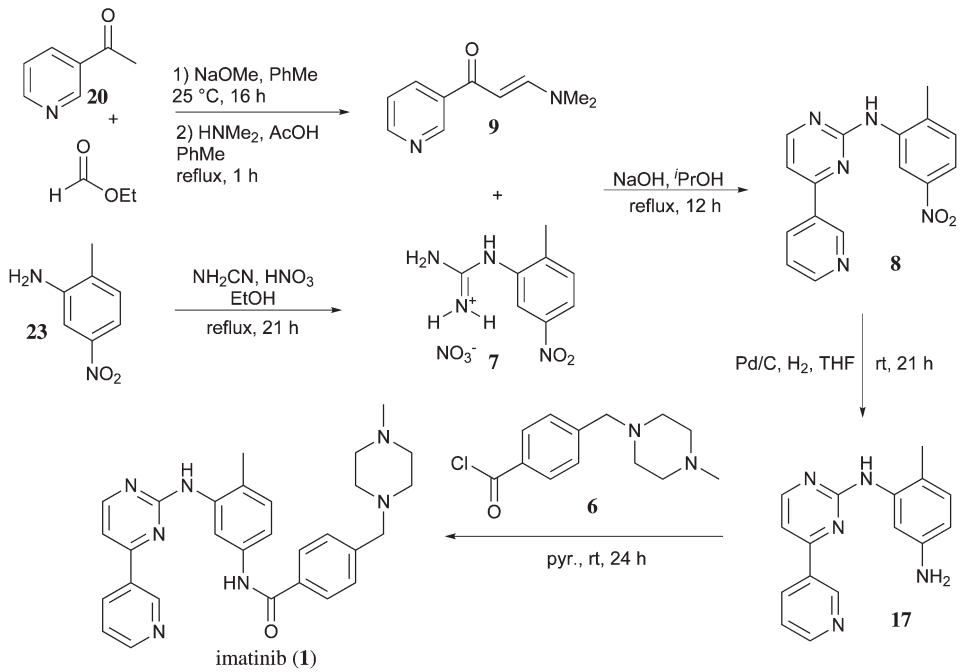


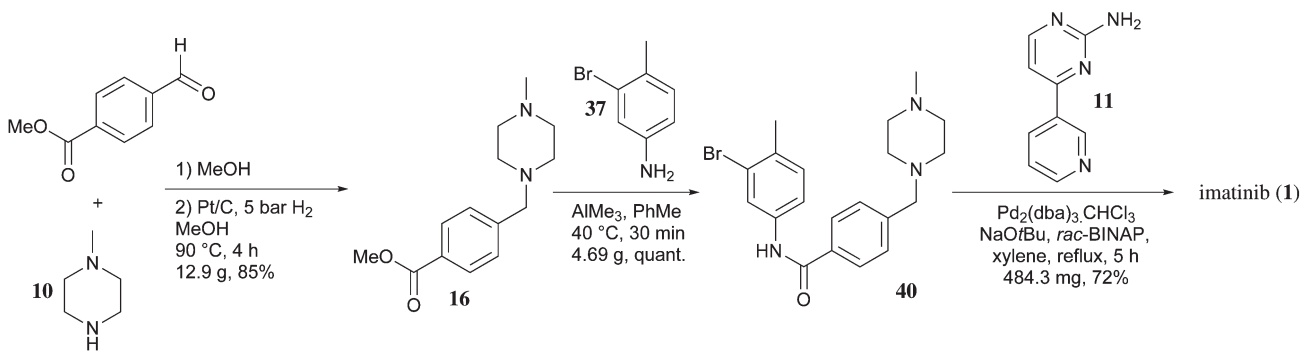
Fig. 3 X-Ray crystal structure binding of imatinib (**1**) with the kinase domain of Abl. Key: carbon (green), nitrogen (blue), oxygen (pink) and sulfur (yellow).

2.1. The original Ciba-Geigy AG discovery route

The first preparation of imatinib (**1**) was published in a patent in 1993 by Zimmermann (Scheme 1)[23,24] and filed by Ciba-Geigy AG (which in 1996 merged with Sandoz to form Novartis). No compound yields were quoted in this patent nor is any information given about the assembly of the key acid chloride **6**.[15] The synthesis takes advantage of precipitation as a purification technique; both guanidinium nitrate **7** and aminopyrimidine **8** are precipitated from the respective reaction mixtures by the addition of insolubilising solvents. The main features of this route are a condensation of the guanidinium salt **7** with enone **9** to form the aminopyrimidine core. This was followed by reduction of the nitro substituent in **8** over palladium on charcoal and amide bond formation with the advanced acid chloride **6** to give the API (**1**).



Scheme 1 Zimmermann's route to imatinib (**1**).



Scheme 2 Novartis' route to imatinib (**1**) utilising a Buchwald–Hartwig coupling of aminopyrimidine **11**.

2.2. Alternative routes and processes developed by Novartis

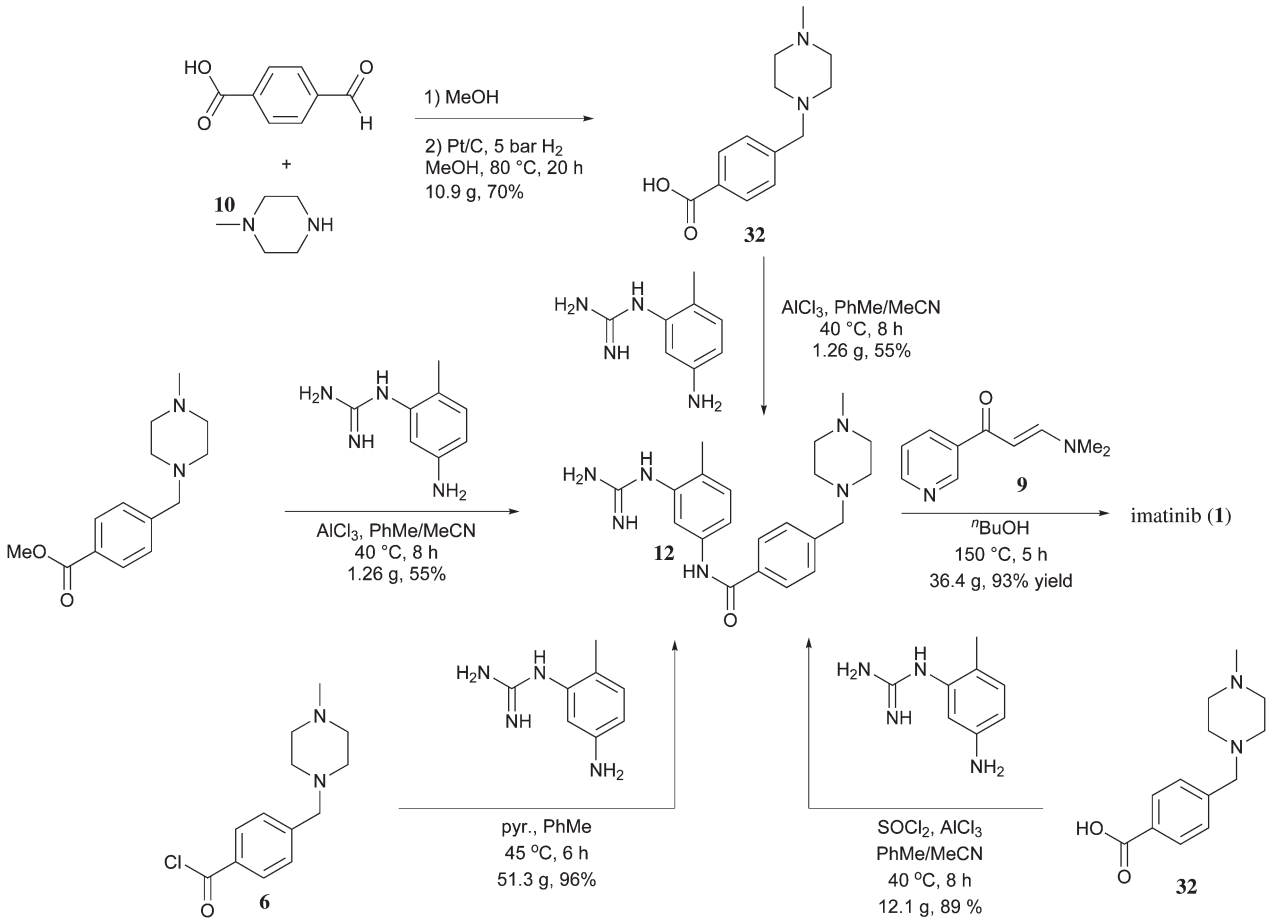
Novartis then went on to patent a number of alternative strategies to **1**.[25] For example, the *N*-methylpiperazine unit **10** was installed early in the synthesis using a reductive amination sequence (Scheme 2). Imatinib (**1**) was then generated by amide formation followed by a Buchwald–Hartwig coupling with aminopyrimidine **11**. While the yield of this final step was given as 72%, the final mass of product reported did not correlate with this figure, and no explanation was afforded. The product also contained unspecified isomers which required separation by reverse-phase preparative HPLC. Again, no yield was given for the final purified product.[15] This lack of detail makes it difficult to properly evaluate this as a truly viable route.

Alternative Novartis routes featured the preparation of the guanidine **12** which was subsequently condensed with enone **9** to form imatinib (**1**) (Scheme 3).[25] This method is common to many other routes and constitutes a simple way to construct the core pyrimidine functionality.

The advanced guanidinium fragment **12** may be generated from the nitro derivative **13** by reduction over a Pt catalyst or transfer hydrogenation from potassium formate followed by guanidine formation with cyanamide in the presence of HCl (Scheme 4).[25] It has also been shown that the aniline intermediate (**14**) can be formed directly by a regioselective amide formation with 3-amino-4-methylaniline (**15**) and ester **16**, however purification of the product required column chromatography making this process interesting but unlikely to be used for large scale production.

2.3. Natco Pharmaceuticals, Cipla and Szakács syntheses

In 2004, Kankan and Rao of Cipla Ltd patented an improved process for the reduction of the nitro group in **8** using $SnCl_2$ in THF or $SnCl_2$ in aqueous hydrochloric



Scheme 3 Novartis' synthesis of imatinib (**1**) *via* guanidinium intermediate **12**.

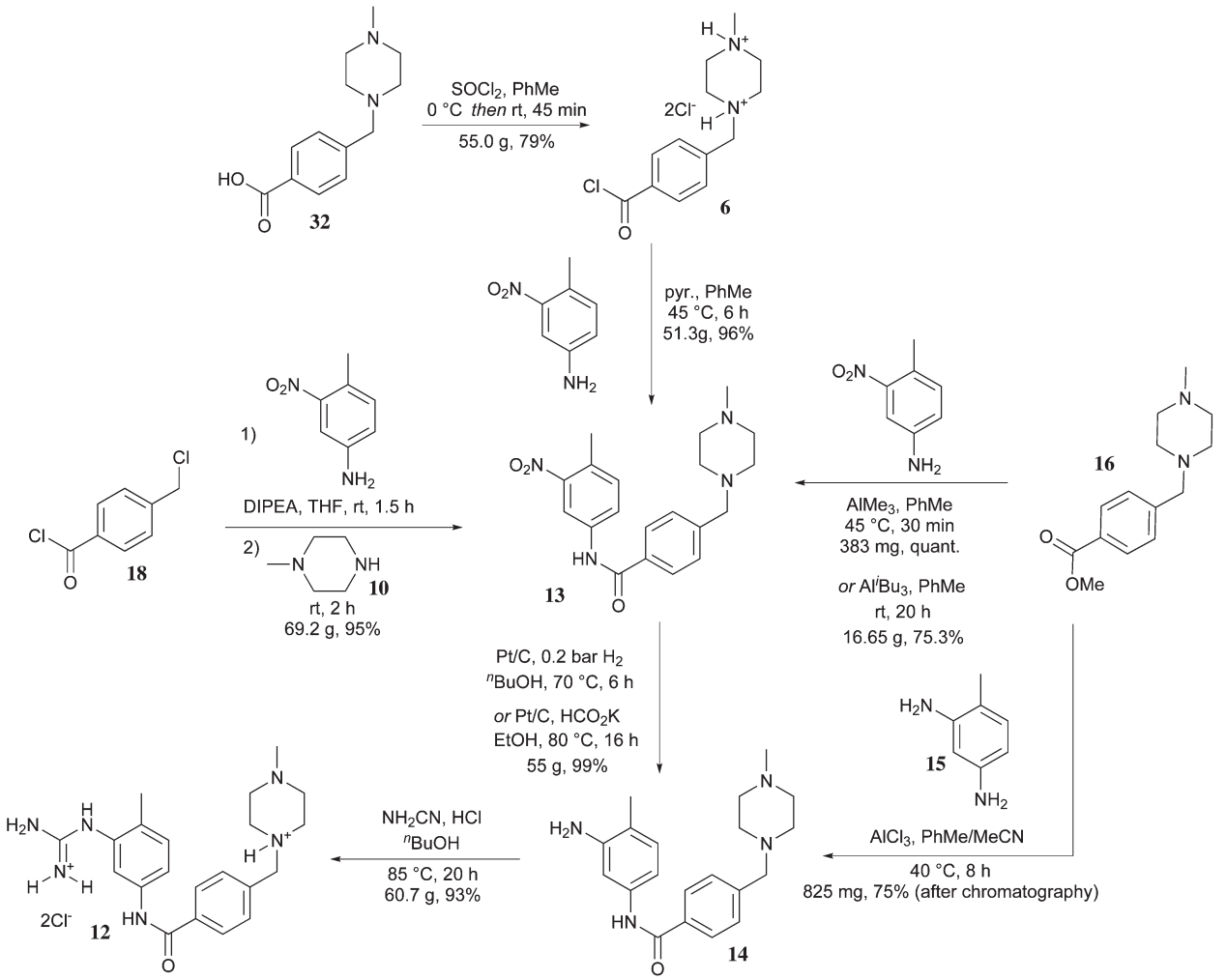
acid.[26] The yield in this step was improved from 40–45% (in the original Zimmermann route, Scheme 1) to 65–70% and the reaction time reduced from 21 h to between 2–4 h. The resulting aniline **17** could then be coupled with the dihydrochloride salt of acid chloride **6** in DMF to yield **1** as its tri-hydrochloride salt (Scheme 5). However, the use of stoichiometric quantities of tin and the subsequent disposal of stannous waste make this route far from ideal.

A subsequent patent[27] from workers at Natco Pharma reinvestigated the original Zimmermann route (Scheme 1) and developed an alternative sequence to overcome some of the problematic steps (Scheme 7). In their hands, Zimmermann's original process gave a very low yield of guanidinium salt **7** (20–25%). This was increased to 41% by simply changing the solvent to the higher boiling ^{n}BuOH and the overall atom economy of the transformation was further improved by recovering unreacted starting material. Also of interest is that the authors claim that the hydrogenation as described in the original patent does produce the desired product aniline **17** (although they did not investigate or characterise the outcome further). Instead they performed the reduction process using $SnCl_2$/HCl. While this new patent also describes the formation of acid chloride **18** from *p*-toluic acid (**19**), it also does not provide a yield for this crucial last step.

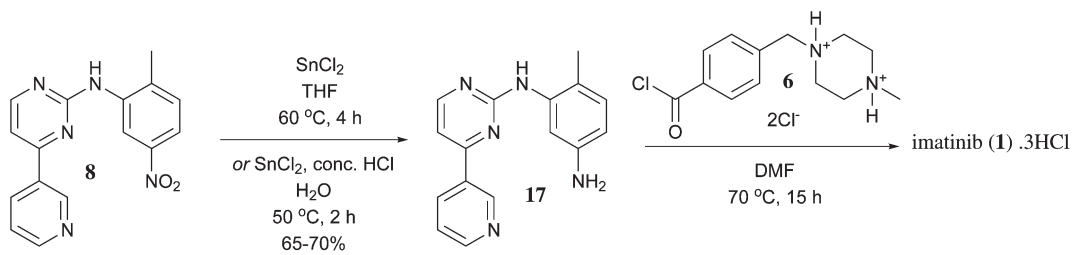
A very similar route has been reported in a subsequent publication by Szakács,[28] with a notably improved yield (81%) of pyrimidine **17** through reduction of the nitro group with $SnCl_2{\cdot}2H_2O$ in concentrated hydrochloric acid at room temperature for 30 min. The publication additionally includes a neat one step procedure for the synthesis of enone **9** from 3-acetylpyridine (**20**) and *N*,*N*-dimethylformamide dimethylacetal (DMF–DMA, **21**) (Scheme 6).

2.4. Szczepek's route

In a further modification to this route (Scheme 8),[29] Szczepek and co-workers found that ion exchange of the hydrochloride salt of **7** to the less soluble nitrate salt of **7** worked more efficiently during the condensation reaction (**9** + **7** → **8**). The coupling partner enone **9** was also formed from DMF–DMA (**21**) in a single step similar to that previously reported[28] but in this case without solvent. Again, yet another alternative reduction of **8** was performed, employing hydrazine over a RANEY® Ni catalyst. The classical amide formation and



Scheme 4 Alternative route to guanidinium **12**.



Scheme 5 Cipla's alternative reduction of intermediate **8**.

chloride displacement using intermediate **17** was then carried out in a similar fashion to the route shown in Scheme 7 but nevertheless required more forcing conditions to achieve the greater yield and reduced reaction time.

A subsequent publication however claimed that this reduction method was problematic yielding a mixture of azo and azoxy compounds that were inseparable from the product by crystallisation.[30] To avoid this problem, these authors conducted the reduction step using the more environmentally sustainable aqueous sodium dithionite to yield **17** in an identical 81% yield (Scheme 10, Method A). An alternative reduction method used a combination of $NaBH_4/CoCl_2$ that resulted in a 71.8% yield (Scheme 10, Method B).[31] More recently a new patent describes a reduction process using hydrazine over a 10% palladium on carbon catalyst to afford **17** in 98% yield (Scheme 10, Method C).[32]

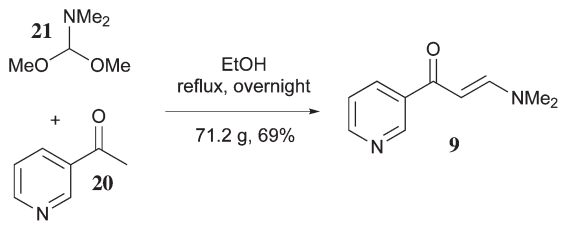
2.5. Zhejiang synthesis

Researchers at the Zhejiang Provincial Academy of Medical Sciences patented a new route to intermediate **8** in 2007 (Scheme 9).[33] They utilised a Negishi coupling previously developed by Simkovsky *et al.*[34] to construct the aminopyrimidine core. This route turned out to be a useful way of assembling the pyridylpyrimidine core, avoiding the high temperature condensation with enone **9** common to many of the previously reported sequences. The subsequent nucleophilic aromatic substitution of **22** with 2-methyl-5-nitroaniline (**23**) proceeded in good yield to provide the key intermediate **8** in just three steps starting from 3-bromopyridine (**24**).

2.6. The Leonetti solid phase synthesis

A solid-phase, microwave assisted preparation of imatinib (**1**) on a polystyrene support has been reported (Scheme 11).[35] The immobilised aldehyde **25** was produced by a chloride displacement of Merrifield's resin with 4-hydroxy-2-methoxybenzaldehyde (Fig. 4). The methoxyphenyl group enables the final product to be cleaved from the resin by acid, following a multi-step sequence involving four discrete microwave steps (Scheme 11).

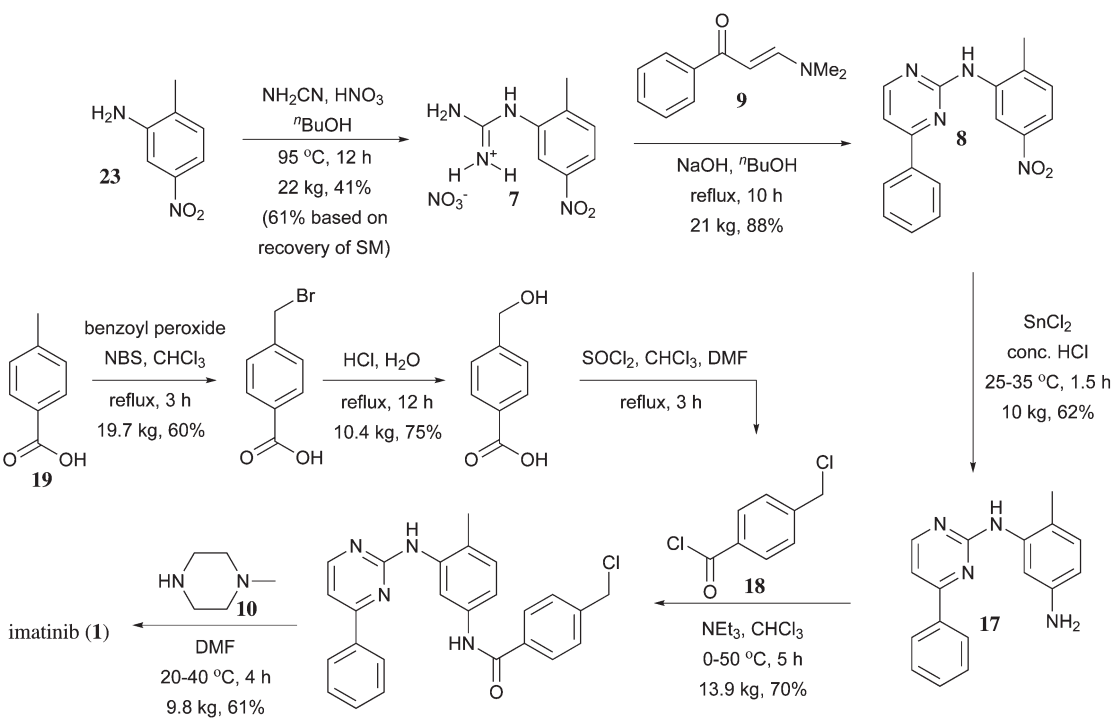
This reaction sequence begins with reductive amination using 4-methyl-3-nitroaniline (**26**) and the polymer supported aldehyde **25**.[35] This was then followed by amide formation, piperazine displacement and nitro reduction to give polymer supported aniline (**27**). Conversion of the aniline (**27**) to the guanidine (**28**) did not proceed well using sodium cyanamide or guanylpyrazole. However, $HgCl_2$ promoted addition of bis (*N*-Alloc) protected *S*-methylpseudothiourea (**29**) was successful. The product (**1**) was then isolated as a free base following cleavage (released with TFA) without the need for further purification. Yields were determined for some individual steps by TFA cleavage of the intermediates. The overall yield of imatinib (**1**) was reported to be "almost 65%" although it is not made clear how this was determined.



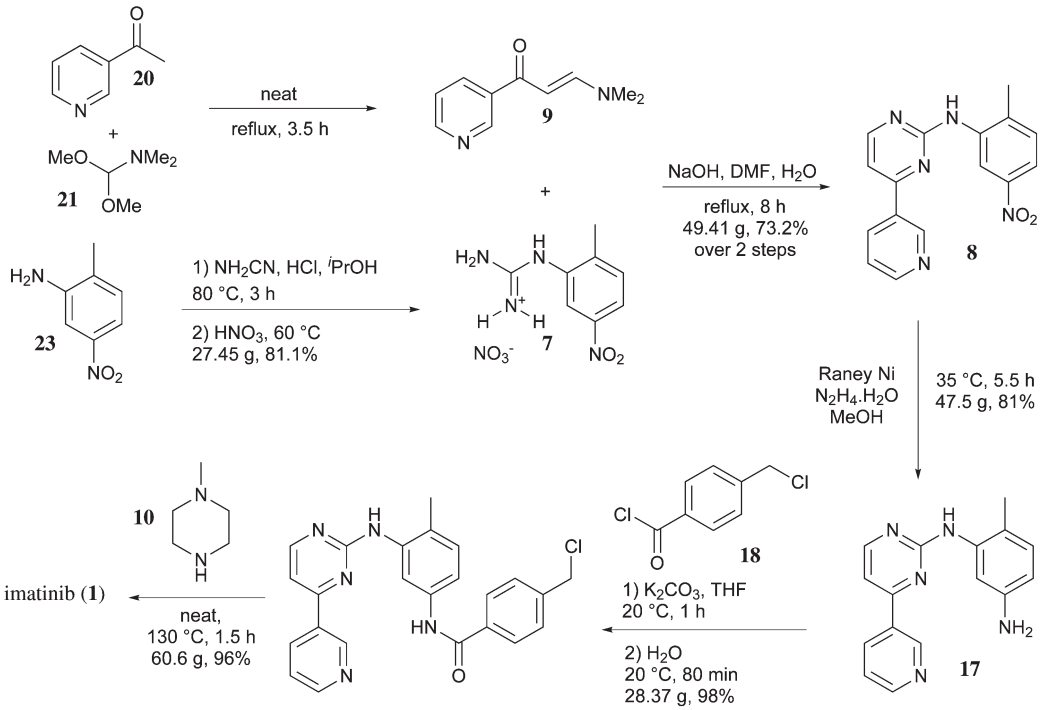
Scheme 6 Szakács synthesis of enone **9**.

2.7. The Liu route

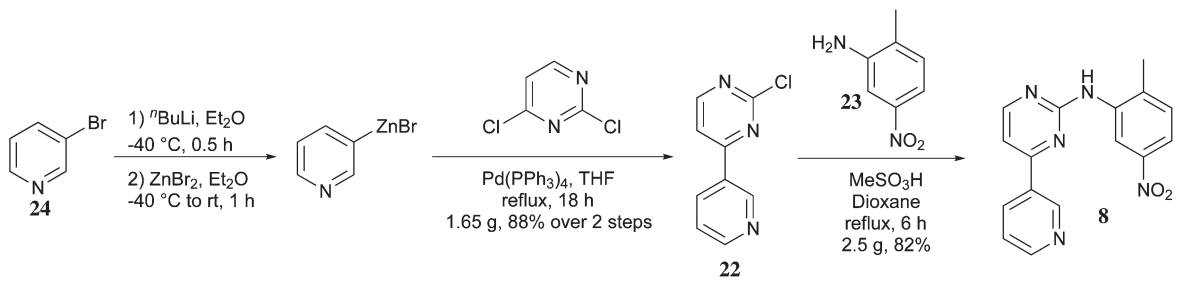
A synthesis sequence designed to be shorter and more environmentally acceptable involves formation of enone **9** from 3-acetylpyridine (**20**) and DMF–DMA (**21**) in a single step in high yields (Scheme 12).[36] The aminopyrimidine derivative **11** could then be generated by reaction of adduct **9** with guanidine nitrate followed by an Ullmann-type coupling to 2-bromo-4-nitrotoluene (**30**).[37,38] Subsequent



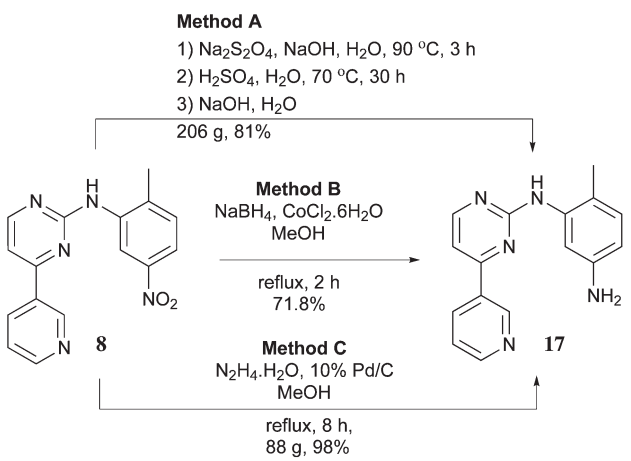
Scheme 7 Natco Pharmaceuticals route to imatinib (**1**).



Scheme 8 Szczepek route to imatinib (**1**).



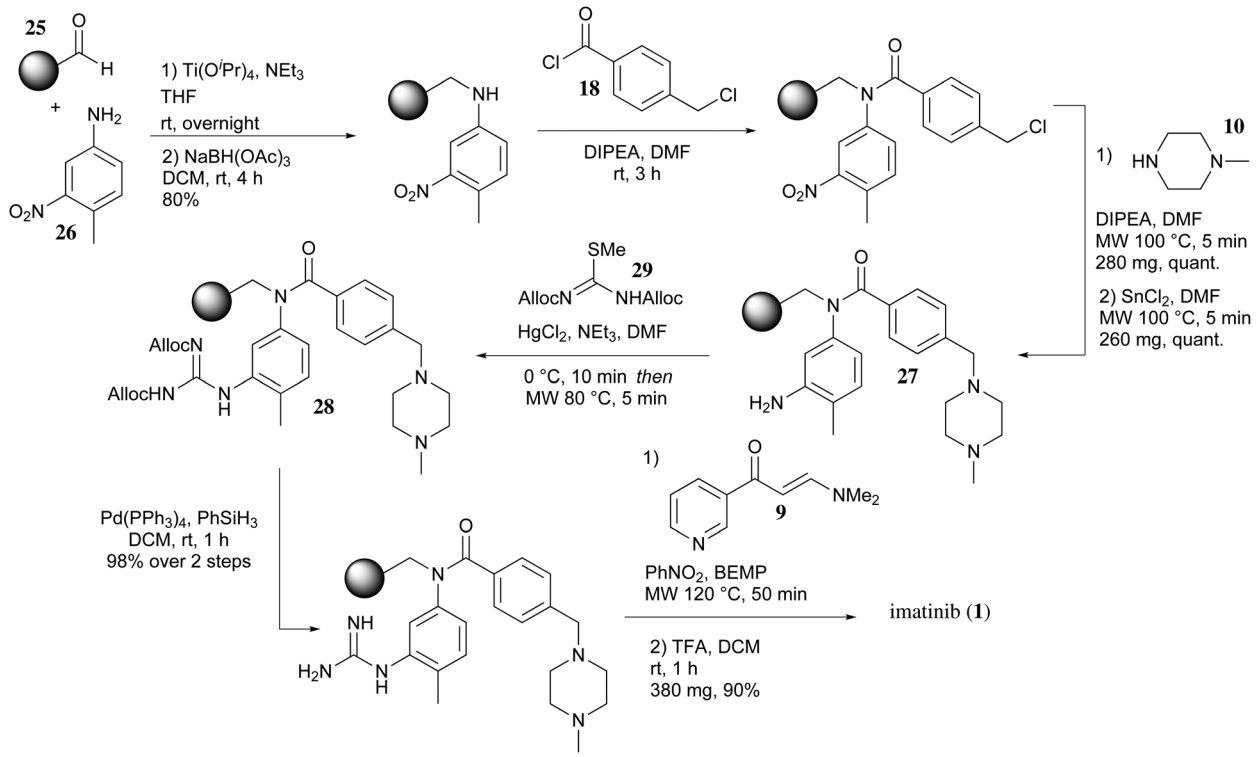
Scheme 9 Negishi coupling in the synthesis of pyrimidine **8**.



Scheme 10 Alternative procedures for the reduction of **8**.

reduction with hydrazine/$FeCl_3$ followed by amide formation yielded the benzylic chloride intermediate **31**. Substitution with *N*-methylpiperazine (**10**) in the final step smoothly forms imatinib (**1**). While this process does benefit from eliminating the need for toxic components such as cyanamide and $SnCl_2$, and expensive Pd and Pt catalysts employed in the previous syntheses, it still utilises highly toxic hydrazine as a reducing agent.

The preparation of the 2-aminopyrimidine (**11**) from 3-acetylpyridine (**20**) has also been described during the synthesis of new anticancer pyrimidines with multiple-kinase inhibitory effects (Scheme 14).[39] While the yields reported are not as high as described earlier in the original Liu process[36] (Scheme 14) the new procedures for work-up and purification do allow isolation of the enone adduct **9** in a particularly facile manner.



Scheme 11 Solid phase synthesis of imatinib (**1**).

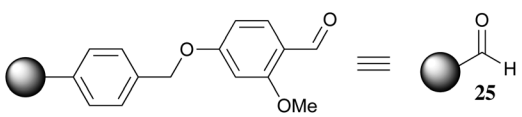


Fig. 4 Solid phase resin **25**.

2.8. Late stage amide coupling as an approach to imatinib synthesis

Most of the previous routes described above rely on the use of an acid chloride in order to form the amide bond of imatinib (**1**). Macdonald and Rossetto on the other hand demonstrated that DCC/HOBt could be used to directly unite aniline **17** with the carboxylic acid **32** (Scheme 13, Method A).[40] This same amide forming method has also been accomplished in similar yields using EDC (Scheme 13, Method B).[41] Ivanov and Shiskov later published a route involving CDI to effect the amide coupling in an improved 87% yield (Scheme 13, Method C).[30] More recent developments in this amide coupling of typical intermediates **17** and **32** have also been patented.[15] For example, triethyl phosphite as a dehydrating agent has been used to achieve the amide coupling in very high yields (Scheme 13, Method D).[42] The uronium salts HATU, HBTU, HCTU and TBTU are also effective in activating the acid coupling, achieving yields greater than 93% (Scheme 13, Method E).[43] These valuable improvements allow a streamlined synthesis to be achieved, avoiding the use of potentially corrosive reagents and by-products. Nevertheless it should be noted that the use of these peptide coupling agents is less satisfactory than other methods owing to waste byproducts being formed.

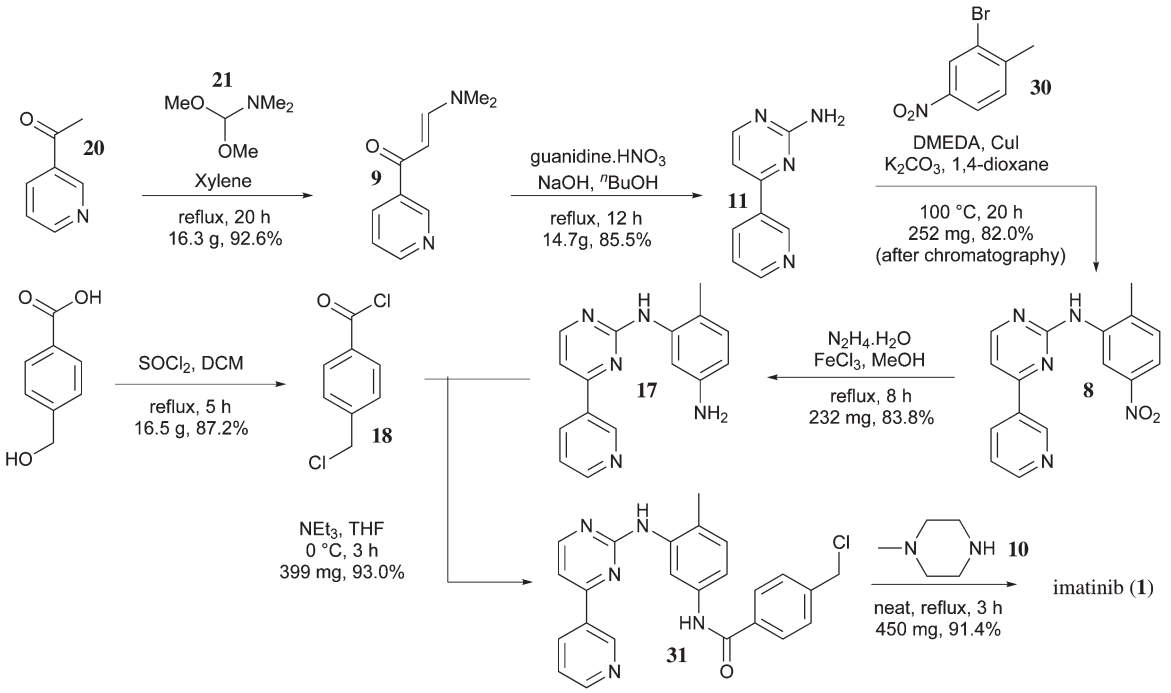
The late stage amide coupling of ester intermediate **16** with aniline **17** has also been described on a reasonable 45 g scale (Scheme 15). A selection of potassium and sodium alkoxide bases were used to promote this coupling. While the reported yields are greater than 81% in all examples, no indication of the reaction times needed to achieve these high yields were reported.[44]

2.9. The Tianjin Weijie synthesis

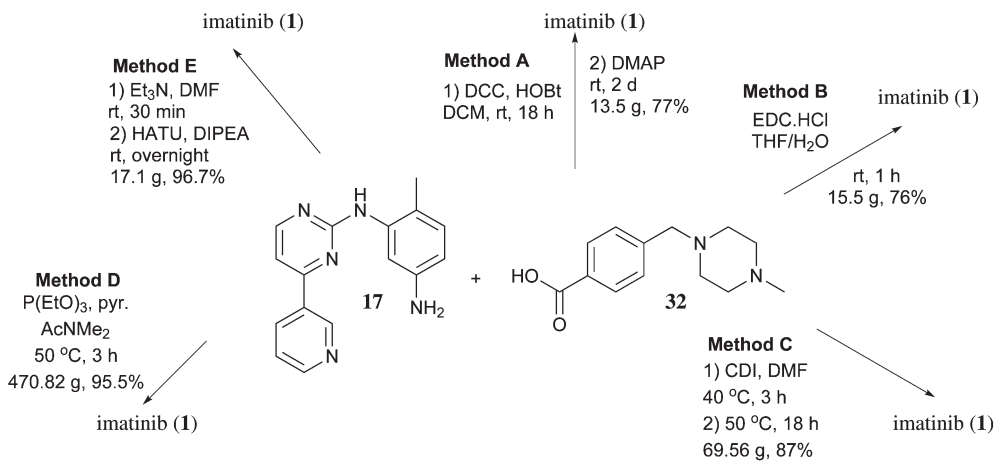
The amide bond may also be introduced at an early stage in the synthesis of imatinib (**1**). Tianjin Weijie Technology have patented a sequence making use of amide **33** as the starting material (Scheme 16).[45] The key step in this approach was the condensation of the advanced guanidine fragment **34** with the commonly used enone (**9**) to form the aminopyrimidine system. In the final stages the benzylic alcohol **35** was mesylated under standard conditions to form an activated leaving group and then displaced with *N*-methylpiperazine (**10**) to give imatinib (**1**) in good yield (85%).

2.10. The Chemagis S_NAr route

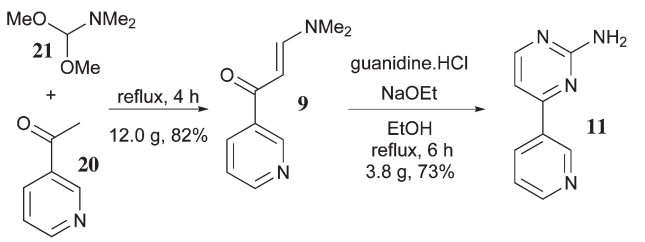
The use of potentially hazardous[46] cyanamide can be avoided by an S_NAr reaction between 2-amino-4-nitrotoluene (**23**) and the chloropyrimidine **22** to form the aminopyrimidine core **17** (Scheme 17).[47] The process developed by Chemagis also avoids



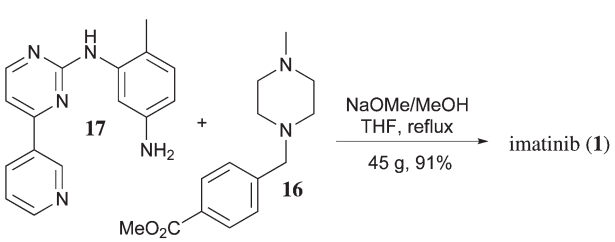
Scheme 12 Synthesis of imatinib (**1**) *via* an Ullmann-type coupling.



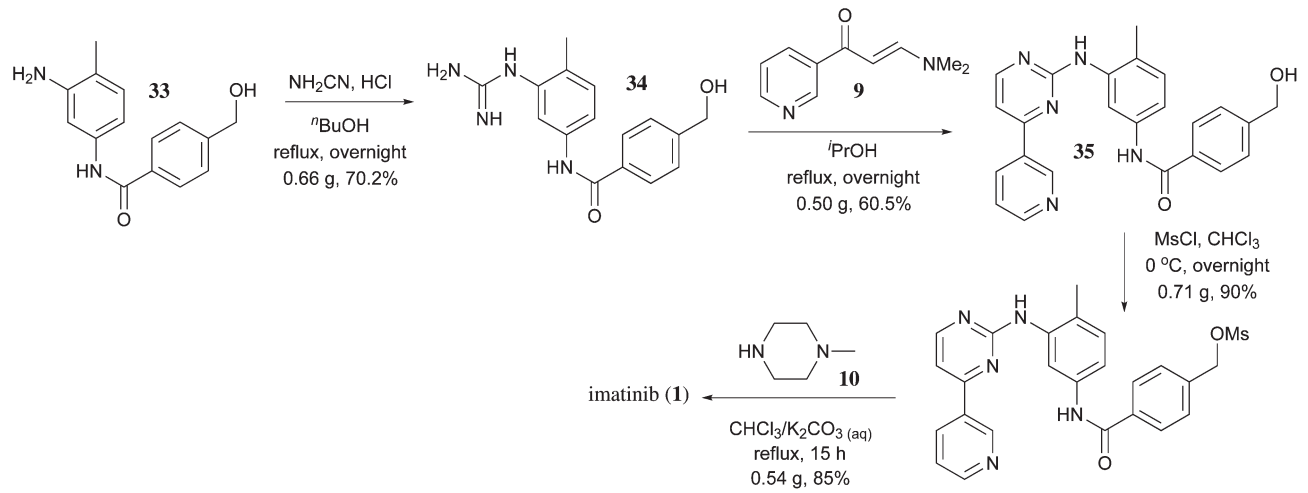
Scheme 13 The formation of imatinib (**1**) by direct carboxylic acid coupling reactions.



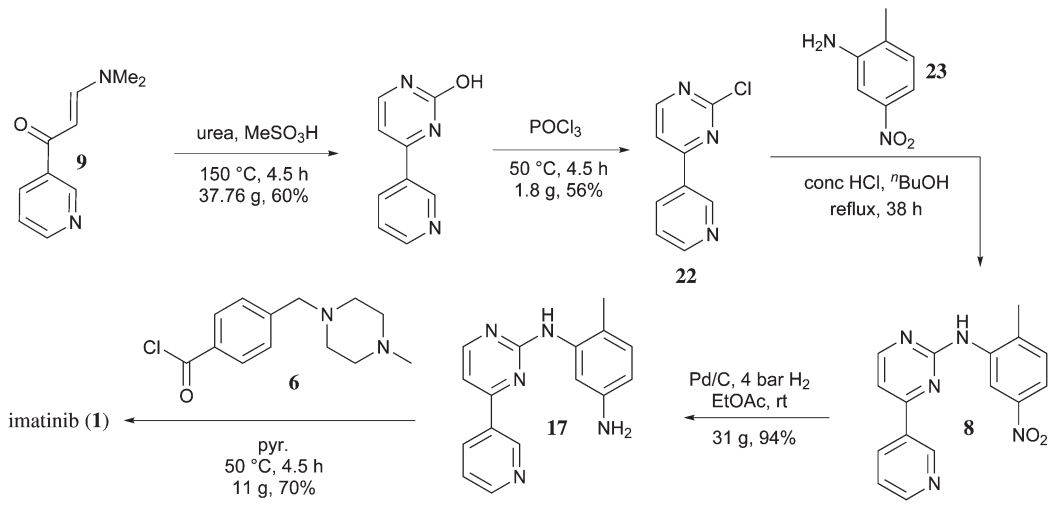
Scheme 14 Synthesis of 2-aminopyrimidine (**11**).



Scheme 15 Alternative methods to perform the amide coupling.



Scheme 16 Preparation of imatinib (**1**).



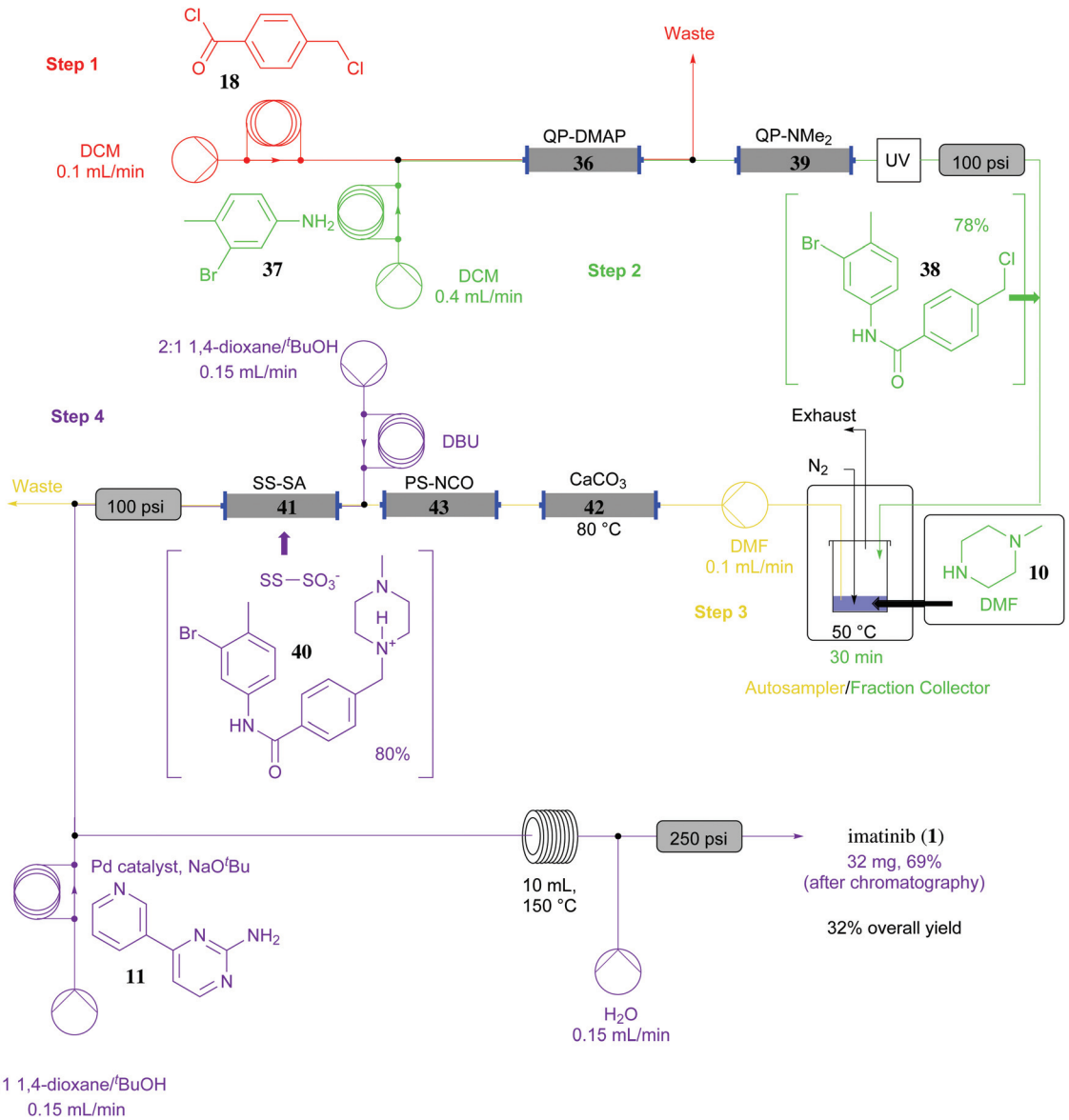
Scheme 17 Synthesis of compound **1** by S_NAr on pyrimidine core **22**.

the handling and manipulation of the guanidine salt common to previous routes. The remaining steps in the synthesis of **1** were performed according to the original patented procedure (Scheme 1). Unfortunately, again no yield[15] was provided for the formation of **8** and in addition, chromatography was apparently required to obtain this nitro intermediate (**8**) in high purity, thereby making this route less suitable for large industrial scale operation.

2.11. The Cambridge flow chemistry synthesis

The Innovative Technology Centre at Cambridge has recently demonstrated a flow chemistry based route to imatinib (**1**) (Scheme 18)[14] and a small library of imatinib analogues[48] (Fig. 5). The first step in this process involved loading the acid chloride **18**, in dichloromethane (DCM), onto a pre-swollen polystyrene-supported DMAP reagent (QP-DMAP, **36**) by using an HPLC pump to flow the solution through a glass column containing the QP-DMAP. The trapped and activated acid chloride was then reacted with aniline **37** in DCM, thus releasing the amide intermediate (**38**) in 78% yield. Unreacted acid was removed by an in-line column containing polystyrene-supported dimethylamine (**39**) as a scavenger. The stream containing the amide **38** was then directed by a fraction collector into a vial containing *N*-methylpiperazine (**10**) and DMF, ready for introduction *via* flow into step 3. A stream of nitrogen gas, in combination with heating, was used to remove the DCM solvent and effect an in-line solvent switch.

The combined reagents in the vial were then used directly in step 3 to form the advanced intermediate **40** which was subsequently trapped on silica-supported sulfonic acid (SS-SA, **41**). Next the S_N2 displacement of the chloride in **38** was achieved by flowing the mixture through a column containing $CaCO_3$ (**42**). Unreacted amide was scavenged by a column containing polystyrene-supported isocyanate (QP-NCO, **43**) to leave



Scheme 18 Reactor set-up for the flow synthesis of imatinib (**1**).

the desired aryl bromide (**40**) trapped on SS-SA (**41**) in 80% yield.

The final step involved a Buchwald coupling with the aminopyrimidine **11**. The trapped aryl bromide (**40**) was released by DBU in a stream of 1,4-dioxane and ^{t}BuOH before being combined with BrettPhos palladium precatalyst[49] and aminopyrimidine **11**, introduced from another injection port. By using a 250 psi back pressure regulator (BPR) it was possible to superheat the reaction to 150 °C for 30 minutes. A stream of water was introduced prior to the BPR to dissolve NaBr that formed in the reaction and prevent blockages. A single brief chromatography was used at the end of the process to provide imatinib (**1**) in 69% yield (32% overall yield).

In a follow on full paper in this journal we have further demonstrated that a library of imatinib analogues can be rapidly generated; each analogue only taking six hours to synthesise and requiring only a single chromatographic purification at the end of the synthesis sequence. Of interest is the fact that the procedure required almost no manual intervention in the chemical processing. Although the route described is clearly not suited to scale up it does provide an attractive alternative for routine analogue preparation.

2.12. The Buchwald synthesis of imatinib

The Buchwald group have also reported a 2-pot, 3-step synthesis of imatinib (**1**) (Scheme 19) using their own BrettPhos palladium precatalyst[49] (**44**) for the final coupling step. This time however an aryl chloride intermediate **45** was utilised instead to provide imatinib (**1**) in 84% yield. Chloro intermediate **45** was prepared in an efficient (73% over two steps)

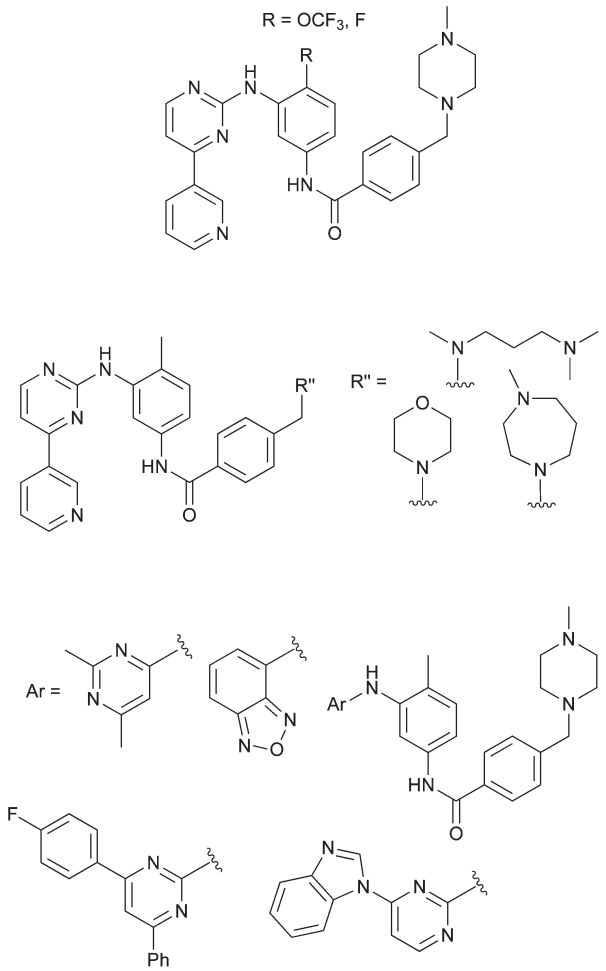


Fig. 5 Analogues of imatinib (**1**).

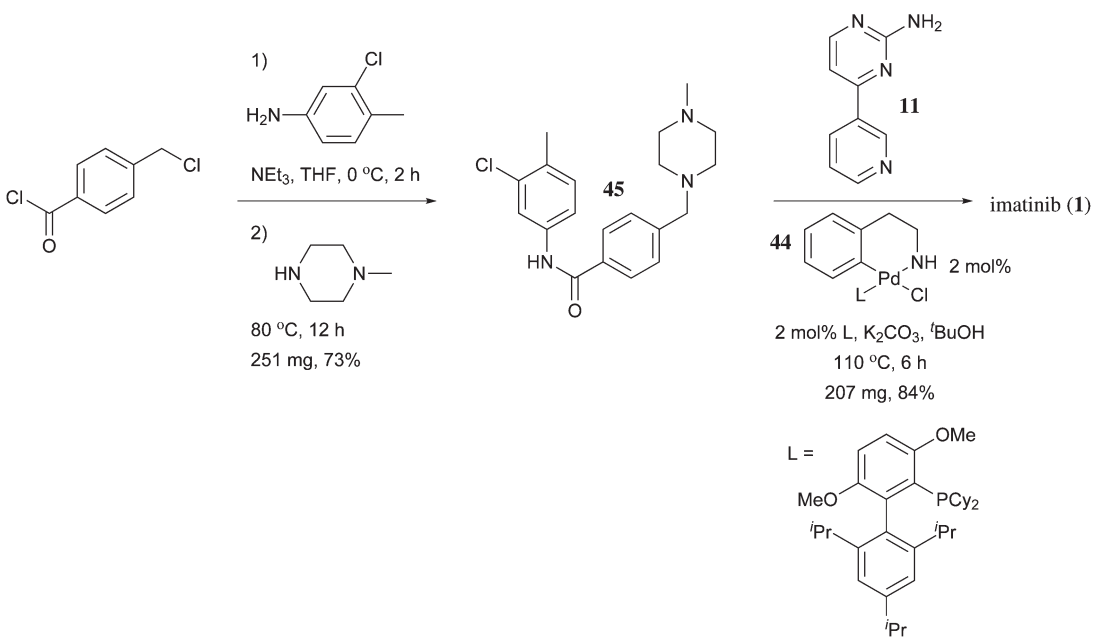
one pot process from commercially available starting materials.[50]

2.13. A "catch–react–release" synthesis of aminopyrimidine 8

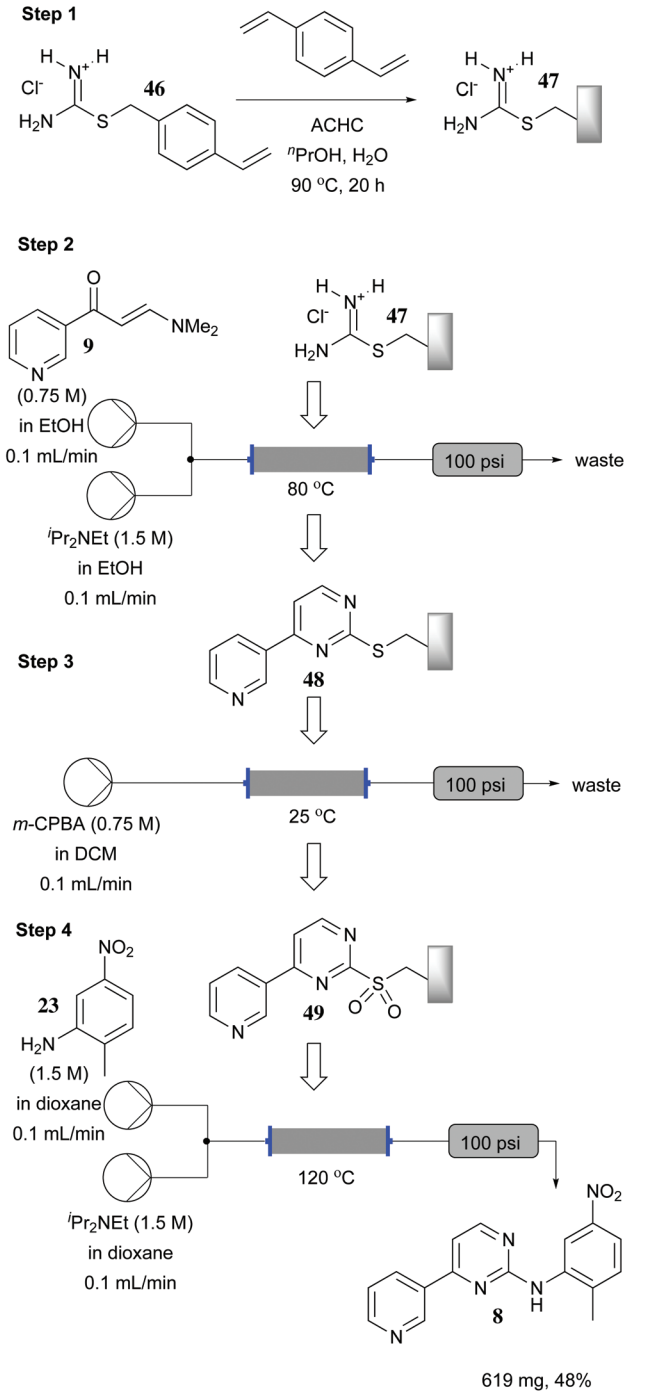
An alternative flow based procedure has recently been developed by our group (Scheme 20).[51] This new route avoids the problems associated with using poorly soluble intermediates in flow by building the pyrimidine core on a monolithic support. In the first step of this synthesis the functionalised monolith was prepared from a homogenised mixture of monomer **46**, divinylbenzene cross-linker, and porogen (a 5 : 1 ^{n}propanol–water mix) (Scheme 20 step 1). Polymerisation was initiated by the addition of 1,1′-azobis(cyclohexanecarbonitrile) (ACHC) and heating to 90 °C for 20 h.

A solution of enaminone **9** and Hünig's base was then eluted through the monolith **47** thereby generating the pyrimidine core **48** (Scheme 20 step 2). Exposing the monolith (**48**) to a flow stream of *m*-CPBA in DCM (Scheme 20 step 3) caused oxidation of the thioether and activated it towards subsequent nucleophilic displacement with amine **23** (Scheme 20 step 4). This substitution however proved to be slow, requiring the reagent solution to be infused into monolith **49** and heated for 2 h before the product could be eluted along with the excess amine. The aminopyrimidine intermediate **8** was then isolated in 48% yield after aqueous extraction and flash column chromatography.

This "catch–react–release" protocol for the synthesis of aminopyrimidine **8** is advantageous due to its containment of malodorous and toxic sulfur-containing byproducts. In addition the process was also easily automated to rapidly generate a library of aminopyrimidines with minimal manual handling.



Scheme 19 The Buchwald synthesis of imatinib (**1**).



Scheme 20 Catch–react–release synthesis of the imatinib aminopyrimidine core (**8**) on a monolithic support.

3. Synthesis of nilotinib

In 2004 Novartis filed a patent on a second generation tyrosine kinase inhibitor as an improved treatment for certain indications of CML.[52] The API nilotinib (**2**), (4-methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide [AMN107, CAS: 641571-10-0], is administered as its hydrochloride salt (monohydrate) in the form of capsules and marketed under the trade name Tasigna (USA, Europe) (Fig. 1). In multiple clinical trials this compound gave an improved profile against drug-resistant CML in particular for the treatment of a specific chromosomal abnormality that is associated with chronic and accelerated phase CML (Philadelphia chromosome positive (Ph^+) CML). This was a major pharmaceutical breakthrough; although almost all CML patients initially treated with imatinib (**1**) demonstrated a positive response (89% survive >5 years)[53] a significant proportion of those with advanced CML eventually suffered relapses. Such drug tolerance and relapse has been ascribed primarily to mutation resistance in the Bcr-Abl gene preventing binding of the original imatinib (**1**) molecule.[54,55] Although elevated drug efflux from the target cells promoted by P-glycoprotein[56] or activation of Lyn, an Src-family protein kinase (SFK)[57,58] have also been additionally implicated. In general nilotinib (**2**) is considered to be about 20 orders of magnitude more potent than imatinib (**1**) as well as being active against all current resistant mutants except for T315I (the gatekeeper mutant).[53,59]

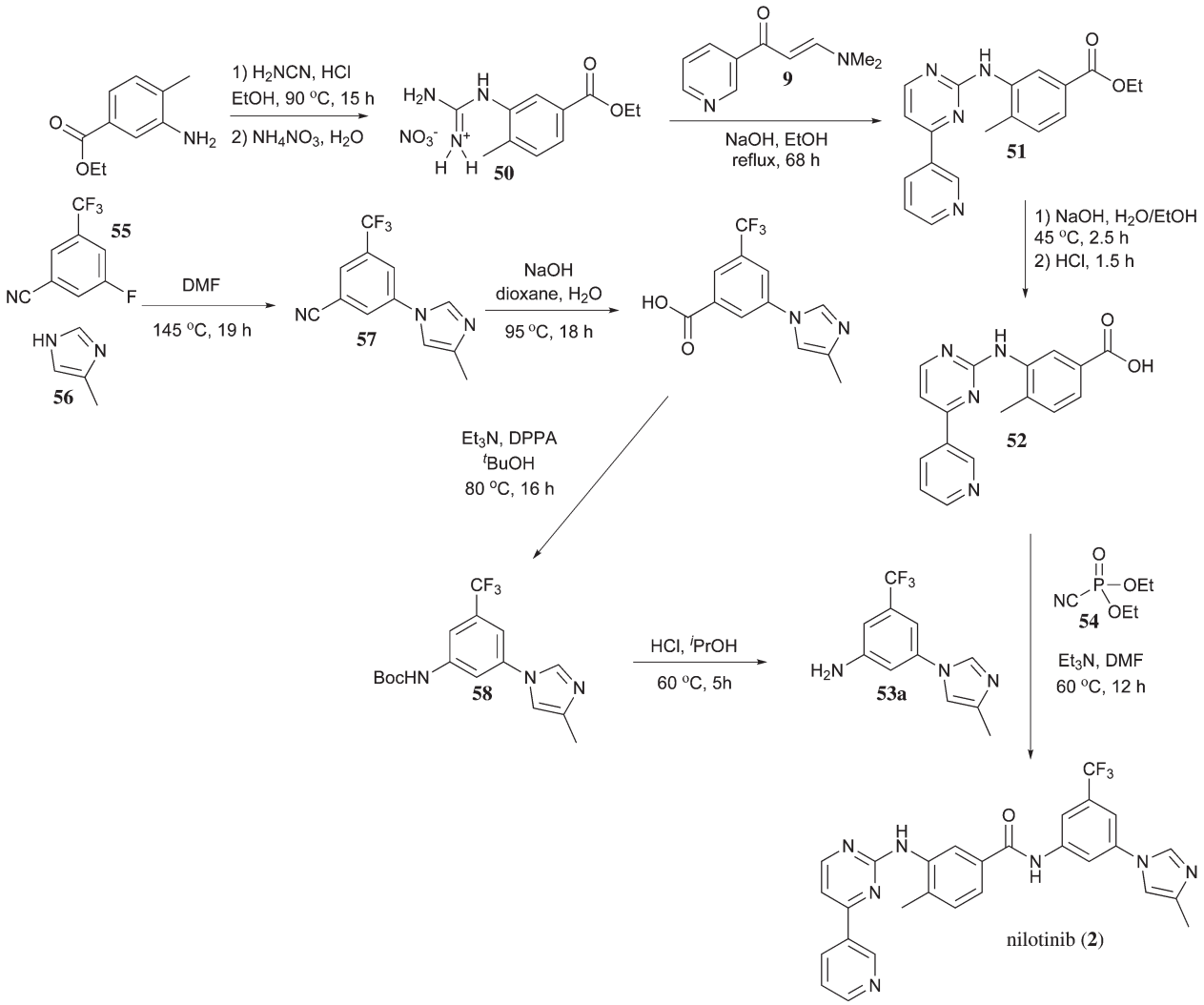
3.1. The original Novartis discovery route

The initial patent on nilotinib (**2**) from Novartis defined the individual synthesis steps and conditions but gave no actual yield data.[15] This patent was primarily concerned with the biological mode of action and application of the molecule.[52] The five step convergent synthesis followed a classical disconnection approach obviously benefiting from the previous synthetic experiences gained when preparing imatinib (**1**) (Scheme 21). Consequently, the initial guanidine forming step was anticipated to be high yielding furnishing the nitric acid salt of **50** which was very insoluble and consequently easily isolated by filtration. Next, a standard condensation reaction between enone (**9**) and the guanidine (**50**), analogous to previous syntheses of imatinib (**1**), generates the 2-aminopyrimidine **51**. The ethyl ester group of compound **51** was then hydrolysed to the corresponding carboxylic acid **52** and coupled with aniline fragment **53a** using diethyl phosphorocyanidate (**54**) as the promoter to yield nilotinib (**3**).

A four step sequence to produce the aniline fragment **53a** starting from the commercially available 3-fluoro-5-trifluorobenzonitrile (**55**) was also described in the same patent.[52] The first step involves nucleophilic aromatic substitution of 4(5)-methylimidazole (**56**) to give benzonitrile intermediate (**57**). No mention is made of the regioselectivity of this reaction.[15] Hydrolysis of the nitrile followed by a Curtius rearrangement in ^{t}BuOH gave the Boc protected aniline (**58**). The desired aniline fragment (**53a**) was obtained after simple acid catalysed deprotection with HCl.

3.2. Novartis synthesis of the aniline intermediate 53a

More specific information about the synthesis of the key aniline intermediate **53a** was disclosed in a detailed patent by Novartis in 2006 which reported several further improvements.[60] The novel electronic and functional distribution of

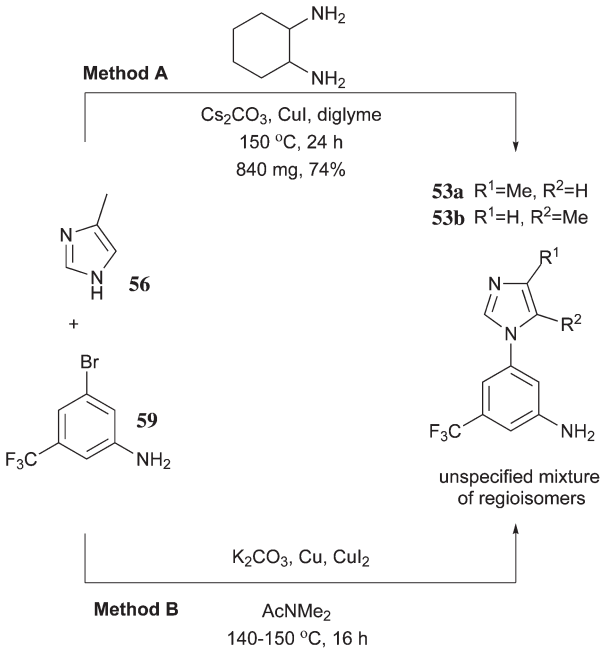


Scheme 21 Novartis primary reported route to nilotinib (**2**).

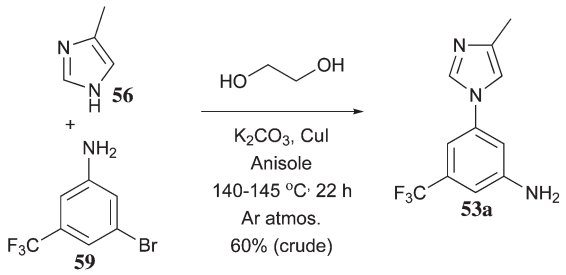
this unit make its synthesis less than trivial and therefore of significant commercial interest. In addition, although the corresponding 4(5)-methylimidazole (**56**) is readily available and can be directly coupled by either S_NAr or metal mediated processes, this often leads to regioisomeric mixtures which require separation. The Novartis patent described a one step method for the preparation of the aniline **53** in 74% yield, using copper(I) catalysis (Scheme 22, Method A). While the regioselectivity of the reaction is not specified,[15] the desired regiomer **53a** was obtained as the major product after column chromatography. A variation of this metal mediated coupling was reported later for the formation of nilotinib analogues by Il-Yang Pharmaceuticals (Scheme 22, Method B).[61] This research group employed a copper(0)/copper(II) catalyst system without metal chelating ligands to obtain **53a.** The procedure, as described, reputedly did not lead to the formation of regioisomer **53b** but fails to report a yield for the process.[15]

A similar copper catalysed process has also been described by Shasun Pharma Solutions in a patent for the general preparation of *N*-aryl compounds. The coupling of the 4(5)-methylimidazole (**56**) and 3-(trifluoromethyl)-5-bromoaniline (**59**) was described although no specific mention of the presence (or absence) of the undesired regioisomer (**53b**) was discussed (Scheme 23).[62] Only a crude yield for the reaction was provided[15] although their choice of anisole as the solvent in this reaction is interesting. This choice is presumably due to anisole having the right combination of low dielectric constant and high boiling point needed to enable the reaction to proceed.

The Novartis 2006 patent also described a number of more elaborate sequences designed to employ alternative starting materials (Scheme 24, routes 1–4).[60] Route 1A reports on a selective bromination of the nitro aromatic **60** using dibromantin **61** as the brominating agent. This initial step gave excellent regioselectivity along with a relatively high yield considering the deactivation of the aromatic ring system. It is therefore unfortunate that the subsequent copper catalysed substitution of the newly installed bromide proceeded in poor



Scheme 22 Preparation of the key coupling fragment **53a**.



Scheme 23 Shasun Pharma Solutions' preparation of aniline fragment **53a**.

yield, although the final hydrogenation over palladium/carbon gave aniline **53a** in comparatively good yield. Alternatively, a nucleophilic aromatic substitution with 4(5)-methylimidazole (**56**) can be used to access the nitro aromatic **62a** (Scheme 24, route 1B).

Route 2 in the scheme employed a slow nitration reaction of the heavily halogenated starting material **63**. This proceeded in excellent yield and selectivity to install the nitro group *meta* to the most electron withdrawing groups (Scheme 24, route 2).[60] Simultaneous reduction of the nitro group and removal of the bromine substituent under standard hydrogenation conditions generated **64**. This was followed by direct nucleophilic aromatic substitution of the fluorine group using the sodium salt of 4(5)-methylimidazole (**56**) in *N*-methylpyrrolidin-2-one (NMP) at an elevated temperature and over an extended reaction time. Despite experimental procedures being reported, once again no actual yields or conversions are recorded for these two steps.[15] One might expect that the S_NAr reaction is low yielding due to the substitution pattern of substituents on this particular substrate. The final product was described as containing at least one other regioisomer, although the desired regioisomer **53a** could be obtained pure after recrystallisation of the bulk mixture albeit again no overall yield is given for this process.

The third route to **53a** also utilised an S_NAr reaction, but on this occasion using a more electron deficient aromatic ring system **55**. This gave a good yield of the corresponding aromatic nitrile **57**.[60] Next, partial hydrolysis to the corresponding amide **63** and performing a modified Hoffmann rearrangement sequence yielded the hydrochloride salt of **53a** in 28% overall yield after acidic work-up (Scheme 24, route 3).

The final route (Scheme 24, route 4) utilised the substitution of an aryl fluoride in the presence of an aryl bromide by 4(5)-methylimidazole (**56**) to generate the residual bromo substituted compound **64a** in moderate yield.[60] A palladium catalysed Buchwald amination then generated the intermediate imine **65a** which was immediately hydrolysed to the aniline product **53a**. The overall yield for the generation of **53a** from this sequence was 35.5%.

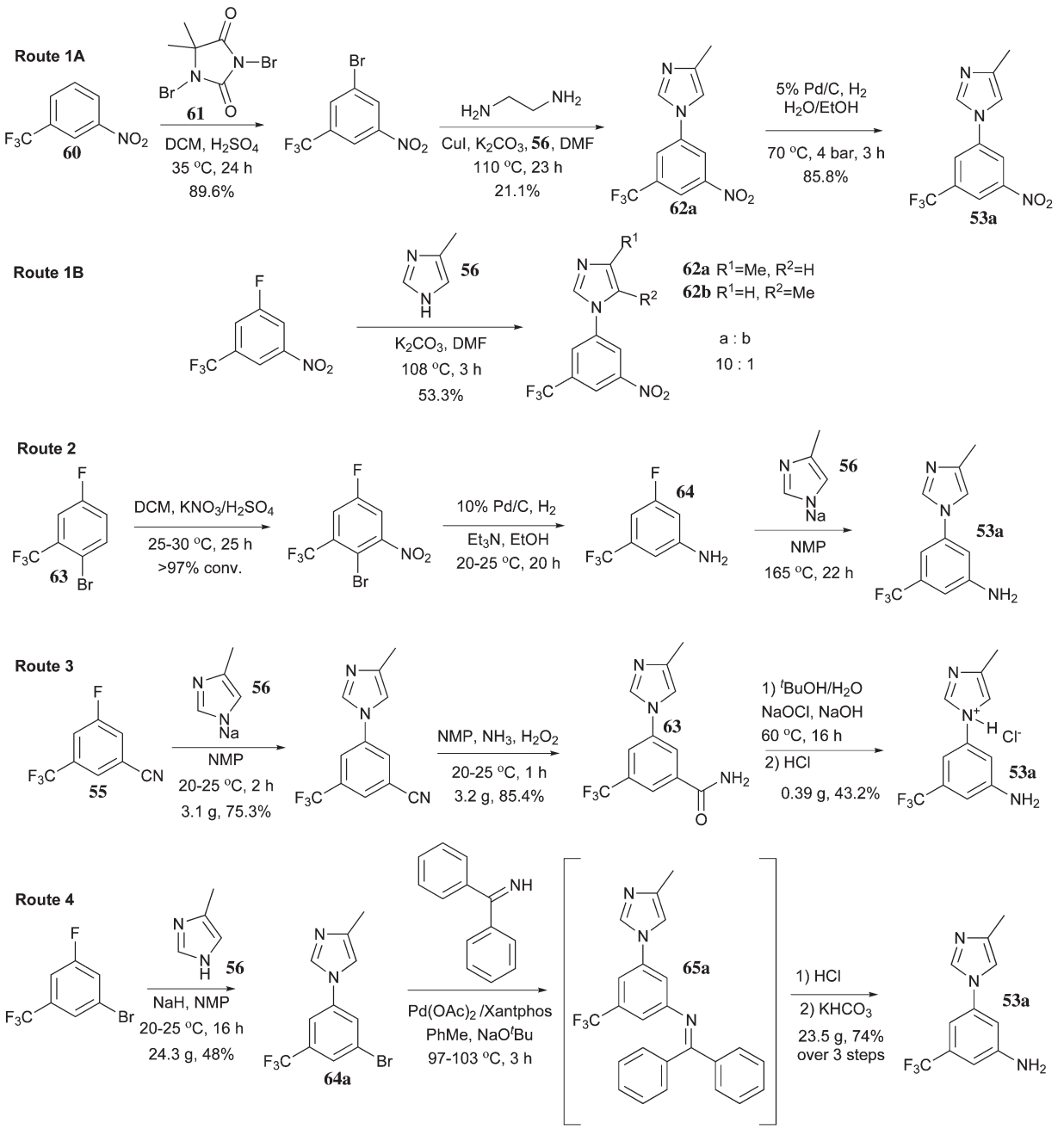
A later Novartis patent describes the preparation of the key intermediate **53a** starting from commercially available dinitro-5-(trifluoromethyl)benzene (**66**) (Scheme 25).[63] In this sequence nucleophilic substitution of the symmetrical starting material with 4(5)-methylimidazole (**56**) is followed by reduction of the associated nitro group in the usual fashion. The substitution step was reported to give a 9 : 1 mixture of regioisomers (**62a** and **62b**) in favour of the undesired product (**62b**). This was subsequently removed by treatment with activated charcoal to give a modest yield of the precursor **62a**. A standard reduction of the nitro group using palladium on charcoal was effective (62%); however, a higher yield of 82.5% was obtained using RANEY® Nickel as the reducing catalyst.

3.3. The direct amide coupling route

About the same time as their patents describing the synthesis of the key aniline fragment **53a** appeared, Novartis demonstrated that it was possible to directly condense the aniline fragment **53a** with methyl ester **67** (Scheme 26).[64] Treatment at room temperature in the presence of potassium *tert*-butoxide gave a good conversion to the final product **2** in 67% isolated yield. This method offers several advantages including the removal of a hydrolysis step (**51** → **52**; Scheme 21) as required in the original route and the need for intermediate acid activation. From an industrial preparation stand point this is an excellent development, shortening the route and removing the need for expensive coupling agents.

3.4. The Ariad Pharmaceuticals route

A further streamlined synthesis of nilotinib by chemists at Ariad Pharmaceuticals (Scheme 27) begins with a number of advanced but commercially available components.[65] The route involves the coupling of 4(5)-methylimidazole (**56**)

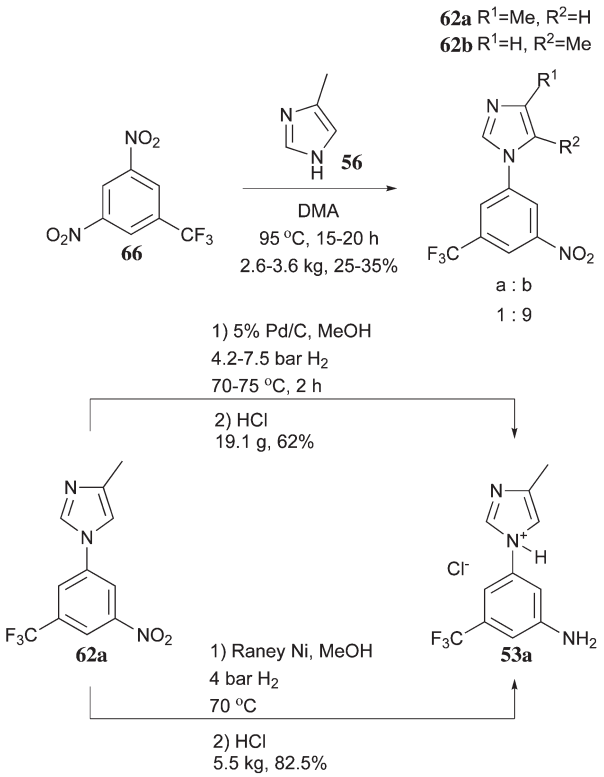


Scheme 24 The alternative Novartis synthetic routes to fragment **53a**.

with 3-bromo-5-trifluoromethylaniline (**59**) using a protocol inspired by chemists at Amgen[66] which gave essentially complete conversion of the bromo starting material to an 85 : 15 (**53a** : **53b**) mixture of the two expected regioisomeric products in favour of the desired material (**53a**). Purification and separation was achieved by column chromatography and recrystallisation. Interestingly, they report that attempts to couple aniline **53a** with 3-iodo-4-methylbenzoic acid using EDCI as the activator either failed or gave moderate yields even at elevated temperatures (<60%). Ultimately, these authors found greater success utilising the commercially available acid chloride **58** which gave a 95% yield of the corresponding amide **68** (an observation which is reminiscent of the original amide coupling in imatinib). The final Buchwald coupling was achieved in 89% yield although despite the previous steps being conducted at gram scale, this was executed on less than 1 mmol scale as a proof of principle of the route. It is our findings that upon repeating this chemistry, scaling of this reaction step is extremely difficult giving widely inconsistent yield on scales above 250 mg.

3.5. The Chen route to nilotinib

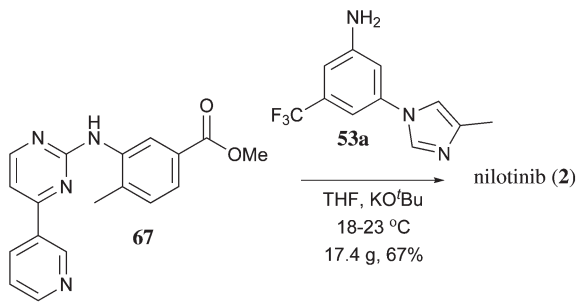
The re-worked synthesis of nilotinib by Chen *et al.*[67] published in 2009 utilises similar conditions to those of Novartis[52] (Scheme 21) and Il-Yang Pharmaceuticals[61] (Scheme 22) to obtain the main fragments **53a** and **51**. However, in an alternative sequence, amine **51** was then protected as a *tert*-butyl carbamate prior to hydrolysis of the ethyl ester. This allowed the coupling of the new acid fragment **69** with the common aniline unit **53a** in an excellent 94% isolated yield (Scheme 28).



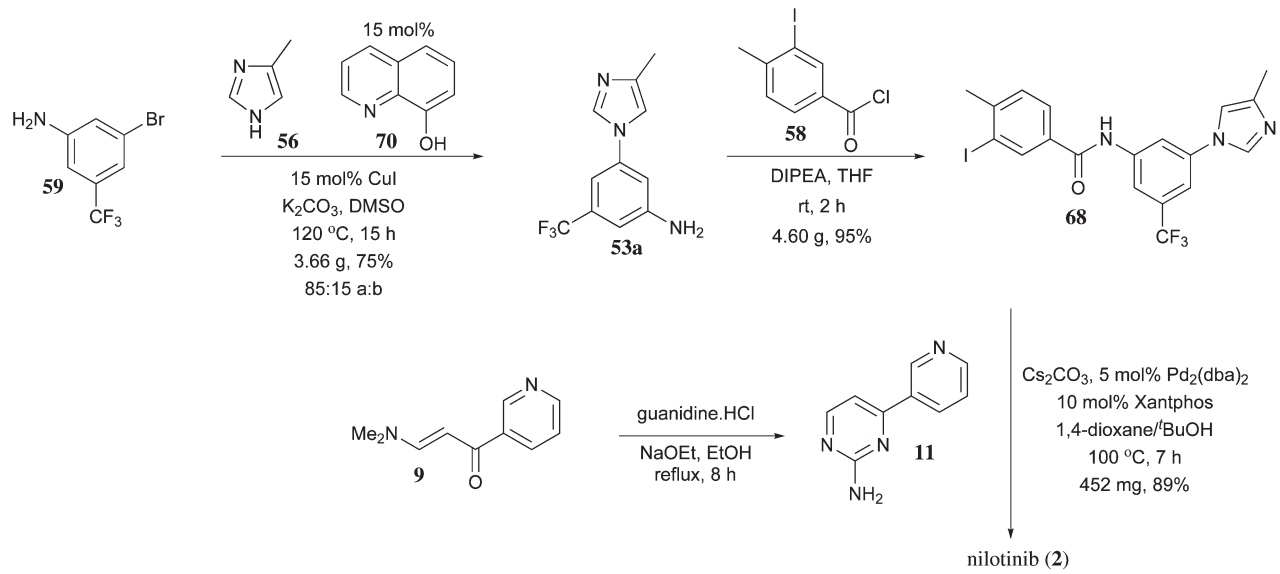
Scheme 25 Preparation of fragment **53a**.

3.6. The Teva Pharmaceuticals synthesis of nilotinib

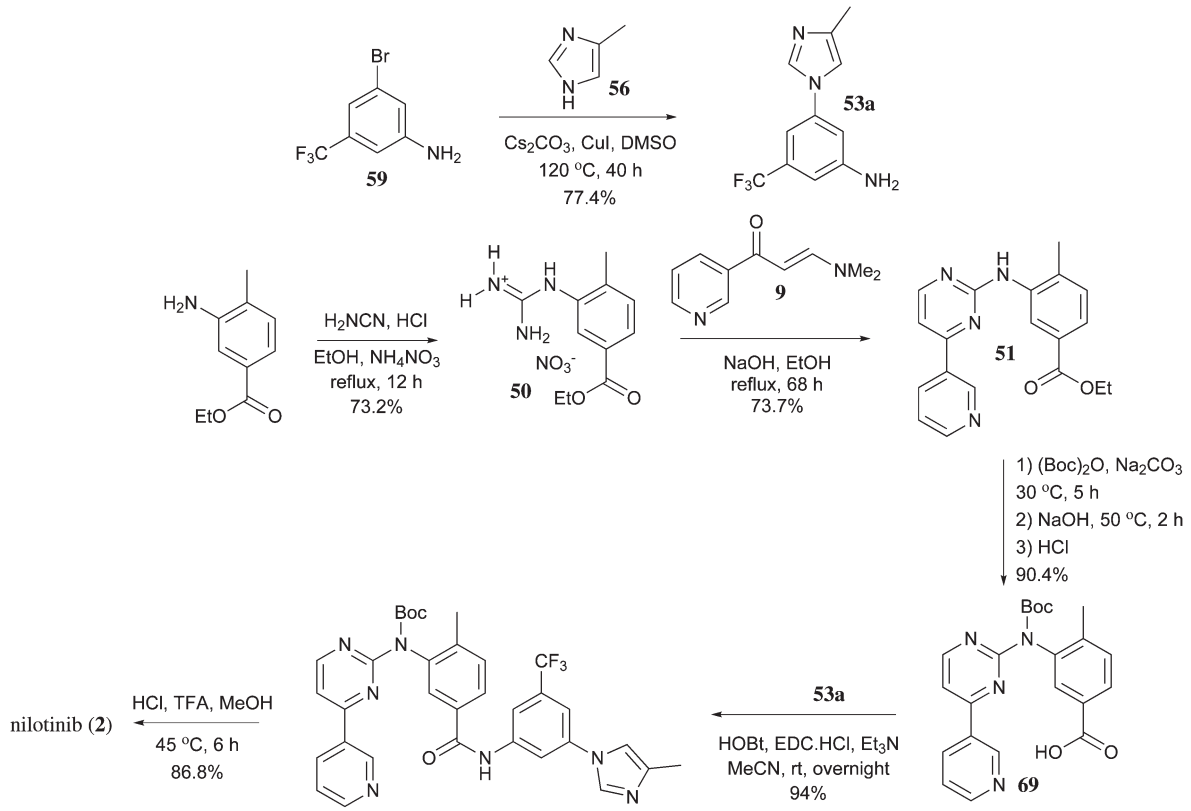
In 2010 Teva Pharmaceuticals patented a new copper catalysed coupling reaction to generate the key aniline intermediate (**53a**) (Scheme 29).[68] The transformation developed by Teva gave improved regioselectivity compared to the previously reported Ariad procedure (Scheme 27).[65] A combination of the chelating ligand, 8-hydroxyquinoline (**70**), copper(I) iodide and a mixture of calcium oxide and sodium hydroxide facilitated the coupling in reasonable yield. The reaction was heated at 120 °C until less than 5% of the 3-bromobenzene derivate (**59**) remained, which took 69 hours at the kilogram scale. The 2.3 kg of solid crude material was purified by precipitation from a concentrated ethyl acetate solution, on addition of petroleum ether, to give 954 g (47.5% yield) of 99.7% purity product. Only a small amount (0.13%) of the 5-methyl regioisomer (**53b**) impurity was detected. The product was



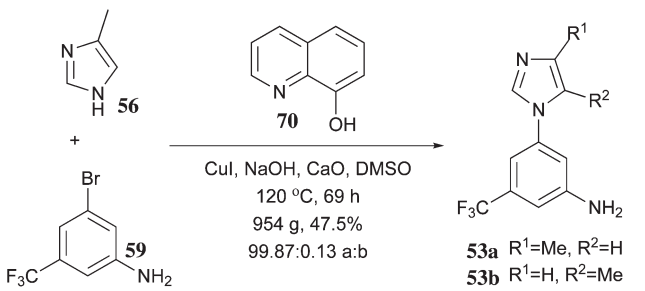
Scheme 26 Direct ester condensation to prepare nilotinib (**2**).



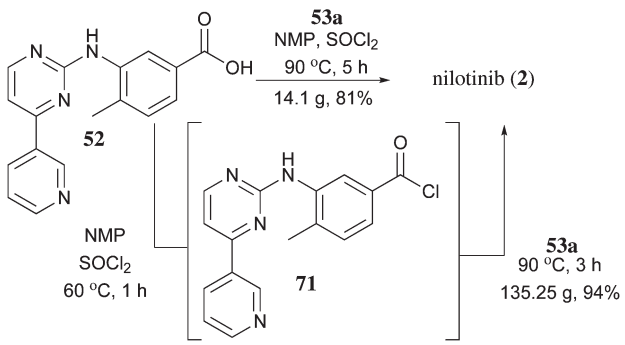
Scheme 27 Ariad Pharmaceuticals synthesis of nilotinib (**2**).



Scheme 28 The Chen route to nilotinib (**2**).



Scheme 29 Large scale synthesis of fragment **53**.

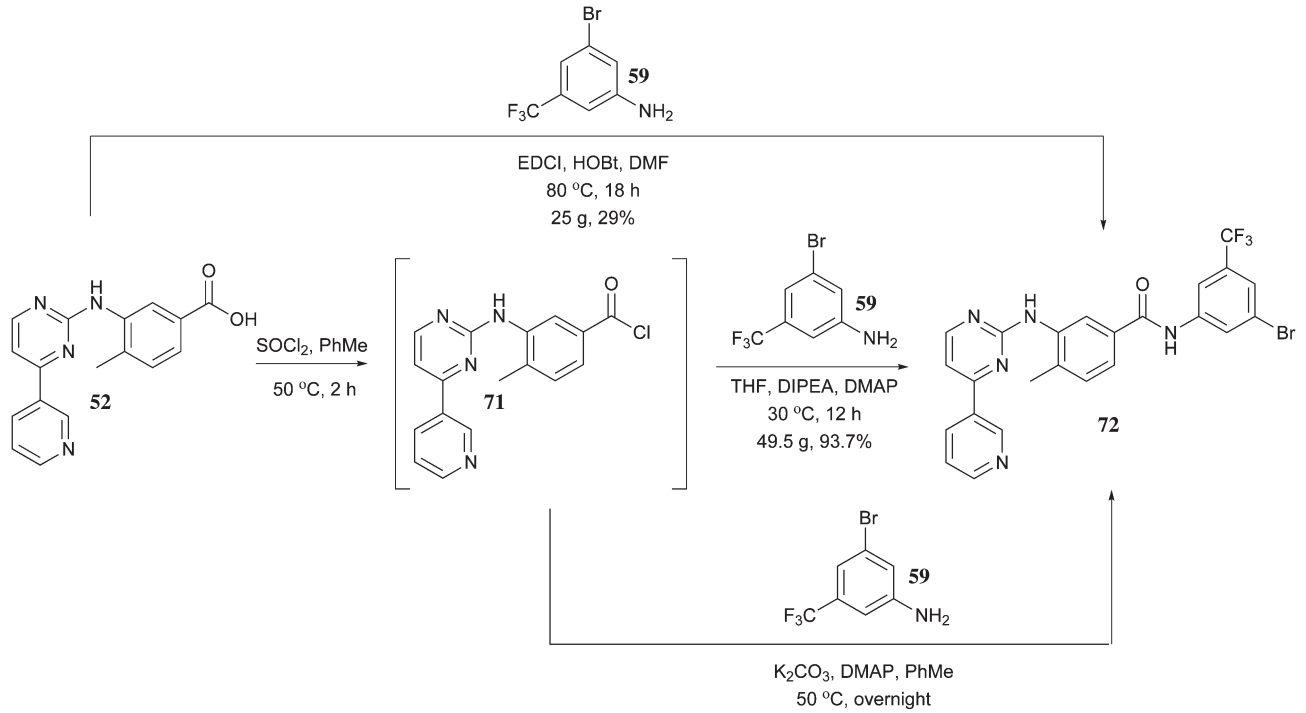


Scheme 30 Assembly of nilotinib (**2**).

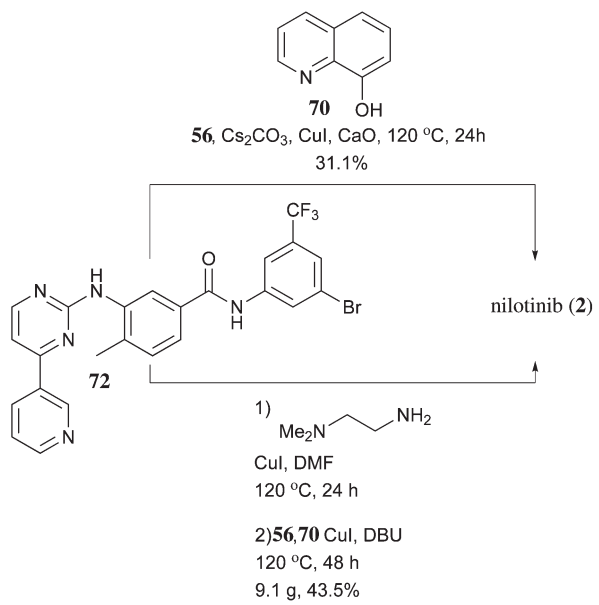
further purified to analytical purity by recrystallisation in a isopropanol–water solution.

Teva's assembly of the final API (**2**) was also described in the same patent (Scheme 30).[68] Notably the use of the diethyl phosphorocyanidate coupling agent **54** used by Novartis (Scheme 21) was avoided, the carboxylic acid **52** being activated *via* its corresponding acid chloride **71** instead. The final amide coupling could be conducted as a one pot process in the presence of the aniline coupling partner (**53a**) to give nilotinib (**2**) in 81% yield. Higher yields (94%) were obtained when the acid chloride **71** was first isolated and then coupled with the aniline **53a**.

An alternative sequence was also described which led to the preparation of the late stage intermediate **72** (Scheme 31).[68] Two main coupling methods were then employed, *via* either the acid chloride intermediate **71** or the HOBt activated ester. Unfortunately, the direct acid coupling procedure using EDCI as the activator gave a low yield of the desired product **72**. Nevertheless, better results were obtained when the acid chloride **71** was used in the coupling reaction, especially when the subsequent amidation process was conducted in THF using DIPEA as the base in the presence of DMAP as a co-catalyst. While a yield was not provided for the alternative amidation using potassium carbonate as base, the product (**72**) was reported to be obtained in 81% purity with only 9% of the acid **52** remaining in the mixture.[15]



Scheme 31 The alternative coupling sequence by Teva to the late stage intermediate **72**.



Scheme 32 Copper catalysed coupling to form nilotinib (**2**).

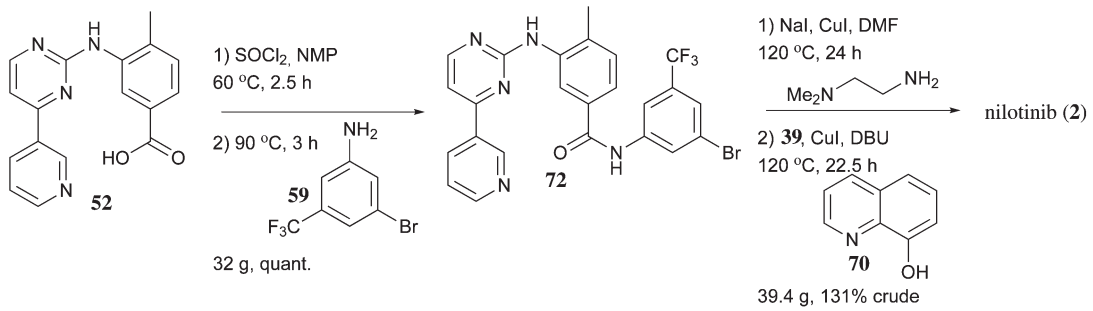
The final coupling (Scheme 32) with 4(5)-methylimidazole (**56**) to yield nilotinib (**2**) utilised similar coupling conditions to that previously described for the simple union to furnish the aniline fragment **53a** (Scheme 29).[68] Unfortunately, this linear route to nilotinib (**2**), although giving good overall yields to compound **72**, still suffers from a low yield (43.5%) in the final step yielding nilotinib (**2**). The crude product was quoted to be obtained in good yield (26.9 g and 69% purity). However, it appears that there were significant losses during subsequent Celite filtrations to purify the product to 99.1% although no indication of the 5-methyl regioisomer as a potential by-product was made.

In a follow up patent,[69] Teva pharmaceuticals scientists published an updated procedure for the final coupling step (Scheme 33). Their coupling conditions included the further addition of sodium iodide leading to a reduced reaction time compared to the previous patent (Scheme 32). It is however difficult to fully assess the effectiveness of this new route since the yield has only been reported as a mass of crude nilotinib. A quick calculation based on the amount of starting material used in this step reveals that there must be significant impurities in their crude product to account for the additional mass obtained.[15]

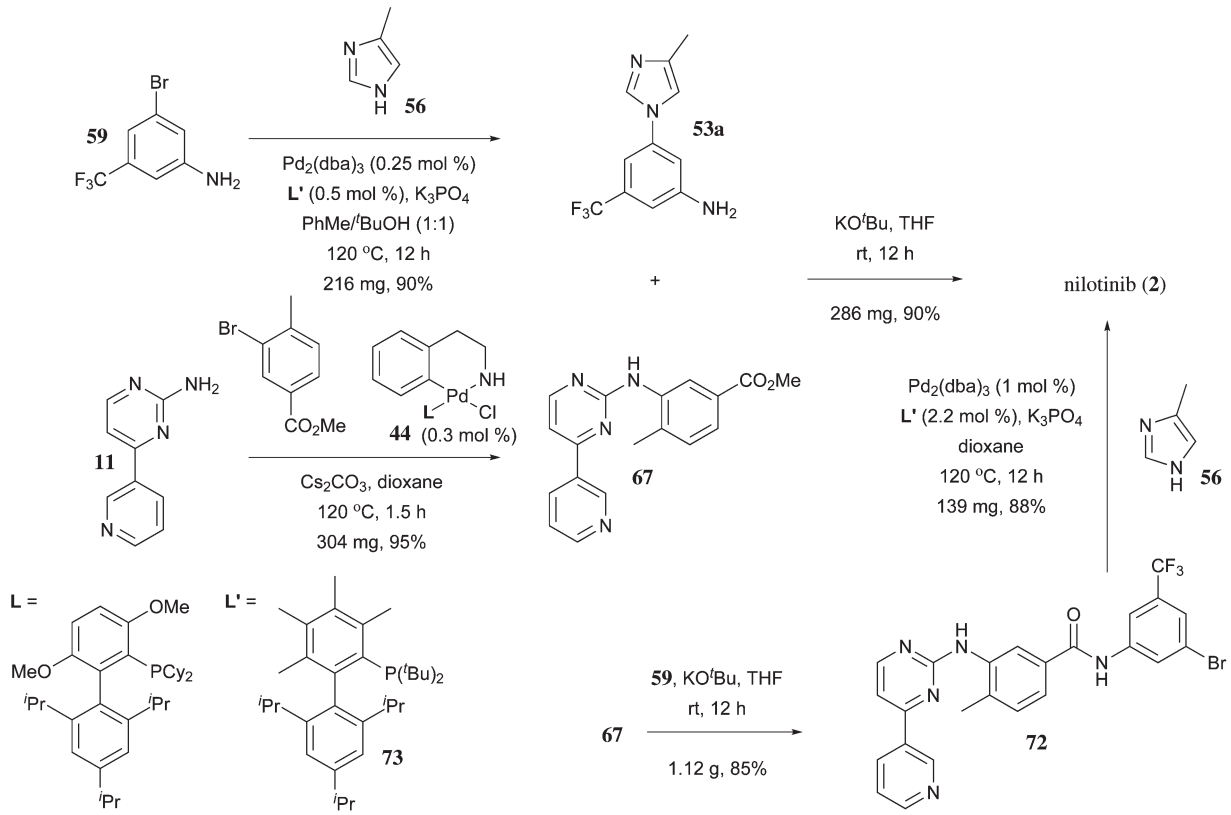
3.7. The Buchwald synthesis of nilotinib

Perhaps a better solution to the regioselectivity problem of the coupling of 4(5)-methylimidazole (**56**) is that reported recently by the Buchwald group.[70] They found that the inhibitory effect of imidazoles on the formation of a catalytic palladium(0)–ligand complex could be overcome by pre-activating $Pd_2(dba)_3$ with ligand **73** prior to the addition of the imidazole. When pre-activated in this way the catalyst system is remarkably effective for the regioselective coupling of unsymmetric imidazoles with aryl bromides, chlorides and triflates.

This methodology was applied to a palladium-catalysed coupling of 4(5)-methylimidazole (**56**) with aryl bromide



Scheme 33 Teva's synthesis of nilotinib (**2**).



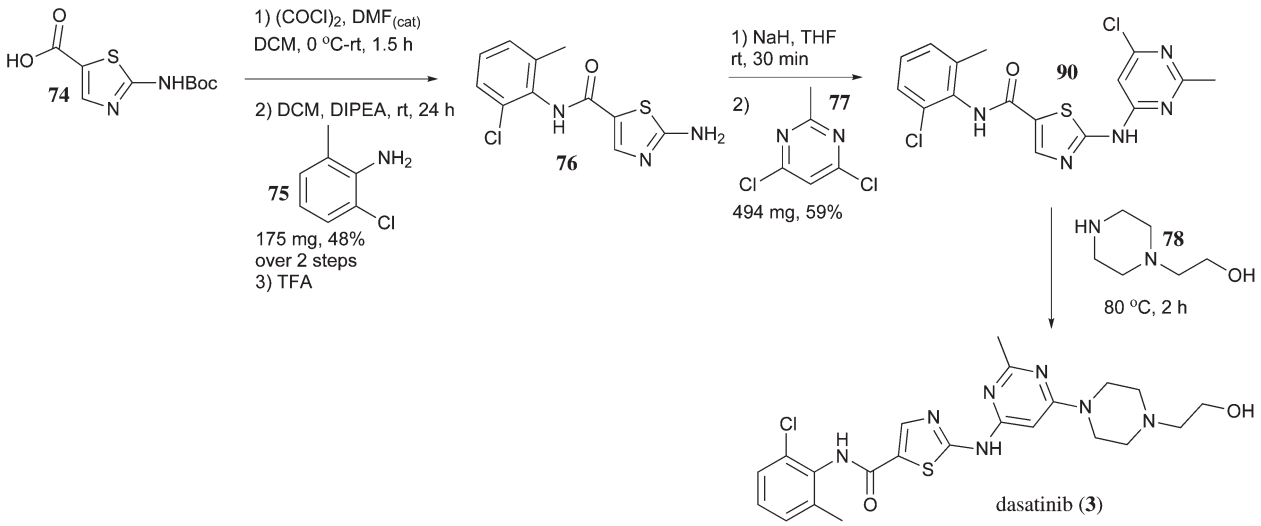
Scheme 34 The Buchwald synthesis of nilotinib (**2**).

intermediate **72** in the final step of a 2-step synthesis of nilotinib from ester intermediate **67** (Scheme 34).[70] It may however be undesirable to use homogeneous transition metal catalysis in the final step of an API synthesis due to the problems associated with removing all traces of the transition metal from the final product. This can be avoided by employing the same palladium catalysed coupling in the initial stages of nilotinib synthesis and was also demonstrated in the same publication.[70]

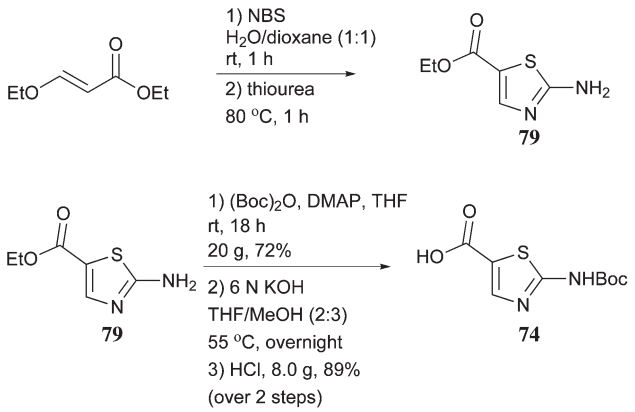
Coupling of 4(5)-methylimidazole (**56**) with the commercially available 3-(trifluoromethyl)-5-bromoaniline (**59**) gave the desired regioisomer **53a** in 90% yield.[70] This is a notable improvement on the slow copper couplings, and low yielding S_NAr reactions previously reported for synthesis of this important intermediate.

4. Synthesis of dasatinib

Dasatinib, (**3**) *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide hydrochloride monohydrate [BMS-354825, CAS 302962-49-8], is produced by Bristol-Myers Squibb (BMS) and sold under the trade name Sprycel (Fig. 1).[71] The compound is



Scheme 35 The BMS original discovery synthesis of dasatinib (**3**).



Scheme 36 Preparation of the protected 2-aminothiazole-5-carboxylate (**74**).

a structurally distinct pharmaceutical substance compared to the related imatinib (**1**) and second generation nilotinib (**2**). Like nilotinib (**2**) it displays increased potency against Bcr-Abl resistant forms of CML and in certain studies it has been indicated as having a 10 fold greater potency than nilotinib (**2**).[72] This increased potency arises from the fact it is a high affinity target for both Src/Abl and c-Kit family tyrosine kinase inhibitors.[73,74]

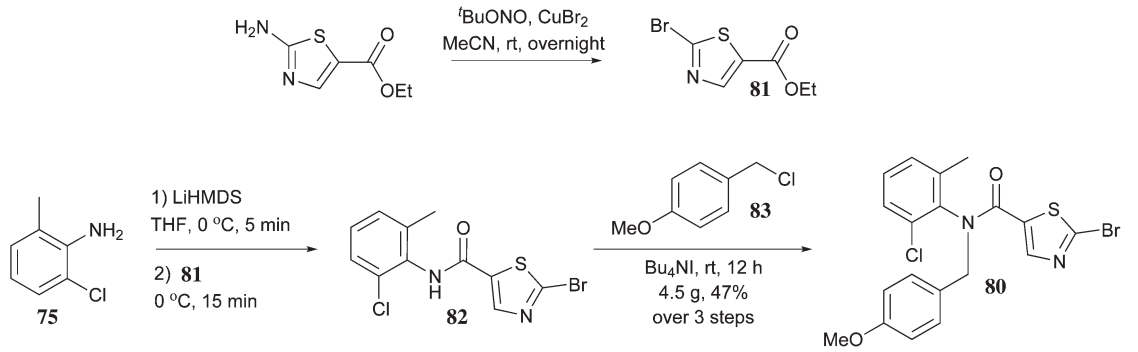
It has been shown that dasatinib (**3**) has high activity against many forms of imatinib (**1**) resistant Bcr-Abl and c-Kit mutants.[74–78] From a molecular understanding gained by analysis of a crystal structure of dasatinib (**3**) bound by the Abl complex it has been shown that there is a greater conformational flexibility in the binding of dasatinib (**3**) to the protein activation loop compared to imatinib (**1**). Furthermore, dasatinib (**3**) forms less general interactions with the rest of the protein loop residues especially at sites where mutation ultimately interferes with imatinib (**1**) specific binding.[79] These less stringent conformational requirements may also explain the increased activity of dasatinib (**3**) against imatinib-resistant forms of c-Kit.

4.1. The Bristol-Myers Squibb (BMS) discovery route

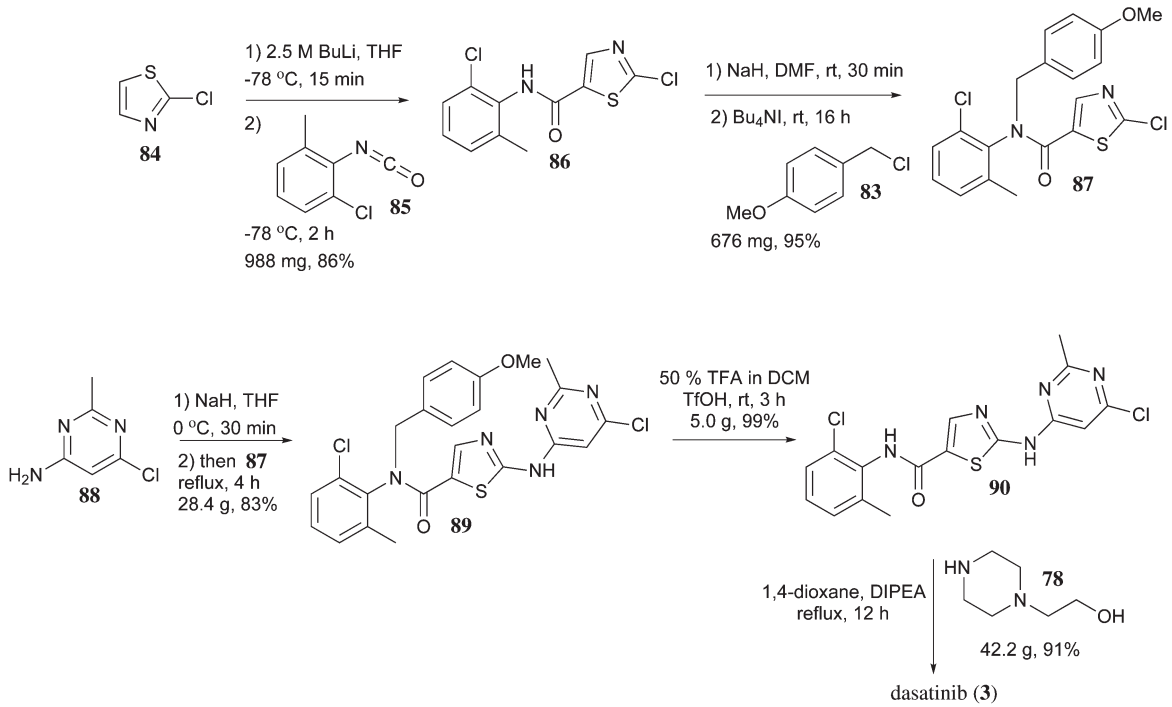
A number of patents describing the synthesis of a large number of cyclic protein kinase inhibitors were released by BMS between 2000 and 2005.[71,80–83] The first published route to dasatinib (**3**) begins with the protected 2-aminothiazole-5-carboxylate **74** (Scheme 35). This material was activated as the acid chloride, coupled with 2-chloro-6-methylaniline (**75**), and deprotected to provide the coupled product **76** in moderate yield. The aniline intermediate **76** was then treated with an excess of sodium hydride and used to displace a chloride from pyrimidine fragment **77**. The final union of the piperazine **78** was conducted under basic anhydrous conditions to give dasatinib (**3**) although again like many previous syntheses, no yield was reported for this final step.

While the preparation of the protected 2-aminothiazole-5-carboxylate (**74**) starting material is not described in the original patents,[15] a method was later published in two medicinal chemistry papers by BMS scientists.[72,84] Ethyl 2-aminothiazole-5-carboxylate (**79**) is commercially available or easily prepared from thiourea in a high yielding (90%) one pot reaction (Scheme 36).[85] The aminothiazole (**79**) was protected as the tertiary butyl carbamate prior to ester hydrolysis to give the material (**74**) required for the discovery route.

Also described was a route to an advanced PMB protected amide fragment **80** (Scheme 37).[71,80–83] Aniline **75** was directly condensed with the thiazole ethyl ester **81** under base catalysed conditions. The resulting secondary amide **82** was then *N*-protected by alkylation with *p*-methoxy benzylchloride (**83**) in modest yield furnishing compound **80.** Although the experimental details were disclosed for the amide coupling and



Scheme 37 Synthesis of an advanced PMB protected amide fragment (**80**).

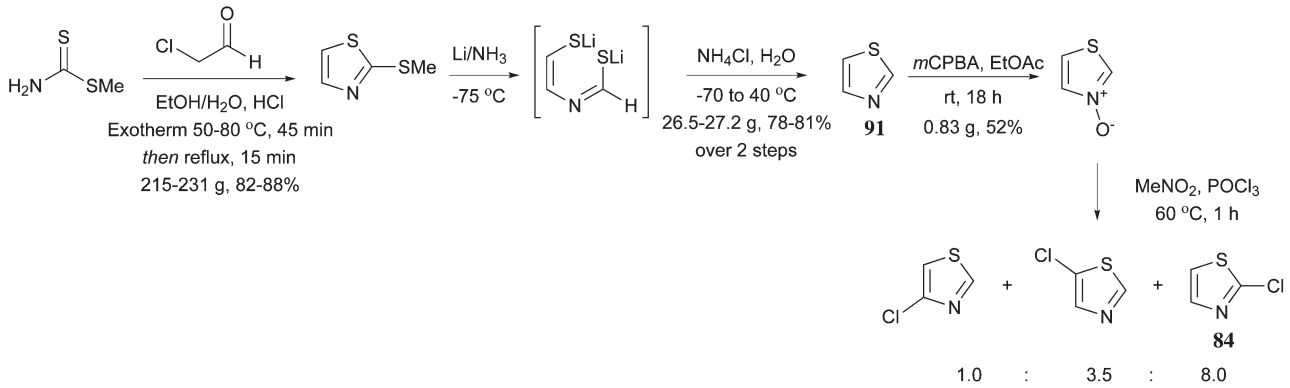


Scheme 38 BMS synthesis of dasatinib (**3**) from 2-chlorothiazole (**84**).

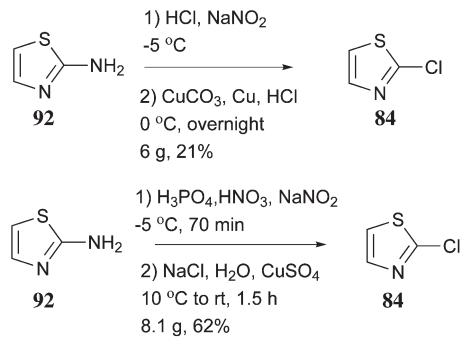
subsequent protection, the generation of bromothiazole **81** is only described briefly with reference to a similar synthesis.[15] The advanced intermediate **80** was also not further elaborated to dasatinib (**3**) but instead used to generate analogue compounds.

4.2. 2-Chlorothiazole as a starting material for dasatinib synthesis

BMS reported the preparation of dasatinib (**3**) in a high overall yield (61%) and on a multigram scale (42.2 g) starting from the basic chlorothiazole species **84** as outlined in Scheme 38.[72,84] An interesting and selective deprotonation of **84** with butyl lithium followed by addition of the resulting lithium anion into isocyanate **85** proceeded smoothly to afford the corresponding amide **86** after work-up. The carboxamide nitrogen atom was then readily protected as its PMB derivative **87** in very high yield. Next, a nucleophilic aromatic substitution of the thiazole 2-chloro substituent by an *in situ* generated sodium salt of 4-amino-6-chloro-2-methylpyrimidine (**88**) yielded the coupled product **89**. Deprotection of the 4-methoxybenzyl *N*-protecting group was realised by treatment of the substrate with a mixture of TfOH/TFA in DCM which allowed isolation of the corresponding chloropyrimidine **90**. Finally, the selective reaction of chloropyrimidine **90** with 1-(2-hydroxyethyl)piperazine (**78**) furnishes dasatinib (**3**), which can be readily converted to the corresponding hydrochloride salt of the API.



Scheme 39 Preparation of the key starting thiazole **84**.



Scheme 40 The Sandmeyer reaction of 2-aminothiazole (**92**).

Although this synthesis is efficient, it employs the proprietary intermediate **84** that is not trivial to access. Indeed, classical approaches such as direct halogenation require harsh conditions, are often laborious and give limited yield along with issues regarding regioselectivity of the process. For example, 1,3-thiazoles are known to undergo electrophilic attack at the 5 or a combination of both the 4 and 5 positions. In order to direct substitution to the 2-position the thiazole ring electronic properties need to be attenuated. The preparation of this key starting material **84** can be achieved in a few steps *via* chlorination of thiazole (**91**)[86,87] although this process is not entirely regioselective and results in a mixture of isomers requiring separation of the desired product through recrystallisation (Scheme 39).

Alternatively, the use of the Sandmeyer reaction with 2-aminothiazole (**92**), can be used to gain access to compound **84** (Scheme 40).[88,89] It should be noted that in both cases steam distillation was required to isolate the final chloro-material **84**.

Interestingly, the direct metallation of 1,3-thiazole (**91**) occurs exclusively at the 2 position. Therefore several derivatives can be prepared by treatment of the anion with various electrophiles. However, very few examples of quenching the intermediate anion with halide sources have been reported. A pseudo lithium–halogen exchange in which trichloroacetyl derivatives[90] (**93**) or tetrahalogenomethane[91] have been used as surrogate halogen donors are amongst the few useful procedures (Scheme 42).

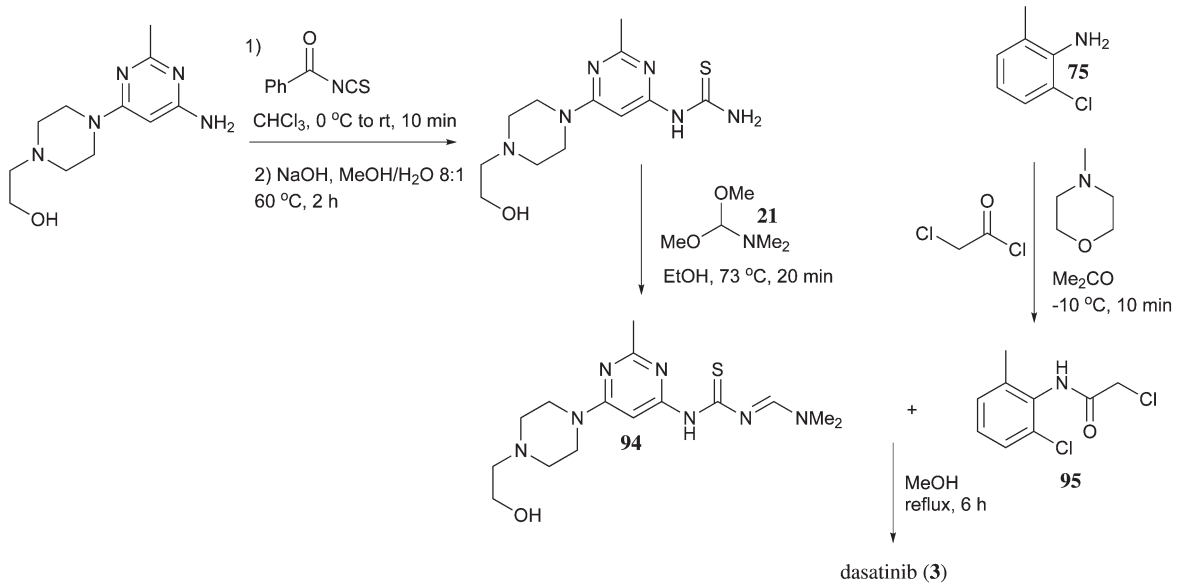
The BMS synthesis of dasatinib **3** (Scheme 38) also makes use of 4-amino-6-chloro-2-methylpyrimidine (**88**) as a starting material.[72,84] This pyrimidine coupling partner has been prepared from the more readily available 4,6-dihydroxy-2-methylpyrimidine (**94**) (Scheme 43).[92] Refluxing the dihydroxy pyrimidine (**94**) in phosphoryl chloride gave the intermediate 4,6-dichloro-2-methylpyrimidine (**77**) which features in many of the later dasatinib (**3**) syntheses. Compound **77** can be mono-aminated by superheating with concentrated ammonium hydroxide in a sealed Carius tube. Heating to higher temperatures resulted in the formation of 4,6-diamino-2-methylpyrimidine.

4.3. The late stage thiazole synthesis

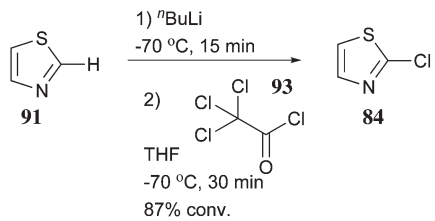
BMS have also proposed an alternative route to dasatinib (**3**) involving a late stage thiazole formation.[93] The patent describes assembling the thiazole unit of dasatinib (**3**) from a α-chloro carbonyl **95** and the *N*,*N*-dimethyl-*N*′-(carbamothioyl)-formimidamide derivative **94** (Scheme 41). While the patent does specify that dasatinib (**3**) can be synthesised by the route described, only general procedures based on the synthesis of analogous molecules were disclosed.

However, in a later work released by BMS, a route to dasatinib (**3**) was described in which the thiazole was also formed late in the synthesis.[94] Here, the substituted thiourea **96** was condensed with enone coupling partner **97** to form the aminothiazole **98** with the pyrimidine ring already in place (Scheme 44). The subsequent substitution reaction with 1-(2-hydroxyethyl)piperazine (**78**) proceeded well to give dasatinib (**3**) in good yield. Finally, the substituted thiourea **96** could obtained by reaction of 4-amino-6-chloro-2-methylpyrimidine (**88**) with ethoxycarbonyl isothiocyanate (**99**) followed by direct ester hydrolysis.

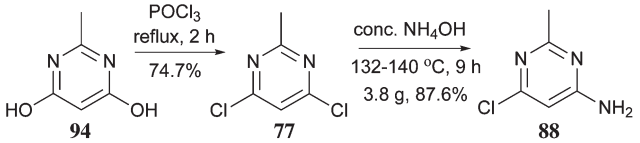
In addition, a coupling of thiourea with the advanced enone (**97**) has also been described (Scheme 44). This was followed by an S_NAr process to add the piperidine ring



Scheme 41 Proposed synthesis of dasatinib (**3**).



Scheme 42 Pseudo lithium–halogen exchange functionalisation of 1,3-thiazole (**91**).



Scheme 43 Synthesis of 4-amino-6-chloro-2-methylpyrimidine (**88**).

and provide the dasatinib precursor (**98**) in an improved 82% yield over the two steps. These same procedures have also been described in a subsequent paper from researchers at BMS.[95]

4.4. The Buchwald–Hartwig coupling approach to dasatinib

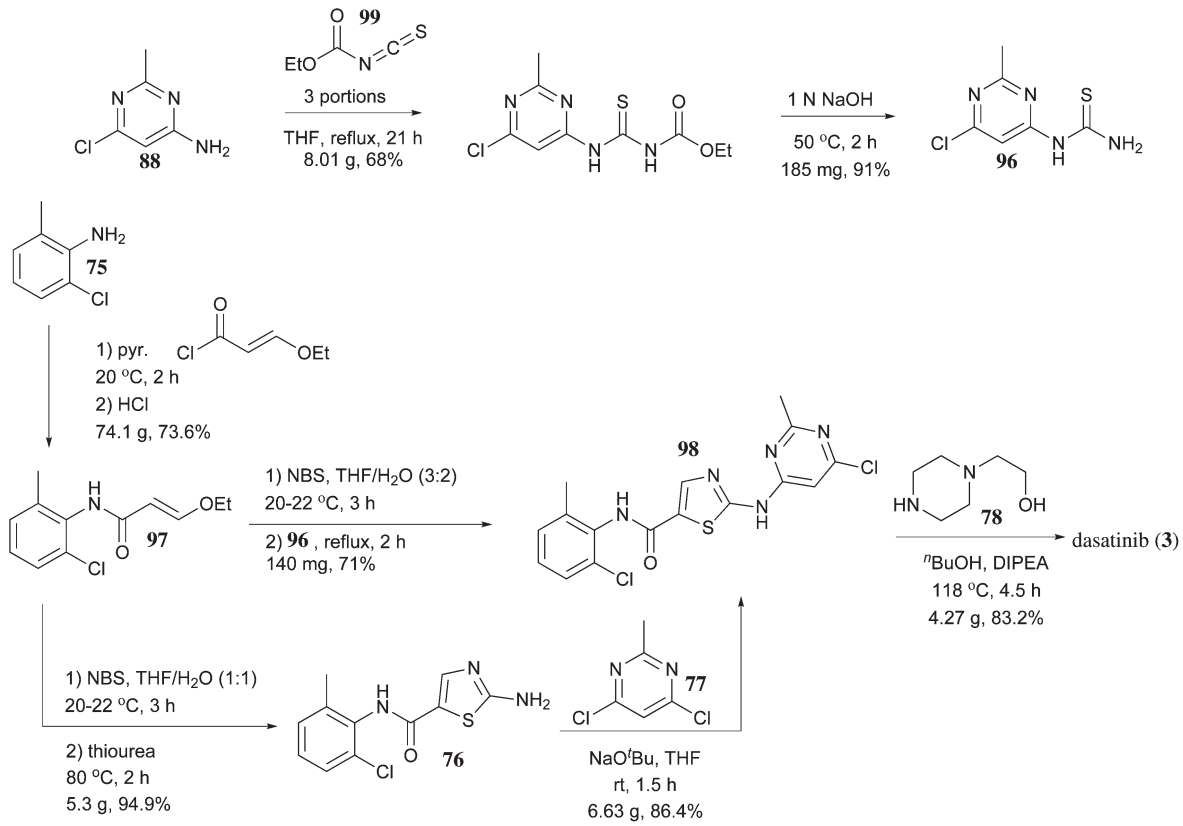
A Buchwald–Hartwig coupling reaction has also been utilised to form dasatinib (**3**) from aminothiazole **76,** 4,6-dichloro-2-methylpyrimidine (**77**) and 1-(2-hydroxyethyl)piperazine (**78**) (Scheme 45). Nucleophilic aromatic substitution of the piperazine (**78**) onto 4,6-dichloro-2-methylpyrimidine (**77**), is followed by Buchwald–Hartwig coupling with the aminothiazole (**76**) to yield dasatinib (**3**) in 80% overall yield.[94]

4.5. The late stage S_NAr reaction of piperazine to form dasatinib

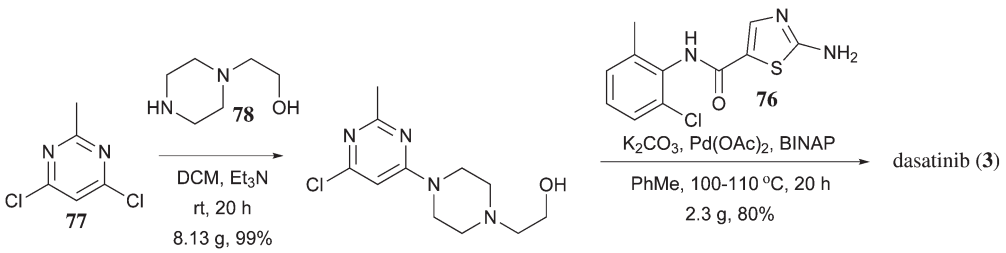
It has been shown that an additional added base is not required for the nucleophilic aromatic substitution of 1-(2-hydroxyethyl)piperazine (**78**) with the advanced pyrimidine (**90**) when the reaction is carried out in DMSO (Scheme 47).[96] The HCl salt or solvate of dasatinib (**3**) could be obtained by precipitation through the addition of isopropanol[96] or DCM[97] respectively. Gore *et al.* have also reinvestigated the conditions of the original BMS route (Scheme 35) to perform this S_NAr process without solvent but using a ten-fold excess of the 1-(2-hydroxyethyl)piperazine (**78**) (Scheme 47) and obtained the monohydrate of dasatinib (**3**) in 70% yield.[98]

4.6. The Nanjing Cavendish Bio-Engineering Technology route to dasatinib

Several methods for forming the amide bond of dasatinib (**3**) have been patented by Nanjing Cavendish Bio-Engineering Technology (Scheme 46). They have shown that the amide coupling step can be performed on elaborate structures such as **99** or simplified precursors such as **100,** as intermediates to dasatinib (**3**) with little variation in the obtained yields. Of the amide coupling methods tested, phenyl dichlorophosphite



Scheme 44 Aminothiazole formation from a substituted thiourea.



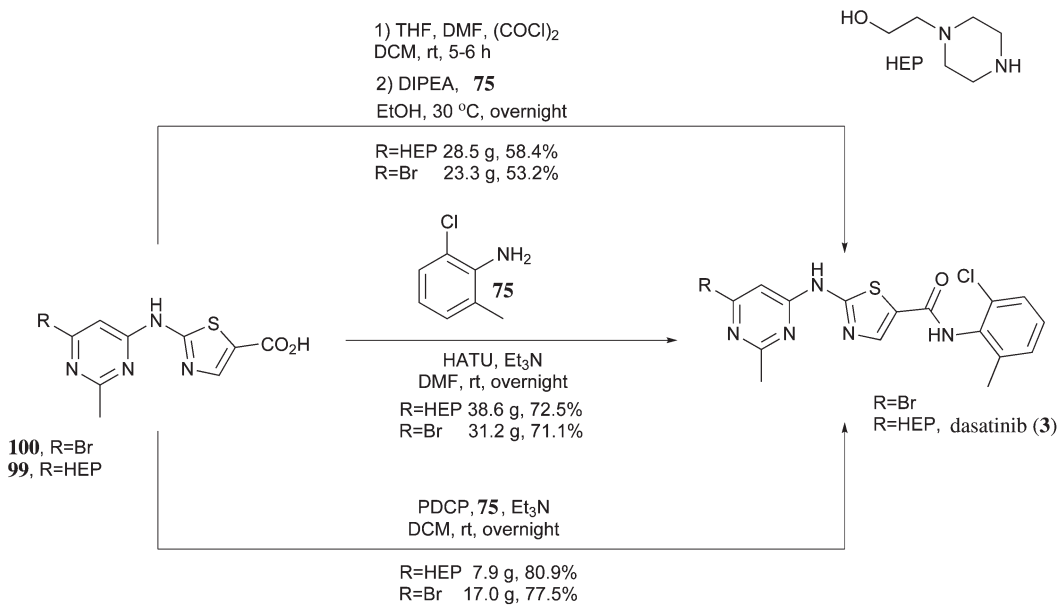
Scheme 45 Buchwald–Hartwig coupling of an aminothiazole (**76**) and a pyrimidine chloride.

(PDCP) proved to be the most effective coupling agent, providing yields over 77.5% in most cases.[99]

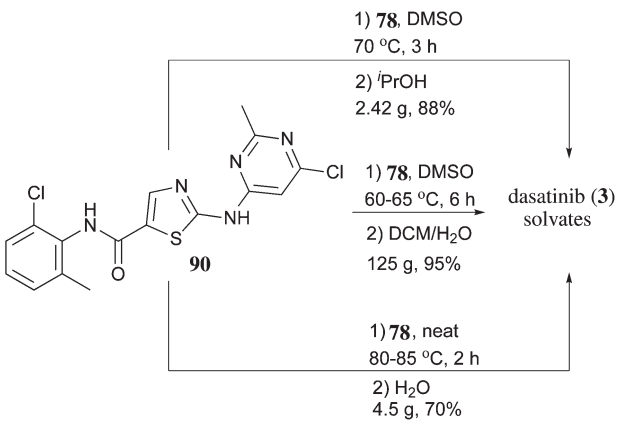
Li has also recently filed a patent describing the same amide coupling for the 6-chloro pyrimidine analogue of **100**.[100] Thionyl chloride was used to activate the acid and achieve the coupling in a modest 65% yield (Scheme 48).

Nanjing Cavendish Bio-Engineering Technology employed their amide coupling procedures (Scheme 46) in a four step linear synthesis of dasatinib (**3**) starting from commercially available 4,6-dichloro-2-methylpyrimidine (**77**) and 1-(2-hydroxyethyl)piperazine (**78,** Scheme 49).[99] Nucleophilic aromatic substitution of the starting materials was followed by Buchwald–Hartwig coupling reaction to install the thiazole ring (**101**), both reactions proceeded in good yield. Next, hydrolysis of the methyl ester (**102**) was achieved by heating the substrate with potassium hydroxide for three hours (96.7% yield, Scheme 49) or alternatively using sodium hydroxide (81.4% yield) at room temperature overnight. Addition of hydrochloric acid gave the acid intermediate **99** which could be subsequently coupled with 2-chloro-6-methylaniline (**75**) as shown in Scheme 46.[99]

An alternative four step synthesis of dasatinib (**101**) has also been reported by the same group (Scheme 50).[99] Nucleophilic aromatic substitution of methyl 2-chlorothiazole-5-carboxylate (**103**) with 6-bromo-2-methylpyrimidin-4-amine



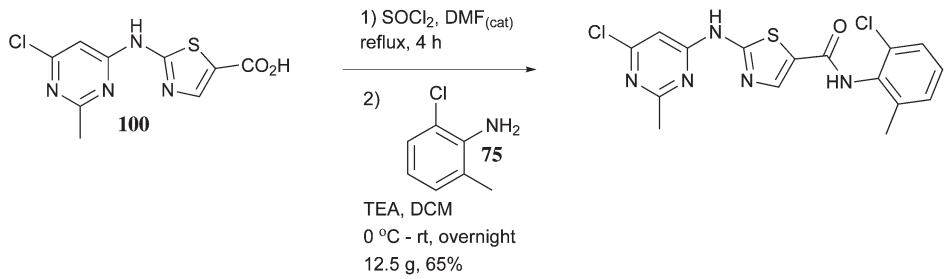
Scheme 46 Methods for forming the amide bond of dasatinib (**3**).



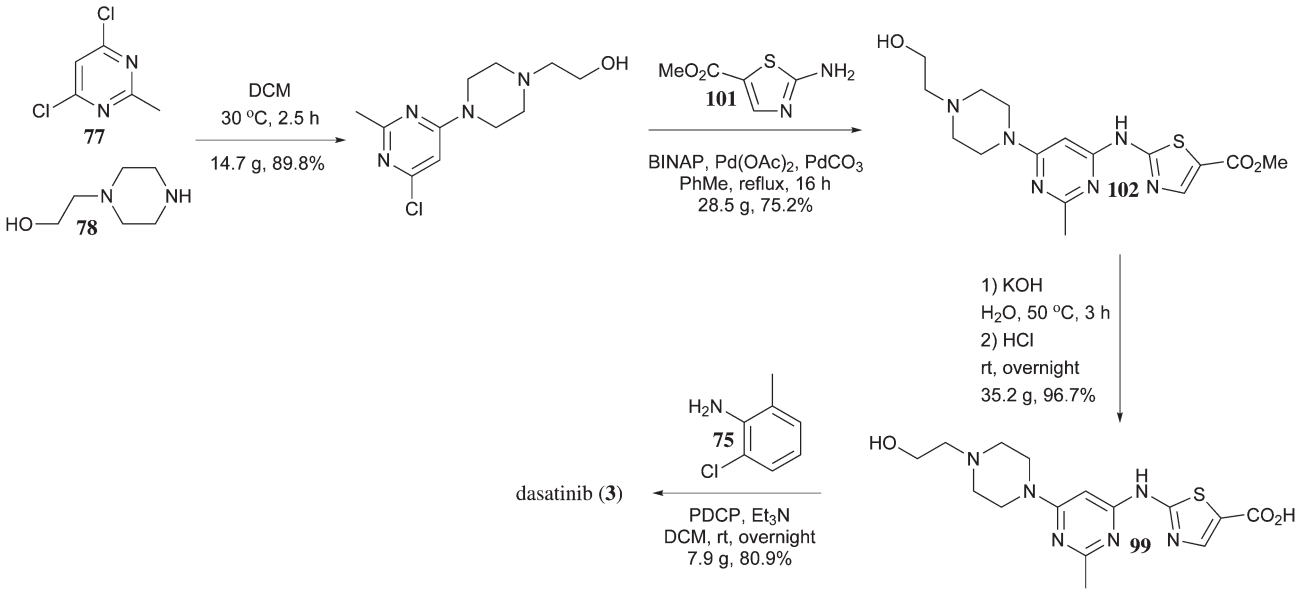
Scheme 47 S_NAr of 1-(2-hydroxyethyl)piperazine (**78**) without added base.

(**103**), followed by ester hydrolysis gave the core intermediate **104** in 78.4% yield. From this intermediate two separate sequences were investigated. Nucleophilic aromatic substitution of the piperazine ring (**78**) onto the pyrimidine (**104**) proceeded in good yield but the following phenyl dichlorophosphite (PDCP) activated amide bond formation was low yielding.[99] It is likely that this was due to poor activation of the methyl ester (**105**) since the same patent gave very good yields when using the free acid **99** under the same reaction conditions (Scheme 49). The alternative ester hydrolysis, amide coupling and S_NAr reaction sequence was more efficient, proceeding in an overall 42% yield over four steps.

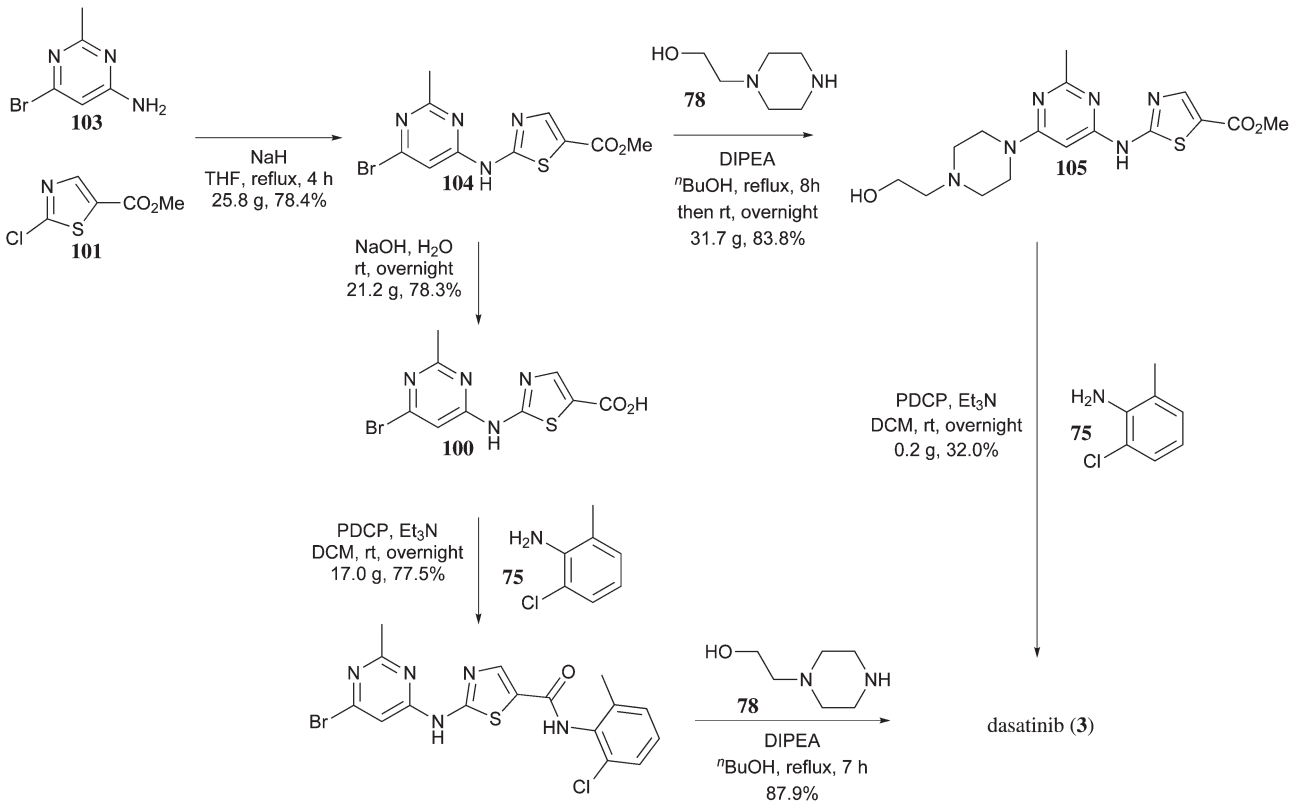
A range of terminal alcohol protection methods were also investigated in the Nanjing patent (Scheme 51).[99] Benzyl,



Scheme 48 Amide coupling by thionyl chloride activation of acid intermediate **100**.

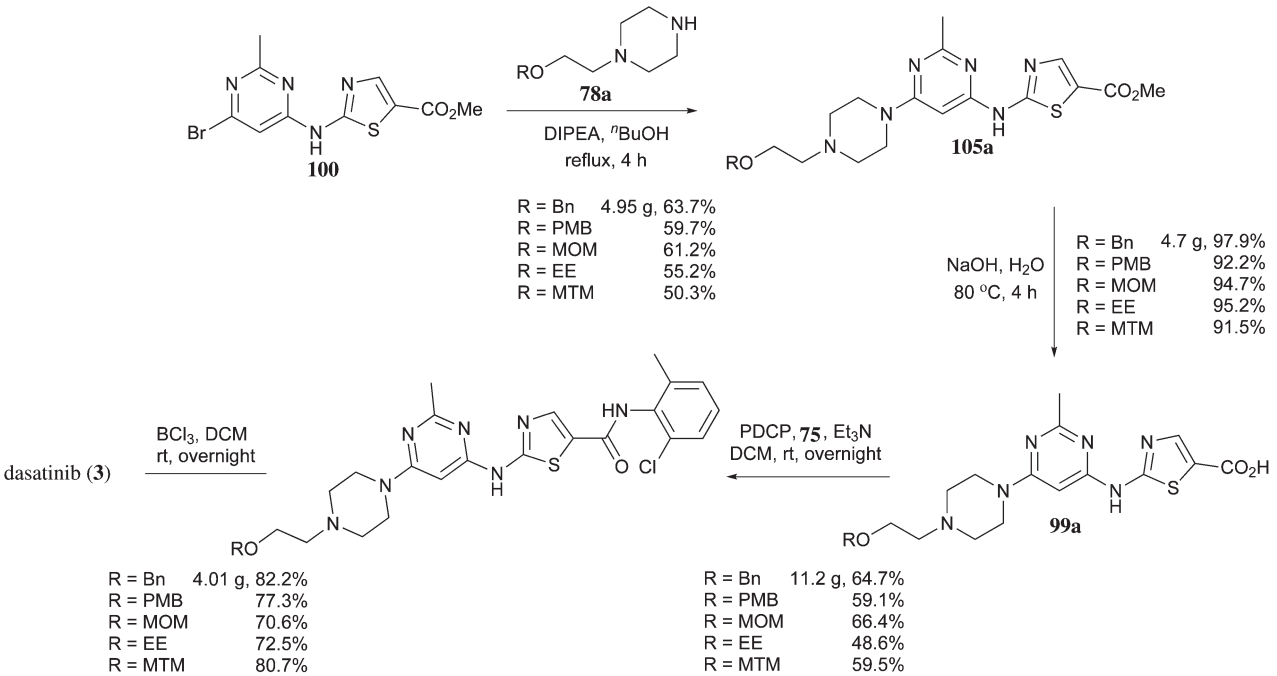


Scheme 49 Nanjing Cavendish Bio-Engineering Technology's synthesis of dasatinib (**3**).

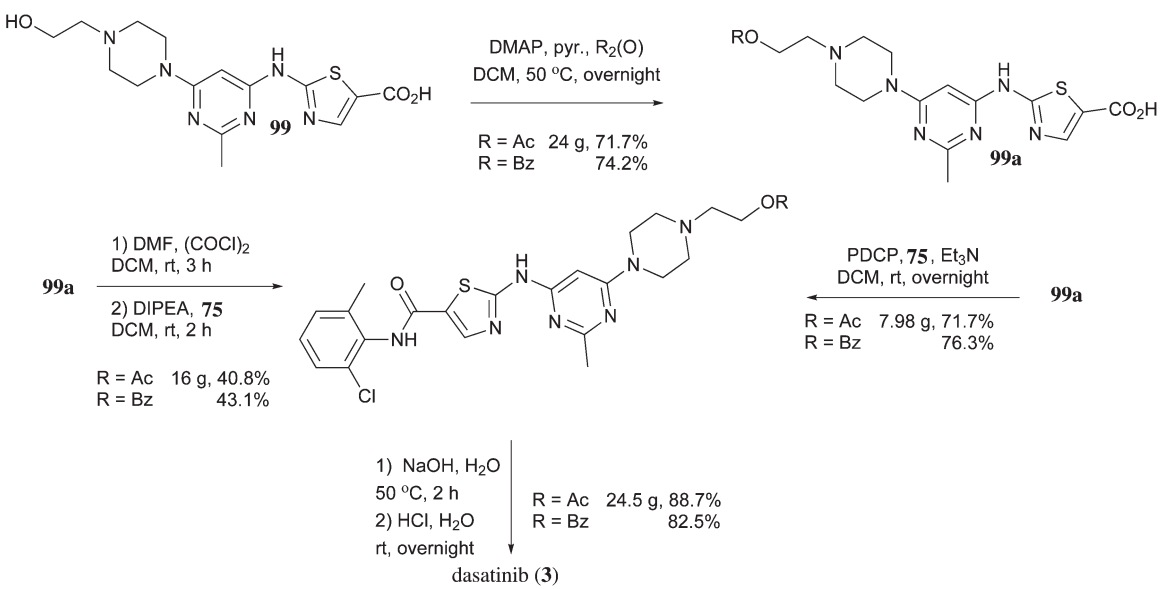


Scheme 50 Alternative sequences in Nanjing Cavendish Bio-Engineering Technology's synthesis of dasatinib (**3**).

paramethoxybenzyl, methoxymethyl ether, ethoxyethyl ether and methylthiomethyl ether protected 1-(2-hydroxyethyl)-piperazines (**78a**) were utilised in an analogous synthesis to that shown in Scheme 50. While the yield for the PDCP activated amide formation was improved using the protected intermediates **105**, it is perhaps more likely that



Scheme 51 Synthesis of dasatinib (**3**) using protected 1-(2-hydroxyethyl)piperazines (**78a**).

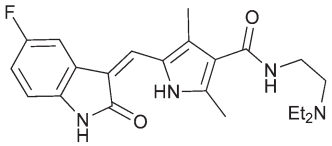
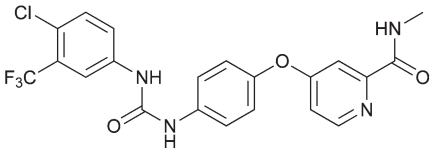
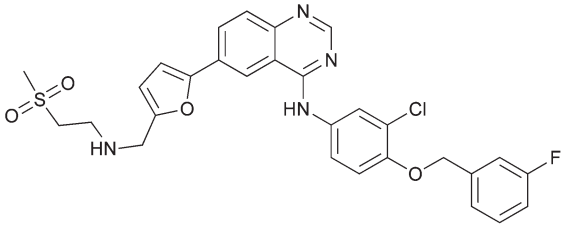
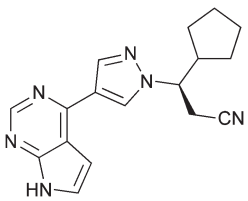
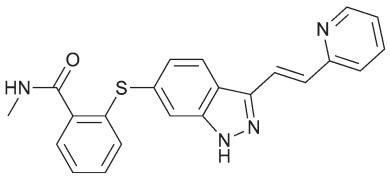
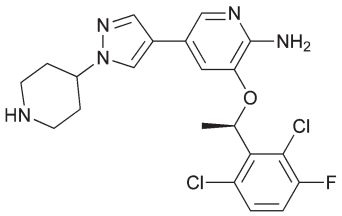
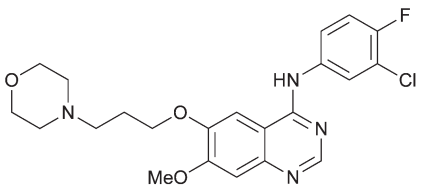


Scheme 52 Acetyl and benzoyl protected route to dasatinib (**3**).

this is as a result of employing the free acid instead of the methyl ester of the 5-thiazole carboxylic acid. However, the reduced yields for the protected 1-(2-hydroxyethyl)-piperazines introduction and the added boron trichloride deprotection step meant that there was no apparent benefit to using these protecting groups in this synthesis.

Benzoyl and acetyl protection methods were also investigated (Scheme 52).[99] While the yields for the PDCP activated amide formation were similar to those of the free alcohol substrate (**99**), the added protection and deprotection steps make this an unattractive route to dasatinib (**3**), especially when compared to their high yielding four step process described in Scheme 49.

Table 1 Other tyrosine kinase inhibiting pharmaceutical agents which are currently on the market or in phase III trials

Molecule	Name	Marketed by	Additional comments
	Sunitinib[101] [SU11248, CAS: 341031-54-7]	Pfizer	Sold under the trade name Sutent.
	Sorafenib[102] [BAY 43-9006, CAS: 284461-73-0]	Bayer	Sold under the trade name Nexavar.
	Lapatinib[103] [GSK 572016, CAS: 231277-92-2]	GlaxoSmithKline	Sold under the trade names Tykerb (US) and Tyverb (Europe).
	Ruxolitinib[104] [INCB 018424, CAS: 941678-49-5]	Incyte	Sold under the trade name Jakafi.
	Axitinb[105] [AG 013736, CAS: 319460-85-0]	Pfizer	Sold under the trade name Inlyta.
	Crizotinib[106] [PF 02341066, CAS: 877399-52-5]	Pfizer	Sold under the trade name Xalkori.
	Gefitinib[107] [ZD 1839, CAS: 184475-35-2]	AstraZeneca and Teva Pharmaceuticals	Sold under the trade name Iressa.

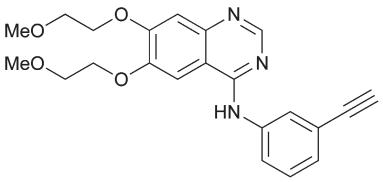
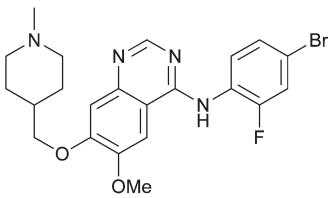
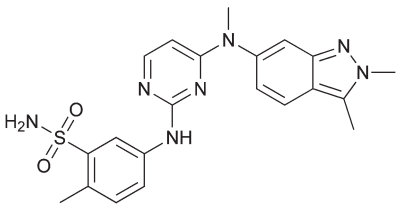
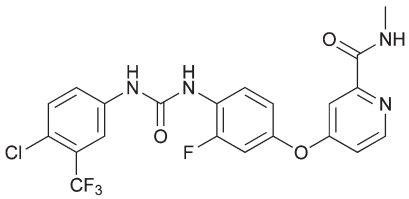
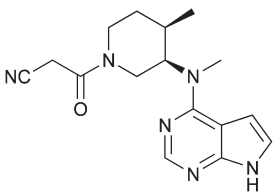
5. Other anticancer pharmaceuticals in the 'tinib' stem class

While imatinib (**1**), nilotinib (**2**) and dasatinib (**3**) may be the only Bcr-Abl inhibitors on the market today they are not the only drugs which inhibit tyrosine kinases. There is an abundance of new candidates appearing in the literature with ever increasing effectiveness as anticancer pharmaceuticals.[2] Tables 1–4 show a number of established tyrosine kinase inhibiting drugs as well as several in phase III clinical trials.

6. Conclusions

In the two decades since the discovery of imatinib (**106**) was first described by Ciba-Geigy AG, there has been intense interest in this API and its analogues. However, much of the subsequent synthetic developments have been limited

Table 2 Other tyrosine kinase inhibiting pharmaceutical agents which are currently on the market or in phase III trials

Molecule	Name	Marketed by	Additional comments
	Erlotinib[108] [NSC 718781, OSI 744, R 1415, CAS: 183321-74-6]	Genentech and OSI Pharmaceuticals (US only), Roche (non-US)	Sold under the trade name Tarceva.
	Vandetanib[109] [CH 331, ZD 6474, CAS: 443913-73-3]	AstraZeneca	Sold under the trade name Caprelsa.
	Pazopanib[110] [GW 786034, CAS: 444731-52-6]	GlaxoSmithKline	Sold under the trade name Votrient.
	Regorafenib[111] [BAY 73-4506, CAS: 755037-03-7]	Bayer and Onyx	Submitted for marketing approval.
	Tofacitinib[112] [formerly tasocitinib, CP 690550, CAS: 477600-75-2]	Pfizer	Submitted for marketing approval.
	Bosutinib[113] [[SKI 606, CAS: 380843-75-4]	Pfizer	Phase III trials were completed in December 2010.

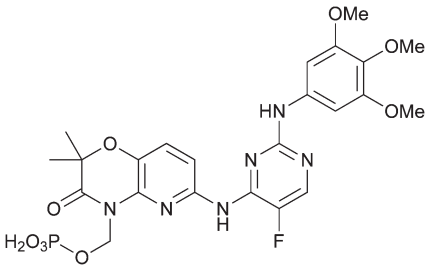
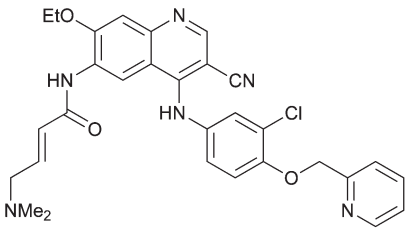
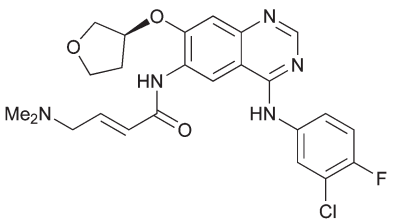
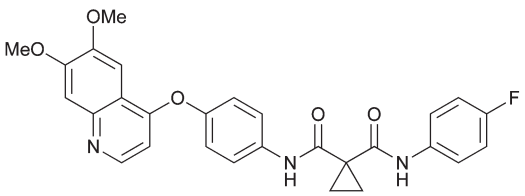
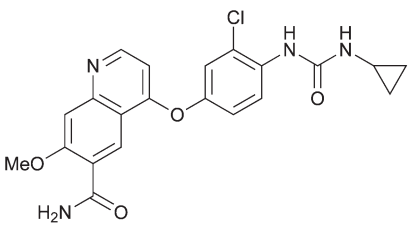
to reinvestigations of the original route described by Zimmermann. The guanidine **7** coupling with the enone **9**, the reduction of nitro intermediate **8** and the subsequent amide coupling have all been extensively optimised and a range of alternative conditions have been reported for these transformations.

After the merger of Ciba Geigy AG with Sandoz, Novartis went on to develop several alternative routes to imatinib (**1**) based on a late stage condensation which built the pyrimidine core from advanced guanidine intermediates. Another notable route makes use of a simplified aminopyrimidine pyridin intermediate (**11**) which has been used in a number of interesting S_NAr and metal catalysed coupling reactions.

Enabling technologies have also been effectively used to produce imatinib and a selection of analogues. Microwave heating was used with great effect by Leonetti and co-workers to improve a number of the steps in their solid phase synthesis of imatinib (**1**). Our own work has also demonstrated the importance of enabling technologies in drug synthesis with our flow chemistry based protocol providing imatinib (**1**) and several analogues quickly and with minimal manual intervention.

The preparation of nilotinib (**2**) follows a similar route to that optimised for imatinib (**1**). The primary differences being the reversal of the acid and amide coupling partners, and the replacement of the piperazine end of the API with an imidazole fragment. The majority of published research from Novartis in this area has been concerned with the preparation of the imidazole fragment which makes up the unique feature of nilotinib (**2**). Preparations of this fragment typically begin with the trifluoromethyl substituent already in place. Copper(I) catalysis or simple S_NAr are commonly used to introduce the 4(5)-methylimidazole substituent. Several nitration/reduction

Table 3 Other tyrosine kinase inhibiting pharmaceutical agents which are currently on the market or in phase III trials

Molecule	Name	Marketed by	Additional comments
	Fostamatinib[114] [R 788, CAS: 901119-35-5]	AstraZeneca and Rigel	In phase III clinical trials.
	Neratinib[115] [HKI 272, CAS: 698387-09-6]	Pfizer, Wyeth and Puma Biotechnology	In phase III clinical trials.
	Afatinib[116] [BIBW 2992, CAS: 850140-72-6]	Boehringer Ingelheim	In phase III clinical trials.
	Cabozantinib[117] [XL 184, BMS 907351, CAS: 849217-68-1]	Exelixis	In phase III clinical trials.
	Lenvatinib[118] [E 7080, ER 203492-00 CAS: 417716-92-8]	Eisai	In phase III clinical trials.

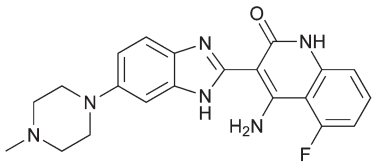
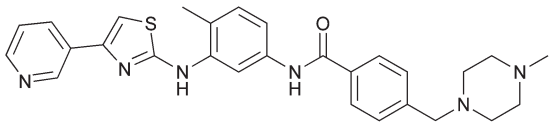
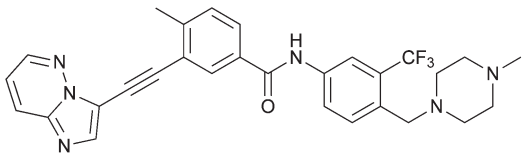
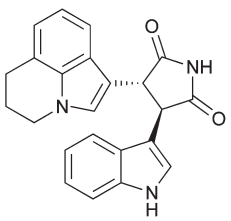
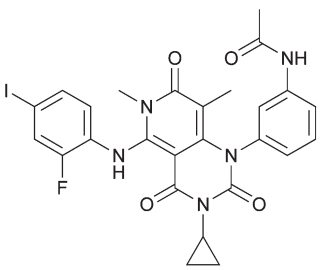
processes, a Hoffmann rearrangement and palladium catalysed Buchwald amination have all been used to introduce the amine substituent required for coupling to the nilotinib core.

The aminopyrimidine pyridin intermediate (**11**), as used in several imatinib (**1**) preparations, has also been used in a Buchwald coupling with an iodo intermediate (**68**) to provide nilotinib (**2**). Teva Pharmaceuticals have also described an alternative linear route to nilotinib (**2**) which couples 4(5)-methylimidazole to advanced intermediate **72**.

Most of the significant developments in the preparation of dasatinib (**3**) have been described by BMS scientists. The key reaction step in all the described routes is the introduction of the thiazole ring. In the original BMS route this was achieved by using a protected 2-aminothiazole-5-carboxylate (**74**) starting material which can be prepared in two steps. Later routes from BMS made use of 2-chlorothiazole as a starting material to obtain dasatinib (**3**) in higher overall yields. While this starting material can be prepared by chlorination, or direct metallation of thiazole (**91**), or by performing the Sandmeyer reaction on 2-aminothiazole (**92**), there is still room for further development of simple procedures to produce this material on a large scale. BMS have also published two routes to dasatinib (**3**) which form the thiazole ring late in the synthesis by condensing thiourea containing intermediates with α-chloro carbonyls or enones.

The introduction of 1-(2-hydroxyethyl)piperazine (**78**) by an S_NAr reaction is common to many of the published routes to

Table 4 Other tyrosine kinase inhibiting pharmaceutical agents which are currently on the market or in phase III trials

Molecule	Name	Marketed by	Additional comments
	Dovitinib[119] [TKI 258, CAS: 405169-16-6]	Novartis	In phase III clinical trials.
	Masitinib[120] [CAS: 790299-79-5]	AB Science	In phase III clinical trials.
	Ponatinib[121] [AP 24534, CAS: 943319-70-8]	Ariad	In phase III clinical trials.
	Tivantinib[122] [ARQ 197, CAS: 905854-02-6]	ArQuele and Daiichi Sankyo	In phase III clinical trials.
	Trametinib[123] [GSK 1120212, JTP 74057, CAS: 871700-17-3]	GlaxoSmithKline	In phase III clinical trials.

dasatinib (**3**). This step of the synthesis has received some attention and a number of alternative procedures have been reported on multigram scales without using added base. Nanjing Cavendish Bio-Engineering Technology have thoroughly investigated the effect of protecting the terminal alcohol, on the amide coupling of 2-chloro-6-methylaniline with simplified and advanced intermediates in several alternative routes.

As yet, no one has reported the use of other enabling methods to prepare either nilotinib (**2**) or dasatinib (**3**). There is clearly a need to make use of the synthetic chemist's modern tools, particularly continuous flow processing, to expedite the efficient preparation of these pharmaceuticals. Many of the routes to these drugs contain steps which require high temperatures and long reaction times. These processes could benefit from the superheating which can be achieved in a pressurised flow reactor. Other opportunities could be found in using cooled continuous flow reactor technology to scale up vigorous reactions which have so far only been utilised on a small laboratory scale. These are just a few of the potential applications of flow processing to the preparation of these important molecules; we expect to see enabling technology taking an increasingly important role in the preparation of tyrosine kinase inhibiting anticancer pharmaceuticals and other small molecular weight drugs.

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