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Development of two synthetic routes to CE-178,253, a CB_1 antagonist for the treatment of obesity

Thomas A. Brandt [b], Stéphane Caron [a], David B. Damon [c], Joseph DiBrino [e], Arun Ghosh [a], David A. Griffith [e], Sandeep Kedia [d], John A. Ragan [a,*], Peter R. Rose [c], Brian C. Vanderplas [a], Lulin Wei [a]

[a] Chemical Research & Development, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06335, USA
[b] Research-API, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06335, USA
[c] Materials Science, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06335, USA
[d] Supply Chain, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06335, USA
[e] Department of Cardiovascular, Metabolic and Endocrine Disease, Pfizer Global Research & Development, Eastern Point Road, Groton, CT, 06335, USA

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In commemoration of Justin DuBois' receipt of the Tetrahedron Advances in Synthesis Award and his valuable contributions to organic synthesis and drug development at Pfizer through his role as friend and consultant

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Thiosemicarbazide

ABSTRACT

CE-178,253 benzenesulfonate (**1**) is a CB_1 antagonist discovered by Pfizer medicinal chemists. Two syntheses of this compound are described. The first, based on the discovery synthesis, involves assembly of an aryl-substituted pyrazolotriazine core onto which the second aryl moiety is installed by a Suzuki coupling; this route has been scaled to provide up to 6 kg of API. A second, more convergent route is also described, which installs the pyrazolotriazine containing both aryl substituents by condensation of a bromoketone with a substituted thiosemicarbazide. This route has been demonstrated on laboratory scale and is viewed as the preferred bond-forming sequence.

1. Introduction

The endocannabinoid system (ECS), and specifically the CB_1 receptor, plays a pivotal role in energy homeostasis.[1] As such, stimulation of the ECS promotes food intake and energy storage and may be chronically overactive in obese subjects.[2,3] In contrast, blockade of the CB_1 receptor decreases food intake and increases energy expenditure, leading to a reduction in body weight.[4–7]

CB_1 receptor antagonists may provide effective therapy options for the management of metabolic disorders, such as obesity. Several CB_1 receptor inverse agonists/antagonists are in clinical development including the diarylpyrazole SR141716A[8] (rimonabant, **2**), the acyclic amide MK-0364[9] (taranabant, **3**), and Pfizer's CP-945,598 (**3**, Fig. 1).[10,11]

1-(7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo-[1,5-*a*][1,3,5]triazin-4-yl)-3-(ethylamino)azetidine-3-carboxamide (CE-178,253, **1**) was identified by Pfizer Discovery chemists as a promising small molecule CB_1 antagonist for the treatment of obesity (Fig. 1).[12] The synthetic challenges associated with this structure included identifying an efficient synthesis of the fused pyrazolotriazinine core, regioselective installation of the two aromatic substituents, and installation of the azetidine side chain. This paper will describe the development and execution of two synthetic routes to this candidate: the first involved synthesis of a mono-substituted pyrazolotriazinine core followed by installation of the second aryl ring through a Suzuki coupling. This bond-forming sequence was designed to efficiently explore the C-8 aryl and C-4 amine SAR since they were introduced from late-stage intermediates. A more convergent route was also identified,

* Corresponding author. Tel.: +1 860 441 6334; fax: +1 860 715 9469.
E-mail address: john.a.ragan@pfizer.com (J.A. Ragan).

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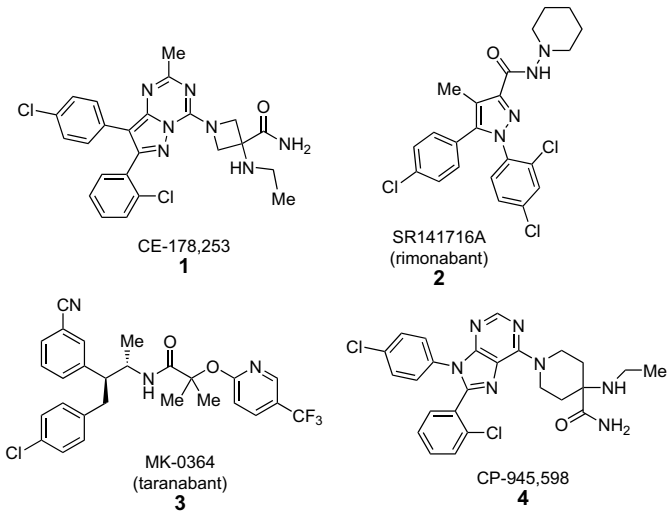


Figure 1. Structures of CB_1 antagonists.

which provided a more efficient synthesis of a late-stage intermediate (pyrazolotrazininone **10**) on laboratory scale. Program reprioritizations prevented us from demonstrating this new route on kilogram scale, but we feel it represents the most promising route to CE-178,253 identified to date.

2. Development and scale-up of the Suzuki route

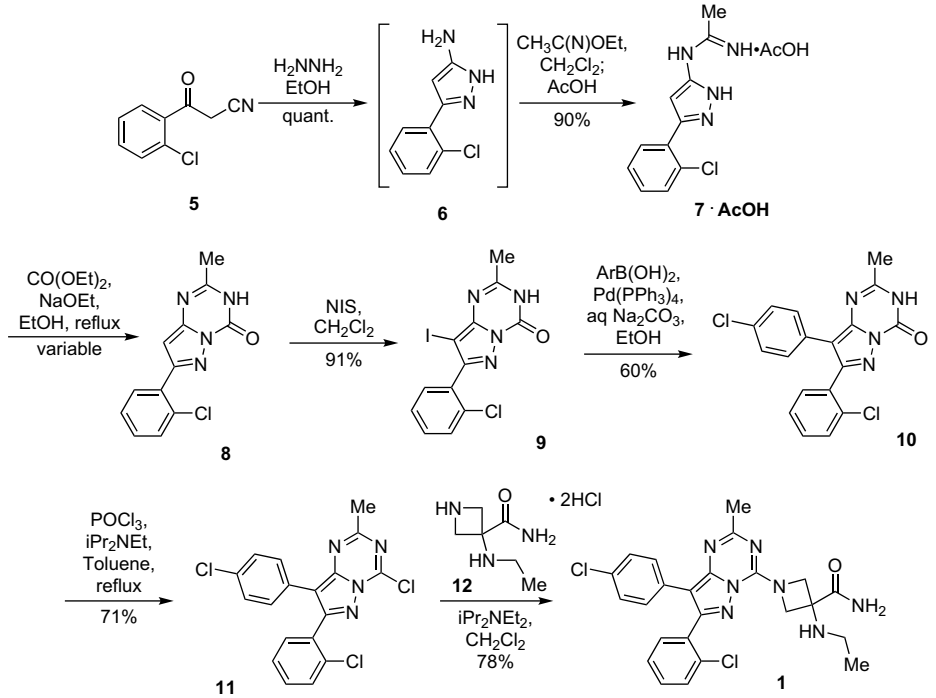
The initial discovery synthesis of **1** is shown in Scheme 1. The cyclization to provide **8** gave variable yields, due in part to impurities present in intermediate **7**. Furthermore, the Suzuki reaction gave significant amounts of a des-iodo side product in addition to moderate yields of triazinone **10**. These issues, the use of chlorinated solvents, and several chromatographic purifications were addressed prior to scale-up.

The synthesis utilized in the first two cGMP (current Good Manufacturing Practice) campaigns is shown in Scheme 2.[10] The first campaign (run in a kilo lab facility) delivered 0.76 kg of API and the second campaign (run in the pilot plant) delivered 5.9 kg of API. Yields in the scheme are for laboratory pilots of the bulk campaign conditions, typically on 20–50 g scale (these are the procedures included in Section 6). These yields were generally within 5–10% of the yields observed on multi-kilogram scale.

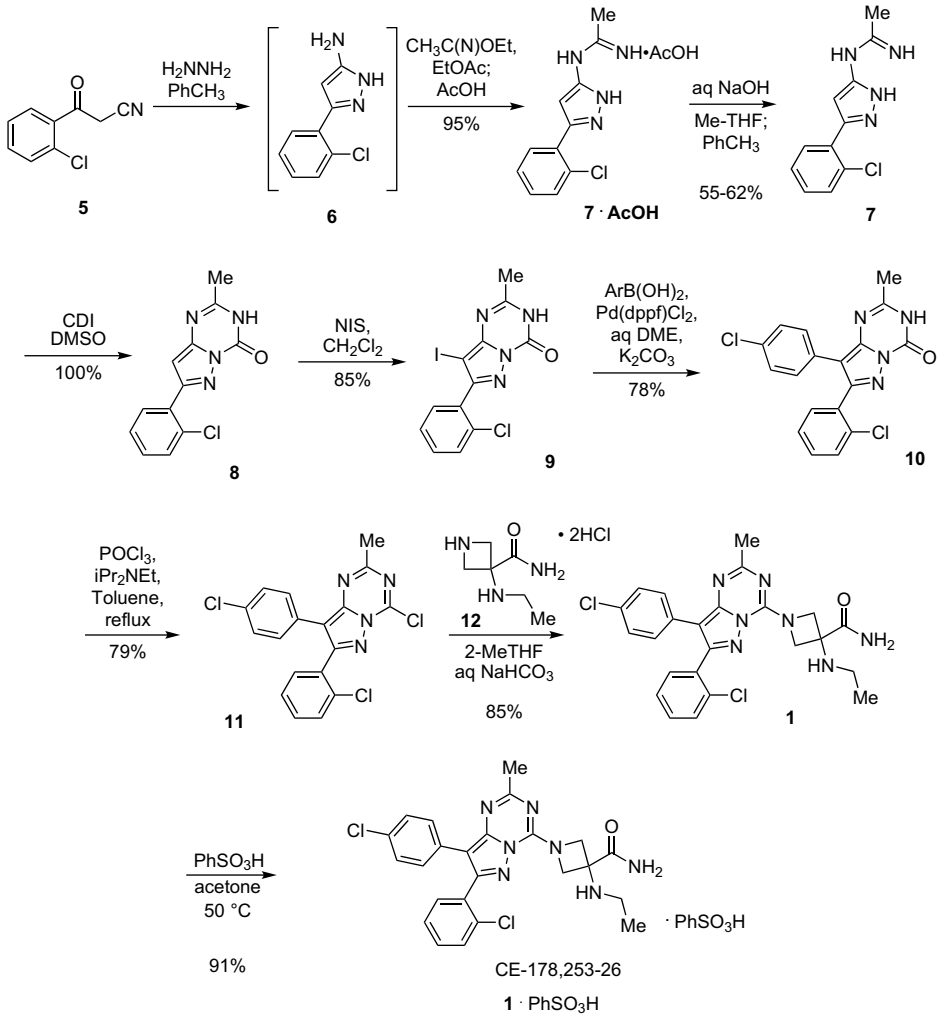
This route begins with the condensation of 2-chlorobenzoyl acetonitrile with hydrazine to form 5-amino-3-(2-chlorophenyl)-1*H*-pyrazole.[13] This reaction was conducted in ethanol for the first cGMP campaign (2 kg scale). HPLC analysis showed rapid hydrazone formation, followed by a slower cyclization to the aminopyrazole (Scheme 3). Upon reaction completion, ethanol was removed by vacuum displacement with ethyl acetate, and this solution was washed with water to remove residual hydrazine.

Upon further scale-up (10–15 kg), it was desirable to identify a water-immiscible reaction solvent such that the excess hydrazine could be removed prior to any distillation operations. 2-Methyltetrahydrofuran served well for hydrazone formation, but subsequent cyclization to the aminopyrazole was sluggish, and did not reach completion after 72 h. Toluene was found to be an adequate replacement for ethanol, providing the desired product after 44 h at reflux. After cooling, excess hydrazine was removed by an aqueous extraction, and the aminopyrazole solution in toluene was carried directly into the acetimidate coupling.

The above reaction solution was treated with ethyl acetimidate, prepared by partitioning ethyl acetimidate hydrochloride between ethyl acetate and saturated aqueous potassium carbonate. Addition of the ethyl acetimidate/ethyl acetate solution to the aminopyrazole/toluene solution, followed by addition of acetic acid, led to precipitation of acetamidine **7** as its acetate salt. The yield for this three-step process (hydrazine cyclization, acetimidate condensation, and salt formation) was seemingly quite high (95% on 15 kg scale), although it was subsequently found that an impurity comprised a portion of the isolated product, inflating the apparent

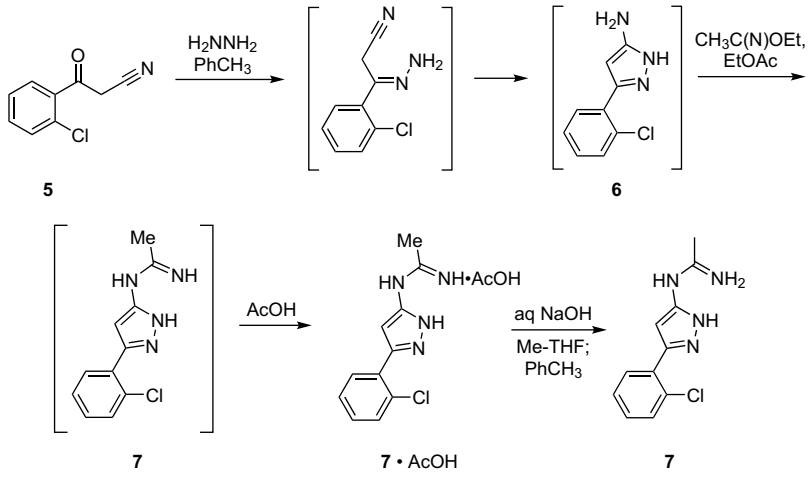


Scheme 1. Initial discovery synthetic route.



Scheme 2. Synthesis used in first and second cGMP campaigns.

yield. The impurity showed two peaks in the ^{1}H NMR in the 1.5–2.5 region, and elemental analysis of the product was low for both carbon and chlorine. The impurity was found to purge in the next operation; treatment of the acetate salt with aqueous sodium hydroxide followed by solvent displacement with 2-methyltetrahydrofuran and toluene lead to precipitation of the free base acetamidine **7** in 53% yield. Thus a 50% overall yield for the sequence from 2-chlorobenzoyl acetonitrile was realized.



Scheme 3. Conversion of 2-chlorobenzoyl acetonitrile to aminopyrazole **6** and acetamidine **7**.

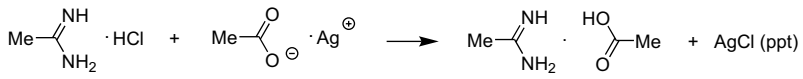
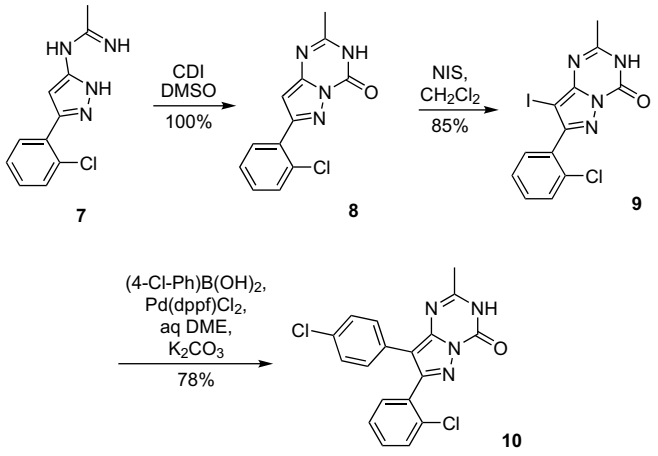


Figure 2. Synthesis of acetamidine acetate from silver acetate and acetamidine hydrochloride.

The impurity present in **7** was subsequently identified as the acetic acid salt of acetamidine ($H_2NC(=NH)CH_3 \cdot CH_3CO_2H$). Its identity was confirmed through an independent synthesis from acetamidine hydrochloride and silver acetate (Fig. 2). The structure is consistent with the extraneous peaks in the ^1H NMR, and also the lowering of both carbon and chlorine in the elemental analysis.

Scheme 4 shows the further processing of acetamidine **7** to pyrazolotriazinone **10**. This sequence commenced by cyclization with carbonyldiimidazole (CDI) in dimethylsulfoxide (DMSO). The choice of solvent was based on the limited solubility of both **7** and **8** in anhydrous organic solvents. Upon reaction completion, the product was isolated by pouring the DMSO solution into aqueous HCl to precipitate the essentially neutral product. This isolation method removes the byproduct imidazole by dissolving it in the aqueous acid, delivering pyrazolotriazinone **8** in >95% yield. The 7-position of the pyrazolotriazinone was then functionalized by reaction with *N*-iodosuccinimide in dichloromethane to form iodide **9**. The product was isolated by dilution with 2-methyltetrahydrofuran, aqueous extraction with aqueous NH_4Cl and aqueous $Na_2S_2O_3$, and distillation to displace the dichloromethane with 2-methyltetrahydrofuran. This resulted in crystallization of the product in 85% yield on laboratory (16 g) scale and 93% yield on pilot plant (14 kg) scale. This intermediate is also an attractive target for impurity control by recrystallization from aqueous THF.



Scheme 4. Synthesis of diarylpyrazolotriazinone **10** from amidine **7**.

The Suzuki coupling to convert iodide **9** to diarylpyrazolotrazinone **10** required significant optimization for preparation of multi-kilogram quantities. Laboratory scale preparations had utilized $Pd(PPh_3)_4$ and NaOH as base. These conditions generated the desired product contaminated with significant levels (5–10%) of the des-iodo product (i.e., previous intermediate **8**, Scheme 4). It was also observed that the reaction stalled after ca. 30 min, with significant reaction progress occurring during this initial 30 min window. These data are consistent with oxidation of the phosphine ligands to $Ph_3P{=}O$ (also observed by LC/MS) to generate a ligand deficient Pd(0) species. This ligand deficient Pd(0) is initially a very active catalyst, until no ligand is available to stabilize the palladium, leading to the observed initial fast reaction and subsequent stalling.

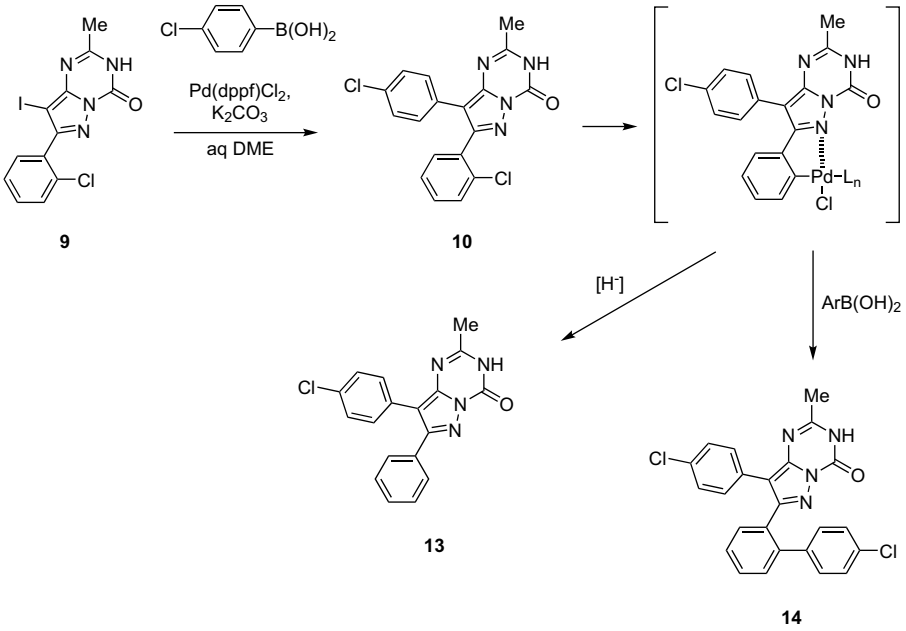
Reaction optimization led to replacement of $Pd(Ph_3P)_4$ with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (dppf=bis(diphenylphosphino)ferrocene), replacement of NaOH with potassium carbonate, use of 20% aqueous dimethoxyethane (DME), and degassing of the reaction solution. Using these conditions, the starting material was consumed in 90 min, and the catalyst load could be reduced to 0.5 mol % (as compared to 5 mol %). For convenience, the reaction was performed with 2 mol % catalyst, thus obviating the need to rigorously degas the solution. Using these conditions on laboratory pilots, two impurities (des-chloro **13** and phenyl insertion product **14**) were observed at 0.8% and 0.4% in final API, respectively (by analysis of their downstream analogues). The des-iodo impurity (**8**) was formed at much lower levels, and purged to undetectable levels in the isolation. A mechanism to account for the formation of these impurities is shown in Scheme 5.

Product isolation was achieved by removal of DME via vacuum distillation, product extraction from the aqueous phase with 2-methyltetrahydrofuran, washing of the organic phase with 1 N NaOH and 1 N HCl, and solvent displacement with methanol to precipitate the product. The isolated yields were 81% on 2 kg scale and 67% on 9 kg scale, with no detectable levels of impurities **13** or **14**. A more efficient impurity purge on larger scale is not something one should anticipate, but it is a happy event when it occurs.

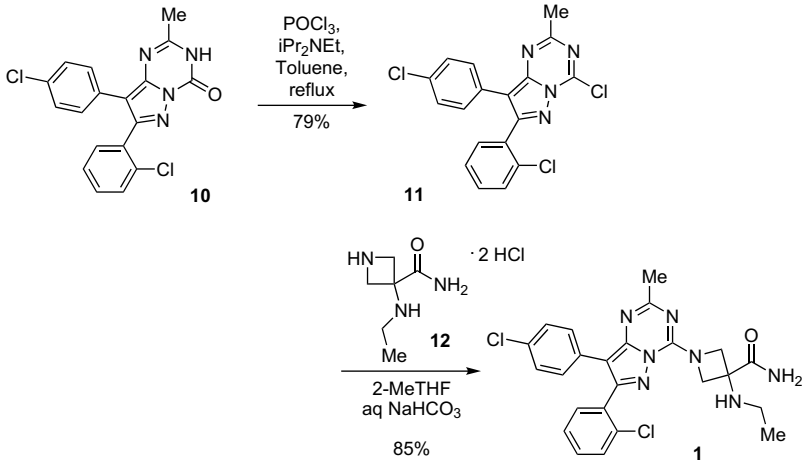
Activation of triazinone **10** as chlorotriazine **11** and coupling to form CE-178,253 (**1**) are shown in Scheme 6. The chlorination was achieved with 2 equiv of phosphorous oxychloride and Hünig's base (*i*-Pr_2NEt) in toluene. Excess $POCl_3$ was required to achieve complete chlorination in reasonable times (use of 1.2 equiv led to incomplete reaction after 18 h). The reaction was quenched by slow addition to half-saturated brine, separation of the organic phase, and washing with aqueous $NaHCO_3$. The product was isolated by partial concentration of the toluene and addition of hexanes, which precipitated chlorotriazine **11** as a canary yellow solid in 75–85% yield on laboratory and multikilogram scales.

For the Kilo-Lab campaign (2 kg scale), chlorotriazine **11** was coupled with azetidine–bis HCl salt **12** using *i*-Pr_2NEt in 3:1 DME/water. Operationally this involved dissolution of chloride **11** and 1 equiv of *i*-Pr_2NEt in DME, and in a separate vessel dissolution of azetidine salt **12**·2HCl[14] in water and addition of 2 equiv of *i*-Pr_2NEt. The aqueous azetidine solution was then added to the chlorotriazine/DME solution at a rate such that the internal temperature remained <25 °C (this addition required 10 min on 2 kg scale). Although lab pilots had shown minimal impurity formation using this method, upon scale-up significant levels of hydrolysis product (**10**) and other unidentified impurities were observed, requiring a rework of the crude product by recrystallization from dichloromethane/MTBE. The resulting isolated yield suffered accordingly (overall yield 42%).

In order to avoid these problems, a two-phase system was developed. Reaction of chlorotriazine **11** and azetidine salt (**12**·2HCl) in a two-phase solvent mixture of 2-methyltetrahydrofuran and aqueous $NaHCO_3$ cleanly provided **1** (CE-178,253) with no detectable levels of hydrolysis product **10**. Product isolation was achieved by separation of the organic phase and solvent displacement at reduced pressure with acetonitrile to precipitate the product as the free base. Laboratory scale experiments provided an 85% yield, and upon scale-up in the pilot plant (6 kg), a 79% isolated yield of CE-178,253 (**1**) was obtained.



Scheme 5. Impurity formation in the Suzuki coupling.

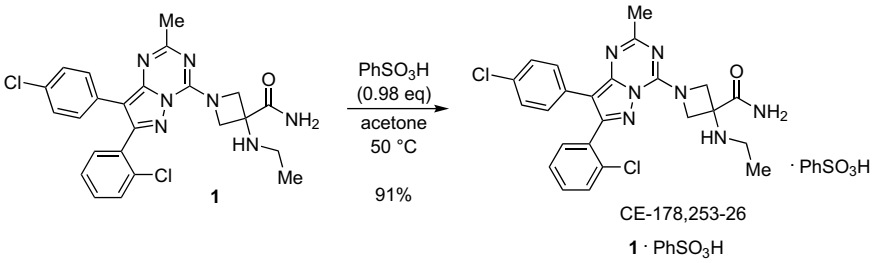


Scheme 6. Chlorination and azetidine coupling to form CE-178,253.

As is frequently the case, final form was a critical issue for this candidate, and several different polymorph, hydrate, and solvate forms of the final API were identified. In the first cGMP campaign (1–2 kg), salt formation was effected by dissolution of the free base in dichloromethane, speck-free filtration, and addition of 98% benzenesulfonic acid. The salt was collected by filtration, and then subjected to a reslurry in 2.5% aqueous acetonitrile; this reslurry provided the desired polymorph (Form A). This material showed good stability in an accelerated API stability program.

The second campaign (8–10 kg) changed the initial solvent from dichloromethane to THF for the speck-free filtration. Technical grade (90%) benzenesulfonic acid was then added as an acetonitrile solution, and THF was displaced by vacuum distillation of the THF/acetonitrile mixture. While successful in laboratory pilots, this method delivered a less stable polymorph (Form C) when performed in the kilo lab. Reslurrying this material in 2.5% aqueous acetonitrile did convert it to Form A, but this conversion was tricky (extended reslurry times led to formation of Form B, which is more stable than Form A, but not desired for formulation development).

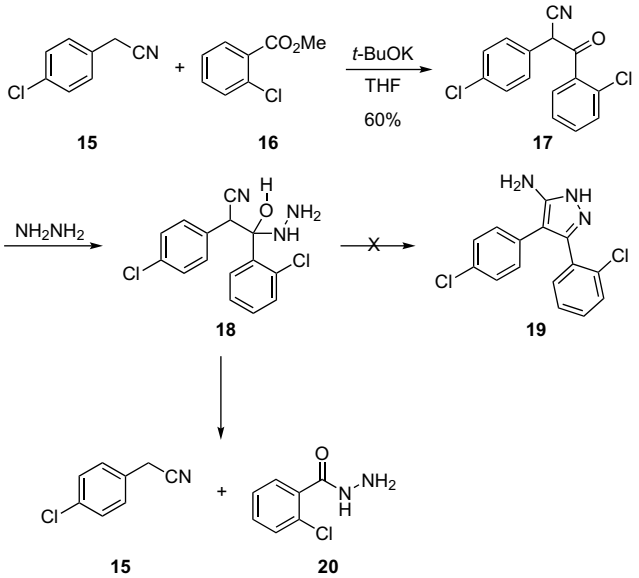
Additional studies on the salt formation delivered two key findings: first, use of the higher purity benzenesulfonic acid (98% vs technical grade 90%) was critical for delivering robust Form A, and second, a more thorough solvent screen found that acetone was preferred as a solvent for the salt formation. Technical grade benzenesulfonic acid (ca. 90%) delivered predominantly Form A, but some additional reflections were observed in the powder X-ray diffraction of this material. Additionally, this material showed reduced stability in accelerated stability studies. While these changes were not incorporated in a bulk campaign, they were successfully demonstrated on laboratory scale (8 g), and this procedure is currently viewed as the optimal salt formation for delivery of robust Form A material (Scheme 7).



Scheme 7. Besylate salt formation.

3. Development of a second generation synthesis: condensation approach

A fundamental inefficiency with the Suzuki route described above is the sequential nature of installing the two aryl substituents. If both aryl groups were present prior to heterocycle formation, a significant improvement in both convergency and efficiency could be realized. Our first approach to realizing this improvement was based on diaryl-substituted keto-nitrile **17** (Scheme 8). It was hoped that the 3,4-diaryl-5-aminopyrazole (**19**) could be prepared from the keto-nitrile by condensation with hydrazine and cyclization (this would be analogous to the conversion of **5** to **6** in the previous route, cf. Scheme 2).



Scheme 8. Keto-nitrile cyclization approach to a 3,4-diaryl-5-aminopyrazole.

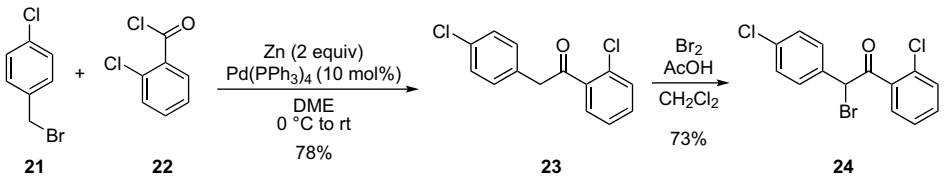
Indeed, condensation of 4-chlorobenzonitrile (**15**) with methyl 2-chlorobenzoate (**16**) provided the known[12] keto-nitrile **17** in good yield. Unfortunately, condensation with hydrazine proved to be unsuccessful. Rather than isolating the desired product (aminopyrazole **19**), an acylhydrazide (**20**) and the benzonitrile (**15**) were generated. We rationalized that upon addition of hydrazine to the ketone, the resulting tetrahedral intermediate (**18**) collapsed through a retro-Claisen mechanism generating acylhydrazide (**20**). Attempts to modify the course of the reaction by modification of the reaction conditions proved to be unsuccessful and this approach was abandoned.

4. Development of a second generation synthesis: sulfur extrusion approach[15]

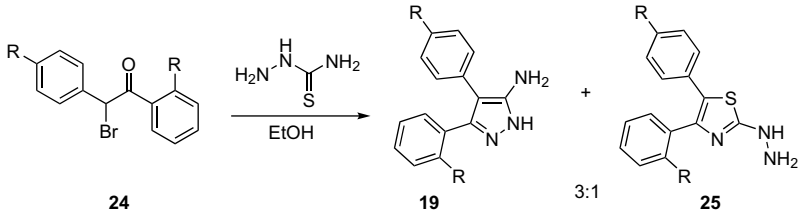
We were intrigued by a previous report that 5-aminopyrazoles could be prepared by the treatment of a 2,3-dihydro-6*H*-1,3,4-thiazine with a base.[16] The pre-requisite α-bromoketone (**24**) was easily prepared in two steps by zinc-mediated coupling[17] of 4-chlorobenzyl bromide (**21**) with 2-chlorobenzoyl chloride (**22**) in 78% yield followed by bromination of ketone **23** with bromine in acetic acid (73% yield) (Scheme 9).

The cyclization was first attempted by reaction of bromoketone (**24**) with thiosemicarbazide in ethanol. A mixture of two products was obtained in a 3:1 ratio, which was in agreement with some previous reports from a different substrate.[18] Although the desired aminopyrazole (**19**) was the major product, attempts to further optimize the reaction to increase the ratio of regioisomers did not lead to any major improvements (Scheme 10).

It was postulated that protection of the thioamide portion of the thiosemicarbazide would allow for chemoselective condensation of the hydrazine moiety with the ketone and result in increased regioselectivity. Several *N*-protected thiosemicarbazides (**26a**–**c**) are commercially available or can be accessed by addition of hydrazine to isothiocyanates (Scheme 11). The *N*-allyl,[19] *N*-benzyl,[20] and *N*-benzydryl[21] derivatives were prepared and evaluated in the cyclodehydration. We were delighted to find that the protected thiosemicarbazides reacted readily with the α-bromoketone (**24**) in ethanol at 0 °C and that upon addition of an excess of aqueous



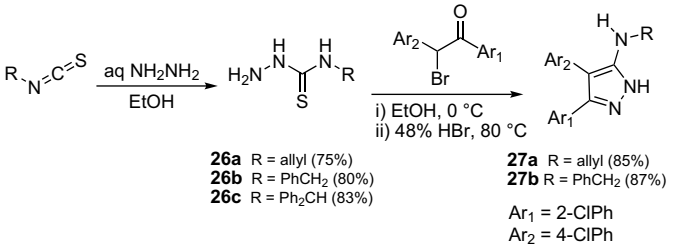
Scheme 9. Synthesis of α-bromoketone **24**.



24 19 25

Scheme 10. A modestly selective aminopyrazole condensation.

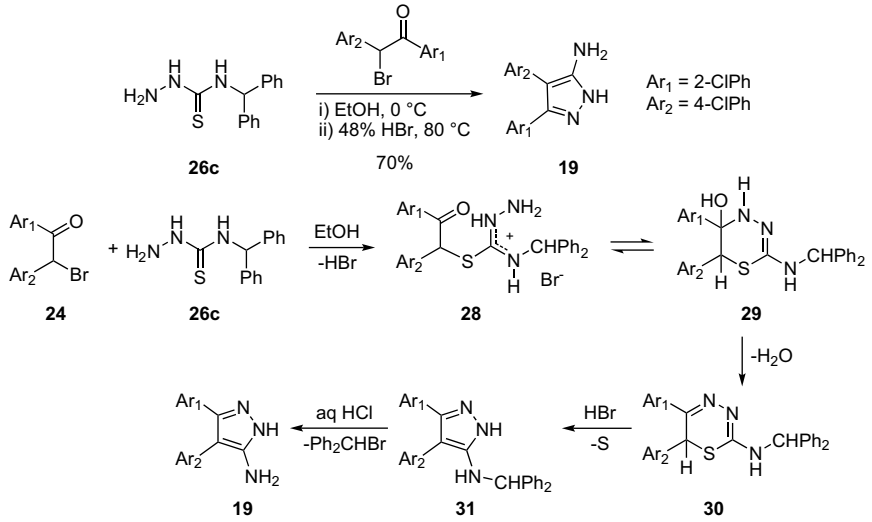
hydrobromic acid, cyclodehydration, and sulfur extrusion proceeded to generate the desired protected 5-aminopyrazoles (**27**) in high overall yield.



Scheme 11. Synthesis of *N*-substituted aminopyrazoles from thiosemicarbazides.

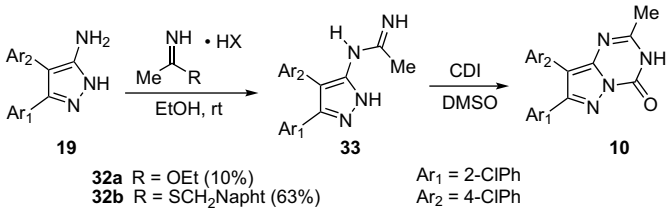
While multiple methods exist for the deprotection of the *N*-allyl (**27a**) and *N*-benzyl (**27b**) derivatives,[22,23] this strategy turned out to be unnecessary. In the case of the *N*-benzhydryl protected substrate (**26c**) the hydrobromic acid present in the reaction proved to be sufficient to cleave the protecting group in situ. This is well precedented for *N*-benzhydryl amines.[24,25] The reaction of α-bromoketone **24** and thiosemicarbazide **26c** afforded the desired compound (**19**) in an overall yield of 70% (Scheme 12). The first step of the sequence likely proceeds by alkylation of the bromide by the sulfur atom to provide **28** with liberation of 1 equiv of HBr. It is precedented that this adduct can be isolated as the HBr salt.[26] The charge distribution in intermediate **28** renders the terminal nitrogen of the hydrazine the most nucleophilic atom for condensation with the ketone providing aminal **29**, which can undergo dehydration to generate the 5,6-diaryl-6*H*-1,3,4-thiadiazin-2-amine **30**. Furthermore, the presence of a protecting group provides an additional steric effect that promotes the high regioselectivity observed. While the original adduct and the aminal can be under equilibrium, formation of the thiadiazine and loss of water should be irreversible. Indeed, it is the only intermediate observed in the sequence (along with some of the sulfur extruded product **31**). Upon addition of additional HBr, conversion to protected aminopyrazole **31** was observed. Deprotection of the benzhydryl group to form **19** was finally achieved in the presence of aqueous HCl.

With the diaryl 5-aminopyrazole **19** in hand, what remained was construction of the second heterocycle. It was expected that preparation of the amidine would be straightforward as for the previous route. To our surprise, reaction of **19** with ethyl acetimidate hydrochloride (**32a**) proceeded in only 10% yield (Scheme 13). We postulated that the fully substituted pyrazole might be too good a leaving group after addition to the imidate. To test this hypothesis, alternative reagents were considered and a thioimidate was selected for evaluation. The naphthylmethyl thiomidiate (**32b**) was chosen because of its known utility in the preparation of amidines and due to the fact that the resulting naphthylmethyl thiol is odorless.[27] Upon reaction of aminopyrazole **19** with *S*-2-naphthylmethyl thioacetimidate hydrobromide (**32b**), a 63% isolated yield of the desired imidate was obtained. To complete the sequence and reach the previously prepared intermediate, condensation of imidate (**33**) with CDI afforded the desired pyrazolotriazinone (**10**). This is a common intermediate with the route



26c 19 24 26c 28 29 30 31 19

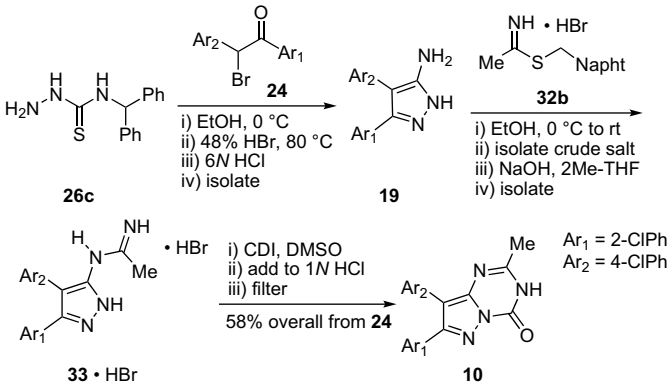
Scheme 12. Mechanism of condensation, cyclization, and sulfur extrusion.



Scheme 13. Conversion of aminopyrazole **19** to pyrazolotrazinone **10**.

described previously (e.g., Scheme 2), and conversion of **10** to **1** can be achieved using the conditions described earlier.

Since many of the reactions provided very clean conversions and the final isolation proved to be robust and reliably provided high quality material, a telescoped process was evaluated in order to avoid isolation of the intermediates. This overall process (Scheme 14) afforded the desired product (**10**) in 58% overall yield from the starting bromoketone (**19**) and thiosemicarbazide (**32b**).



Scheme 14. Telescoped process for conversion of bromoketone **24** to pyrazolotrazinone **10**.

5. Conclusions

Two routes to CE-178,253 (**1**) have been developed. The first involves construction of the pyrazolotriazine **8** containing one of the two aryl moieties; the second aryl group is then installed through an iodination/Suzuki coupling sequence. This route was successfully scaled to 6 kg in the pilot plant. A more convergent route was also developed that formed the diaryl-substituted aminopyrazole **22** by coupling of a thiosemicarbazide (**20c**) with an α-bromoketone (**16**). This route was demonstrated on laboratory scale, and offers more efficient access to pyrazolotriazinone **10** (five steps from 2-chlorobenzoyl chloride or three steps from the bromoketone **16**, versus six steps from 2-chlorobenzoyl acetonitrile via the previous route). Both routes are attractive in requiring no chromatographic purifications.

6. Experimental section

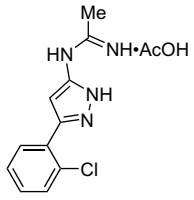
6.1. General

GC/MS data were obtained on a Hewlett–Packard 5971 with an MSD detector using an HP-1 column (12 m×0.2 mm×0.33 μm); flow 1 mL/min; injector temp 280 °C; oven temp 133 °C; initial hold for 0.1 min, then ramp to 310 °C at 19 °C/min, hold for 1.65 min. Mass spectral data were obtained on a Micromass ZMD mass spectrometer with flow injection analysis and atmospheric pressure chemical ionization (APCI). HPLC analyses were performed on two different systems:

- System A: Zorbax SB-C8 column, 10:90 gradient to 90:10 acetonitrile/aqueous over 10 min, aqueous=0.5% $HClO_4$; flow rate=1.5 mL/min, 40 °C, 210 nm detection; t_R (**7**)=4.4 min, (**8**)=5.0 min, (**9**)=5.7 min, (**10**)=7.0 min, (**11**)=8.7 min, (**1**)=6.3 min.
- System B: identical to System A, except that the aqueous phase consisted of 2 mL phosphoric acid and 1 g SDS dissolved in sufficient water to bring the total volume to 1 L; t_R (**10**)=7.5 min, (**19**)=3.6 min.

Commercial reagents and solvents were purchased from the following suppliers and used as-received unless otherwise noted. Benzenesulfonic acid (>98%), dichloromethane, diisopropylethylamine (Hünig's base), dimethoxyethane (DME, anhydrous), dimethylsulfoxide (anhydrous), ethyl acetimidate hydrochloride, hydrazine hydrate, methanol, 2-methyltetrahydrofuran, phosphorous oxychloride, and toluene were purchased from Aldrich. 2-Chlorobenzoyl acetonitrile and carbonyldiimidazole (CDI) were purchased from Lancaster. Ethyl acetate, glacial acetic acid, concentrated HCl, methyl *tert*-butyl ether (MTBE), potassium carbonate, and sodium bicarbonate were purchased from J.T. Baker. *N*-Iodosuccinimide and sodium thiosulfate ($Na_2S_2O_3$) were purchased from Fisher/Acros. 4-Chlorophenylboronic acid was purchased from Alfa Aesar. Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ was purchased from Strem Chemicals.

6.1.1. *N-(3-(2-Chlorophenyl)-1H-pyrazol-5-yl)acetamidine acetate (7·AcOH)*

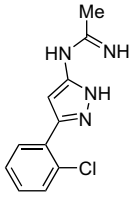


A 2 L, four-neck round bottom flask equipped with an overhead stirrer, reflux condenser with nitrogen inlet, temperature probe, and addition funnel was flushed with nitrogen, and charged with toluene (1.0 L). Stirring was initiated, and hydrazine hydrate (20.3 mL, 418 mmol, 1.5 equiv) was added from the addition funnel over a period of 5 min. The reaction mixture was then heated to an internal temperature of 90–95 °C. ^{1}H NMR and GC/MS analysis indicated the following conversions to aminopyrazole **6**: 1 h (18%), 3 h (29%), 20 h (75%), 25 h (82%), 44 h (92%); GC retention times were as follows: **5** (2.29 min); intermediate hydrazone (2.97 min); **6** (3.83 min). After 44 h, the reaction mixture was cooled to 30 °C, diluted with 500 mL of half-saturated brine, and stirred vigorously for 5 min. The reaction mixture was transferred to a 2 L separatory funnel and the aqueous phase was separated. The organic phase was washed with brine (250 mL). The combined organic phases were transferred to a 2 L flask, rinsing with 50 mL of toluene. The flask was equipped with a short path distillation head, and was heated to distill off ca. 500 mL of solvent, then cooled to 20 °C. In a separate flask, K_2CO_3 (115 g, 834 mmol, 3.0 equiv) was dissolved in 250 mL water, and ethyl acetimidate hydrochloride (85.9 g, 695 mmol, 2.5 equiv) was added over 2–3 min. Ethyl acetate was added (350 mL), and the two-phase system was stirred vigorously for 5 min. The mixture was transferred to a 1 L separatory funnel, and the aqueous phase (plus some undissolved solids) was

removed. The resulting ethyl acetimidate free base solution was added to the above reaction mixture in a steady stream (addition of ca. 370 mL solution required 5 min). Glacial acetic acid (24 mL, 420 mmol, 1.5 equiv) was then added over 2–3 min. The reaction flask was placed in an ice bath, and a few seed crystals of the product were added (200–300 mg). Solids came out quickly and were granulated for 3 h. The solids were collected by filtration, rinsing with 3×50 mL ethyl acetate. After air-drying overnight, the product was obtained as a tan solid (77.65 g, 263 mmol, 95%).

IR (thin film) cm^{-1} 3226, 2877, 1529, 1488, 1409, 752, 729, 652, 562. ^1H NMR (CD_3OD): δ 7.60–7.56 (m, 2H), 7.46–7.43 (m, 2H), 6.47 (s, 1H), 4.9 (br s, 4H), 2.42 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6) (12 of 13 signals observed): δ 179.1, 126.6, 148.1, 141.1, 132.2, 130.5, 130.4, 128.0, 127.4, 97.0, 23.0, 18.1. Several attempts to obtain satisfactory elemental analysis of this material were unsuccessful; note, however, that proof of purity by elemental analysis was obtained for the corresponding free base that was isolated in the next reaction (**7**).

6.1.2. *N-(3-(2-Chlorophenyl)-1H-pyrazol-5-yl)acetamidine (**7**)*

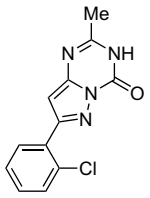


A 1 L, single-neck round bottom flask with a magnetic stir bar and a temperature probe was charged with *N*-(3-(2-chlorophenyl)-1*H*-pyrazol-5-yl)acetamidine acetate (**7**·AcOH) (50.0 g, 170 mmol) and 2-methyltetrahydrofuran (500 mL), and stirring was initiated. Aqueous NaOH (2 N, 340 mL, 680 mmol, 4.0 equiv) was added, and the two-phase system was stirred for 5 min (no significant exotherm was observed during this addition). The reaction mixture was transferred to a 1 L separatory funnel, rinsing with 50 mL 2-methyltetrahydrofuran. The aqueous phase was removed and the organic phase was washed with 300 mL of half-saturated brine. The aqueous phase was separated, and the organic layer was transferred to a 1 L, four-neck round bottom flask equipped with a short path distillation head. Atmospheric distillation was initiated, and approximately two-thirds of the volume was displaced with toluene (350 mL) added in several smaller portions during the distillation. Solids began to precipitate, and the distillation head temperature gradually increased from 72 to 82 °C. The slurry was cooled, and the solids were collected, rinsing with pentane. After air-drying overnight, product was collected as tan solids: 21.95 g (93.5 mmol, 55%), mp 197.5–199.5 °C.

Concentration of the mother liquors to a volume of 30–40 mL provided a second crop of 2.64 g (11.2 mmol, 6.6%). Combined yield for the two crops: 24.6 g (105 mmol, 62%). The purity of the second crop was slightly diminished from the first crop, and attempts to recrystallize offered no significant improvement. Consequently, upon scale-up, no attempts to recover a second crop were pursued.

IR (thin film) cm^{-1} 3414, 1621, 1561, 1460, 1289, 1049, 796, 754, 722. ^1H NMR (CD_3OD): δ 7.61–7.59 (m, 1H), 7.63–7.61 (m, 1H), 7.41–7.34 (m, 2H), 6.32 (s, 1H), 4.9 (br s, 3H), 2.10 (s, 3H). ^{13}C NMR (DMSO-d_6) (due to limited solubility of **7**, only 9 of 11 signals were observed): δ 157.5, 131.6, 130.94, 130.88, 129.9, 129.2, 127.9, 95.7, 23.7. MS (CI): 235 (100). Anal. Calcd for $C_{11}H_{12}ClN_4$: C, 56.06; H, 5.13; N, 23.77. Found: C, 56.11; H, 4.82; N, 23.80.

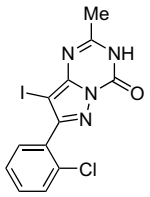
6.1.3. *7-(2-Chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (**8**)*



A 250 mL, 3-neck round bottom flask equipped with a nitrogen inlet, internal temperature probe, addition funnel, glass stopper, and magnetic stir bar was charged with 13.0 g of *N*-(3-(2-chlorophenyl)-1H-pyrazol-5-yl)acetamidine (**7**) (55.4 mmol) and 40 mL of DMSO, and stirred at room temperature. The addition funnel was charged with CDI (9.88 g, 60.9 mmol, 1.1 equiv) dissolved in 40 mL of DMSO. The CDI solution was added to the reaction mixture dropwise over 20 min, such that the internal temperature did not rise above 22 °C (this required periodic cooling with an ice bath). Aliquots were analyzed by removing ca. 0.2 mL of the reaction solution and quenching into 3:1 acetonitrile-water. HPLC analysis of the organic phase showed the following reaction progress (System A): 1 min (5.3% starting material, 90.1% product); 30 min (0.3% starting material, 97.6% product). No further conversion was observed after 2.5 h. The reaction mixture was then added over 15 min to a chilled (14 °C) solution of 1 N HCl (122 mL). White solids began to precipitate from solution near the beginning of the addition. The slurry was stirred for an additional 30 min at 14 °C, and the solids were collected by filtration, rinsing with five 30 mL portions of water. The solids were dried overnight in a 40 °C vacuum oven (20–30 mm) with a nitrogen sweep. The product was isolated as an off-white solid (14.62 g, 56.1 mmol, 100% yield).

IR (thin film) cm^{-1} 3073, 2954, 1727, 1634, 1443, 1377, 1040, 809, 747. ^1H NMR (DMSO-d_6): δ 7.81–7.77 (m, 1H), 7.56–7.54 (m, 1H), 7.45–7.42 (m, 2H), 6.75 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 155.3, 154.4, 149.9, 144.7, 132.4, 131.8, 131.7, 131.3, 131.0, 128.1, 99.2, 21.5. MS (APCI): 261 (100). Anal. Calcd for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; N, 21.49. Found: C, 55.10; H, 3.38; N, 21.46.

6.1.4. *7-(2-Chlorophenyl)-8-iodo-2-methylpyrazolo[1,5-a]-[1,3,5]triazin-4(3H)-one (**9**)*

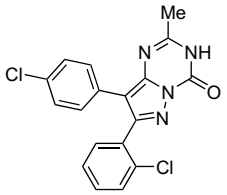


A 500 mL, three-neck round bottom flask equipped with an internal temperature probe, nitrogen inlet, glass stopper, and magnetic stir bar was charged with 7-(2-chlorophenyl)-2-methylpyrazolo[1,5-*a*][1,3,5]triazin-4(3*H*)-one (**8**) (13.2 g, 50.6 mmol) and dichloromethane (210 mL). To this stirred slurry was added *N*-iodosuccinimide (12.5 g, 55.6 mmol, 1.1 equiv) in a single portion (a modest, 2–3 °C exotherm was observed following the addition). After 3 h, HPLC analysis showed complete conversion (System A). The solution was diluted with 65 mL of 2-methyltetrahydrofuran and 112 mL of 15% aqueous NH_4Cl, leading to a homogeneous solution. The reaction solution was transferred to a 500 mL separatory funnel, rinsing with 8 mL of dichloromethane. The lower organic phase was separated, and the aqueous phase (containing a small amount of an emulsion) was temporarily retained. The organic phase was washed with 86 mL of aqueous $Na_2S_2O_3$ (1 M) and then

86 mL of brine. Approximately half of the organic phase was added to a 300 mL, three-neck round bottom flask equipped with a distillation head, internal thermometer, and magnetic stir bar. Dichloromethane was distilled at atmospheric pressure, while slowly adding the remainder of the reaction solution. The final volume was ca. 75 mL. The solution was cooled to ambient temperature, and 130 mL of MTBE was added. The resulting slurry was stirred overnight, and the solids were collected by filtration, rinsing with 10 mL of MTBE. After air-drying overnight, the product was isolated as white solids (16.7 g, 43.2 mmol, 85%).

IR (thin film) cm^{-1} 3062, 2942, 1722, 1621, 1562, 1423, 763, 746, 674. ^1H NMR (DMSO-d_6): δ 7.60 (dd, J=7.9, 1.2 Hz, 1H), 7.52 (dt, J=1.8, 7.6 Hz, 1H), 7.45 (dt, J=1.3, 7.5 Hz, 1H), 7.39 (dd, J=7.5, 1.7 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (DMSO-d_6) (10 of 12 signals observed): δ 157.4, 157.0, 133.4, 132.6, 132.4, 131.8, 130.2, 127.8, 21.7. MS (APCI): 387 (50). Anal. Calcd for $C_{12}H_8ClN_4IO$: C, 37.28; H, 2.09; N, 14.49. Found: C, 37.15; H, 1.89; N, 14.35.

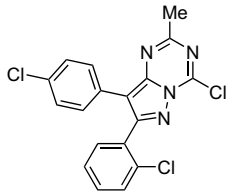
6.1.5. 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (10)



A 250 mL, three-neck round bottom flask equipped with an overhead stirrer, internal temperature probe, and reflux condenser with a nitrogen inlet was flushed with nitrogen, and then charged with 7-(2-chlorophenyl)-8-iodo-2-methylpyrazolo[1,5-*a*][1,3,5]triazin-4(3*H*)-one (**9**) (7.50 g, 19.4 mmol), 4-chlorophenylboronic acid (4.55 g, 29.1 mmol, 1.5 equiv), and potassium carbonate (5.36 g, 38.8 mmol, 2.0 equiv). The flask was flushed again with nitrogen and then charged sequentially with Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (0.32 g, 0.39 mmol, 2 mol %), dimethoxyethane (75 mL), and water (19.3 mL). Stirring was initiated, leading to a homogeneous solution. The flask was then placed in an oil bath and heated to reflux (80 °C) for 18 h. Analysis by HPLC (System A) showed 14% starting material (**9**), 74% product (**10**), and 11% of the des-iodo product (**8**) by uncorrected area%. Further heating did lead to further conversion, but for this experiment the reaction was halted at this point to confirm that unconsumed starting material would purge during product isolation. The reaction flask was cooled to room temperature, and the reflux condenser was replaced with a short path distillation head. The flask was then re-heated in the oil bath. Distillation commenced at a pot temperature of 110 °C and head temperature of 78 °C (DME forms a 10% water azeotrope with bp 78.5 °C). Over the course of the distillation, the head temperature remained at 78–80 °C, and the pot temperature rose to 123 °C. When the head temperature began to fall and distillation slowed, heating was stopped, and the distillation pot was cooled to ambient temperature. The volume of distillate collected was 55 mL. After cooling to 50 °C, the reaction solution was diluted with 2-methyltetrahydrofuran (150 mL) and 1 N NaOH (40 mL). The internal temperature was 40 °C after these additions and 5 min additional stirring. The reaction solution was transferred to a 500 mL, three-neck round bottom flask equipped with a nitrogen inlet, distillation head, and internal temperature probe. The flask was heated in an oil bath to distill off 2-methyltetrahydrofuran. During this distillation, solids began to precipitate. The head temperature was at 71–75 °C during distillation, and ca. 100 mL of distillate was collected. Methanol (50 mL) was added and the slurry was heated to reflux for 60 min (this was an attempt to remove a black, insoluble material present on the walls of the flask, but the material was still present after 60 min at reflux). The slurry was cooled and the solids were collected by filtration, rinsing with 25–50 mL of methanol. After air-drying, the product was obtained as a gray solid (5.60 g, 15.1 mmol, 78% yield), mp >300 °C. HPLC analysis (System A) showed relatively good purge of the two impurities (98.5% product, 0.4% starting material **9**, and 0.4% des-iodo product **8**).

IR (thin film) cm^{-1} 3071, 2946, 1578, 1556, 1490, 1429, 1383, 1326, 962, 835, 678, 582. ^1H NMR (DMSO-d_6): δ 7.53–7.43 (m, 4H), 7.33–7.26 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6) (15 of 16 signals observed): δ 156.3, 153.4, 146.5, 144.6, 133.3, 132.7, 131.9, 131.8, 130.8, 130.4, 130.0, 129.0, 128.2, 110.2, 21.8. MS (APCI): 371 (100), 373 (60). Anal. Calcd for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 15.09. Found: C, 57.91; H, 3.06; N, 15.01.

6.1.6. 4-Chloro-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine (11)

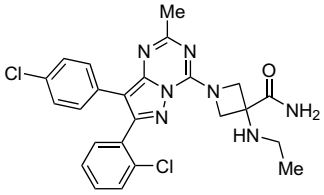


A 1 L, four-neck round bottom flask equipped with an overhead stirrer, reflux condenser, nitrogen inlet, internal thermometer, and a glass stopper was flushed with nitrogen and charged with 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-*a*]-[1,3,5]triazin-4(3*H*)-one (**10**) (35.0 g, 94.3 mmol) and toluene (455 mL). Stirring was initiated, leading to a dark gray slurry. Diisopropylethylamine (34.4 mL, 197 mmol, 2.1 equiv) was charged, and phosphorous oxychloride (17.7 mL, 189 mmol, 2.0 equiv) was then added over 45 s, leading to visible production of HCl but no exotherm. The reaction mixture was then heated with a heating mantle to an internal temperature of 80 °C and held at that temperature for 17 h. HPLC analysis (System A) showed 2% starting material remaining. A separate, 2 L, three-neck round bottom flask with a nitrogen inlet, addition funnel, and overhead stirrer was charged with 350 mL of half-saturated brine. The reaction solution was then added to this rapidly stirred brine solution. The rate of addition was adjusted and intermittent ice-bath cooling was applied such that the internal temperature remained <30 °C. The addition required 25 min, and the two-phase system was stirred for an additional 15 min after complete addition. The two-phase system was then filtered through a ca. 2″ bed of Celite in a Buchner funnel to remove flocculent solids from the aqueous phase. The Celite bed was rinsed with four 10 mL portions of toluene. The filtered reaction mixture was transferred to a separatory funnel and the phases were separated. The organic layer was washed with aqueous $NaHCO_3$ (200 mL) and brine (175 mL). The phase separations were somewhat slow, requiring occasional gentle swirling of the lower aqueous phase over a period of 30–60 min. The organic phase was concentrated by rotary evaporation (40 °C water bath, 35–40 mm). Upon concentration to 175 mL, solids began forming in the toluene. The flask was removed from the rotovap, a magnetic stir bar was added, and 225 mL of hexanes were added, leading to a slurry that was granulated overnight. The solids were collected by filtration on a 9 cm Buchner funnel equipped with filter paper and house vacuum. After air-drying, the product was isolated as a bright yellow solid (29.0 g, 74.4 mmol, 79%), mp >300 °C.

IR (thin film) cm^{-1} 3074, 2953, 1728, 1628, 1579, 836, 741, 582. ^1H NMR (DMSO-d_6): δ 7.53–7.43 (m, 4H), 7.33–7.26 (m, 4H), 2.35 (s, 3H).

^{13}C NMR (DMSO-d_6) (15 of 16 signals observed): δ 156.3, 153.4, 146.5, 144.6, 133.3, 132.7, 131.9, 130.8, 130.4, 129.9, 129.0, 128.2, 110.2, 21.8. Several attempts to obtain mass spectral and analytical data for this compound were unsuccessful.

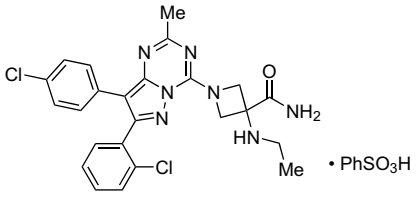
*6.1.7. 1-(7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl)-3-(ethylamino)azetidine-3-carboxamide (**1**)*



A 1 L, three-neck round bottom flask equipped with an overhead stirrer, internal thermometer, nitrogen inlet, and glass stopper was charged with 4-chloro-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-*a*][1,3,5]triazine (**11**) (18.2 g, 46.8 mmol) and 3-(ethylamino)azetidine-3-carboxamide bis-hydrochloride (**12**·2HCl) (10.6 g, 49.1 mmol, 1.05 equiv).[14] 2-Methyltetrahydrofuran (275 mL) and water (138 mL) were added, and stirring was initiated, leading to dissolution of the solids into a two-phase system. In a separate flask, sodium bicarbonate (12.6 g, 150 mmol, 3.2 equiv) was dissolved in water (137 mL); the resulting solution was added to the reaction mixture over 1–2 min through a funnel. The reaction flask was placed in a room temperature water bath to moderate the modest exotherm observed during the addition, and stirring was continued for 2 h. HPLC analysis (System A) showed >99% conversion. The reaction mixture was transferred to a 1 L separatory funnel and the aqueous phase was removed (phases were slow to separate throughout the workup; agitation with a wooden dowel and/or addition of small quantities of brine were helpful in speeding separation). The organic phase was washed with two portions of 275 mL water. The organic phase was then transferred to a 500 mL round bottom flask and concentrated by rotary evaporation (30 °C water bath, 40–50 mm) to ca. 75 mL, resulting in a hazy, light brown solution. Acetonitrile (250 mL) was added with stirring, leading to precipitation of white solids after a few minutes. The resulting slurry was stirred overnight at ambient temperature. The solids were collected by filtration, rinsing with 50 mL of cold acetonitrile. After air-drying, the product was obtained as a yellow-white solid (21.0 g, 42.3 mmol, 90%). This material was recrystallized by dissolution in THF (190 mL) and treatment with 1.0 g activated carbon for 60 min. The slurry was filtered through a 2″ pad of Celite in a 90 mm Buchner funnel. The cleary, light yellow filtrate was concentrated by rotary evaporation (30 °C water bath, 40–50 mm) to a volume of 50–75 mL (clear solution). Addition of 175 mL acetonitrile with stirring led to precipitation of white solids, which were granulated overnight. The solids were collected by filtration, rinsing with 50 mL of cold acetonitrile. After drying in a vacuum oven for 48 h (38 °C, 25 mm, nitrogen bleed), product was obtained as a white solid (19.8 g, 39.9 mmol, 85%), mp 234.0–235.7 °C.

IR (thin film) cm^{-1} 3430, 3266, 3183, 2964, 1684, 1575, 1562, 1527, 1426, 1284, 1227, 1093, 1016, 778, 602. ^{1}H NMR (DMSO-d_6): δ 7.54–7.41 (m, 4H), 7.36–7.28 (m, 4H), 4.92 (d, J=10.0 Hz, 1H), 4.60 (d, J=10.0 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 4.08 (d, J=9.6 Hz, 1H), 2.90 (br t, J=6.9 Hz, 1H), 2.47–2.35 (m, 2H), 2.39 (s, 3H), 1.00 (t, J=7.1 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 174.5, 164.6, 153.2, 148.8, 147.8, 133.4, 133.0, 132.8, 131.7, 131.3, 131.2, 130.4, 129.6, 128.9, 128.2, 106.0, 63.3, 60.2, 58.7, 38.5, 26.3, 15.9. MS (APCI): 496 (100), 498 (75). Anal. Calcd for $C_{24}H_{23}Cl_2N_7O_2$: C, 58.07; H, 4.67; N, 19.75. Found: C, 57.99; H, 4.66; N, 19.43.

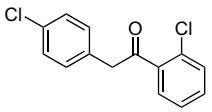
6.1.8. 1-(7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl)-3-(ethylamino)azetidine-3-carboxamide benzenesulfonate (1·PhSO$_3$H)



To a 500 mL, four-neck jacketed flask attached to a Biotage AS 4100 automated reactor system with an overhead stirrer, Lasentec FBRM probe, external J-Kem syringe pump, reflux condenser, and internal temperature probe were added 1-(7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-*a*][1,3,5]triazin-4-yl)-3-(ethylamino)azetidine-3-carboxamide (**1**) (8.00 g, 16.1 mmol) and 160 mL of acetone. The slurry was heated to 50 °C and held for 30 min, at which time partial dissolution of the free base was observed. In a separate flask, benzenesulfonic acid (>98% purity, 2.54 g, 15.8 mmol) was dissolved in 80 mL of acetone. Upon dissolution, this solution was transferred to the syringe pump and added to the free base/acetone slurry over a period of 30–60 min. The resulting slurry was maintained at 50 °C with stirring for 2 h, then allowed to cool to 20 °C over a period of 2–4 h and granulated at that temperature for an additional 16–24 h. An aliquot of the slurry was removed for DSC analysis, to confirm that the desired Form A was present. The solids were then collected by filtration (90 mm Buchner funnel equipped with filter paper and attached to house vacuum), rinsing with 40 mL acetone. After air-drying, the solids were dried in a vacuum oven for 24 h at 40–50 °C with a nitrogen bleed. Product was isolated as a white solid (9.60 g, 14.7 mmol, 91%), mp 256.2–259.6 °C.

IR (thin film) cm^{-1} 3330, 3161, 3015, 2813, 1707, 1620, 1597, 1579, 1444, 1171, 1123, 1016, 610. ^{1}H NMR (DMSO-d_6): δ 9.6 (br s, 2H), 8.4 (br s, 1H), 8.1 (br s, 1H), 7.56–7.48 (m, 4H), 7.33 (s, 4H), 7.27–7.25 (m, 3H), 5.20 (d, J=12.0 Hz, 1H), 5.00 (d, J=11.6 Hz, 1H), 4.63 (d, J=11.6 Hz, 1H), 4.52 (d, J=11.6 Hz, 1H), 3.1–3.0 (br m, 2H), 2.44 (s, 3H), 1.20 (t, J=7.1 Hz, 3H). ^{13}C NMR (DMSO-d_6) (22 of 26 signals observed): δ 168.2, 164.5, 153.5, 148.9, 147.6, 133.4, 132.8, 131.9, 131.5, 131.0, 130.5, 129.7, 129.1, 128.2, 126.1, 106.4, 60.9, 59.4, 57.1, 39.4, 26.3, 12.4. Anal. Calcd for $C_{30}H_{29}Cl_2N_7O_4S$: C, 55.05; H, 4.47; N, 14.98. Found: C, 54.93; H, 4.35; N, 14.93.

*6.1.9. 1-(2-Chlorophenyl)-2-(4-chlorophenyl)ethanone (**23**)*

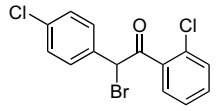


To a suspension of zinc (30 mesh, 18.0 g, 275 mmol) and Pd(PPh$_3$)$_4$ (2.00 g, 1.73 mmol) in DME (50 mL) at ambient temperature was added a solution of 2-chlorobenzoyl chloride (**22**) (23.8 g, 136 mmol) in DME (50 mL). The reaction mixture was cooled to 0 °C and a solution of 4-chlorobenzyl bromide (**21**) (28.3 g, 138 mmol) in DME (100 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and EtOAc (200 mL) was added to the crude product. The EtOAc solution was washed with 2 N HCl (100 mL) and brine (100 mL), concentrated

to a solid, and triturated with hexanes (200 mL). The solids were collected by filtration to afford 1-(2-chlorophenyl)-2-(4-chlorophenyl)ethanone (**23**) (28.0 g, 78%). The melting point of the product (mp=62–64 °C) was in accordance with the reported data from an alternative synthesis.[28]

^{1}H NMR ($CDCl_3$): δ 7.20–7.44 (m, 8H), 4.26 (s, 2H).

*6.1.10. 2-Bromo-1-(2-chlorophenyl)-2-(4-chlorophenyl)-ethanone (**24**)*



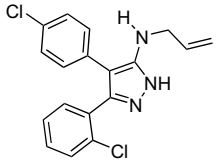
To a solution of 1-(2-chlorophenyl)-2-(4-chlorophenyl)-ethanone (**23**) (21.1 g, 79.7 mmol) in CH_2Cl_2 (200 mL) was added a solution of bromine (14.3 g, 89.6 mmol) in AcOH (200 mL). The reaction mixture was stirred overnight and water (200 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The organic extracts were combined and washed with H_2O (200 mL). The organic extracts were concentrated and the crude product was triturated in hexanes (250 mL) to afford 2-bromo-1-(2-chlorophenyl)-2-(4-chlorophenyl)ethanone (**24**) (20.0 g, 73%) as a pale yellow solid, mp=91–94 °C.

IR (thin film) cm^{-1} 3065, 1698, 1567, 1473, 1321, 1119, 853, 670. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.3 Hz, 2H), 7.32 (d, J=8.3 Hz, 2H), 7.27–7.40 (m, 4H), 6.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (13 of 14 signals were observed): δ 194.5, 137.2, 135.6, 133.5, 132.6, 131.1, 131.1, 130.8, 130.6, 130.4, 129.3, 127.3, 52.2. Anal. Calcd for $C_{14}H_9BrCl_2O$: C, 48.88; H, 2.64. Found: C, 48.84; H, 2.44.

6.2. General procedure for the preparation of *N*-protected pyrazol-5-amine

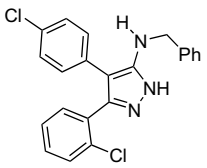
Bromoketone **24** (5 mmol) and 4-allyl or 4-benzylthiosemicarbazide (**26a** or **26b**) (5 mmol) were added to EtOH (60 mL) at 0 °C. The suspension was allowed to warm to room temperature overnight. HBr (1 mL of a 48% aqueous solution) was added and the reaction mixture was heated to 80 °C for 4 h. HCl (5 mL of a 6 N solution) was added and heating was continued for 16 h. The mixture was cooled to ambient temperature and concentrated. The residue was partitioned between EtOAc (50 mL) and 2 N NaOH (25 mL). The mixture was filtered and the layers were separated. The organic layer was concentrated and the crude product purified by chromatography on silica gel (4:1 EtOAc/hexanes) to afford the desired product.

*6.2.1. N-Allyl-3-(2-chlorophenyl)-4-(4-chlorophenyl)-1H-pyrazol-5-amine (**27a**)*



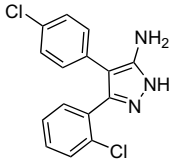
Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J=7.9 Hz, 1H), 7.29–7.14 (m, 6H), 7.08 (d, J=8.3 Hz, 2H), 6.06–5.97 (m, 1H), 5.26 (dd, J=7.4, 1.2 Hz, 1H), 5.14 (dd, J=10.4, 1.2 Hz, 1H), 3.94 (d, J=5.4 Hz, 2H).

*6.2.2. N-Benzyl-3-(2-chlorophenyl)-4-(4-chlorophenyl)-1H-pyrazol-5-amine (**27b**)*



Yield 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.22 (m, 11H), 7.16 (d, J=8.6 Hz, 2H), 4.50 (d, J=5.6 Hz, 2H), 4.00 (br t, J=5.6 Hz, 1H).

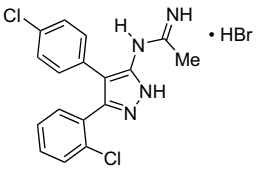
*6.2.3. 3-(2-Chlorophenyl)-4-(4-chlorophenyl)-1H-pyrazol-5-amine (**19**)*



Bromoketone **24** (3.41 g, 9.95 mmol) and 4-benzhydrylthiosemicarbazide (**26c**) (2.58 g, 10.0 mmol) were added to EtOH (120 mL) at 0 °C. The suspension was allowed to warm to room temperature overnight. HBr (2 mL of a 48% aqueous solution) was added and the reaction mixture was heated to 80 °C for 4 h. HCl (10 mL of a 6 N solution) was added and heating was continued for 16 h. The mixture was cooled to room temperature and concentrated. The residue was partitioned between EtOAc (100 mL) and 2 N NaOH (50 mL). The mixture was filtered and the layers were separated. The organic layer was concentrated and the crude product purified by chromatography on silica gel (4:1 EtOAc/hexanes) to afford 3-(2-chlorophenyl)-4-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**19**) as a slightly tan solid (2.10 g, 70%), mp 156–157 °C.

IR (thin film) cm^{-1} 3425, 1603, 1563, 1347, 1175, 1125, 865, 780, 630. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J=8.3 Hz, 2H), 7.22 (d, J=8.7 Hz, 2H), 7.16–7.30 (m, 5H), 7.09 (d, J=9 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8, 133.1, 132.7, 132.6, 132.5, 130.7, 130.5, 130.2, 130.0, 129.9, 129.7, 129.2, 128.6, 128.3, 127.4. Anal. Calcd for $C_{15}H_{11}Cl_2N_3$: C, 59.23; H, 3.65; N, 13.81. Found: C, 58.98; H, 3.57; N, 13.61.

*6.2.4. N-(3-(2-Chlorophenyl)-4-(4-chlorophenyl)-1H-pyrazol-5-yl)acetamidine hydrobromide (**33**·HBr)*



To a stirred solution of 3-(2-chlorophenyl)-4-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**19**) (606 mg, 1.99 mmol) in EtOH (10 mL) at 0 °C was added *S*-2-naphthylmethyl thioacetimidate hydrobromide (622 mg, 2.10 mmol). The reaction mixture was allowed to warm to room temperature overnight, concentrated under reduced pressure, and dissolved in MeOH (4 mL). The solution was added to *i*-Pr_2O (30 mL) and the resulting solids were filtered and dried to afford the title compound (531 mg, 63%), mp 228–230 °C.

Compound **33** was characterized as the free base. IR (thin film) cm^{-1} 3092, 3014, 1613, 1550, 1482, 1269, 1199, 1118, 946, 771, 659,

540. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (br s, 1H), 7.52–7.18 (m, 8H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) (7 of 15 signals observed): δ 133.1, 130.6, 130.4, 128.3, 128.3, 128.2, 30.2. Anal. Calcd for $C_{15}H_{11}Cl_2N_3$: C, 59.14; H, 4.09; N, 16.23. Found: C, 59.44; H, 4.47; N, 15.33.

6.2.5. Telescoped conversion of bromoketone **24** to pyrazolotriazinone **10**

Bromoketone **24** (10.26 g, 30.0 mmol) was dissolved in ethanol (360 mL, some warming required for dissolution) and cooled to 0 °C. To this turbid solution was added *N*-benzhydrylthiosemicarbizide **26c** (8.10 g, 31.5 mmol), and the resulting suspension was allowed to warm to room temperature and stirred overnight. The slurry was then treated with 30 mL of 6 N HCl and warmed in an 80 °C oil bath for 24 h. At this point TLC and HPLC analyses showed complete formation of 5-aminopyrazole **19**. The slurry was cooled to room temperature, and a flocculent white precipitate was removed by filtration. The filtrate was concentrated and dried by concentration from 400 mL toluene added in several portions on a rotary evaporator. The resulting salt (**8**·HCl) was free based by partitioning between 100 mL of 2 N NaOH and 100 mL of 2-methyltetrahydrofuran. The layers were separated, and the aqueous phase was washed with an additional 100 mL of 2-methyltetrahydrofuran. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give ca. 8 g of free base **8** as an amorphous solid. This material was dissolved in ethanol (130 mL) and cooled in an ice bath. *S*-2-Naphthylmethylthioacetimidate hydrobromide **32b** (7.47 g, 25.2 mmol, 1.05 equiv based on 80% yield of **8**) was added, and the mixture was stirred and allowed to warm to ambient temperature overnight. The solvent was removed by rotary evaporation and the residue was dissolved in 25 mL of methanol. This slurry was poured into 250 mL of isopropyl ether, and the resulting solids were collected by filtration and air-dried to provide 8.2 g of **33**·HBr. The salt was free based in 100 mL of 2 N NaOH and 100 mL of 2-methyltetrahydrofuran. The layers were separated and the aqueous phase was extracted with an additional 100 mL of 2-methyltetrahydrofuran. The combined organics were dried over $MgSO_4$, filtered, and evaporated to provide the free base **33**. This material was dissolved in DMSO (100 mL) and treated with carbonyldiimidazole (3.73 g, 23 mmol). The resulting solution was stirred at room temperature for 3 h. It was then poured into 500 mL of 1 N HCl solution, which precipitated the product (**10**). The solids were collected by filtration, washed with water, and dried overnight in a vacuum oven (30 °C, 20–30 mm). The title product (**10**) was obtained as an off-white solid (6.4 g, 58% overall yield), spectral data for which matched that reported in the previous procedure.

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