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Preclinical optimization of gp120 entry-antagonists as anti-HIV-1 agents with improved cytotoxicity and ADME properties through rational design, synthesis, and antiviral evaluation

Francesca Curreli[a], Shahad Ahmed[a], Sofia M. Benedict Victor[a], Ildar R. Iusupov[b], Pavel O. Markov[b], Alexander V. Kurkin[b], Andrea Altieri[b], Asim K. Debnath*[a]

[a]Laboratory of Molecular Modeling & Drug Design, Lindsley F. Kimball Research Institute, New York Blood Center, 310 E 67th Street, New York, NY 10065, USA

[b]EDASA Scientific, Scientific Park, Moscow State University, Leninskie Gory Bld. 75, 77-101b, 119992 Moscow, Russia

*Corresponding author

Keywords

HIV-1, ENV-pseudovirus, gp120 entry-antagonist, cytotoxicity, broad-spectrum, structure-activity relationship (SAR), selectivity index (SI), ADME

ABSTRACT

We previously reported a milestone in the optimization of NBD-11021, an HIV-1 gp120 antagonist, by developing a new and novel analog, NBD-14189 (**Ref1**), which showed antiviral activity against HIV-1_{HXB2}, with an IC_{50} of 89 nM. However, cytotoxicity remained high, and the ADME data showed relatively poor aqueous solubility. To optimize these properties, we replaced the phenyl ring in the compound with a pyridine ring and synthesized a set of 48 novel compounds. One of the new analogs, NBD-14270 (**8**), showed a marked improvement in cytotoxicity, with a 3-fold and 58-fold improvements in SI values compared with that of **Ref1** and NBD-11021, respectively. Furthermore, the *in vitro* ADME data clearly showed improvements in aqueous solubility and other properties compared with those for **Ref1**. The data for **8** indicated that the pyridine scaffold is a good bioisostere for phenyl, allowing the further optimization of this molecule.

INTRODUCTION

According to the Joint United Nations Programme on HIVAIDS (UNAIDS) report, published in 2018, 37 million people are living with HIV, and almost 2 million new infections are diagnosed each year. Despite the availability of more than 30 Food and Drug Administration (FDA)-approved drugs for acquired immunodeficiency syndrome (AIDS) treatment, AIDS remains a major global public health concern; although, combination antiretroviral therapies (cART) can help manage this devastating disease. However, no vaccine has yet been developed to manage the transmission of the human immunodeficiency virus (HIV), and despite many years of effort, no cure has been identified for HIV. Therefore, drug-based treatments remain the only option for those who have been infected with the virus. Furthermore, HIV patients must engage in life-long therapy regimens. Unfortunately, due to the very high heterogeneity among HIV strains, drug-associated toxicities and difficulties with adherence often result in treatment failure. Long-term use of HIV treatment drugs may also lead to the emergence of drug-resistant HIV. As a result, treatment-experienced patients may exhaust their treatment options. Therefore, the development of novel drugs, with fewer side effects and high antiviral potencies against a large array of drug-resistant HIV-1, is urgently needed. To achieve this goal, the continued discovery of new classes of drugs that target novel HIV components is critical.

HIV fusion and attachment (often collectively termed as “entry”) are the most critical steps necessary for HIV to initiate its life cycle in the host cell[1-4]. Despite the importance of these steps, only two FDA-approved drugs target the HIV-1 entry pathway: Fuzeone (Enfuvirtide), which targets HIV-1 glycoprotein 41 (gp41), and Maraviroc, which targets C-C chemokine receptor type 5 (CCR5) co-receptors. Thus far, no FDA-approved drugs target the HIV-1 envelope glycoprotein gp120. However, the potential of gp120 as a drug target was validated by reports describing several highly potent HIV-1 attachment inhibitors, from Bristol-Meyer Squibs (BMS)[5-13], our group, and others[14-18]. One of the BMS attachment inhibitors, known as Fostemsavir (BMS-663068), is currently in an advanced stage of clinical

development and demonstrated success in a recent Phase III clinical trial (Bright Study). Until recently, the target site of this class of attachment inhibitors being developed by BMS was uncertain. In 2017, Pancera et al. reported first the X-ray crystal structures of these inhibitors, with a trimeric HIV-1 envelope[19]. Interestingly, these crystal structures showed that the binding pocket for this class of inhibitors was distinct from the Phe43 cavity induced by the cluster of differentiation 4 (CD4), the cellular receptor that binds to gp120. In contrast, Madani et al. first suggested that NBD-556, which our group identified and reported in 2005[13], binds to the highly conserved Phe43 cavity[20]. In 2012, we solved the X-ray crystal structure of NBD-556 bound to gp120, confirming that NBD-556 binds to the Phe43 cavity[11]. Unfortunately, NBD-556 was shown to be a CD4-agonist that could enhance HIV-1 infection in CD4-CCR5+ cells[20]. This undesirable trait motivated us to use the insights gained from the crystal structure to modify the structure of NBD-556, to convert this compound into a gp120 entry-antagonist. We were successful and reported the first gp120 entry-antagonist, NBD-11021, in 2012[21]. Subsequently, a series of X-ray structures, showing gp120 entry-antagonists bound to monomeric gp120, have confirmed that these antagonists also bind to the Phe43 cavity[9, 11, 12, 22].

Recently, we reported the successful design of our most advanced gp120 antagonist, NBD-14189 (**Ref1, Figure 1**), which was tested against a large panel of HIV-1 Env-pseudotyped viruses, representing a diverse set of clinical isolates and multiple HIV subtypes[10]. **Ref1** showed remarkable antiviral potency (as low as 63 nM), indicating that this compound has broad-spectrum inhibitory activity against HIV-1[10]. Furthermore, this inhibitor had ADME properties comparable to BMS-626529, a prodrug of which, BMS-663068, is currently undergoing Phase III clinical trials[10]. However, the *in vitro* ADME and cellular toxicity data confirmed that further improvements could be made to the cellular toxicity of **Ref1**, to improve the selectivity index (SI = CC_{50}/IC_{50}) and to the ADME properties, especially, aqueous solubility. Towards that goal, we replaced the phenyl group in Region I (**Figure 1**) with a pyridine moiety, a unique aromatic ring. The use of pyridine as a bioisostere of aromatic rings has been reported in the fields of medicinal chemistry and drug discovery to improve aqueous

solubility, stability, and the ability to form H-bonds[23-25]. Here, we report the detailed synthesis, structure-activity relationships (SARs), antiviral activities, and ADME properties of a large set of pyridine-based analogs, with considerable improvement over the most potent gp120 entry-antagonists previously reported by our group. This study explored a new scaffold in Region I that resulted in many improved properties while still displaying potent antiviral activity.

CHEMISTRY

The syntheses of the novel inhibitors are described in **Schemes 1-7**. First, we prepared a series of 5-arylpyrrole-2-carboxylic acids with pyridine pharmacophoric fragment or its bioisosteres - pyrimidine and pyridazine (**Scheme 1**). Acids **S4 a-h** were prepared using the general scheme involving Suzuki coupling of pyridine/pyrimidine/pyridazine halogenides with N-Boc-2-pyrrole boronic acid, followed by Boc cleavage, acylation, and semi-haloform reaction[26]. Aryl bromides and aryl chlorides were commercially available. Acid **S8** was prepared using a general procedure A involving Suzuki coupling of 4-Bromo-2-fluoropyridine and with N-Boc-2-pyrrole boronic acid, followed by Boc cleavage (MeOH-HCl) afforded the 2-methoxy-4-(1H-pyrrol-2-yl)pyridine **S6** in good yield (67%), which was then subjected first to an acylation and then to a semi-haloform reaction[8, 21, 27-29].

5-Aryl-3-methyl-1H-pyrrole-2-carboxylic acids were prepared using commercially available reagents (2-bromo-5-(trifluoromethyl)pyridine or 2-bromo-5-chloropyridine) and known compound N-Boc-β-iododehydroamino acid methyl esters **R4** as per the reported procedure[29] (**Scheme 3**). This one-pot, two-step procedure occurs by a Sonogashira coupling followed by a 5-endo-dig-cyclization, which involves the nitrogen atom of the dehydroamino acid.

The Suzuki approach could not be used with the methylpyrrole intermediates **S15** and **S16** due to chemical feasibility issues related to the synthesis of the methyl pyrrole boc-protected derivative needed as a substrate. Except for **S23**, **S32,** and **S37**, all the required intermediary protected secondary amines have been prepared using an enantioselective pathway reported previously[9]. Instead, **S23** and **S32**, due to the extended and different side

chains, have been prepared accordingly to **Schemes 4** and **5**, respectively, but still exploiting the enantioselective step as per the *General Procedure E*. While the synthetic approach for **S37** is depicted on **Scheme 6**, it was obtained as a racemate. Since the corresponding final compound **31** showed no improvement in anti-HIV-1 activity, but rather a loss of activity, therefore no attempts were wasted in the isolation of the corresponding enantiomers.

The synthesis of all final 48 pyridine analogs (**1**-**48, Table 1**) was performed as per Scheme 7. The amines **S38-S40** were prepared using a method described in our earlier work. Similarly, amines **S41**-**S43 and S44 and S45** were synthesized, starting from the appropriate thiazole derivative and following the protocols as reported earlier[10, 28]r

All the alloc protected intermediates were worked-up as per the *general procedure H[10],* and the corresponding alloc products (**1a-48a**) were used directly in the next step without characterization.

RESULTS AND DISCUSSION

Optimization strategy

In recent years, we have made significant progress converting NBD-556, the first-in-class CD4-agonist, into gp120 entry-antagonists, such as NBD-11021, NBD-14010, and **Ref1**, while simultaneously dramatically improving the anti-HIV potencies of these new molecules (**Figure 1**)[9, 10, 21]. Despite this success, we realized that our most potent inhibitor, **Ref1**, still requires further improvements in cytotoxicity and SI values. Furthermore, the *in vitro* ADME study indicated that **Ref1** requires improved solubility[10]. Poor aqueous solubility can lead to slow drug absorption, which may result in the poor bioavailability of drugs. Therefore, we reasoned that improved aqueous solubility and reduced toxicity are urgently necessary for our best inhibitors. However, the X-ray crystal structures of CD4 bound to gp120 and those of Phe43 cavity-targeted inhibitors bound to gp120 have confirmed that the hydrophobic cavity where Phe43 binds is narrow[9, 22]; therefore, the structural manipulation of the phenyl ring in our best inhibitors required careful consideration. We used a pyridine scaffold as a bioisostere, replacing the phenyl ring, due to its aromatic characteristics and increased basicity compared

with the phenyl ring, to improve aqueous solubility, minimize reactive metabolite formation, and mitigate toxicity liability[23-25]. While this article was in preparation, Kobayakawa et al. reported successful improvements in aqueous solubility and cytotoxicity by replacing the phenyl ring of NBD-556 with a pyridine scaffold[30].

Anti-HIV-1 screening and structure-activity relationships (SARs)

Our previously reported data for **Ref1**, the best gp120 entry-antagonist that we have identified to date, showed an anti-HIV-1 activity of 89 nM against HIV-1_{HXB2}; however, **Ref1** showed high cytotoxicity, with a SI value of 246[10]. Furthermore, although the SI value was considered to be reasonable, the cytotoxicity and ADME data indicated that further improvements in cytotoxicity and ADME properties, especially aqueous solubility, were necessary to develop this molecule into a preclinical candidate for further assessment. Until recently, our group and others have avoided altering the phenyl group in Region I (**Figure 1**) because all of the X-ray crystal structures of this class of compounds bound to HIV-1 gp120 have confirmed that this hydrophobic ring was inserted deep inside the Phe43 cavity, which is surrounded by hydrophobic residues. Pyridine was used by BMS as a substitute for the phenyl ring in the inhibitor that prevents the attachment of HIV gp120 to CD4 host cells, which led to the development of the potent clinical candidate BMS-488043[24]. BMS-488043 showed a better pharmacokinetic profile, including improved solubility, and better metabolic profiles than previously described inhibitors. To explore other alternative bioisosteres, we opted to utilize a pyridine scaffold for replacing the phenyl ring (**Figure 1**).

We made a concerted effort to synthesize pyridine analogs for some of our most active phenyl-containing inhibitors, produced 48 novel pyridine-based compounds, and determined comprehensive SARs for these compounds. In general, we observed that cytotoxicity improved considerably for these compounds compared with **Ref1** and a structurally similar analog, NBD-14136[10] (**Ref2, Figure 1**), irrespective of the position of "N" within the pyridine ring. The introduction of CH_2OH or higher congeners at position R_1 (**15-34**) improved cytotoxicity, but antiviral activity was dependent on other substituents in Regions I, II, and III.

For example, the introduction of the CH_3 group at positions R_4 and R_5 in Region III generally retained antiviral potency, but the toxicities of these compounds were higher (**9-12, 23, and 24**). An electron-withdrawing substituent at position R_7 generally improved or maintained antiviral potency; however, antiviral activity reduced considerably when an electron-donating substituent, such as CH_3, was introduced at position R_7 (**19 and 20**).

Although fluorine is an electron-withdrawing substituent and is hydrophobic, its presence at R_7 reduced antiviral activity, most likely due to its small size. When the "N" atom in pyridine was at positions Y or W (see the structures in **Table 1**), the antiviral potencies of these compounds dropped dramatically. Similarly, the presence of a bulkier group at position R_8 also had detrimental effects on antiviral activity, most likely due to steric limitations in the narrow hydrophobic cavity.

Interestingly, the presence of a CH_3 group at position R_6 improved antiviral activity, with no detrimental effects on toxicity. We also introduced a branched alcohol group ($CHOHCH_2OH$) at position R_1, which resulted in the loss of antiviral activity (**13, 14, and 29, 30**), although the cytotoxicity of these compounds remained low (higher CC_{50} values). Similarly, we introduced longer alcohol groups, such as $(CH_2)_2OH$ (**25, 26**) and $(CH_2)_3OH$ (**27, 28**) at R_1, and observed no substantial reductions in antiviral activity; however, cytotoxicity was somewhat higher for some of these compounds (**25**, **26** and **28**).

The most notable improvements we observed were for NBD-14270 (**8**), with an IC_{50} of 0.16 μM and a CC_{50} of 109.3 μM. The IC_{50} of **8** reduced by approximately 2-fold compared with **Ref1**, while the cytotoxicity (CC_{50}) improved by approximately 5-fold. However, the activity and cytotoxicity of **8** improved by 2-fold and 2.5-fold, respectively, compared with those for **Ref2**. The SI value for **Ref1** was 246, whereas the SI value for **8** reached 683, an almost 3-fold improvement. This remarkable improvement in the cytotoxicity and SI values prompted more in-depth assessments of the antiviral potency and ADME properties of this inhibitor.

Kobayakawa et al., in their recent report describing the replacement of the phenyl ring with pyridine, also showed measurable improvements in cytotoxicity for their pyridine analogs of NBD-556[30]. However, the closest analog of NBD-556 (5-chloro-2-substituted pyridine)

showed an antiviral potency (IC_{50}) reduction of approximately 358-fold, whereas the cytotoxicity (CC_{50}) improved by approximately 3-fold. Besides, some other reported analogs, such as 2-chloro-4-substituted pyridine and 2-chloro-5-substituted pyridine, showed antiviral potency reductions of 13-fold and 23-fold, respectively, whereas the cytotoxicity improvements were also approximately 3-fold for these compounds[30].

The new generation of inhibitors showed entry antagonist traits

Our first-generation NBD-compound, NBD-556 [13], was reported to facilitate HIV infection into CD4-negative cells that expressed the coreceptor CCR5 by mimicking CD4 and inducing a conformational change in gp120, promoting CCR5 binding and enhancing HIV-1 entry[31, 32]. Subsequently, we verified that our new inhibitors did not possess this undesirable trait and behaved as entry antagonists[9, 10]. In this study, we initially tested all 48 pyridine-containing molecules in a single-cycle assay against HIV-1_{HXB2}. We selected **8,** which exhibited the best anti-HIV-1 activity and a higher SI value (SI = 683), and NBD-14235 (**33),** which has a SI of 243 and close structural similarity to **8** to confirm that they are HIV-1 gp120 entry-antagonists. CD4-negative and CCR5-positive Cf2TH-CCR5 cells were infected with the recombinant CD4-dependant HIV-1_{ADA} virus, in the presence of escalating concentrations of these inhibitors. NBD-556 was used as a control. As shown in **Figure 2**, NBD-556 significantly enabled the infection of the Cf2Th-CCR5 cells, whereas **8** and **33** did not, indicating that these compounds maintained the HIV-1 entry antagonist property. Additionally, these compounds did not show toxicity at the doses used in this assay. We used these two molecules for further antiviral evaluation.

Antiviral activities of 8 and 33 against a large and diverse panel of HIV-1 Env-pseudotyped clinical isolates.

We previously reported systematic improvements in the anti-HIV-1 activities of our gp120 entry-antagonists against a large panel of diverse HIV-1 Env-pseudotyped clinical isolates[10].

Some of our best inhibitors against HIV-1_{HXB2} showed broad-spectrum antiviral activities against these clinical isolates[9, 10, 21, 27]. We selected **8** and **33** to evaluate the anti-HIV-1 activity against a set of 50 HIV-1 clinical isolates belonging to diverse subtypes, including primary, transmitted, and early founder HIV-1 isolates and a selection of 12 recombinant HIV-1 clones. Except for two dual-tropic (CCR5/CXCR4) clinical isolates, all of the clones tested use the CCR5 co-receptor for entry. We compared the antiviral activity of the new generation of inhibitors with that of the previously described inhibitor **Ref2**[10], which has structural similarity to **8**. **33** exhibited anti-HIV-1 activity similar to that of **Ref2**, as demonstrated by their overall mean IC_{50} values and their antiviral activities against the different HIV subtypes **(Table 2)**. The overall mean IC_{50} value for **Ref2** was 0.39 ± 0.02 μM (IC_{50} values ranged from 0.19-0.79 μM), whereas the overall mean IC_{50} value determined for **33** was 0.43 ± 0.02 μM (IC_{50} values ranged from 0.13-0.99 μM). **Ref2** showed better antiviral activities against subtype D viruses (mean IC_{50} value of 0.26 ± 0.03 μM), whereas **33** showed better antiviral activities against subtype C and D viruses (mean IC_{50} values of 0.37 ± 0.03 μM and 0.35 ± 0.07 μM, respectively). In contrast, the respective SI values (CC_{50}/IC_{50}) determined for the panel of pseudoviruses were higher for **33** than for **Ref2,** with 1.5–2.1-fold improvements, depending on the viral subtype. Furthermore, this new generation compounds exhibited a better cytotoxicity profile (**8**: CC_{50} of 109.3 ± 2 μM and **33**: CC_{50} of 85 ± 3 μM) than that for **Ref2** (CC_{50} of 42.4 ± 1.0 μM). **8** showed better SI values than both **Ref2** and **33,** as well as better anti-HIV-1 activities and a better cytotoxicity profile. The overall mean IC_{50} value for **8** was 0.18 ± 0.008 μM (IC_{50} values ranged from 0.11-0.33 μM). Except for subtype A (mean IC_{50} value of 0.22 ± 0.003 μM), **8** worked equally well against all of the subtypes tested (mean IC_{50} value of 0.17-0.18 μM). The SI value calculated using the overall mean IC_{50} value was 607.2, and depending on the viral subtype, the SI values varied from 497 to 643, representing 4.9–5.6-fold improvements compared with **Ref2**. Overall, **8** and **33** were active against all of the tested clinical isolates, regardless of the viral subtypes (A-D), indicating that these compounds have broad-spectrum inhibitory activity, unlike BMS-378806, an early stage attachment inhibitor, which despite its low nM potency showed weaker activity against A, C and D subtypes[33]. Furthermore, **8** and **33**, similar to earlier

reports for **Ref2**, were poorly active against the pseudovirus VSV-G, which was used here as a control, suggesting that the inhibitory activities of these compounds are specific to HIV-1. Additionally, **8** and **33** did not induce toxicity in the U87-CD4-CXCR4 cell line at the doses used for this assay.

Moreover, we tested the anti-HIV-1 activity of **8** and **33** against an HIV-1 panel, comprised of paired infant and maternal clones belonging to subtypes A and D/A. These HIV clones were isolated from chronically infected mothers and their respective infected infants[34]. Previous studies have shown that vertically transmitted HIV infant variants were more difficult to neutralize using combinations of broadly neutralizing antibodies (bNAbs) 2G12, biz, 2F5, and 4E10[34]. In this study, we found that **Ref2**, **8,** and **33** equally neutralized both the infant and maternal HIV-1 variants (**Table 3**), as shown by their overall mean IC_{50} values and the means for infant and maternal viruses. **8,** the most effective compound with an overall mean IC_{50} value of 0.37 ± 0.07 μM, was slightly more efficient against the maternal clones (mean IC_{50} value of 0.31 ± 0.04 μM) than against the infant clones (mean IC_{50} value of 0.43 ± 0.07 μM). These findings suggest that the new gp120 entry-antagonists can neutralize both infant and maternal HIV-1 variants.

Inhibitory activity of 8 and 33 against a large panel of FDA-approved-drug-resistant viruses

To further evaluate the neutralizing activities of **8** and **33**, we assessed these compounds against a large set of drug-resistant viruses, including 5 Enfuvirtide (T-20)-resistant viruses, 7 multi-drug, non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant viruses, which carry mutations that confer resistance to both NNRTIs and nucleoside inhibitors (NRTIs), 3 Raltegravir-resistant viruses, and 9 protease inhibitor(PI)-resistant viruses (**Table 4**). As a reference, the activities of the gp120 entry-antagonists were assessed against the reconstructed wild type (WT) HIV-1_{NL4-3} clone, from which the drug-resistant clones were obtained. For this assay, the WT HIV-1_{NL4-3} control virus or the drug-resistant viruses were

pretreated with the gp120 entry-antagonists and then used to infect TZMb-l cells. We found that **8** and **33** both inhibited WT HIV-1_{NL4-3}, with IC_{50} values of 2.1 and 1.1 μM, respectively. Moreover, both compounds neutralized the T-20-resistant viruses, with IC_{50} values similar to the IC_{50} values determined for the control virus, WT HIV-$1_{NL4-3.}$ Similar results were observed for the NNRTI-resistant viruses, and in some cases, the drug-resistant viruses appeared to be more sensitive to the gp120 entry-antagonists than the WT virus. The Raltegravir-resistant viruses and the PI-resistant viruses were also highly sensitive to **8** and **33**, as shown by their low IC_{50} values. For **33**, the IC_{50} values detected against these clones were 1.8–10.5-fold lower than the IC_{50} value detected for WT HIV-1_{NL4-3}, and for **8,** the IC_{50} values were 1.8–11.7-fold lower than the IC_{50} value detected for WT HIV-1_{NL4-3}. In conclusion, we found that **8** and **33** were active against all of the tested drug-resistant viruses, indicating that these compounds could potentially be successfully used in combination with other antiviral agents.

However, we are currently conducting experiments to identify the possible generation of drug-resistant mutants in response to the use of the most potent gp120 entry-antagonists examined in this study.

gp120 entry-antagonists inhibited cell-to-cell HIV-1 transmission

Another important feature described for the earlier generation of gp120 entry-antagonists was their ability to inhibit cell-to-cell HIV-1 transmission[10], which has been reported to be more efficient than HIV-1 cell-free infection[35, 36]. Multiple viral particles can be transmitted to non-infected cells simultaneously. Additionally, cell-to-cell HIV-1 transmission *in vitro* has been shown to be resistant to some potent, bNAbs, including CD4 binding site (CD4bs) antibodies[36-38] and NRTIs, but not to other antiretrovirals, including entry inhibitors, NNRTIs, and protease inhibitors[39].

Here, we evaluated the activities of the new generation of gp120 entry-antagonists, **8** and **33**, against cell-to-cell HIV-1 transmission and compared their activities to that of **Ref2,** which has previously been reported to inhibit cell-to-cell HIV-1 transmission[10] H9 cells,

chronically infected with HIV-1_{IIIB} (CXCR4-tropic), and MOLT-4 cells, chronically infected with HIV-1_{ADA} (CCR5-tropic), were used as donor cells, and TZM-bl cells were used as acceptor cells. BMS-626529 was used as a control treatment drug. Our results (**Table 5**) indicated that both **8** and **33** have similar activities to that for the previous generation compound, **Ref2,** against cell-to-cell HIV transmission. All of the tested compounds, including BMS-626529, showed better activities against the CXCR4-tropic virus HIV-1_{IIIB} than against the CCR5-tropic virus HIV-$1_{ADA.}$ In particular, the IC_{50} values for the gp120 entry-antagonists calculated against HIV-1_{IIIB} in the CXCR4-tropic assay were 1-fold lower than the IC_{50} values calculated against HIV-1_{ADA} in the CCR5-tropic assay.

***In vitro* ADME assessment**

The *in vitro* assessment of ADME properties has played an important role, especially for the pharmaceutical industry, in reducing the drug attrition rate. In 1997, the major causes of failure for drugs that advanced to clinical trials were poor ADME properties[40]. However, the judicious use of ADME assessments during the early stages of drug development has dramatically improved the failure rate of drugs during recent years[41]. Drug failures during the later stages of drug development can be very costly. Therefore, the major goal of the pharmaceutical industry with regards to drug development programs is to “fail early, fail cheaply[41].” Therefore, we also adopted *in vitro* ADME assessments in our early optimization phase of developing these entry-antagonists as future clinical candidates. We previously reported the ADME properties of our most active inhibitor, **Ref1**, which targets the Phe43 cavity of gp120, and compared our results with the data obtained for BMS-626529, a prodrug of which is showing promising results in Phase III clinical trials[10]. The ADME properties of **Ref1** indicated room for further improvements.

Since this is the first time we decide to use pyridine scaffold as aromatic ring in Region I and this bioisostere was used before in medicinal chemistry to improve physicochemical and ADME properties, it was also imperative for us to evaluate these properties by selecting one of our most active inhibitors, **8**, which has a better cytotoxicity profile and SI values than the

other compounds examined in this study, and compared with **Ref1** previously reported[10]. The data presented in **Table 6** shows that **8** (a pyridine analog) has approximately 3-fold improved solubility compared with **Ref1** (a phenyl analog) and BMS-626529, which was expected and was the basis of the design strategy used in this study. Since these inhibitors are expected to be used orally, we performed the Caco-2 bidirectional permeability experiment [apical to basolateral (A-B) and basolateral to apical (B-A) across the Caco-2 cell monolayer], which can be used to measure the efflux ratio and predict the human intestinal permeability of orally administered drugs. The data shown in **Table 6** indicates that the apparent permeabilities of **8** and the clinical candidate, BMS-626529, are similar. However, the permeability of **Ref1** was poor compared with both of these inhibitors. We used digoxin, a P-gp substrate, as a positive control to identify whether active efflux was mediated by P-gp. It is apparent that the efflux of **8**, **Ref1** and digoxin was mediated by P-gp. However, we were unable to directly compare the effects of P-gp inhibitors on permeability parameters because different P-gp inhibitors were used in the current study (1 μM valsopodar) and the previous study (100 μM verapamil)[10]. However, the data confirmed that all three compounds had efflux ratios greater than 2, suggesting the potential involvement of an efflux transporter, which can mediate the transport of these inhibitors from the basolateral side to the apical side. Interestingly, the efflux ratios for all three cases were reduced in the presence of a P-gp inhibitor. For **8**, BMS-626529, and digoxin (positive control) the efflux ratios were reduced to less than 2, indicating that these compounds could be P-gp substrates. However, for **Ref1,** the efflux ratio was not reduced to less than 2, indicating the possible involvement of other transporters, such as breast cancer-resistant protein (BCRP) or multi-drug resistance-associated protein 2 (MRP2).

We also examined the metabolic stability of **8** in the human liver microsome because the liver is the primary site of drug metabolism. The data in **Table 6** shows that **8** has the highest stability (93.5%) among the examined compounds, followed by **Ref1**, whereas BMS-626529 was metabolized to some degree (71.5%) in our earlier study. The clearance data (Cl_{int}) indicated that all three compounds are low-clearance compounds, and **8** had a half-life longer than 120 minutes. We did not calculate half-life data in our earlier reported study. It is

worthwhile to mention that compounds with high clearance values may not be considered favorable because they may be cleared rapidly from the body, and the drugs may have a short duration of action and may need multiple dosing. We also examined the protein-binding potential of these inhibitors in human plasma. The data indicated that both **8** and **Ref1** were highly bound (>99%), whereas BMS-626529 had a binding potential of 86.9%.

The oxidative biotransformation of many lipophilic drugs into hydrophilic counterparts is critical, facilitating the elimination of drugs from the body. The cytochrome P450 enzyme system plays a critical role in these oxidative biotransformation reactions associated with drug metabolism. More than 50 CYP450 enzymes have been identified, but CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 metabolize almost 80 percent of all drugs. Therefore, we decided to use this set of eight CYP450 enzymes to determine whether any of our potent inhibitors have inhibitory effects that may help predict potential drug-drug interactions when co-administered with other treatment agents. Earlier, we reported the inhibitory effects of **Ref1** and BMS-626529, which showed no inhibitory activities for doses as high as 25 μM. In this study, we escalated the tested doses to as high as 100 μM, and our most potent inhibitor, **8,** showed no inhibition at > 50 μM dose levels against CYP1A2, CYP2B6, and CYP3A. No inhibitory activities were observed against the other CYP450 enzymes at the 100 μM dose level.

CONCLUSIONS

Here, we reported a significant shift in the design of gp120 antagonists, based on our previously reported and optimized inhibitor, **Ref1**. The phenyl ring in this class of inhibitors has been accepted to represent the critical moiety for antiviral potency because this ring is located deep inside the narrow hydrophobic cavity, according to X-ray crystallography data. In this study, we deployed pyridine, a bioisostere of phenyl, as a scaffold to replace the phenyl ring. We synthesized 48 novel compounds and determined a comprehensive SAR to identify the best possible gp120 entry-antagonists that display improved cytotoxicity and ADME properties. We identified the two best inhibitors, **8** and **33**, as determined by antiviral activity

against HIV-$1_{HXB2.}$ These inhibitors were confirmed to be gp120 entry-antagonists and showed broad-spectrum activity against a large panel of HIV-1 Env-pseudotyped viruses, representing diverse subtypes. Although the antiviral potency of these two new inhibitors remained similar to that for **Ref1**, the cytotoxicity of **8** was substantially improved, with an overall SI value of 607 against 50 diverse clinical isolates. This improvement was quite substantial compared to the SI value for **33**, which was 198. The ADME data for **8** also showed a considerable improvement in aqueous solubility. All other ADME properties for **8** were comparable to those for the clinical candidate BMS-626529, a prodrug of which is currently being tested in Phase III clinical trials. Overall, the pyridine substitution of the phenyl ring has been the most effective alteration in our quest to identify a clinically relevant gp120 antagonist. This finding is expected to improve the antiviral potency, cytotoxicity, and ADME properties of this class of inhibitors for subsequent preclinical studies.

EXPERIMENTAL SECTION

Cells and viruses

TZM-bl cells [42], U87CD4+CXCR4+ cells [43], HIV-1 IIIB, infected H9 Cells [44], and MOLT-4 CCR5+ Cells [45] were obtained through the NIH ARP. HEK 293T cells were purchased from ATCC. CD4-negative Cf2Th-CCR5+ cells and Env expression vector pSVIIIenv-ADA were kindly provided by Dr. J. G. Sodroski [46]. HIV-1 Env molecular clone expression vector pHXB2-env (X4) DNA was also obtained through the NIH ARP [47]. HIV-1 Env molecular clones of gp160 genes for HIV-1 Env pseudovirus production were obtained as follows: clones representing the standard panels A, A/D, A2/D, D, and C (QB099.391M.Env.B1) were obtained through the NIH ARP from Dr. J. Overbaugh [48, 49]. The HIV-1 Env molecular clones panel of subtype A/G, A/E, and G Env clones were obtained through the NIH ARP from Drs. D. Ellenberger, B. Li, M. Callahan, and S. Butera [50]. The HIV-1 Env panel of standard reference subtype B Env clones was obtained through the NIH ARP from Drs. D. Montefiori, F. Gao and M. Li (PVO, clone 4 (SVPB11) TRO, Clone 11 (SVPB12), QH0692, clone 42 (SVPB6),

SC422661, clone B (SVPB8)); from Drs. B. H. Hahn and J. F. Salazar-Gonzalez (pRHPA4259, clone 7 (SVPB14)); from Drs. B. H. Hahn and D. L. Kothe (pTHRO4156 clone 18 (SVPB15), pCAAN5342 clone A2 (SVPB19)) [51, 52]. The subtype B clones pWEAUd15.410.5017, p1058_11.B11.1550, p1054.TC4.1499, p1006_11.C3.1601, p1056.TA11.1826 and p9021_14.B2.4571 were obtained through the NIH ARP from Drs. B. H. Hahn, B. F. Keele, and G. M. Shaw [53]. The subtype C HIV-1 reference panel of Env clones was also obtained through the NIH ARP from Drs. D. Montefiori, F. Gao, S. A. Karim, and G. Ramjee (Du172.17); from Drs. D. Montefiori, F. Gao, C. Williamson, and S. A. Karim (Du422.1), from Drs. B. H. Hahn, Y. Li and J. F. Salazar-Gonzalez (ZM197M.PB7; ZM214M.PL15, ZM249M.PL1); from Drs. E. Hunter and C. Derdeyn (ZM53M.PB12; ZM109F.PB4); from Drs. L. Morris, K. Mlisana, and D. Montefiori, (CAP210.2.00.E8) [54-56]. The HIV-1 Subtype C Panel of Indian gp160 Env Clones HIV-16055-2 clone 3, HIV-16936-2 clone 21, HIV-25711-2 clone 4 and HIV-225925-2 clone 22 were obtained through the NIH ARP from Drs. R. Paranjape, S. Kulkarni and D. Montefiori [50]. The panel of paired Infant and maternal HIV-1 Env Molecular Clones were obtained through the NIH ARP from Dr. J. Overbaugh [57]. The Env pseudotyped genes of BG505.T332N, KNH1144, and B41 were kindly provided by Dr. J. P. Moore of the Weil Cornell Medical College, NY.

The Env-deleted proviral backbone plasmids pNL4-3.Luc.R-.E-DNA (from Dr. N. Landau) [58, 59], the pSG3Δ^{env} DNA (from Drs. J. C. Kappes and X. Wu) [42, 52] and the pNL4-3 (from Dr. Malcolm Martin) [60] were obtained through the NIH ARP Division of AIDS, NIAID, NIH. The following molecular clones were also obtained through the NIH ARP, Division of AIDS, NIAID, NIH: the panel of Enfuvirtide (T-20) resistant viruses from Trimeris, Inc. [60, 61]; the panel Multi-Drug Resistant NNRTI Infectious Clones from Dr. R. Shafer [62]; the Raltegravir-resistant infectious molecular clones from Dr. R. Shafer and E. Reuman, M.S [63] and the multi-drug Protease inhibitor-resistant infectious clones from Dr. R. Shafer [64].

MLV gag-pol-expressing vector pVPack-GP, Env-expressing vector pVPack-VSV-G, and a pFB-Luc vector were obtained from Stratagene (La Jolla, CA).

Pseudovirus preparation

Pseudoviruses capable of single-cycle infection were prepared as previously described [27, 31]. Briefly, 5 x 10^6 HEK293T cells were transfected with an HIV-1 Env-deleted pro-viral backbone plasmid pSG3$^{\Delta env}$ or pNL4-3.Luc.R-.E- DNA, and an HIV-1 Env-expression plasmid by using FuGENE6 (Promega). The control VSV-G pseudovirus was prepared by transfecting the HEK293T cells with a combination of the Env-expressing plasmid pVPack-VSV-G, the MLV gag-pol-expressing plasmid pVPack-GP, the pFB-Luc plasmid, and FuGENE6. Pseudovirus-containing supernatants were collected two days after transfection, filtered, tittered, and stored in aliquots at −80 °C.

Measurement of antiviral activity

Single-cycle infection assay in TZM-bl cells. The antiviral activity of the gp120 entry-antagonists was evaluated in single-cycle infection assay by infecting TZM-bl cells with HIV-1 pseudotyped with the Env from the lab-adapted HIV-1_{HXB-2} (CXCR4-tropic). Additionally, **Ref2**, **33**, and **8** were tested against a large group of HIV-1 pseudotyped with the Env from the panel of clinical isolates as previously described [27, 31]. Briefly, TZM-bl cells were plated at 1 x 10^4 / well in a 96-well tissue culture plate and cultured overnight. On the following day, HIV-1 pseudovirus was pre-treated with graded concentrations of the small molecules for 30 min and added to the cells. Following three days of incubation, the cells were washed and lysed with 50 µl of lysis buffer (Promega). 20 µl of the lysates were transferred to a white plate and mixed with the luciferase assay reagent (Promega). The luciferase activity was measured immediately with a Tecan Spark reader, and the percent inhibition by the compounds and the IC_{50} (the half-maximal inhibitory concentration) values were calculated using the GraphPad Prism software.

Single-cycle infection assay in U87-CD4-CXCR4 cells. The antiviral activity of **Ref2**, **33**, and **8** was tested against the control pseudovirus VSV-G in U87-CD4-CXCR4 cells. Briefly, U87-CD4-CXCR4 cells were plated in a 96-well tissue culture plate at 1 x 10^4/well and cultured

at 37 ºC. The following day, aliquots of pseudovirus pre-treated with graded concentrations of the small molecules for 30 min, were added to the cells and incubated for three days. Cells were washed and lysed with 40 µl of lysis buffer. The lysates were then transferred to a white plate and mixed with the luciferase assay reagent. The luciferase activity was immediately measured to calculate the percent of inhibition and IC_{50} values by using the GraphPad Prism software.

Assay in Cf2Th-CCR5 cells

CD4-negative Cf2Th-CCR5 cells were plated at 6×10^3 cells/well in a 96-well tissue culture plate and incubated at 37 C. The cells were infected with the recombinant CD4-dependent pseudovirus HIV-1_{ADA} as previously described [18]. Briefly, aliquots of HIV-1_{ADA} pseudovirus pre-treated with graded concentrations of compounds for 30 min were added to the cells and cultured for 48 h. Cells were washed with PBS and lysed with 40 µl of cell lysis reagent. Lysates were transferred to a white 96-well plate and mixed with the luciferase assay reagent. The luciferase activity was immediately measured to obtain the relative infection compared to the untreated control. The Relative virus infectivity indicates the ratio of the amount of infection detected in the presence of the compounds and the amount of infection detected in the absence of the compounds.

Measurement of antiviral activity against drug-resistant viruses in TZM-bl cells

The antiviral activity of the gp120 entry-antagonists against a panel of drug-resistant viruses was evaluated by infecting TZM-bl cells. Briefly, TZM-bl cells were plated at 10^4/well in a 96 well plate and cultured overnight. On the following day, HIV-1 drug-resistant viruses were pre-treated with graded concentrations of the small molecules for 30 min and added to the cells. Following 48 h incubation, the cells were washed and lysed. The cellular lysates were transferred to a white plate, and the luciferase activity was immediately measured with a Tecan Spark reader. The percent inhibition by the compounds and the IC_{50} values were calculated using the GraphPad Prism software, as reported above.

Cell-to-Cell HIV-1 Transmission

The cell-to-cell HIV-1 transmission inhibition assay was performed as previously described [65, 66], with few modifications. Briefly, TZM-bl cells (used as acceptor cells**)** were plated at 10^4/well in a 96 well plate 24 h before the assay. As transmitting cells, we used H9 cells chronically infected with HIV-1_{IIIB} at 2 × 10^3 cells/well for the CXCR4-tropic assay and MOLT-4/CCR5 cells chronically infected with HIV-1_{ADA} at 2 × 10^3 cells/well for the CCR5-tropic assay. The transmitting cells were pre-treated with 200 µg/mL mitomycin C (Sigma) for 1 h at 37 °C, washed with PBS, and incubated with the acceptor cells in the presence of escalating concentrations of compounds for 24 h. Therefore, the cells were washed and lysed. The lysates were mixed with the luciferase assay reagent. The luciferase activity was immediately measured to calculate the percent of inhibition and IC_{50} values by using the GraphPad Prism software.

Evaluation of cytotoxicity

TZM-bl cells and U87-CD4-CXCR4 cells. The cytotoxicity of the gp120 entry-antagonists in TZM-bl and U87-CD4-CXCR4 cells was measured by using the colorimetric CellTiter 96® AQueous One Solution Cell Proliferation Assay (MTS) (Promega) following the manufacturer's instructions. Briefly, the cells were plated at 1 x 10^4 / well and cultured at 37 °C. Following overnight incubation, the cells were incubated with 100 µl of the compounds at graded concentrations and cultured for three days. The MTS reagent was added to the cells and incubated for four h at 37 ºC. The absorbance was recorded at 490 nm. The percent of cytotoxicity and the CC_{50} (the concentration for 50 % cytotoxicity) values were calculated as above.

Cf2Th-CCR5 cells. The cytotoxicity of the small molecules in Cf2Th-CCR5 cells was also measured with the colorimetric CellTiter 96® AQueous One Solution Cell Proliferation Assay. Briefly, Cf2Th-CCR5 cells were plated in a 96-well plate and cultured at 37 °C overnight. Next, the cells were incubated with 100 µl of the compounds at graded concentrations and cultured

for 48 h. The MTS reagent was added to the cells, and 4 h later, the absorbance was recorded at 490 nm. The percent of cytotoxicity and the CC_{50} values were calculated as above.

In vitro ADME study

Details of the *In vitro* ADME study and data analyses can be found in the "Supplemental Information."

Chemistry

General. We used commercial reagents and solvents without further purification. We also performed all reactions in the air atmosphere unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC Silica gel plates (60 F254), using a UV light for visualization and basic aqueous potassium permanganate or iodine fumes as a developing agent. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 instrument with operating frequency of 400 and 100 MHz, respectively, and calibrated using residual undeuterated chloroform (δH = 7.28 ppm) and CDCl3 (δC = 77.16 ppm) or undeuterated DMSO (δH = 2.50 ppm) and DMSO-d6 (δC = 39.51 ppm) as internal references. The following abbreviations are used to set multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The purity of the final compounds was checked by LCMS in a Shimadzu LCMS-2010A using three types of detection systems such as EDAD, ELSD, and UV and was found to be ≥95%.

General procedure A: for Suzuki coupling

To a solution containing appropriate bromide (or chloride) (50 mmol, 1 equiv), (1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid (50 mmol, 1 equiv) in THF-H_2O (1:1, 100 mL), Na_2CO_3 (100 mmol, 2 equiv) and $Pd(Ph_3P)Cl_2$ (1 mol. %) were added under a nitrogen atmosphere. The mixture was stirred at reflux for 8-15 h (TLC-control). After cooling to the room temperature, water (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic

layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography using the hexane-EtOAc mixture as eluent afforded the desired compound. Compounds **S1a-h** were obtained following the ***general procedure A***. Compounds **S1g** and **S1h** were obtained from the corresponding chlorides.

Tert-butyl 2-(5-methylpyridin-2-yl)-1H-pyrrole-1-carboxylate (*S1a*)

Eluent: Hex-EtOAc (from 10:1 to 5:1), Rf=0.2 (5:1, Hex-EtOAc). Yield = 63%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.37 (s, 9 H), 2.34 (s, 3 H), 6.22 (t, *J*=3.3 Hz, 1 H), 6.36 (dd, *J*=3.2, 1.7 Hz, 1 H), 7.28 (d, *J*=8.1 Hz, 1 H), 7.33 (dd, *J*=3.2, 1.8 Hz, 1 H), 7.48 (dd, *J*=7.9, 1.8 Hz, 1 H), 8.42 - 8.45 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.3, 27.6 (3C), 83.5, 110.5, 115.3, 123.2, 123.2, 131.3, 134.2, 136.3, 149.2, 149.3, 150.2.

Tert-butyl 2-(5-chloropyridin-2-yl)-1H-pyrrole-1-carboxylate (S1b)

Eluent: Hex-EtOAc (from 20:1 to 10:1), Rf=0.3 (10:1, Hex-EtOAc). Yield = 84%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.41 (s, 9 H), 6.25 (t, *J*=3.3 Hz, 1 H), 6.43 (dd, *J*=3.3, 1.7 Hz, 1 H), 7.34 - 7.38 (m, 2 H), 7.66 (dd, *J*=8.4, 2.5 Hz, 1 H), 8.57 (d, *J*=2.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.8 (3C), 84.1, 110.8, 116.3, 124.0, 124.3, 130.2, 133.1, 135.6, 147.8, 149.2, 151.0.

Tert-butyl 2-(5-fluoropyridin-2-yl)-1H-pyrrole-1-carboxylate (*S1c*)

Eluent: Hex-EtOAc (from 20:1 to 10:1), Rf=0.3 (10:1, Hex-EtOAc). Yield = 68%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.39 (s, 9 H), 6.23 (t, *J*=3.3 Hz, 1 H), 6.39 (dd, *J*=3.3, 1.7 Hz, 1 H), 7.35 (dd, *J*=3.2, 1.7 Hz, 1 H), 7.39 (d, *J*=1.8 Hz, 1 H), 7.40 - 7.42 (m, 1 H), 8.47 (t, *J*=1.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.7 (3C), 83.9, 110.6, 115.8, 122.7 (d, *J*=18.6 Hz), 123.6, 124.6 (d, *J*=4.2 Hz), 133.1, 137.0 (d, *J*=23.8 Hz), 149.2 (d, *J*=1.5 Hz), 149.3, 158.4 (d, *J*=256.0 Hz).

Tert-butyl 2-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-1-carboxylate (*S1d*)

Eluent: Hex-EtOAc (from 30:1 to 20:1), Rf=0.3 (30:1, Hex-EtOAc). Yield = 65%.

^{1}H NMR ($CDCl_3$, 400 MHz): 1.42 (s, 9 H), 6.28 (t, *J*=3.3 Hz, 1 H), 6.54 (dd, *J*=3.4, 1.7 Hz, 1 H), 7.40 (dd, *J*=3.2, 1.7 Hz, 1 H), 7.54 (d, *J*=8.2 Hz, 1 H), 7.92 (dd, *J*=8.3, 2.2 Hz, 1 H), 8.87 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.6 (3C), 84.3, 110.9, 117.3, 122.8, 123.8 (q, *J*=272.0 Hz), 124.4 (q, *J*=33.0 Hz), 124.8, 132.9 (q, *J*=3.5 Hz), 133.0, 145.8 (q, *J*=4.1 Hz), 149.1, 156.0 (q, *J*=1.5 Hz).

Tert-butyl 2-(6-chloropyridin-3-yl)-1H-pyrrole-1-carboxylate (*S1e*)

Eluent: Hex-EtOAc (from 20:1 to 10:1), Rf=0.4 (10:1, Hex-EtOAc). Yield = 76%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.44 (s, 9 H), 6.25 - 6.29 (m, 2 H), 7.33 (d, *J*=8.2 Hz, 1 H), 7.41 (t, *J*=2.5 Hz, 1 H), 7.66 (dd, *J*=8.2, 2.5 Hz, 1 H), 8.38 (d, *J*=2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.8 (3C), 84.6, 111.1, 116.1, 123.1, 123.8, 129.3, 130.0, 139.4, 149.0, 149.5, 150.0.

Tert-butyl 2-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrrole-1-carboxylate (S1f)

Eluent: Hex-EtOAc (from 30:1 to 20:1), Rf=0.5 (30:1, Hex-EtOAc). Yield = 84%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.43 (s, 9 H), 6.30 (t, *J*=3.3 Hz, 1 H), 6.32 - 6.35 (m, 1 H), 7.45 (dd, *J*=3.2, 1.8 Hz, 1 H), 7.68 (d, *J*=8.1 Hz, 1 H), 7.86 (dd, *J*=8.1, 1.8 Hz, 1 H), 8.72 (d, *J*=1.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 27.7 (3C), 84.8, 111.3, 116.8, 119.5 (q, *J*=2.8 Hz), 121.8 (q, *J*=273.9 Hz), 124.3, 130.0, 133.2, 137.3, 146.3 (q, *J*=34.8 Hz), 148.9, 150.0.

Tert-butyl 2-(6-(trifluoromethyl)pyridazin-3-yl)-1H-pyrrole-1-carboxylate (*S1g*)

Eluent: Hex-EtOAc (from 20:1 to 5:1), Rf=0.4 (5:1, Hex-EtOAc). Yield = 61%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.45 (s, 9 H), 6.35 (t, *J*=3.4 Hz, 1 H), 6.73 (dd, *J*=3.4, 1.6 Hz, 1 H), 7.48 (dd, *J*=3.2, 1.7 Hz, 1 H), 7.75 - 7.79 (m, 2 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 27.8 (3C), 85.1, 111.6, 119.2, 121.7 (q, *J*=274.2 Hz), 122.8 (q, *J*=2.4 Hz), 125.8, 127.7, 129.9, 148.9, 149.5 (q, *J*=35.0 Hz), 157.2.

Tert-butyl 2-(5-chloropyrimidin-2-yl)-1H-pyrrole-1-carboxylate (*S1h*)

Eluent: Hex-EtOAc (from 30:1 to 20:1), Rf=0.5 (30:1, Hex-EtOAc). Yield = 58%..

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.44 (s, 9 H), 6.26 (t, *J*=3.3 Hz, 1 H), 6.78 (dd, *J*=3.4, 1.7 Hz, 1 H), 7.35 (dd, *J*=3.1, 1.7 Hz, 1 H), 8.67 (s, 2 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 27.8 (3C), 84.3, 110.9, 118.8, 125.7, 128.4, 131.8, 149.2, 155.2 (2C), 158.8.

General procedure B: for Boc-deprotection

To a solution containing Boc-protected compound (30 mmol) in MeOH (15 mL, 2M solution), 1M HCl solution in MeOH (45 mL) was added in a one portion. The mixture was stirred at reflux for 7-8 h. After cooling to the room temperature, solvent was evaporated. Then 10% aqueous K_2CO_3 (50 mL) was added carefully (CO_2 evolution) and mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude product was used in the next step without purification. Compound **S2a-h** were obtained following the ***general procedure B***.

5-Methyl-2-(1H-pyrrol-2-yl)pyridine (S2a)

Yield= 94 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.33 (s, 3 H), 6.31 - 6.35 (m, 1 H), 6.72 - 6.75 (m, 1 H), 6.89 - 6.91 (m, 1 H), 7.48 (dd, *J*=8.2, 1.9 Hz, 1 H), 7.53 (d, *J*=8.1 Hz, 1 H), 8.27 - 8.38 (m, 1 H), 10.73 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.2, 106.8, 109.9, 118.1, 119.9, 129.9, 131.8, 137.4, 148.5, 148.9.

5-Chloro-2-(1H-pyrrol-2-yl)pyridine (S2b)

Yield= 92 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.31 - 6.34 (m, 1 H), 6.71 - 6.74 (m, 1 H), 6.92 (td, *J*=2.6, 1.4 Hz, 1 H), 7.50 (d, *J*=8.6 Hz, 1 H), 7.60 (dd, *J*=8.6, 2.4 Hz, 1 H), 8.42 (d, *J*=2.2 Hz, 1 H), 9.90 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 107.9, 110.6, 118.9, 120.5, 128.3, 130.7, 136.4, 147.7, 148.9.

5-Fluoro-2-(1H-pyrrol-2-yl)pyridine (S2c)

Yield= 93 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.33 (dd, *J*=6.2, 2.7 Hz, 1 H), 6.66 - 6.71 (m, 1 H), 6.88 - 6.94 (m, 1 H), 7.38 (td, *J*=8.5, 2.8 Hz, 1 H), 7.56 (dd, *J*=8.8, 4.3 Hz, 1 H), 8.35 (d, *J*=2.8 Hz, 1 H), 9.96 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 107.1, 110.3, 119.1 (d, *J*=4.1 Hz), 120.2, 123.9 (d, *J*=19.3 Hz), 130.9, 136.7 (d, *J*=23.9 Hz), 147.4 (d, *J*=3.2 Hz), 157.8 (d, *J*=253.2 Hz).

2-(1H-Pyrrol-2-yl)-5-(trifluoromethyl)pyridine (*S2d*)

Eluent: Hex-EtOAc (from 20:1 to 10:1), Rf=0.5 (10:1, Hex-EtOAc). Yield = 88%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.32 - 6.37 (m, 1 H), 6.80 - 6.86 (m, 1 H), 6.94 - 7.03 (m, 1 H), 7.61 (d, *J*=8.4 Hz, 1 H), 7.83 (dd, *J*=8.4, 2.1 Hz, 1 H), 8.71 (s, 1 H), 9.74 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 109.6, 111.0, 117.6, 121.6 122.9 (q, *J*=33.0 Hz), 124.0 (q, *J*=271.6 Hz), 130.5, 133.7 (q, *J*=3.5 Hz), 146.1 (q, *J*=4.4 Hz), 153.5 (q, *J*=1.5 Hz).

2-Chloro-5-(1H-pyrrol-2-yl)pyridine (*S2e*)

Yield = 93%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.33 - 6.37 (m, 1 H), 6.57 - 6.60 (m, 1 H), 6.94 - 6.98 (m, 1 H), 7.32 (d, *J*=8.4 Hz, 1 H), 7.74 (dd, *J*=8.3, 2.6 Hz, 1 H), 8.52 (d, *J*=2.4 Hz, 1 H), 8.84 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 107.9, 110.6, 120.8, 124.5, 127.4, 128.2, 134.2, 144.6.

5-(1H-Pyrrol-2-yl)-2-(trifluoromethyl)pyridine (*S2f*)

Yield = 92%

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.29 - 6.41 (m, 1 H), 6.64 - 6.74 (m, 1 H), 6.92 - 7.04 (m, 1 H), 7.63 (d, *J*=8.2 Hz, 1 H), 7.89 (dd, *J*=8.2, 1.8 Hz, 1 H), 8.82 (d, *J*=1.8 Hz, 1 H), 9.32 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 109.2, 111.0, 120.9 (q, *J*=2.9 Hz), 121.8, 121.8 (q, *J*=273.7 Hz), 127.2, 131.5, 131.7, 144.7 (q, *J*=35.1 Hz), 144.9.

3-(1H-Pyrrol-2-yl)-6-(trifluoromethyl)pyridazine (*S2g*)

Yield = 95%

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.25 - 6.29 (m, 1 H), 7.07 - 7.14 (m, 2 H), 8.10 (d, *J*=9.0 Hz, 1 H), 8.20 (d, *J*=9.0 Hz, 1 H), 12.15 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 110.5, 112.7, 122.0 (q, *J*=273.5 Hz), 122.9, 124.2, 124.8 (q, *J*=2.2 Hz), 126.9, 147.3 (q, *J*=33.7 Hz), 154.8.

5-Chloro-2-(1H-pyrrol-2-yl)pyrimidine (*S2h*)

Yield = 90%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.20 (s, 1 H), 6.93 (d, *J*=1.8 Hz, 1 H), 6.97 (s, 1 H), 8.78 (s, 2 H), 11.77 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 110.1, 112.3, 123.2, 125.7, 129.4, 155.6 (2C), 157.1.

General procedure C: for acylation

Crude pyrrole from the previous step (1 equiv) was dissolved in CH_2Cl_2 (0.5 M solution), and pyridine (1.2 equiv) was added, followed by dropwise addition of TFAA (1.2 equiv). After completion of the addition, the mixture was stirred for 1 h, and the solvent was evaporated. The product was triturated in aqueous, and the precipitate was filtered, washed with aqueous twice, and dried on a filter. Compound **S3a-h** were obtained following the ***general procedure C***.

2,2,2-Trifluoro-1-(5-(5-methylpyridin-2-yl)-1H-pyrrol-2-yl)ethanone (*S3a*)

Yield = 89%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.34 (s, 3 H), 7.05 (d, *J*=4.2 Hz, 1 H), 7.28 (dd, *J*=3.9, 1.9 Hz, 1 H), 7.75 (dd, *J*=8.0, 1.4 Hz, 1 H), 8.09 (d, *J*=8.1 Hz, 1 H), 8.49 - 8.52 (m, 1 H), 12.87 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 17.8, 111.8, 117.0 (q, *J*=290.3 Hz), 120.6, 122.9 (q, *J*=3.5 Hz), 126.1, 133.4, 137.8, 142.6, 145.3, 149.8, 168.1 (q, *J*=35.0 Hz).

1-(5-(5-Chloropyridin-2-yl)-1H-pyrrol-2-yl)-2,2,2-trifluoroethanone (*S3b*)

Yield = 94%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.09 (dd, 1 H), 7.29 (dt, *J*=4.1, 2.0 Hz, 1 H), 8.07 (dd, *J*=8.6, 2.5 Hz, 1 H), 8.23 (d, *J*=8.6 Hz, 1 H), 8.69 (d, *J*=2.4 Hz, 1 H), 13.04 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 112.5, 117.0 (q, *J*=290.25 Hz), 122.0, 122.7 (q, *J*=3.5 Hz), 126.6, 130.7, 137.0, 141.5, 146.7, 148.3, 168.5 (q, *J*=35.0 Hz).

2,2,2-Trifluoro-1-(5-(5-fluoropyridin-2-yl)-1H-pyrrol-2-yl)ethanone (*S3c*)

Yield = 91%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.04 (dd, J=4.1, 2.3 Hz, 1 H), 7.28 (dt, J=4.1, 2.0 Hz, 1 H), 7.87 (td, J=8.8, 2.9 Hz, 1 H), 8.27 (dd, J=8.9, 4.4 Hz, 1 H), 8.65 (d, J=2.8 Hz, 1 H), 12.96 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 112.0, 117.0 (q, *J*=289.9 Hz), 122.4 (d, *J*=4.8 Hz), 122.7 (q, *J*=3.5 Hz), 124.1 (d, *J*=19.0 Hz), 126.4, 138.0 (d, *J*=24.5 Hz), 141.8, 144.9 (d, *J*=3.9 Hz), 158.7 (d, *J*=256.2 Hz), 168.3 (q, *J*=35.0 Hz).

2,2,2-Trifluoro-1-(5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrol-2-yl)ethanone (*S3d*)

Yield = 92%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.19 (dd, *J*=4.0, 2.2 Hz, 1 H), 7.27 - 7.32 (m, 1 H), 8.33 (dd, *J*=8.4, 1.7 Hz, 1 H), 8.40 (d, *J*=8.3 Hz, 1 H), 8.99 (s, 1 H), 13.19 (br. s., 1 H)

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 113.7, 117.2 (q, *J*=289.8 Hz), 120.9, 122.7 (q, *J*=1.5 Hz), 124.0 (q, *J*=271.5 Hz), 124.5 (q, *J*=32.2 Hz), 127.5, 135.1, 141.2, 146.7, 152.0, 169.1 (q, *J*=34.4 Hz).

1-(5-(6-Chloropyridin-3-yl)-1H-pyrrol-2-yl)-2,2,2-trifluoroethanone (*S3e*)

Yield = 87%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.08 (dd, *J*=4.2, 2.4 Hz, 1 H), 7.33 (dt, *J*=4.1, 2.0 Hz, 1 H), 7.64 (d, *J*=8.4 Hz, 1 H), 8.43 (dd, *J*=8.4, 2.6 Hz, 1 H), 9.02 (d, *J*=2.4 Hz, 1 H), 13.14 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 111.9, 117.1 (q, *J*=289.9 Hz), 123.2 (q, *J*=3.3 Hz), 124.5, 125.5, 126.8, 137.0, 139.1, 147.6, 150.2, 168.3 (q, *J*=35.0 Hz).

2,2,2-Trifluoro-1-(5-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrrol-2-yl)ethanone (S3f)

Yield = 93%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.14 (d, *J*=4.3 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 7.96 (d, *J*=8.3 Hz, 1 H), 8.61 (dd, *J*=8.2, 1.8 Hz, 1 H), 9.32 (d, *J*=1.7 Hz, 1 H), 13.24 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 112.6, 116.9 (q, *J*=289.8 Hz), 120.8 (q, *J*=2.2 Hz), 121.6 (q, *J*=273.7 Hz), 122.9 (q, *J*=3.7 Hz), 127.2, 129.1, 135.1, 138.4,145.7 (q, *J*=34.4 Hz), 147.7, 168.5 (q, *J*=35.1 Hz).

2,2,2-Trifluoro-1-(5-(6-(trifluoromethyl)pyridazin-3-yl)-1H-pyrrol-2-yl)ethanone (*S3g*)

Yield = 85%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.34 - 7.39 (m, 2 H), 8.39 (d, *J*=9.0 Hz, 1 H), 8.70 (d, *J*=9.0 Hz, 1 H), 13.50 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 114.1, 116.7 (q, J=289.8 Hz), 121.6 (q, J=274.0 Hz), 122.3 (q, J=3.1 Hz), 125.4 (q, J=2.0 Hz), 125.5, 128.0, 137.8, 149.2 (q, J=34.1 Hz), 153.8, 169.1 (q, J=35.4 Hz).

1-(5-(5-Chloropyrimidin-2-yl)-1H-pyrrol-2-yl)-2,2,2-trifluoroethanone (S3h)

Yield = 86%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.10 (d, *J*=3.9 Hz, 1 H), 7.24 (s, 1 H), 8.97 (s, 2 H), 13.07 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 114.2, 116.7 (q, *J*=289.8 Hz), 122.2 (q, *J*=2.9 Hz), 127.2, 129.2, 139.6, 155.3, 156.2 (2C), 168.7 (q, *J*=35.1 Hz).

General procedure D: for haloform reaction

Appropriate trifluoroethanone (1 equiv) was added to a solution of NaOH (5 equiv) in dioxane-H_2O mixture (1:1, 0.5M solution). The resulting reaction mixture was refluxed for 20 h and cooled to the room temperature. A concentrated aqueous HCl solution (~12 M, 5 equiv) was added dropwise. The resulting precipitate was filtered off, washed with H_2O and dried on filter. Compound **S4a-h** were obtained following the ***general procedure D***.

5-(5-Methylpyridin-2-yl)-1H-pyrrole-2-carboxylic acid (*S4a*)

Yield = 82%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.28 (s, 3 H), 6.77 - 6.84 (m, 2 H), 7.61 (dd, *J*=8.1, 2.1 Hz, 1 H), 7.88 (d, *J*=8.1 Hz, 1 H), 8.38 (d, *J*=1.8 Hz, 1 H), 11.69 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 17.9, 109.2, 116.5, 119.1, 124.8, 131.6, 136.4, 137.6, 147.1, 149.7, 162.0.

5-(5-Chloropyridin-2-yl)-1H-pyrrole-2-carboxylic acid (S4b)

Yield = 73%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.78 - 6.93 (m, 2 H), 7.94 (dd, *J*=8.6, 2.4 Hz, 1 H), 8.06 (d, *J*=8.6 Hz, 1 H), 8.58 (d, *J*=2.2 Hz, 1 H), 11.96 (br. s., 1 H), 12.57 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 110.3, 116.2, 120.3, 125.8, 128.8, 135.0, 136.8, 147.9, 148.2, 161.8.

5-(5-Fluoropyridin-2-yl)-1H-pyrrole-2-carboxylic acid (S4c)

Yield = 85%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.80 - 6.85 (m, 2 H), 7.74 (td, *J*=8.8, 2.9 Hz, 1 H), 8.08 (dd, *J*=8.8, 4.3 Hz, 1 H), 8.53 (d, *J*=2.8 Hz, 1 H), 11.86 (br. s., 1 H), 12.52 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 109.7, 116.3, 120.6 (d, *J*=4.4 Hz), 124.1 (d, *J*=18.8 Hz), 125.1, 135.4, 137.4 (d, *J*=24.0 Hz), 146.4 (d, *J*=3.7 Hz), 158.0 (d, *J*=253.4 Hz), 161.8.

5-(5-(Trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxylic acid S4d)

Yield = 80%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.76 - 6.95 (m, 1 H), 6.95 - 7.08 (m, 1 H), 8.12 - 8.31 (m, 2 H), 8.89 (s, 1 H), 12.18 (br. s., 1 H), 12.71 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 111.7, 116.3, 119.0, 122.7 (q, *J*=32.2 Hz), 124.0 (q, *J*=272.2 Hz), 126.7, 134.4 (q, *J*=3.7 Hz), 134.8, 146.2 (q, *J*=4.4 Hz), 153.1, 161.8.

5-(6-Chloropyridin-3-yl)-1H-pyrrole-2-carboxylic acid (S4e)

Yield = 91%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.73 - 6.89 (m, 2 H), 7.52 (d, *J*=8.4 Hz, 1 H), 8.29 (dd, *J*=8.4, 2.6 Hz, 1 H), 8.90 (d, *J*=2.4 Hz, 1 H), 12.26 (br. s., 1 H), 12.51 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 109.2, 116.4, 124.2, 125.5, 127.1, 132.0, 135.7, 146.3, 148.2, 161.8.

5-(6-(Trifluoromethyl)pyridin-3-yl)-1H-pyrrole-2-carboxylic acid (S4f)

Yield =80%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.84 - 6.87 (m, 1 H), 6.87 - 6.90 (m, 1 H), 7.85 (d, *J*=8.3 Hz, 1 H), 8.45 (dd, *J*=8.3, 1.5 Hz, 1 H), 9.20 (d, *J*=1.2 Hz, 1 H), 12.40 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 110.5, 116.6, 120.9 (q, *J*=2.9 Hz), 243.9 (q, *J*=273.7 Hz), 126.5, 130.8, 131.8, 133.5, 144.2 (q, *J*=33.7 Hz), 146.7, 161.9.

5-(6-(Trifluoromethyl)pyridazin-3-yl)-1H-pyrrole-2-carboxylic acid (S4g)

Yield = 87%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.91 (dd, *J*=3.9, 2.3 Hz, 1 H), 7.20 (dd, *J*=3.9, 2.4 Hz, 1 H), 8.27 (d, *J*=9.0 Hz, 1 H), 8.57 (d, *J*=9.0 Hz, 1 H), 12.55 (br. s., 1 H), 12.83 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 112.7, 116.4, 121.9 (q, *J*=273.7 Hz), 123.9, 125.1 (q, *J*=2.2 Hz), 127.9, 131.7, 148.2 (q, *J*=33.7 Hz), 154.7, 161.6.

5-(5-Chloropyrimidin-2-yl)-1H-pyrrole-2-carboxylic acid (S4h)

Yield = 75 %.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 6.81 (d, *J*=3.7 Hz, 1 H), 6.96 (d, *J*=3.7 Hz, 1 H), 8.87 (s, 2 H), 11.63 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 112.7, 115.7, 127.4, 128.1, 132.9, 155.9 (2C), 156.2, 161.7.

tert-Butyl 2-(2-fluoropyridin-4-yl)-1H-pyrrole-1-carboxylate (S5)

Compound **S5** was obtained following the ***general procedure A***. Yield = 67%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.45 (s, 9 H), 6.24 - 6.27 (m, 1 H), 6.36 (dd, *J*=3.3, 1.7 Hz, 1 H), 6.88 - 6.91 (m, 1 H), 7.14 - 7.17 (m, 1 H), 7.41 (dd, *J*=3.2, 1.7 Hz, 1 H), 8.16 (d, *J*=5.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.7, 84.9, 109.0 (d, *J*=38.3 Hz), 111.2, 117.0, 121.6 (d, *J*=3.9 Hz), 124.8, 131.2 (d, *J*=3.9 Hz), 146.6 (d, *J*=15.5 Hz), 147.1 (d, *J*=8.9 Hz), 148.8, 163.6 (d, *J*=237.2 Hz).

2-Methoxy-4-(1H-pyrrol-2-yl)pyridine (S6)

Compound **S6** was obtained following the ***general procedure B***. Yield 92%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.96 (s, 3 H), 6.31 - 6.36 (m, 1 H), 6.68 - 6.74 (m, 1 H), 6.78 (d, *J*=1.2 Hz, 1 H), 6.93 (s, 1 H), 6.99 (dd, *J*=5.5, 1.5 Hz, 1 H), 8.11 (d, *J*=5.5 Hz, 1 H), 8.89 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 53.7, 103.8, 109.0, 110.7, 112.3, 121.0, 129.3, 142.4, 147.3, 165.1.

2,2,2-Trifluoro-1-(5-(2-methoxypyridin-4-yl)-1H-pyrrol-2-yl)ethanone (S7)

Compound **S7** was obtained following the ***general procedure C***. Yield = 78%

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.88 (s, 3 H), 7.10 (dd, *J*=4.2, 2.4 Hz, 1 H), 7.28 (dt, *J*=4.0, 1.9 Hz, 1 H), 7.46 (s, 1 H), 7.54 (dd, *J*=5.4, 1.4 Hz, 1 H), 8.21 (d, *J*=5.4 Hz, 1 H), 13.12 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 53.4, 106.5, 112.4, 114.0, 116.9 (q, *J*=290.1 Hz), 122.8 (q, *J*=3.5 Hz), 126.8, 139.6, 140.2, 147.7, 164.5, 168.5 (q, *J*=35.0 Hz).

5-(2-Methoxypyridin-4-yl)-1H-pyrrole-2-carboxylic acid (S8)

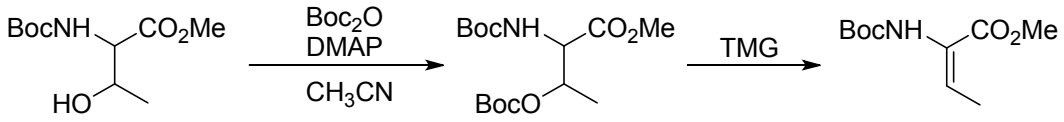
Compound **S8** was obtained following the ***general procedure D***. Yield = 93%.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.86 (s, 3 H), 6.80 - 6.84 (m, 1 H), 6.84 - 6.88 (m, 1 H), 7.35 (s, 1 H), 7.43 (dd, *J*=5.5, 1.4 Hz, 1 H), 8.11 (d, *J*=5.5 Hz, 1 H), 12.26 (br. s., 1 H), 12.56 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 53.2, 104.9, 110.2, 113.2, 116.2, 125.9, 133.5, 141.3, 147.2, 161.7, 164.5.

Synthesis of Reagent Methyl 2-((tert-butoxycarbonyl)amino)-3-iodobut-2-enoate (R4)

Methyl 2-((tert-butoxycarbonyl)amino)but-2-enoate (R3)

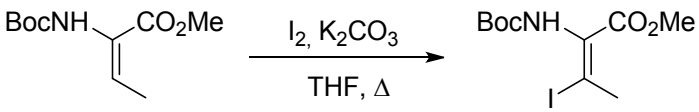


R1 **R2** **R3**

DMAP (3.64 g, 0.1 equiv.) was added to a solution of the N-Boc acid methyl ester **R1** (69.59 g, 1 equiv.) in dry acetonitrile (300 mL), followed by di-tert-butyl dicarbonate (65.0 g, 1.0 equiv.) with rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/n-hexane, 1:1) until all the reactants had been consumed. TMG (3.44 mL, 0.1 equiv) was then added, stirring was continued, and the reaction was followed by TLC. When all the reactants had been consumed, evaporation at reduced pressure gave a residue that was partitioned between CH_2Cl_2 (300 mL) and 5% HCl (200 mL). The organic phase was thoroughly washed with NaHCO3 and dried with Na_2SO_4. Removal of the solvent afforded the corresponding N-Boc-dehydroamino acid methyl ester. M = 63.88 g.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (s, 9 H), 1.82 (d, J=7.2 Hz, 3 H), 3.78 (s, 3 H), 6.00 (br. s, 1 H), 6.69 (q, J=7.0 Hz, 1 H).

Methyl 2-((tert-butoxycarbonyl)amino)-3-iodobut-2-enoate (R4)



R3 **R4**

A flask was charged with the dehydroamino acid derivative **R3** (63.88 g, 48.4 mmol), K_2CO_3 (81.7 g, 2 equiv.), and THF (400 mL). I_2 (90.9 g, 1.2 equiv.) was added, and the reaction mixture was heated at reflux for ~4 h. After the system had cooled to room temperature, the

reaction mixture was quenched with a 10% solution of Na2SO3 (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was subjected to column chromatography (eluent hexanes/EtOAc, 10:1). M = 52.2 g.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.47 (s, 9 H), 2.74 (s, 3 H), 3.83 (s, 3 H), 6.17 (br. s, 1 H).

5-(Trifluoromethyl)-2-((trimethylsilyl)ethynyl)pyridine (S9)

In a pressurized vessel equipped with magnetic stirring bar containing solution of 2-bromo-5-(trifluoromethyl)pyridine (30 g; 133 mmol, 1 equiv) in Et_3N (265 mL), TMS-acetylene (26.07 g, 36.8 mL, 265 mmol, 2 equiv.), $Pd(Ph_3P)Cl_2$ (0.93 g; 1 mol. %), CuI (0.51 g; 2 mol. %) were added under argon atmosphere. It was heated to 50-60 °C and the mixture was stirred at this temperature for 6-8 h (TLC-control). Aqueous (500 ml) was added and extracted with hexane (3×150 mL). Combined extracts were washed with water and dried with anhydrous sodium sulfate. Solvent was removed by rotary evaporation and the residue was purified using column chromatography (eluent: Hexane-EtOAc, 30:1, Rf = 0.5 in hexane-EtOAc 30:1). M = 15.6 g. Yield = 48%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.28 (s, 9 H), 7.55 (d, *J*=8.2 Hz, 1 H), 7.87 (dd, *J*=8.2, 2.2 Hz, 1 H), 8.81 (s, 1 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= -0.4 (3C), 98.2, 102.5, 123.3 (q, *J*=272.2 Hz), 125.6 (q, *J*=33.3 Hz), 126.9, 133.4 (q, *J*=3.1 Hz), 146.5, 146.8 (q, *J*=3.8 Hz).

5-Chloro-2-((trimethylsilyl)ethynyl)pyridine (S10)

In a pressurized vessel equipped with magnetic stirring bar containing solution of 2-bromo-5-chloropyridine (20 g; 104 mmol, 1 equiv) in Et_3N (210 mL), TMS-acetylene (20.42 g, 28.8 mL, 208 mmol, 2 equiv.), $Pd(Ph_3P)Cl_2$ (0.73 g; 1 mol. %), CuI (0.4 g; 2 mol. %) were added under argon atmosphere. It was heated to 50-60 °C and the mixture was stirred at this temperature for 6-8 h (TLC-control). Aqueous (500 ml) was added and extracted with hexane (3×150 mL). Combined extracts were washed with aqueous and dried with anhydrous sodium sulfate. Solvent was removed by rotary evaporation and the residue was purified using column

chromatography (eluent: Hexane-EtOAc, 30:1, Rf = 0.4 in hexane-EtOAc 30:1). M = 16.7 g. Yield = 74%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.27 (s, 9 H), 7.40 (d, *J*=8.4 Hz, 1 H), 7.62 (dd, *J*=8.4, 2.4 Hz, 1 H), 8.52 (d, *J*=2.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= -0.3 (3c), 96.1, 102.6, 127.8, 131.5, 135.9, 141.0, 148.9.

1-tert-Butyl 2-methyl 3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-1,2-dicarboxylate (S11)

To the solution of **S9** (9.81 g, 40 mmol, 1 equiv) in DMF (200 mL), triethylamine trihydrofluoride (1.98 g, 2 mL, 12 mmol, 0.3 equiv) was added and mixture was stirred for 1 h under argon atmosphere. Then methyl (E)-2-(tert-butoxycarbonylamino)-3-iodo-but-2-enoate (13.75 g, 1 equiv.), $Pd(Ph_3P)Cl_2$ (1.42 g; 5 mol. %), CuI (0.77 g; 10 mol. %) and Cs_2CO_3 (26.27 g; 80 mmol, 2 equiv.) were added under argon atmosphere. It was heated to 70-80 °C and the mixture was stirred at this temperature for 10-15 h (TLC-control). Aqueous (300 ml) was added and extracted with Et_2O (3×150 mL). Combined extracts were washed with aqueous and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography using hexane-EtOAc mixture (20:1) as eluent. M = 7.1 g, Yield 46%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.64 (s, 9 H), 2.34 (s, 3 H), 3.89 (s, 3 H), 6.52 (s, 1 H), 7.64 (d, *J*=8.1 Hz, 1 H), 7.89 (d, *J*=7.8 Hz, 1 H), 8.73 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 13.1, 27.4 (3C), 51.5, 85.1, 114.1, 120.5, 123.1, 123.6 (q, *J*=272.2 Hz), 124.3 (q, *J*=32.9 Hz),129.2, 133.2, 133.6 (q, *J*=2.9 Hz), 145.1 (q, *J*=4.4 Hz), 149.9, 152.5, 161.2.

1-tert-Butyl 2-methyl 5-(5-chloropyridin-2-yl)-3-methyl-1H-pyrrole-1,2-dicarboxylate (S12)

To the solution of **S10** (13.1 g, 62 mmol, 1 equiv) in DMF (310 mL), triethylamine trihydrofluoride (3.01 g, 3.05 mL, 12 mmol, 0.3 equiv) was added and mixture was stirred for 1 h under argon atmosphere. Then methyl (E)-2-(tert-butoxycarbonylamino)-3-iodo-but-2-enoate (21.31 g, 1 equiv.), $Pd(Ph_3P)Cl_2$ (1.32 g; 3 mol. %), CuI (1.2 g; 10 mol. %) and Cs_2CO_3

(40.7 g; 125 mmol, 2 equiv.) were added under argon atmosphere. It was heated to 70-80 °C and the mixture was stirred at this temperature for 10-15 h (TLC-control). Aqueous (300 ml) was added and extracted with Et_2O (3×150 mL). Combined extracts were washed with aqueous and brine, dried over Na_2SO_4, filtered, and concentrated. M = 8.95 g, Yield 41%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.61 (s, 9 H), 2.33 (s, 3 H), 3.87 (s, 3 H), 6.41 (s, 1 H), 7.49 (d, *J*=8.5 Hz, 1 H), 7.65 (dd, *J*=8.5, 2.4 Hz, 1 H), 8.45 (d, *J*=2.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.3, 27.5 (3C), 51.6, 85.1, 113.2, 122.0, 122.4, 129.5, 130.5, 133.9, 136.3, 147.3, 147.8, 150.1, 161.4.

Methyl 3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxylate (S13)

To a solution of **S11** (5.87 g, 15 mmol, 1 equiv) in CH_2Cl_2 (50 ml) TFA (11 g, 7.4 mL, 76 mmol, 5 equiv) was added in one portion and mixture was stirred overnight. Then solvent was evaporated and 10% aqueous K_2CO_3 was added and mixture was extracted with CH_2Cl_2 (3x100 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography using hexane-EtOAc mixture (10:1) as eluent. M = 3.96 g. Yield 91 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.40 (s, 3 H), 3.90 (s, 3 H), 6.62 (d, *J*=2.8 Hz, 1 H), 7.61 (d, *J*=8.3 Hz, 1 H), 7.87 (dd, *J*=8.4, 2.1 Hz, 1 H), 8.76 (s, 1 H), 10.01 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 400 MHz): δ= 12.8, 51.4, 112.1, 118.4, 121.5, 123.7 (q, *J*=272.2 Hz), 124.1 (q, *J*=32.9 Hz), 129.6, 132.4, 133.8 (q, *J*=3.7 Hz), 146.4 (q, *J*=4.4 Hz), 152.1, 161.6.

Methyl 5-(5-chloropyridin-2-yl)-3-methyl-1H-pyrrole-2-carboxylate (S14)

To a solution of **S12** (8.25 g, 24 mmol, 1 equiv) in CH_2Cl_2 (100 ml) TFA (13.4 g, 9.0 mL, 118 mmol, 5 equiv) was added in a one portion and mixture was stirred overnight. Then solvent was evaporated and 10% aqueous K_2CO_3 was added and mixture was extracted with CH_2Cl_2 (3x100 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography using hexane-EtOAc mixture (10:1) as eluent. M = 5.76 g. Yield 98 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.38 (s, 3 H), 3.88 (s, 3 H), 6.50 (d, *J*=2.6 Hz, 1 H), 7.46 (d, *J*=8.4 Hz, 1 H), 7.62 (dd, *J*=8.5, 2.4 Hz, 1 H), 8.45 (d, *J*=2.2 Hz, 1 H), 9.89 (br. s., 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 12.9, 51.4, 110.9, 119.8, 120.7, 129.7, 129.9, 132.7, 136.5, 147.4, 148.2, 161.7.

Sodium 3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxylate (S15)

To a solution of **S13** (3.96 g, 14 mmol, 1 equiv) in mixture of dioxane-H_2O (1:1, 30 mL), NaOH (0.61 g, 15 mmol, 1.1 equiv) was added in one portion and reaction mixture was stirred at reflux for 10-12 h (TLC-control). Mixture was evaporated to a volume of 10-20 mL, precipitate was filtered, washed with ether (2x50 mL) and dried under reduced pressure. M = 3.21 g. Yield 79 %.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.28 (s, 3 H), 6.72 (s, 1 H), 7.92 (d, *J*=8.6 Hz, 1 H), 8.01 (d, *J*=8.6 Hz, 1 H), 8.75 (s, 1 H), 10.34 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 12.8, 113.1, 118.0, 121.0 (q, *J*=32.2 Hz), 122.5, 124.2 (q, *J*=271.5 Hz), 127.8, 131.3, 133.7 (q, *J*=2.2 Hz), 145.8 (q, *J*=3.7 Hz), 153.9, 167.1.

5-(5-Chloropyridin-2-yl)-3-methyl-1H-pyrrole-2-carboxylic acid (S16)

To a solution of **S14** (5.7 g, 22 mmol, 1 equiv) in mixture of dioxane-H_2O (1:1, 60 mL), NaOH (1.06 g, 25 mmol, 1.1 equiv) was added in a one portion and reaction mixture was stirred at reflux for 10-12 h (TLC-control). Then sodium-salt solution was acidified by addition of equivalent amount of HCl (12M, 2.08 mL, 1.1 equiv.) and precipitate was filtered. M = 5.1 g. Yield 95 %.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.29 (s, 3 H), 6.70 (s, 1 H), 7.89 (d, *J*=8.3 Hz, 1 H), 7.98 (d, *J*=8.4 Hz, 1 H), 8.53 (s, 1 H), 11.28 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 12.8, 112.2, 120.2, 123.1, 126.9, 128.5, 132.2, 136.7, 147.8, 148.2, 163.1.

Thiazole-5-carbaldehyde (S17)

A solution of DMSO (16.96 g, 15.4 mL, 217 mmol, 2.5 equiv) in CH_2Cl_2 (100 mL) was added dropwise to a solution of oxalyl chloride (13.23 g, 8.94 mL, 104 mmol, 1.2 equiv) in CH_2Cl_2 (100 mL) at –70 to –80 °C. The resulting solution was stirred for 10 minutes, and a solution of

alcohol (10 g, 87 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added dropwise at the same temperature. After 15 min, Et_3N (35.15 g, 48.3 mL, 347 mmol, 4 equiv) was added dropwise, and 5 minutes later, the reaction mixture was allowed to warm to r.t. The reaction mixture was quenched with aqueous (300 mL), and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated in *vacuo* (bath temperature not exceeding 45-50 °C). The purification by flash chromatography (hexanes/EtOAc, 3:1) afforded aldehyde as a slightly brown oil. M = 7.05 g. Yield = 72%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 8.48 (s, 1 H), 9.07 (s, 1 H), 10.04 (d, *J*=1.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 139.4, 151.6, 160.1, 182.3.

5-Vinylthiazole (S18)

To the suspension of $Ph_3P^+MeI^-$ (25.74 g, 64 mmol, 1.1 equiv) in THF (70 ml), tBuOK (7.16 g, 64 mmol, 1.1 equiv) was added in a one portion. The mixture was refluxed for 1 h and cooled to room temperature. Aldehyde **S17** (6.55 g, 58 mmol, 1 equiv) in THF (50 ml) was added dropwise under cooling with an aqueous bath. The solvent was evaporated (bath temperature not exceeding 35 °C), and the residue was triturated in ether and filtered. The filtrate was evaporated, and the crude product was purified by flash chromatography using hexane-EtOAc mixture (3:1) as eluent (Rf = 0.5in hexane-EtOAc 3:1). M = 4.79 g. Yield = 74%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 5.29 (d, *J*=10.9 Hz, 1 H), 5.57 (d, *J*=17.3 Hz, 1 H), 6.82 (dd, *J*=17.3, 10.9 Hz, 1 H), 7.74 (s, 1 H), 8.63 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 117.2, 126.5, 138.0, 141.6, 151.7.

1-(Thiazol-5-yl)ethane-1,2-diol (S19)

To a solution of alkene **S18** (4.7 g, 42 mmol, 1 equiv) in acetone-aqueous (4:1, 50 mL), NMO monohydrate (6.29 g, 47 mmol, 1.1 equiv.) and potassium osmate (VI) dehydrate (0.16 g, 1 mol. %) were added in a one portion. Mixture was refluxed for 10-12 h (TLC-control) and cooled to the room temperature. Solvent was evaporated and crude product was purified by

flash chromatography using pure EtOAc as eluent (Rf = 0.2 in EtOAc). M = 2.83 g. Yield = 46 %.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.44 - 3.50 (m, 1 H), 3.51 - 3.58 (m, 1 H), 4.85 (q, *J*=5.6 Hz, 1 H), 5.00 (t, *J*=5.8 Hz, 1 H), 5.80 (d, *J*=4.7 Hz, 1 H), 7.77 (s, 1 H), 8.96 (s, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ=66.9, 68.0, 139.5, 142.0, 153.1.

5-(2,2,3,3,8,8,9,9-Octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)thiazole (*S20*)

To a solution of alcohol **S19** (2.83 g, 19 mmol, 1 equiv.) DMF (50 mL), imidazole (5.31 g, 78 mmol, 4 equiv) was added in one portion, followed by portion-wise addition of TBSCl (8.81 g, 58 mmol, 3 equiv). The reaction mixture was stirred overnight at 50-60 ˚C, cooled to the room temperature, diluted with aqueous (100 ml), and extracted with EtoAc (3 x 50 mL). The combined organic phases were washed with aqueous (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated to give an oil, which was purified by flash chromatography using Hexane-EtOAc (10:1) as eluent (Rf = 0.3 in 10:1 Hexane-EtOAc). M = 5.87 g. Yield = 80%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.02 - 0.03 (m, 9 H), 0.10 (s, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 3.58 (dd, *J*=9.9, 6.3 Hz, 1 H), 3.75 (dd, *J*=9.9, 5.9 Hz, 1 H), 5.01 (t, *J*=6.1 Hz, 1 H), 7.76 (s, 1 H), 8.73 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= -5.4, -5.4, -4.9, -4.7, 18.3, 18.5, 25.8 (3C), 26.0 (3C), 69.2, 70.4, 139.6, 141.7, 152.6.

General Procedure E: for 1,2-Addition

The appropriate thiazole (1.3 equiv) was dissolved in THF (1M) and cooled to −78 °C. At this temperature, n-BuLi (2.5 M, 1.4 equiv.) was added dropwise under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at −78 °C, and appropriate imine (1 equiv) was added dropwise as a solution in THF (1M). The reaction mixture was slowly (∼1 h) warmed to 0 °C and poured into aqueous (5 mL per 1 g thiazole). The biphasic mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered,

and evaporated to give a brown oil which was purified by column chromatography. Eluent: hexanes/EtOAc (10:1, 5:1, 1:1, 0:1).

General Procedure F: for Amine Deprotection:

A 1 M HCl−MeOH solution was prepared by the dropwise addition of AcCl (1.5 equiv) to a MeOH. The resulting solution was cooled to ambient temperature and added to a flask containing an appropriately protected compound (1 equiv). After dissolution, the reaction mixture was stirred for 1 h, evaporated, dissolved in CH_2Cl_2, and washed with 10% aqueous K_2CO_3. The organic layer was dried over Na_2SO_4, filtered, and evaporated and loaded on silica. Eluting with CH_2Cl_2/MeOH (50:1) provided pure amine as a yellow oil.

General procedure G: for TBDPS-protection:

Diol (1 equiv.) was dissolved in CH_2Cl_2 (10 mL per 1 g), and imidazole (1.2 equiv) was added in one portion, followed by a portion-wise addition of TBDPSCl (1.1 equiv). The reaction mixture was stirred overnight, diluted with aqueous (10 ml per 1 g), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, filtered, and evaporated to give an oil, which was purified by flash chromatography using Hexane-EtOAc mixture (1:1 and 0:1) as eluent.

Allyl allyl(2-amino-2-(4-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)thiazol-2-yl)ethyl)carbamate (S23-fS and S23-fR)

Compounds **S23-fS** and **S23-fR** were obtained following in succession the ***general procedure E, F and G*** from **S20** (compounds **S21**, **S22**, were considered pure enough and used directly in the next steps without any further purifications)

S23-fS: M = 2.94 g. Yield (over three steps) = 30%.

S23-fR: M = 1.81 g. Yield (over three steps) = 27%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.08 (s, 9 H), 2.43 (br. s., 3 H), 3.51 - 4.00 (m, 6 H), 4.40 - 4.54 (m, 1 H), 4.60 (d, *J*=4.2 Hz, 2 H), 5.03 (dd, *J*=7.1, 4.1 Hz, 1 H), 5.07 - 5.17 (m, 2 H), 5.20

(dd, *J*=10.5, 1.3 Hz, 1 H), 5.29 (dd, *J*=17.2, 1.4 Hz, 1 H), 5.67 - 5.83 (m, 1 H), 5.85 - 5.98 (m, 1 H), 7.36 - 7.49 (m, 6 H), 7.55 (s, 1 H), 7.61 - 7.68 (m, 4 H).

Methyl 2-(thiazol-4-yl)acetate (*S24*)

The compound (S24) was prepared by following a published procedure[67]

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.72 (s, 3 H), 3.89 (s, 2 H), 7.24 (d, *J*=1.8 Hz, 1 H), 8.76 (d, *J*=1.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 36.6, 52.2, 116.1, 149.5, 152.8, 170.7.

2-(Thiazol-4-yl)ethanol (*S25*)

A solution of ester **S24** (0.481 mol) in THF (480 mL) was added dropwise to a suspension of LiAlH4 (0.500 mmol, 1.0 equiv) in THF (480 mL) at 0 °C. The reaction mixture was stirred for 60 min at 0 °C. It was then quenched by successive addition of EtOAc (100 mL), aqueous (37 mL), 10% NaOH (37 mL) solution, and aqueous (74 mL) (the temperature should not exceed 0 °C). The precipitate was filtered and washed several times with THF. The filtrate was evaporated to give **S25**, which was used without further purifications

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.03 (t, *J*=5.9 Hz, 2 H), 3.43 (br. s., 1 H), 3.93 (t, *J*=5.9 Hz, 2 H), 7.04 - 7.05 (m, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 33.9, 61.5, 114.1, 152.8, 155.2.

2-(Thiazol-4-yl)ethyl methanesulfonate (*S26*)

To a solution of corresponding alcohol **S25** (2.14 mmol) and triethylamine (0.36 mL, 2.59 mmol) in anhydrous dichloromethane (6 mL), kept to 0 °C, under an inert nitrogen atmosphere, was added mesyl chloride (2.31 mmol). The reaction was maintained at 0 °C during the first hour, followed by warming to room temperature, under vigorous stirring and nitrogen atmosphere for 3 h. Then, the solution was extracted with dichloromethane (3 .x. 30 mL), and the combined organic extracts were washed with a 10% aqueous HCl solution, brine, dried over Na_2SO_4, filtered and evaporated. The obtained residue was separated by

chromatography on silica gel eluting with dichloromethane, followed by chloroform to yield the desired O-mesylated derivative. Yield: 78%

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.89 (s, 3 H), 3.24 (t, *J*=6.5 Hz, 2 H), 4.56 (t, *J*=6.5 Hz, 2 H), 7.13 (d, *J*=1.3 Hz, 1 H), 8.76 (d, *J*=1.8 Hz, 1 H).

4-Vinylthiazole (*S27*)

To a mixture of **S26** (7.41 mmol) and TEA (5 mL) in DCM (50 mL) was added DBU (5 mL) slowly at 0 °C. The mixture was stirred at r.t overnight and then diluted with 50 mL of DCM, washed with 2N HCl x 3 times and x 1 brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by prep-TLC to give **S27**. Yield: 58%

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 5.39 (dd, *J*=10.9, 1.5 Hz, 1 H), 6.09 (dd, *J*=17.3, 1.5 Hz, 1 H), 6.77 (dd, *J*=17.3, 10.9 Hz, 1 H), 7.14 (d, *J*=1.8 Hz, 1 H), 8.76 (d, *J*=1.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 114.9, 116.9, 129.5, 152.9, 155.1.

1-(Thiazol-4-yl)ethane-1,2-diol (*S28*)

To a solution of alkene **S27** (42 mmol, 1 equiv) in acetone-aqueous (4:1, 50 mL), NMO monohydrate (47 mmol, 1.1 equiv.) and potassium osmate (VI) dehydrate (0.16 g, 1 mol. %) were added in a one portion. The mixture was refluxed for 10-12 h (TLC-control) and cooled to the room temperature. The solvent was evaporated and the crude product was purified by flash chromatography (Eluent: EtOAc). Yield 70%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.77 (dd, *J*=11.4, 7.2 Hz, 1 H), 3.91 (dd, *J*=11.5, 3.4 Hz, 1 H), 4.72 (br. s., 1 H), 4.99 (dd, *J*=6.9, 3.3 Hz, 1 H), 5.25 (br. s., 1 H), 7.32 (d, *J*=1.9 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 66.4, 71.3, 115.2, 153.6, 157.5.

4-(2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)thiazole (*S29*)

To a solution of alcohol **S28** (19 mmol, 1 equiv.) DMF (50 mL), imidazole (5.31 g, 78 mmol, 4 equiv) was added in one portion, followed by portion-wise addition of TBSCl (8.81 g, 58 mmol, 3 equiv). The reaction mixture was stirred overnight at 50-60 ˚C, cooled to the room temperature, diluted with aqueous (100 mL), and extracted with EtoAc (3 x 50 mL). The combined organic phases were washed with aqueous (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated to give an oil, which was purified by flash chromatography using Hexane-EtOAc (10:1) as eluent. Yield = 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.01 - 0.04 (m, 9 H), 0.11 (s, 3 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 3.68 (dd, *J*=10.2, 7.2 Hz, 1 H), 3.93 (dd, *J*=10.2, 3.8 Hz, 1 H), 5.03 (dd, *J*=7.0, 3.6 Hz, 1 H), 7.28 (d, *J*=1.9 Hz, 1 H), 8.75 (d, *J*=2.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= -5.3, -5.2, -4.8, -4.5, 18.4, 18.5, 26.0 (3C), 26.1 (3C), 68.5, 73.8, 114.8, 152.3, 159.3.

Allyl N-allyl-N-[2-[4-[1,2-bis[[tert-butyl(dimethyl)silyl]oxy]ethyl]thiazol-2-yl]-2-(tert-butylsulfinylamino)ethyl]carbamate (S30)

Compounds **S30**-fR and **S30**-fS were obtained following the general procedure E

Allyl N-allyl-N-[2-amino-2-[4-(1,2-dihydroxyethyl)thiazol-2-yl]ethyl]carbamate (S31)

Compounds **S31**-fR and **S31**-fS were obtained following the general procedure F

Allyl N-allyl-N-[2-amino-2-[4-[2-[tert-butyl(diphenyl)silyl]oxy-1-hydroxy-ethyl]thiazol-2-yl]ethyl]carbamate (S32)

Compounds **S32**-fR and **S32**-fS were obtained following the general procedure G

Synthesis of compound **S33** was reported earlier[10]

1-(4-(((tert-Butyldimethylsilyl)oxy)methyl)thiazol-2-yl)ethanone (*S34*)

To a solution of thiazole **S33** (49.06 g, 214 mmol, 1 equiv) in THF (210 mL), BuLi (2.5M in hexane, 85.55 mL, 1.2 equiv) was added dropwise at -78 °C under argon atmosphere. After

the end of the addition, the mixture was stirred for 10 min, then the solution of *N*-methoxy-*N*-methyl-acetamide (24.26 g, 235 mmol, 1.1 equiv) in THF (50 mL) was added dropwise. The resulting mixture was stirred overnight and poured into a saturated solution of NH_4Cl (400 mL). The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography using hexane-EtOAc (10:1) as eluent. M = 44.39 g. Yield = 76%.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 0.12 (s, 6 H), 0.94 (s, 9 H), 2.67 (s, 3 H), 4.90 (d, *J*=1.1 Hz, 2 H), 7.54 (t, *J*=1.1 Hz, 1 H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ = -5.3 (2C), 18.5, 26.0 (3C), 26.1, 62.2, 121.5, 159.7, 166.8, 191.8.

2-Amino-2-(4-(((tert-butyldimethylsilyl)oxy)methyl)thiazol-2-yl)propanenitrile (S35)

To the solution of **S34** (44.39 g, 164 mmol, 1 equiv) in MeOH-NH_3 (330 mL), NaCN (16.0 g, 327 mmol, 2 equiv) and NH_4Cl (35.0 g, 654 mmol, 4 equiv) were added. Mixture was stirred for 4-5 days, then aqueous (600 ml) was added and extracted with DCM (3x200 mL). Combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated. The obtained crude product was purified by flash chromatography using hexane-EtOAc mixture (3:1) as eluent. Compound was obtained in racemic form. M = 16.46 g. Yield = 34%.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 0.12 (s, 6 H), 0.95 (s, 9 H), 1.92 (s, 3 H), 2.42 (br. s., 2 H), 4.86 (d, *J*=1.2 Hz, 2 H), 7.21 (t, *J*=1.2 Hz, 1 H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ = -5.3 (2C), 18.4, 26.0 (3C), 30.3, 52.6, 62.3, 114.8, 121.9, 158.2, 170.6.

2-(4-(((tert-Butyldimethylsilyl)oxy)methyl)thiazol-2-yl)propane-1,2-diamine (S36)

A solution of **S35** (16.46 g, 55 mmol, 1 equiv) in Et_2O (55 mL) was added dropwise to a suspension of $LiAlH_4$ (6.31 g, 166 mmol, 3 equiv.) in Et_2O (55 mL) at -10 °C. The reaction

mixture was stirred for 12 h at 0 °C. It was then quenched by successive addition of aqueous (7 mL), 10% NaOH (7 mL) solution, and aqueous (7 mL) (the temperature should not exceed 0 °C). The precipitate was filtered and washed several times with Et_2O. The filtrate was evaporated to give diamine **S36**, which was purified by flash chromatography using pure EtOAc and $CHCl_3$-MeOH saturated with NH_3 (10:1) as eluents). M = 9.13 g. Yield = 55%.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 0.09 (s, 6 H), 0.92 (s, 9 H), 1.46 (s, 3 H), 1.61 (br. s., 4 H), 2.76 (d, J=12.8 Hz, 1 H), 3.15 (d, J=12.8 Hz, 1 H), 4.81 (d, J=1.2 Hz, 2 H), 7.06 (t, J=1.2 Hz, 1 H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ = -5.2 (2C), 18.5, 26.0 (3C), 28.1, 53.9, 58.1, 62.5, 113.5, 157.3, 179.8.

tert-Butyl (2-amino-2-(4-(((tert-butyldimethylsilyl)oxy)methyl)thiazol-2-yl)propyl)carbamate (S37)

To a solution of diamine **S36** (9.13 g, 30 mmol, 1 equiv) in CH_2Cl_2 (300 ml), a solution of Boc_2O (6.93 g, 32 mmol, 1.05 equiv.) in CH_2Cl_2 (300 ml) was added dropwise at 0 °C. Mixture was stirred for overnight and then solvent was evaporated. Crude product was used in the next step without purification. M = 12.1 g. Yield = 100 %.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 0.11 (s, 6 H), 0.94 (s, 9 H), 1.42 (s, 9 H), 1.48 (s, 3 H), 1.85 (br. s., 2 H), 3.43 - 3.60 (m, 2 H), 4.80 (d, J=1.2 Hz, 2 H), 5.07 (br. s., 1 H), 7.09 (t, J=1.2 Hz, 1 H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ = -5.2 (2C), 18.5, 26.0 (3C), 28.2, 28.5 (3C), 51.6, 57.5, 62.4, 79.6, 114.2, 156.6, 157.1, 179.1.

General Procedure H: for Amide Coupling

DIPEA (1 equiv) was added to an appropriate acid (1 equiv) followed by DMF (10 mL per 1 g of acid) and then HBTU (1 equiv). The resulting solution was stirred for 10 min and added to a solution of appropriate amine (1 equiv) in DMF (10 mL per 1 g of amine) in several portions. The reaction mixture was stirred overnight; DMF was evaporated, and the residue was

dissolved in DCM (50 mL per 1 g of crude product) and successively washed with 5% aqueous NaOH and 10% tartaric acid solutions (25 mL per 1 g of crude product). The organic layer was dried over Na_2SO_4, filtered, evaporated, and dry loaded on silica. Eluting with hexanes/EtOAc (1:1, then pure EtOAc) gave the target compounds. The products were used in the next step without analysis.

General Procedure I: for Deprotection

To a solution containing protected compound (1 equiv) and N,N-dimethyl barbituric acid (NDMBA, 3 equiv) in MeOH (0.1M solution), PPh_3 (10 mol %) was added under a nitrogen atmosphere followed by $Pd(dba)_2$ (5 mol %). The mixture was stirred for 1 day under reflux. After cooling, 50 mL of DCM was added, and the organic phase was shaken with 10% aqueous K_2CO_3 (50 mL) to remove the unreacted NDMBA. The organic layer was separated, and the aqueous layer was extracted with DCM/EtOH (~4:1, (2−4) × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (eluent: DCM/MeOH (saturated with NH_3~7M), 10:1) afforded amine as a slightly brown or yellowish solid.

N-(2-Amino-1-(5-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-chloropyridin-2-yl)-1H-pyrrole-2-carboxamide (*1** & **2*)

Compounds **1** and **2** were obtained following the ***general procedure H*** and ***I*** from amine **S39** and acid **S4b**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

1: M = 507 mg. Yield = 33% (over two steps). rt = 1.035 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 378 Da.

2: M = 335 mg. Yield = 22% (over two steps). rt = 1.022 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 378 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.68 (br. s., 2 H), 2.97 (dd, *J*=13.2, 7.9 Hz, 1 H), 3.11 (dd, *J*=13.3, 5.3 Hz, 1 H), 4.59 (d, *J*=4.2 Hz, 2 H), 5.12 - 5.20 (m, 1 H), 5.46 (t, *J*=5.3 Hz, 1 H), 6.88

- 6.94 (m, 2 H), 7.54 (s, 1 H), 7.89 - 8.01 (m, 2 H), 8.52 - 8.64 (m, 1 H), 8.80 (d, *J*=7.5 Hz, 1 H), 11.89 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 45.8, 54.7, 55.8, 109.7, 114.3, 120.4, 128.4, 128.5, 133.4, 136.9, 139.1, 140.1, 147.6, 148.4, 160.0, 171.8.

HRMS (ESI) calcd for $C_{16}H_{17}ClN_5O_2S$ $[M+H]^+$ 378.0786, found 378.0787.

N-(2-Amino-1-(5-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-chloropyridin-2-yl)-3-methyl-1H-pyrrole-2-carboxamide (3 & 4)

Compounds **3** and **4** were obtained following the ***general procedure H*** and ***I*** from amine **S39** and acid **S16**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

3: M = 412 mg. Yield = 26% (over two steps). rt = 1.112 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 392 Da.

4: M = 284 mg. Yield = 18% (over two steps). rt = 1.140 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 392 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 2.31 (s, 3 H), 3.00 (dd, *J*=13.2, 8.1 Hz, 1 H), 3.13 (dd, *J*=13.3, 5.1 Hz, 1 H), 4.60 (s, 2 H), 5.13 - 5.23 (m, 1 H), 5.49 (br. s., 1 H), 6.76 (s, 1 H), 7.55 (s, 1 H), 7.82 - 7.87 (m, 1 H), 7.92 - 7.96 (m, 1 H), 8.59 (d, *J*=2.3 Hz, 1 H), 8.76 (d, *J*=7.5 Hz, 1 H), 11.80 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 13.1, 45.7, 54.2, 55.8, 111.9, 120.4, 123.5, 127.2, 128.4, 131.2, 136.9, 139.1, 140.1, 147.4, 148.3, 160.8, 172.0.

HRMS (ESI) calcd for $C_{17}H_{19}ClN_5O_2S$ $[M+H]^+$ 392.0942, found 392.0942.

N-(2-Amino-1-(5-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (5 & 6)

Compounds **5** and **6** were obtained following the ***general procedure H*** and ***I*** from amine **S39** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

5: M = 262 mg. Yield = 38% (over two steps). rt = 1.260 min. Purity = 100 %. LC-MS: m/z $[M+H]^+$ = 412 Da.

6: M = 162 mg. Yield = 24% (over two steps). rt = 1.265 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 412 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 3.02 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.15 (dd, *J*=13.4, 5.4 Hz, 1 H), 4.62 (s, 2 H), 5.15 - 5.26 (m, 1 H), 5.51 (br. s., 1 H), 6.99 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 7.56 (s, 1 H), 8.12 (d, *J*=8.4 Hz, 1 H), 8.19 (dd, *J*=8.6, 2.1 Hz, 1 H), 8.81 - 8.97 (m, 2 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 45.8, 54.7, 55.8, 111.2, 114.3, 118.9, 122.4 (q, *J*=32.1 Hz), 124.0 (q, *J*=271.5 Hz), 129.4, 133.1, 134.4 (q, *J*=3.2 Hz), 139.1, 140.1, 146.0 (q, *J*=4.0 Hz), 153.2, 159.9, 171.7.

HRMS (ESI) calcd for $C_{17}H_{17}F_3N_5O_2S$ $[M+H]^+$ 412.1050, found 412.1048.

N-(2-amino-1-(5-(hydroxymethyl)thiazol-2-yl)ethyl)-3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (7 & 8)

Compounds **8** and **7** were obtained following the ***general procedure H*** and ***I*** from amine **S39** and the sodium salt **S15**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

8: M = 358 mg. Yield = 40% (over two steps). rt = 1.202 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

7: M = 253 mg. Yield = 28% (over two steps). rt = 1.208 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.93 (br. s., 2 H), 2.33 (s, 3 H), 3.00 (dd, *J*=13.2, 8.0 Hz, 1 H), 3.12 (dd, *J*=13.3, 5.1 Hz, 1 H), 4.61 (s, 2 H), 5.13 - 5.22 (m, 1 H), 5.50 (br. s., 1 H), 6.91 (s, 1 H), 7.56 (s, 1 H), 8.00 (d, *J*=8.4 Hz, 1 H), 8.19 (dd, *J*=8.5, 2.1 Hz, 1 H), 8.80 (d, *J*=7.2 Hz, 1 H), 8.89 (s, 1 H), 12.00 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 13.1, 45.7, 54.2, 55.8, 113.4, 119.0, 122.3 (q, *J*=32.4 Hz), 124.0 (q, *J*=271.8 Hz), 124.6, 127.3, 130.9, 134.4 (q, *J*=3.3 Hz), 139.1, 140.1, 145.8 (q, *J*=4.1 Hz), 153.1 (q, *J*=1.1 Hz), 160.8, 171.8.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_2S$ $[M+H]^+$ 426.1206, found 426.1216.

N-(2-Amino-1-(5-(hydroxymethyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (9 & 10)

Compounds **9** and **10** were obtained following the ***general procedure H*** and ***I*** from amine **S45** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (20:1 and 10:1).

9: M = 434 mg. Yield = 25% (over two steps). rt = 1.204 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

10: M = 252 mg. Yield = 15% (over two steps). rt = 1.218 min. Purity = 96%. LC-MS: m/z $[M+H]^+$ = 440 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.10 (s, 3 H), 1.14 (s, 3 H), 4.63 (s, 2 H), 5.29 (d, *J*=4.9 Hz, 1 H), 5.51 (br. s., 1 H), 6.96 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.8 Hz, 1 H), 7.58 (s, 1 H), 8.11 (d, *J*=8.4 Hz, 1 H), 8.20 (dd, *J*=8.4, 2.2 Hz, 1 H), 8.64 (d, *J*=7.2 Hz, 1 H), 8.88 - 8.92 (m, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 27.6, 28.3, 52.8, 55.8, 59.7, 111.2, 115.1, 119.1, 122.4 (q, *J*=32.2 Hz), 124.0 (q, *J*=272.1 Hz), 129.3, 133.2, 134.5 (q, *J*=3.2 Hz), 138.7, 140.3, 145.9 (q, *J*=4.1 Hz), 153.3, 159.4, 169.9.

HRMS (ESI) calcd for $C_{19}H_{21}F_3N_5O_2S$ $[M+H]^+$ 440.1363, found 440.1359.

N-(2-Amino-1-(5-(hydroxymethyl)thiazol-2-yl)-2-methylpropyl)-3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (11 & 12)

Compounds **11** and **12** were obtained following the ***general procedure H*** and ***I*** from amine **S45** and the sodium salt **S15**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (20:1 and 10:1).

11: M = 609 mg. Yield = 32% (over two steps). rt = 1.268 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 454 Da.

12: M = 674 mg. Yield = 33% (over two steps). rt = 1.306 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 454 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.09 (s, 3 H), 1.14 (s, 3 H), 2.32 (s, 3 H), 4.63 (d, *J*=3.5 Hz, 2 H), 5.28 (s, 1 H), 5.45 - 5.56 (m, 1 H), 6.91 (s, 1 H), 7.58 (s, 1 H), 8.00 (d, *J*=8.4 Hz, 1 H), 8.19 (dd, *J*=8.6, 2.2 Hz, 1 H), 8.50 (br. s., 1 H), 8.86 - 8.92 (m, 1 H), 12.24 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 13.4, 27.6, 28.1, 52.9, 55.8, 59.2, 113.6, 119.2, 122.3 (q, *J*=32.3 Hz), 124.0 (q, *J*=271.8 Hz) 124.5, 127.5, 131.0, 134.4 (q, *J*=3.1 Hz), 138.7, 140.3, 145.8 (q, *J*=4.1 Hz), 153.2, 160.4, 170.1.

HRMS (ESI) calcd for $C_{20}H_{23}F_3N_5O_2S$ $[M+H]^+$ 454.1519, found 454.1519.

N-(2-Amino-1-(5-(1,2-dihydroxyethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (13 & 14)

Compounds **13** and were **14** obtained from amine **S23** and acid **S4d**, following in sequence the ***general procedure H***, ***I,*** and the TBDPS cleavage as described below. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

TBDPS cleavage: To a solution of TBDPS-protected compound (1 equiv) in THF (0.1M), solution of TBAF trihydrate (1.1 equiv) in THF (0.1M) was added in one portion. The mixture was stirred for 1-2 h at room temperature (TLC-control) and concentrated. Purification by flash chromatography using $CHCl_3$-MeOH saturated with NH_3 mixture (5:1 and 3:1) as eluent.

Note that compounds **13** & **14** were obtained as diastereisomeric mixture of 2 single compounds having the absolute configuration of the chiral carbon **a** as fR for **13** and fS for **14**.

13: M = 221 mg. Yield = 27% (over three steps). rt = 1.107 min. Purity = 97%. LC-MS: m/z $[M+H]^+$ = 442 Da.

14: M = 485 mg. Yield = 41% (over three steps). rt = 1.160 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 442 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 2.99 (dd, 1 H), 3.13 (dd, *J*=13.2, 5.2 Hz, 1 H), 3.42 (ddd, *J*=10.7, 5.7, 2.4 Hz, 1 H), 3.50 (dd, *J*=10.8, 6.1 Hz, 1 H), 4.75 (t, *J*=5.8 Hz, 1 H), 4.96 (br. s.,

1 H), 5.14 - 5.24 (m, 1 H), 5.71 (br. s., 1 H), 6.98 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 7.57 (s, 1 H), 8.13 (d, *J*=8.4 Hz, 1 H), 8.20 (dd, *J*=8.6, 2.1 Hz, 1 H), 8.83 - 8.93 (m, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= (45.8, 45.8), 54.6, 66.7, (68.1, 68.1), 111.3, 114.3, 119.0, 122.4 (q, *J*=32.3 Hz), 124.0 (q, *J*=271.8 Hz), 129.4, 133.2, 134.5 (q, *J*=3.3 Hz), (138.6, 138.6), (141.4, 141.4), 146.0 (q, *J*=4.1 Hz), (153.2, 153.2), 159.9, (171.0, 171.1).

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$ 442.1155, found 442.1155.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-chloropyridin-2-yl)-1H-pyrrole-2-carboxamide (15 & 16)

Compounds **15** and **16** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4b**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

15: M = 518 mg. Yield = 34% (over two steps). rt = 1.074 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 378 Da.

16: M = 381 mg. Yield = 25% (over two steps). rt = 1.079 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 378 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.73 (br. s., 2 H), 2.99 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.12 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.54 (s, 2 H), 5.17 - 5.24 (m, 1 H), 5.30 (br. s., 1 H), 6.85 - 6.97 (m, 2 H), 7.29 (s, 1 H), 7.89 - 8.00 (m, 2 H), 8.59 (s, 1 H), 8.83 (d, *J*=7.7 Hz, 1 H), 11.91 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.8, 54.3, 59.8, 109.7, 114.2, 114.3, 120.4, 128.4, 128.6, 133.5, 136.9, 147.6, 148.4, 157.7, 160.0, 172.0.

HRMS (ESI) calcd for $C_{16}H_{17}ClN_5O_2S$ $[M+H]^+$ 378.0786, found 378.0786.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-fluoropyridin-2-yl)-1H-pyrrole-2-carboxamide (17 & 18)

Compounds **17** and **18** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4c**.. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

17: M = 420 mg. Yield = 31% (over two steps). rt = 0.987 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 362 Da.

18: M = 325 mg. Yield = 24% (over two steps). rt = 1.001 min. Purity = 96%. LC-MS: m/z $[M+H]^+$ = 362 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.78 (br. s., 2 H), 2.99 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.12 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.54 (d, *J*=3.0 Hz, 2 H), 5.17 - 5.24 (m, 1 H), 5.30 (br. s., 1 H), 6.84 (d, *J*=3.9 Hz, 1 H), 6.92 (d, *J*=3.8 Hz, 1 H), 7.28 (s, 1 H), 7.77 (td, *J*=8.8, 2.9 Hz, 1 H), 7.99 (dd, *J*=8.9, 4.4 Hz, 1 H), 8.55 (d, *J*=2.9 Hz, 1 H), 8.80 (d, *J*=7.8 Hz, 1 H), 11.82 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 45.9, 54.4, 59.8, 109.0, 114.1, 114.2, 120.6 (d, *J*=4.6 Hz), 124.3 (d, *J*=19.0 Hz), 128.0, 133.7, 137.0 (d, *J*=24.0 Hz), 146.6 (d, *J*=3.7 Hz), 157.7, 157.9 (d, *J*=252.5 Hz), 160.1, 172.1.

HRMS (ESI) calcd for $C_{16}H_{17}FN_5O_2S$ $[M+H]^+$ 362.1081, found 362.1080.

***N*-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-methylpyridin-2-yl)-1H-pyrrole-2-carboxamide (19** and **20)**

Compounds **19** and **20** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4a**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

19: M = 357 mg. Yield = 35% (over two steps). rt = 0.829 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 358 Da.

20: M = 254 mg. Yield = 25% (over two steps). rt = 0.773 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 358 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.71 (br. s., 2 H), 2.30 (s, 3 H), 2.99 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.12 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.54 (s, 2 H), 5.16 - 5.25 (m, 1 H), 5.32 (br. s., 1 H), 6.81 (d, *J*=3.8 Hz, 1 H), 6.90 (d, *J*=3.8 Hz, 1 H), 7.29 (s, 1 H), 7.63 (dd, *J*=8.2, 2.0 Hz, 1 H), 7.79 (d, *J*=8.1 Hz, 1 H), 8.41 (d, *J*=1.7 Hz, 1 H), 8.82 (d, *J*=7.8 Hz, 1 H), 11.78 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 17.8, 46.0, 54.5, 59.8, 108.3, 114.0, 114.3, 118.7, 127.4, 131.0, 134.6, 137.4, 147.2, 149.2, 157.6, 160.0, 172.2.

HRMS (ESI) calcd for $C_{17}H_{20}N_5O_2S$ $[M+H]^+$ 358.1332, found 358.1337.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (21 & 22)

Compounds **21** and**22** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4d**.. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

21: M = 410 mg. Yield = 41% (over two steps). rt = 1.269 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 412 Da.

22: M = 312 mg. Yield = 32% (over two steps). rt = 1.266 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 412 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.00 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.14 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.55 (s, 2 H), 5.18 - 5.26 (m, 1 H), 5.32 (br. s., 1 H), 6.98 (d, *J*=3.8 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 7.29 (s, 1 H), 8.13 (d, *J*=8.4 Hz, 1 H), 8.20 (dd, *J*=8.6, 1.7 Hz, 1 H), 8.84 - 8.96 (m, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.9, 54.4, 59.8, 111.2, 114.1, 114.3, 118.9, 122.3 (q, *J*=32.2 Hz), 124.0 (q, *J*=272.2 Hz), 129.4, 133.1, 134.4 (q, *J*=2.9 Hz), 146.0 (q, *J*=3.7 Hz), 153.2, 157.7, 159.8, 171.8.

HRMS (ESI) calcd for $C_{17}H_{17}F_3N_5O_2S$ $[M+H]^+$ 412.1050, found 412.1056.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (23 & 24)

Compounds **23** and **24** were obtained following the ***general procedure H*** and ***I*** from amine **S44** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (20:1 and 10:1).

23: M = 321 mg. Yield = 26% (over two steps). rt = 1.248 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

24: M = 208 mg. Yield = 17% (over two steps). rt = 1.234 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.08 (s, 3 H), 1.13 (s, 3 H), 4.57 (s, 2 H), 5.10 - 5.50 (m, 2 H), 6.96 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 7.32 (s, 1 H), 8.09 (d, *J*=8.4 Hz, 1 H), 8.18 (dd, *J*=8.6, 2.1 Hz, 1 H), 8.65 (d, *J*=7.2 Hz, 1 H), 8.87 - 8.91 (m, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 27.5, 28.3, 52.8, 59.4, 59.8, 111.2, 114.4, 115.1, 119.1, 122.4 (q, *J*=32.2 Hz), 124.0 (q, *J*=271.6 Hz), 129.3, 133.2, 134.5 (q, *J*=3.2 Hz), 145.9 (q, *J*=4.1 Hz), 153.3, 157.3, 159.4, 169.9.

HRMS (ESI) calcd for $C_{19}H_{21}F_3N_5O_2S$ $[M+H]^+$ 440.1363, found 440.1359.

N-(2-Amino-1-(4-(2-hydroxyethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (25 & 26)

Compounds and **25** and **26** were obtained following the ***general procedure H*** and ***I*** from amine **S41** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

25: M = 490 mg. Yield = 43% (over two steps). rt = 1.198 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

26: M = 368 mg. Yield = 32% (over two steps). rt = 1.153 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.85 (t, *J*=6.9 Hz, 2 H), 3.01 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.15 (dd, *J*=13.2, 5.1 Hz, 1 H), 3.71 (t, *J*=6.8 Hz, 2 H), 4.69 (br. s., 1 H), 5.19 - 5.27 (m, 1 H), 6.99 (d, *J*=3.8 Hz, 1 H), 7.05 (d, *J*=3.8 Hz, 1 H), 7.18 (s, 1 H), 8.12 (d, *J*=8.4 Hz, 1 H), 8.19 (dd, *J*=8.4, 1.7 Hz, 1 H), 8.89 (s, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 34.9, 46.0, 54.6, 60.2, 111.2, 114.1, 114.3, 118.9, 122.3 (q, *J*=32.4 Hz), 124.0 (q, *J*=271.8 Hz), 129.4, 133.1, 134.4 (q, *J*=3.3 Hz), 146.0 (q, *J*=4.2 Hz), 153.2 (q, *J*=1.1 Hz), 154.1, 159.9, 171.3.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_2S$ $[M+H]^+$ 426.1206, found 426.1204.

N-(2-Amino-1-(4-(3-hydroxypropyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (27 & 28)

Compounds **27** and **28** were obtained following the ***general procedure H*** and ***I*** from amine **S42** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

27: M = 483 mg. Yield = 34% (over two steps). rt = 1.226 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

28: M = 727 mg. Yield = 39% (over two steps). rt = 1.220 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.73 - 1.83 (m, 2 H), 2.71 (t, *J*=7.7 Hz, 2 H), 2.99 (dd, *J*=13.2, 7.9 Hz, 1 H), 3.13 (dd, *J*=13.2, 5.1 Hz, 1 H), 3.44 (t, *J*=6.3 Hz, 2 H), 4.50 (br. s., 1 H), 5.17 - 5.24 (m, 1 H), 6.98 (d, *J*=3.9 Hz, 1 H), 7.06 (d, *J*=3.9 Hz, 1 H), 7.14 (s, 1 H), 8.13 (d, *J*=8.5 Hz, 1 H), 8.21 (dd, *J*=8.5, 2.1 Hz, 1 H), 8.84 - 8.94 (m, 2 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 27.6, 32.1, 46.0, 54.6, 60.2, 111.2, 113.1, 114.3, 118.9, 122.3 (q, *J*=32.4 Hz), 124.0 (q, *J*=271.8 Hz), 129.4, 133.1, 134.4 (q, *J*=3.1 Hz), 146.0 (q, *J*=4.2 Hz), 153.2, 156.6, 159.9, 171.5.

HRMS (ESI) calcd for $C_{19}H_{21}F_3N_5O_2S$ $[M+H]^+$ 440.1363, found 440.1377.

N-(2-Amino-1-(4-(1,2-dihydroxyethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (29 & 30)

Compounds **29** and **30** were obtained), from amine **S32** and acid **S4d,** following in sequence, the ***general procedure H***, ***I,*** and the TBDPS cleavage (below). Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

TBDPS cleavage: To a solution of TBDPS-protected compound (1 equiv) in THF (0.1M), solution of TBAF trihydrate (1.1 equiv) in THF (0.1M) was added in one portion. The mixture was stirred for 1-2 h at room temperature (TLC-control) and concentrated. Purification by flash chromatography using $CHCl_3$-MeOH saturated with NH_3 mixture (5:1 and 3:1) as eluent.

Note that compounds **29** & **30** were obtained as diastereisomeric mixture of 2 single compounds having the absolute configuration of the chiral carbon **a** as fR for **29** and fS for **30**.

29: M = 358 mg. Yield = 29% (over two steps). rt = 1.143 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 442 Da.

30: M = 238 mg. Yield = 19% (over two steps). rt = 1.124 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 442 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 3.00 (ddd, *J*=13.2, 7.8, 2.1 Hz, 1 H), 3.10 - 3.18 (m, 1 H), 3.49 (ddd, *J*=10.9, 7.1, 2.0 Hz, 1 H), 3.71 (dt, *J*=10.9, 4.1 Hz, 1 H), 4.65 (dd, *J*=6.8, 4.2 Hz, 1 H), 4.72 (br. s., 1 H), 5.16 - 5.26 (m, 1 H), 5.35 (br. s., 1 H), 6.98 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 7.29 - 7.32 (m, 1 H), 8.13 (d, *J*=8.4 Hz, 1 H), 8.20 (dd, *J*=8.6, 2.1 Hz, 1 H), 8.84 - 8.94 (m, 2 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 45.7, 54.3, (65.8, 65.9), (71.3, 71.4), 111.3, 114.3, (114.5, 114.5), 118.9, 121.9 (q, *J*=32.4 Hz), 124.0 (q, *J*=271.8 Hz), 129.4, 133.2, 134.5 (q, *J*=3.3 Hz), 146.0 (q, *J*=4.2 Hz), 153.2 (q, *J*=1.1 Hz), (158.4, 158.5), (159.9, 159.9), (171.5, 171.5).

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$ 442.1155, found 442.1172.

***N*-(1-Amino-2-(4-(hydroxymethyl)thiazol-2-yl)propan-2-yl)-3-methyl-5-(5-(trifluoromethyl)-pyridin-2-yl)-1*H*-pyrrole-2-carboxamide (31)**

Compound **31** (racemate) was obtained following the ***general procedure H*** and ***I*** from amine **S37** and the sodium salt **S15**. The compound was purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (20:1 and 10:1).

M = 190 mg. Yield = 12%. rt = 1.271 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 440 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.74 (s, 3 H), 2.25 (s, 3 H), 2.92 (d, *J*=13.2 Hz, 1 H), 3.12 (d, *J*=13.2 Hz, 1 H), 4.51 (d, *J*=5.1 Hz, 2 H), 5.26 (t, *J*=5.7 Hz, 1 H), 6.88 (s, 1 H), 7.21 - 7.23 (m, 1 H), 7.99 (d, *J*=8.4 Hz, 1 H), 8.18 (dd, *J*=8.6, 2.3 Hz, 1 H), 8.28 (s, 1 H), 8.86 - 8.89 (m, 1 H), 12.02 (br. s., 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 13.1, 23.5, 51.8, 59.9, 60.5, 113.5, 113.8, 119.0, 122.2 (q, *J*=32.3 Hz), 122.6, 125.4, 126.5, 130.6, 134.4 (q, *J*=3.3 Hz), 145.8 (q, *J*=4.1 Hz), 153.2 (q, *J*=1.3 Hz), 156.8, 160.5, 176.6.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_2S$ $[M+H]^+$ 440.1363, found 440.1373.

N-(1-Amino-2-(4-(hydroxymethyl)thiazol-2-yl)propan-2-yl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (32

Compound **32** (racemate) was obtained following the ***general procedure H*** and ***I*** from amine **S37** and acid **S4d**. The compound was purified using column chromatography on silica gel. Eluent $CHCl_3$/MeOH saturated with NH_3 (10:1 and 5:1).

M = 332 mg. Yield = 38%. rt = 1.205 min. Purity = 98%. LC-MS: m/z $[M+H]^+$ = 426 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 1.76 (s, 3 H), 2.94 (d, *J*=13.3 Hz, 1 H), 3.14 (d, *J*=13.3 Hz, 1 H), 4.52 (s, 2 H), 5.29 (br. s., 1 H), 6.90 (d, *J*=3.9 Hz, 1 H), 7.04 (d, *J*=3.9 Hz, 1 H), 7.23 (s, 1 H), 8.10 (d, *J*=8.4 Hz, 1 H), 8.19 (dd, *J*=8.6, 2.2 Hz, 1 H), 8.40 (s, 1 H), 8.85 - 8.92 (m, 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 23.5, 51.7, 59.9, 60.6, 111.2, 113.8, 114.3, 118.9, 122.3 (q, *J*=32.3 Hz), 124.0 (q, *J*=271.8 Hz), 130.0, 132.9, 134.4 (q, *J*=3.1 Hz), 145.9 (q, *J*=4.2 Hz), 153.3, 156.9, 159.6, 176.4.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_2S$ $[M+H]^+$ 426.1206, found 426.1217.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (33 & 34)

Compounds **33** and **34** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and sodium salt **S15**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

33: M = 248 mg. Yield = 33% (over two steps). rt = 1.333 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

34: M = 162 mg. Yield = 22% (over two steps). rt = 1.328 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 426 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 2.33 (s, 3 H), 3.00 (dd, *J*=13.2, 7.7 Hz, 1 H), 3.12 (dd, *J*=13.3, 5.1 Hz, 1 H), 4.55 (s, 2 H), 5.18 - 5.26 (m, 1 H), 5.34 (br. s., 1 H), 6.90 (s, 1 H), 7.29

(s, 1 H), 7.98 (d, *J*=8.6 Hz, 1 H), 8.17 (dd, *J*=8.6, 2.2 Hz, 1 H), 8.81 (d, *J*=6.8 Hz, 1 H), 8.86 - 8.90 (m, 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 13.1, 46.1, 54.4, 59.8, 113.4, 114.0, 119.0, 122.3 (q, *J*=32.2 Hz), 124.0 (q, *J*=272.1 Hz), 124.6, 127.3, 130.9, 134.4 (q, *J*=3.2 Hz), 145.8 (q, *J*=4.1 Hz), 153.1, 157.7, 160.7, 172.2.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_2S$ $[M+H]^+$ 426.1206, found 426.1213

N-(2-Amino-1-(4,5-bis(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (35 & 36)

Compounds **35** and **36** were obtained following the ***general procedure H*** and ***I*** from amine **S40** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (15:1 and 3:1).

35; (fR): M = 468 mg. Yield = 38% (over two steps). rt = 1.221 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 442 Da.

36; (fS): M = 290 mg. Yield = 24% (over two steps). rt = 1.225 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 442 Da.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ= 2.99 (dd, *J*=13.1, 7.9 Hz, 1 H), 3.07 - 3.15 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.46 (s, 2 H), 4.65 (s, 2 H), 5.08 (br. s., 1 H), 5.12 - 5.19 (m, 1 H), 5.45 (br. s., 1 H), 6.97 (d, *J*=3.9 Hz, 1 H), 7.05 (d, *J*=3.9 Hz, 1 H), 8.13 (d, *J*=8.4 Hz, 1 H), 8.20 (dd, *J*=8.6, 2.0 Hz, 1 H), 8.84 - 8.91 (m, 1 H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ= 45.5, 54.1, 55.1, 57.4, 111.2, 114.3, 118.9, 122.3 (q, *J*=32.1 Hz), 124.0 (q, *J*=271.5 Hz), 129.4, 133.1, 134.4 (q, *J*=3.2 Hz), 136.3, 146.0 (q, *J*=4.0 Hz), 150.8, 153.2, 159.8, 169.0.

HRMS (ESI) calcd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$ 442.1155, found 442.1151.

N-(2-Amino-1-(thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxamide (37 & 38)

Compounds **37** and **38** were obtained following the ***general procedure H*** and ***I*** from amine **S43** and acid **S4d**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

37; (fR): M = 220 mg. Yield = 30% (over two steps). rt = 1.230 min. Purity = 95%. LC-MS: m/z $[M+H]^+$ = 382 Da.

38; (fS): M = 342 mg. Yield = 45% (over two steps). rt = 1.236 min. Purity = 96%. LC-MS: m/z $[M+H]^+$ = 382 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.03 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.16 (dd, *J*=13.2, 5.3 Hz, 1 H), 5.22 - 5.31 (m, 1 H), 6.98 (d, *J*=3.8 Hz, 1 H), 7.06 (d, *J*=3.8 Hz, 1 H), 7.61 (d, *J*=3.2 Hz, 1 H), 7.77 (d, *J*=3.2 Hz, 1 H), 8.13 (d, *J*=8.5 Hz, 1 H), 8.20 (dd, *J*=8.5, 2.0 Hz, 1 H), 8.80 - 9.01 (m, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.9, 54.5, 111.2, 114.2, 118.9, 119.6, 122.3 (q, *J*=32.4 Hz), 124.0 (q, *J*=271.8 Hz), 129.3, 133.1, 134.4 (q, *J*=3.3 Hz), 142.4, 145.9 (q, *J*=4.1 Hz), 153.2 (q, *J*=1.3 Hz), 159.8, 172.1.

HRMS (ESI) calcd for $C_{16}H_{15}F_3N_5OS$ $[M+H]^+$ 382.0944, found 382.0952.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(6-chloropyridin-3-yl)-1H-pyrrole-2-carboxamide (39 & 40)

Compounds **39** and **40** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4e**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

39; (fR): M = 375 mg. Yield = 24% (over two steps). rt = 1.044 min. Purity = 96%. LC-MS: m/z $[M+H]^+$ = 378 Da.

40; (fS): M = 387 mg. Yield = 28% (over two steps). rt = 0.999 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 378 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.72 (br. s., 2 H), 2.99 (dd, *J*=13.2, 7.9 Hz, 1 H), 3.13 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.52 (s, 2 H), 5.16 - 5.23 (m, 1 H), 5.28 (br. s., 1 H), 6.76 (d, *J*=3.9 Hz, 1

H), 7.04 (d, *J*=3.9 Hz, 1 H), 7.27 (s, 1 H), 7.51 (d, *J*=8.5 Hz, 1 H), 8.25 (dd, *J*=8.5, 2.6 Hz, 1 H), 8.61 (d, *J*=8.1 Hz, 1 H), 8.86 (d, *J*=2.4 Hz, 1 H), 12.07 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.5, 54.2, 59.8, 108.7, 112.8, 114.1, 124.2, 127.3, 128.3, 130.6, 135.3, 146.0, 147.8, 157.6, 160.4, 172.2.

HRMS (ESI) calcd for $C_{16}H_{17}ClN_5O_2S$ $[M+H]^+$ 378.0786, found 378.0786.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrrole-2-carboxamide (41 & 42)

Compounds **41** and **42** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4f**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

41; (fR): M = 240 mg. Yield = 33% (over two steps). rt = 1.246 min. Purity = 100 %. LC-MS: m/z $[M+H]^+$ = 412 Da.

42; (fS): M = 290 mg. Yield = 40% (over two steps). rt = 1.262 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 412 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.03 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.16 (dd, *J*=13.2, 5.4 Hz, 1 H), 4.55 (s, 2 H), 5.20 - 5.28 (m, 1 H), 5.36 (br. s., 1 H), 6.93 (d, *J*=3.9 Hz, 1 H), 7.11 (d, *J*=3.9 Hz, 1 H), 7.30 (s, 1 H), 7.88 (d, *J*=8.3 Hz, 1 H), 8.47 (dd, *J*=8.3, 1.7 Hz, 1 H), 8.71 (d, *J*=7.8 Hz, 1 H), 9.22 (d, *J*=1.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.6, 54.4, 59.8, 109.9, 113.0, 114.2, 120.8 (q, *J*=2.6 Hz), 121.9 (q, *J*=273.5 Hz), 129.2, 130.4, 130.9, 132.9, 143.7 (q, *J*=33.9 Hz), 146.3, 157.7, 160.4, 172.1.

HRMS (ESI) calcd for $C_{17}H_{17}F_3N_5O_2S$ $[M+H]^+$ 412.1050, found 412.1054.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(6-(trifluoromethyl)pyridazin-3-yl)-1H-pyrrole-2-carboxamide (43 & 44)

Compounds **43** and **44** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4g**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

43; (fR): M = 322 mg. Yield = 42% (over two steps). rt = 1.095min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 413 Da.

44; (fS): M = 193 mg. Yield = 25% (over two steps). rt = 1.065min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 413 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 3.01 (dd, *J*=13.1, 7.8 Hz, 1 H), 3.14 (dd, *J*=13.2, 5.3 Hz, 1 H), 4.55 (s, 2 H), 5.20 - 5.28 (m, 1 H), 5.32 (br. s., 1 H), 7.03 (d, *J*=3.9 Hz, 1 H), 7.22 (d, *J*=3.9 Hz, 1 H), 7.30 (s, 1 H), 8.24 (d, *J*=9.0 Hz, 1 H), 8.48 (d, *J*=9.0 Hz, 1 H), 8.97 (d, *J*=7.1 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.7, 54.3, 59.8, 112.7, 114.2, 114.4, 121.8 (q, *J*=273.7 Hz), 124.0, 125.2 (q, *J*=1.7 Hz), 130.1, 130.6, 148.1 (q, *J*=33.9 Hz), 154.5, 157.7, 159.7, 171.6.

HRMS (ESI) calcd for $C_{16}H_{16}F_3N_6O_2S$ $[M+H]^+$ 413.1002, found 413.1000.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(5-chloropyrimidin-2-yl)-1H-pyrrole-2-carboxamide (45 & 46)

Compounds **45** and **46** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S4h**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (10:1 and 5:1).

45; (fR): M = 186 mg. Yield = 24% (over two steps). rt = 1.078 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 379 Da.

46; (fS): M = 124 mg. Yield = 16% (over two steps). rt = 1.099min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 379 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 2.99 (dd, *J*=13.2, 7.8 Hz, 1 H), 3.12 (dd, *J*=13.3, 5.3 Hz, 1 H), 4.55 (s, 2 H), 5.16 - 5.26 (m, 1 H), 5.31 (br. s., 1 H), 6.91 (d, *J*=3.8 Hz, 1 H), 6.99 (d, *J*=3.8 Hz, 1 H), 7.29 (s, 1 H), 8.90 (s, 2 H), 8.97 (d, *J*=7.2 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 46.1, 54.5, 59.8, 112.5, 114.1, 114.9, 127.3, 129.7, 132.2, 155.9 (2C), 156.3, 157.7, 159.5, 171.8.

HRMS (ESI) calcd for $C_{15}H_{16}ClN_6O_2S$ $[M+H]^+$ 379.0738, found 379.0745.

N-(2-Amino-1-(4-(hydroxymethyl)thiazol-2-yl)ethyl)-5-(2-methoxypyridin-4-yl)-1H-pyrrole-2-carboxamide (47 & 48)

Compounds **47** and **48** were obtained following the ***general procedure H*** and ***I*** from amine **S38** and acid **S8**. Compounds were purified using column chromatography on silica gel. Eluent $CHCl_3$-MeOH saturated with NH_3 (20:1 and 10:1).

47; (fR): M = 485 mg. Yield = 32% (over two steps). rt = 0.838 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 374 Da.

48; (fS): M = 423 mg. Yield = 28% (over two steps). rt = 0.839 min. Purity = 100%. LC-MS: m/z $[M+H]^+$ = 374 Da.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 1.74 (br. s., 2 H), 3.00 (dd, *J*=13.1, 7.9 Hz, 1 H), 3.14 (dd, *J*=13.2, 5.3 Hz, 1 H), 3.85 (s, 3 H), 4.54 (s, 2 H), 5.18 - 5.25 (m, 1 H), 5.30 (br. s., 1 H), 6.87 (d, *J*=3.9 Hz, 1 H), 7.03 (d, *J*=3.9 Hz, 1 H), 7.29 (t, *J*=1.0 Hz, 1 H), 7.30 (d, *J*=0.9 Hz, 1 H), 7.41 (dd, *J*=5.5, 1.4 Hz, 1 H), 8.10 (d, *J*=5.4 Hz, 1 H), 8.66 (d, *J*=7.9 Hz, 1 H), 12.07 (br. s., 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 45.7, 53.2, 54.5, 59.8, 104.5, 109.8, 112.9, 113.1, 114.1, 128.7, 132.1, 141.5, 147.2, 157.6, 160.4, 164.5, 172.2.

HRMS (ESI) calcd for $C_{17}H_{20}N_5O_3S$ $[M+H]^+$ 374.1281, found 374.12

ASSOCIATED CONTENT

Supporting Information

ADME (Experimental details), Supplemental Figures (Figure S1 and Figure S2), Molecular formula strings (CSV)

AUTHOR INFORMATION

Corresponding Author

*Phone: 001-212-570-3373. Fax: 001-212-570-3168. E-mail: adebnath@nybc.org.

ORCID

Asim K. Debnath: 0000-0003-2761-0506

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

HIV-1, human immunodeficiency virus type 1; Env, envelope; AIDS, acquire immunodeficiency syndrome; VSV-G, vesicular stomatitis virus-G; ADMET, absorption, distribution, metabolism, and excretion; TBDPSCl, tert-Butyl(chloro)diphenylsilane; DCM, dichloromethane; DIPEA, N,N-diisopropylethylamine; HBTU, N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)-uronium hexafluorophosphate; NDMBA, N,N-dimethyl barbituric acid; TBSCl, tert-butyldimethylsilyl chloride; Alloc, allyloxycarbonyl

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Figures

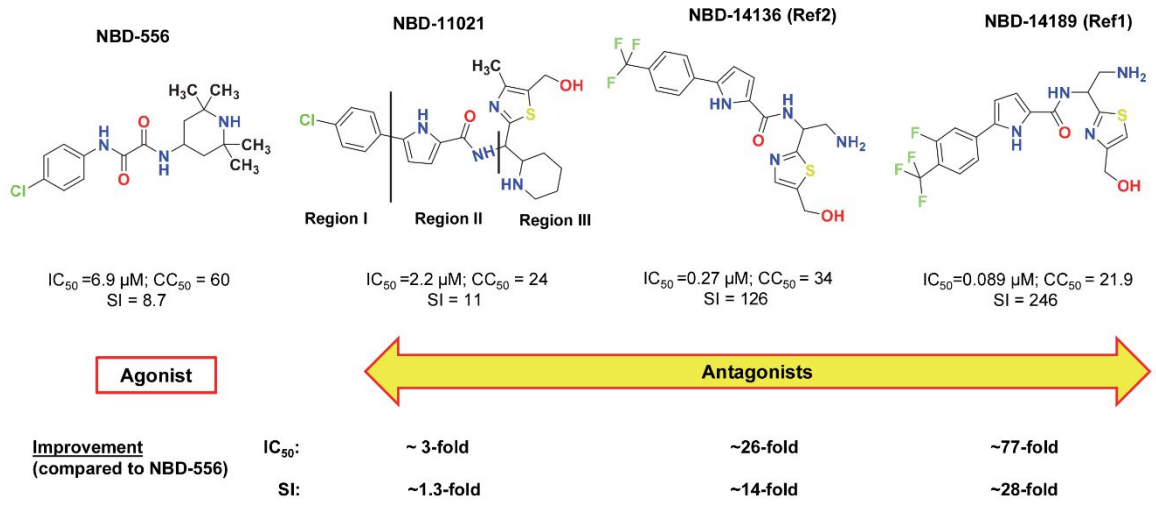


Figure 1. Chronology of improvement of anti-HIV-1 activity (IC50 against HIV-1HXB2) and Selectivity Index (SI)

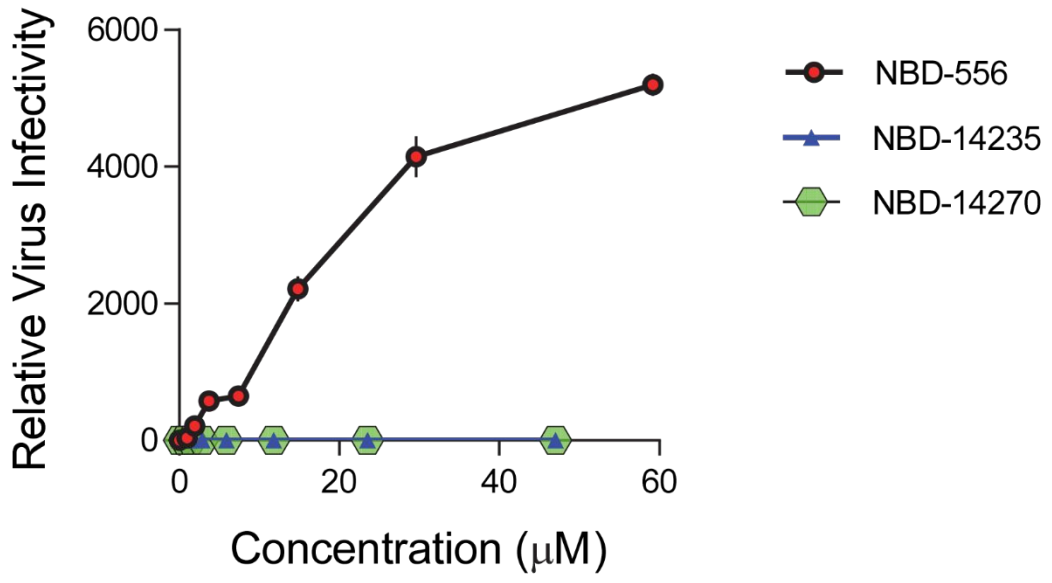
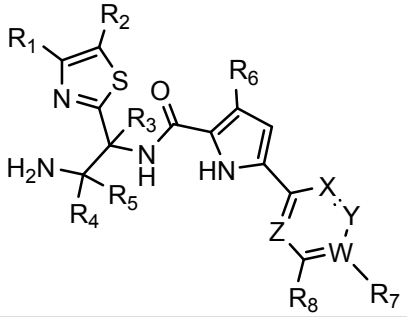


Figure 2. Infectivity of Cf2Th−CCR5 cells by CD4-dependent HIV-1_{ADA}. Cf2Th−CCR5 cells were infected with CD4-dependent HIV-1_{ADA} in the presence of **8** and **33**. NBD-556 was used as a control. The Relative virus infectivity designates the ratio of the amount of infection detected in the presence of the compounds and the amount of infection detected in the absence of the compounds. Three independent experiments were performed in triplicate, and the graph is representative of one experiment. The toxicity of the compounds against these cells was evaluated to calculate the CC_{50} values: for NBD-556 the CC_{50} was > 60, for **8** and **33** it was > 47. All the values represent the mean ± standard deviation

Table 1. Anti-HIV-1 activity (IC_{50}) and cytotoxicity (CC_{50}) of gp120 entry-antagonists in single-cycle (TZM-bl cells) assay



No. (enantiomer)	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	X	Y	Z	W	μM[a]	
													IC_{50}	CC_{50}
Ref1 (S)	CH_2OH	H	H	H	H	H	CF_3	F	CH	CH	CH	CH	0.089±0.001	21.9±0.5
Ref2 (R)	H	CH_2OH	H	H	H	H	CF_3	H	CH	CH	CH	CH	0.27±0.02	42.4±1.0
1 (R)	H	CH_2OH	H	H	H	H	Cl	H	N	CH	CH	CH	0.85±0.1	144±7.5
2 (S)	H	CH_2OH	H	H	H	H	Cl	H	N	CH	CH	CH	2.7±0.7	142±1.7
3 (R)	H	CH_2OH	H	H	H	CH3	Cl	H	N	CH	CH	CH	1.2±0.1	98.3±4
4 (S)	H	CH_2OH	H	H	H	CH_3	Cl	H	N	CH	CH	CH	2.4±0.2	95±3.6
5 (R)	H	CH_2OH	H	H	H	H	CF_3	H	N	CH	CH	CH	0.96±0.1	>122
6 (S)	H	CH_2OH	H	H	H	H	CF_3	H	N	CH	CH	CH	1.2±0.3	>122
7 (R)	H	CH_2OH	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	0.36±0.01	92.8±2.4
8 (S)	H	CH_2OH	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	0.16±0.004	109.3±2
9 (R)	H	CH_2OH	H	CH_3	CH_3	H	CF_3	H	N	CH	CH	CH	0.52±0.09	74±3.6
10 (S)	H	CH_2OH	H	CH_3	CH_3	H	CF_3	H	N	CH	CH	CH	0.5±0.09	42.4±4.1
11 (R)	H	CH_2OH	H	CH_3	CH_3	CH_3	CF_3	H	N	CH	CH	CH	0.6±0.2	35.3±2
12 (S)	H	CH_2OH	H	CH_3	CH_3	CH_3	CF_3	H	N	CH	CH	CH	0.43±0.05	37.5±2.2
13 (R)	H	$CHOHCH_2OH$	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	2.1±0.3	>113
14 (S)	H	$CHOHCH_2OH$	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	5.9±0.6	>113

15 (R)	CH_2OH	H	H	H	H	H	Cl	H	N	CH	CH	CH	5±0.5	>132
16 (S)	CH_2OH	H	H	H	H	H	Cl	H	N	CH	CH	CH	1.7±0.3	>132
17 (R)	CH_2OH	H	H	H	H	H	F	H	N	CH	CH	CH	>11	>138
18 (S)	CH_2OH	H	H	H	H	H	F	H	N	CH	CH	CH	>11	>138
19 (R)	CH_2OH	H	H	H	H	H	CH_3	H	N	CH	CH	CH	9.6±1.2	>140
20 (S)	CH_2OH	H	H	H	H	H	CH_3	H	N	CH	CH	CH	>11	>140
21 (R)	CH_2OH	H	H	H	H	H	CF_3	H	N	CH	CH	CH	0.59±0.07	94.3±8.6
22 (S)	CH_2OH	H	H	H	H	H	CF_3	H	N	CH	CH	CH	0.3±0.04	77.9±9.9
23 (R)	CH_2OH	H	H	CH_3	CH_3	H	CF_3	H	N	CH	CH	CH	1.7±0.04	61±6.5
24 (S)	CH_2OH	H	H	CH_3	CH_3	H	CF_3	H	N	CH	CH	CH	0.58±0.05	59±10
25 (R)	$(CH_2)_2OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	1.7±0.1	100±7
26 (S)	$(CH_2)_2OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	0.76±0.04	91±3.6
27 (R)	$(CH_2)_3OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	2.3±0.3	>114
28 (S)	$(CH_2)_3OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	0.89±0.12	81.2±1.3
29 (R)	$CHOHCH_2OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	5.2±0.9	>113
30 (S)	$CHOHCH_2OH$	H	H	H	H	H	CF_3	H	N	CH	CH	CH	3.8±0.2	>113
31-rac	CH_2OH	H	CH_3	H	H	CH_3	CF_3	H	N	CH	CH	CH	2.6±0.4	>68.3
32-rac	CH_2OH	H	CH_3	H	H	H	CF_3	H	N	CH	CH	CH	5.1±0.4	>70.5
33 (R)	CH_2OH	H	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	0.35±0.02	85±3
34 (S)	CH_2OH	H	H	H	H	CH_3	CF_3	H	N	CH	CH	CH	1.1±0.1	85±4
35 (R)	CH_2OH	CH_2OH	H	H	H	H	CF_3	H	N	CH	CH	CH	1.8±0.3	>113
36 (S)	CH_2OH	CH_2OH	H	H	H	H	CF_3	H	N	CH	CH	CH	>13	>113
37 (R)	H	H	H	H	H	H	CF_3	H	N	CH	CH	CH	2±0.2	89.3±1

38 (S)	H	H	H	H	H	H	CF_3	H	N	CH	CH	CH	1.2±0.03	93.6±1.5
39 (R)	CH_2OH	H	H	H	H	H	Cl	H	CH	N	CH	CH	>11	>132
40 (S)	CH_2OH	H	H	H	H	H	Cl	H	CH	N	CH	CH	>11	>132
41 (R)	CH_2OH	H	H	H	H	H	CF_3	H	CH	N	CH	CH	12.7±2.8	>122
42 (S)	CH_2OH	H	H	H	H	H	CF_3	H	CH	N	CH	CH	11.9±1.9	>122
43 (R)	CH_2OH	H	H	H	H	H	CF_3	H	N	N	CH	CH	>12	>73
44 (S)	CH_2OH	H	H	H	H	H	CF_3	H	N	N	CH	CH	>12	>73
45 (R)	CH_2OH	H	H	H	H	H	Cl	H	N	CH	N	CH	>15.8	>66
46 (S)	CH_2OH	H	H	H	H	H	Cl	H	N	CH	N	CH	>15.8	>66
47 (R)	CH_2OH	H	H	H	H	H		OCH_3	CH	CH	CH	N	>11	>133
48 (S)	CH_2OH	H	H	H	H	H		OCH_3	CH	CH	CH	N	>11	>133
BMS-626529	-												<1 nM	>100

[a] The reported IC_{50} and CC_{50} values represent the means ± standard deviations (n = 3).

Table 2. Neutralization Activity of gp120 entry-antagonists against a Panel of HIV-1 Env Pseudoviruses

			IC_{50} μM[a]		
Subtype	**NIH #**	**ENVs**	**Ref2**	**33**	**8**
A	11887	Q259ENV.W6	0.46±0.06[c]	0.4±0.05	0.23±0.03
	11888	QB726.70M.ENV.C4	0.31±0.07	0.63±0.1	0.22±0.01
	11890	QF495.23M.ENV.A1	0.44±0.05	0.47±0.05	0.14±0.003
	11891	QF495.23M.ENV.A3	0.26±0.04[c]	0.71±0.17	0.33±0.01
		BG505-T332N	0.41±0.03	0.27±0.007	0.124±0.005
		KNH1144	0.62±0.08	0.74±0.06	0.26±0.02
A/D	11901	QA790.204I.ENV.A4	0.29±0.01	0.36±0.03	0.14±0.003
	11904	QA790.204I.ENV.E2	0.41±0.03	0.36±0.02	0.16±0.03
A2/D	11905	QG393.60M.ENV.A1	0.34±0.02	0.42±0.03	0.22±0.002
	11906	QG393.60M.ENV.B7	0.6±0.005	0.5±0.04	0.17±0.03
A/G	11591	CRF02_AG Clone 211	0.58±0.05	0.38±0.04	0.23±0.04
	11594	CRF02_AG clone 250	0.41±0.01	0.42±0.01	0.21±0.01
	11595	CRF02_AG clone 251	0.36±0.06	0.39±0.03	0.12±0.01
	11598	CRF02_AG clone 255	0.33±0.01	0.66±0.03	0.22±0.01
	11599	CRF02_AG clone 257	0.39±0.01	0.74±0.1	0.16±0.002
	11600	CRF13_cpx clone 258	0.52±0.07	0.52±0.1	0.14±0.003
	11602	CRF02_AG clone 266	0.51±0.06	0.75±0.05	0.23±0.01
AE	11603	CRF01_AE clone 269	0.52±0.02	0.41±0.2	0.138±0.01
B		B41	0.36±0.04	0.38±0.05	0.136±0.001
	11018	QH0692, clone 42	0.27±0.01[c]	0.99±0.05	0.28±0.02
	11022	PVO, clone 4	0.41±0.06	0.33±0.04	0.11±0.03
	11023	TRO, clone 11	0.39±0.02	0.45±0.03	0.23±0.005
	11036	RHPA4259 clone 7	0.37±0.07	0.24±0.09	0.15±0.01
	11037	THRO4156 clone 18	0.32±0.02	0.15±0.03	0.16±0.02
	11038	CAAN5342 clone A2	0.22±0.03	0.38±0.07	0.13±0.005
	11058	SC422661.8	0.32±0.08	0.16±0.01	0.13±0.01
	11560	1006_11.C3.1601	0.58±0.06	0.27±0.01	0.139±0.003
	11561	1054.TC4.1499	0.25±0.02	0.39±0.02	0.23±0.01
	11562	1056.TA11.1826	0.58±0.01	0.71±0.1	0.13±0.006
	11563	1058 11.B11.1550[b]	0.29±0.02	0.49±0.06	0.28±0.01
	11572	9021_14.B2.4571	0.36±0.08	0.57±0.13	0.11±0.03
	11578	WEAUd15.410.5017[b]	0.76±0.04	0.54±0.04	0.22±0.002
C	11307	Du172, clone 17	0.3±0.03	0.27±0.02	0.19±0.002
	11308	Du422, clone 1	0.63±0.09	0.42±0.01	0.23±0.01
	11309	ZM197M.PB7, SVPC6	0.27±0.01	0.31±0.03	0.13±0.006
	11310	ZM214M.PL15, SVPC7	0.24±0.007	0.26±0.005	0.13±0.005

	11312	ZM249M.PL1, SVPC10	0.55±0.07	0.44±0.1	0.18±0.01
	11313	ZM53M.PB12, SVPC11	0.54±0.03	0.57±0.3	0.28±0.002
	11314	ZM109F.PB4	0.29±0.01	0.47±0.01	0.28±0.003
	11317	CAP210.2.00.E8, SVPC17	0.47±0.03	0.14±0.05	0.115±0.002
	11502	HIV-16055-2, clone 3	0.29±0.06	0.29±0.09	0.12±0.006
	11504	HIV-16936-2, clone 21	0.47±0.05	0.48±0.1	0.21±0.04
	11506	HIV-25711-2, clone 4	0.26±0.02	0.32±0.03	0.17±0.01
	11507	HIV-225925-2, clone 22	0.24±0.02	0.46±0.04	0.17±0.01
	11908	QB099.391M.ENV.B1	0.42±0.05	0.33±0.05	0.118±0.002
D	11911	QA013.70I.ENV.H1	0.32±0.01	0.55±0.04	0.25±0.01
	11912	QA013.70I.ENV.M12	0.22±0.01	0.25±0.02	0.16±0.02
	11916	QD435.100M.ENV.B5	0.3±0.01	0.37±0.03	0.13±0.01
	11918	QD435.100M.ENV.E1	0.19±0.04	0.24±0.01	0.136±0.002
G	11596	CRF02_G clone 252	0.26±0.03	0.13±0.01	0.11±0.01
Mean ± SEM (μM):		**Overall** (n=50) **SI**	0.39±0.02 **108.7**	0.43±0.02 **198.4**	0.18±0.008 **607.2**
		Subtype A (n=6) **SI**	0.42±0.05 **101**	0.54±0.08 **158**	0.22±0.003 **496.8**
		Subtype A_{rec} (n=12) **SI**	0.44±0.03 **96.4**	0.49±0.04 **174.1**	0.18±0.01 **607.2**
		Subtype B (n=14) **SI**	0.39±0.04 **108.7**	0.43±0.06 **198.4**	0.17±0.02 **642.9**
		Subtype C (n=13) **SI**	0.38±0.04 **111.6**	0.37±0.03 **230.5**	0.18±0.02 **607.2**
		Subtype D (n=4) **SI**	0.26±0.03 **163.1**	0.35±0.07 **243.7**	0.17±0.03 **642.9**
Control	VSV-G[d]	IC_{50}	>20	>20	>20
		CC_{50}	46.3±10.6	>94	>94
IC_{50} (Color Code)			≤0.2	>0.2 ≤0.5	>0.5

[a] The reported IC_{50} values represent the means ± standard deviations (n = 3).
[b] R5X4-tropic virus all the rest are CCR5-tropic viruses.
[c] Data previously published[10]
[d] VSV-G was tested in U87-CD4-CCR5 cells

Table 3. Neutralization activity of gp120 entry-antagonists against an HIV-1 panel of Paired Infant (B) and Maternal (M) Env Molecular Clones.

			IC_{50} (μM)[a]		
Subtype	**NIH #**	**ENV**	**Ref2**	**33**	**8**
A	**11518-B**	BG505.W6M.ENV.C2	0.92±0.16	1.38±0.2	0.57±0.06
A	**11528-M**	MG505.W0M.ENV.A2	0.93±0.07	1.6±0.08	0.47±0.08.
A	**11519-B**	B1206.W6P.ENV.A1A	0.75±0.06	1.8±0.07	0.53±0.05
A	**11531-M**	MI206.W0M.ENV.D1	0.7±0.02	1±0.02	0.28±0.01
A	**11521-B**	BJ613.W6M.ENV.E1	0.8±0.07	0.94±0.14	0.26±0.01
A	**11535-M**	MJ613.W0M.ENV.A2	0.5±0.05	0.63±0.07	0.31±0.07
D/A	**11524-B**	BL035.W6M.ENV.C1	0.52±0.16	0.54±0.04	0.42±0.01
D/A	**11538-M**	ML035.W0M.ENV.G2	0.59±0.08	0.86±0.05	0.23±0.01
A	**11525-B**	BL274.W6M.ENV.A3	0.63±0.12	0.84±0.09	0.37±0.05
A	**11540-M**	ML274.W0M.ENV.B1	0.66±0.1	0.88±0.06	0.25±0.03
Mean ± SEM (μM): Overall (n=10)			0.7±0.05	1.05±0.13	0.37±0.04
Infant (B) (n=5)			0.72±0.07	1.1±0.22	0.43±0.07
Mother (M) (n=5)			0.68±0.07	0.99±0.16	0.31±0.04

[a] The reported IC_{50} values represent the means ± standard deviations (n = 3).

Table 4. Inhibitory activity of **8** and **33** against a large panel of FDA approved drug-resistant viruses

	NIH catalog#	Major mutations[a]	33 IC_{50} (μM)[b]	Fold increase/ Sensitive	8 IC_{50} (μM)[b]	Fold increase/ Sensitive
NL4-3 WT (wild-type)	#114	-	2.1±0.1	-	1.1±0.04	-
ENTRY (Enfuvirtide)-resistant	#9498	V38A, N42T	1.5±0.2	Sensitive	0.94±0.1	Sensitive
	#9490	V38A	1.9±0.1	Sensitive	0.94±0.02	Sensitive
	#9496	V38E, N42S	1.6±0.2	Sensitive	0.89±0.1	Sensitive
	#9491	N42T, N43K	2.5±0.2	Sensitive	0.47±0.02	Sensitive
	#9489	D36G	0.73±0.1	Sensitive	0.71±0.01	Sensitive
Multi-drug (NNRTI)- resistant	#12227	K101P, K103N	0.48±0.01	Sensitive	0.23±0.01	Sensitive
	#12229	L100I, K103N	2.9±0.1	1.38	2.4±0.2	2.18
	#12231	K103N, Y181C	0.42±0.04	Sensitive	0.26±0.02	Sensitive
	#12233	K101E, Y181V	3.7±0.3	1.76	2.4±0.07	2.18
	#12237	Y181C, G190A	3.5±0.5	1.66	2±0.1	1.82
	#12241	K101E, G190S	1.7±0.3	Sensitive	0.47±0.01	Sensitive
	#12243	L100I, M230L	4.5±0.05	2.14	2.3±0.05	2.09
Integrase (Raltegravir-resistant)	#11847	G140S, Q148H	0.2±0.04	Sensitive	0.23±0.005	Sensitive
	#11850	E92Q, N155H	0.72±0.22	Sensitive	0.3±0.03	Sensitive
	#11851	N155H	0.26±0.1	Sensitive	0.094±0.005	Sensitive
Multiple-PI-r	#11800	11I, 32I, 33F, 46I, 47V, 54M, 58E, 73S, 84V, 89V, 90M	0.28±0.05	Sensitive	0.16±0.07	Sensitive
	#11801	10F, 33F, 43T, 46L, 54V, 82A, 84V, 90M	0.31±0.16	Sensitive	0.19±0.1	Sensitive
	#11803	33F, 43T, 46I, 48V, 50V, 54S, 82A	1.2±0.2	Sensitive	0.61±0.2	Sensitive
	#11804	32I, 46I, 47V, 84V	0.51±0.07	Sensitive	0.26±0.04	Sensitive
	#11805	48V, 53L, 54V, 82A, 90M	1±0.1	Sensitive	0.27±0.14	Sensitive

	#11807	32I, 33F, 47A, 82A, 90M	0.58±0.1	Sensitive	0.12±0.02	Sensitive
	#11808	10F, 11I, 33F, 43T, 46L, 54V, 73S, 82A, 84V, 89V, 90M	0.47±0.1	Sensitive	0.73±0.1	Sensitive
	#12465	46I, 54V, 58E, 74P, 82L, 90M	1±0.2	Sensitive	0.42±0.1	Sensitive
	#12466	32I, 33F, 43T, 46I, 47V, 54M, 73S, 82A, 89V, 90M	0.47±0.1	Sensitive	0.24±0.09	Sensitive

[a] Mutants were reported here as per the data obtained from https://www.aidsreagent.org/ and associated references indicated in the Experimental Section.
[b] The reported IC_{50} values represent the means ± standard deviations (n = 3).

Table 5. Inhibitory activity against Cell-to-Cell HIV transmission by the gp120 entry-antagonists.

Compound	IC_{50} (μM)[a]	
	TZMb-l/H9-HIV-1_{IIIB}	**TZMb-l/MolT-HIV-1_{ADA}**
Ref2	0.46±0.2	0.89±0.14
33	0.45±0.1	1.2±0.4
8	0.47±0.1	0.92±0.13
BMS-626529	0.02±0.005	~0.2

[a]The reported IC_{50} values represent the means ± standard deviation (SD), n=3.

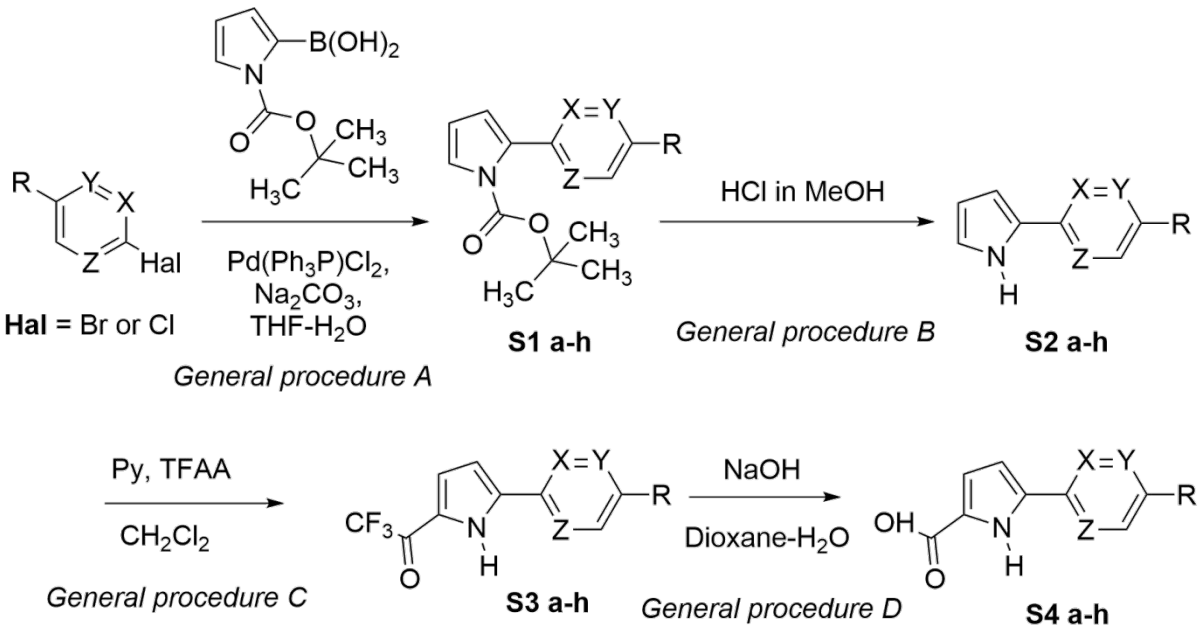
Table 6. in vitro ADME profile of the most potent inhibitor **8**

Assay performed	in vitro ADMET	Compound		BMS-626529[a]	Positive control used in the study (Digoxin)
		8	Ref1[a]		
Solubility (mg/mL)	Phosphate buffer, pH7.4	0.734	0.042 – 0.214	0.047 – 0.237	-
Caco-2 permeability (mean P_{app}, x 10^{-6} cm/sec)	A-to-B	6.51	0.602	9.27	0.483
	B-to-A	20.3	17.7	32.0	10.3
	Efflux Ratio	3.12	30.5	3.46	21.2
(+ 1μM Valspodar)	A-to-B	14.0	0.777[b]	13.5[b]	2.00
	B-to-A	10.5	10.9[b]	22.7[b]	2.06
	Efflux Ratio	0.755	14.4[b]	1.69[b]	1.03
Metabolic Stability (human liver microsomes)	parent compound remaining at 120 min (% of 0 min)	93.5	88.5	71.5	-
	Cl_{int} (mL/min/mg protein)	<0.0116	0.0018	0.0052	-
	Half-life (min)	>120	-	-	-
Protein binding (human plasma)	% bound	99.2	99.0	86.9	-
Cytochrome P450 inhibition, IC_{50} (μM)	CYP1A2 (Phenacetin)	70.1	> 25	> 25	-
	CYP2B6 (Bupropion)	85.4	> 25	> 25	-
	CYP2C8 (Amodiaquine)	> 100	> 25[c]	> 25[c]	-
	CYP2C9 (Diclofenac)	> 100	> 25	> 25	-
	CYP2C19 (S-Mephenytoin)	> 100	> 25	> 25	-
	CYP2D6 (Bufuralol)	> 100	> 25	> 25	-
	CYP3A (Testosterone)	> 62.2	> 25	> 25	-
	CYP3A (Midazolam)	> 100	> 25	> 25	-

[a,b,c,]The data were from Ref. *Eur J med Chem, 154, 367(2018)*

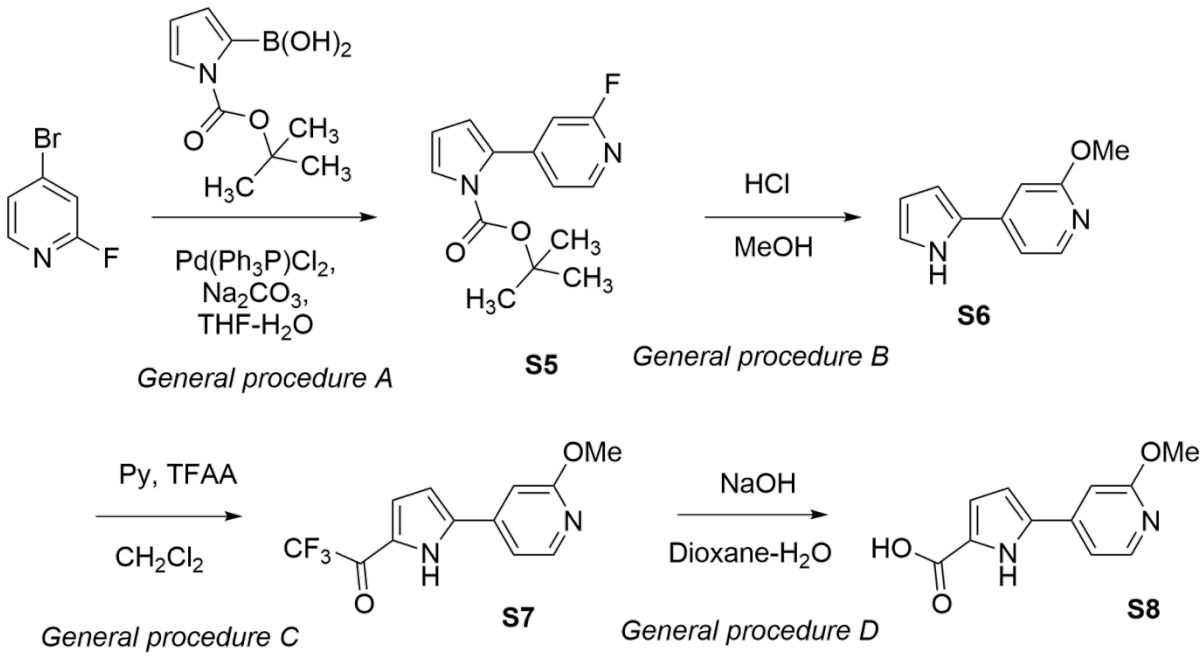
[b],100 μM verapamil was used as a P-gp inhibitor

[c,] Paclitaxel was used as a substrate

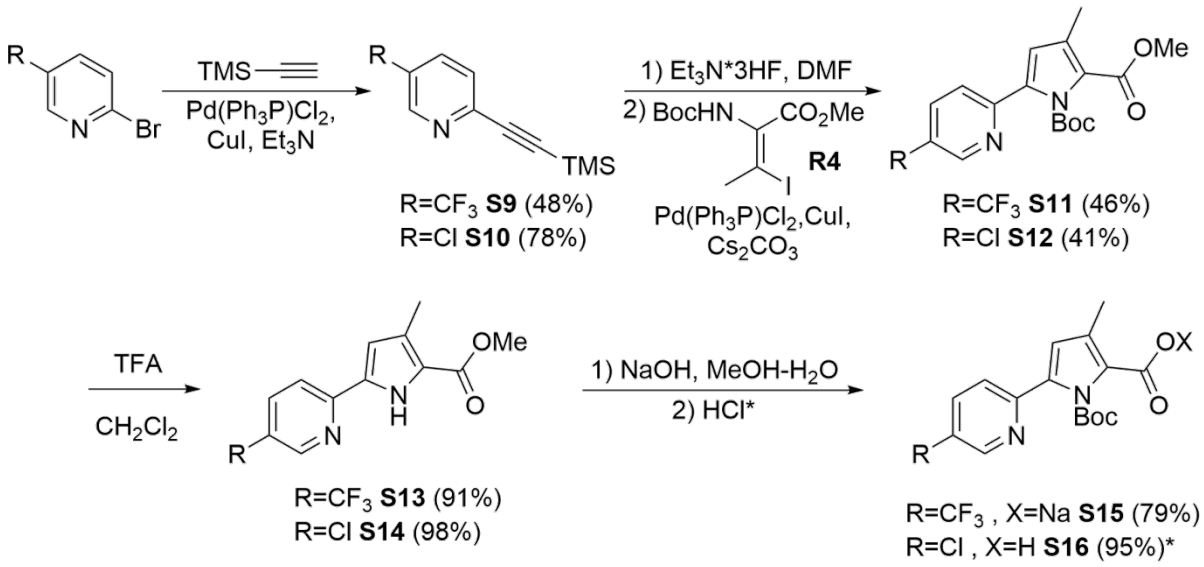


a) X=N, Y=Z=CH, R=Me
b) X=N, Y=Z=CH, R=Cl
c) X=N, Y=Z=CH, R=F
d) X=N, Y=Z=CH, R=CF_3
e) Y=N, X=Z=CH, R=Cl
f) Y=N, X=Z=CH, R=CF_3
g) X=Y=N, Z=CH, R=CF_3:
h) X=Z=N, Y=CH, R=Cl

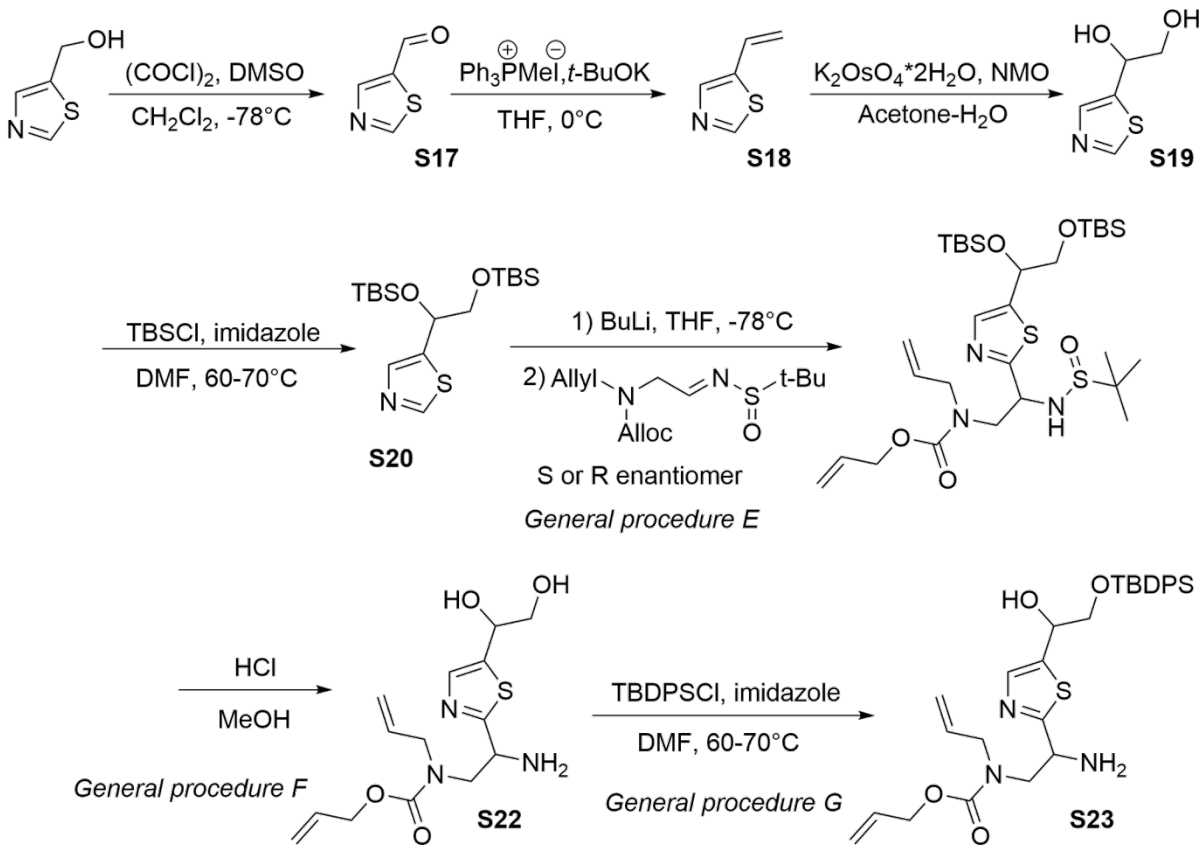
Scheme 1. Synthesis of intermediate acids



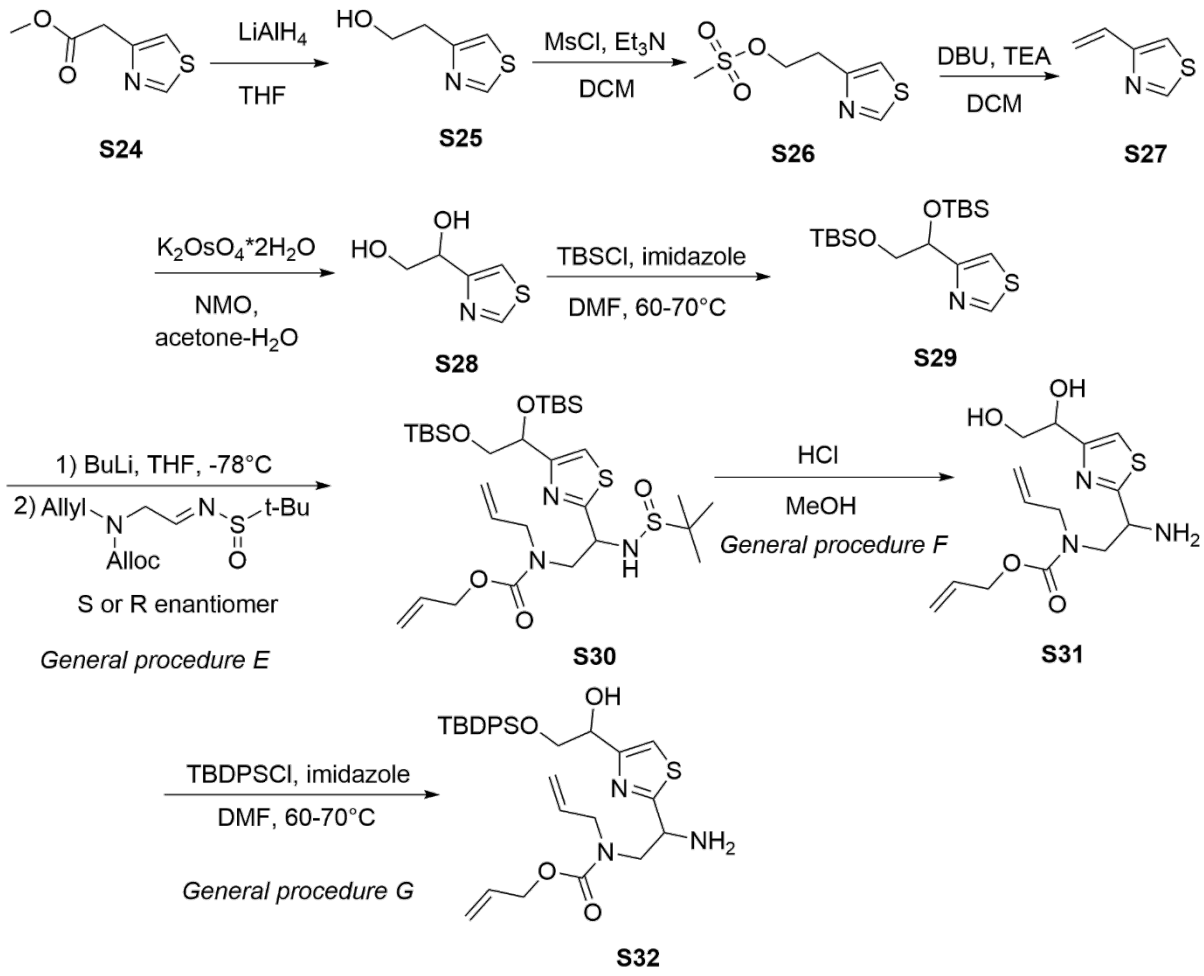
Scheme 2. Synthesis of 5-(2-methoxypyridin-4-yl)-1H-pyrrole-2-carboxylic acid



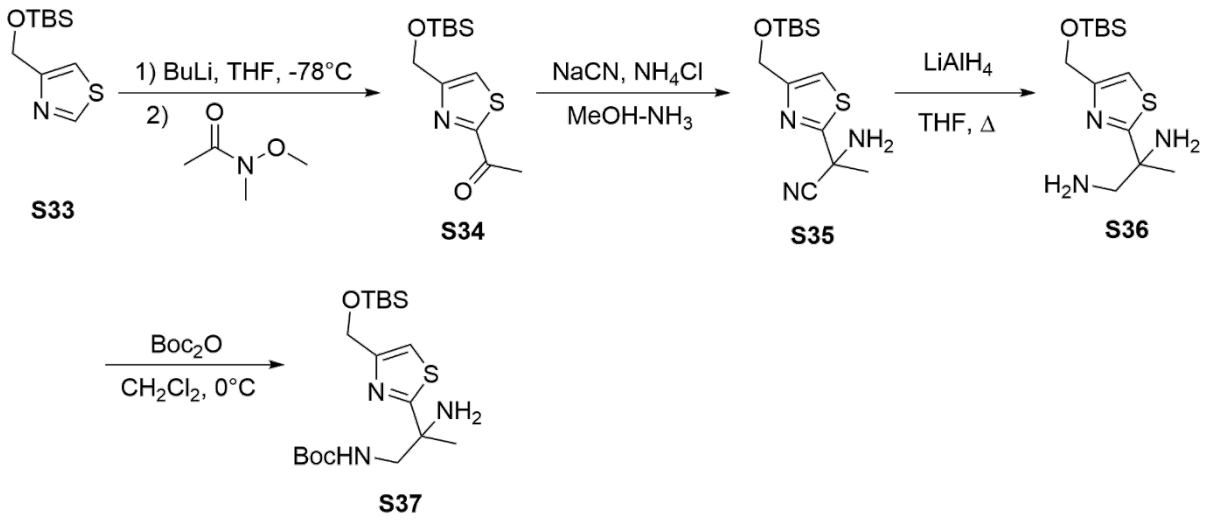
Scheme 3. Synthesis of 5-(5-substituted-2-yl)-3-methyl-1H-pyrrole-2-carboxylic acid and Na salt. (*) acidification step performed only for **S16**



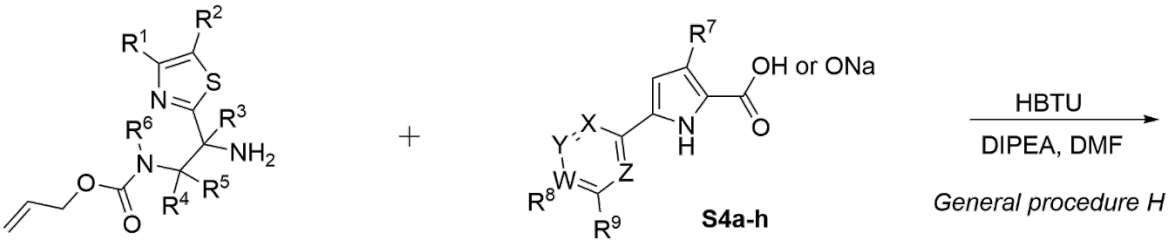
Scheme 4. Synthesis of allyl allyl(2-amino-2-(4-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)thiazol-2-yl)ethyl)carbamate (**S23 fS** and **S23 fR**). Note all enantiomer compounds derived from the stereo-controlled addition of the allyl N-allyl-N-[(2E)-2-tert-butylsulfinyliminoethyl]carbamate with absolute configuration S, have been specified with the **fS** descriptor; and all enantiomer compounds derived from the stereo-controlled addition of the allyl N-allyl-N-[(2E)-2-tert-butylsulfinyliminoethyl]carbamate with the absolute configuration R have been specified with the **fR** descriptor as per previous works[10].



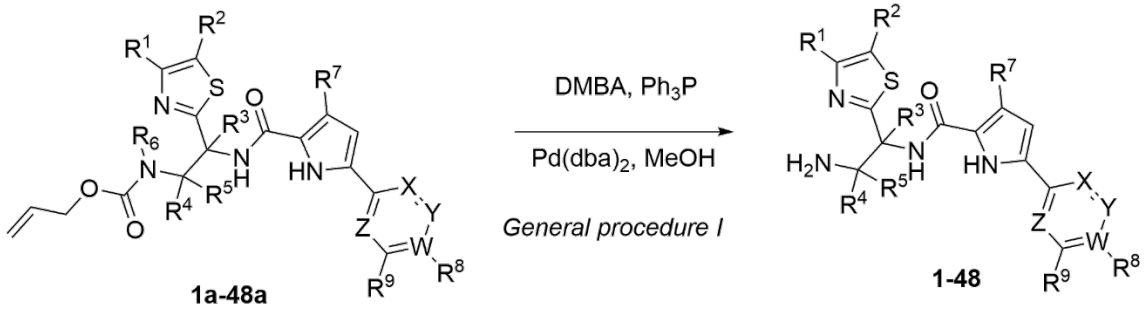
Scheme 5. Synthesis of allyl N-allyl-N-[2-amino-2-[4-[2-[tert-butyl(diphenyl)silyl]oxy-1-hydroxy-ethyl]thiazol-2-yl]ethyl]carbamate (**S32 fR** and **S32 fS**).



Scheme 6: Synthesis of tert-butyl (2-amino-2-(4-(((tert-butyldimethylsilyl)oxy)methyl)thiazol-2-yl)propyl)carbamate (**S37**).



R^1=CH_2OH, R^2=H, R^3=H, R^4=H, R^5=H, R^6=allyl **S38**
R^1=H, R^2=CH_2OH, R^3=H, R^4=H, R^5=H, R^6=allyl **S39**
R^1=CH_2OH, R^2=CH_2OH, R^3=H, R^4=H, R^5=H, R^6=allyl **S40**
R^1=$(CH_2)_2OH$, R^2=H, R^3=H, R^4=H, R^5=H, R^6=allyl **S41**
R^1=$(CH_2)_3OH$, R^2=H, R^3=H, R^4=H, R^5=H, R^6=allyl **S42**
R^1=H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=allyl **S43**
R^1=$C(CH_3)_2OH$, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H **S44**
R^1=H, R^2=$C(CH_3)_2OH$, R^3=H, R^4=H, R^5=H, R^6=H **S45**



Scheme 7: Synthesis of HIV-1 inhibitors 1-48 in Table-1.

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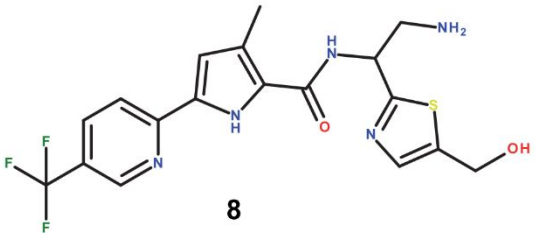
HIV-1 gp120 entry-antagonist



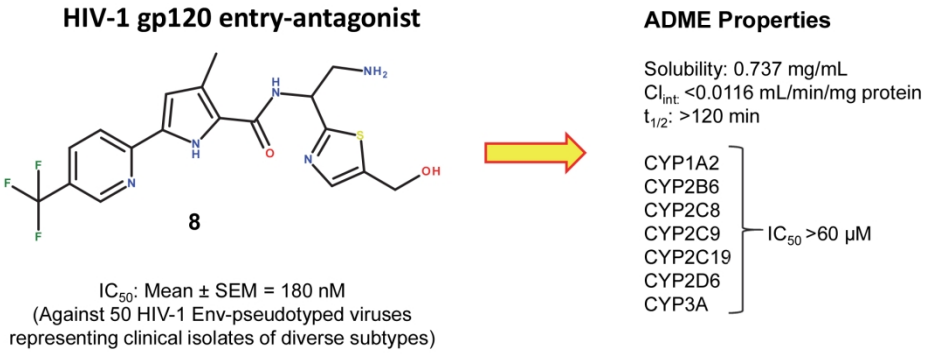
8

IC_{50}: Mean ± SEM = 180 nM
(Against 50 HIV-1 Env-pseudotyped viruses representing clinical isolates of diverse subtypes)

ADME Properties

Solubility: 0.737 mg/mL
Cl_{int}: <0.0116 mL/min/mg protein
$t_{1/2}$: >120 min

CYP1A2
CYP2B6
CYP2C8
CYP2C9
CYP2C19
CYP2D6
CYP3A
} IC_{50} >60 μM



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