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# Heterocycle amide isosteres: an approach to overcoming resistance for HIV-1 Integrase strand transfer inhibitors

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*Departments of Discovery Chemistry and Discovery Infectious Diseases, Bristol-Myers Squibb Research & Development, Wallingford, CT 06492, USA*

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ABSTRACT

A series of heterocyclic pyrimidinedione-based HIV-1 integrase inhibitors was prepared and screened for activity against purified integrase enzyme and/or viruses modified with the following mutations within integrase: Q148R, Q148H/G140S and N155H. These are mutations that result in resistance to the first generation integrase inhibitors raltegravir and elvitegravir. Based on consideration of drug-target interactions, an approach was undertaken to replace the amide moiety of the first generation pyrimidinedione inhibitor with azole heterocycles that could retain potency against these key resistance mutations. An imidazole moiety was found to be the optimal amide substitute and the observed activity was rationalized with the use of calculated properties and modeling. Rat pharmacokinetic (PK) studies of the lead imidazole compounds demonstrated moderate clearance and moderate exposure.

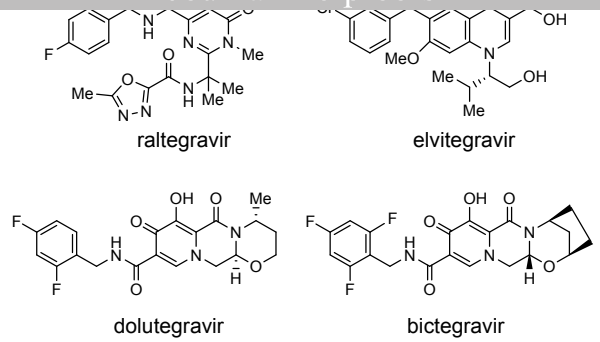


HIV-1 infection remains a persistent global health problem. In recent years, treatment advances have dramatically improved the prognosis for HIV-1-infected patients, transforming what was once untreatable into a manageable chronic disease. However, due to issues associated with resistance and tolerability, there remains a need for new treatment agents.[1] HIV-1 integrase, one of three vital enzymes encoded in the virus genome, is an attractive target for antiviral treatment.[2-5] Currently, 1st generation integrase inhibitors raltegravir, and elvitegravir, and the 2nd generation integrase inhibitors dolutegravir and bictegravir are approved for use in HIV-1-infected individuals, in combination with other agents (Figure 1).[6-9] Despite their success, raltegravir and elvitegravir suffer from relatively low barriers for the development of resistance mutations.[7,8] The ability to be used against viruses resistant to first generation integrase inhibitors is the goal of 2nd generation HIV-1 integrase inhibitors.*

Incorporation of transcribed viral DNA into the host genome is a critical part of the HIV-1 life cycle and is mediated by the integrase enzyme.[10] HIV-1 integrase catalyzes this process via two separate reactions. The first of these, termed 3'-processing, involves the cleavage of two base pair nucleotides from the 3'-ends of the reverse transcribed viral DNA. The second catalyzed reaction, termed strand transfer, involves the insertion of the 3'-processed viral DNA into the host genome. Active site inhibitors act by inhibiting the strand transfer step and are designated as integrase strand transfer inhibitors (INSTIs).

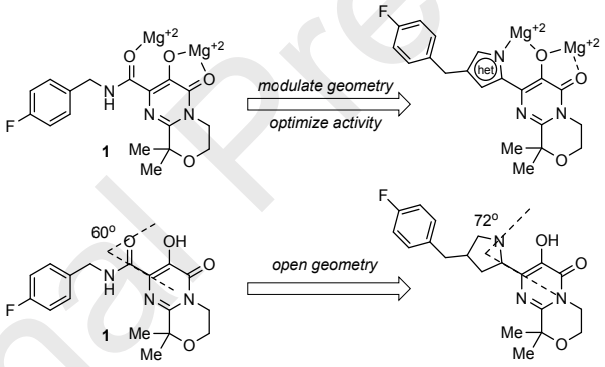
**Figure 1**. HIV-1 strand transfer inhibitors.

* Corresponding author. Tel.: 203-677-7755; e-mail: kevin.peese@bms.com.



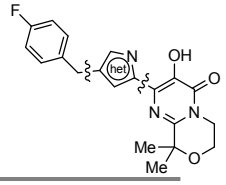

Pyrimidinedione amides, including raltegravir and compound **1**, bind to the integrase enzyme by coordination of two active site $Mg^{2+}$ atoms via the "two-metal binding model".[11,12] Once bound in the active site, the compounds do not allow the host DNA to bind. A primary and robust raltegravir clinical resistance pathway involves mutation of the Q148 residue which confers >25-fold reduction in potency.[13] Mutation at this site affects the affinity of the enzyme for $Mg^{2+}$ and allows the host DNA to compete better compared to first generation inhibitors for binding into the active site.[14] However, mutations involving the Q148 pathway display impaired replication, and require a secondary mutation to restore virus growth. For the Q148H mutant, the secondary mutation G140S is necessary to restore fitness. The reduced $Mg^{2+}$ affinity of the Q148 mutants suggests a slightly altered coordinating environment surrounding the $Mg^{2+}$ atoms and, by extension, a structural shift of the position of the $Mg^{2+}$. Since integrase strand transfer inhibitors chelate two $Mg^{2+}$ ions in the active site, such a shift would likely also affect the binding capacity of active site strand transfer inhibitors including the first generation pyrimidinedione amide **1**. To address the proposed altered structure of the binding site of the Q148 mutants, an approach involving the use of azole heterocycles to replace the amide was initiated within the pyrimidinedione chemotype exemplified by **1**. This change was anticipated to afford a more open geometry that would exhibit greater tolerance of the altered active site of Q148 mutants (Figure 2). The proximal nitrogen of azole heterocycles would allow for $Mg^{2+}$ chelation in a similar fashion to the amide oxygen of the parent amide.[11] Optimization of the azole would then be expected to restore activity compromised through the altered geometry of the metal binding template. This strategy was especially attractive given that resistance coverage of the azole series may be additive with other orthogonal structural modifications. Our efforts toward implementation of this strategy are detailed herein.

**Figure 2**. Strategic approach to heterocycles as a metal coordinators.




The use of heterocycles to mimic an amide is well-explored in the literature and has been independently pursued in the context of HIV-1 integrase inhibitors.[15-21] Within a bicyclic pyrimidinedione series, azole amide isosteres were explored in order to optimize wild type integrase inhibitory activity.[16] Further extension of this work demonstrated that thiazoles, in cooperation with other chemical modifications, were active against raltegravir-resistant mutants.[17] In addition to this example, in the context of a hydroxynaphthyridine series oxadiazoles were established as competent replacements for the amide portion of the metal binding motif.[18,19] Another study also evaluated oxadiazoles as a chemotype for inhibition of the wild-type integrase enzyme.[20] The work described herein focused on the utility of azole isosteres as a strategy specifically to improve activity compared to first generation resistant mutants, while retaining activity against wild-type integrase.

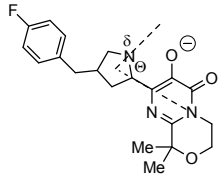
A series of azole heterocycle derivatives were prepared and evaluated for antiviral activity against $NL_{4-3}$ virus in a cellular assay (Table 1). Generally, the majority of heterocycles were tolerated with wild-type potencies within 5-fold of the parent amide (e.g., **2**, **3**, **5**, **6**, **8**, vs. **1**). Exceptions included pyrazole **4**, oxadiazole **7**, and triazole **9** which all lost substantial activity against the wild-type virus. Attachment of the benzyl group via *N* or *C* had only minor effects on potency against wild type virus, as exemplified by comparing **5** and **6**. Establishing potent activity toward the first generation resistance mutations Q148R, G140S/Q148H, and N155H proved to be more challenging. While most heterocycles offered incremental improvements in potency compared with the parent amide, imidazole and thiazole replacements provided the most substantial improvement, with the imidazole replacement having the best profile (**5** and **6**). Of the resistant mutants evaluated, N155H was consistently the least challenging followed by Q148R, and finally G140S/Q148H. During this survey, we also evaluated some basic substitution patterns of the heterocycle ring. For example, a methyl group was well tolerated on the southern position (compare **10** vs. **5** and **11** vs. **9**). In contrast, methyl or Cl substitution at the northwest position led to a complete loss of potency (**12** vs. **8**, **13** vs. **5**). In addition, the regio-connectivity of the benzyl group to the heterocycle was also found to be critical. The *N*-methyl imidazole **14** forces the benzyl group to be connected through the northwest position in order to preserve the metal binding motif of the heterocycle. This substitution pattern, however, resulted in complete loss of activity.



| Compound | heterocycle | $EC_{50}$ (μM)[a] | $EC_{50}$ (μM)[a] Q148R | $EC_{50}$ (μM)[a] G140S/Q148H | $EC_{50}$ (μM)[a] N155H | CC50 (μM)[a] |
|---|---|---|---|---|---|---|
| **1** |  | 0.003 | 0.30 | >8 | 0.14 | >100 |
| **2** |  | 0.022 | 0.33 | 6.9 | 0.088 | 5.3 |
| **3** |  | 0.003 | 0.091 | 0.54 | 0.034 | 2.5 |
| **4** |  | 0.12 | 3.0 | 4.2 | 0.26 | 7.1 |
| **5** |  | 0.006 | 0.033 | 0.32 | 0.002 | 4.4 |
| **6** |  | 0.004 | 0.026 | 0.32 | 0.009 | 3.2 |
| **7** |  | 0.39 | 0.19 | >40 | 1.3 | 99 |
| **8** |  | 0.007 | 0.22 | 3.7 | 0.016 | 18 |
| **9** |  | 0.081 | 1.5 | >40 | 4.0 | 44 |
| **10** |  | 0.010 | 0.061 | 0.53 | 0.036 | 1.6 |
| **11** |  | 0.081 | 0.45 | 1.1 | NA | 35 |
| **12** |  | >30[b] | NA | NA | NA | >100 |
| **13** |  | >64[b] | NA | NA | NA | 29 |
| **14** |  | 9.3[b] | NA | NA | NA | 7.0 |

a) Antiviral activity assayed in an HIV infectivity cellular assay; b) Integrase activity assayed in an in vitro enzyme binding assay.

Our hypothesis suggested that inhibitors with a wider geometry than the parent pyrimidinedione amide series exemplified by **1** would be more capable of binding to the active site of first generation resistant integrases. Indeed, most heterocycles evaluated show a much improved ratio ($EC_{50}$ mutant/$EC_{50}$ wt) against the integrase mutants (Table 2). To better understand the altered potential of the heterocycle series to chelate $Mg^{2+}$, we calculated the "bite angle" and partial charge of the $Mg^{2+}$-coordinating nitrogen. The calculated values of *N*-partial charge, with the exception of triazole **8**, generally tracked with fold-change compared to the wild type. Imidazoles **5** and **6** showed among the highest partial negative charge on the nitrogen, -0.58 and -0.57, respectively, and the least fold-changes. Triazole **8** exhibited excellent wild type activity but surprisingly weak activity against the resistant viruses given the high partial charge on the nitrogen of -0.60. The calculated results concerning the "bite angle" were more ambiguous. The larger bite angle relative to the parent amide **1** likely does contribute to increased activity against the resistant integrases. However, within the series, subtle differences in bite angle did not track with resistance activity. The azoles, with the exception of thiazole **3**, had a bite angle of 70–74°. Thiazole **3** had a bite angle of 67°, closest to the parent amide **1**, and may account for the excellent wild-type inhibitory activity. Imidazoles have previously been calculated to bind well to $Mg^{2+}$ in protein environments with an affinity matching or exceeding the corresponding amide.[22] This result agrees well with our findings and provides precedent for the use of imidazole in a $Mg^{2+}$ chelation capacity.



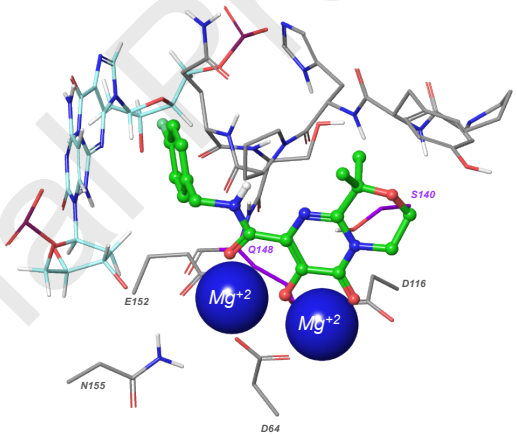
**Tabl**

| Compound | Q148R fold[b] | G140S/Q148H fold[b] | N155H fold[b] | Bite angle (θ) | *N* partial charge |
|---|---|---|---|---|---|
| **1** | 99 | >2666 | 47 | 60.5 | -0.60 (*O*) |
| **2** | 15 | 318 | 4 | 70.8 | -0.48 |
| **3** | 30 | 177 | 11 | 67.4 | -0.51 |
| **4** | 26 | 36 | 22 | 72.1 | -0.54 |
| **5** | 6 | 54 | 0.3 | 71.8 | -0.58 |
| **6** | 7 | 80 | 2 | 73.4 | -0.57 |
| **7** | 0.5 | >100 | 3 | 70.5 | -0.40 |
| **8** | 34 | 563 | 2 | 72.2 | -0.60 |
| **9** | 19 | >500 | 49 | 71.7 | -0.40 |

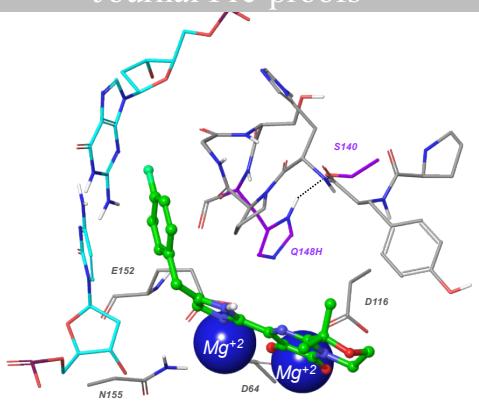
a) calculated using Schrodinger Maestro Elements; b) $EC_{50}$ mutant/$EC_{50}$ wild type.

We also modeled the active sites of the wild-type integrase with amide **1** bound and the G140S/Q148H integrase with imidazole **5** bound based upon the published structure of the closely related prototype foamy virus (PFV) integrase.[23,24] The modeling reveals a distinct structural difference between the binding sites of the wild-type integrase and the G140S/Q148H mutant (Figure 4). The binding pocket of the wild-type enzyme places the benzyl group of **1** tightly between Q148 and E152. Mutation of glutamine148 to histidine, however, resulted in a more open pocket that is no longer well occupied by the benzyl amide of **1**, a result that was also supported by recent literature.[25] In contrast, the more extended geometry of imidazole **5** is able to occupy much of this increased space thereby resulting in increased antiviral activity. Overall, the improved resistance coverage of the heterocycle series is likely due to a combination of the wider geometry of the azoles and its effect on $Mg^{2+}$ binding coupled with better steric occupation of the mutant active site. Within the heterocycle series, imidazole is likely the most active due to having the highest partial charge on the azole nitrogen suggesting optimum $Mg^{2+}$ binding.

**Figure 4**. Models of amide **1** bound to wild type integrase and imidazole **5** bound to G140S/Q148H integrase.




Compound **1** bound to PFV integrase (3S3N) wild type



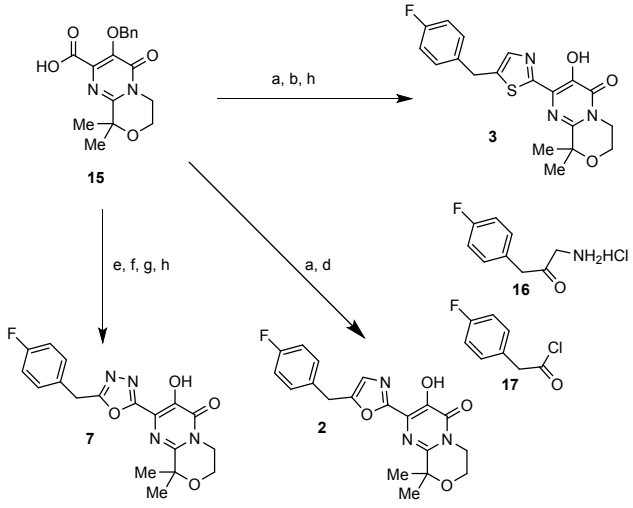

Imidazole **5** bound to PFV integrase (3S3N) Q148H_G140S

Four heterocycles were advanced into rat IV PK studies (Table 3). Imidazole analogs **5** and **10** were both found to have low clearance (CL) and very low volume of distribution (Vss), resulting in moderate plasma exposures. In contrast, imidazole **6** and triazole **8**, for which the 4-fluorobenzyl group point of attachment is through a nitrogen atom, were found to have high CL and moderate Vss, resulting in low exposure.

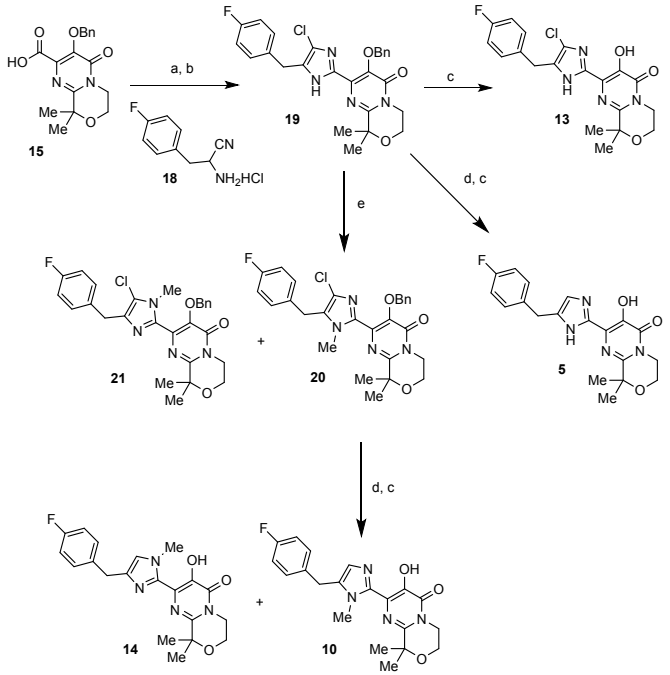
**Table 3.** Rat IV PK of lead analogs (1 mg/kg)

| Compound | CL (L/min/kg) | Vss (L/kg) | AUC (nM*h) |
|---|---|---|---|
| **5** | 10 | 0.3 | 4550 |
| **10** | 11 | 0.5 | 3918 |
| **6** | 127 | 3.5 | 353 |
| **8** | 52 | 1.5 | 872 |

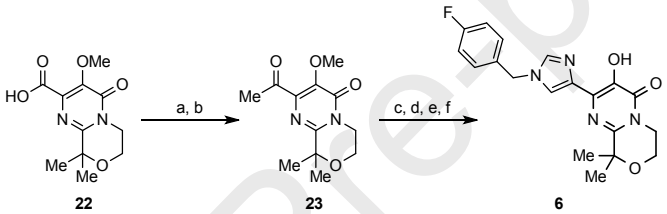
The series of heterocycles detailed above were readily prepared by published methods from the key starting compounds **15** and **22**.[26] Oxazole **2** was prepared *via* amidation of acid **15** with amino ketone **16** and dehydrative cyclization with concomitant debenzylation (Scheme 1). Thiazole **3** was prepared *via* an analogous sequence utilizing Lawesson's reagent-mediated thiodehydrative cyclization followed by TFA mediated debenzylation. Oxadiazole **7** was also synthesized using an analogous sequence utilizing acyl hydrazide **17** in place of aminoketone **16**. Imidazoles **5**, **10**, **13**, and **14** were prepared *via* published methodology by Zhong *et al*. (Scheme 2).[27] Amide formation from acid **15** with aminonitrile **18**, followed by dehydrative chlorocyclization provided chloroimidazole **19**. This pivotal intermediate was subjected alternatively to deprotection, dechlorination/ deprotection, alkylation/deprotection, or alkylation/dechlorination/deprotection to provide chloroimidazole **13**, imidazole **5**, methylated chloroimidazoles **20** and **21**, and methylated imidazoles **10** and **14**, respectively. Isomeric imidazole **6** was prepared *via* conversion of acid **22** to methyl ketone **23** followed by bromination, cyclization, benzylation, and deprotection (Scheme 3). Triazoles **8** and **9** were prepared by conversion of acid **15** to thioamide **24** followed by activation, cyclization, and concomitant debenzylation with either acylhydrazide **25** or formylhydrazide **26** to provide triazole **8** and **9**, respectively (Scheme 4). Methyltriazole **11** was prepared in a similar sequence by conversion of acid **15** to methylthioamide **27**, followed by methylation and cyclization with accompanying debenzylation to give methyltriazole **11** (Scheme 5). Finally, pyrazole **4** was prepared by conversion of acid **15** to diketone **28** followed by hydrazine mediated cyclization and deprotection to deliver pyrazole **4** (Scheme 6).



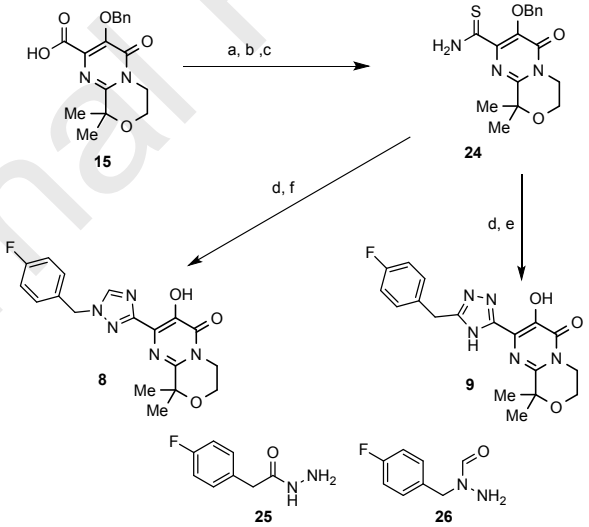
**Sche** t; (e) $(COCl)_2$, DMF, DCM; hydrazine, DCM. (f) **17**, TEA, DCM; (g) $PPh_3$, $Cl_3CCCl_3$, DIPEA, $CH_3CN$, heat; (h) TFA.



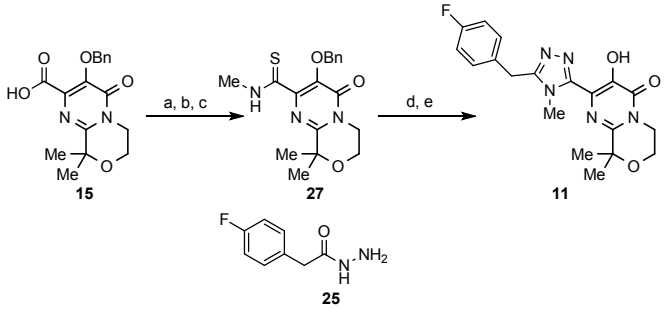
**Scheme 2.** Reagents: (a) $(COCl)_2$, DMF, DCM; **18**, DIPEA, DCM; (b) $PPh_3$, $CCl_4$, MeCN, 45 °C; (c) LiCl, DMF, 120 °C; (d) $H_2$, 10% Pd/C, MeOH (e) NaH, THF; MeI.

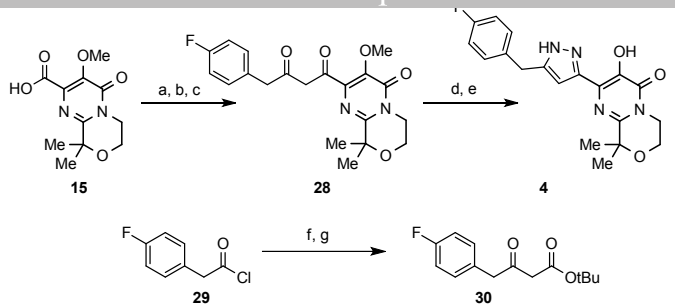


**Scheme 3.** Reagents: (a) $(COCl)_2$, DMF, DCM; NHMe(OMe)HCl, TEA, DCM; (b) MeMgBr, THF, 0 °C; (c) $CuBr_2$, THF, 50 °C; (d) formamide, 140 °C; (e) NaH, then 4-*F*-BnBr, THF; (f) $BBr_3SMe_2$, DCE, 80 °C.



**Scheme 4.** Reagents: (a) $(COCl)_2$, DMF, DCM; (b) $NH_4OH$, DCM; (c) Lawesson's reagent, THF, 70 °C; (d) MeI, MeCN, 50 °C; (e) **25**, DMF, 140 °C; (f) **26**, DMF, 140 °C.






**Scheme 6.** Reagents: (a) $(COCl)_2$, DMF, DCM; (b) **30**, NaH, THF; (c) TFA, 60 °C; (d) hydrazine hydrate, EtOH, reflux; (e) $BBr_3$, DCM; (f) Meldrum's acid, pyridine, DCM; (g) *t*-BuOH, heat.

Interestingly, a previous study examining the use of azoles in the context of integrase inhibitors found thiazoles to be optimal, a finding that likely reflects the study's focus on wild-type activity.[16,17] Our work also demonstrates that thiazoles are excellent amide substitutes in wild-type enzyme inhibitors; however, consideration of resistant mutants indicated that imidazoles exhibit broader polymorph coverage. Indeed, thiazole was superior to imidazole only for the wild-type. For the three resistance mutations evaluated (Q148R, G140S/Q148H, and N155H), imidazole was consistently more effective.

In conclusion, we have identified a promising set of heterocycle amide isosteres in the pyrimidinedione series that have increased capacity for resistance coverage. Against the most resistant mutant G140S/Q148H, coverage was much improved although still not optimal. However, the heterocycle series may prove useful in combination with other structural modifications to improve resistance coverage. The best of these compounds, **5** and **10**, were both found to have moderate exposure in a rat IV PK screen demonstrating the viability of this class of structure modification to the parent pyrimidinedione series.

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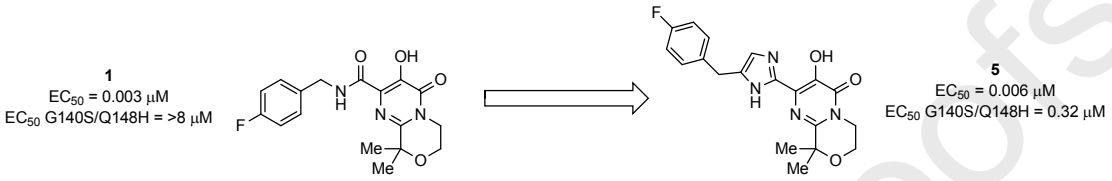


## Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

## Graphical Abstract

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