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Carbamoyl Pyridone HIV-1 Integrase Inhibitors 2. Bi- and Tri-cyclic Derivatives Result in Superior Antiviral and Pharmacokinetic Profiles

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Abstract

This work is a continuation of our initial discovery of a potent monocyclic carbamoyl pyridone human immunodeficiency virus type-1 (HIV-1) integrase inhibitor that displayed favorable antiviral and pharmacokinetic properties. We report herein a series of bicyclic carbamoyl pyridone analogs to address conformational issues from our initial SAR studies. This modification of the core unit succeeded to deliver low nM potency in standard antiviral assays. An additional hydroxyl substituent on the bicyclic scaffold provides remarkable improvement of antiviral efficacies against clinically relevant resistant viruses. These findings led to additional cyclic tethering of the naked hydroxyl group resulting tricyclic carbamoyl pyridone inhibitors to address remaining issues and deliver potential clinical candidates. The tricyclic carbamoyl pyridone derivatives described herein served as the immediate lead in molecules to the next generation integrase inhibitor dolutegravir which is currently in late stage clinical evaluation.

KEYWORDS

HIV-1 integrase, two-metal binding pharmacophore, molecular design, carbamoyl pyridone inhibitor, dolutegravir, DTG, S/GSK1349572, S/GSK572

1. Introduction

HIV-1 integrase (IN) is a virally encoded enzyme essential for replication that catalyzes the integration of viral DNA into the host chromatin. As a result of this unique retroviral step, IN has become an attractive target for drug discovery.¹ In 2007, raltegravir² (RAL) (figure 1) became the first approved HIV-1 IN inhibitor (INI) thus opening up a new class of antiretroviral agents and it has since become a preferred first line agent as part of the highly active antiretroviral therapy (HAART) treatment guidelines since 2009.³ RAL requires a 400 mg twice daily dose and has given rise to clear signature mutation pathways (N155H, Q148H/K/R-G140S and Y143C).⁴ Elvitegravir⁵ (EVG) (figure 1) is a second INI which was approved in 2012. EVG allows for a once daily dose of 150 mg, however, this requires co-administration of CYP3A inhibitor as a PK

booster.⁶ Additionally, EVG has significant cross resistance with RAL in both the N155 and Q148 mutation pathways.⁷ While both RAL and EVG are valued additions to the HAART armamentarium, there remains significant room for differentiation and improvement. It was our vision that a next generation INI would have to address attributes in the areas of overall dose burden, dosing interval,⁸ potency against resistant mutations and genetic barrier to resistance. Thus it was with these goals that we set out to design a novel scaffold that would deliver clear value for patients. The work presented herein is the second in a series of manuscripts to elaborate on the evolution of our scaffold design in pursuit of true next generation properties that ultimately resulted in the discovery of dolutegravir (DTG) (figure 1) to deliver low dose, once daily unboosted PK and exceptional resistance properties.⁹ We recently reported on the twometal pharmacophore¹⁰ driven design of a carbamovl pyridone INI **1** shown in Figure 2a.¹¹ This compound showed remarkable antiviral potency against wild-type HIV-1 virus from just the minimum pharmacophore elements consisting of C2 carboxylate and C3 hydroxy pyridone moiety as a basic chelating unit and a benzyl carboxyamide unit to occupy the hydrophobic region. Although the potency against some clinically relevant mutant viruses were comparable to the prior generation INIs and insufficient for further development, this agent showed encouraging PK properties with a $T_{1/2}$ of 4.7 hours and robust plasma drug levels well in excess of the protein adjusted IC₅₀ (^{MT4}PAIC₅₀) at 24 hours after oral dosing in rat PK studies. The initial monocyclic carbamoyl pyridone inhibitor 1 has an ester unit at the C2 position to coordinate with a metal cofactor in the catalytic active site of the enzyme. We sought to explore further chemical space adjacent to the requisite pharmacophore elements in hopes of addressing the potential risk of chemical or metabolic stabilities of the ester unit as well as attempting to improve on the remaining deficiencies around resistance profile. We initially tried amide derivatives including primary, secondary and tertiary amides. Potentially the amide modification could provide an

additional benefit in antiviral potency due to slightly higher basicity of carbonyl lone pair favorable to coordinate with magnesium cofactors in the active site. However potencies were remarkably reduced in both enzymatic and antiviral assays, presumably because the amide analog causes an undesired intramolecular hydrogen bond between the central OH and amide NH moiety (in the case of primary and secondary amide examples) or more generally simply disrupts the coplanarity of the metal chelation motif due to steric hindrance of the amide and the pyridone NH as shown in Figure 2b. Eitherway, this distortion of the chelating unit critical for effective binding to the adjoining two metal cofactors was not productive during the simple ester to amide modification. An intramolecular tethering design was adopted as shown in Figure 2c as a logical next step in the development of the carbamoyl pyridone SAR in order to fix the metal chelation motif into a desired co-planar orientation for effective metal coordination.







Figure 1. HIV-1 integrase inhibitors.



Figure 2. (a) The monocyclic carbamoyl pyridone lead inhibitor **1**. (b) Unfavorable intramolecular hydrogen bonding and steric hindrance potentially disrupt the co-planarity of the metal chelation motif by amide modifications. (c) A logical approach toward the cyclization modification to fix the metal chelation motif into a co-planar orientation.

2. Chemistry

All tested compounds were prepared through the key N1 acetaldehyde unit using one of the strategies outlined in Figure 3. Series A and B were accessed through imine formation which underwent enamine tautomerization and led to the unsaturated analogs (Series A) and upon reduction the saturated counterparts (Series B). Condensation of the N1 acetaldehyde with a pendent amide let to the hydroxyl containing Series C. Finally, access to the tricyclic Series D or E was envisioned to result from condensation of the acetaldehyde functionalized core with an

aminoalcohol or diamine which could then close to form a fused amide group and facilitate the tricyclic ring formation.



Figure 3. Conceptual synthetic approach toward bi- and tri-cyclic analogs.

The key synthetic divergence points were chosen as the benzyl protected intermediates **13**, **14** (Scheme 1). These were chosen due to the potential for mild and selective modification of the core and C2 carboxyl moiety to support our synthetic strategies outlines in Figure 3. In addition, the benzyl protect central hydroxyl would be stably protected and able to be exposed chemoselectively in a last step to produce the fully functionalized metal binding moiety. The commercially available maltol **2** was protected as its benzyl ether followed by pyrone to pyridone conversion via amination with ammonia to provide intermediate **4**. C5 bromination was followed

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by palladium catalyzed carbonylation to give the methyl ester **6**. After acetyl protection of 4hydroxyl, oxidation of the pyridine nitrogen with *m*-CPBA was performed followed by thermal rearrangement of the resultant *N*-oxide in acetic anhydride to give the corresponding C2hydroxymethyl derivative **9**. The acetoxy unit was selectively removed with anhydrous sodium methoxide followed by amination with 4-fluorobenzylamine on the C5 ester to provide **11**. The C2 alcohol was oxidized in a stepwise manner to produce the corresponding carboxylic acid **13**. Condensation with methanol was performed to conclude preparation of intermediate **14**.





^{*a*}Reagents and conditions: (a) BnBr, K₂CO₃, DMF, 80 °C; (b) NH₃, 2 M NaOH, ethanol, 90 °C; (c) *N*-bromosuccinimide, acetnitrile, rt; (d) Pd(OAc)₂, 1,3-bis(diphenylphosphino)propane, Et₃N, CO, methanol, DMF, 80 °C; (e) Ac₂O, 130 °C; (f) *m*-CPBA, chloroform, rt; (g) Ac₂O, 130 °C; (h) MeONa, methanol, rt; (i) 4-fluorobenzylamine, DMF, 120 °C; (j) MnO₂, chloroform, 60 °C; (k) NaCl, sulfamic acid, THF-water, rt; (l) HOBt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, Et₃N, methanol, DMF, reflux.

The synthesis of series A and B are shown in Scheme 2. *N*-allylation of **14** and oxidative cleavage with osmium tetroxide and sodium metaperiodate gave the corresponding acetaldehyde intermediate **16**. After formation of an imine with a primary amine, intramolecular cyclization

proceeded using microwave heating to provide 17. Acidic deprotection of 17 served to deprotect the above mentioned benzyl ether and preserve the unsaturation to give the target series A derivatives **18a-f**. Subjecting **17** to hydrogenolysis conditions also resulted in removal of the benzyl ether while concomitantly reducing the newly formed ring to give the partially saturated compounds **19a-f** (series B).

Scheme 2. Synthesis of series A and B^a



^{*a*}Reagents and conditions: (a) 3-bromopropen, Cs_2CO_3 , DMF, rt; (b) potassium osmate dihydrate, sodium metaperiodate, 1,4-dioxane, rt; (c) amine, dichloromethane, 140 °C microwave; (d) TFA, rt; (e) H₂, 10% Pd-C, DMF-methanol, rt.

Synthesis of series C is shown in Scheme 3. After amidation of the carboxylic acid **13** with a primary amine, *N*-allylation was performed to give intermediate **21**. Oxidative cleavage of the double bond resulted in formation of hemi-aminal derivatives **22**, hydrogenolytic deprotection concluded the sequence to produce compound **23**.





^{*a*}Reagents and conditions: (a) HOBt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, Et₃N, DMF, reflux; (b) 3-bromopropen, Cs₂CO₃, DMF, rt; (c) potassium osmate dihydrate, sodium metaperiodate, 1,4-dioxane, rt; (d) 10% Pd-C, DMF-methanol, rt.

Series D and E compounds were synthesized as shown in Scheme 4. The aldehyde **16** was condensed with an amino-alcohol (series D) or diamine (series E) to generate the corresponding cyclic (hemi)-aminal moiety, and direct heating under microwave irradiation promoted intramolecular cyclization to provide the corresponding tricyclic compounds **24–36**. Additional modification on the secondary amine of **34** allowed introducing acetyl- or sulfonyl- functional group. Subsequent deprotection completed preparation of compounds **37–48**.

Scheme 4. Synthesis of series D and E^a



^{*a*}Reagents and conditions: (a) amino-alcohol, dichloromethane, 140 °C microwave; (b) diamine, dichloromethane, 140 °C microwave; (c) Ac₂O, cat. DMAP, pyridine, rt; (d) MsCl, DMAP, pyridine, rt; (e) 10% Pd-C, methanol, rt.

3. Results and Discussion

3.1. Antiviral profiles of bicyclic series A and B.

Inhibitory activities of series A and B are summarized in Table 1. Slightly improved antiviral potencies against wild type HIV-1 virus from the initial compound **1** were observed while the uniformly high selectivity index over cytotoxicity to indicate a true antiviral effect was maintained. Although variation on R did not have a significant influence on antiviral potency, modifications toward hydrophilic substituents appeared to have a negative impact on potency as seen in compounds **19b**, **18c** and **19c**. Potency shifts in presence of human serum albumin (HSA) resulted in a very acceptable protein adjustment to the IC_{50} (^{MT4}PAIC₅₀). Comparison of series A (unsaturated) and series B (saturated) resulted in no significant difference in potency for the R groups that were examined, however slightly larger protein shift was observed for the unsaturated analogs. The saturated series B also had a slightly improved profile (vs. series A) against the

Q148K site directed mutant virus across the R substitutents examined. An improvement of fold change against the Q148K mutant compared to the original monocyclic compound **1** was observed in compounds which have an ethereal R group (**18a**, **19a**, **18d**, **19d** and **19e**), however the data still left room for improvement to achieve our original differentiation goals.

Table 1. Antiviral profiles of series A and B.^{*a*}

F O N R **18[a-f]**; unsaturated bridge OH O R **18[a-f]**; saturated bridge

| compd | R | MT-4/MTT ^b wild type IC ₅₀ (nM) | MT-4/MTT ^b MT-4/MTT ^c d type IC ₅₀ (nM) CC ₅₀ (nM) | | ^{MT4} PAIC ₅₀ ^e (nM) | potency shift ^f |
|-------------|-----------------------|--|---|--------------|--|-------------------------------|
| 1 | - | 10 ± 2.9 | 19000 ± 850 | 200 ± 25 | 120 | 12 |
| 18 a | فو | 1.6 ± 1.1 | >200000 | 35 ± 6.8 | 27 | 17 |
| 19a | / OMe | 5.9 ± 0.044 | 52000 ± 8300 | 18 ± 2.5 | 18 | 3.1 |
| 18b | 6 | 6.6 ± 1.5 | 36000 ± 4100 | >250 | 20 | 3 |
| 19b | , , N O | 21 ± 5.5 | 160000 ± 25000 | NT | 34 | 1.6 |
| 18c | 0 8 | 35 ± 8.8 | >200000 | NT | 144 | 4.1 |
| 19c | NMe ₂ | 26 ± 7.9 | >200000 | NT | 62 | 2.4 |
| 18d | فر | 4.3 ± 1.4 | 49000 ± 19000 | 39 ± 14 | 19 | 4.4 |
| 19d | | 4.2 ± 1.0 | 30000 ± 1900 | 9.9 ± 1.3 | 13 | 3.1 |
| 18e | <i>y</i> ² | 4.4 ± 1.6 | 2400 ± 710 | >250 | 48 | 11 |
| 19e | OPh | 6.8 ± 3.7 | 10000 ± 1300 | 17 ± 6.9 | 65 | 9.5 |
| 18f | 4~ | 12 ± 3.1 | >200000 | >250 | 156 | 13 |
| 19f | , <u> </u> | 6.5 ± 2.9 | >240000 | >250 | 29 | 4.4 |

^{*a*}Data represent the mean \pm s.d. from independent three experiments. ^{*b*}Anti-HIV activities using MT-4 cells. ^{*c*}Cytotoxicity using MT-4 cells. ^{*d*}Fold change against the resistant variant. ^{*e*}Protein adjusted antiviral potencies based on MT-4/MTT IC₅₀. ^{*f*}Potency shift in presence of human serum albumin.

3.2. Antiviral profiles of hydroxyl series C and tricyclic series D and E.

A remarkable potency improvement against the O148K variant was observed from hydroxyl compound 23 (3.8 nM IC_{50} vs. wild type with a 2.1 fold reduction against Q148K). This potency profile combined with a very modest 3.7 fold shift in presence of HSA served as encouragement for further exploration. However as is discussed in next section, the series C compound did not show sufficient oral bioavailability. Moreover the hemi-aminal chiral center is not configurationally stable and interconverts on a moderate time scale (minutes to hours) resulting in lose of enantiomeric purity after chiral purification. Additional series C derivatives wherein the R substituent was modified are not shown herein but delivered similar virological and PK profiles and hence were not further improvements to justify continued pursuit. Although we abandoned further exploration of series C, the hydroxyl substitution on the saturated bridge provided impetus to address the perceived PK and configurational stability issues. In order to address the immediate issue of configurational stability, two series of tricyclic analogs were devised whereby the hemi-aminal was effectively 'locked down' into a third ring such that equilibration through an open chain intermediate would not be feasible. The oxygen and nitrogen containing third ring analogs, series D and E respectively, showed high antiviral potencies against wild-type virus and excellent selectivity over cytotoxicity as previously observed (Table 2). The ring size (five-, six- and seven-member) does not affect antiviral efficacy for the wild type virus regardless of hemi-aminal or aminal analog, however the five-membered analogs 37 and 40 lost potency against the mutant. Although the series E aminal unit does not appear to impact potency or resistance profile significantly, hydrophilic functional groups as seen in 47 and 48 do begin to erode the antiviral activity.

Table 2. Antiviral profiles of series C, D and E^a



| compd | Y | n | R | MT-4/MTT ^b wild type IC ₅₀ (nM) | MT-4/MTT ^c CC ₅₀ (nM) | Q148K ^d (FC) | ^{MTT} PAIC ₅₀ ^e (nM) | potency shift ^f |
|-------|---|---|--------------------|---|---|----------------------------|--|-------------------------------|
| 23 | - | - | - | 3.8 ± 0.53 | 83000 ± 22000 | 2.1 ± 0.50 | 14.1 | 3.7 |
| 37 | 0 | 0 | - | 2.7 ± 0.63 | 72000 ± 24000 | 19 ± 5.1 | 140.4 | 52 |
| 38 | 0 | 1 | - | 3.4 ± 1.1 | 18000 ± 1600 | 2.8 ± 0.32 | 26.9 | 7.9 |
| 39 | 0 | 2 | - | 2.9 ± 0.70 | 26000 ± 7000 | 2.2 ± 1.2 | 22.0 | 7.6 |
| 40 | Ν | 0 | isopropyl | 2.3 ± 0.55 | 8000 ± 2500 | 39 ± 7.4 | 7.8 | 3.4 |
| 41 | Ν | 1 | methyl | 3.8 ± 0.96 | 20000 ± 3000 | 4.7 ± 1.0 | 16.3 | 4.3 |
| 42 | N | 1 | isopropyl | 7.5 ± 0.42 | 7200 ± 790 | 9.1 ± 1.7 | 32.3 | 4.3 |
| 43 | Ν | 1 | thiazol-2-ylmethyl | 3.3 ± 0.91 | 2800 ± 820 | 4.2 ± 1.6 | 12.9 | 3.9 |
| 44 | Ν | 1 | 2-methoxyethyl | 5.2 ± 1.3 | 9800 ± 2200 | 5.7 ± 0.47 | 20.3 | 3.9 |
| 45 | Ν | 2 | methyl | 6.4 ± 3.7 | >200000 | 4.2 ± 1.0 | 31.4 | 4.9 |
| 46 | Ν | 2 | isobutyl | 5.4 ± 0.92 | 13000 ± 5000 | 3.2 ± 1.1 | 91.8 | 17 |
| 47 | Ν | 1 | acetyl | 29 ± 4.2 | >200000 | NT | 58.0 | 2 |
| 48 | N | 1 | methanesulfonyl | 43 ± 22 | >220000 | NT | 120.4 | 2.8 |

^{*a*}Data represent the mean \pm s.d. from independent three experiments. ^{*b*}Anti-HIV activities using MT-4 cells. ^{*c*}Cytotoxicity using MT-4 cells. ^{*d*}Fold change against the resistant variant. ^{*e*}Protein adjusted antiviral potencies based on MT-4/MTT IC₅₀. ^{*f*}Potency shift in presence of human serum albumin.

3.3. Efficacy against additional RAL signature pathways and rat PK profiles of 18a, 19a,

23 and 38.

Antiviral potency against clinically relevant RAL resistant mutants (Q148K, N155H and Y143R) and rat PK profiles are summarized in Table 3. The bicyclic analogs **18a**, **19a**, hydroxyl examples **23**, and tricyclic analog **38** showed a low fold change against the N155H and Y143R site directed mutants. As was discussed above, the tricyclic derivatives furthermore succeeded in

improving efficacy against Q148K which was the primary remaining issue left unaddressed by monocyclic lead analog **1**. Low dose rat PK profiles resulted in low CLt (1 mL/min/kg) and moderate to long $T_{1/2}$ estimates (3-17 hours) in every compound in Table 3. Although the moderate to low oral bioavailability of the hydroxyl derivative **23** raised concerns, the tricyclic analog **38** delivered a yet further improved $T_{1/2}$ accompanied with an oral bioavailability of 50%. The rat 24 hour plasma concentration (C₂₄) of 7127 ng/mL from a 5 mg/kg oral dose robustly covered the ^{MT4}PAIC₅₀ of 10 ng/mL. No remarkable CYP inhibition nor metabolic concerns were identified during in vitro studies.

Although these virological advances and promising PK profile of the tricyclic series D were significant toward our goal, this data set was from racemate. As an initial approach to understand contributions of the individual enantiomers toward the antiviral profile, the isomers were isolated after chiral chromatographic separation of the O-benzyl protected precursor 25 to give the enantiopure benzyl ethers 25R and 25S. Subsequent deprotection via hydrogenolysis provided the pure individual enantiomers **38***R* and **38***S* as shown in Figure 4. We were initially concerned that the hemi-aminal stability would be an issue but no interconversion or chemical stability issues were observed with the purified isomers of **38**. Notably the isomers had almost identical antiviral activity against wild type virus however significantly differed in their loss of activity against a Q148K mutation. The S derivative displayed only a 2 fold potency change while the R analog had a 10 fold shift in potency. The isomers also showed different protein binding shifts with the S isomer showing a near 50 fold shift while the R isomer had a very modest 5 fold loss of potency in the presence of HSA. These differences in protein binding on potency also suggest a different PK profile might be expected to arise as well. These preliminary data on the purified isomers demonstrated excellent potency and previous PK data from the racemate 38 was

consistent with once daily PK potential with a low risk for CYP450 interaction and the need for a boosting agent.

| Cmpd. | Q148K (FC) | N155H (FC) | Y143R (FC) | CLt (mL/min/kg) | T1/2 (hours) | Vdss (mL/Kg) | %F | C24 / ^{MT4} PAIC50 |
|-------------|--------------------|-------------------|--------------------|--------------------|-----------------|-----------------|--------------|--------------------------------|
| RAL | 83 ± 6.6^b | 8.4 ± 1.8^{b} | 16 ± 3.9^{b} | - | - | - | - | - |
| EVG | >1700 ^b | 25 ± 7.8^{b} | 1.8 ± 0.16^{b} | - | - | - | - | - |
| 1 | 200 ± 25 | 21 ± 8.9 | 1.5 ± 0.59 | 1.2 ± 0.41 | 4.7 ± 0.15 | 200 ± 38 | 53 ± 20 | 3.4 |
| 18 a | 35 ± 6.8 | 3.7 ± 1.0 | 1.6 ± 0.40 | 0.02 ± 0.00 | 11 ± 2.6 | 15 ± 1.1 | 40 ± 7.1 | 2600 |
| 19a | 18 ± 2.5 | 1.5 ± 0.16 | 1.5 ± 0.12 | 0.51 ± 0.04 | 3.4 ± 0.28 | 120 ± 6 | 41 ± 2.7 | 27 |
| 23 | 2.1 ± 0.50 | 1.5 ± 0.054 | 1.5 ± 0.28 | 0.24 ± 0.02 | 7.6 ± 0.2 | 140 ± 13 | 14 ± 6.3 | 117 |
| 38 | 2.8 ± 0.32 | 1.6 ± 0.75 | 1.6 ± 0.85 | 0.10 ± 0.03 | 17 ± 6.7 | 130 ± 11 | 51 ± 8.5 | 685 |

Table 3. Resistance profile against RAL resistant mutants and PK parameters in rat.^a

^{*a*}Data represent the mean \pm s.d. FC; fold change. ^{*b*}Data reported in reference 9.



Figure 4. Chiral separation of the compound 38.

5. Conclusions

The carbamoyl pyridone scaffold was optimized through series' of bicyclic and tricyclic analogs for the inhibition of HIV-1 IN utilizing a divergent synthetic strategy from a key *N*-pyridonyl-acetaldehyde intermediate. We have demonstrated the addition of a second and third ring have added significant attributes to the carbamoyl pyridone core scaffold in terms of antiviral activity against both wild-type and key resistant mutants. Furthermore, protein binding

effects as well as in vitro and in vivo PK profiles were taken into consideration in resulting in the optimization to the tricyclic analogs **38**. As such the tricyclic series D was identified as a true next generation INI series which appeared to deliver on our original differentiation goals centered on resistance and once daily PK. Further optimization of the individual enantiomers of compounds such as **38** will be the subject of future publications.

6. Experimental section

6.1. Chemistry

 Reactions were carried out under a nitrogen atmosphere with anhydrous solvents. Melting points were collected up to 300 °C with a Stanford Research Systems Optimelt for every crystalized sample. Purity of samples tested were assessed using combustion analyses or LC/MS/UV/ELSD, and the analytical data confirmed the purities to be \geq 95%. Combustion analyses were performed with a Yanaco CORDER MT-6 and a DIONEX ICS-2000, LC/MS/UV were with Waters Acquity SQD System. Microwave irradiation was performed with Biotage Initiator. ¹H NMR spectra were measured on a Varian MERCURY or Gemini 300MHz spectrometer in a solution of either CDCl₃ or DMSO- d_6 , using tetramethylsilane as the internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard.

3-Benzyloxy-2-methylpyran-4-one (3). Maltol **2** (189 g, 1.5 mol) was dissolved in DMF (1890 mL), and benzyl bromide (184 mL, 1.5 mol) was added. After stirring the solution at 80 °C for 15 minutes, potassium carbonate (228 g, 1.65 mol) was added, and the mixture was stirred for 1 hour. After the reaction solution was cooled to room temperature, inorganic salt was filtered off, and the filtrate was evaporated in vacuo. To the precipitated inorganic salt was added THF (1000 mL), and the salt was filtered off. The filtrate was again evaporated in vacuo to obtain the

 product (329 g, quant.) as colorless solid. ¹H NMR (CDCl₃) δ 2.09 (s, 3H), 5.15 (s, 2H), 6.36 (d, J = 5.6 Hz, 1H), 7.29–7.41 (m, 5H), 7.60 (d, J = 5.6 Hz, 1H).

3-Benzyloxy-2-methyl-1*H***-pyridine-4-one (4).** The compound **3** (162 g, 750 mmol) was dissolved in ethanol (487 mL), and aqueous ammonia (28%, 974 mL) and a 6 M aqueous sodium hydroxide solution (150 mL, 900 mmol) was added. After strring the reaction solution at 90 °C for 1 hour, the solution was cooled to under ice-cooling, and ammonium chloride (58 g, 1.08 mol) was added. The solution was extracted with chloroform, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was evaporated in vacuo, then isopropylalcohol and diethyl ether were added to the residue. Precipitated solid was filtered to obtain the product (69.1 g, 43% yield) as pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 2.05 (s, 3H), 5.04 (s, 2H), 6.14 (d, *J* = 7.2 Hz, 1H), 7.31–7.42 (m, 5H), 7.46 (d, *J* = 7.2 Hz, 1H), 11.29 (brs, 1H).

3-Benzyloxy-5-bromo-2-methyl-1*H***-pyridine-4-one (5).** The compound **4** (129 g, 599 mmol) was suspended in acetonitrile (1300 mL), and *N*-bromosuccinimide (117 g, 659 mmol) was added. After stirring at room temperature for 1.5 hours precipitated crystals were filtered and washed with acetonitrile and diethyl ether to obtain the product (154 g, 88% yield) as colorless solid. ¹H NMR (DMSO-*d*₆) δ 2.06 (s, 3H), 5.04 (s, 2H), 7.32–7.42 (m, 5H), 8.03 (d, *J* = 5.5 Hz, 1H), 11.82 (brs, 1H).

Methyl 5-benzyloxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (6). To a solution of the compound **5** (88.0 g, 300 mmol), Pd(OAc)₂ (13.4 g, 60.0 mmol) and 1,3-bis(diphenylphosphino)propane (30.8 g, 516 mmol) in DMF (660 mL) were added methanol (264 mL) and triethylamine (210 mL, 1.50 mol) at room temperature. The interior of a reaction vessel was replaced with CO, and the solution was stirred at room temperature for 30 minutes, then stirred at 80 °C for 18 hours. To a mixture of ethyl acetate (1500 mL), an aqueous saturated

 ammonium chloride solution (1500 mL) and water (1500 mL) stirred under ice-cooling the reaction solution was added. Precipitates were filtered and washed with water (300 mL), ethyl acetate (300 mL) and diethyl ether (300 mL) to obtain the product (44.9 g, 55% yield) as colorless solid. ¹H NMR (DMSO- d_6) δ 2.06 (s, 3H), 3.72 (s, 3H), 5.02 (s, 2H), 7.33–7.42 (m, 5H), 8.07 (s, 1H).

Methyl 4-acetoxy-5-benzyloxy-6-methylnicotinate (7). After a solution of the compound 6 (19.1 g, 70.0 mmol) in acetic anhydride (134 mL) was stirred at 130 °C for 40 minutes, the acetic anhydride was evaporated in vacuo to obtain the product (19.9 g, 90% yield) as flesh colored solid. ¹H NMR (CDCl₃) δ 2.29 (s, 3H), 2.52 (s, 3H), 3.89 (s, 3H), 4.98 (s, 2H), 7.36–7.41 (m, 5H), 8.85 (s, 1H).

Methyl 4-acetoxy-5-benzyloxy-6-methyl-1-oxynicotinate (8). To a solution of the compound 7 (46.2 g, 147 mmol) in chloroform (370 mL) was added 65% *m*-CPBA (42.8 g, 161 mmol) in portions under ice-cooling, and the solution was stirred at room temperature for 90 minutes. To the reaction solution was added a 10% aqueous potassium carbonate solution, and the mixture was stirred for 10 minutes. The solution was extracted with chloroform, and the organic layer was washed with successively with a 10% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The residual precipitate was washed with diisopropyl ether to obtain the product (42.6 g, 87% yield) as colorless solid. ¹H NMR (CDCl₃) δ 2.30 (s, 3H), 2.41 (s, 3H), 3.90 (s, 3H), 5.02 (s, 2H), 7.37–7.39 (m, 5H), 8.70 (s, 1H).

Methyl 4-acetoxy-6-acetoxymethyl-5-benzyloxynicotinate (9). To acetic anhydride (500 mL) which had been heated at 130 °C was added the compound **8** (42.6 g, 129 mmol) over 2 minutes, and the mixture was stirred for 20 minutes. The acetic anhydride was evaporated in vacuo to

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obtain the product (49.6 g, quant.) as black oil. ¹H NMR (CDCl₃) δ 2.10 (s, 3H), 2.28 (s, 3H), 3.91 (s, 3H), 5.07 (s, 2H), 5.20 (s, 2H), 7.35–7.41 (m, 5H), 8.94 (s, 1H).

Methyl 5-benzyloxy-6-hydroxymethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (10). To a solution of the compound **9** (9.50 g, 25.4 mmol) in methanol (50 mL) was added a 28 wt% sodium methoxide methanol solution (7.35 mL, 38.1 mmol) under ice-cooling. The solution was stirred at room temperature for 30 minutes. To an ice-cooled sat. ammonium chloride aqueous solution the reaction solution were added and stirred for 30 minutes. Precipitated crystals were filtered, and washed with water and diethyl ether to obtain the product (4.68 g, 64% yield) as colorless solid. ¹H NMR (DMSO-*d*₆) δ 3.72 (s, 3H), 4.37 (s, 2H), 5.06 (s, 2H), 5.72 (s, 1H), 7.34–7.40 (m, 5H), 8.06 (s, 1H), 11.47 (brs, 1H).

5-Benzyloxy-N-(4-fluorobenzyl)-6-hydroxymethyl-4-oxo-1,4-dihydropyridine-3-

carboxamide (11). To a solution of the compound **10** (289 mg, 1.0 mmol) in DMF (3 mL) was added 4-fluorobenzylamine (126 μ L, 1.10 mmol). The mixture was stirred at 120 °C for 1.5 hours. After the reaction solution was cooled to room temperature, 2 M aq HCl (6 mL) was added. The solution was extracted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo to obtain the product (198 mg, 52% yield) as colorless solid. ¹H NMR (DMSO-*d*₆) δ 4.45 (d, *J* = 5.0 Hz, 2H), 4.52 (d, *J* = 6.0 Hz, 2H), 5.09 (s, 2H), 5.84 (t, *J* = 5.0 Hz, 1H), 7.14–7.20 (m, 2H), 7.35–7.40 (m, 7H), 8.30 (s, 1H), 10.72 (t, *J* = 6.0 Hz, 1H), 11.97 (s, 1H).

5-Benzyloxy-*N***-(4-fluorobenzyl)-6-formyl-4-oxo-1,4-dihydropyridine-3-carboxamide (12).** To a suspension of the compound **11** (9.80 g, 25.6 mmol) in chloroform (490 mL) manganese dioxide (49.0 g) was added. The mixture was stirred at room temperature for 1 hour, then stirred at 60 °C for 20 minutes. The manganese dioxide was filtrated off under celite filtration, and

 washed with chloroform heated at 50 °C. The filtrate was evaporated in vacuo to obtain the product (8.20 g, 84% yield) as pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 4.53 (d, *J* = 5.8 Hz, 2H), 5.38 (s, 2H), 7.15–7.21 (m, 2H), 7.35–7.46 (m, 7H), 8.33 (s, 1H), 9.90 (s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 12.49 (s, 1H).

3-Benzyloxy-5-(4-fluorobenzylcarbamoyl)-4-oxo-1,4-dihydropyridine-2-carboxylic acid (13). To an aqueous solution (105 mL) of sodium chlorite (7.13 g, 78.8 mmol) and sulfamic acid (7.65 g, 78.8 mmol) was added a solution of the compound **12** (15.0 g, 39.4 mmol) in THF (630 mL) under ice-cooling. The mixture was stirred at room temperature for 1 hour, and water (2500 L) was added to the reaction solution. The precipitated crystals were filtered, and washed with diethyl ether to obtain the product (14.0 g, 90% yield) as colorless solid. ¹H NMR (DMSO-*d*₆) δ 4.52 (d, *J* = 5.8 Hz, 2H), 5.13 (s, 2H), 7.14–7.19 (m, 2H), 7.31–7.40 (m, 5H), 7.47–7.49 (m, 2H), 8.31 (d, *J* = 4.5 Hz, 1H), 10.44 (t, *J* = 5.8 Hz, 1H), 12.47 (brs, 1H).

Methyl 3-benzyloxy-5-(4-fluorobenzylcarbamoyl)-4-oxo-1,4-dihydropyridine-2carboxylate (14). The compound 13 (12.0 g, 30.3 mmol), 1-(3-dimethylaminopropyl)-3ethylcarbodiimide hydrochloride (6.96 g, 36.3 mmol) and 1-hydroxybenzotriazole (4.91 g, 36.3 mmol) in DMF (180 mL) was stirred at room temperature for 1.5 hours. To the mixture methanol (180 mL) and triethylamine (9.29 mL, 66.7 mmol) were added, and the mixture was heated to reflux for 1.5 hours. The reaction solution was diluted with ethyl acetate, then washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution, and an aqueous saturated sodium chloride solution. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The residual precipitate was washed with diethyl ether to obtain the product (8.74 g, 70% yield) as colorless crystals. ¹H NMR (DMSO- d_6) δ 3.85 (s, 3H), 4.52 (d, J = 6.0 Hz, 2H), 5.15 (s, 2H), 7.13–7.21 (m, 2H), 7.31–7.47 (m, 7H), 8.33 (s, 1H), 10.41 (t, J = 6.0 Hz, 1H), 12.59 (s, 1H).

Methyl 1-allyl-3-benzyloxy-5-(4-fluorobenzylcarbamoyl)-4-oxo-1,4-dihydropyridine-2carboxylate (15). To a solution of the compound 14 (6.79 g, 16.5 mmol) 3-bromopropene (2.15 mL, 24.8 mmol) and Cs₂CO₃ (8.09 g, 24.8 mmol) in DMF (54 mL) was added, and the mixture was stirred at room temperature for 4.5 hours. To the reaction solution was added an aq. ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and an aq. saturated sodium chloride solution. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The residual precipitate was washed with diethyl ether to obtain the product (6.15 g, 83% yield) as colorless solid. ¹H NMR (CDCl₃) δ 3.76 (s, 3H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 5.20–5.37 (m, 2H), 5.25 (s, 2H), 5.80–5.93 (m, 1H), 6.98–7.04 (m, 2H), 7.31–7.35 (m, 7H), 8.45 (s, 1H), 10.41 (m, 1H).

Methyl 3-benzyloxy-5-(4-fluorobenzylcarbamoyl)-4-oxo-1-(2-oxoethyl)-1,4dihydropyridine-2-carboxylate (16). To a solution of the compound 15 (7.6 g, 16.9 mmol) in 1,4-dioxane (228 mL) was added an aqueous solution (38 mL) of potassium osmate dihydrate (372 mg, 1.01 mmol), and sodium metaperiodate (14.5 g, 67.6 mmol) was further added. After stirring at room temperature for 2 hours the reaction solution was added to a vessel to which ethyl acetate (300 mL) and water (300 mL) had been added, while stirring. The organic layer was washed with water, a 5% aq. sodium hydrogen sulfite solution and an aq. saturated sodium chloride solution. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo, and the residual precipitate was washed with diethyl ether to obtain the product (5.39 g, 71% yield) as colorless solid. ¹H NMR (CDCl₃) δ 3.74 (s, 3H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.87 (s, 2H), 5.27 (s, 2H), 6.98–7.04 (m, 2H), 7.30–7.40 (m, 7H), 8.39 (s, 1H), 9.58 (s, 1H), 10.38 (s, 1H).

9-Benzyloxy-2-(2-methoxyethyl)-1,8-dioxo-1,8-dihydro-2H-pyrid[1,2-a]pyrazine-7-

carboxylic acid 4-fluorobenzylamide (17a). To a solution of the compound **16** (400 mg, 0.884 mmol) in dichloromethane (12 mL) were added 2-methoxyethylamine (77.0 μ L, 0.884 mmol) and acetic acid (18 μ L). After stirring at room temperature for 5 minutes, the reaction was performed at 140 °C for 30 minutes in a microwave reaction apparatus. The solvent was evaporated in vacuo, and the residue was subjected to silica gel column chromatography. Fractions eluting with toluene-acetone were collected and evaporated in vacuo to obtain the product (226 mg, 54% yield) as a yellow solid. ¹H NMR (CDCl₃) δ 3.35 (s, 3H), 3.65 (t, *J* = 5.2 Hz, 2H), 3.98 (t, *J* = 5.2 Hz, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 5.28 (s, 2H), 6.57 (s, 2H), 6.98–7.04 (m, 2H), 7.30–7.38 (m, 5H), 7.637.67 (m, 2H), 8.59 (s, 1H), 10.60–10.64 (m, 1H).

9-Benzyloxy-2-[2-(morpholin-4-yl)ethyl]-1,8-dioxo-1,8-dihydro-2H-pyrido[1,2-

a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (17b). ¹H NMR (CDCl₃) δ 2.59 (s, 4H), 2.74 (s, 2H), 3.73 (s, 4H), 3.95 (s, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 5.28 (s, 2H), 6.53 (d, *J* = 6.0 Hz, 1H), 6.63 (d, *J* = 6.0 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 7.26–7.38 (m, 5H), 7.64 (d, *J* = 6.9 Hz, 2H), 8.61 (s, 1H), 10.61 (t, *J* = 5.4 Hz, 1H).

9-Benzyloxy-2-dimethylcarbamoylmethyl-1,8-dioxo-1,8-dihydro-2H-pyrido[1,2-

a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (17c). ¹H NMR (CDCl₃) δ 3.01 (s, 3H), 3.13 (s, 3H), 4.59 (s, 2H), 4.63 (d, *J* = 6.0 Hz, 2H), 5.26 (s, 2H), 6.42 (d, *J* = 6.0 Hz, 1H), 6.64 (d, *J* = 6.0 Hz, 1H), 6.98–7.05 (m, 2H), 7.16–7.36 (m, 5H), 7.60–7.66 (m, 2H), 8.60 (s, 1H), 10.59 (brt, *J* = 6.0 Hz, 1H).

9-Benzyloxy-2-(2-isopropoxyethyl)-1,8-dioxo-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (17d). ¹H NMR (CDCl₃) δ 1.12 (d,** *J* **= 6.0 Hz, 6H), 3.51– 3.59 (m, 1H), 3.68 (t,** *J* **= 4.8 Hz, 2H), 3.96 (t,** *J* **= 4.8 Hz, 2H), 4.62 (d,** *J* **= 6.0 Hz, 2H), 5.28 (s,**

9-Benzyloxy-1,8-dioxo-2-(2-phenoxyethyl)-1,8-dihydro-2*H***-pyrido**[**1,2-a**]**pyrazine-7carboxylic acid 4-fluorobenzylamide (17e).** ¹H NMR (CDCl₃) δ 4.17–4.20 (m, 2H), 4.25–4.28 (m, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 5.28 (s, 2H), 6.60–6.66 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.95–7.04 (m, 2H), 7.28–7.37 (m, 8H), 7.64 (d, *J* = 7.0 Hz, 2H), 8.59 (s, 1H), 10.60 (brs, 1H).

9-Benzyloxy-2-cyclohexyl-1,8-dioxo-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (17f). ¹H NMR (CDCl₃) δ 1.15–1.92 (m, 10H), 4.62 (d,** *J* **= 6.1 Hz, 2H), 4.70–4.78 (m, 1H), 5.27 (s, 2H), 6.43 (d,** *J* **= 6.4 Hz, 1H), 6.69 (d,** *J* **= 6.3 Hz, 1H), 7.01– 7.16 (m, 2H), 7.18–7.37 (m, 5H), 7.66–7.68 (m, 2H), 8.63 (s, 1H), 10.67 (t,** *J* **= 5.5 Hz, 1H).**

9-Hydroxy-2-(2-methoxyethyl)-1,8-dioxo-1,8-dihydro-2H-pyrido[1,2-a]pyrazine-7-

carboxylic acid 4-fluorobenzylamide (18a). To the compound **17a** (140 mg, 0.293 mmol) was added trifluoroacetic acid (1.4 mL) under ice-cooling. The mixture was stirred at 0 °C for 5 minutes and at room temperature for 1.5 hours. The solvent was evaporated in vacuo and the residue was diluted with chloroform and ice water. The organic layer was washed with an aq. saturated sodium bicarbonate solution, a 10% aq. citric acid solution and water. The organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The residual crystals were recrystallized with dichloromethane-ethanol to obtain the product (89.0 mg, 79% yield) as yellow crystals. mp 223–224 °C; ¹H NMR (DMSO-*d*₆) δ 3.25 (s, 3H), 3.58 (t, *J* = 5.4 Hz, 2H), 3.92 (t, *J* = 5.1 Hz, 2H), 4.53 (d, *J* = 5.7 Hz, 2H), 6.87 (d, *J* = 6.3 Hz, 1H), 7.14 (t, *J* = 9.0 Hz, 2H), 7.33–7.38 (m, 2H), 7.47 (d, *J* = 6.0 Hz, 1H), 8.77 (s, 1H), 10.56 (t, *J* = 6.0 Hz, 1H), 12.00 (brs, 1H). Anal. Calcd for C₁₉H₁₈FN₃O₅: C, 58.91; H, 4.68; F, 4.90; N, 10.85. Found: C, 58.68; H, 4.63; F, 4.73; N, 10.80.

9-Hydroxy-2-[2-(morpholin-4-yl)ethyl]-1,8-dioxo-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (18b).** mp 212–215 °C; ¹H NMR (DMSO-*d*₆) δ 2.51 (s, 4H), 2.38 (s, 2H), 3.55 (s, 4H), 3.90 (s, 2H), 4.55 (d, *J* = 6.0 Hz, 2H), 6.95 (d, *J* = 6.3 Hz, 2H), 7.17 (t, *J* = 8.7 Hz, 2H), 7.35–7.40 (m, 2H), 7.50 (d, *J* = 6.3 Hz, 1H), 8.78 (s, 1H), 10.58 (t, *J* = 6.3 Hz, 1H), 12.10 (s, 1H). LC/MS: *m/z* 443 [M + H]⁺.

2-Dimethylcarbamoylmethyl-9-hydroxy-1,8-dioxo-1,8-dihydro-2*H***-pyrido**[**1,2-a**]**pyrazine-7-carboxylic acid 4-fluorobenzylamide (18c).** mp >300 °C; ¹H NMR (DMSO-*d*₆) δ 2.87 (s, 3H), 3.03 (s, 3H), 4.55 (d, *J* = 6.0 Hz, 2H), 4.71 (s, 2H), 6.80 (d, *J* = 6.3 Hz, 1H), 7.16 (m, 2H), 7.38 (m, 2H), 7.48 (d, *J* = 6.3 Hz, 1H), 8.82 (s, 1H), 10.54 (brt, *J* = 6.0 Hz, 1H), 11.83 (s, 1H). Anal. Calcd for C₂₀H₁₉FN₄O₅(H₂O)_{0.4}: C, 56.98; H, 4.73; F, 4.51; N, 13.29. Found: C, 57.03; H, 4.44; F, 4.50; N, 13.13.

9-Hydroxy-2-(2-isopropoxyethyl)-1,8-dioxo-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (18d).** mp 209-210 °C; ¹H NMR (DMSO-*d*₆) δ 1.06 (d, *J* = 6.3 Hz, 6H), 3.54–3.64 (m, 3H), 3.90 (t, *J* = 5.4 Hz, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 6.89 (d, *J* = 6.3 Hz, 1H), 7.13–7.19 (m, 2H), 7.35–7.39 (m, 2H), 7.47 (d, *J* = 6.3 Hz, 1H), 8.77 (s, 1H), 10.58 (t, *J* = 5.7 Hz, 1H), 12.04 (brs, 1H). Anal. Calcd. for C₂₁H₂₂FN₃O₅: C, 60.72; H, 5.34; F, 4.57; N, 10.12. Found: C, 60.78; H, 5.29; F, 4.34; N, 10.11.

9-Hydroxy-1,8-dioxo-2-(2-phenoxyethyl)-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (18e). mp 237–239 °C; ¹H NMR (CDCl₃) δ 4.18–4.21 (m, 2H), 4.26–4.29 (m, 2H), 4.62 (d,** *J* **= 5.7 Hz, 2H), 6.57 (d,** *J* **= 6.3 Hz, 1H), 6.71 (d,** *J* **= 6.3 Hz, 1H), 6.86 (d,** *J* **= 8.1 Hz, 2H), 6.97–7.02 (m, 3H), 7.29–7.35 (m, 4H), 8.56 (s, 1H), 10.58 (t,** *J* **= 5.7 Hz, 1H), 11.84 (brs, 1H). Anal. Calcd for C₂₄H₂₀FN₃O₅: C, 64.14; H, 4.49; F, 4.23; N, 9.35. Found: C, 64.46; H, 4.50; F, 4.01; N, 9.12.**

2-Cyclohexyl-9-hydroxy-1,8-dioxo-1,8-dihydro-2*H***-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (18f). mp >300 °C; ¹H NMR (DMSO-***d***₆) δ 1.15–1.84 (m, 10H), 4.43–4.49 (m, 1H), 4.53 (d,** *J* **= 5.8 Hz, 2H), 7.05 (d,** *J* **= 6.4 Hz, 1H), 7.13–7.19 (m, 2H), 7.34– 7.39 (m, 2H), 7.53 (d,** *J* **= 6.4 Hz, 1H), 8.79 (s, 1H), 10.61 (t,** *J* **= 5.8 Hz, 1H), 12.23 (brs, 1H). LC/MS:** *m/z* **412 [M + H]⁺.**

9-Hydroxy-2-(2-methoxyethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (19a). The compound 17a (157 mg, 0.329 mmol) was dissolved in DMF (18 mL) and methanol (1 mL), 10% palladium-carbon powder (31 mg) was added, and the mixture was stirred at room temperature for 20 hours under hydrogen atmosphere. The reaction solution was filtered with celite, and the filtrate was evaporated in vacuo. The residue was dissolved in chloroform, and insoluble residue was filtered with celite again, and the filtrate was evaporated in vacuo. The residual crystals were recrystallized from dichloromethanemethanol to obtain the product (66 mg, 52% yield) as brown crystals. mp 197–199 °C; ¹H NMR (DMSO-***d***₆) \delta 3.27 (s, 3H), 3.55 (t,** *J* **= 5.1 Hz, 2H), 3.68 (t,** *J* **= 5.1 Hz, 2H), 3.79 (s, 2H), 4.36 (s, 2H), 4.51 (d,** *J* **= 5.7 Hz, 2H), 7.15 (t,** *J* **= 8.7 Hz, 2H), 7.32–7.37 (m, 2H), 8.38 (s, 1H), 10.46 (t,** *J* **= 5.4 Hz, 1H), 12.41 (s, 1H). LC/MS:** *m/z* **390 [M + H]⁺.**

9-Hydroxy-2-[2-(morpholin-4-yl)ethyl]-1,8-dioxo-1,3,4,8-tetrahydro-2*H***-pyrido[1,2a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (19b). mp 205–207 °C; ¹H NMR (DMSOd₆) δ 2.43 (s, 2H), 2.50 (s, 4H), 3.54 (s, 4H), 3.63 (s, 2H), 3.81 (s, 2H), 4.40 (s, 2H), 4.52 (d,** *J* **= 6.0 Hz, 2H), 7.16 (t,** *J* **= 9.0 Hz, 2H), 7.33–7.37 (m, 2H), 8.43 (s, 1H), 10.45 (t,** *J* **= 5.7 Hz, 1H), 12.48 (s, 1H). LC/MS:** *m/z* **445 [M + H]⁺.**

2-Dimethylcarbamoylmethyl-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2*H***-pyrido**[1,2a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (19c). mp 245 °C; ¹H NMR (CDCl₃) δ 3.00

(s, 3H), 3.08 (s, 3H), 3.83–3.87 (m, 2H), 4.37–4.41 (m, 2H), 4.42 (s, 2H), 4.60 (s, 2H), 6.98–7.04 (m, 2H); 7.30–7.34 (m, 2H), 8.33 (s, 1H). LC/MS: *m/z* 417 [M + H]⁺.

 9-Hydroxy-2-(2-isopropoxyethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2*H***-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluorobenzylamide (19d).** mp 210–212 °C; ¹H NMR (DMSO-*d*₆) δ 1.08 (d, *J* = 6.0 Hz, 6H), 3.54–3.66 (m, 5H), 3.79–3.83 (m, 2H), 4.35–4.39 (m, 2H), 4.52 (d, *J* = 6.0 Hz, 2H), 7.12–7.18 (m, 2H), 7.32–7.37 (m, 2H), 8.40 (s, 1H), 10.44 (t, *J* = 6.0 Hz, 1H), 12.42 (brs, 1H). Anal. Calcd for C₂₁H₂₄FN₃O₅(H₂O)_{0.3}: C, 59.65; H, 5.86; F, 4.49; N, 9.94. Found: C, 59.58; H, 5.63; F, 4.40; N, 9.96.

9-Hydroxy-1,8-dioxo-2-(2-phenoxyethyl)-1,3,4,8-tetrahydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (19e). mp 200–201 °C; ¹H NMR (CDCl₃) δ 3.96–4.02 (m, 4H), 4.20–4.28 (m, 4H), 4.60 (d,** *J* **= 6.0 Hz, 2H), 6.86–6.89 (m, 2H), 6.96–7.02 (m, 3H), 7.28– 7.34 (m, 4H), 8.31 (s, 1H), 10.43 (brs, 1H), 12.15 (brs, 1H). Anal. Calcd for C₂₄H₂₀FN₃O₅: C, 63.85; H, 4.91; F, 4.21; N, 9.31. Found: C, 63.72; H, 4.93; F, 4.07; N, 9.29.**

2-Cyclohexyl-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2*H***-pyrido[1,2-a]pyrazine-7carboxylic acid 4-fluorobenzylamide (19f). mp >300 °C; ¹H NMR (DMSO-***d***₆) δ 1.03–1.81 (m, 10H), 3.69–3.72 (m, 2H), 4.29–4.36 (m, 3H), 4.52 (d,** *J* **= 6.1 Hz, 2H), 7.13–7.19 (m, 2H), 7.33– 7.37 (m, 2H), 8.43 (s, 1H), 10.47 (t,** *J* **= 5.8 Hz, 1H), 12.59 (brs, 1H). LC/MS:** *m/z* **414 [M + H]⁺.**

3-Benzyloxy- N^5 -(**4-fluorobenzyl**)- N^2 -(**2-methoxyethyl**)-**4-oxo**-**1**,**4-dihydropyridine**-**2**,**5**dicarboxamide (20). Using the compound **13**, compound **20** was synthesized according to the method of synthesizing the compound **14**. ¹H NMR (CDCl₃) δ 3.27 (s, 3H), 3.76–3.40 (m, 2H), 3.47–3.52 (m, 2H), 4.63 (d, J = 6.1 Hz, 2H), 5.48 (s, 2H), 6.99–7.05 (m, 2H), 7.33–7.45 (m, 7H), 8.54–8.58 (m, 1H), 8.62 (d, J = 6.7 Hz, 1H), 10.44–10.48 (m, 1H).

1-Allyl-3-benzyloxy- N^5 -(4-fluorobenzyl)- N^2 -(2-methoxyethyl)-4-oxo-1,4-dihydropyridine-2,5-dicarboxamide (21). Using the compound 20, compound 21 was synthesized according to

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the method of synthesizing a compound **15**. ¹H NMR (CDCl₃) δ 3.21 (s, 3H), 3.32–3.35 (m, 2H), 3.38–3.45 (m, 2H), 4.58–4.61 (m, 4H), 5.14–5.30 (m, 4H), 5.82–5.93 (m, 1H), 6.72 (brs, 1H), 6.98–7.04 (m, 2H), 7.30–7.39 (m, 7H), 8.41 (s, 1H), 10.43–10.47 (m, 1H).

9-Benzyloxy-N-(4-fluorobenzyl)-3-hydroxy-2-(2-methoxyethyl)-1,8-dioxo-2,3,4,8-

tetrahydro-1*H*-pyrido[1,2-a]pyrazine-7-carboxamide (22). Using the compound 21, compound 22 was synthesized according to the method of synthesizing a compound 16. ¹H NMR (CDCl₃) δ 3.07–3.17 (m, 1H), 3.42 (s, 3H), 3.44–3.49 (m, 1H), 3.61–3.69 (m, 1H), 4.11–4.17 (m, 4H), 4.26–4.31 (m, 1H), 4.43–4.49 (m, 1H), 4.59–4.62 (m, 2H), 5.00–5.08 (m, 2H), 5.20 (d, *J* = 9.9 Hz, 1H), 5.34 (d, *J* = 9.9 Hz, 1H), 6.98–7.04 (m, 2H), 7.30–7.35 (m, 5H), 7.60–7.63 (m, 2H), 8.38 (s, 1H), 10.45–10.49 (m, 1H).

3,9-Dihydroxy-2-(2-methoxyethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrid[1,-2-

a]**pyrazine-7-carboxylic acid 4-fluorobenzylamide (23).** According to the method of synthesizing **19**, compound **23** was synthesized from **22**. mp 163–164 °C; ¹H NMR (CDCl₃) δ 3.24–3.32 (m, 1H), 3.46 (s, 3H), 3.52–3.57 (m, 1H), 3.72–3.80 (m, 1H), 4.17–4.39 (m, 3H), 4.62 (d, *J* = 5.8 Hz, 2H), 5.12 (s, 1H), 5.80 (brs, 1H), 6.97–7.03 (m, 2H), 7.30–7.35 (m, 2H), 8.32 (s, 1H), 10.36–10.38 (m, 1H), 12.02 (brs, 1H). Anal. Calcd for C₁₉H₂₀FN₃O₆: C, 56.29; H, 4.97; F, 4.69; N, 10.37. Found: C, 56.13; H, 4.99; F, 4.55; N, 10.34.

7-Benzyloxy-*N*-(4-fluorobenzyl)-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-[1,3]oxazino[3,2d]pyrido[1,2-a]pyrazine-9-carboxamide (25). To the solution of the compound 16 (200 mg, 0.442 mmol) in dichloromethane (5 mL) 3-aminopropane-1-ol (35.0 μ L, 0.511 mmol) and acetic acid (10.0 mg, 0.167 mmol) were added. The reaction was performed with a microwave reaction apparatus at 140 °C for 30 minutes. After cooled to room temperature, solvent was evaporated in vacuo, the residue was subjected to silica gel column chromatography, and fractions eluting with chloroform-methanol were collected and concentrated to obtain the product (173 mg, 74% yield)

as colorless solid. ¹H NMR (CDCl₃) δ 1.62–1.67 (m, 1H), 1.91–-2.07 (m, 1H), 3.07 (dt, *J* = 12.9, 3.3 Hz, 1H), 3.84 (dt, *J* = 11.7, 2.4 Hz, 1H), 4.11–4.20 (m, 2H), 4.32 (dd, *J* = 13.8, 3.3 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 2H), 4.71–4.78 (m, 1H), 5.01 (t, *J* = 4.2 Hz, 1H), 5.26 (d, *J* = 9.9 Hz, 1H), 5.31 (d, *J* = 9.9 Hz, 1H), 7.00–7.07 (m, 2H), 7.32–7.42 (m, 5H), 7.64–7.66 (m, 2H), 8.39 (s, 1H), 10.45 (brs, 1H).

6-Benzyloxy-N-(4-fluorobenzyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-

d]**pyrido**[**1,2-a**]**pyrazine-8-carboxamide (24).** ¹H NMR (DMSO-*d*₆) δ 3.52–3.62 (m, 1H), 3.78– 3.91 (m, 1H), 4.01–4.12 (m, 2H), 4.24–4.31 (m, 1H), 4.50–4.62 (m, 2H), 4.88 (dd, *J* = 3.3, 12.0 Hz, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 5.21 (d, *J* = 10.2 Hz, 1H), 5.31 (dd, *J* = 9.9, 3.3 Hz, 1H), 7.19 (t, *J* = 8.7 Hz, 2H), 7.32–7.42 (m, 5H), 7.58 (d, *J* = 6.6 Hz, 2H), 8.64 (s, 1H), 10.49–10.54 (t, *J* = 6.3 Hz, 1H).

1-Benzyloxy-2,11-dioxo-2,5,5a,7,8,9,10,11-octahydro-6-oxa-4a,10a-

diazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (26). ¹H NMR (CDCl₃) δ 1.55–1.60 (m, 1H), 1.77–1.91 (m, 2H), 2.03–2.13 (m, 1H), 3.13–3.22 (m, 1H), 3.64–3.81 (m, 2H), 4.15–4.21 (m, 1H), 4.31–4.37 (m, 1H), 4.39–4.48 (m, 1H), 4.63 (t, *J* = 6.0 Hz, 2H), 4.99 (t, *J* = 2.4 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 5.41 (d, *J* = 10.2 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.20–7.40 (m, 5H), 7.63–7.65 (m, 2H), 8.40 (s, 1H), 10.49–10.54 (m, 1H).

6-Benzyloxy-*N***-(4-fluorobenzyl)-1-isopropyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1***H***imidazo[1,2-d]pyrido[1,2-a]pyrazine-8-carboxamide (27). ¹H NMR (DMSO-***d***₆) δ 1.06 (d,** *J* **= 6.3 Hz, 3H), 1.16 (d,** *J* **= 6.3 Hz, 3H), 2.77–2.85 (m, 1H), 2.98–3.07 (m, 1H), 3.15–3.22 (m, 1H), 3.54–3.58 (m, 2H), 3.87 (t,** *J* **= 11.4 Hz, 1H), 4.48–4.57 (m, 3H), 4.81–4.85 (m, 1H), 5.06 (d,** *J* **= 10.2 Hz, 1H), 5.20 (d,** *J* **= 10.2 Hz, 1H), 7.19 (t,** *J* **= 9.0 Hz, 2H), 7.31–7.42 (m, 5H), 7.57 (d,** *J* **= 7.8 Hz, 2H), 8.62 (s, 1H), 10.49 (t,** *J* **= 6.0 Hz, 1H).**

5-Benzyloxy-1-methyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7carboxylic acid 4-fluorobenzylamide (28). ¹H NMR (CDCl₃) δ 1.61–1.68 (m, 2H), 2.31 (s, 3H), 2.85–2.93 (m, 1H), 3.06–3.11 (m, 1H), 4.32–4.39 (m, 2H), 4.58–4.66 (m, 3H), 4.69–4.79 (m, 2H), 5.32 (s, 2H), 7.02–7.08 (m, 2H), 7.33–7.42 (m, 5H), 7.64–7.66 (m, 2H), 8.41 (s, 1H), 10.50 (brs, 1H).

5-Benzyloxy-1-isopropyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (29). ¹H NMR (DMSO-*d*₆) δ 0.95–0.99 (m, 6H), 1.52– 1.56 (m, 1H), 1.64–1.69 (m, 1H), 2.49–2.56 (m, 1H), 2.89–2.98 (m, 2H), 2.32–2.41 (m, 1H), 2.40–2.55 (m, 1H), 3.68–3.70 (m, 2H), 4.36 (brs, 1H), 4.54–4.59 (m, 1H), 4.88–4.93 (m, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 7.18–7.24 (m, 2H), 7.35–7.45 (m, 5H), 7.58–7.62 (m, 2H), 8.78 (s, 1H), 10.52 (t, *J* = 6.0 Hz, 1H).

5-Benzyloxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (30). ¹H NMR (CDCl₃) δ 1.67–1.71 (m, 1H), 2.00–2.13 (m, 1H), 2.84–2.97 (m, 2H), 3.19–3.23 (m, 1H), 4.13 (s, 2H), 4.35–4.38 (m, 2H), 4.56–4.67 (m, 3H), 4.71–4.80 (m, 1H), 5.29 (d, *J* = 9.9 Hz, 1H), 5.36 (d, *J* = 9.9 Hz, 1H), 7.03–7.08 (m, 2H), 7.24 (d, *J* = 3.3 Hz, 1H), 7.34–7.42 (m, 5H), 7.66–7.69 (m, 2H), 7.79 (d, *J* = 3.3 Hz, 1H), 8.05 (brs, 1H), 10.49 (t, *J* = 6.0 Hz, 1H).

5-Benzyloxy-1-(2-methoxyethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (31). ¹H NMR (CDCl₃) δ 1.56-1.65 (m, 1H), 1.82–1.95 (m, 1H), 2.62–2.70 (m, 1H), 2.80–2.92(m, 3H), 2.98–3.05 (m, 1H), 3.28–3.34 (m, 1H), 3.34 (s, 3H), 3.58–3.65 (m, 1H), 4.28 (dd, *J* = 13.8 Hz, 3.6 Hz, 1H), 4.38 (brs, 1H), 4.53–4.59 (m, 1H), 4.63 (d, *J* = 6.0 Hz, 2H), 4.69–4.76 (m, 1H), 5.29 (s, 2H), 7.00–7.05 (m, 2H), 7.30–7.38 (m, 5H), 7.63–7.66 (m, 2H), 8.38 (s, 1H), 10.53 (t, *J* = 6.0 Hz, 1H).

1-Benzyloxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-

 triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (32). ¹H NMR (CDCl₃) δ 1.55–1.87 (m, 4H), 2.28 (s, 3H), 2.69–2.83 (m, 2H), 3.07–3.16 (m, 1H), 4.16–4.40 (m, 4H) 4.57–4.70 (m, 2H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.39 (d, *J* = 10.2 Hz, 1H), 7.01–7.07 (m, 2H), 7.29–7.39 (m, 5H), 7.61–7.64 (m, 2H), 8.38 (s, 1H), 10.56 (t, *J* = 5.4 Hz, 1H).

1-Benzyloxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-

triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (33). ¹H NMR (CDCl₃) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.57–1.71 (m, 4H), 1.79–1.86 (m, 1H), 2.31 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.62 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.75–2.95 (m, 2H), 3.02– 3.09 (m, 1H), 4.06–4.21 (m, 2H), 4.33–4.40 (m, 1H), 4.48–4.51 (m, 1H), 4.56–4.70 (m, 2H), 5.28 (d, *J* = 9.9 Hz, 1H), 5.32 (d, *J* = 9.9 Hz, 1H), 7.04 (t, *J* = 8,7 Hz, 2H), 7.31–7.40 (m, 5H), 7.63 (d, *J* = 6.6 Hz, 2H), 8.36 (s, 1H), 10.54 (t, *J* = 6.0 Hz, 1H).

5-Benzyloxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-

carboxylic acid 4-fluorobenzylamide (34). ¹H NMR (CDCl₃) δ 1.67–1.80 (m, 2H), 2.80–2.90 (m, 1H), 2.95–3.05 (m, 1H), 3.16–3.21 (m, 1H), 3.98 (dd, *J* = 13.2, 8.4 Hz, 1H), 4.23 (dd, *J* = 3.9 Hz, 1H), 4.55 (dd, *J* = 8.1, 3.9 Hz, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 4.65–4.68 (m, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 5.27 (d, *J* = 10.2 Hz, 1H), 7.00–7.06 (m, 2H), 7.33–7.41 (m, 5H), 7.63–7.66 (m, 2H), 8.37 (s, 1H), 10.47 (t, *J* = 5.7 Hz, 1H).

1-Acetyl-5-benzyloxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7carboxylic acid 4-fluorobenzylamide (35). To the solution of the compound 34 (150 mg, 0.315 mmol) in pyridine (1.5 mL), acetic anhydride (60.0 μ L, 0.630 mmol) and catalytic amount of DMAP were added. After stirring for 5 hours at room temperature, 2 M aq HCl (20 mL) was added to the reaction and extracted with ethyl acetate. The combined organics were washed with water and dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was

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recrystallized with chloroform to give the product (126 mg, 77% yield) as orange solid. ¹H NMR (DMSO- d_6) δ 1.85–2.18 (m, 2H), 2.18 (s, 3H), 2.45–2.54 (m, 1H), 2.83–2.94 (m, 1H), 3.28–3.36 (m, 1H), 4.40–4.57 (m, 5H), 5.07 (d, J = 10.2 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 6.10 (brs, 1H), 7.19 (t, J = 8.7 Hz, 2H), 7.34–7.43 (m, 5H), 7.59 (d, J = 6.9 Hz, 2H), 8.64 (s, 1H), 10.49 (d, J = 5.7 Hz, 1H).

5-Benzyloxy-1-methanesulfonyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (36). To the solution of the compound 34 (150 mg, 0.315 mmol) in pyridine (1.5 mL), methanesulfonyl chloride (37.0 μ L, 0.473 mmol) and catalytic amount of DMAP were added. After stirring for 3.5 hours at room temperature, 2 M aq HCl was added to the reaction and extracted with ethyl acetate. The combined organics were washed with water and dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was recrystallized with chloroform-diisopropyl ether to give the product (86.0 mg, 49% yield) as colorless crystals. ¹H NMR (DMSO-*d*6) δ 1.78–1.87 (m, 1H), 1.95–2.02 (m, 1H), 2.98–3.08 (m, 1H), 3.20 (s, 3H), 3.40–3.53 (m, 1H), 3.58–3.67 (m, 1H), 4.48–4.64 (m, 4H), 4.74–4.85 (m, 1H), 5.08–5.17 (m, 2H), 5.59–5.63 (m, 1H), 7.21 (t, *J* = 9.0 Hz, 2H), 7.36–7.44 (m, 5H), 7.59–7.66 (m, 2H), 8.58 (s, 1H), 10.47 (t, *J* = 6.3 Hz, 1H).

5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1-oxa-3a,8a-diazacyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide (37). mp 272–274 °C; ¹H NMR (DMSO-*d*₆) δ 3.59– 3.67 (m, 1H), 3.72–3.81 (m, 1H), 3.98–4.10 (m, 2H), 4.27–4.35 (m, 1H), 4.52 (d, *J* = 7.2 Hz, 2H), 4.92 (dd, *J* = 12.3, 12.3 Hz, 1H), 5.27 (dd, *J* = 9.9, 3.6 Hz, 1H), 7.11–7.20 (m, 2H), 7.30– 7.40 (m, 2H), 8.49 (s, 1H), 10.32 (t, *J* = 5.6 Hz, 1H), 11.53 (s, 1H). Anal. Calcd for C₁₈H₁₆FN₃O₅: C, 57.91; H, 4.32; F, 5.09; N, 11.26. Found: C, 57.78; H, 4.28; F, 4.97; N, 11.25.

5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2*H*-1-oxa-4a,8a-diazaanthracene-7-

carboxylic acid 4-fluorobenzylamide (38). mp 259–259 °C; ¹H NMR (DMSO-*d*₆) δ 1.60–1.67

(m, 1H), 1.72–1.85 (m, 1H), 3.25 (td, J = 12.8, 3.5 Hz, 1H), 3.86–3.93 (m, 1H), 4.06 (dd, J = 11.4, 4.2 Hz, 1H), 4.44–4.57 (m, 5H), 5.28 (t, J = 3.8 Hz, 1H), 7.13–7.18 (m, 2H), 7.33–7.37 (m, 2H), 8.51 (s, 1H), 10.36 (t, J = 6.0 Hz, 1H), 12.47 (s, 1H). Anal. Calcd for C₁₉H₁₈FN₃O₅: C, 58.91; H, 4.68; F, 4.90; N, 10.85. Found: C, 58.86; H, 4.65; F, 4.74; N, 10.85.

1-Hydroxy-2,11-dioxo-2,5,5a,7,8,9,10,11-octahydro-6-oxa-4a,10a-

diazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (39). mp 242–244 °C; ¹H NMR (DMSO- d_6) δ 1.40–2.00 (m, 4H), 3.20–3.30 (m, 1H), 3.66–3.77 (m, 2H), 4.14–4.23 (m, 1H), 4.38–4.41 (m, 1H), 4.52 (d, J = 6.3 Hz, 2H), 4.58–4.63 (m, 1H), 5.34 (brs, 1H), 7.15 (t, J = 9.0 Hz, 2H), 7.33–7.37 (m, 2H), 8.50 (s, 1H), 10.39 (brs, 1H), 12.14 (s, 1H). Anal. Calcd for C₂₀H₂₀FN₃O₅(H₂O)_{0.3}: C, 59.05; H, 5.10; F, 4.67; N, 10.33. Found: C, 59.15; H, 4.95; F, 4.52; N, 10.30.

5-Hydroxy-1-isopropyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-

triazacyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide (40). mp 232–234 °C; ¹H NMR (DMSO- d_6) δ 1.03 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 2.70–2.90 (m, 1H), 2.90–3.10 (m, 1H), 3.12–3.30 (m, 1H), 3.40–3.66 (m, 2H), 3.82 (t, J = 10.8 Hz, 1H), 4.40–4.60 (m, 3H), 4.90 (d, J = 12.3 Hz, 1H), 7.10–7.20 (m, 2H), 7.30–7.40 (m, 2H), 8.45 (s, 1H), 10.39 (t, J = 5.4 Hz, 1H), 11.60 (s, 1H). Anal. Calcd for C₂₁H₂₃FN₄O₄: C, 60.86; H, 5.59; F, 4.58; N, 13.52. Found: C, 60.61; H, 5.51; F, 4.47; N, 13.43.

5-Hydroxy-1-methyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7carboxylic acid 4-fluorobenzylamide (41). mp 252–253 °C; ¹H NMR (DMSO-*d*₆) δ 1.56–1.75 (m, 2H), 2.22 (s, 3H), 2.50–2.55 (m, 1H), 2.90–3.10 (m, 2H), 4.17 (brs, 1H), 4.39–4.42 (m, 2H), 4.52 (d, *J* = 6.0 Hz, 2H), 4.74–4.78 (m, 1H), 7.13–7.17 (m, 2H), 7.33–7.37 (m, 2H), 8.61 (s, 1H),

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10.40 (t, J = 6.0 Hz, 1H), 12.54 (s, 1H). Anal. Calcd for C₂₀H₂₁FN₄O₄: C, 59.99; H, 5.29; F, 4.74; N, 13.99. Found: C, 59.61; H, 5.30; F, 4.55; N, 13.81.

5-Hydroxy-1-isopropyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (42). mp 220 °C; ¹H NMR (DMSO-*d*₆) δ 0.94 (d, *J* = 9.6 Hz, 6H), 1.53–1.67 (m, 2H), 2.92–3.30 (m, 3H), 4.32–4.40 (m, 4H), 4.52 (d, *J* = 5.7 Hz, 2H), 4.89 (d, *J* = 14.1 Hz, 1H), 7.16 (t, *J* = 9.0 Hz, 2H), 7.35 (dd, *J* = 9.0, 6.3 Hz, 2H), 8.61 (s, 1H), 10.46 (s, 1H), 12.55 (s, 1H). Anal. Calcd for C₂₂H₂₅FN₄O₄(H₂O)_{1.0}: C, 59.18; H, 6.10; F, 4.26; N, 12.55. Found: C, 59.13; H, 5.76; F, 4.07; N, 12.41.

5-Hydroxy-6,10-dioxo-1-(thiazol-2-yl)methyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (43). mp 214–215 °C; ¹H NMR (DMSO- d_6) δ 1.54–1.72 (m, 2H), 2.75–2.81 (m, 1H), 2.95–3.07 (m, 2H), 3.80 (d, J = 16.0 Hz, 1H), 4.37 (d, J = 16.4 Hz, 1H), 4.44–4.51 (m, 4H), 4.69 (brs, 1H), 4.89–4.93 (m, 1H), 7.13–7.17 (m, 2H), 7.32–7.35 (m, 2H), 7.55 (d, J = 3.2 Hz, 1H), 7.69 (d, J = 3.2 Hz, 1H), 8.37 (s, 1H), 10.36 (t, J = 6.0 Hz, 1H), 12.50 (s, 1H). Anal. Calcd for C₂₃H₂₂FN₅O₄S(H₂O)_{0.4}: C, 56.29; H, 4.68; F, 3.87; N, 14.27; S, 6.53. Found: C, 56.49; H, 4.59; F, 3.78; N, 14.12; S, 6.25.

5-Hydroxy-1-(2-methoxyethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (44). mp 147 °C; ¹H NMR (DMSOd₆) δ 1.56–1.74 (m, 2H), 2.53–2.58 (m, 1H), 2.66–3.10 (m, 4H), 3.18 (s, 3H), 3.41–3.39 (m, 2H), 4.37–4.52 (m, 5H), 4.73–4.80 (m, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 7.33–7.37 (m, 2H), 8.56 (s, 1H), 10.40 (t, *J* = 6.0 Hz, 1H), 12.62 (s, 1H). LC/MS: *m/z* 445 [M + H]⁺.

1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5*H***-4a,6,10a-triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (45).** mp 230–231 °C; ¹H NMR (DMSO-*d*₆) δ 1.47–1.53 (m, 1H), 1.62–1.78 (m, 3H), 2.29 (s, 3H), 2.77–2.81 (m,

2H), 4.05–4.10 (m, 1H), 4.35–4.40 (m, 1H), 4.54–4.64 (m, 3H), 4.70 (s, 1H), 7.18–7.22 (m, 2H), 7.30–7.34 (m, 1H), 7.47–7.52 (m, 1H), 8.49 (s, 1H), 10.47 (d, J = 6.0 Hz, 1H), 12.44 (s, 1H). Anal. Calcd for C₂₁H₂₃FN₄O₄: C, 60.86; H, 5.59; F, 4.58; N, 13.52. Found: C, 60.46; H, 5.57; F, 4.52; N, 13.23.

1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-

triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide (46). mp 221–223 °C; ¹H NMR (DMSO- d_6) δ 0.81 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 1.45–1.78 (m, 5H), 2.36–2.54 (m, 2H), 2.27–2.93 (m, 2H), 3.17–3.23 (m, 1H), 4.03–4.06 (m, 1H), 4.32–4.56 (m, 4H), 4.82–4.85 (m, 1H), 7.13–7.17 (m, 2H), 7.30–7.37 (m, 2H), 8.48 (s, 1H), 10.42 (t, J = 6.0 Hz, 1H), 12.53 (s, 1H). Anal. Calcd for C₂₄H₂₉FN₄O₄(H₂O)_{0.3}: C, 62.40; H, 6.46; F, 4.11; N, 12.13. Found: C, 62.50; H, 6.34; F, 4.22; N, 11.97.

1-Acetyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7carboxylic acid 4-fluorobenzylamide (47). mp 290 °C; ¹H NMR (DMSO-*d*₆) δ 1.78–2.14 (m, 2H), 2.14 (s, 3H), 2.80–3.00 (m, 2H), 4.05–4.15 (m, 1H), 4.30–4.60 (m, 3H), 4.51 (d, *J* = 5.7 Hz, 2H), 5.99 (s, 1H), 7.15 (t, *J* = 9.0 Hz, 2H), 7.30–7.40 (m, 2H), 8.37 (s, 1H), 10.46 (s, 1H), 12.28 (s, 1H). Anal. Calcd for C₂₁H₂₁FN₄O₅(H₂O)_{0.5}: C, 57.66; H, 5.07; F, 4.34; N, 12.81. Found: C, 57.53; H, 4.90; F, 4.20; N, 12.64.

5-Hydroxy-1-methanesulfonyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-

triazaanthracene-7-carboxylic acid 4-fluorobenzylamide (48). mp 257–259 °C; ¹H NMR (DMSO-*d*₆) δ 1.80–1.96 (m, 2H), 3.02–3.58 (m, 2H), 3.16 (s, 3H), 4.52 (d, *J* = 5.7 Hz, 2H), 4.50–4.60 (m, 1H), 4.70–4.80 (m, 1H), 5.56 (s, 1H), 7.16 (t, *J* = 9.0 Hz, 2H), 8.36 (s, 1H), 10.39 (s, 1H). LC/MS: *m/z* 465 [M + H]⁺.

6.2. Biological Assay and PK studies in rats

All biological and PK studies were performed with the same manner described in our previous paper.¹¹

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Abbreviations used

CYP3A, Cytochrome P450, family 3, subfamily A; HOBt, 1-hydroxybenzotriazole; rt, room temperature; NaOMe, sodium methoxide; MnO₂, manganese dioxide; TFA, trifluoroacetic acid; BnBr, benzyl bromide; CO, carbon monooxide; 10% Pd-C, palladium carbon; Pd(OAc)₂, palladium diaceate; Ac₂O, acetic anhydride; MsCl, methanesulfonyl chloride; NaOH, sodium hydroxide; DMAP, *N*,*N*-dimethylaminopyridine; Et₃N, triethylamine; NH₃, ammonia; CDCl₃, deuterated chloroform; DMSO- d_6 , deuterated DMSO; HCl, hydrogen chloride; Na₂CO₃, sodium

carbonate; Cs₂CO₃, cesium carbonate; K₂CO₃, potassium carbonate; Na₂SO₄, sodium sulfate; Et₂O, diethyl ether; NaHSO₃, sodium hydrogen sulfite.

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