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# Synthesis and biological evaluation of pyridinone analogues as novel potent HIV-1 NNRTIs

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ABSTRACT

A novel 2-pyridinone scaffold was rationally designed and synthesized based on the active anti-HIV agent **1** (LAM-*trans*) via an efficient method. The biological results revealed that some target compounds inhibited HIV-1 reverse transcriptase in the lower micromolar concentration range ($IC_{50}$ 0.089–0.68 μm). Notably, the most promising compound **25b** exhibited extremely potent inhibitory activity against HIV-1 replication with an $EC_{50}$ value of 0.0563 μM and the viral selectivity index amounted to 3466.8. Molecular modeling studies were performed, and some SARs were rationalized.



## 1. Introduction

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) has been identified as an important viral target for the discovery and development of anti-HIV therapeutic agents. Accordingly, two functionally distinct classes of HIV-1 RT inhibitors (nucleoside and non-nucleoside) have been developed and are being used clinically. Especially, non-nucleoside RT inhibitors (NNRTIs), with high antiviral potency and the favorable pharmacokinetic properties, have gained an important role in clinical use, and become an indispensable component in HAART regimen.[1–4] So far, five NNRTIs have gained approval for clinical use: nevirapine (NVP), delavirdine (DLV), efavirenz (EFV), etravirine (ETR) and rilpivirine (RPV). Like other types of anti-HIV drugs, the therapeutic efficacy of NNRTIs is weakened by the emergence of mutants, in vitro and in vivo, that show cross-resistance to other structurally unrelated drugs.[5–7] Therefore, it is important to develop new NNRTIs which can effectively inhibit the existing drug-resistant viral strains.

Among the structurally diverse NNRTIs, pyridinone scaffolds demonstrated high potency against HIV-1 wild type and drug-resistant strains.[8] A contribution from our laboratories to this effort was the development of pyridinone derivatives, especially the compound **1** (LAM-*trans*) (Fig. 1) which was highly effective against a panel of RTIs-resistant strains with single (Y181C and K103 N) and double (A17) mutations in RT with high selectivity index (SI), and would be identified as a promising lead compound.[9]

Preliminary structure and activity relationship (SAR) on this series has revealed that the substituents on the C-3, C-4 and C-6 of the pyridinone ring were very important for antiviral activity.[10] The docking results displayed that the C-6 side chain could be located at the region similar to that of the N-1 side chain of compound **2** (TNK-651), and form the π-π interaction with the Tyr318 and Pro236 residues.

Encouraged by these promising results, we were inspired to carry out the optimization program on this scaffold which was focused on the C-3 and C-4 positions (Fig. 1) with an efficient synthetic strategy, while keeping the above mentioned key interaction features required for RT inhibition.

Based on our previous study, substituent with steric or lipophilic character on the C-3 position would be beneficial for the

*Abbreviations:* HIV, human immunodeficiency virus; NNRTIs, non-nucleoside reverse transcriptase inhibitors; SARs, structure and activity relationships; HAART, highly active antiretroviral therapy; RT, reverse transcriptase; NVP, nevirapine; DLV, delavirdine; EFV, efavirenz; ETR, etravirine; RPV, rilpivirine; RTIs, reverse transcriptase inhibitors; NIS, *N*-iodosuccinimide; NBS, *N*-bromosuccinimide; DMF, *N*,*N*-dimethylformamide; NNBP, non-nucleoside binding pocket; PDB, protein database; SI, selectivity index.

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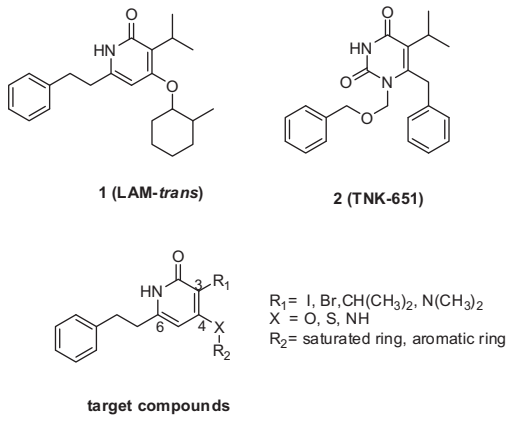



**Figure 1.** Structure of typical NNRTIs and the target compounds.

inhibitory activity. Therefore, according to the isosteric principle, the isopropyl and the *N*,*N*-dimethyl as the preferred substituents were introduced on this position, and expected to 'trigger' the conformation of the C-4 substituent with the improved anti-HIV-1 RT activity.[11] Moreover, the halogen substituent could form a halogen bond with the carbonyl of the Tyr181 residue and act as a vehicle to incorporate diverse functionality at C-3 of the pyridinone ring.

The optimization on C-4 position, which is surrounded by the aromatic residues Tyr188, Phe227, and Trp229 in the hydrophobic binding pocket, was carried out by introducing saturated and aromatic rings to provide the opportunity to compare the influence on anti-HIV activity. Considering the modification on linker was little concerned. We incorporated an oxygen, sulfur or nitrogen atom, with different electro negativity, into the bridging site to obtain more SAR information about this category compounds.

To explore the relationships between structure and activity of the target compounds, we synthesized a series of novel pyridinone derivatives (Fig. 1), and tested their HIV-1 RT inhibitory potency. The active compounds were further evaluated in vitro against the HIV-1 laboratory-adapted strain (SF33) on TZM-bl cell lines.

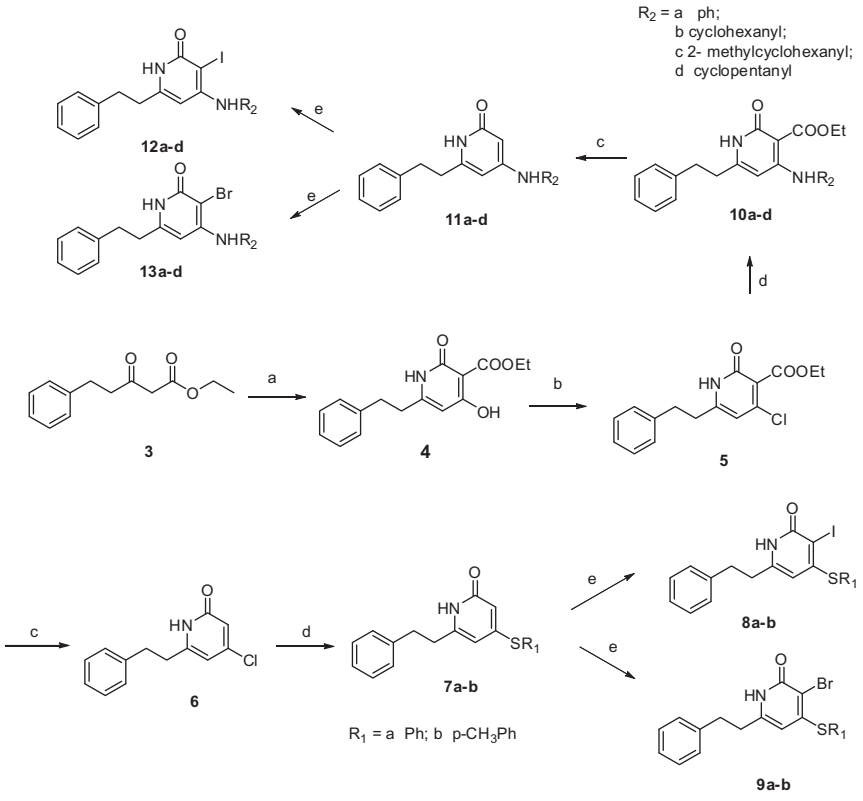
## 2. Results and discussion

### 2.1. Chemistry

Almost all the target compounds had been synthesized from the common intermediate **4**, which was conveniently prepared through condensation of ethyl 3-oxo-5-phenyl pentanoate **3** with diethylmalonate in the presence of ammonia (Scheme 1).[9]

Chlorination with phosphorus oxychloride and benzyltriethylammonium chloride provided the requisite 4-chloro-3-carbethoxy-2-pyridinone **5**, which reacted with the corresponding aryl mercaptan or amine to afford 4-thioaryl and 4-amino substituent pyridinones respectively in a Michael addition/retro-Michael process.[12] The transformation would be beneficial with an electron withdrawing group on the C-3 position of pyridinone ring. Subsequently, the 4-amino pyridinone anologues **10a–d** were subjected to 2N HCl and then halogenated with NIS or NBS to give the target compound **12a–d** and **13a–d** successively. However, considering 3-carbethoxy-4-thioaryl pyridinone, the yield of hydrolysis-decarboxylation was unacceptable (30%). Therefore, we adjusted the sequence of reactions. The compound **5** involved decarboxylation of the C-3 ester group prior to reaction with the corresponding aryl mercaptan to afford the **7a–b** with improved yield (70%), which were converted to **8a–b** and **9a–b** by reaction with NIS or NBS, respectively.

For the preparation of the aryloxy analogue, the approach did not appear sufficiently effective. Based on the report of Kappe




**Scheme 1.** Reagents and reaction conditions: (a) $NH_3$/MeOH, diethyl malonate/EtONa, reflux, 5 d, yield 33%; (b) $POCl_3$, benzyltriethylammoniumchloride, $CH_3CN$, rt, 12 h, yield 80%; (c) 2 N HCl, reflux, 2 d, yields 65–76%; (d) Corresponding $HSR_1$ or $H_2NR_2$, ethanol, reflux, 2 d, yields 62–76%; (e) NIS/NBS, THF, rt, 8 h, yields 90–96%.

and El-Mariah,[13] reaction of 4-hydroxy substituted pyridinone **14** with (dichloroiodo)benzene led to rapid formation of dipole, which was isolated and then heated in dry DMF to take rearrangement to the 3-iodo-6-phenethyl-4-phenoxy-2-pyridinone **15**. The aryloxy and iodo substituents were introduced adjacent to each other on the pyridinone nucleus successively, and the target compound **15** was conveniently obtained with high yield (95%) (Scheme 2).[14]

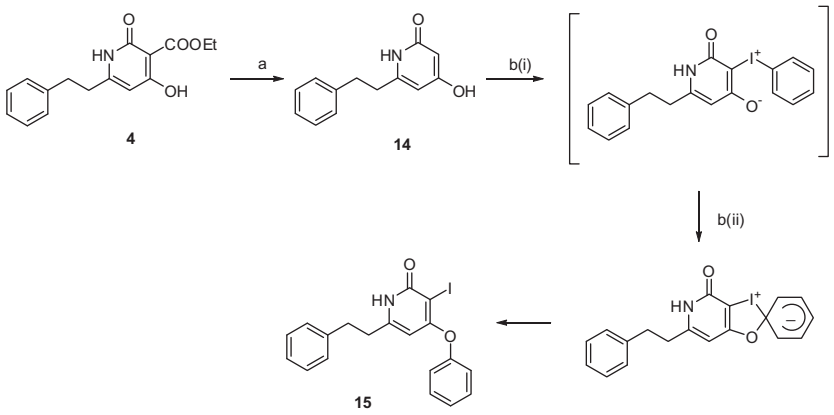
Introducing the *N*,*N*-dimethyl moiety on the C-3 position was performed as illustrated in Scheme 3. Treatment of 4-hydroxy-6-phenethyl-2-pyridinone (**14**) with fuming nitric acid in acetic acid afforded the 3-nitro product **16**, which reacted with methylsufonyl chloride in triethylamine to give the bismesylated compound **17**. Subsequently, the nucleophilic substitution reaction took place on the C-4 position selectively to afford the compound **18**[15] which was treated under mild hydrolysis condition with sodium methoxide in $CH_3OH$ to provide the intermediate **19**. Hydrogenation of the nitro group, using Pd/C as the catalytic agent, provided the amine **20** with 90% yield, which was following converted to the target compound **21** successfully under reductive alkylation conditions.

Further modifications on the C-3 position, with isopropyl moiety, were carried out according to Scheme 4, in which **5** was used as the starting material. Concerning the linker with different atoms (oxygen or sulfur atom), the synthetic routes are slightly different. 4-Chloro-3-carbethoxy-2-pyridinone **5** was treated with $K_2CO_3$ in DMF or $Et_3N$ in ethanol, and then reacted with phenol or thiophenol alternatively to afford **22a**–**b**. Conversion of **22** to **23** involved ester reduction using MeLi leading to the expected tertiary alcohol derivative **23**, which was followed by reaction with acetic anhydride or thionyl chloride to provide **24a**–**b**.[16] The 3-propylene derivatives were hydrogenated to yield the target compounds **25a**–**b** bearing isopropyl moiety on the C-3 position.

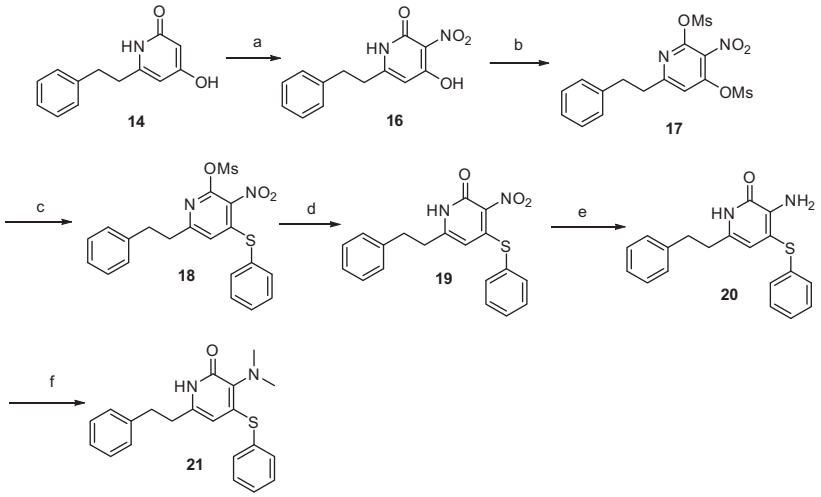
## 2.2. Biological evaluation

The target compounds were initially evaluated in enzymatic tests for their ability to inhibit highly purified recombinant HIV-1 RT using a poly(ra)/oligo(dT)15 as homopolymer template with nevirapine as a reference compound. The assay results are summarized in Table 1, some compounds exhibited promising inhibition with $IC_{50}$ values, which are much better than NVP.

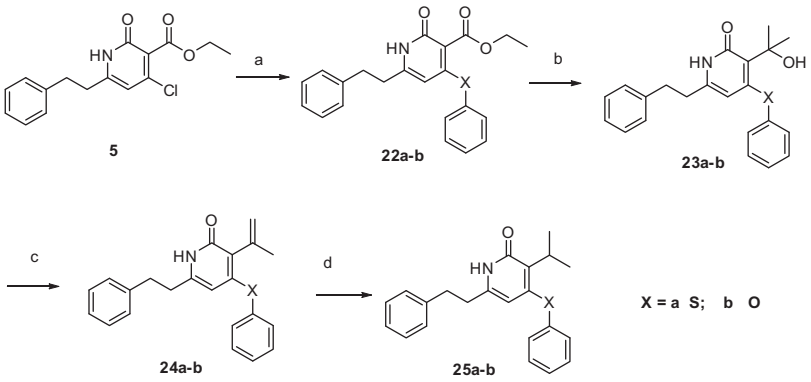
Firstly, comparison of the inhibitory activity of compounds modified at the C-3, we found that the substituent with iodine (**8a** $IC_{50}$ = 20.29 μM,) was superior to bromine (**9a** $IC_{50}$ = 57.14 μM), as shown in Table 1. In addition, the isopropyl moiety could initiate the 'trigger action' required for improved activity. As we expected, the inhibitory activity was improved enormously (**25a**




**Scheme 2.** Reagents and reaction conditions: (a) 2N HCl, reflux, 2 d, yield 73%; (b) (i) $Na_2CO_3$, $H_2O$, room temperature, (dichloroiodo)benzene; (ii) DMF, reflux, 2 h, yield 95%.

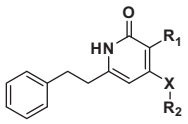



**Scheme 3.** Reagents and reaction conditions: (a) nitric acid fuming, acetic acid, 80 °C, 2 min, yield 75%; (b) methanesulfonyl chloride, triethylamine, $CH_2Cl_2$, 12 h, yield 85%; (c) thiophenol, triethylamine, $CH_2Cl_2$, 12 h, yield 72%; (d) $CH_3ONa/CH_3OH$, reflux, 1 h, yield 70%; (e) $H_2$, Pd/C, $CH_2Cl_2$, room temperature, 2 d, yield 75%; (f) $NaBH_3CN$, HCHO, HOAc, $CH_3CN$, 1 h, yield 80%.




**Scheme 4.** Reagents and reaction conditions: (a) benzenethiol, triethylamine, ethanol, reflux, 2 d, yield 83%; or phenol, $K_2CO_3$, DMF, reflux, 8 h, yield 89%; (b) MeLi, THF, −78 °C, 12 h, yield 70–71%; (c) $SOCl_2$, THF, room temperature, 12 h, yield 70%; or $(CH_3CO)_2O$, reflux, 1 h, yield 80%; (d) $H_2$, Pd/C, $CH_2Cl_2$, room temperature, 4 d, yield 80–95%.

**Table 1**
HIV-1 RT inhibitory activity of target compounds[a]



| Compds | $R_1$ | $R_2$ | X | $IC_{50}$[a] (μM) | Compds | $R_1$ | $R_2$ | X | $IC_{50}$[a] (μM) |
|---|---|---|---|---|---|---|---|---|---|
| **8b** | I | *p*-$CH_3$Ph | S | 12.03 | **9b** | Br | *p*-$CH_3$Ph | S | 16.89 |
| **12b** | I | Cyclohexanyl | NH | 15.22 | **13b** | Br | Cyclohexanyl | NH | 40.26 |
| **12c** | I | 2-Methylcyclohexanyl[c] | NH | 0.42 | **13c** | Br | 2-Methylcyclohexanyl[c] | NH | 0.68 |
| **12d** | I | Cyclopentanyl | NH | 24.01 | **12d** | Br | Cyclopentanyl | NH | 43.34 |
| **12a** | I | Ph | NH | 8.14 | **13a** | Br | Ph | NH | 11.35 |
| **8a** | I | Ph | S | 20.29 | **9a** | Br | Ph | S | 57.14 |
| **15** | I | Ph | O | 0.29 | **21** | *N*,*N*-Dimethyl | Ph | S | 15.21 |
| **25b** | Isopropyl | Ph | O | 0.089 | **25a** | Isopropyl | Ph | S | 0.093 |
| NVP[b] | | | | 4.65 | | | | | |

[a] Effective dose (μM) of the compounds required to inhibit HIV-1 RT activity by 50%. Data represent mean values for three separate experiments; variation among triplicate samples was less than 15%.
[b] Nevirapine (NVP) was used as the reference compounds.
[c] Mixture of stereoisomers.

$IC_{50}$ = 0.093 μM, **25b** $IC_{50}$ = 0.089 μM), which illustrated that the overall steric and lipophilic characteristics were clearly beneficial for the inhibitory activity. However, according to the isosteric principle, we used the *N*,*N*-dimethyl (**21** $IC_{50}$ = 15.21 μM) to replace the isopropyl and found that the activity was decreased significantly.

Secondly, we turned our attention to the linker on the C-4 position. With the oxygen bridge (**15** $IC_{50}$ = 0.29 μM), the inhibitory activity was more 28 times and 72 times than that of nitrogen (**12a** $IC_{50}$ =8.14 μM) and sulfur (**8a** $IC_{50}$ = 20.90 μM), respectively (Table 1). One possible explanation for this result was that the oxygen atom, with its favorable electro negativity, could provide the better interaction with the NNIBP.[10] Additionally, when a methyl moiety was introduced to the *para*-position of the benzene ring, the inhibitory activity was improved.

Finally, an investigation of the **$R_2$** substituent was performed. As shown in Table 1, **12a**–**d**, which contained rings ranging from phenyl, cyclopentyl to cycloheptyl, were evaluated against HIV-1 RT. The biological results displayed that the substituent with a phenyl ring was superior to both that of cyclopentyl and cyclohexyl. Notably, a methyl-bearing moiety on the cycle ring (**12c**), which is a mixture of stereoisomers, had the inhibitory activity superior to the other compounds. There would be differences in the conformational contribution of the cyclic moiety to the binding of the inhibitors to RT. For the cyclopentanyl substituted compound, the decreased inhibitory activity could be a result of the unfavorable steric interactions with the enzyme.

**Table 2**
Antiviral activity of compounds on HIV-$1_{SF33}$ infection in TZM-bl cell lines[a]

| Compds | $EC_{50}$ (μM)/HIV-$1_{SF33}$ | $CC_{50}$ (μM) | SI[c] |
|---|---|---|---|
| **15** | 0.150 ± 0.001 | 180.754 | 1205 |
| **12c** | 2.710 ± 0.001[b] | 50.161 | 18.5 |
| **13c** | 13.680 ± 0.003[b] | 130.905 | 9.6 |
| **25a** | 0. 136 ± 0.001 | 135.775 | 998.3 |
| **25b** | 0.0563 ± 0.001 | 195.182 | 3466.8 |
| NVP[d] | 0.190 ± 0.001 | 204.003 | 1073.7 |

[a] Each compound was tested in triplicate, and the data were presented as the mean ± SD.
[b] Mixture of stereoisomers.
[c] SI was calculated based on the $CC_{50}$ for TZM-bl cell and $EC_{50}$ for inhibiting infection by HIV-$1_{SF33}$.
[d] Nevirapine (NVP) was used as the reference compound.

Subsequently, the anti-HIV-1 activity and cytotoxicity of the compounds **15**, **12c**, **13c**, **25a** and **25b** were determined in parallel using nevirapine as reference compound. As illustrated in Table 2, some compounds were capable of inhibiting wild-type virus infection by HIV-$1_{SF33}$ in TZM-bl cell with $EC_{50}$ values in the lower micromolar concentration range (0.0563–2.71 μM). Notably, **25b** was the most promising compound. It exhibited extremely potent

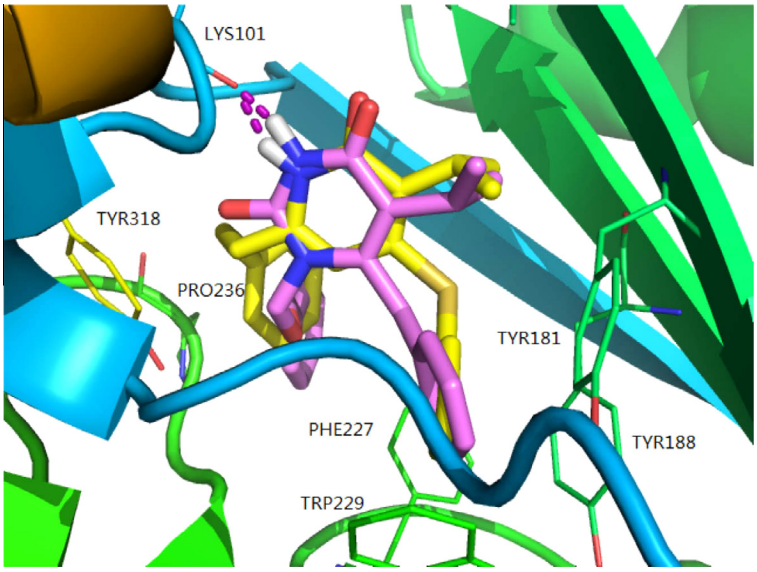



**Figure 2.** Superimposed stereoview of the docked **2** (purple) and **25a** (yellow) with 1RT2. The Hydrogen bonds are shown as purple dashed lines.

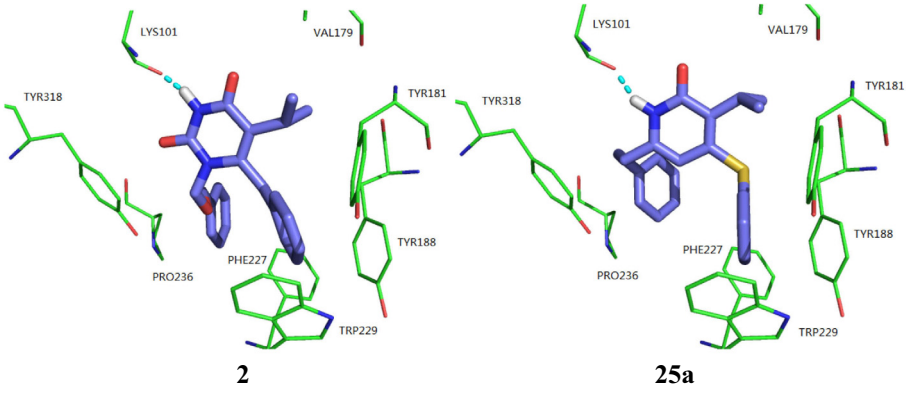



**Figure 3.** Docking results of **2** (TNK-651) and **25a** into the 1RT2 NNBP. Hydrogen bonds are shown as cyan dashed lines.

inhibitory activity against HIV-1 replication with an $EC_{50}$ value of 0.0563 μM and the viral selectivity amounted to 34,668, which is much better than NVP.

## 3. Computational modeling

In addition, molecular modeling studies were carried out to elucidate the effect of structural features on anti-HIV activity. The target compound **25a** was flexibly docked into the binding site of HIV-1 RT (PDB 1RT2), using the GOLD 3.0.1 docking program. The results displayed that **25a** adopted the approximate conformation comparable to that of the **2**/RT complex (Fig. 2).

Inspection of the **25a**/RT complex (Fig. 3), the compound could establish several ligand-receptor interactions as that of **2**, which may be characterized as the hydrogen bond with the backbone NH of Lys101, the favorable π-stacking interaction with Tyr188 and the 'trigger action' of the isopropyl group.

Recently, the existence of a halogen bond was regarded as one of the important interactions leading to improve the anti-HIV-1 activity.[17] Upon inspection of the docking result of **15**/RT (Fig. 4), the halogen bond was observed. The iodine atom of **15** is only 3.14 Å away from the carbonyl oxygen of Tyr188, which is less than the van der waals contact distance of 3.55 Å.

Overall, the combination of hydrophobic and π-stacking interactions may favor the binding of the 2-pyridinone scaffold to RT.

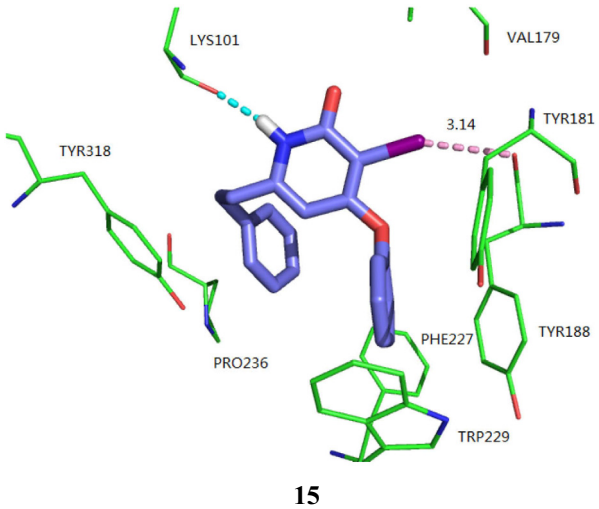



**Figure 4.** Docking results of **15** into the 1RT2 NNBP. The Hydrogen bond is shown as a cyan dashed line, and halogen bond is shown as a pink dashed line.

## 4. Conclusion

In summary, through rational design we have generated the novel 2-pyridinone derivatives as inhibitors of HIV-1 RT in compar-

ison with nevirapine and also explored the SAR. Interestingly, the biological studies revealed that several 2-pyridinone derivatives showed activity in the low micromolecular range with $EC_{50}$ values ranging from 0.0563 to 2.71 μM. Notably **25a** and **25b** displayed the best profile against HIV-1 both in enzyme and cell-based assays. These results appear to confirm that the isopropyl moiety on the C-3 would be beneficial to improve the antiviral activity. It is worth mentioning that, the SI values of the derivatives for inhibiting HIV-$1_{SF33}$ infection are in the range of 18.5–3466.8. Because of their excellent potency, the biological and the structural data would serve as a valuable guide to the further optimization of the anti-HIV activity of the 6-phenethyl pyridinone family.

## 5. Experimental section

### 5.1. Chemistry

The structural characterization was performed with an NMR spectrometer and a high resolution mass spectrometer (HRMS). NMR spectra were recorded on a Bruker Avance 300 or Avance 500 with tetramethylsilane (TMS) as an internal standard, and chemical shifts are reported in (ppm). Melting points were determined on a WBS-1B type digital melting-point apparatus and are uncorrected. All the reactions monitoring were performed with TLC which was performed on aluminum-backed silica gel plates (60 F254) with spots visualized by UV detection. Silica gel H (200–300 mesh or 500 mesh) was used for the column chromatography and silica gel was used for TLC plates. Unless otherwise stated, all reagents were purchased from commercial companies. When necessary, they were purified and dried by standard methods. Organic solutions were dried over anhydrous sodium sulfate.

#### 5.1.1. Ethyl 3-oxo-5-phenylpentanoate (3)[9]

Hydrocinnamoyl chloride (11.2 mL, 75.6 mmol) was added dropwise to a solution of Meldrum's acid (10.9 g, 75.6 mmol) and pyridine (12.4 mL) in $CH_2Cl_2$ (140 mL) at 0 °C. The solution was stirred for 30 min at 0 °C and then was allowed to room temperature for 24 h. The reaction mixture was washed with 10% aqueous HCl (2 × 50 mL) and $H_2O$ (50 mL) separately. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was dissolved in EtOH (100 mL) and heated to reflux for 24 h. The mixture was concentrated under reduced pressure to give the dark oily residue which was purified by flash chromatography using EtOAc/petroleum ether (1:50 V/V) as the eluent to give required compound **3**.

Yield 95%; yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.17–7.29 (m, 5H, Ar*H*), 4.16 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 3.41 (s, 2H, COC$H_2$CO), 2.85–2.92 (m, 4H, ArC$H_2$C$H_2$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$).

#### 5.1.2. Ethyl 4-hydroxy-2-oxo-6-phenethyl-1,2-dihydropyridine-3-carboxylate (4)[9]

A mixture of compound **3** (5 g, 24.0 mmol) and 12.8 M $NH_3$ in MeOH (100 mL) was heated to reflux for 8 h under $N_2$. After cooling, the mixture was concentrated to dryness to provide ethyl 3-amino-5-phenylpent-2-enoate which was used without further purification.

To a solution of 1.2 g (48.0 mmol) of sodium in 40 mL of ethanol was added a solution of 7.0 mL (48.0 mmol) of diethyl malonate in 20 mL of ethanol. The resulting yellow mixture was heated to reflux for 2 h. After cooling, another solution of 5.0 g (24.0 mmol) of ethyl 3-amino-5-phenylpent- 2-enoate in 24 mL of ethanol was added. The mixture was refluxed for 5 d, and then acidified with 2 N HCl. The precipitate was filtered, washed with water and dried to yield the compound **4**.

Yield 33%; white solid; mp 192–193 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 12.58 (s, 1H, O*H*), 11.51 (br s, 1H, N*H*), 7.18–7.31 (m, 5H, Ar*H*), 5.81 (s, 1H, pyridinone *H*), 4.26 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 2.86–2.90 (m, 2H, ArC$H_2$CH$_2$), 2.69–2.73 (m, 2H, ArCH$_2$C$H_2$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 172.82, 170.57, 161.14, 154.97, 140.68, 128.78, 126.61, 98.53, 97.52, 61.09, 34.54, 34.09, 14.58; MS (ESI): *m*/*z*, 288.50 [M+H]$^+$.

#### 5.1.3. Ethyl 4-chloro-2-oxo-6-phenethyl-1,2-dihydropyridine-3-carboxylate (5)

To a solution of compound **4** (4.6 g, 16.0 mmol) and benzyltriethylammonium chloride (14.5 g, 64.0 mmol) in acetonitrile (50 mL) was added phosphorus oxychloride (2.3 mL, 24.0 mmol). The obtained mixture was stirred at room temperature for 24 h. After evaporation of the solvent, 10 mL of ice water was added, and a white precipitate formed, which was collected and recrystallized with ethanol to give compound **5**.

Yield 80%; white solid; mp 147–149 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.64 (br s, 1H, N*H*), 7.21–7.35 (m, 5H, Ar*H*), 6.19 (s, 1H, pyridinone *H*), 4.41 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 2.98–3.03 (m, 2H, ArC$H_2$CH$_2$), 2.85–2.90 (m, 2H, ArCH$_2$C$H_2$), 1.33 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 163.98, 162.43, 150.79, 146.37, 128.59, 128.50, 126.53, 139.70, 121.66, 107.64, 61.90, 35.48, 34.99, 14.11; MS (ESI): *m*/*z*, 306.40 [M+H]$^+$.

#### 5.1.4. 4-Chloro-6-phenethylpyridin-2(1*H*)-one (6)

A solution of the compound **5** (5.0 g, 16.4 mmol) in 2 N HCl (50 mL) was refluxed for 2 d. After the reaction was completed (TLC), $Na_2CO_3$ was added to adjust the mixture to neutral. The resulting white precipitate was filtered, washed with water and dried to give the compound **6**. Yield 72%; white solid; mp 147–149 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.34 (br s, 1H, N*H*), 7.23–7.34 (m, 5H, Ar*H*), 6.49 (d, *J* = 1.6 Hz, 1H, pyridinone *H*), 6.09 (d, *J* = 1.6 Hz, 1H, pyridinone *H*), 3.00–3.05 (m, 2H, ArC$H_2$CH$_2$), 2.87–2.92 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 165.28, 149.66, 148.96, 128.57, 128.49, 126.48, 139.78, 116.06, 107.43, 35.01, 34.80; MS (ESI): *m*/*z*, 234.27 [M+H]$^+$.

### 5.2. General procedure for the synthesis of the compounds 7a–b

To a solution of compound **6** (2.8 g, 12.0 mmol) and the corresponding benzenethiol (1.3 mL, 13.0 mmol) in 20 mL of ethanol was added triethylamine (1 mL, 7.2 mmol). The obtained mixture was heated to reflux for 2 d. After completion of the reaction as indicated by TLC, the mixture was cooled and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **7a**–**b**.

#### 5.2.1. 6-Phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (7a)

Yield 65%; white solid; mp 180–182 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.97 (br s, 1H, N*H*), 7.17–7.54 (m, 10H, Ar*H*), 5.91 (s, 1H, pyridinone *H*), 5.84 (s, 1H, pyridinone *H*), 2.94–2.98 (m, 2H, ArC$H_2$CH$_2$), 2.79–2.83 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 164.77, 156.66, 147.82, 135.53, 129.89, 128.53, 128.46, 126.30, 116.05, 110.60, 140.04, 107.31, 104.38, 34.84, 34.64; MS (ESI): *m*/*z*, 308.54 [M+H]$^+$.

#### 5.2.2. 6-Phenethyl-4-(*p*-tolylthio)pyridin-2(1*H*)-one (7b)

Yield 62%; white solid; mp 104–106 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.96 (br s, 1H, N*H*), 7.17–7,42 (m, 10H, Ar*H*), 5.87 (s, 1H, pyridinone *H*), 5.83 (s, 1H, pyridinone *H*), 2.93–2.97 (m, 2H, ArC$H_2$CH$_2$), 2.78–2.82 (m, 2H, ArCH$_2$C$H_2$), 2.43 (s, 3H, ArC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 164.82, 157.20,

147.70, 140.10, 135.60, 130.67, 128.54, 128.43, 126.26, 125.00, 140.25, 110.31, 104.18, 34.76, 34.62, 21.35; MS (ESI): *m*/*z*, 322.40 $[M+H]^+$.

### 5.3. General procedure for the synthesis of the compounds 8a–b and 9a–9b

The compound **7a**–**7b** (2.0 mmol) was dissolved in 10 mL anhydrous THF, and NIS (NBS) (2.0 mmol) was added to the mixture, which was protected from light and stirred at room temperature overnight. After evaporating the solvent, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **8a**–**b** and **9a**–**b**.

#### 5.3.1. 3-Iodo-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (8a)

Yield 91%; white solid; mp 225–227 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 11.85 (br s, 1H, N*H*), 7.01–7.57 (m, 10H, Ar*H*), 5.06 (s, 1H, pyridinone *H*), 2.66–2.68 (m, 2H, ArC$H_2$CH$_2$), 2.52–2.57 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 159.90, 158.29, 153.39, 140.33, 135.66, 130.73, 130.62, 130.33, 128.73, 126.57, 148.02, 107.17, 102.16, 34.12, 34.07; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{16}$INOS $[M+H]^+$: 434.3059, found 434.0071.

#### 5.3.2. 3-Iodo-6-phenethyl-4-(p-tolylthio)pyridin-2(1*H*)-one (8b)

Yield 92%; white solid; mp 216–218 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.11 (br s, 1H, N*H*), 7.20–7.42 (m, 10H, Ar*H*), 5.32 (s, 1H, pyridinone *H*), 2.88–2.92 (m, 2H, ArC$H_2$CH$_2$), 2.69–2.73 (m, 2H, ArCH$_2$C$H_2$), 2.46 (s, 3H, ArC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 161.86, 161.35, 147.55, 140.04, 135.70, 130.78, 128.71, 128.41, 126.93, 140.60, 126.24, 103.93, 35.31, 34.99, 21.49; HRMS (ESI): *m*/*z*, calcd. for $C_{20}H_{18}$INOS $[M+H]^+$: 448.3325, found 448.0224.

#### 5.3.3. 3-Bromo-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (9a)

Yield 95%; white solid; mp 204–207 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.04 (br s, 1H, N*H*), 7.18–7.55 (m, 10H, Ar*H*), 5.32 (s, 1H, pyridinone *H*), 2.86–2.90 (m, 2H, ArC$H_2$CH$_2$), 2.69–2.73 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 160.41, 156.30, 146.45, 135.88, 130.75, 130.22, 129.95, 129.36, 128.64, 128.53, 139.91, 126.26, 103.73, 35.38, 34.95; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{16}$BrNOS $[M+H]^+$: 386.0136, found 386.0204.

#### 5.3.4. 3-Bromo-6-phenethyl-4-(p-tolylthio)pyridin-2(1*H*)-one (9b)

Yield 96%; white solid; mp 209–211 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.89 (br s, 1H, N*H*), 7.18–7.41 (m, 10H, Ar*H*), 5.33 (s, 1H, pyridinone *H*), 2.86–2.90 (m, 2H, ArC$H_2$CH$_2$), 2.69–2.73 (m, 2H, ArCH$_2$C$H_2$), 2.46 (s, 3H, ArC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 160.19, 156.98, 146.26, 139.84, 135.84, 130.77, 128.60, 128.43, 126.29, 140.68, 125.62, 103.84, 35.25, 34.87, 21.46; HRMS (ESI): *m*/*z*, calcd. for $C_{20}H_{18}$BrNOS $[M+H]^+$: 400.3320, found 400.0370.

### 5.4. General procedure for the synthesis of the compounds 10a–d

To a solution of the compound **5** (3.9 g, 13.0 mmol) in 30 mL of ethanol was added triethylamine (1 mL). Then, the corresponding aniline (13.5 mmol) was added dropwise. The obtained mixture was heated to reflux for 2 d. The mixture was monitored by TLC to ensure the progress of the reaction. The reaction mixture was subsequently diluted with water (50 mL), acidified with HCl and extracted with $CH_2Cl_2$. Finally, the organic layer was washed with water and the organic phase was concentrated to dryness, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **10a**–**d** as the white solids.

#### 5.4.1. Ethyl 2-oxo-6-phenethyl-4-(phenylamino)-1,2-dihydropyridine-3-carboxylate (10a)

Yield 73%; white solid; mp 190–192 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.88 (br s, 1H, N*H*), 7.05–7.37 (m, 10H, Ar*H*), 5.70 (s, 1H, pyridinone *H*), 4.34 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 3.86 (s, 1H, ArN*H*), 2.98–3.03 (m, 2H, ArC$H_2$CH$_2$), 2.78–2.82 (m, 2H, ArCH$_2$C$H_2$), 1.32 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.20, 164.39, 159.43, 151.86, 140.03, 129.44, 128.54, 128.44, 126.27, 125.99, 125.37, 138.23, 125.26, 94.72, 60.46, 35.16, 34.13, 14.34; MS (ESI): *m*/*z*, 385.48 $[M+Na]^+$.

#### 5.4.2. Ethyl 4-(cyclohexylamino)-2-oxo-6-phenethyl-1,2-dihydropyridine-3-carboxylate (10b)

Yield 75%; white solid; mp 213–215 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 11.93 (br s, 1H, N*H*), 9.36 (br s, 1H, cyclohexyl N*H*), 7.17–7.30 (m, 5H, Ar*H*), 5.44 (s, 1H, pyridinone *H*), 4.28 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 3.26–3.28 (m, 1H, NHC*H*), 3.02–3.06 (m, 2H, ArC$H_2$CH$_2$), 2.83–2.87 (m, 2H, ArCH$_2$C$H_2$), 1.26–1.86 (m, 13H, C$H_3$ + cyclohexyl *H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.44, 164.40, 159.74, 151.52, 128.53, 128.40, 126.25, 140.20, 93.23, 91.54, 59.95, 51.05, 32.78, 25.50, 24.44, 35.07, 34.15, 14.38; MS (ESI): *m*/*z*, 369.45 $[M+H]^+$.

#### 5.4.3. Ethyl 4-((2-methylcyclohexyl)amino)-2-oxo-6-phenethyl-1,2-dihydropyridine-3-carboxylate (10c)

Yield 70%; white solid; mp 177–180 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.11 (br s, 1H, N*H*), 9.34 (d, *J* = 8 Hz, 1H, cyclohexyl N*H*), 7.17–7.28 (m, 5H, Ar*H*), 5.41 (s, 1H, pyridinone *H*), 4.28 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 3.48–3.52 (m, 1H, NHC*H*), 3.03–3.07 (m, 2H, ArC$H_2$CH$_2$), 2.83–2.87 (m, 2H, ArCH$_2$C$H_2$), 0.87–1.85 (m, 15H, C$H_3$ + cyclohexyl *H* + cyclohexyl C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.55, 164.51, 160.34, 140.27, 128.55, 128.37, 126.22, 151.50, 93.18, 91.36, 59.89, 57.86, 53.00, 38.44, 33.22, 25.48, 25.18, 19.42, 35.07, 34.15, 14.37; MS (ESI): *m*/*z*, 383.46 $[M+H]^+$.

#### 5.4.4. Ethyl 4-(cyclopentylamino)-2-oxo-6-phenethyl-1,2-dihydropyridine-3-carboxylate (10d)

Yield 76%; white solid; mp 190–192 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.04 (br s, 1H, N*H*), 9.36 (d, *J* = 6 Hz, 1H, cyclopentyl N*H*), 7.19–7.30 (m, 5H, Ar*H*), 5.51 (s, 1H, pyridinone *H*), 4.26 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 3.75–3.80 (m, 1H, NHC*H*), 3.03–3.07 (m, 2H, ArC$H_2$CH$_2$), 2.84–2.88 (m, 2H, ArCH$_2$C$H_2$), 1.48–1.97 (m, 8H, cyclopentyl *H*), 1.27 (t, *J* = 7.2 Hz, 3H, C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 170.41, 164.28, 160.28, 151.63, 128.51, 128.41, 126.26, 140.20, 93.71, 91.62, 59.97, 54.03, 33.56, 23.93, 35.12, 34.14, 14.36; MS (ESI): *m*/*z*, 355.70 $[M+H]^+$.

### 5.5. General procedure for the synthesis of the compounds 11a–d

A solution of the compounds **10a**–**d** (16.4 mmol) in 2 N HCl (30 mL) was heated to reflux for 2 d. When the reaction was completed (TLC), the mixture was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was chromatographed on a silica gel column with EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **11a**–**d**.

#### 5.5.1. 6-Phenethyl-4-(phenylamino)pyridin-2(1*H*)-one (11a)

Yield 76%; white solid; mp 268–270 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 10.91 (br s, 1H, N*H*), 8.60 (s, 1H, ArN*H*), 7.01–7.34 (m, 10H, Ar*H*), 5.70 (s, 1H, pyridinone *H*), 5.52 (s, 1H, pyridinone *H*), 2.85–2.89 (m, 2H, ArC$H_2$CH$_2$), 2.62–2.66 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 164.75, 154.15, 148.45, 141.14, 129.65, 128.85, 128.78, 126.52, 123.28, 121.57, 140.74, 97.14, 92.50, 34.77, 34.56; MS (ESI): *m*/*z*, 291.26 $[M+H]^+$.

#### 5.5.2. 4-(Cyclohexylamino)-6-phenethylpyridin-2(1*H*)-one (11b)

Yield 72%; white solid; mp 290–292 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 10.37 (br s, 1H, N*H*), 7.16–7.30 (m, 5H, Ar*H*),

6.23 (d, $J$ = 7.6 Hz, 1H, cyclohexyl N*H*), 5.48 (s, 1H, pyridinone *H*), 4.94 (s, 1H, pyridinone *H*), 3.08–3.10 (m, 1H, NHC*H*), 2.80–2.85 (m, 2H, ArC$H_2$CH$_2$), 2.52–2.57 (m, 2H, ArCH$_2$C$H_2$), 1.07–1.85 (m, 10H, cyclohexyl *H*); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 156.31, 147.14, 141.22, 128.66, 126.38, 113.32, 128.72, 102.49, 96.10, 50.54, 32.56, 25.82, 24.88, 34.79, 34.59; MS (ESI): *m*/*z*, 297.25 [M+H]$^+$.

#### 5.5.3. 4-((2-Methylcyclohexyl)amino)-6-phenethylpyridin-2(1*H*)-one (11c)

Yield 65%; white solid; mp 233–236 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.01 (br s, 1H, N*H*), 7.20–7.31 (m, 5H, Ar*H*), 5.42 (s, 1H, pyridinone *H*), 5.33 (s, 1H, pyridinone *H*), 3.96 (d, $J$ = 8.4 Hz, 1H, cyclohexyl N*H*), 3.46 (m, 1H, NHC*H*), 2.98–3.02 (m, 2H, ArC$H_2$CH$_2$), 2.77–2.81 (m, 2H, ArCH$_2$C$H_2$), 0.87–2.08 (m, 12H, cyclohexyl *H* + cyclohexyl C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 166.48, 156.86, 147.79, 128.63, 128.38, 126.14, 140.57, 97.65, 89.71, 57.28, 52.52, 38.77, 32.98, 25.65, 25.30, 19.32, 34.92, 34.54; MS (ESI): *m*/*z*, 311.30 [M+H]$^+$.

#### 5.5.4. 4-(Cyclopentylamino)-6-phenethylpyridin-2(1*H*)-one (11d)

Yield 75%; white solid; mp 143–145 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 10.39 (br s, 1H, N*H*), 7.17–7.31 (m, 5H, Ar*H*), 6.36 (d, $J$ = 6.4 Hz, 1H, cyclopentyl N*H*), 5.48 (s, 1H, pyridinone *H*), 4.94 (s, 1H, pyridinone *H*), 3.51–3.64 (m, 1H, NHC*H*), 2.81–2.85 (m, 2H, ArC$H_2$CH$_2$), 2.53–2.58 (m, 2H, ArCH$_2$C$H_2$), 1.22–1.90 (m, 8H, cyclopentyl *H*); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 164.70, 156.74, 141.30, 128.77, 126.48, 146.99, 96.82, 89.07, 53.31, 32.64, 24.12, 34.69, 34.49; MS (ESI): *m*/*z*, 283.26 [M+H]$^+$.

### 5.6. General procedure for the synthesis of the compounds 12a–d and 13a–d

Compound **11a**–**d** (2.0 mmol) was dissolved in 10 mL anhydrous THF, and NIS (NBS) (2.1 mmol) was added portionwise to the mixture, which was protected from light and stirred at room temperature overnight. After evaporating the solvent, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **12a**–**d** and **13a**–**d**.

#### 5.6.1. 3-Iodo-6-phenethyl-4-(phenylamino)pyridin-2(1*H*)-one (12a)

Yield 92%; white solid; mp 212–214 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 11.36 (br s, 1H, N*H*), 7.53 (s, 1H, ArN*H*), 7.01–7.33 (m, 10H, Ar*H*), 5.56 (s, 1H, pyridinone *H*), 2.79–2.83 (m, 2H, ArC$H_2$CH$_2$), 2.59–2.63 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 161.82, 154.95, 148.14, 140.18, 129.59, 128.90, 128.73, 126.49, 124.56, 123.75, 140.78, 95.26, 71.22, 34.57, 34.35; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{17}IN_2O$ [M+H]$^+$: 417.2555, found 417.0459.

#### 5.6.2. 4-(Cyclohexylamino)-3-iodo-6-phenethylpyridin-2(1*H*)-one (12b)

Yield 93%; yellow solid; mp 156–158 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.42 (s, 1H, N*H*), 7.20–7.37 (m, 5H, Ar*H*), 5.50 (s, 1H, pyridinone *H*), 4.93 (d, $J$ = 7.6 Hz, 1H, cyclohexyl N*H*), 3.28–3.30 (m, 1H, NHC*H*), 2.99–3.04 (m, 2H, ArC$H_2$CH$_2$), 2.84–2.88 (m, 2H, ArCH$_2$C$H_2$), 0.86–1.93 (m, 10H, cyclohexyl *H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 155.89, 148.68, 140.50, 128.42, 126.18, 111.32, 128.83, 93.71, 51.71, 35.63, 35.29, 33.21, 29.71, 25.47, 24.55; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{23}IN_2O$ [M+H]$^+$: 423.3032, found 423.0928.

#### 5.6.3. 3-Iodo-4-((2-methylcyclohexyl)amino)-6-phenethylpyridin-2(1*H*)-one (12c)

Yield 95%; yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.77 (br s, 1H, N*H*), 7.18–7.40 (m, 5H, Ar*H*), 5.48 (s, 1H, pyridinone *H*), 4.82 (d, $J$ = 8.4 Hz, 1H, cyclohexyl N*H*), 3.55–3.56 (m, 1H, NHC*H*), 3.02–3.06 (m, 2H, ArC$H_2$CH$_2$), 2.86–2.92 (m, 2H, ArCH$_2$C$H_2$), 0.90–1.95 (m, 12H, cyclohexyl *H* + cyclohexyl C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 162.96, 156.35, 148.90, 140.66, 128.91, 128.39, 148.78, 126.13, 93.54, 67.00, 58.51, 53.48, 38.89, 25.50, 25.30, 19.44, 35.75, 35.39; HRMS (ESI): *m*/*z*, calcd. for $C_{20}H_{25}IN_2O$ [M+H]$^+$ 437.3298, found 437.1086.

#### 5.6.4. 4-(Cyclopentylamino)-3-iodo-6-phenethylpyridin-2(1*H*)-one (12d)

Yield 91%; yellow solid; mp 191–193 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.80 (br s, 1H, N*H*), 7.21–7.42 (m, 5H, Ar*H*), 5.59 (s, 1H, pyridinone *H*), 4.95 (d, $J$ = 6.8 Hz, 1H, cyclopentyl N*H*), 3.80–3.88 (m, 1H, NHC*H*), 3.02–3.07 (m, 2H, ArC$H_2$CH$_2$), 2.85–2.89 (m, 2H, ArCH$_2$C$H_2$), 1.48–2.07 (m, 8H, cyclopentyl *H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 162.96, 156.41, 148.88, 128.90, 128.41, 126.15, 140.67, 93.81, 66.97, 54.72, 33.79, 23.82, 35.84, 35.48; HRMS (ESI): *m*/*z*, calcd. for $C_{18}H_{21}IN_2O$ [M+H]$^+$ 409.2766, found 409.0764.

#### 5.6.5. 3-Bromo-6-phenethyl-4-(phenylamino)pyridin-2(1*H*)-one (13a)

Yield 95%; white solid; mp 188–190 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.06 (br s, 1H, N*H*), 7.10–7.42 (m, 10H, Ar*H*),6.71 (s, 1H, ArN*H*), 5.84 (s, 1H, pyridinone *H*), 3.00–3.04 (m, 2H, ArC$H_2$CH$_2$), 2.81–2.85 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 162.06, 151.83, 147.73, 140.43, 129.60, 128.83, 128.43, 126.17, 125.62, 124.28, 138.50, 95.11, 91.89, 35.73, 35.24; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{17}BrN_2O$ [M+H]$^+$ 369.2551, found 369.0599.

#### 5.6.6. 3-Bromo-4-(cyclohexylamino)-6-phenethylpyridin-2(1*H*)-one (13b)

Yield 92%; yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.49 (br s, 1H, N*H*), 7.20–7.31 (m, 5H, Ar*H*), 5.58 (s, 1H, cyclohexyl N*H*), 5.01 (s, 1H, pyridinone *H*), 3.24–3.26 (m, 1H, NHC*H*), 3.01–3.05 (m, 2H, ArC$H_2$CH$_2$), 2.87–2.91 (m, 2H, ArCH$_2$C$H_2$), 1.21–1.92 (m, 10H, cyclohexyl *H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 160.72, 153.13, 147.74, 128.72, 128.47, 126.28, 140.21, 94.73, 89.17, 51.55, 33.18, 25.40, 24.59, 35.47, 35.07; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{23}BrN_2O$ [M+H]$^+$ 375.3027, found 375.1068.

#### 5.6.7. 3-Bromo-4-((2-methylcyclohexyl)amino)-6-phenethylpyridin-2(1*H*)-one (13c)

Yield 96%; yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.73 (br s, 1H, N*H*), 7.20–7.38 (m, 5H, Ar*H*), 5.54 (s, 1H, pyridinone *H*), 4.83 (d, $J$ = 8.8 Hz, 1H, cyclohexyl N*H*), 3.01–3.05 (m, 2H, ArC$H_2$CH$_2$), 2.84–2.88 (m, 2H, ArCH$_2$C$H_2$), 0.91–1.94 (m, 13H, cyclohexyl *H* + cyclohexyl C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 161.43, 153.47, 147.67, 128.85, 128.40, 126.15, 140.61, 93.89, 89.44, 58.14, 38.93, 34.38, 33.90, 25.52, 25.33, 19.39, 35.83, 35.33; HRMS (ESI): *m*/*z*, calcd. for $C_{20}H_{25}BrN_2O$ [M+H]$^+$ 389.3293, found 389.1225.

#### 5.6.8. 3-Bromo-4-(cyclopentylamino)-6-phenethylpyridin-2(1*H*)-one (13d)

Yield 91%; white solid; mp 178–180 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.80 (br s, 1H, N*H*), 7.20–7.39 (m, 5H, Ar*H*), 5.63 (s, 1H, pyridinone *H*), 4.96 (d, $J$ = 6.4 Hz, 1H, cyclopentyl N*H*), 3.77–3.83 (m, 1H, NHC*H*), 3.01–3.05 (m, 2H, ArC$H_2$CH$_2$), 2.84–2.88 (m, 2H, ArCH$_2$C$H_2$), 1.46–2.05 (m, 8H, cyclopentyl *H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 161.44, 153.47, 147.80, 128.81, 128.41, 126.16, 140.60, 94.21, 89.53, 54.41, 33.79, 23.82, 35.86, 35.38; HRMS (ESI): *m*/*z*, calcd. for $C_{18}H_{21}BrN_2O$ [M+H]$^+$ 361.2761, found 361.0903.

#### 5.6.9. 4-Hydroxy-6-phenethylpyridin-2(1*H*)-one (14)

A solution of the compound **4** (4.7 g, 16.4 mmol) in 2 N HCl (10 mL) was heated to reflux for 2 d. After the reaction was completed, $Na_2CO_3$ was added to adjust the mixture to neutral. A white precipitate formed and was filtered off. The solid was recrystallized from ethanol to give the compound **14**.

Yield 73%; white solid; mp 272–274 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 11.23 (br s, 1H, N*H*), 10.52 (s, 1H, O*H*), 7.16–7.30 (m, 5H, Ar*H*), 5.65 (s, 1H, pyridinone *H*), 5.40 (s, 1H, pyridinone *H*), 2.83–2.88 (m, 2H, ArC$H_2$CH$_2$), 2.63–2.68 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 168.12, 165.46, 149.66, 128.81, 128.76, 126.53, 141.07, 98.44, 96.63, 34.52; MS (ESI): *m*/*z*, 214.18 $[M-H]^-$.

#### 5.6.10. 3-Iodo-6-phenethyl-4-phenoxypyridin-2(1*H*)-one (15)

Dichloroiodobenzene (2.7 g, 10.0 mmol) was suspended in water (20 mL) containing sodium carbonate (1.0 g, 9.1 mmol) and stirred for 30 min at room temperature. To this mixture, a solution of compound **14** (2 g, 9.0 mmol) in water (20 mL) containing also sodium carbonate (1.0 g, 9.1 mmol) was added. After stirring for 1 h at room temperature, the precipitate was filtered off, washed with water, dried in vacuo, and suspended in DMF (20 mL). After heating under reflux for 2 h, the solvent was removed in vacuo. The residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **15**.

Yield 95%; white solid; mp 200–202 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 11.97 (br s, 1H, N*H*), 6.95–7.44 (m, 10H, Ar*H*), 5.45 (s, 1H, pyridinone *H*), 2.77–2.81 (m, 2H, ArC$H_2$CH$_2$), 2.64–2.66 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 166.81, 162.80, 154.39, 150.54, 130.69, 128.84, 128.73, 126.56, 125.42, 119.96, 140.54, 97.24, 76.73, 34.57, 34.30; HRMS (ESI): *m*/*z*, calcd. for $C_{19}H_{16}INO_2$ $[M+H]^+$ 418.2403, found 418.0307.

#### 5.6.11. 4-Hydroxy-3-nitro-6-phenethylpyridin-2(1*H*)-one (16)

A suspension of the compound **14** (5.0 g, 23.2 mmol) in 40 mL of acetic acid was stirred at 80 °C until the solution was clear. The nitric acid fuming (1 mL, 23.3 mmol) was added dropwise. The mixture was stirred for 5 min at 80 °C; 50 mL of ice water was added immediately, and the yellow precipitate formed and was filtered off. The solid was washed with water to give the compound **16**.

Yield 75%; yellow solid; mp 244–245 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm) 11.91 (br s, 1H, N*H*), 7.18–7.32 (m, 5H, Ar*H*), 5.82 (s, 1H, pyridinone *H*), 2.84–2.89 (m, 2H, ArC$H_2$CH$_2$), 2.69–2.74 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm) 161.98, 157.26, 152.50, 128.82, 126.68, 140.59, 125.98, 97.39, 34.59, 34.26; MS (ESI): *m*/*z*, 259.32 $[M-H]^-$.

#### 5.6.12. 2-(Methanesulfonyloxy)-3-nitro-6-(2-phenylethyl) pyridin-4-yl methanesulfonate (17)

To a solution of compound **16** (2.8 g, 12.0 mmol) and methanesulfonyl chloride (1.5 mL, 19.0 mmol) in 40 mL of $CH_2Cl_2$ was added triethylamine (1 mL, 7.2 mmol). The obtained mixture was stirred at room temperature until TLC indicated that the starting material was no longer present. The reaction mixture was diluted with water (35 mL), and extracted with $CH_2Cl_2$. The organic layer was washed with water and the organic phase was concentrated to dryness. The residue was purified by column chromatography using EtOAc/petroleum ether (1:5 V/V) as the eluent to give the compound **17**.

Yield 85%; yellow solid; mp 133–135 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.16–7.33 (m, 6H, Ar*H* + pyridinone *H*), 3.51 (s, 3H, C$H_3$), 3.32 (s, 3H, C$H_3$), 3.18–3.23 (m, 2H, ArC$H_2$CH$_2$), 3.08–3.12 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 164.54, 149.87, 148.94, 139.62, 128.71, 128.38, 126.56, 115.52, 41.72, 34.62, 39.52, 39.48; MS (ESI): *m*/*z*, 417.35 $[M+H]^+$.

#### 5.6.13. 3-Nitro-6-phenethyl-4-(phenylthio)pyridin-2-yl methanesulfonate (18)

To a solution of compound **17** (4.2 g, 10 mmol) in 50 mL of $CH_2Cl_2$ was added thiophenol (1.1 mL, 10.1 mmol) dropwise. Then 1 mL of triethylamine was added. The obtained mixture was stirred at room temperature overnight. When the reaction was complete (TLC), the solution was washed with 1N HCl (25 mL) and sat. aq $NaHCO_3$ (25 mL) successively. The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using EtOAc/petroleum ether (1:2 V/V) as the eluent to give the compound **18**.

Yield 72%; yellow solid; mp 160–162 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.01–7.56 (m, 10H, Ar*H*), 6.32 (s, 1H, pyridinone *H*), 3.52 (s, 3H, C$H_3$), 2.88–2.94 (m, 4H, ArC$H_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 161.20, 151.16, 148.94, 130.90, 130.48, 128.55, 128.33, 127.81, 126.32, 139.87, 135.63, 119.66, 41.67, 39.05, 34.53; MS (ESI): *m*/*z*, 431.39 $[M+H]^+$.

#### 5.6.14. 3-Nitro-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (19)

To a solution of 0.2 g (10.0 mmol) of sodium in 50 mL of methanol was added compound **18** (4.3 g, 10.0 mmol). The mixture was heated to reflux for 2 h. When the reaction was complete (TLC), the mixture was subsequently diluted with water (30 mL), acidified with HCl and extracted with $CH_2Cl_2$. Finally, the organic phase was concentrated to dryness. The residue was purified by flash chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **19**.

Yield 70%; yellow solid; mp 213–215 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.23 (br s, 1H, N*H*), 7.10–7.56 (m, 10H, Ar*H*), 5.44 (s, 1H, pyridinone *H*), 2.85–2.89 (m, 2H, ArC$H_2$CH$_2$), 2.72–2.76 (m, 2H, ArCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 157.44, 156.43, 151.18, 135.77, 130.81, 130.23, 128.62, 128.48, 126.53, 139.07, 104.12, 35.54, 34.50; MS (ESI): *m*/*z*, 353.40 $[M+H]^+$.

#### 5.6.15. 3-Amino-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (20)

To a pressure reaction bottle were added compound **19** (50 mg, 0.1 mmol) and Pd/C (0.07 mmol) in 15 mL of $CH_2Cl_2$. The mixture was placed under hydrogen (1 atm) and stirred at room temperature for 2 d. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **20**.

Yield 75%; yellow solid; mp 130–133 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.50 (br s, 1H, N*H*), 7.19–7.32 (m, 10H, Ar*H*), 5.93 (s, 1H, pyridinone *H*), 2.95–2.99 (m, 2H, ArC$H_2$CH$_2$), 2.77–2.81 (m, 2H, ArCH$_2$C$H_2$), 1.28 (s, 2H, N$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 144.41, 140.56, 133.44, 129.29, 128.48, 128.44, 126.83, 126.19, 118.57, 136.32, 133.79, 109.89, 35.31, 34.62; MS (ESI): *m*/*z*, 323.49 $[M+H]^+$.

#### 5.6.16. 3-(Dimethylamino)-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (21)

$NaBH_3CN$ (40 mg, 0.6 mmol) was added portionwise at room temperature to a solution of the compound **20** (50 mg, 0.2 mmol) and HCHO (37% in $H_2O$, 1.4 mmol) in $CH_3CN$ (10 mL). The mixture was stirred at room temperature for 15 min before slow addition of HOAc (0.5 mL). The reaction was stirred at room temperature for 1 h, then basified with 10% aqueous $K_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography using

EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **21**.

Yield 80%; yellow solid; mp 194–196 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 12.93 (br s, 1H, N*H*), 7.18–7.52 (m, 10H, Ar*H*), 5.28 (s, 1H, pyridinone *H*), 2.90–2.94 (m, 2H, ArC$H_2$C$H_2$), 2.87 (s, 6H, NC$H_3$C$H_3$), 2.67–2.71 (m, 2H, ArC$H_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 162.05, 153.49, 140.40, 131.98, 131.21, 129.49, 129.24, 128.47, 128.38, 144.67, 135.76, 126.20, 102.69, 41.81, 29.71, 35.08, 34.93; HRMS (ESI): *m*/*z*, calcd. for $C_{21}H_{22}N_2OS$ $[M+H]^+$ 351.4772, found 351.1523.

### 5.6.17. Ethyl 2-oxo-6-phenethyl-4-(phenylthio)-1,2-dihydropyridine-3-carboxylate (22a)

A mixture of the compound **5** (3.7 g, 12.0 mmol) and benzenethiol (1.3 mL, 13.0 mmol) in 50 mL of ethanol was stirred until homogeneity. 1 mL of triethylamine was added dropwise. The obtained mixture was heated to reflux for 2 d. After cooling and removing the solvent, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **22a**.

Yield 83%; white solid; mp 178–180 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.23 (br s, 1H, N*H*), 7.10–7.49 (m, 10H, Ar*H*), 5.45 (s, 1H, pyridinone *H*), 4.40 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 2.84–2.88 (m, 2H, ArC$H_2$C$H_2$), 2.69–2.73 (m, 2H, ArC$H_2$C$H_2$), 1.33 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 165.83, 162.07, 158.21, 149.91, 135.52, 129.98, 129.86, 129.78, 128.43, 126.29, 139.80, 115.27, 104.51, 61.41, 35.23, 34.40, 14.23; MS (ESI): *m*/*z*, 380.68 $[M+H]^+$.

### 5.6.18. Ethyl 2-oxo-6-phenethyl-4-phenoxy-1,2-dihydropyridine-3-carboxylate (22b)

To a suspension of the compound **5** (0.1 g, 0.3 mmol) in 20 mL of anhydrous DMF was added $K_2CO_3$ (70 mg, 0.5 mmol). Then, phenol (0.04 g, 0.5 mmol) was added. The mixture was heated to reflux for 8 h carefully. After cooling, the reaction mixture was subsequently diluted with water (20 mL), acidified with HCl and extracted with $CH_2Cl_2$. The organic phase was concentrated to dryness. The residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **22b**.

Yield 89%; white solid; mp 182–184 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.40 (br s, 1H, N*H*), 7.02–7.42 (m, 10H, Ar*H*), 5.53 (s, 1H, pyridinone *H*), 4.35 (q, *J* = 7.2 Hz, 2H, OC$H_2$CH$_3$), 2.93–2.97 (m, 2H, ArC$H_2$C$H_2$), 2.78–2.83 (m, 2H, ArC$H_2$C$H_2$), 1.28 (t, *J* = 7.2 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 165.87, 164.66, 164.24, 153.91, 139.87, 128.55, 128.47, 126.30, 125.43, 130.00, 120.67, 97.48, 61.33, 35.72, 34.83, 14.17; MS (ESI): *m*/*z*, 364.35 $[M+H]^+$.

## 5.7. General procedure for the synthesis of the compounds 23a–b

The compound **22a**–**b** (2.0 mmol) was dissolved in 10 mL of dry THF. After cooling to −78 °C, a total of 7 mL (20 mmol) of methyllithium (3 M) was added in one portion. The reaction mixture was kept at -78 °C for 1 h and at 0 °C for 2 h, then 12 h at room temperature. The reaction was ended with 2 mL of water and slowly neutralized with cold 1 N HCl. The organic layer was separated, and the aqueous phase was extracted twice with 10 mL of ethyl acetate. The combined organic solution was subsequently washed with sodium bicarbonate and brine, and dried over the anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compounds **23a**–**b**.

### 5.7.1. 3-(2-Hydroxypropan-2-yl)-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (23a)

Yield 70%; yellow solid; mp 126–129 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.11 (br s, 1H, N*H*), 7.07–7.45 (m, 10H, Ar*H*), 5.59 (s, 1H, pyridinone *H*), 5.46 (s, 1H, O*H*), 2.82–2.91 (m, 2H, ArC$H_2$C$H_2$), 2.64–2.71 (m, 2H, ArC$H_2$C$H_2$), 2.06 (s, 3H, C$H_3$), 1.81 (s, 3H, C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 151.16, 144.21, 139.81, 135.19, 134.97, 129.75, 129.60, 129.39, 128.44,128.37, 135.59, 126.30, 107.77, 60.39, 34.56, 34.37, 29.91, 21.04; MS (ESI): *m*/*z*, 364.47 $[M-H]^-$.

### 5.7.2. 3-(2-Hydroxypropan-2-yl)-6-phenethyl-4-phenoxypyridin-2(1*H*)-one (23b)

Yield 71%; white solid; mp 168–170 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.35 (br s, 1H, N*H*), 8.00 (s, 1H, O*H*), 6.90–7.40 (m, 10H, Ar*H*), 5.59 (s, 1H, pyridinone *H*), 2.97–3.01 (m, 2H, ArC$H_2$-CH$_2$), 2.80–2.84 (m, 2H, ArC$H_2$C$H_2$), 1.70 (s, 6H, COHC$H_3$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 167.62, 162.73, 154.53, 139.60, 130.08, 128.55, 128.52, 126.36, 124.60, 119.90, 147.29, 119.65, 101.02, 72.47, 34.74, 30.26; MS (ESI): *m*/*z*, 348.40 $[M-H]^-$.

### 5.7.3. 6-Phenethyl-4-(phenylthio)-3-(prop-1-en-2-yl)pyridin-2(1*H*)-one (24a)

To a solution of the compound **23a** (40 mg, 0.1 mmol) in 20 mL of anhydrous THF, the thionyl chloride (0.02 mL, 0.2 mmol) was added in one portion. The mixture was stirred at room temperature overnight. After the evaporation of the solvent, the residue was dissolved in 10 mL of dichloromethane. This solution was basified with a cold sodium bicarbonate solution, washed with brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the compound **24a**.

Yield 70%; white solid; mp 183–185 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.18–7.49 (m, 10H, Ar*H*), 5.48 (s, 1H, pyridinone *H*), 5.46 (s, 1H, C=C$H_2$), 5.11 (s, 1H, C=C$H_2$), 2.86–2.90 (m, 2H, ArC$H_2$C$H_2$), 2.66–2.70 (m, 2H, ArC$H_2$C$H_2$), 2.13 (s, 3H, C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 162.12, 157.63, 151.68, 145.80,140.21, 135.22, 131.00, 129.60, 129.31, 128.53, 128.37, 140.32, 126.23, 118.47, 104.11, 35.40, 34.87, 21.56; MS (ESI): *m*/*z*, 348.61 $[M+H]^+$.

### 5.7.4. 6-Phenethyl-4-phenoxy-3-(prop-1-en-2-yl)pyridin-2(1*H*)-one (24b)

The compound **23b** (40 mg, 0.1 mmol) was dissolved in 10 mL of acetic anhydride. The mixture was heated to reflux for 1 h. After cooling, the reaction mixture was subsequently diluted with water (10 mL), extracted with $CH_2Cl_2$. Finally, the organic layer was washed with water and the organic phase was concentrated to dryness. The residue was purified by column chromatography using EtOAc/petroleum ether (1:5 V/V) as the eluent to give the compound **24b**.

Yield 80%; colorless liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 6.97–7.41 (m, 10H, Ar*H*), 6.32 (s, 1H, pyridinone *H*), 5.34 (s, 1H, C=C$H_2$), 5.07 (s, 1H, C=C$H_2$), 2.91–2.98 (m, 4H, ArC$H_2$C$H_2$), 2.07 (s, 3H, C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.11, 169.12, 159.92, 164.26,154.67, 136.55, 130.10, 128.47, 128.32, 125.93, 125.08, 120.30, 117.80, 109.43, 39.53, 35.52, 21.03; MS (ESI): *m*/*z*, 332.47 $[M+H]^+$.

## 5.8. General procedure for the synthesis of the compounds 25a–b

To a pressure reaction bottle were added **24a**–**b** (0.08 mmol) and Pd/C (0.08 mmol) in 15 mL of $CH_2Cl_2$. The mixture was placed under hydrogen (1 atm) and stirred at room temperature overnight. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography using EtOAc/petroleum ether (1:1 V/V) as the eluent to give the target products **25a**–**b**.

#### 5.8.1. 3-Isopropyl-6-phenethyl-4-(phenylthio)pyridin-2(1*H*)-one (25a)

Yield 80%; yellow solid; mp 138–140 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.17–7.46 (m, 10H, Ar*H*), 5.47 (s, 1H, pyridinone *H*), 3.40–3.47 (m, 1H, $CHCH_3CH_3$), 2.89–2.93 (m, 2H, $ArCH_2CH_2$), 2.65–2.69 (m, 2H, $ArCH_2CH_2$), 1.43 (d, $J$ = 6.8 Hz, 6H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 163.32, 149.45, 144.52,134.48, 131.63, 129.75, 129.52, 128.82, 128.47, 128.37, 140.43, 126.17, 104.97, 34.94, 34.86, 29.79, 19.29; HRMS (ESI): *m*/*z*, calcd. for $C_{22}H_{23}NOS$ $[M+H]^+$ 350.4891, found 350.1563.

#### 5.8.2. 3-Isopropyl-6-phenethyl-4-phenoxypyridin-2(1*H*)-one (25b)

Yield 95%; white solid; mp 189–191 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 13.28 (br s, 1H, N*H*), 6.95–7.40 (m, 10H, Ar*H*), 5.58 (s, 1H, pyridinone *H*), 3.53–3.61 (m, 1H, $CHCH_3CH_3$), 2.99–3.04 (m, 2H, $ArCH_2CH_2$), 2.78–2.82 (m, 2H, $ArCH_2CH_2$), 1.38 (d, $J$ = 6.8 Hz, 6H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 166.59, 163.17, 155.54, 146.61, 129.85, 128.58, 128.40, 126.19, 123.91, 121.39, 140.52, 119.28, 99.53, 35.41, 35.19, 24.54, 20.23; HRMS (ESI): *m*/*z*, calcd. for $C_{22}H_{23}NO_2$ $[M+H]^+$ 334.4235, found 334.1802.

### 5.9. Biological testing assays

#### 5.9.1. Assay for measuring the inhibitory activity of compounds against HIV-1 RT

Oligo(dT) (TaKaRa Co., Japan) was immobilized via its 5′-terminal phosphate to Covalink-NH microtiter plates (NUNC Co., Denmark). The biotin-dUTP was incorporated by reverse transcriptase (Sigma). Briefly, a serial concentration of inhibitor was added to the mixture, which contained 1 mol/L Tris-HCl (pH 8.3), 1 mol/L $MgCl_2$, 1 mol/L KCl, 0.5 mol/L DTT (D,L,-dithiothreitol), 1% BSA (Albumin Bovine V), 5 mg/mL poly (A), 5 mmol/L biotin-11-dUTP, and 0.1 mmol/L dTTP. The reaction mixture was incubated at 37 °C for 1 h and washed with a buffer containing 100 mmol/L Tris–HCl (pH 7.5), 0.1 mol/L NaCl, 0.1 mol/L $MgCl_2$, and 0.02% Tween-20. After 100 μL of 1% BSA was added to each well and incubated at room temperature for another 1 h, the plate was washed with the same buffer. Before further incubation at 37 °C for 1 h, 50 μL of SA-ALP (Alkaline Phosphatase Streptavidin) solution was added per well and washed again as above. Finally, 100 μL of PNPP (p-nitrophenyl phosphate, disodium) (1 mg/mL, pH 9.5) was added and incubated at 37 °C for 30 min. The reaction was stopped by addition of 0.5 M NaOH. The inhibitory activity of the compounds was detected and quantified using a colorimetric streptavidin-alkaline phosphatase reporter system.

#### 5.9.2. Assay for measuring the inhibitory activity of compounds on HIV-$1_{SF33}$ infectious

TZM-bl cells, HIV-$1_{SF33}$ were obtained from the NIH AIDS Research and Reference Reagent Program (Germantown, MD). The inhibitory activity of target compounds on infection by a laboratory-adapted HIV-1 strain SF33 were tested in TZM-bl cells. Briefly, TZM-bl cells ($4 \times 10^4$/well) were infected by addition of 200 $TCID_{50}$ of HIV-1, followed by incubation for 2 h at 37 °C before addition of compounds at serial dilutions. After further incubation at 37 °C for 7 days, p24 was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Vironostika HIV-1 Microelisa system; BioMérieux; Marcy l'Etoile, France).The concentration of a compound for inhibiting 50% viral replication ($EC_{50}$) was determined by nonlinear regression using GraphPad Prism 5.01.

#### 5.9.3. Assessment of in vitro cytotoxicity in MT-4 cells

An XTT assay, as previously described,[18] was used to assess the cytotoxicity of target compounds to MT4 cells. Briefly, a compound at graded concentrations was added to MT4 cells ($5 \times 10^4$/well), followed by incubation at 37 °C for 3 days. Ten microliters of CCK-8 reagent were added to the cells. After incubation at 37 °C for 4 h to allow color development of the XTT formazan product, the absorbance of each well was then read at 450 nm in a Victor2 1420 Multilabel Counter (Wallace-PerkinElmer Life and Analytical Sciences Inc., Boston, MA). The percent of cytotoxicity and $CC_{50}$ (concentration causing 50% cytotoxicity) were calculated as previously described.[19]

### 5.10. Molecular modeling

The docking studies were conducted by using software GOLD 3.0.1 and the protein crystal structures of wild type RT/1 complex (PDB ID: 1RT2). Following the default setting of Chemscore in the software tool, top scored docked poses were visually inspected for each ligand in the DS 2.5 based on relevant molecules. The radius of the binding site sphere was defined by the original ligand as 12.4 Å.

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