Tetrahedron 68 (2012) 4838–4845

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile isocyanide-based one-pot three-component regioselective synthesis of highly substituted pyridin-2(1*H*)-one derivatives at ambient temperature

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ARTICLE INFO

Article history:
Received 24 December 2011
Received in revised form 21 March 2012
Accepted 30 March 2012
Available online 13 April 2012

Keywords:
Multicomponent reactions
Isocyanides
DMAD
N-Arylidene-2-cyanoacetohydrazides
Pyridin-2-one derivatives

ABSTRACT

A novel one-pot three-component regioselective synthesis of highly substituted pyridin-2-one derivatives starting from simple and readily available starting materials is described. The reactive zwitterionic intermediate generated by the addition of an isocyanide to dimethyl acetylenedicarboxylate (DMAD) was trapped with *N*-arylidene-2-cyanoacetohydrazides to afford the title compounds in moderate to good yields at room temperature without using any catalyst and other additives.

1. Introduction

The development of simple synthetic routes toward widely used organic compounds from readily available starting materials is one of the major tasks in organic synthesis. Multicomponent reactions (MCRs), by virtue of their convergence, facile execution, and generally high yields of products, have attracted much attention from the point of combinatorial chemistry.[1,2]

Moreover, the rich and fascinating chemistry that stems from MCR provides a robust approach for the synthesis of diverse and complex 'drug-like' heterocyclic compounds. Particularly, isocyanide-based multicomponent reactions (IMCRs) have occupied a major position in multicomponent reactions in recent years.[3]

The initially formed zwitterionic intermediate from DMAD and isocyanides has been shown to undergo further reaction with different electrophilic reagents, leading to a variety of complex heterocyclic compounds. Due to the unique reactivity of the isocyanide functional group, there are many reactions reported in the literature involving isocyanides and DMAD.[4] These reactions have been the subject of detailed investigation by a number of research groups.[5–7] Although significant progress has been made in IMCRs,[8] there is still a high demand for new processes aimed at the rapid assembly of heterocyclic molecules.

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry.[9] Functionalized pyridin-2(1*H*)-ones and their dihydro- and tetrahydro derivatives, as privileged heterocyclic scaffolds, represent an important class of organic heterocycles for their presence in numerous natural products and synthetic organic compounds with diverse bio-, physio-, and pharmacological activities, such as antibacterial[10] and antifungal[11] activities, anti-cancer/antitumor,[12] and HIV-reverse transcriptase inhibitors.[13] Due to their diverse range of biological activities, pyridin-2(1*H*)-ones are recognized as privileged structures making these structural motifs attractive targets for library preparation.[14]

Though many literature reported synthetic approaches for pyridin-2(1*H*)-ones,[15] to the best of our knowledge, so far, there have been no reports on the application of *N*-arylidene-2-cyanoacetohydrazides along with isocyanides and DMAD to synthesize pyridin-2-one derivatives. In continuing our interest in IMCRs,[16] and based on our previous endeavors in exploring novel and practical MCRs to synthesize useful heterocyclic compounds,[17] herein we outline a facile and efficient synthetic approach for the construction of highly substituted pyridin-2(1*H*)-ones.

2. Results and discussion

Our approach toward the design and development of new domino and multicomponent procedures involves the use of *N*-arylidene-2-cyanoacetohydrazides **3** that contains a number of chemically distinct functionalities, which could be selectively

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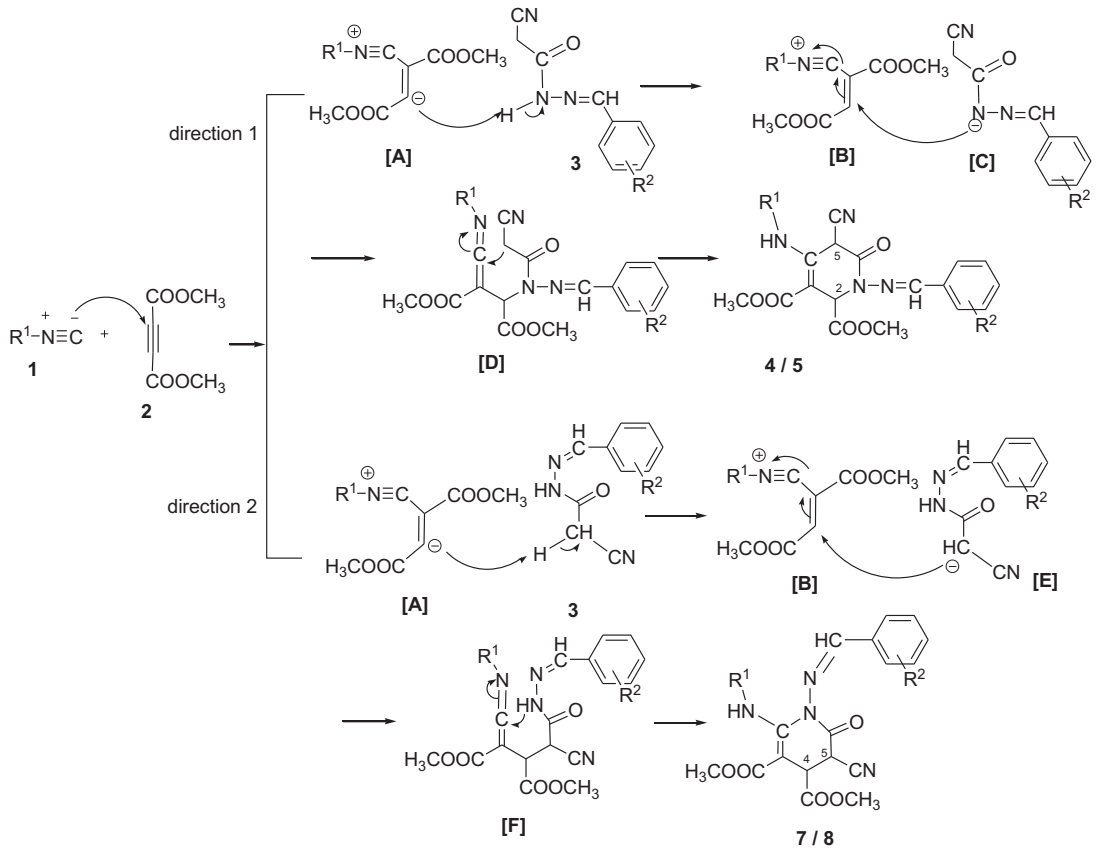
doi:10.1016/j.tet.2012.03.124

reacted with isocyanides **1** and DMAD **2** to generate molecular diversity.

The zwitterionic intermediate **[A]** derived from isocyanides **1** and DMAD **2** could react with *N*-arylidene-2-cyanoacetohydrazides **3** in two manners (Scheme 1). In direction 1, the **[A]** captures the NH



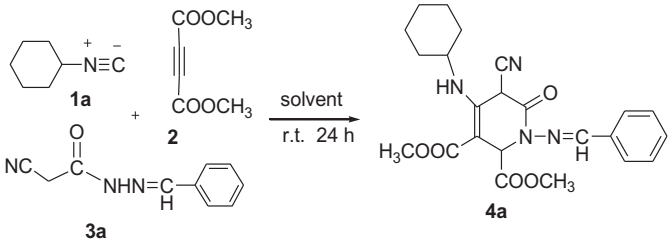
Scheme 1.

of **3** to produce **[B]**, meanwhile the resulting anion **[C]** is produced from **3**, which would then react with the cation **[B]** through Michael addition to give intermediate **[D]**, which undergoes intramolecular cyclization to deliver dimethyl 1-(arylideneamino)-5-cyano-4-(alkylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylates **4**/**5**. In direction 2, however, the **[A]** abstracts a proton of methylene of **3** to give **[B]**, but the resulting anion **[E]** instead of **[C]** is obtained from **3**, which would then reacts with the cation **[B]** to give the intermediate **[F]**, next, an intramolecular cyclization of **[F]** leads to the formation of (*Z*)-dimethyl 1-(arylideneamino)-5-cyano-2-(alkylamino)-6-oxo-1,4,5,6-tetrahydropyridine-3,4-dicarboxylates **7**/**8**.

In our experiment, the reaction of cyclohexyl isocyanide **1a** with DMAD **2** and *N*-benzylidene-2-cyanoacetohydrazide **3a** occurred smoothly in CH_2Cl_2 at room temperature without any catalyst to afford dimethyl 1-(benzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate **4a** exclusively in good yield of 70%. And the structure of **4a** was deduced on the basis of ^{1}H NMR spectrum, where two singlets at δ=4.73 and 5.51 ppm for 2-CH and 5-CH were identified, respectively. Whereas two doublets for 4-CH and 5-CH due to coupling interaction should be observed if another regioisomer **7a** would be formed. These results indicated that the reaction proceeded as the direction 1 rather than the direction 2; and also suggested that our three-component reaction is highly regioselective.

Choosing an appropriate solvent is of crucial importance for the successful synthesis. Firstly, we examined the effects of various solvents on the reaction using **1a**, **2**, and **3a** as model substrates at room temperature without using any catalyst for 24 h (Table 1). The results showed that the reaction did not occur in ethanol even

Table 1
Optimization of solvents for the synthesis of **4a**



Entry	Solvent	Time (h)	Isolated yield (%)
1	EtOH	24	—
2	MeOH	24	18
3	CH_2Cl_2	24	70
4	CH_3CN	24	55
5	THF	24	65
6	Toluene	24	40
7	Acetone	24	30

though the reaction time was prolonged to 48 h (Table 1, entry 1); and in methanol also gave only 18% yield (Table 1, entry 2). Then CH_2Cl_2, acetonitrile, THF, toluene, and acetone were examined at ambient temperature under catalyst-free conditions; the corresponding product **4a** was obtained in yields of 70%, 55%, 65%, 40%, and 30%, respectively (Table 1, entries 3–7). It was then concluded that CH_2Cl_2 was the optimal solvent for this reaction. However, subsequently prolonging the reaction time cannot promote the reaction. So the optimized conditions were CH_2Cl_2 as a solvent at room temperature without using any catalyst.

To evaluate the use of this approach, a variety of **3** and **1** were employed to react with **2** under the optimized conditions. Initially, to test the scope of substrates **3**, cyclohexyl isocyanide **1a** and **2** were used as model substrates (Table 2, entries 1–19). As indicated in Table 2, **3** bearing either electron-withdrawing or electron-donating substituents on the aryl ring could be converted smoothly to their corresponding products in good to excellent yields. However, the position of substituents also has some influence on the reaction. The results suggested that the substituents at *para*- and *meta*-positions afforded higher yields than those counterparts at *ortho*-position (Table 2, entries 2, 5, and 8).

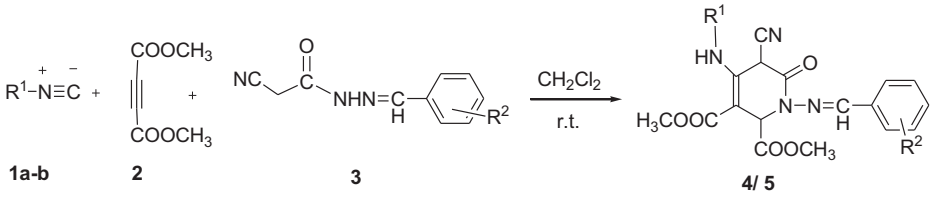
As for the isocyanide component of the multicomponent reaction, we adopted initially cyclohexyl isocyanide, ethyl isocyanideacetate. In all these cases, the reactions conducted smoothly to give the corresponding products, respectively. The results are summarized in Table 2.

The structures of the products **4**/**5** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data. Take **4a**, for example. In its IR spectrum, a strong absorption at 2201 cm^{-1} was subject to C≡N group. The two strong characteristic bands of ester carbonyl groups were found at 1731 and 1686 cm^{-1}, respectively. The carbonyl group on the tetrahydropyridine ring appeared at 1629 cm^{-1} as a strong peak. The imine group was found at 1653 cm^{-1} as a medium peak.

The ^{1}H NMR spectrum of **4a** consisted of a multiplet at δ 1.26–2.04 ppm for the cyclohexyl ring, two singlets at δ 3.73, 3.78 ppm for two CH_3O groups, a multiplet at δ 3.62 ppm for cyclohexyl CH linked to NH, two singlets at δ 4.73, 5.51 ppm for CH–CN, CH–CO_2Me, respectively; the characteristic signals at δ 7.42–7.69 ppm for aromatic ring, a singlet at δ 7.83 ppm for CH=N, and a broad singlet at δ 8.32 ppm for NH group. In the ^{13}C NMR spectrum, the peak at δ 169.0 ppm was assigned to the carbonyl resonance on the tetrahydropyridine ring. The two ester carbonyl signals were visible at δ 156.9, 158.8 ppm, respectively. The cyano carbon signal appeared at δ 117.3 ppm and the two methoxy carbons were observed at δ 52.3, 53.0 ppm, respectively. The signal at δ 55.4 was attributed to the carbon atom of cyclohexyl ring adjacent to the nitrogen. All other signals were also in good agreement with the proposed structure.

Encouraged by the success of the above reactions, we replaced **1a** and **1b** with *tert*-butyl isocyanide **1c** to investigate this reaction with **2** and **3a** under the same conditions as described above.

Table 2
The synthesis of compounds **4a**–**s** and **5a**–**g**



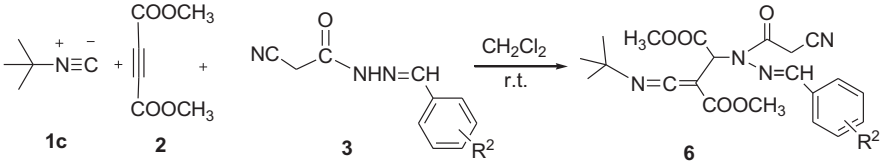
1a, R^1 = cyclohexyl; **1b**, R^1 = ethoxycarbonylmethyl

Entry	1	3	R^2	Product	Time (h)	Isolated yield (%)
1	**1a**	**3a**	H	**4a**	24	60
2	**1a**	**3b**	4-F	**4b**	18	72
3	**1a**	**3c**	4-Cl	**4c**	18	68
4	**1a**	**3d**	4-Br	**4d**	18	67
5	**1a**	**3e**	3-F	**4e**	20	65
6	**1a**	**3f**	3-Cl	**4f**	20	66
7	**1a**	**3g**	3-Br	**4g**	20	64
8	**1a**	**3h**	2-F	**4h**	22	50
9	**1a**	**3i**	2-Cl	**4i**	22	46
10	**1a**	**3j**	2,3-Cl_2	**4j**	19	70
11	**1a**	**3k**	4-NO_2	**4k**	18	71
12	**1a**	**3l**	3-NO_2	**4l**	20	62
13	**1a**	**3m**	4-CF_3	**4m**	20	72
14	**1a**	**3n**	4-CH_3	**4n**	24	63
15	**1a**	**3o**	3-CH_3	**4o**	24	59
16	**1a**	**3p**	4-OCH_3	**4p**	26	58
17	**1a**	**3q**	3-OCH_3	**4q**	26	66
18	**1a**	**3r**	3,4-OCH_3	**4r**	28	68
19	**1a**	**3s**	3,4-OCH_2O	**4s**	28	65
20	**1b**	**3a**	H	**5a**	24	61
21	**1b**	**3b**	4-F	**5b**	20	75
22	**1b**	**3c**	4-Cl	**5c**	20	70
23	**1b**	**3e**	3-F	**5d**	20	68
24	**1b**	**3k**	4-NO_2	**5e**	19	73
25	**1b**	**3n**	4-CH_3	**5f**	22	55
26	**1b**	**3p**	4-OCH_3	**5g**	22	50

Unfortunately, the intramolecular nucleophilic attack by the methylene group on the activated allenyl moiety did not occur, and the isolated compound was intermediate **6a**. Then, other seven *N*-arylidene-2-cyanoacetohydrazides **3** were employed to verify this reaction (Table 3). The results were in accordance with **3a**, which may be subject to the steric hindrance of *tert*-butyl group.

The structures of the products **6** were characterized from their IR, ^{1}H NMR, and ^{13}C NMR and HRMS spectra. The IR spectrum of **6a** exhibited a strong absorption at 2091 cm^{-1} corresponding to N=C=C stretching vibration. The mass spectrum of **6a** displayed the molecular ion ([M+H]$^+$) peak at *m*/*z*=413.1815, which is consistent with dimethyl 2-(2-benzylidene-1-(2-cyanoacetyl)hydrazinyl)-3-((*tert*-butylimino)methylene)succinate.

Table 3
The synthesis of compounds **6a**–**h**



Entry	3	R^2	Product	Time (h)	Isolated yield (%)
1	**3a**	H	**6a**	24	70
2	**3b**	4-F	**6b**	20	76
3	**3c**	4-Cl	**6c**	20	74
4	**3d**	4-Br	**6d**	20	71
5	**3g**	3-Br	**6e**	20	67
6	**3h**	2-F	**6f**	21	65
7	**3l**	3-NO_2	**6g**	20	68
8	**3p**	4-OCH_3	**6h**	24	65

The structures of all compounds **6** were unequivocally established by X-ray monocrystal diffraction analysis of **6g** (Fig. 1).[18]

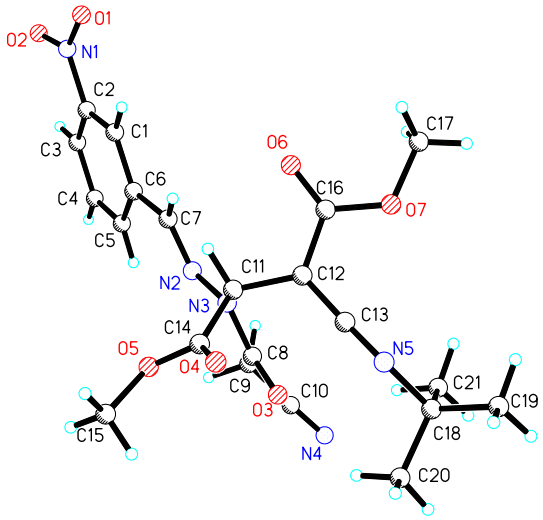


Fig. 1. The X-ray crystal structure of **6g**.

3. Conclusion

In conclusion, we have successfully described a novel one-pot three-component reaction for the synthesis of highly substituted pyridin-2-one derivatives. The present procedure has advantages, such as the ready availability of the starting materials, easy workup procedure, mild reaction conditions, good functional group tolerance, highly regioselectivity, and moderate to good yields. Undoubtedly, this synthetic strategy opens a convenient, effective way to construct the pyridin-2-one derivatives. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

4. Experimental section

4.1. General

All the reagents were purchased from local suppliers and used without purification. Melting points were recorded on an RY-1 microscopic melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on 500 MHz and ^{13}C NMR spectra were recorded on 125 MHz in $CDCl_3$ or DMSO-d_6 by using a Bruker Avance 500 spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS as internal standard. IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer and only major peaks are reported in cm^{-1}. HRMS were performed on Ultima Global and Varian spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on Rigaku Saturn 724+ CCD instrument. The *N*-arylidene-2-cyanoacetohydrazides **3** were synthesized by the aromatic aldehydes and 2-cyanoacetohydrazide.[19]

4.2. General procedure for the preparation of products 4a–s, 5a–g, and 6a–h

A mixture of isocyanides **1** (1.0 mmol), DMAD **2** (1.0 mmol), and *N*-arylidene-2-cyanoacetohydrazides **3** (1.0 mmol) was stirred in CH_2Cl_2 for the appropriate reaction time at room temperature. After completion of the reaction, as indicated by TLC The solvent was removed under vacuum, and the residue was separated by column chromatography (silica gel, petroleum ether/EtOAc, 8:1, v/v) to give the product **4a**–**s**, **5a**–**g**, and **6a**–**h**.

*4.2.1. Dimethyl 1-(benzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4a**).* White powder, mp 185–187 °C; IR (KBr, cm^{-1}): 3447, 2930, 2851, 2201, 1731, 1686, 1629, 1467, 1411, 1324, 1283, 1099, 774, 721, 690; δ_H (500 MHz, $CDCl_3$): 1.26–2.04 (m, 10H, 5× CH_2 of cyclohexyl), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.90 (m, 1H, CH of cyclohexyl), 4.73 (s, 1H, CH–CN), 5.51 (s, 1H, CH–COO), 7.42–7.69 (m, 5H, ArH), 7.83 (s, 1H, CH=N), 8.32 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.2,

53.0, 55.4, 70.5, 117.3, 127.5, 128.8, 130.7, 133.3, 142.9, 156.9, 158.8, 166.8, 169.0; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{27}N_4O_5$, 439.1981; found, 439.1969.

*4.2.2. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(4-fluorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4b**).* White powder, mp 186–188 °C; IR (KBr, cm^{-1}): 3446, 2937, 2854, 2209, 1738, 1691, 1508, 1463, 1412, 1329, 1286, 1200, 1098, 838, 776, 728; δ_H (500 MHz, $CDCl_3$): 1.22–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.94 (m, 1H, CH of cyclohexyl), 4.70 (s, 1H, CH–CN), 5.48 (s, 1H, CH–COO), 7.09–7.13 (t, J=8.5 Hz, 2H, ArH), 7.66–7.69 (m, 2H, ArH), 7.81 (s, 1H, CH=N), 8.31 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.7, 50.8, 51.2, 52.4, 53.0, 55.5, 70.6, 116.0 (d, $^2J_{CF}$=22 Hz), 117.1, 129.4 (d, $^3J_{CF}$=8.0 Hz), 129.6, 141.8, 156.9, 158.7, 164.2 (d, $^1J_{CF}$=251 Hz), 166.8, 168.9; HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{23}H_{25}FN_4O_5Na$, 479.1701; found, 479.1698.

*4.2.3. Dimethyl 1-(4-chlorobenzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4c**).* White powder, mp 185–187 °C; IR (KBr, cm^{-1}): 3263, 2930, 2856, 2206, 1746, 1727, 1690, 1635, 1461, 1408, 1294, 1097, 762; δ_H (500 MHz, $CDCl_3$): 1.20–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.94 (m, 1H, CH of cyclohexyl), 4.71 (s, 1H, CH–CN), 5.49 (s, 1H, CH–COO), 7.39–7.40 (d, J=8.0 Hz, 2H, ArH), 7.61–7.63 (d, J=8.0 Hz, 2H, ArH), 7.79 (s, 1H, CH=N), 8.31 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.4, 53.0, 55.7, 70.5, 117.0, 128.6, 129.1, 131.9, 136.7, 141.2, 156.9, 158.6, 166.8, 168.8; HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{23}H_{25}ClN_4O_5Na$, 495.1406; found, 495.1404.

*4.2.4. Dimethyl 1-(4-bromobenzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4d**).* White powder, mp 193–197 °C; IR (KBr, cm^{-1}): 3445, 2930, 2851, 2204, 1731, 1687, 1636, 1468, 1411, 1324, 1289, 1098, 819, 774, 722; δ_H (500 MHz, $CDCl_3$): 1.20–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.93 (m, 1H, CH of cyclohexyl), 4.89 (s, 1H, CH–CN), 5.75 (s, 1H, CH–COO), 7.54 (s, 4H, ArH), 7.77 (s, 1H, CH=N), 8.32 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.3, 53.2, 55.7, 70.5, 117.1, 125.1, 128.9, 132.1, 132.3, 141.5, 156.8, 158.6, 166.8, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}BrN_4O_5$, 517.1087; found, 517.1093.

*4.2.5. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3-fluorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4e**).* White powder, mp 182–184 °C; IR (KBr, cm^{-1}): 3446, 2930, 2860, 2201, 1735, 1687, 1630, 1467, 1410, 1326, 1268, 1221, 1101, 775, 723; δ_H (500 MHz, $CDCl_3$): 1.26–2.04 (m, 10H, 5× CH_2 of cyclohexyl), 3.74 (s, 3H, OCH_3),3.78 (s, 3H, OCH_3), 3.95 (m, 1H, CH of cyclohexyl), 4.73 (s, 1H, CH–CN), 5.49 (s, 1H, CH–COO), 7.11–7.13 (m, 1H, ArH), 7.36–7.43 (m, 3H, ArH), 8.14 (s, 1H, CH=N), 8.33 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.9, 50.8, 51.3, 52.3, 53.1, 55.9, 70.6, 113.6 (d, $^2J_{CF}$=22 Hz), 117.0, 117.6 (d, $^2J_{CF}$=21 Hz), 123.7, 130.5, 135.6, 141.2, 156.8, 158.6, 163.0 (d, $^1J_{CF}$=246 Hz), 166.8, 168.8; HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{23}H_{25}FN_4O_5Na$, 479.1701; found, 479.1705.

*4.2.6. Dimethyl 1-(3-chlorobenzylideneamino)-5-cyano-2-(cyclohexylamino)-6-oxo-1,4,5,6-tetrahydropyridine-3,4-dicarboxylate (**4f**).* White powder, mp 186–182 °C; IR (KBr, cm^{-1}): 3448, 2930, 2859, 2201, 1731, 1687, 1630, 1467, 1409, 1324, 1101, 775, 719; δ_H (500 MHz, $CDCl_3$): 1.36–2.05 (m, 10H, 5× CH_2 of cyclohexyl), 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.98 (m, 1H, CH of cyclohexyl), 4.75 (s, 1H, CH–CN), 5.50 (s, 1H, CH–COO), 7.35–7.41 (m, 2H, ArH), 7.55–7.56 (d, J=7.5 Hz, 1H, ArH), 7.68 (s, 1H, ArH), 7.77 (s, 1H, CH=N), 8.31 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.4, 25.3, 33.4, 33.8, 50.9, 51.3, 52.4, 53.2, 56.1, 70.5, 117.0, 125.8, 127.3, 130.1, 130.6, 135.1, 135.2, 141.2, 156.9, 158.6, 166.8, 168.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}ClN_4O_5$, 473.1592; found, 473.1586.

*4.2.7. Dimethyl 1-(3-bromobenzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4g**).* White powder, mp 170–171 °C; IR (KBr, cm^{-1}): 3446, 2929, 2848, 2201, 1731, 1687, 1634, 1459, 1408, 1322, 1099, 787, 775, 726; δ_H (500 MHz, $CDCl_3$): 1.36–2.08 (m, 10H, 5× CH_2 of cyclohexyl), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.97 (m, 1H, CH of cyclohexyl), 4.78 (s, 1H, CH–COO), 5.53 (s, 1H, CH–CN), 7.30–7.79 (m, 4H, ArH), 7.86 (s, 1H, CH=N), 8.32 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.3, 53.1, 56.0, 70.4, 117.0, 123.0, 126.1, 130.2, 130.3, 133.5, 135.4, 141.0, 156.8, 158.5, 166.7, 168.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}BrN_4O_5$, 517.1087; found, 517.1061.

*4.2.8. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(2-fluorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4h**).* White powder, mp 180–182 °C; IR (KBr, cm^{-1}): 3442, 2932, 2856, 2208, 1746, 1691, 1636, 1460, 1408, 1294, 1097, 762; δ_H (500 MHz, $CDCl_3$): 1.23–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.94 (m, 1H, CH of cyclohexyl), 4.73 (s, 1H, CH–CN), 5.52 (s, 1H, CH–COO), 7.11 (t, J=9.0 Hz, 1H, ArH), 7.20 (t, J=7.5 Hz, 1H, ArH), 7.40 (q, J=6.5 Hz, 1H, ArH), 7.88 (t, J=7.0 Hz, 1H, ArH), 8.07 (s, 1H, CH=N), 8.29 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.2, 53.0, 55.8, 70.6, 115.9 (d, $^2J_{CF}$=21 Hz), 117.0, 121.3 (d, $^3J_{CF}$=9.2 Hz), 124.5, 126.8, 132.1 (d, $^3J_{CF}$=8.0 Hz), 136.0, 156.9, 158.7, 161.5 (d, $^1J_{CF}$=251 Hz), 166.8, 168.8; HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{23}H_{25}FN_4O_5Na$, 479.1701; found, 479.1703.

*4.2.9. Dimethyl 1-(2-chlorobenzylideneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4i**).* White powder, mp 182–184 °C; IR (KBr, cm^{-1}): 3448, 2944, 2851, 2204, 1739, 1692, 1626, 1462, 1414, 1321, 1299, 1103, 760, 718; δ_H (500 MHz, $CDCl_3$): 1.28–1.80 (m, 10H, 5× CH_2 of cyclohexyl), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.97 (m, 1H, CH of cyclohexyl), 4.77 (s, 1H, CH–CN), 5.54 (s, 1H, CH–COO) 7.30–7.96(m, 4H, ArH), 8.28 (s, 1H, CH=N), 8.32 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.5, 53.0, 55.9, 70.4, 117.1, 127.2, 127.4, 129.9, 130.9, 131.5, 134.6, 139.5, 156.8, 158.7, 166.8, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}ClN_4O_5$, 473.1592; found, 473.1599.

*4.2.10. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3,4-dichlorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine -2,3-dicarboxylate (**4j**).* White powder, mp 190–193 °C; IR (KBr, cm^{-1}): 3440, 2933, 2856, 2208, 1743, 1691, 1636, 1462, 1409, 1297, 1100, 775; δ_H (500 MHz, $CDCl_3$): 1.22–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.95 (m, 1H, CH of cyclohexyl), 4.73 (s, 1H, CH–CN), 5.49 (s, 1H, CH–COO), 7.49–7.53 (m, 2H, ArH), 7.73(s, 1H, ArH), 7.77 (s, 1H, CH=N), 8.32 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.2, 33.8, 50.8, 51.3, 52.4, 53.2, 56.2, 70.3, 116.9, 126.3, 129.0, 130.9, 133.4, 134.7, 139.9, 156.8, 158.4, 166.8, 168.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{25}Cl_2N_4O_5$, 507.1202; found, 507.1215.

*4.2.11. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(4-nitrobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4k**).* Yellow powder, mp 201–202 °C; IR (KBr, cm^{-1}): 3446, 2933, 2853, 2208, 1736, 1693, 1637, 1521, 1460, 1405, 1342, 1142, 1102, 845; δ_H (500 MHz, $CDCl_3$): 1.19–2.11 (m, 10H, 5× CH_2 of cyclohexyl), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.94 (m, 1H, CH of cyclohexyl), 4.78 (s, 1H, CH–CN), 5.55 (s, 1H, CH–COO), 7.84–8.29 (m, 5H, ArH, CH=N), δ_C (125 MHz, DMSO-d_6): 24.7, 25.1, 33.0, 33.5,

51.2, 51.7, 51.8, 53.7, 55.6, 72.3, 117.7, 124.4, 129.2, 140.2, 142.7, 148.6, 156.9, 159.2, 166.6, 169.0; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}N_5O_7$, 484.1832; found, 484.1845.

*4.2.12. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3-nitrobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4l**).* Yellow powder, mp 169–170 °C; IR (KBr, cm^{-1}): 3447, 2930, 2854, 2206, 1731, 1687, 1638, 1532, 1471, 1410, 1383, 1287, 1103, 774, 725; δ_H (500 MHz, DMSO-d_6): 1.33–2.01 (m, 10H, 5× CH_2 of cyclohexyl), 3.67 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.82 (m, 1H, CH of cyclohexyl), 5.04 (s, 1H, CH–CN), 5.82 (s, 1H, CH–COO), 7.73 (t, J=8.0 Hz, 1H, ArH), 8.12–8.13 (d, J=7.0 Hz, 1H, ArH), 8.25–8.28 (dd, J_1=8.0 Hz, J_2=1.5 Hz, 1H, ArH), 8.33–8.34(d, J=7.5 Hz, 1H, ArH), 8.40 (s, 1H, CH=N), 8.61 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 24.7, 25.1, 33.0, 33.5, 51.2, 51.7, 51.8, 53.7, 55.3, 72.5, 117.7, 123.3, 125.2, 130.8, 133.4, 135.9, 143.2, 148.7, 156.9, 159.3, 166.6, 169.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{23}H_{26}N_5O_7$, 484.1832; found, 484.1845.

*4.2.13. Dimethyl 5-cyano-4-(cyclohexylamino)-6-oxo-1-(4-(trifluoromethyl)benzylideneamino)-1,2,5,6-tetrahydro pyridine-2,3-dicarboxylate (**4m**).* White powder, mp 196–198 °C; IR (KBr, cm^{-1}): 3445, 2930, 2860, 2208, 1731, 1688, 1610, 1468, 1410, 1325, 1101, 1067, 837, 755, 725; δ_H (500 MHz, DMSO-d_6): 1.17–1.93 (m, 10H, 5× CH_2 of cyclohexyl), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.76 (m, 1H, CH of cyclohexyl), 5.01 (s, 1H, CH–CN), 5.83 (s, 1H, CH–COO), 7.78–7.79 (d, J=8.0 Hz, 2H, ArH), 8.03–8.05 (d, J=8.0 Hz, 2H, ArH), 8.14 (s, 1H, NH), 8.29 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6): 24.7, 25.1, 33.0, 33.5, 51.1, 51.7, 53.6, 55.2, 72.3, 117.8, 123.4, 126.1, 128.8, 130.5, 137.9, 143.5, 156.8, 159.3, 166.6, 169.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{26}F_3N_4O_5$, 507.1855; found, 507.1859.

*4.2.14. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(4-methylbenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4n**).* White powder, mp 168–170 °C; IR (KBr, cm^{-1}): 3440, 2931, 2857, 2205, 1745, 1731, 1690, 1634, 1463, 1410, 1320, 1286, 1099, 815, 775, 720; δ_H (500 MHz, $CDCl_3$): 1.37–2.07 (m, 10H, 5× CH_2 of cyclohexyl), 2.38 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.94 (m, 1H, CH of cyclohexyl), 4.71 (s, 1H, CH–CN), 5.49 (s, 1H, CH–COO), 7.21–7.23 (d, J=8.0 Hz, 2H, ArH), 7.56–7.68 (d, J=8.5 Hz, 2H, ArH), 7.81 (s, 1H, CH=N) 8.31 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 21.5, 24.3, 25.2, 33.3, 33.8, 50.8, 51.2, 52.2, 53.0, 55.1, 70.5, 117.4, 127.5, 129.6, 130.6, 141.2, 143.2, 156.9, 158.8, 166.9, 169.1; HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{24}H_{28}N_4O_5Na$, 475.1952; found, 475.1950.

*4.2.15. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3-methylbenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4o**).* White powder, mp 186–182 °C; IR (KBr, cm^{-1}): 3448, 2930, 2859, 2201, 1732, 1689, 1633, 1467, 1410, 1324, 1101, 775, 724; δ_H (500 MHz, DMSO-d_6): 1.21–2.08 (m, 10H, 5× CH_2 of cyclohexyl), 2.40 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.77 (m, 1H, CH of cyclohexyl), 4.93 (s, 1H, CH–CN), 5.78 (s, 1H, CH–COO), 7.25–7.27 (d, J=8.0 Hz, 1H, ArH), 7.32 (t, J=7.5 Hz, 1H, ArH), 7.59–7.61 (d, J=7.5 Hz, 1H, ArH), 7.66 (s, 1H, CH=N), 8.14 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 21.3, 24.7, 25.2, 33.0, 33.5, 51.1, 51.7, 53.6, 54.5, 72.2, 117.9, 125.6, 128.5, 129.2, 131.8, 133.9, 138.6, 145.5, 156.9, 159.5, 166.6, 169.3; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{29}N_4O_5$, 453.2138; found, 453.2145.

*4.2.16. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(4-methoxybenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4p**).* White powder, mp 201–202 °C; IR (KBr, cm^{-1}): 3443, 2931, 2851, 2201, 1744, 1729, 1688, 1634, 1515, 1466, 1412, 1324, 1254, 1099, 830; δ_H (500 MHz, $CDCl_3$): 1.35–2.05 (m, 10H, 5× CH_2 of cyclohexyl), 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, $ArOCH_3$), 3.94 (m, 1H, CH of cyclohexyl), 4.68 (s, 1H, CH–CN), 5.47 (s, 1H, CH–COO), 6.93–6.94 (d, J=8.5 Hz, 2H, ArH), 7.62–7.64 (d, J=8.5 Hz, 2H, ArH), 7.81 (s, 1H, CH=N), 8.31 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 24.6, 25.1, 33.0, 33.4, 51.0, 51.6, 51.7, 53.5, 53.7, 55.8, 72.2, 118.2, 126.5, 129.9, 133.7, 145.5, 156.8, 159.5, 161.7, 166.5, 169.4; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{29}N_4O_6$, 469.2087; found, 469.2066.

*4.2.17. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3-methoxybenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4q**).* White powder, mp 169–170 °C; IR (KBr, cm^{-1}): 3450, 2930, 2857, 2202, 1732, 1687, 1635, 1467, 1410, 1322, 1285, 1099, 784, 775, 729; δ_H (500 MHz, $CDCl_3$): 1.26–2.08 (m, 10H, 5× CH_2 of cyclohexyl), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, *m*-OCH_3), 3.98 (m, 1H, CH of cyclohexyl), 4.76 (s, 1H, CH–CN), 5.54 (s, 1H, CH–COO), 7.00–7.02 (m, 1H, ArH), 7.26–7.30 (m, 2H, ArH), 7.35–7.38 (m, 1H, ArH), 7.83 (s, 1H, CH=N), 8.36 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.3, 25.2, 33.3, 33.8, 50.8, 51.3, 52.2, 53.1, 55.3, 55.4, 70.6, 111.7, 117.0, 117.3, 120.0, 129.9, 134.6, 142.8, 156.8, 158.7, 159.9, 166.8, 169.0; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{29}N_4O_6$, 469.2087; found, 469.2073.

*4.2.18. Dimethyl 5-cyano-4-(cyclohexylamino)-1-(3,4-dimethoxybenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4r**).* White powder, mp 110–112 °C; IR (KBr, cm^{-1}): 3425, 2935, 2856, 2206, 1748, 1639, 1539, 1514, 1266, 1167, 1144, 1024, 813, 745; δ_H (500 MHz, $CDCl_3$): 1.22–1.98 (m, 10H, 5× CH_2 of cyclohexyl), 3.36 (m, 1H, CH of cyclohexyl), 3.76 (s, 3H, $OOCH_3$), 3.83 (s, 3H, $OOCH_3$), 3.91 (s, 3H, $ArOCH_3$), 3.94 (s, 3H, $ArOCH_3$), 4.39 (s, 1H, CH–CN), 5.23 (s, 1H, CH–COO), 6.85–6.87 (d, J=8.0 Hz, 1H, ArH), 7.13–7.16 (dd, J_1=8.0 Hz, J_2=1.5 Hz, 1H, ArH), 7.34 (s, 1H, CH=N), 9.12 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$):24.8, 33.1, 34.4, 44.1, 53.6, 53.9, 55.9, 63.4, 108.5, 110.7, 115.9, 122.6, 127.7, 149.2, 151.2, 153.7, 158.3, 160.4, 166.3, 169.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{25}H_{31}N_4O_7$, 499.2193; found, 499.2185.

*4.2.19. Dimethyl 1-(benzo[d][1,3]dioxol-5-ylmethyleneamino)-5-cyano-4-(cyclohexylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**4s**).* White powder, mp 138–140 °C; IR (KBr, cm^{-1}): 3442, 2950, 2859, 2204, 1742, 1652, 1607, 1452, 1400, 1256, 1151, 1033, 818, 742; δ_H (500 MHz, $CDCl_3$): 1.19–1.97 (m, 10H, 5× CH_2 of cyclohexyl), 3.35 (m, 1H, CH of cyclohexyl), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.38 (s, 1H, CH–CN), 5.18 (s, 1H, CH–COO), 6.85–6.87 (m, 3H, ArH,CH_2), 6.78–6.79 (d, J=8.0 Hz, 1H, ArH), 7.03–7.04 (dd, J_1=8.0 Hz, J_2=1.5 Hz, 1H, ArH), 7.29 (s, 1H, CH=N), 9.12 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 24.6, 24.8, 32.9, 34.2, 53.6, 53.7, 60.3, 63.6, 101.3, 105.6, 108.1, 115.5, 124.1, 129.4, 148.1, 149.5, 153.1, 158.5, 160.5, 166.2, 169.7; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{24}H_{27}N_4O_7$, 483.1880; found, 483.1879.

*4.2.20. Dimethyl 1-(benzylideneamino)-5-cyano-4-(2-ethoxy-2-oxoethylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5a**).* White powder, mp 159–161 °C; IR (KBr, cm^{-1}): 3435, 2982, 2955, 2206, 1742, 1694, 1637, 1474, 1412, 1208, 1110, 758, 694; δ_H (500 MHz, $CDCl_3$): 1.31 (t, J=7.0 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.15–4.19 (dd, J_1=6.0 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.27 (q, J=7.0 Hz, 2H, OCH_2), 4.32–4.37 (dd, J_1=6.0 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.74 (s, 1H, CH–CN), 5.53 (s, 1H, CH–COO), 7.41–7.43 (m, 3H, ArH), 7.67–7.69 (m, 2H, ArH), 7.84 (s, 1H, CH=N), 8.62 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.8, 51.7, 52.2, 53.2, 55.8, 62.0, 72.7, 117.1, 127.6, 128.9, 130.8, 133.2, 143.1, 158.4, 166.5, 168.8, 168.9, 171.2; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{23}N_4O_7$, 443.1567; found, 443.1576.

*4.2.21. Dimethyl 5-cyano-4-(2-ethoxy-2-oxoethylamino)-1-(4-fluorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5b**).* White powder, mp 170–173 °C; IR (KBr, cm^{-1}): 3435, 2982, 2850, 2206, 1744, 1691, 1636, 1474, 1408, 1233, 1112, 839; δ_H (500 MHz, $CDCl_3$): 1.31 (t, J=7.0 Hz, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.14–4.19 (dd, J_1=5.7 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.28 (q, J=7.0 Hz, 2H, OCH_2), 4.32–4.37 (dd, J_1=5.7 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.71 (s, 1H, CH–CN), 5.50 (s, 1H,

CH–COO), 7.09–7.12 (m, 2H, ArH), 7.66–7.69 (m, 2H, ArH), 7.82 (s, 1H, CH=N), 8.64 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.9, 51.6, 52.4, 53.2, 55.9, 62.0, 72.9, 116.1 (d, $^2J_{CF}$=22 Hz), 116.9, 129.5(2c), 142.0, 158.3, 164.2 (d, $^1J_{CF}$=250 Hz), 166.4, 168.8, 168.9, 171.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{22}FN_4O_7$, 461.1473; found, 461.1462.

*4.2.22. Dimethyl 1-(4-chlorobenzylideneamino)-5-cyano-4-(2-ethoxy-2-oxoethylamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5c**).* White powder, mp 179–180 °C; IR (KBr, cm^{-1}): 3442, 2954, 2852, 2208, 1741, 1695, 1636, 1474, 1408, 1210, 1111, 822; δ_H (500 MHz, $CDCl_3$): 1.32 (t, J=7.0 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.15–4.19 (dd, J_1=5.7 Hz, J_2=18.0 Hz, 1H, C(O)CH_2N), 4.28 (q, J=7.0 Hz, 2H, OCH_2), 4.33–4.38 (dd, J_1=5.7 Hz, J_2=18.0 Hz, 1H, C(O)CH_2N), 4.73 (s, 1H, CH–CN), 5.51 (s, 1H, CH–COO), 7.39–7.40 (d, J=8.5 Hz, 2H, ArH), 7.61–7.63 (d, J=8.0 Hz, 2H, ArH), 7.86 (s, 1H, CH=N) 8.62 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.9, 51.6, 52.4, 53.3, 56.1, 62.0, 72.8, 116.9, 128.7, 129.2, 131.8, 136.8, 141.8, 146.3, 158.3, 166.4, 168.7, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{22}ClN_4O_7$, 477.1177; found, 477.1189.

*4.2.23. Dimethyl 5-cyano-4-(2-ethoxy-2-oxoethylamino)-1-(3-fluorobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5d**).* White powder, mp 168–170 °C; IR (KBr, cm^{-1}): 3448, 2956, 2852, 2209, 1739, 1694, 1640, 1473, 1409, 1210, 1111, 777, 689; δ_H (500 MHz, $CDCl_3$): 1.31 (t, J=7.5 Hz, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.14–4.19 (dd, J_1=6.0 Hz, J_2=18.2 Hz, 1H, C(O)CH_2N), 4.28 (q, J=7.5 Hz, 2H, OCH_2), 4.33–4.38 (dd, J_1=6.0 Hz, J_2=18.2 Hz, 1H, C(O)CH_2N), 4.74 (s, 1H, CH–CN), 5.51 (s, 1H, CH–COO), 7.37–7.42 (m, 4H, ArH), 7.82 (s, 1H, CH=N) 8.64 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.9, 51.6, 52.4, 53.3, 56.3, 62.0, 72.9, 113.7 (d, $^2J_{CF}$=22.7 Hz), 116.8, 117.7 (d, $^2J_{CF}$=21 Hz), 123.7, 130.5, 135.5, 141.5, 157.0, 158.2, 164.0 (d, $^1J_{CF}$=246 Hz), 166.4, 168.6, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{22}FN_4O_7$, 461.1473; found, 461.1465.

*4.2.24. Dimethyl 5-cyano-4-(2-ethoxy-2-oxoethylamino)-1-(4-nitrobenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5e**).* Yellow powder, mp 197–199 °C; IR (KBr, cm^{-1}): 3434, 2925, 2853, 2209, 1734, 1700, 1637, 1522, 1472, 1408, 1345, 1216, 1109, 845; δ_H (500 MHz, $CDCl_3$): 1.31 (t, J=7.0 Hz, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.13–4.18 (dd, J_1=6.0 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.28 (q, J=7.0 Hz, 2H, OCH_2), 4.33–4.38 (dd, J_1=6.0 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.77 (s, 1H, CH–CN), 5.55 (s, 1H, CH–COO), 7.82–7.84 (d, J=8.5 Hz, 2H, ArH), 7.87 (s, 1H, CH=N), 8.26–8.28 (d, J=8.5 Hz, 2H, ArH), 8.61 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.9, 51.7, 52.4, 53.5, 57.2, 62.1, 72.7, 116.4, 124.2, 128.1, 139.1, 139.7, 148.7, 157.9, 168.3, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{22}N_5O_9$, 488.1418; found, 488.1425.

*4.2.25. Dimethyl 5-cyano-4-(2-ethoxy-2-oxoethylamino)-1-(4-methylbenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5f**).* White powder, mp 178–180 °C; IR (KBr, cm^{-1}): 3439, 2958, 2923, 2206, 1741, 1693, 1636, 1474, 1415, 1209, 1111, 812; δ_H (500 MHz, $CDCl_3$): 1.31 (t, J=7.0 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.14–4.19 (dd, J_1=5.7 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.27 (q, J=7.0 Hz, 2H, OCH_2), 4.32–4.37 (dd, J_1=5.7 Hz, J_2=18.5 Hz, 1H, C(O)CH_2N), 4.72 (s, 1H, CH–CN), 5.50 (s, 1H, CH–COO), 7.21–7.22 (d, J=8.0 Hz, 2H, ArH), 7.56–7.58 (d, J=8.0 Hz, 2H, ArH), 7.82 (s, 1H, CH=N), 8.60 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 21.5, 42.9, 51.6, 52.2, 53.2, 55.5, 62.0, 72.6, 117.3, 127.7, 129.6, 130.6, 141.3, 143.5, 157.0, 158.5, 166.6, 168.9, 171.1; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{25}N_4O_7$, 457.1723; found, 457.1735.

*4.2.26. Dimethyl 5-cyano-4-(2-ethoxy-2-oxoethylamino)-1-(4-methylbenzylideneamino)-6-oxo-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (**5g**).* White powder, mp 173–175 °C; IR (KBr, cm^{-1}): 3439, 2955, 2920, 2208, 1737, 1693, 1637, 1515, 1473, 1411, 1254, 1111, 832; δ_H (500 MHz, $CDCl_3$): 1.32 (t, J=7.5 Hz, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, Ar–OCH_3), 4.15–4.20 (dd, J_1=5.7 Hz, J_2=18.2 Hz, 1H, C(O)CH_2N), 4.28 (q, J=7.5 Hz, 2H, OCH_2), 4.32–4.37 (dd, J_1=5.7 Hz, J_2=18.2 Hz, 1H, C(O)CH_2N), 4.69 (s, 1H, CH–CN), 5.49 (s, 1H, CH–COO), 6.92–6.94 (d, J=9.0 Hz, 2H, ArH), 7.62–7.64 (d, J=9.0 Hz, 2H, ArH), 7.82 (s, 1H, CH=N), 8.65 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$): 14.1, 42.9, 51.5, 52.4, 53.1, 55.2, 55.4, 62.0, 73.0, 114.4, 117.3, 126.0, 129.3, 143.7, 145.2, 157.0, 158.5, 161.9, 166.5, 168.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{25}N_4O_8$, 473.1672; found, 473.1685.

*4.2.27. (E)-Dimethyl 2-(2-benzylidene-1-(2-cyanoacetyl)hydrazinyl)-3-((tert-butylimino)methylene)succinate (**6a**).* White powder, mp 119–121 °C; IR (KBr, cm^{-1}): 2979, 2261, 2091, 1761, 1701, 1624, 1429, 1369, 1106, 1013, 872, 794, 757, 689; δ_H (500 MHz, DMSO-d_6), 1.40 (s, 9H, C(CH_3)$_3$), 3.60 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2–CN), 6.12 (s, 1H, CH–COO), 7.47–7.49 (m, 2H, ArH), 7.76–7.77 (m, 2H, ArH), 8.34 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.8, 30.0, 52.0, 53.0, 53.2, 60.4, 62.6, 116.1, 127.9, 129.3, 130.8, 134.2, 143.5, 163.8, 165.2, 167.5, 169.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{25}N_4O_5$, 413.1825; found, 413.1815.

*4.2.28. (E)-Dimethyl 2-((tert-butylimino)methylene)-3-(1-(2-cyanoacetyl)-2-(4-fluorobenzylidene)hydrazinyl)succinate (**6b**).* White powder, mp 124–126 °C; IR (KBr, cm^{-1}): 2978, 2955, 2259, 2079, 1752, 1693, 1512, 1433, 1267, 1237, 1177, 1109, 1014, 847, 770; δ_H (500 MHz, DMSO-d_6), 1.39 (s, 9H, C(CH_3)$_3$), 3.60 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2–CN), 6.10 (s, 1H, CH–COO), 7.32 (t, J=9.0 Hz, 2H, ArH), 7.80–7.83(m, 2H, ArH), 8.35 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.8, 30.1, 52.1, 53.1, 53.3, 60.5, 62.7, 116.2, 116.4 (d, $^2J_{CF}$=22 Hz), 130.2(d, $^3J_{CF}$=8.0 Hz), 130.9, 142.5, 163.7, 163.8 (d, $^1J_{CF}$=248 Hz), 165.2, 167.5, 169.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}FN_4O_5$, 431.1731; found, 431.1720.

*4.2.29. (E)-Dimethyl 2-((tert-butylimino)methylene)-3-(2-(4-chlorobenzylidene)-1-(2-cyanoacetyl)hydrazinyl)succinate (**6c**).* White powder, mp 119–122 °C; IR (KBr, cm^{-1}): 2980, 2251, 2077, 1750, 1693, 1435, 1265, 1176, 1104, 1013, 831, 769; δ_H (500 MHz, DMSO-d_6), 1.40 (s, 9H, C(CH_3)$_3$), 3.60 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2–CN), 6.11 (s, 1H, CH–COO), 7.53–7.55 (d, J=8.5 Hz, 2H, ArH), 7.77–7.78 (d, J=7.5 Hz, 2H, ArH), 8.35 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.9, 30.1, 52.1, 53.1, 53.3, 60.5, 62.7, 116.2, 129.5, 129.6, 133.2, 135.4, 142.3, 163.7, 165.3, 167.5, 169.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}ClN_4O_5$, 447.1435; found, 447.1439.

*4.2.30. (E)-Dimethyl 2-(2-(4-bromobenzylidene)-1-(2-cyanoacetyl)hydrazinyl)-3-((tert-butylimino)methylene)succinate (**6d**).* White powder, mp 128–130 °C; IR (KBr, cm^{-1}): 2956, 2920, 2247, 2063, 1733, 1688, 1434, 1367, 1312, 1267, 1176, 1102, 1009, 828, 769; δ_H (500 MHz, $CDCl_3$), 1.49 (s, 9H, C(CH_3)$_3$), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2–CN), 5.73 (s, 1H, CH–COO), 7.57–7.58 (m, 4H, ArH), 8.16 (s, 1H, CH=N); δ_C (125 MHz, $CDCl_3$) 25.5, 30.1, 51.9, 53.3, 54.0, 58.7, 62.7, 114.0, 125.0, 129.1, 132.1, 132.6, 142.6, 160.2, 163.8, 167.1, 170.6; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}BrN_4O_5$, 491.0930; found, 491.0920.

*4.2.31. (E)-Dimethyl 2-(2-(3-bromobenzylidene)-1-(2-cyanoacetyl)hydrazinyl)-3-((tert-butylimino)methylene)succinate (**6e**).* White powder, mp 140–143 °C; IR (KBr, cm^{-1}): 2975, 2261, 2077, 1759, 1695, 1435, 1266, 1177, 1108, 1069, 1015, 872, 700, 719, 689; δ_H (500 MHz, DMSO-d_6), 1.40 (s, 9H, C(CH_3)$_3$), 3.61 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.47 (s, 2H, CH_2–CN), 6.11 (s, 1H, CH–COO), 7.45 (t, J=8.0 Hz, 1H, ArH), 7.65–7.66 (d, J=8.0 Hz, 1H, ArH), 7.72–7.74 (d, J=8.0 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 8.33 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.9, 30.0, 52.0, 53.1, 53.3, 60.4,

62.6, 116.1, 122.7, 127.3, 129.9, 131.4, 133.4, 136.5, 141.9, 163.6, 165.4, 167.4, 169.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}BrN_4O_5$, 491.0930; found, 491.0936.

*4.2.32. (E)-Dimethyl 2-((tert-butylimino)methylene)-3-(1-(2-cyanoacetyl)-2-(2-fluorobenzylidene)hydrazinyl)succinate (**6f**).* White powder, mp 166–168 °C; IR (KBr, cm^{-1}): 2977, 2259, 2076, 1756, 1697, 1612, 1436, 1264, 1177, 1109, 1037, 1016, 872, 764; δ_H (500 MHz, DMSO-d_6), 1.40 (s, 9H, $C(CH_3)_3$), 3.61 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.43 (s, 2H, CH_2–CN), 6.17 (s, 1H, CH–COO), 7.28–7.33 (m, 2H, ArH), 7.50–7.54 (m, 1H, ArH), 8.00 (t, J=7.5 Hz, 1H, ArH), 8.45 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.9, 30.1, 52.1, 53.2, 53.3, 60.2, 62.7, 116.1, 116.5 (d, $^2J_{CF}$=20 Hz), 121.8 (d, $^3J_{CF}$=9.1 Hz), 125.4, 127.7, 132.9, 136.4, 161.5(d, $^1J_{CF}$=250 Hz), 163.5, 165.5, 167.5, 169.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}FN_4O_5$, 431.1731; found, 431.1726.

*4.2.33. (E)-Dimethyl 2-((tert-butylimino)methylene)-3-(1-(2-cyanoacetyl)-2-(3-nitrobenzylidene)hydrazinyl)succinate (**6g**).* Yellow powder, mp 134–136 °C; IR (KBr, cm^{-1}): 2985, 2261, 2091, 1759, 1694, 1529, 1437, 1271, 1178, 1111, 1020, 871, 773,675; δ_H (500 MHz, DMSO-d_6), 1.39 (s, 9H, $C(CH_3)_3$), 3.59 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2–CN), 6.13 (s, 1H, CH–COO), 7.76 (t, J=8.0 Hz, 1H, ArH), 8.20–8.22 (d, J=8.0 Hz, 1H, ArH), 8.27–8.29 (dd, J_1=8.0 Hz, J_2=2.0, 1H, CH=N), 8.49–8.51 (m, 2H, ArH); δ_C (125 MHz, DMSO-d_6) 26.0, 30.1, 52.1, 53.3, 53.4, 60.4, 62.7, 116.1, 122.5, 125.2, 131.0, 133.7, 136.0, 141.5, 148.8, 163.5, 165.5, 167.4, 169.9; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{21}H_{24}N_5O_7$, 458.1676; found, 458.1685.

*4.2.34. Dimethyl 2-((tert-butylimino)methylene)-3-(1-(2-cyanoacetyl)-2-(4-methoxybenzylidene)hydrazinyl)succinate (**6h**).* White powder, mp 166–168 °C; IR (KBr, cm^{-1}): 3010, 2959, 2259, 2103, 1748, 1687, 1655, 1607, 1515, 1436, 1254, 1176, 1109, 1031, 876, 833, 770; δ_H (500 MHz, DMSO-d_6), 1.37 (s, 9H, $C(CH_3)_3$), 3.59 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.80 (s, 3H, $ArOCH_3$), 4.36 (s, 2H, CH_2–CN), 6.04 (s, 1H, CH–$COOCH_3$), 7.00–7.02 (d, J=8.5 Hz, 2H, ArH), 7.68–7.70 (d, J=9.0 Hz, 2H, ArH), 8.24 (s, 1H, CH=N); δ_C (125 MHz, DMSO-d_6) 25.7, 30.0, 52.0, 53.0, 53.2, 55.8, 60.5, 62.6, 114.8, 116.2, 126.7, 129.6, 143.4, 161.5, 164.0, 164.9, 167.6, 169.8; HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{22}H_{27}N_4O_6$, 443.1931; found, 443.1926.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Nos. 20872074 and 21072110), and the Natural Science Foundation of Shandong Province (Nos. Z2008B03 and ZR2010BM007).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.124. These data include MOL files and InChiKeys of the most important compounds described in this

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18. Crystallographic data for **6g** have been deposited in the Cambridge Crystallographic Data Centre with the deposition number CCDC 798675. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44 (0) 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).
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