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ORIGINAL ARTICLE

Regioselective four-component synthesis of new tetrazolo[1,5-a]quinoline-based 2-amino-1,4-dihydropyridine and pyridin-2(1*H*)-one derivatives using nano-ZnO catalysis

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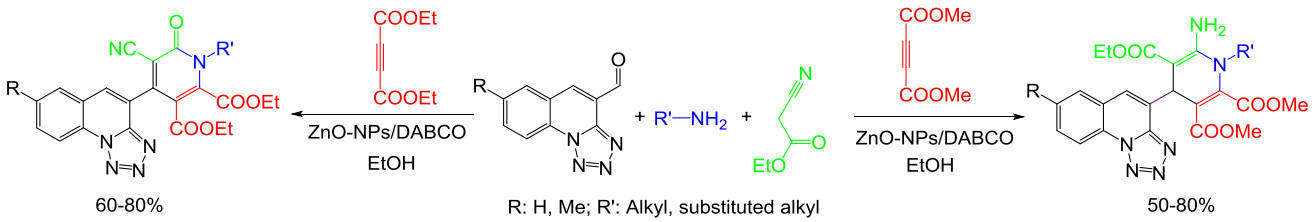
Abstract

Four-component reaction between primary amines, dialkylacetylendicarboxylates, tetrazolo[1,5-a] quinoline-4-carbaldehyde and ethyl-2-cyanoacetate in the presence of 1,4-diaza-bicyclo[2.2.2]octane and zinc oxide nanoparticles results to the regioselective production of new tetrazolo[1,5-a]quinoline-based 2-amino-1,4-dihydropyridine or pyridin-2(1*H*)-one derivatives in good to high yields. The selectivity of the catalyzed reaction toward the generation of the dihydropyridine or pyridin-2(1*H*)-one derivatives was found to be strongly dependent on the size of the alkyl groups in the ester moieties of the acetylenic esters. According to single-crystal X-ray diffraction and NMR studies, the pyridin-2(1*H*)-one derivatives involve a restricted rotation around the C–C bond connecting the tetrazoloquinoline and dihydropyridinone cyclic systems.

Graphical abstract



Keywords Tetrazolo[15-a]quinoline-4-carbaldehyde · Dialkylacetylendicarboxylate · Ethyl-2-cyanoacetate · Zinc oxide nanoparticles · Enaminone · Atropisomer · MCRs

Introduction

Quinoline derivatives are members of an important class of heterocyclic compounds that exhibit different biological and pharmacological activities [1]. Another class of bioactive compounds is related to tetrazole and its derivatives [2]. Since the fusion of quinoline and tetrazole can improve the biological activity of quinolone [3–5], fused tetrazole and quinoline structures, e.g., substituted tetrazoloquinoline rings, have been used for diverse pharmacological purposes, such as anti-inflammatory [6], antimicrobial [7, 8], antitubercular [9], antifungal [10], antitumor [11] and pregnancy-interceptive [12] activities. Conversely, pyridin-2(1*H*)-one and 1,4-dihydropyridine derivatives are members of an important class of nitrogen-containing heterocycles and they have a wide variety of biological and pharmacological properties. For example, milrinone (**I**, Fig. 1) and perampanel (**II**, Fig. 1), which are two pyridine-2(1*H*)-one derivatives, are used as a cardiotonic agent and for the treatment of Parkinson's disease, respectively. Also, the 1,4-dihydropyridine derivatives that are shown in Fig. 1, **III** and **IV**, are reported as anticancer and calcium chan-

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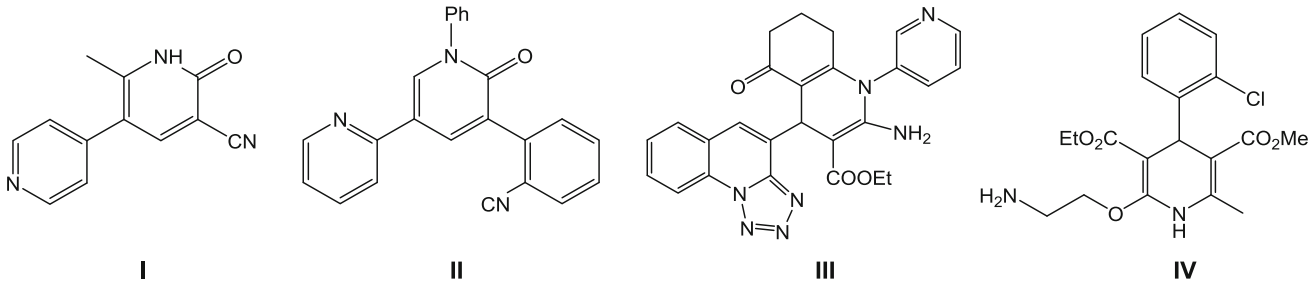
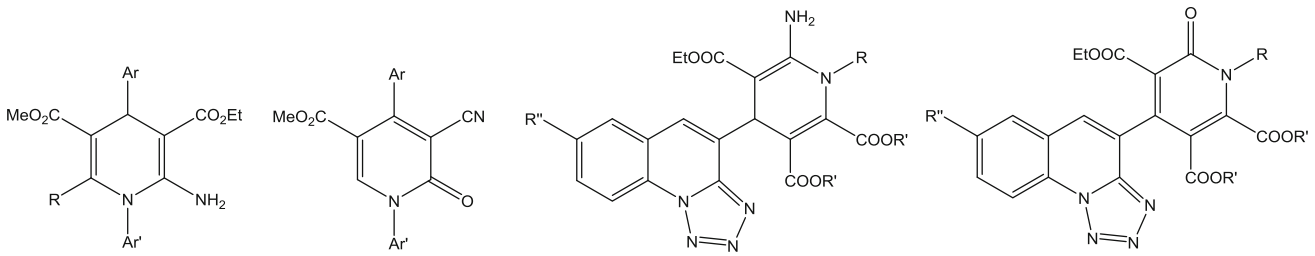


I II III IV

Fig. 1 Examples of pyridin-2(1*H*)-one and 1,4-dihydropyridine-based bioactive compounds



1 2 3 4

1: R = H , CO_2Me
1,**2**: Ar and Ar': phenyl and substituted phenyl

3, **4**: R and R' = alkyl or substituted alkyl and R" = H, Me

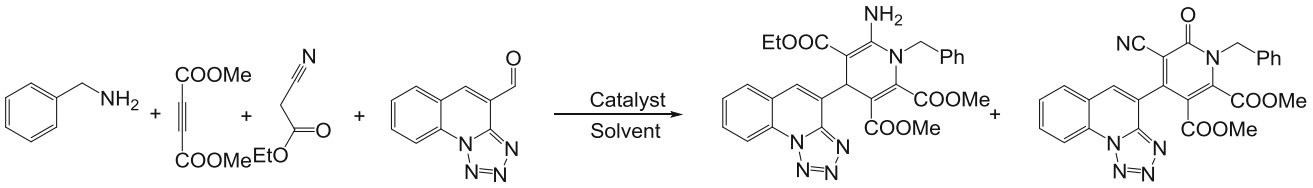
Fig. 2 Structures of the reported and target polysubstituted dihydropyridine and 2-pyridinone compounds

nel blocker agents, respectively. As a result of the wide range of biological activities of 2-aminohydropyridines and 2-pyridinones, various methods have been suggested for the synthesis of these structures [13–16]. Yan et al. [17] reported a four-component reaction between aromatic aldehydes, malononitrile, arylamines and dimethyl acetylenedicarboxylate (DMAD) for the synthesis of polysubstituted dihydropyridines **1** (R = CO_2Me; Fig. 2). Later, when methyl propiolate was used instead of DMAD, compounds **1** (R = H) and **2** were produced [18].

In continuation of our research on heterocyclic synthesis using enaminones [19–22], we decided to use the approach of Yan et al. for the synthesis of compounds **3** and **4** (Fig. 2). Unfortunately, we found that Yan's methodology cannot efficiently proceed with tetrazolo[1,5-a]quinoline-4-carbaldehyde and aliphatic primary amines. To find a solution, we reviewed the literature and found that zinc oxide nanoparticles (ZnO NPs) can interact with carbonyl and nitrile groups and accelerate various Michael addition reactions, condensation reactions between aldehydes and CH-acids and intramolecular cyclization reactions [23–31]. Therefore, we considered ZnO NPs as catalyst for the synthesis of tetrazolo[1,5-a]quinolone-based 2-amino-1,4-dihydropyridine and pyridin-2(1*H*)-one derivatives (Fig. 2; **3** and/or **4**) via the one-pot regioselective four-component reaction of primary amines with dialkylacetylendicarboxylates (DAAD), tetrazolo[1,5-a]quinoline-4-carbaldehyde and ethyl-2-cyanoacetate. During this study, we found that the regioselectivity of the reaction depends on the size of the alkyl groups in the ester moieties of the acetylenic esters and the dihydropyridines **3** or 2-pyridinones **4** can be obtained by applying an appropriate acetylenic ester.

Results and discussion

The one-pot reaction between benzyl amine, DMAD, ethyl-2-cyanoacetate and tetrazolo[1,5-a]quinoline-4-carbaldehyde was selected as a model reaction. As illustrated in Scheme 1, compounds **3** and **4** are the products expected from this reaction [17, 18]. To optimize the regioselectivity of the reaction, the influence of various solvents, bases, base to ZnO ratios and reaction times was studied on our model reaction. Table 1 presents a summary of the optimization results. As presented in Table 1, the reaction does not proceed in the absence of any catalyst under the solvent-free condition or in the presence of the ethanol solvent, within 48 h reaction time (entries 1 and 2). A comparison of the results of entries 1 and 2 with those of entries 3–6, which were performed in the presence of K_2CO_3, Et_3N, ZnO NPs and 1,4-diaza-bicyclo [2.2.2]octane (DABCO), revealed that the highest reaction yield was obtained in the presence of DABCO. Also, it was observed that the reaction is solvent sensitive and the best yield can be obtained by carrying out the reaction in ethanol (entries 6–12). However, as shown in Table 1 (entries 6–9), solvent selection does not determine



3a **4a**

Scheme 1 Reaction between benzylamine, DMAD, tetrazolo[1,5-a]quinoline-4-carbaldehydes and ethyl-2-cyanoacetate

Table 1 Screening of solvent, catalyst and catalyst amount for the model reaction

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield of **3a** (%)[a]	Yield of **4a** (%)[a]
1	–	–[b]	48	–	–
2	–	Ethanol	48	–	–
3	K_2CO_3 (100)	Ethanol	4	Trace	–
4	Et_3N (100)	Ethanol	10	Trace	Trace
5	ZnO NPs (20)	Ethanol	4	Trace	Trace
6	DABCO (100)	Ethanol	4	40	35
7	DABCO (100)	DMSO	4	40	30
8	DABCO (100)	TBAB[c]	4	35	35
9	DABCO (100)	Methanol	4	37	22
10	DABCO (100)	THF	24	–	–
11	DABCO (100)	CH_2Cl_2	24	–	–
12	DABCO (100)	H_2O	24	–	–
13	DABCO (100)/ZnO NPs (10)	Ethanol	1	70	15
14	DABCO (100)/ZnO NPs (20)	Ethanol	1	80	10
15	DABCO (100)/ZnO NPs (30)	Ethanol	1	80	10
16	DABCO (25)/ZnO NPs (20)	Ethanol	1.5	60	20
17	DABCO (50)/ZnO NPs (20)	Ethanol	1	70	20
18	DABCO (200)/ZnO NPs (20)	Ethanol	1	80	10

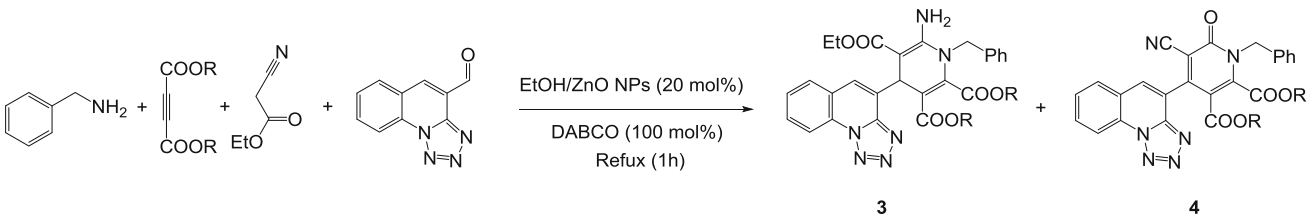
[a]Isolated yields
[b]Room temperature reaction
[c]Reaction in 100 mol% of tetra-*n*-butylammonium bromide at 90 °C

which of the two products, i.e., **3a** or **4a**, is more likely to be produced. Conversely, compared with **4a**, the production of **3a** can be greatly improved with the use of ZnO NPs and DABCO combined (entries 13–15). Finally, changing the ratio of DABCO to ZnO NPs revealed that the highest efficiency can be achieved when the reaction is performed in the presence of an equimolar amount of DABCO and 20 mol% ZnO NPs (entries 13–18).

Surprisingly, further investigation showed that selectivity toward products **3** or **4** strongly depends on the size of the alkyl groups in the ester moieties of the acetylenic esters when the reaction occurs in the presence of DABCO and ZnO NPs. Table 2 shows that the maximum yield of **3** can be obtained when the acetylenic esters contain methyl groups while the highest yield of **4** corresponds to the acetylenic esters that contain ethyl groups. The application of di-*tert*-butyl acetylenedicarboxylate does not give **3** or **4** products. These observations imply that the size of the alkyl groups on the acetylenic esters play a key role in the performance and regioselectivity of the studied reaction (see Table 2).

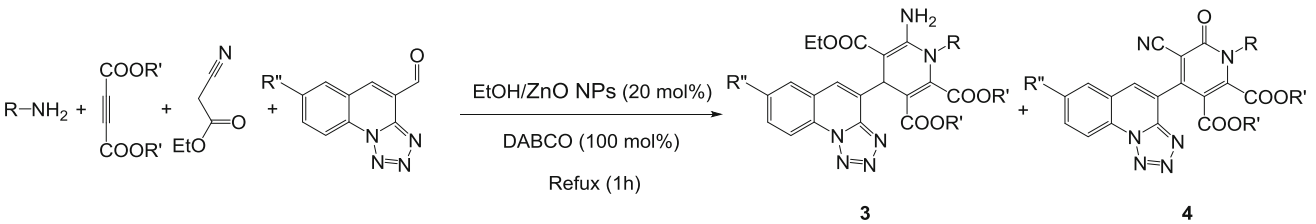
On the basis of the above findings, several regioselective four-component reactions between primary amines, DAAD, ethyl-2-cyanoacetate and tetrazolo[1,5-a]quinoline-4-carbaldehydes were examined in the presence of an

Table 2 Regioselective reaction between benzylamine, DAAD, tetrazolo[1,5-a]quinoline-4-carbaldehyde and ethyl-2-cyanoacetate



Entry	R	Compd **3**	Yield (%)	Compd **4**	Yield (%)
1	Me	**3a**	80	**4a**	10
2	Et	**3b**	30	**4b**	60
3	*t*-Bu	**3c**	–	**4c**	–

Table 3 Regioselective synthesis of tetrazolo[1,5-a]quinine-based 2-amino-1,4-dihydropyridine and pyridin-2(1*H*)-one derivatives



Entry	R	R′	R″	Compd **3**	Yield (%)[a]	Compd **4**	Yield (%)[a]
1	Bnzyl	Me	H	**3a**	80	**4a**	10
2	Bnzyl	Et	H	**3b**	30	**4b**	60
3	Bnzyl	Me	Me	**3d**	60	**4d**	–[b]
4	Phenethyl	Me	H	**3e**	70	**4e**	–[b]
5	4-Methoxyphenethyl	Me	H	**3f**	75	**4f**	–[b]
6	Propyl	Me	H	**3g**	50	**4g**	–[b]
7	Phenethyl	Et	H	**3h**	–[b]	**4h**	75
8	4-Methoxyphenethyl	Et	H	**3i**	–[b]	**4i**	60
9	4-Methoxyphenethyl	Et	Me	**3j**	–[b]	**4j**	60
10	*i*-Pr	Et	H	**3k**	–[b]	**4k**	70
11	*i*-Bu	Et	H	**3l**	–[b]	**4l**	55

[a]Isolated yields
[b]No product isolated due to the lack of product formation

equimolar amount of DABCO and 20 mol% of ZnO NPs in ethanol. The results are presented in Table 3. Based on Table 3, 2-amino-1,4-dihydropyridine derivatives are the major products when the reactions are carried out using DMAD (Table 3, entries 1 and 3–6) while the 2-pyridinone derivatives are the major products when using DEAD (Table 3, entries 2 and 7–11).

The structures of the produced 2-amino-1,4-dihydropyridine derivatives were determined based on their CHN, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. For example, the ^{1}H NMR spectrum of **3g** showed two triplets ($\delta = 1.00$ ppm with $^3J_{HH} = 7.5$ Hz, and $\delta = 1.12$ ppm with $^3J_{HH} = 7.3$ Hz) for the two methyl protons of the propyl and ethyl moieties. The methylene protons of the propyl moiety ($CH_3CH_2CH_2$) showed a multiplet at δ = 1.88–2.04 ppm and the methoxy groups of **3g** appeared as two singlets at $\delta = 3.59$ and 3.88 ppm. The NCH_2 and OCH_2 protons were revealed as two multiplets at δ = 3.56–3.66 ppm and $\delta = 3.96$–4.05 ppm, respectively. The methine proton of **3g** exhibited a sharp singlet at δ = 5.49 ppm. The NH_2 protons of **3g** resulted in a broad singlet at $\delta = 6.64$ ppm and the CH-6 aromatic proton displayed a triplet ($\delta = 7.64$ ppm with $^3J_{HH} = 8.3$ Hz). The CH-4 aromatic proton gave a singlet at $\delta = 7.75$ ppm and the CH-7

aromatic proton exhibited a triplet ($\delta = 7.78$ ppm with $^3J_{HH} = 8.3$ Hz). Also, the CH-5 and CH-8 protons of **3g** produced two doublets ($\delta = 7.9$ ppm with $^3J_{HH} = 8.3$ Hz and $\delta = 8.63$ ppm with $^3J_{HH} = 8.5$ Hz, respectively). In addition, the ^{13}C NMR spectrum of **3g** showed 24 distinct resonances that corroborate the proposed structure (see the "Experimental" section) and the mass spectrum of **3g**, illustrated a molecular ion peak at the expected *m/z* value, i.e., 498.

The IR, ^{1}H and ^{13}C NMR, MS and elemental analysis techniques were used to characterize the structures of the highly functionalized **4a, 4b** and **4h** to **4l** 2-pyridinones. The structure of **4i** was also confirmed by single-crystal X-ray diffraction. In the ^{1}H NMR spectrum of **4b**, the benzylic protons clearly exhibited an AB quartet system ($\delta_A = 5.28$ and $\delta_B = 5.54$ with $J_{AB} = 15.2$ Hz). In the meantime, in the ^{1}H NMR spectrum of **4i**, the NCH_2 protons were found to be diatereotopic, which means that they appeared as two multiplets at two different chemical shifts ($\delta = 4.10$ ppm and $\delta = 4.25$ ppm). Diastereotopicity was also observed in the case of the NCH_2 protons of **4b** due to the restricted rotation around the C–C bond connecting the tetrazoloquinoline and dihydropyridinone cyclic systems. Moreover, the ^{13}C NMR spectra of **4b** and **4i** showed 28 and 30 distinct signals, respectively. These ^{1}H and ^{13}C NMR results are consistent with the nonplanar structures of these pyridinones. Figure 3 shows the ORTEP representation of **4i** in which it can be observed that the pyridinone ring is forced out of the plane of the tetrazoloquinoline ring by twisting about 58°.

In this study, the mechanism proposed for generation of the 2-amino-1,4-dihydropyridine and 2-pyridinone derivatives (Scheme 2) is similar to the mechanism suggested by Yan et al. [17, 18]. The difference is that our proposed mechanism considers the presence of ZnO NPs. As aforementioned, the application of ZnO NPs can accelerate Michael addition and cyclization of the intermediates [23–28]. The reaction starts with the addition of primary amines to the electron-deficient acetylenic ester to form enaminocarbonyl compound **5** [32]. In parallel, Knoevenagel condensation of tetrazolo[1,5-a]quinoline-4-carbaldehyde with ethyl cyanoacetate occurs under the catalytic effect of DABCO and ZnO to generate intermediate **6** [29]. Then, Michael addition of the enaminone (**5**) to the condensed intermediate, i.e., compound **6**, produces intermediate **7** [30]. In intermediate **7**, when the alkyl groups of the acetylenic ester are methyl (**7a**), intramolecular nucleophilic addition of the imino group to the triple bond of the nitrile in the presence of Zno forms a cyclic intermediate **8** [31]. Finally, tautomerization of the imino group to the amino form results in the production of 2-amino-1,4-dihydropyridine **3**. On the other hand, in intermediate **7**, when the alkyl groups of the acetylenic ester are ethyl (**7b**), the imino group attacks the ester group to produce a cyclic intermediate **9**. Dehydrogenation of intermediate **9** in air gives 2-pyridinone (**4**), as the final product [18].

Conclusions

In summary, we have described a convenient route for the synthesis of new tetrazolo[1,5-a]quinolone-based 2-amino-1,4-dihydropyridine and pyridin-2(1*H*)-one derivatives through one-pot regioselective four-component reactions between tetrazolo[1,5-a]quinoline-4-carbaldehydese, ethyl-2-cyanoacetate, primary amines and DAAD, in the presence of DABCO and a catalytic amount of ZnO NPs. This approach provides good to high yields within 1 h of reaction time.

Experimental

Tetrazolo[1,5-a]quinoline-4-carbaldehyde was prepared according to the literature [33, 34]. Zinc oxide nanopowder (99%, 10–30 nm, CAS: 1314-13-2) was obtained from US Research Nanomaterials, Inc. Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerl) and were used without further purification. Melting points (uncorrected) were measured using a Stuart SMP-3 apparatus. Elemental analyses for C, H and N were performed using a Eager 300 for EA1112. IR spectra were recorded using a FT-IR Perkin Elmer RXI. NMR spectra were recorded on a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^{1}H and 62.9 MHz for ^{13}C) using $CDCl_3$ as solvent. Abbreviation of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Coupling constant (J) is expressed in Hz. Mass spectra were recorded on an Agilent-5975C VL mass spectrometer operating at an ionization potential of 70 eV.

General procedure

To a magnetically stirred solution of 2 mmol tetrazolo[1,5-a]quinoline-4-carbaldehyde in 5 mL ethanol was added 2 mmol ethyl-2-cyanoacetate and 2 mmol DABCO. The reaction mixture was stirred for 5 min at reflux temperature, then 0.4 mmol of ZnO NPs was add to the reaction mixture. Then, a solution of a primary amine (2 mmol) and DAAD (2 mmol) in 2 mL of ethanol was added to the reaction mixture. The reaction mixture was then allowed to reflux for 1 h. After completion, the solvent was removed under reduce pressure. Then, 10 mL of chloroform followed by 10 mL of water were added to the reaction mixture and the organic layer was separated using a separatory funnel. The organic phase was dried over calcium chloride, filtered, the solvent removed under reduced pressure and the resulting crude product was purified by column chromatography.

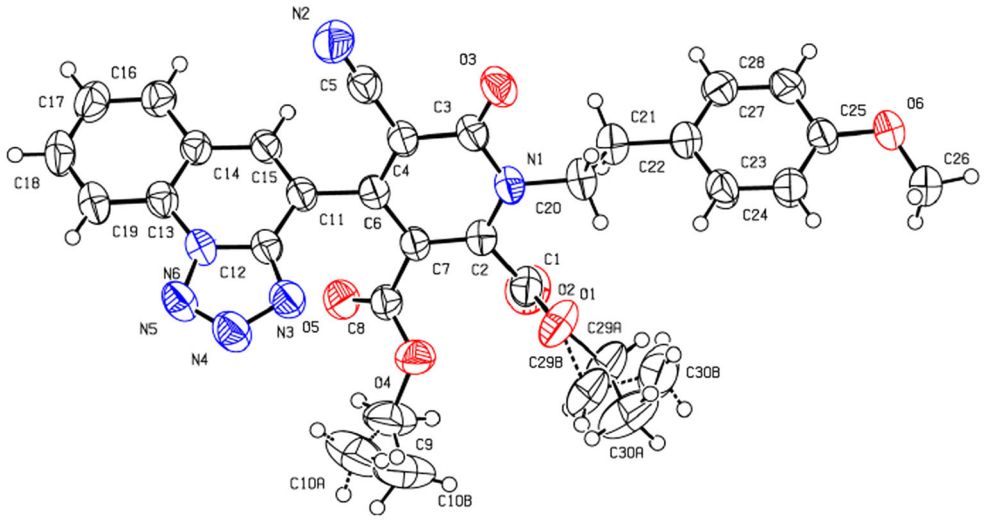
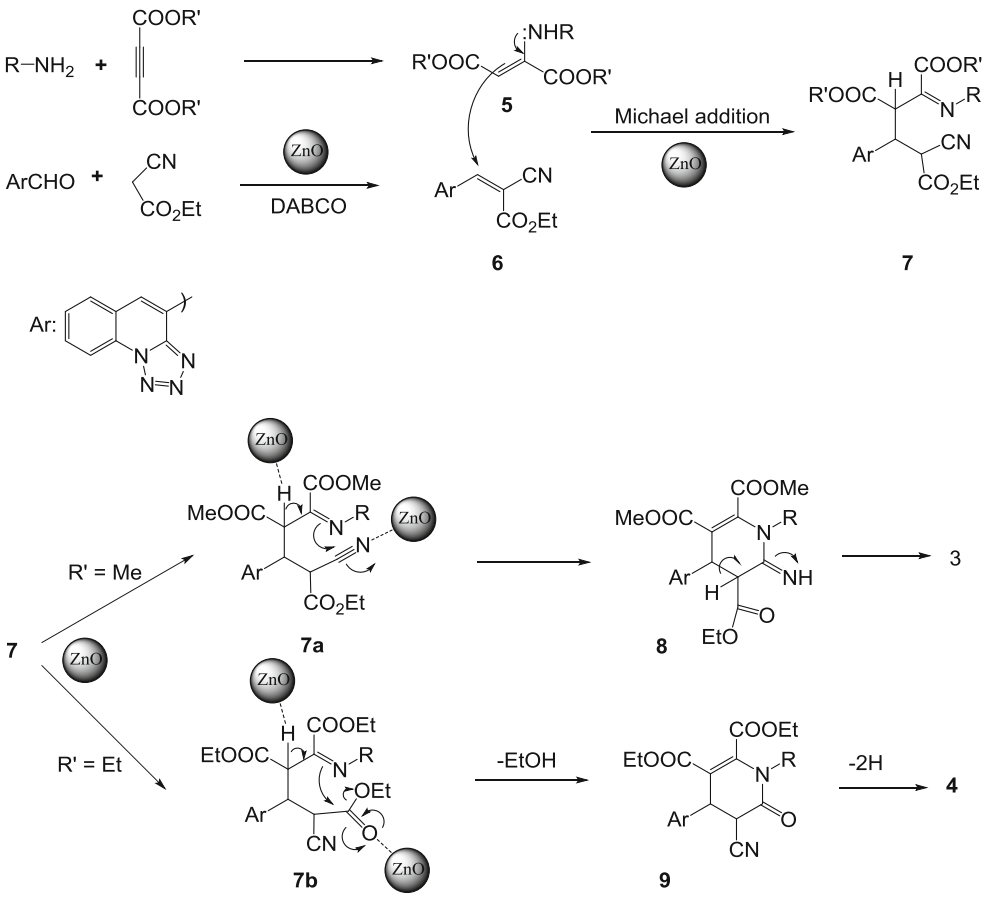


Fig. 3 ORTEP representation of **4i**



Scheme 2 Proposed mechanism for formation of the 2-amino-1,4-dihydropyridine and 2-pyridinone derivatives in the presence of DABCO/ZnO NPs

5-Ethyl 2,3-dimethyl 6-amino-1-benzyl-1,4-dihydro -4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5-tricarboxylate (3a)

Yellow powder; mp: 215–217 °C; 0.867 g, yield: 80%. IR (KBr) (υ_{max}/cm^{-1}): 3469, 3271, 3033, 2981, 1735, 1707, 1656, 1500, 1210, 761. Ms: *m/z* (%) = 542 (M^+, 14), 469 (25), 441 (12), 373 (10), 105 (25), 83 (100), 97 (73), 57 (10). Anal. Calcd for $C_{28}H_{26}N_6O_6$ (542.3): C, 61.99; H, 4.83; N, 15.49. Found C, 61.74; H, 5.02; N, 15.02. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.16 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.63 and 3.64 (2 s, 6H, 2OCH_3), 4.01 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2), 5.13 (AB quartet, δ_A = 5.00, δ_B = 5.25, J_{AB} = 18.3 Hz, NCH_2), 5.46 (s, H, CH), 6.41 (bs, 2H, NH_2), 7.34–7.52 (m, 5H, 5CH, Ar), 7.64 (t, 1H, $^3J_{HH}$ = 8.0 Hz, CH-6, Ar), 7.78–7.84 (m, 2H, 2CH, Ar), 7.92 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH-5, Ar), 8.64 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH_3), 36.6 (CH), 52.0 (NCH_2 and OCH_3), 52.9 (OCH_3), 59.4 (OCH_2), 78.2 (NH_2–C=*C*), 104.7 (N–C=*C*), 116.7 (CH-6), 124.2 (C), 126.3 (2CH), 127.7 (CH-5), 128.1 and 128.7 (2CH), 129.2 (2CH), 129.6 and 129.9 (2C), 130.1 (CH-8), 130.2 (CH-4), 136.0, 144.6, 147.3, and 155.1 (4C), 165.0, 166.1, and 169.0 (3 C=O).

Triethyl 6-amino-1-benzyl-1,4-dihydro-4 -(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5-tricarboxylate (3b)

Yellow powder; mp: 187–190 °C; 0.342 g, yield: 30%. IR (KBr) (υ_{max}/cm^{-1}): 3486, 3252, 3032, 2984, 1733, 1702, 1653, 1499, 1206, 758. Ms: *m/z* (%) = 497 (M^+ - CO_2Et, 19), 459 (17), 430 (10), 401 (7), 309 (8), 204 (12), 91 (100), 65 (10). Anal. Calcd for $C_{30}H_{30}N_6O_6$ (570.2): C, 63.15; H, 5.30; N, 14.73. Found C, 62.45; H, 5.42; N, 14.85. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.06 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.52 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2CH_3), 3.40–4.14 (m, 6H, 3OCH_2), 5.14 (AB quartet, δ_A = 5.04, δ_B = 5.25, $^2J_{HH}$ = 18.5 Hz, NCH_2), 5.47 (s, H, CH), 6.42 (bs, 2H, NH_2), 7.33–7.52 (m, 5H, 5CH, Ar), 7.66 (t, 1H, $^3J_{HH}$ = 7.5 Hz, CH-6, Ar), 7.78, (t, 1H, $^3J_{HH}$ = 7.5 Hz, CH-7, Ar), 7.79 (s, 1H, CH-4, Ar), 7.91 (d, 1H, $^3J_{HH}$ = 7.8 Hz, CH-5, Ar), 8.65 (d, 1H, $^3J_{HH}$ = 8.3 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.4, 14.0, and 14.4 (3CH_3), 36.8 (CH), 51.6 (NCH_2), 59.3, 60.7, and 62.2 (3OCH_2), 78.0 (NH_2–C=*C*), 104.8 (N–C=*C*), 116.7 (CH-6), 124.1 (C), 126.2 (2CH), 127.7 (CH-5), 128.0 (CH-7), 128.6 (CH), 129.1 (2CH), 129.7 and 129.9 (2C), 130.0 (CH-8), 130.3 (CH-4), 136.2, 144.4, 147.4, and 155.3 (4C), 164.4, 166.5, and 169.1 (3 C=O).

5-Ethyl 2,3-dimethyl 6-amino-1-benzyl-1, 4-dihydro-4-(7-methyltetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5 tricarboxylate (3d)

Yellow powder; mp: 233–236 °C; 0.667 g, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3422, 3277, 3031, 2982, 1747, 1708, 1656, 1496, 1211, 806. Ms: *m/z* (%) = 483 (M^+ - CO_2Et, 7), 455 (5), 415 (5), 310 (11), 254 (20), 223 (20), 196 (20), 91 (100), 65 (17). Anal. Calcd for $C_{29}H_{28}N_6O_6$ (556.2): C, 62.58; H, 5.07; N, 15.10. Found C, 62.32; H, 5.18; N, 14.88. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.19 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 2.56 (s, 3H, CH_3), 3.62 and 3.64 (2 s, 6H, 2OCH_3), 4.01 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2), 5.12 (AB quartet, δ_A = 5.00, δ_B = 5.25, J_{AB} = 18.8 Hz, NCH_2), 5.45 (s, H, CH), 6.41 (bs, 2H, NH_2), 7.33–7.71 (m, 8H, 8CH, Ar), 8.50 (d, 1H, $^3J_{HH}$ = 8.5 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 14.5 and 21.4 (2CH_3), 36.6 (CH), 51.9 (NCH_2 and OCH_3), 52.8 (OCH_3), 59.3 (OCH_2), 78.3 (NH_2–C=*C*), 104.9 (N–C=*C*), 116.4 (CH-6), 124.2 (C), 126.3 (2CH), 128.1 and 128.2 (2CH), 129.1 (2CH), 129.5 (C), 130.0 (CH-8), 131.5 (CH-4), 136.1, 137.8, 140.01, 144.5, 147.1, and 155.1 (6C), 164.9, 166.0, and 169.0 (3 C=O).

5-Ethyl 2,3-dimethyl 6-amino-1,4-dihydro-1-phenethyl-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5-tricarboxylate (3e)

Yellow powder; mp: 234.7–235.6 °C; 0.778 g, yield: 70%. IR (KBr) (υ_{max}/cm^{-1}): 3450, 3218, 3035, 2972, 1733, 1707, 1658, 1505, 1210, 752. Ms: *m/z* (%) = 483 (M^+ - CO_2Et, 23), 455 (19), 365 (19), 319 (28), 206 (16), 172 (47), 140 (38), 105 (100), 77 (24). Anal. Calcd for $C_{29}H_{28}N_6O_6$ (556.2): C, 62.58; H, 5.07; N, 15.10. Found C, 62.30; H, 5.16; N, 14.92. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.13 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.15–3.22 (m, 2H, CH_2Ph), 3.62 and 3.93 (2 s, 6H, 2OCH_3), 3.98–4.06 (m, 4H, 2CH_2), 5.45 (s, 1H, CH), 6.29 (bs, 2H, NH_2), 7.26–7.38 (m, 5H, 5CH, Ar), 7.64 (t, 1H, $^3J_{HH}$ = 7.8 Hz, CH-6, Ar), 7.76 (s, 1H, CH-4, Ar), 7.78 (t, 1H, $^3J_{HH}$ = 7.5 Hz, CH-7, Ar), 7.91 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH-5, Ar), 8.62 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 14.4 (CH_3), 36.1 (CH), 36.5 (CH_2Ph), 49.8 (NCH_2), 51.9 and 53.2 (2OCH_3), 59.4 (OCH_2), 78.5 (NH_2–C=*C*), 104.8 (N–C=*C*), 116.7 (CH-6), 124.1 (C), 127.2 (CH-5), 127.6 (CH-7), 128.6 (CH), 128.9 (2CH), 129.1 (2CH), 129.3 and 129.9 (2C), 130.0 and 130.2 (2CH), 137.8, 144.3, 147.2, and 154.4 (4C), 165.2, 166.0, and 169.2 (3 C=O).

5-Ethyl 2,3-dimethyl 1-(4-methoxyphenethyl)-6-amino-1,4-dihydro-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5-tricarboxylate (3f)

Yellow powder; mp: 218–220 °C; 0.879 g, yield: 75%. IR (KBr) (υ_{max}/cm^{-1}): 3401, 3199, 2980, 2950, 1751, 1710, 1652, 1500, 1225, 789. Ms: *m*/*z* (%) = 513 (M^+ - CO_2Et, 15), 379 (10), 319 (13), 292 (66), 238 (73), 194 (18), 134 (100), 91 (61), 55 (43). Anal. Calcd for $C_{30}H_{30}N_6O_6$ (586.2): C, 61.43; H, 5.15; N, 14.33. Found C, 61.19; H, 5.26; N, 14.55. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.12 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.09–3.13 (m, 2H, CH_2Ph), 3.61, 379, and 3.92 (3 s, 9H, 3OCH_3), 4.00–4.13 (m, 4H, NCH_2 and OCH_2), 5.44 (s, 1H, CH), 6.28 (bs, 2H, NH_2), 6.87 (d, 2H, $^3J_{HH}$ = 8.0 Hz, 2CH, Ar), 7.19 (d, 2H,$^3J_{HH}$ = 8.0 Hz, 2CH, Ar), 7.64 (t, 1H, $^3J_{HH}$ = 7.5 Hz, CH-6, Ar), 7.75 (s, 1H, CH-4, Ar), 7.75 (t, 1H, $^3J_{HH}$ = 7.8 Hz, CH-7, Ar), 7.90 (d, 1H, $^3J_{HH}$ = 7.8 Hz, CH-5, Ar), 8.61 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ(ppm) = 14.4 (CH_3), 35.1 (CH), 36.5 (CH_2Ph), 50.1 (NCH_2), 51.9, 53.1, and 55.2 (3OCH_3), 59.3 (OCH_2), 78.4 (NH_2–C=*C*), 104.9 (N–C=*C*), 114.5 (2CH), 116.7 (CH-6), 124.1 (C), 127.7 (CH-5), 128.7 (CH-7), 129.7 (C) 129.8 (2C), 129.9 (2CH), 130.0 and 130.2 (2CH), 144.2, 147.3, 154.6, and 158.7 (4C), 165.3, 166.0, and 169.1 (3 C=O).

5-Ethyl 2,3-dimethyl 6-amino-1,4-dihydro-1-propyl-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3,5-tricarboxylate (3g)

Yellow powder; mp: 189–203 °C; 0.494 g, yield: 50%. IR (KBr) (υ_{max}/cm^{-1}): 3450, 3216, 2973, 1733, 1707, 1658, 1505, 1210, 752. Ms: *m*/*z* (%) = 494 (M^+, 38), 421 (100), 393 (81), 319 (71), 194 (76), 149 (81), 97 (73), 57 (99). Anal. Calcd for $C_{24}H_{26}N_6O_6$ (494.2): C, 58.29; H, 5.30; N, 16.99. Found C, 58.05; H, 5.42; N, 16.33. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.00 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.12 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3), 1.88–2.04 (m, 2H, CH_2), 3.59 (s, 3H, OCH_3), 3.56–3.66 (m, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 3.96–4.05 (m, 2H, OCH_2), 5.49 (s, 1H, CH), 6.64 (bs, 2H, NH_2), 7.64 (t, 1H, $^3J_{HH}$ = 8.3 Hz, CH-6, Ar), 7.75 (s, 1H, CH-4, Ar), 7.78 (t, 1H, $^3J_{HH}$ = 8.3 Hz, CH-7, Ar), 7.90 (d, 1H, $^3J_{HH}$ = 8.3 Hz, CH-5, Ar), 8.63 (d, 1H, $^3J_{HH}$ = 8.5 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 11.5 and 14.4 (2CH_3), 23.4 (CH_2), 36.2 (CH), 49.3 (NCH_2), 51.9 and 53.0 (2OCH_3), 59.4 (OCH_2), 78.3 (NH_2–C=*C*), 104.2 (N-C=*C*), 116.7 (CH-6), 124.2 (C), 127.7 (CH-5), 128.6 (CH-7), 129.9 (C), 130.0 (CH-8), 130.2 (CH-4), 130.5, 144.1, 147.3, and 154.0 (4C), 165.1, 166.1, and 169.3 (3 C=O).

Diethyl 1-benzyl-5-cyano-1,6-dihydro-6-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3-dicarboxylate (4b)

White crystals; mp: 150–153 °C; 0.626, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3058, 2231, 1736, 1727, 1673, 1281, 1241, 1021, 764. Ms: *m*/*z* (%) = 522 (M^+, 2), 419 (4), 359 (2), 315 (2), 288 (3), 260 (2), 231 (2), 204 (2), 177 (3), 134 (100), 91 (23), 65 (5). Anal. Calcd for $C_{28}H_{22}N_6O_5$ (522.1): C, 64.36; H, 4.24; N, 16.08. Found C, 63.75; H, 4.37; N, 15.82. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.68 (t, 3H, $^3J_{HH}$ = 6.7 Hz, CH_3), 1.12 (t, 3H, $^3J_{HH}$ = 6.7 Hz, CH_3), 3.75–3.81 (m, 2H, OCH_2), 4.22 (q, 2H, $^3J_{HH}$ = 7 Hz, OCH_2), 5.41 (ABq, δ_A = 5.28, δ_B = 5.54, J_{AB} = 15.2 Hz, NCH_2), 7.32 (m, 5H, 5CH, Ar), 7.78 (t, 1H, $^3J_{HH}$ = 7.7 Hz, CH-6, Ar), 7.97 (t, 1H, $^3J_{HH}$ = 7.7 Hz, CH-7, Ar), 8.09 (d, 1H, $^3J_{HH}$ = 11.5 Hz, CH-5, Ar), 8.12 (s, 1H, CH-4, Ar), 8.7(d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.1, 13.3 (2CH_3), 50.5 (NCH_2), 62.3 and 63.7 (2OCH_2), 107.5, 109.1, and 113.6 (3C), 117.0 (CH), 120.9 and 123.2 (2C), 127.8 (2CH), 128.5 and 128.6 (2CH), 128.8 (2CH), 129.9 (CH), 130.8 (C), 132.6, 133.0(2CH), 133.7, 146.0, 148.5, and 151.9 (4C), 158.4, 160.9, and 162.4 (3 C=O).

Diethyl 5-cyano-1,6-dihydro-6-oxo-1-phenethyl-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3-dicarboxylate (4h)

White crystals; mp: 177–180 °C; 0804 g, yield: 75%. IR (KBr) (υ_{max}/cm^{-1}): 3028, 2229, 1735, 1717, 1689, 1308, 1243, 1190, 1016, 766. Ms: *m*/*z* (%) = 536 (M^+, 6), 492 (3), 464 (3), 404 (3), 360 (4), 316 (15), 288 (36), 260 (15), 177 (6), 134 (100), 104 (75), 77 (17), 51 (6). Anal. Calcd for $C_{29}H_{24}N_6O_5$ (536.1): C, 64.92; H, 4.51; N, 15.66. Found C, 64.30; H, 4.76; N, 14.97. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.65 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 1.44 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 3.15 (t, 2H, $^3J_{HH}$ = 8.5 Hz, CH_2Ph), 3.80–3.82 (m, 2H, OCH_2), 4.12 and 4.30 (2 m, 2H, NCH_2), 4.51 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2), 7.25–7.36 (m, 5H, 5CH, Ar), 7.79 (t, 1H, $^3J_{HH}$ = 7.7 Hz, CH-6, Ar), 7.98 (t, 1H, $^3J_{HH}$ = 8.0 Hz, CH-7, Ar), 8.09 (s, 1H, CH-4, Ar), 8.11 (d, 1H, $^3J_{HH}$ = 8 Hz CH-5, Ar), 8.74 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.1, 13.8, (2CH_3), 34.7 (CH_2Ph), 50.6 (NCH_2), 62.2 and 64.0 (2OCH_2), 107.2, 109.3 and 113.6 (3C), 117.0 (CH), 121.2 and 123.3 (2C), 127.2 and 128.6 (2CH), 128.8, (2CH), 128.9 (2CH), 129.9 (CH), 130.8 (C), 132.6 and 132.7 (2CH), 136.8, 146.1, 149.0, and 151.9 (4C), 158.1, 161.1, and 162.2 (3 C=O).

Diethyl 1-(4-methoxyphenethyl)-5-cyano-1,6-dihydro-6-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3-dicarboxylate (4i)

White crystals; mp: 192–197 °C; 0.679 g, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3053, 1739, 1673, 1314, 1242, 1182,765. MS: *m*/*z* (%) = 566 (M^+, 2), 521 (2), 231 (2), 204 (2), 177 (3), 134 (100), 122 (14), 91 (7), 89 (5), 65 (2). Anal. Calcd for $C_{30}H_{26}N_6O_6$ (566.1): C, 63.60; H, 4.63; N, 14.83. Found C, 62.98; H, 4.72; N, 14.32. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.657 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 1.44 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 3.08 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2Ph), 3.81 (bs, 5H, OCH_3, $OCH_{2,}$), 4.10 and 4.25 (2 m, 2H, NCH_2), 4.49–4.52 (m, 2H, OCH_2), 6.89 (d, 2H, $^3J_{HH}$ = 8.0 Hz, 2CH, Ar), 7.22 (d, 2H, $^3J_{HH}$ = 8.2 Hz, 2CH, Ar), 7.80 (t, 1H, $^3J_{HH}$ = 6.5 Hz, CH-6, Ar), 7.99 (t, 1H, $^3J_{HH}$ = 6.7 Hz, CH-7, Ar), 8.09 (s, 2H, 2CH-4, 5, Ar), 8.75 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.1 and 13.8 ($2CH_3$), 33.8 (CH_2Ph), 50.5 (NCH_2), 55.3 (OCH_3), 62.2 and 64.0 ($2OCH_2$), 107.2, 109.3 and 113.6 (3C), 114.3 (2CH), 117.0 (CH), 121.2 and 123.2 (2C), 128.6 (CH), 128.6 (C), 129.8 (3CH), 130.8 (C), 132.6 (2CH), 146.1, 149.0, 151.8, and 158.1 (4C), 158.8, 161.1, and 162.2 (3 C=O).

X-ray crystal-structure of ***4i****. Structure-determination and refinement of data* Formula ($C_{30}H_{26}N_6O_6$): *F*w = 566.57, monoclinic, space group *P*21/n, Z = 4, *a* = 9.5087 (19) Å, *b* = 21.965 (4) Å, *c* = 14.004 (3) Å, α = 90°, β = 105.74 (3)°, γ = 90°, *V* = 2815.2 (10) Å^3, D_{calcd} = 1.337 g cm^{-3}, *R* (reflections) = 0.0635(4208), wR2 (reflections) = 0.1626 (4897), Mo (λ = 0.71073 Å), *T* = 293 K. The crystallographic data of **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1560095. Copies of the data can be obtained free of charge (http://www.ccdc.cam.ac.uk/data_request/cif, deposit@ccdc.cam.ac.uk).

Diethyl 1-(4-methoxyphenethyl)-5-cyano-1,6-dihydro-4-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-6-oxopyridine-2,3-dicarboxylate (4j)

White crystals; mp: 199–200 °C; 0.696 g, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3045, 2231, 1734, 1717, 1687, 1304, 1246, 1188, 1021, 828. Ms: *m*/*z* (%) = 580 (M^+, 2), 535 (2), 507 (2), 431 (2), 274 (4), 245 (4), 177 (10), 134 (100), 122 (35), 91 (20), 51 (12).Anal. Calcd for $C_{31}H_{28}N_6O_6$ (580.2): C, 64.13; H, 4.86; N, 14.47. Found C, 63.52; H, 5.04; N, 14.15. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.63 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 1.43 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 2.51 (s, 3H, CH_3), 3.08 (t, 2H, $^3J_{HH}$ = 8 Hz, CH_2Ph), 3.79 (bs, 5H, OCH_3, OCH_2), 4.07 and 4.26 (2 m, 2H, NCH_2), 4.50 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2), 6.89 (d, 2H, $^3J_{HH}$ = 8 Hz, 2CH, Ar), 7.22 (d, 2H, $^3J_{HH}$ = 8.2 Hz, 2CH, Ar), 7.80 (d, 1H, $^3J_{HH}$ = 8.5 Hz, CH-7, Ar), 7.86 (s, 1H, CH, Ar), 8.02 (s, 1H, CH-4, Ar), 8.61 (d, 1H, $^3J_{HH}$ = 8.5 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.1, 13.8, and 21.4 ($3CH_3$), 33.8 (CH_2Ph), 50.8 (NCH_2), 55.3 (OCH_3), 62.1 and 64.0 ($2OCH_2$), 107.2, 109.3 and 113.6 (3C), 114.3 (2CH), 116.7 (CH), 121.0 and 123.3 (2C), 128.7 (CH), 128.8 (C), 129.4 (CH), 129.8 (2CH), 132.5, 134.0 (2CH), 139.1, 145.9, 148.9, 152.0, and 158.1 (5C), 158.8, 161.1, and 162.3 (3 C=O).

Diethyl 5-cyano-1,6-dihydro-1-isopropyl-6-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3-dicarboxylate (4k)

White crystals; mp: 191–192 °C; 0.663 g, yield: 70%. IR (KBr) (υ_{max}/cm^{-1}): 3043, 2230, 1743, 1726, 1675, 1309, 1230, 1184, 763. Ms: *m*/*z* (%) = 474 (M^+, 18), 446 (9), 404 (55), 331 (100), 287 (28), 260 (85), 231 (88), 204 (31), 177 (38), 151 (10), 115 (6), 89 (5), 63 (3).Anal. Calcd for $C_{24}H_{22}N_6O_5$ (474.1): C, 60.75; H, 4.67; N, 17.71. Found C, 60.17; H, 4.83; N, 17.35. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.59 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.43 (t, 3H, $^3J_{HH}$ = 7 Hz, CH_3), 1.71 (d, 3H, $^3J_{HH}$ = 6.5 Hz, CH_3), 1.74 (d, 3H, $^3J_{HH}$ = 5.2 Hz, CH_3), 3.75–3.80 (m, 2H, OCH_2), 4.27 (m, 1H, NCH), 4.46–4.52 (m, 2H, OCH_2), 7.81 (t, 1H, $^3J_{HH}$ = 8.7 Hz, CH-6, Ar), 7.97 (t, 1H, $^3J_{HH}$ = 8.2 Hz,CH-7, Ar), 8.05 (s, 1H, CH-4, Ar), 8.07 (d, 1H, $^3J_{HH}$ = 9 Hz, CH-5, Ar), 8.73 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.0, 13.8, 19.2, and 19.3 ($4CH_3$), 59.0 (NCH), 62.0 and 63.7 ($2OCH_2$), 107.1, 109.9, and 113.7 (C), 116.9 (CH), 121.2 and 123.3 (2C), 128.6 and 129.8 (2CH), 130.7 (C), 132.5 (2CH), 146.1, 149.5, and 151.3 (3C), 158.4, 161.5, and 162.4 (3 C=O).

Diethyl 5-cyano-1,6-dihydro-1-isobutyl-6-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)pyridine-2,3-dicarboxylate (4l)

White crystals; mp: 170–172 °C; 0.537 g, yield: 55%. IR (KBr) (υ_{max}/cm^{-1}): 3048, 2232, 1751, 1728, 1672, 1315, 1280, 1241, 77. Ms: *m*/*z* (%) = 488 (M^+, 6), 433 (100), 404 (49), 359 (15), 331 (52), 287 (20), 260 (40), 231 (46), 204 (15), 177 (18), 134 (6), 91 (2), 57 (9). Anal. Calcd for $C_{25}H_{24}N_6O_5$ (488.2): C, 61.47; H, 4.95; N, 17.20. Found C, 60.89; H, 5.14; N, 16.93. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 0.64 (t, 3H, $^3J_{HH}$ = 6.5 Hz, CH_3), 098 (d, 6H, $^3J_{HH}$ = 3.5 Hz, $2CH_3$), 1.40 (t, 3H, $^3J_{HH}$ = 6.7 Hz, CH_3), 2.27 (m, 1H, CH), 3.74–3.80 (m, 2H, OCH_2), 3.88–4.11 (m, 2H, NCH_2), 4.45 (q, 2H, $^3J_{HH}$ = 6.5 Hz, OCH_2), 7.77 (t, 1H, $^3J_{HH}$ = 7.5 Hz, CH-6, Ar), 7.96 (t, 1H, $^3J_{HH}$ = 7.7 Hz, CH-7, Ar), 8.08 (d, 1H, $^3J_{HH}$ = 8.5 Hz, CH5, Ar), 8.10 (s, 1H, CH-4, Ar), 8.72 (d, 1H, $^3J_{HH}$ = 8.2 Hz, CH-8, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 13.1, 13.8, 20.0, and 20.1 ($4CH_3$), 28.1 (CH), 54.8 (NCH_2), 62.2, 63.8 ($2OCH_2$), 107.3, 109.9, and 113.8 (3C), 116.9 (CH), 121.1, 123.2 (2C),

128.6 and 129.9 (2CH), 130.7 (C), 132.6 and 132.8 (2CH), 146.1, 149.0, and 151.6 (3C), 158.6, 161.0, and 162.4 (3 C=O).

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