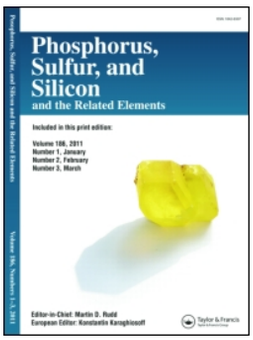

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# Synthesis of thiazolo[3,2-*a*]pyridines via an unusual Mannich-type cyclization

Victor V. Dotsenko[a,b], Ivan S. Bushmarinov[c], Alexander S. Goloveshkin[c], Elena A. Chigorina[d], Konstantin A. Frolov[a], and Sergey G. Krivokolysko[a]

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**ABSTRACT**

The Mannich-type reaction of *N*-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates with 3-(1,3-benzodioxol-5-yl)-2-methylpropanal (ocean propanal) and *p*-toluidine afforded 7-aryl-2-(1,3-benzodioxol-5-ylmethyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyridine-8-carbonitriles in modest (25–46%) yields. The structure of the key compound was confirmed by X-ray crystal structure analysis.

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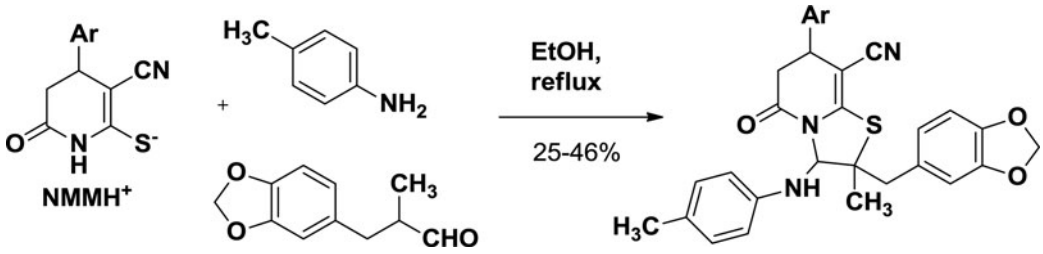
Thiazolo[3,2-*a*]pyridines; aminomethylation; Mannich reaction; X-ray studies; bis(pyrid-2-yl)disulfides

**GRAPHICAL ABSTRACT**




## Introduction

3-Cyanopyridine-2(1*H*)-thiones and related thiolates are known as useful and versatile building blocks in organic chemistry.[1–10] Recently it was shown that pyridine-2(1*H*)-thiones and related thiolates easily react with primary amines and formaldehyde HCHO to give, depending on the reaction conditions, stoichiometry and the nature of the reagents, a wide range of heterocyclic systems including pyrido[1,2-*a*][1,3,5]triazines **1**,[11,12] dipyridotetrazocines **2**,[13] pyrido[2,1-*b*][1,3,5]thiadiazines **3–5**,[14–22] diazabicyclo[3.3.1]non-3-enes **6**,[21] 3,7-diazabicyclo[3.3.1]nonanes **7**[23–25] or tetraazatricyclo[7.3.1.0$^{2,7}$]tridec-2-enes **8**[26–31] (Scheme 1).

As was previously shown,[14,15,20–22] easily available pyridine-2-thiolates **9** smoothly react with HCHO and $RNH_2$ under mild conditions without any catalyst to form pyrido[2,1-*b*][1,3,5]thiadiazines **10** (Scheme 2). However, the Mannich reaction of thiolates **9** with other aliphatic aldehydes (such as acetaldehyde) resulted in resinification, and the formation of deeply colored complex mixtures, presumably owing to the side process of aldol-type condensations which is competing with aminomethylation.[22] The only exception is the reaction of compounds **9** with *p*-substituted anilines and isobutyraldehyde leading to the unusual Mannich products, thiazolo[3,2-*a*]pyridines; this reaction was reported in our preliminary communication.[32] In the reaction of thiolates **9** with aromatic aldehydes and benzyl amine, only benzylammonium salts **11** were isolated. No Mannich-type products were obtained when thiolates **9** were reacted with amines and aromatic aldehydes.[22]

## Results and discussion

In the present paper we report on the unusual Mannich-type reaction of thiolates **9** with the model amine, *p*-toluidine **12** and accessible $\alpha,\alpha$-disubstituted aldehyde-3-(1,3-benzodioxol-5-yl)-2-methylpropanal **13** (so-called "ocean propanal"). Surprisingly, when the reagents were heated in EtOH under reflux, thiazolo[3,2-*a*]pyridines **14a-e** were obtained in modest (25–46%) yields (Scheme 3).

The unusual fact of the formation of thiazolopyridine core in the aminomethylation process clearly reveals the special character of the Mannich reaction of pyridine-2-thiolates with $\alpha,\alpha$-disubstituted aldehydes and amines. A plausible mechanism has

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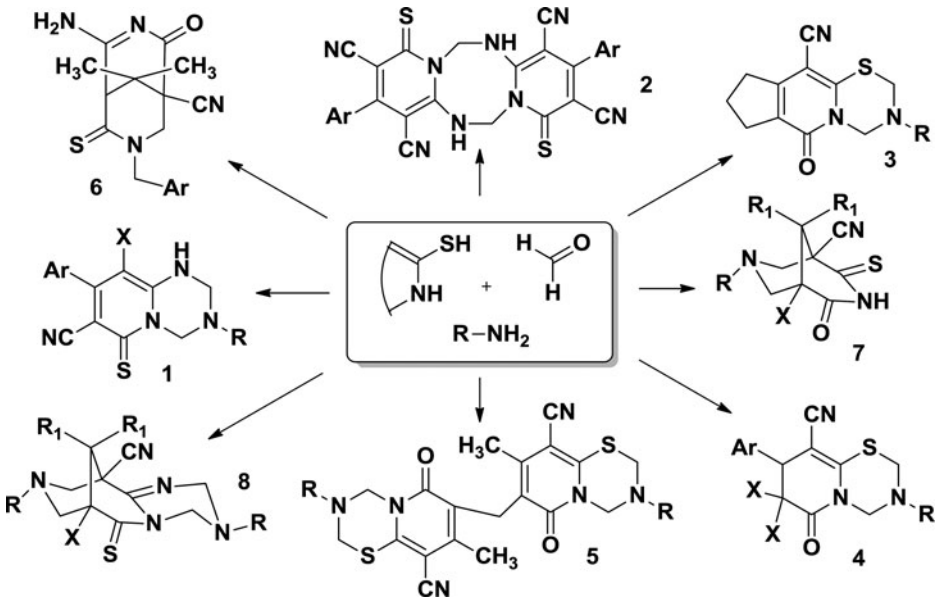
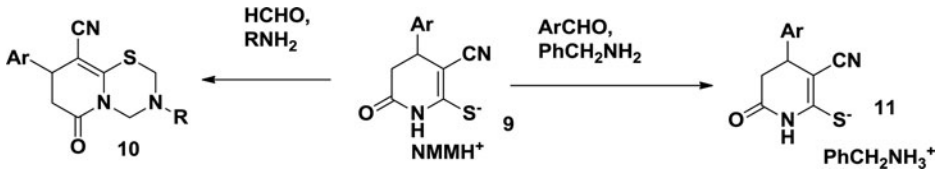


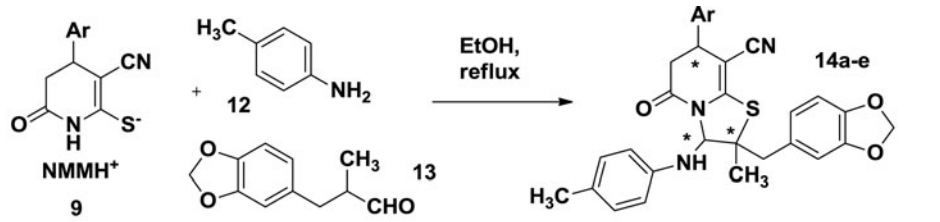
**Scheme 1.** The aminomethylation of pyridine-2(1*H*)-thiones and related species. X = electron-withdrawing group (CN, COOMe, COOEt).



**Scheme 2.** The aminomethylation of thiolates **9** (NMM = N-methylmorpholine).

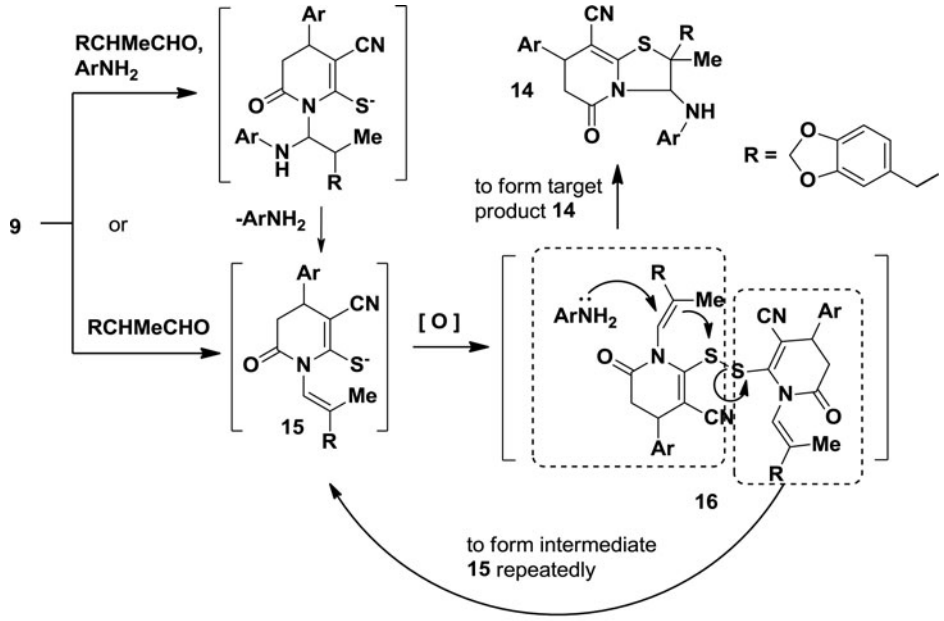
been suggested for the reaction. One may assume that on the first step of the cascade process N-aminoalkylation take place to form the intermediate **15** which can be oxidized by air to give disulfide intermediate **16**. The reaction did not proceed in the absence of air. Disulfide **16** can undergo an intramolecular S–S bond cleavage to give thiazolopyridine **14** and thiolate **15**. The latter upon the action of oxygen gives disulfide **16** which reacts repeatedly to afford thiazolopyridine **14** and thiolate **15** and so on (Scheme 4).

Evidently, the structure of the aldehyde component is a crucial factor that determines the specifics of the reaction: on the one hand, $\alpha,\alpha$-disubstituted aldehydes are able to form stable and active enamide/enamine species, on the other, they almost cannot react by self-condensation to form competing side products. The proposed mechanism was supported by the observation that thiolates **9**[33] and related compounds (e.g., [34]) can be oxidized in air to form corresponding 2,2′-*bis*(pyridyl)disulfides **17**. It is noteworthy that S–S bond in disulfides **17** could be easily cleaved by C-nucleophiles.[33] One may suggest the alternative mechanism which is based on the homolytic cleavage of disulfide bond. However, the homolysis of strong S–S bond with dissociation energy of 55–75 kcal/mol usually requires more harsh conditions and higher temperatures,[35] therefore the homolytic mechanism should be excluded. Additional supporting evidence for the proposed mechanism was obtained from the reaction of ocean propanal and *p*-toluidine with 2,2′-*bis*(pyridyl)disulfide **17a** which was obtained by the oxidation of thiolate **9a** with iodine.[33] Thiazolopyridine **14a** was obtained in 38% yield (Scheme 5).

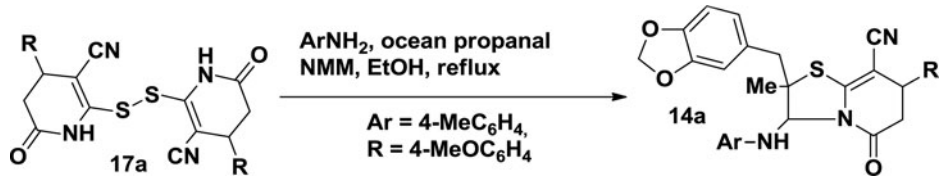


Ar = 4-$MeOC_6H_4$ (**a**); Ar = 2-$EtOC_6H_4$ (**b**); Ar = 2-furyl (**c**); Ar = 4-$BrC_6H_4$ (**d**); Ar = 4-BnO-3-$MeOC_6H_3$ (**e**).

**Scheme 3.** The reaction of thiolates **9** with ocean propanal and *p*-toluidine. Ar = 4-$MeOC_6H_4$ (**a**); Ar = 2-$EtOC_6H_4$ (**b**); Ar = 2-furyl (**c**); Ar = 4-$BrC_6H_4$ (**d**); Ar = 4-BnO-3-$MeOC_6H_3$ (**e**).




**Scheme 4.** Proposed mechanism for the formation of thiazolopyridines **14**.




**Scheme 5.** Synthesis of thiazolopyridine **14a** from disulfide **17a**.

Presumably, the modest yields of thiazolopyridines **14** are due to the multi-step mechanism of the reaction and competing side reactions. Since both ocean propanal **13** and thiolates **9** are racemates, the products have three chiral centers and are isolated as a complex mixture of diastereoisomers which cannot be easily separated. Compounds **14** are easily soluble in $Me_2CO$, EtOAc, DMSO and hot MeCN but sparingly soluble in alcohols. The structure of compounds **14a-e** was confirmed by $^1$H NMR, $^{13}$C APT NMR, IR, mass-spectrometry and LCMS data. The analysis of NMR spectra of compounds **14** revealed a complex mixture presumably due to the formation of diastereomers based on the presence of three stereogenic centers. In the IR spectra, the presence of a secondary amine moiety was confirmed by the appearance of the intense and sharp absorption bands exhibited at $\nu$ 3330 cm$^{-1}$. The IR spectra also revealed the conjugated nitrile adsorption bands and lactam C=O bands. The mass spectra showed peaks $[M + H]^+$ and $[M–ArNH_2]^+$. Since it was difficult to elucidate the structure of compounds **14** unequivocally from the spectral data, the structure of thiazolo[3,2-*a*]pyridine **14c** has been studied by X-ray single crystal methods (Fig. 1). The compound **14c** is a racemate (space group $P2_1/c$); the relative configuration of stereo centers was determined as 2*R*∗, 3*S*∗, 7*R*∗. In the bicyclic core, the cycle N1-C5-C6-C7-C8 = C8A has a *sofa* conformation with C6 lying 0.526(2) Å out of the plane of the remaining atoms (standard deviation 0.082 Å). The fragment S1-C2-C3-N1-C8A has an envelope conformation with C3 out of the plane of the other thiazole ring atoms by 0.520(2) Å. The lengths of bonds C–S & C–N have the expected[36] values. In a crystal, molecules of **14c** form centrosymmetric dimers, which are linked by hydrogen bonds N3-H3···N2 (N3···N2 3.034(2) Å, N3-H3···N2 160.5(17)°).

In summary, we have demonstrated that the Mannich reaction of N-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-thiolates **9** with ocean propanal and *p*-toluidine leads to the unexpected formation of functionalized

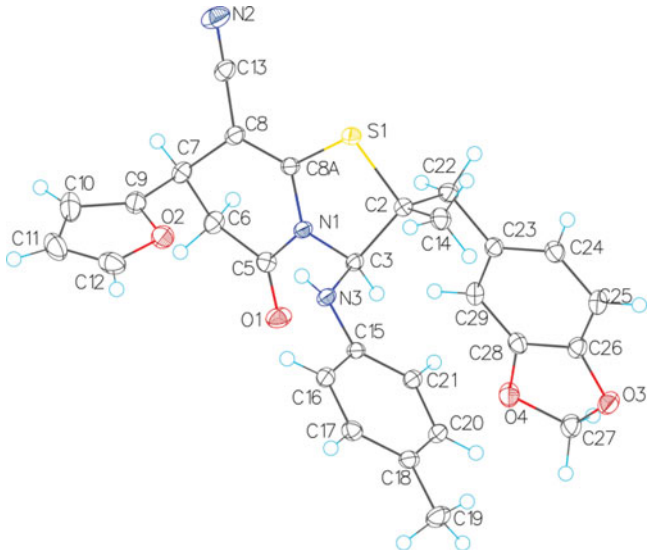



**Figure 1.** The structure of compound **14c**. Vibrational ellipsoids are shown at the 50% probability level.

thiazolo[3,2-*a*]pyridines. The structures of the new compounds was unambiguously confirmed by spectral data and X-ray analysis. As far as we know, the reaction demonstrates a new approach towards the construction of thiazolo[3,2-*a*]pyridine ring system. Further studies to expand the scope of the reaction and optimize the conditions are currently underway and will be published elsewhere.

## Experimental

The IR spectra were recorded on an IKS-29 (LOMO, USSR) instrument in Nujol mulls. NMR $^1$H spectra were recorded on a Bruker DPX-400 (400.4 MHz) and Bruker DRX-500 (500.07 MHz) instruments in DMSO-$d_6$ using TMS as an internal standard. NMR $^{13}$C and $^{13}$C APT spectra were recorded on a Bruker DRX-500 (125.76 MHz) device in DMSO-$d_6$ with TMS as an internal standard. Mass spectra of compounds **14a-c** (EI, 70 eV) were obtained on a MX-1321 spectrometer by direct inlet. LCMS analysis for compound **14a** was obtained on a PE SCIEX API 150EX mass spectrometer (API–ES) following separation on a Shimadzu LC-10AD liquid chromatography system with Waters XBridge C18 3.5 $\mu$m (4.6 × 150 mm) column, equipped with Shimadzu SP D-10A UV-Vis detector ($\lambda_{max}$ 220 and 254 nm) and Sedex 75 ELSD detector. C,H,N-analyses were performed on a Carlo Erba Strumentazione 1106 analyzer. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silicagel after Pitra with luminescent indicator for UV 254 on the aluminium foil, binder – starch) in the acetone–hexane (1:1) system; spots were visualized with iodine vapors and UV light. Ocean propanal **13** is commercially available reagent (Parchem). The Supplemental Materials contains additional experimental details and sample $^1$H, $^{13}$C NMR, mass and LC-MS spectra for compounds 14 (Figures S1–S18).

Starting thiolates **9** were obtained by the known method[14,20,22,37,38] as follows: a mixture of an aromatic aldehyde (0.05 mol), finely powdered cyanothioacetamide[39] (5.0 g, 0.05 mol), EtOH (35–40 mL) and 5–7 drops of N-methylmorpholine were stirred until cyanothioacetamide had dissolved and yellow (or orange) crystalline 3-aryl-2-cyanoprop-2-enethioamide started to precipitate. Then Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (7.5 g, 0.052 mol) and N-methylmorpholine (8.3 mL, 0.075 mol) were added, and the mixture was gently refluxed for 2−4 h. The solution was evaporated to a syrup, whereupon it was treated with acetone (50 mL). The light yellow (or beige) precipitate of the corresponding thiolate **9** was filtered off and washed with cold EtOH and acetone. The compounds were used without further purification.

*Thiazolo[3,2-a]pyridine-8-carbonitriles **14a-e** (General procedure).* *p*-Toluidine **12** (330 mg, 3.08 mmol) and ocean propanal **13** (1.7 mL, 10.2 mmol) were added to the suspension of thiolate **9a-e** (2.4 mmol) in the mixture of EtOH (12 mL) and water (2 mL). The mixture was heated under reflux for 10–15 h. The heavy red oil formed was separated by decantation and then dissolved in boiling *n*-BuOH (20 mL). The solution was left to stand at 25°C in a loosely stoppered flask. The crystalline solid which slowly (1–3 months) precipitate from the solution was filtered off and recrystallized from either BuOH or *i*-PrOH–MeCN. Compounds **14a-c** were obtained as colorless crystals, compounds **14d,e**—as yellow viscous oils.

*Synthesis of thiazolo[3,2-a]pyridine 5a from disulfide **17a**.* To the solution of ocean propanal **13** (1.7 mL, 10.2 mmol), p-toluidine **12** (300 mg, 3.08 mmol) and 0.3 mL (2.73 mmol) of *N*-methylmorpholine in 96% EtOH (15 mL), 0.62 g (1.2 mmol) of disulfide **17a** (0.62 g, 1.2 mmol) were added. The mixture were heated under reflux for 20 h, the precipitated yellowish solid was filtered off and recrystallized from BuOH to give 490 mg (38%) of thiazolo[3,2-*a*]pyridine **14a**. The physical data and spectra are in agreement with the data obtained for the sample of **14a** prepared from thiolate **9a**.

*2-(1,3-Benzodioxol-5-ylmethyl)-7-(4-methoxyphenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile **14a**, mixture of diastereomers*. White crystalline solid, yield was 46% (*n*-BuOH). IR spectrum (nujol): 3330 (NH), 2195 (C≡N), 1680 (C=O) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ 1.41–1.53 (m, 3H, 2-$CH_3$), 2.12–2.15 (m, 3H, ArMe), 2.29–2.42 (m, 1H, *cis*-H-6), 2.84–2.94 (m, 1H, 2-$CH_2$Ar), 3.04–3.12 (m, 1H, 2-$CH_2$Ar), 3.16–3.26 (m, 1H, *trans*-H-6), 3.69–3.75 (m, 3H, $OCH_3$), 3.85–3.92 (m, 1H, H-7), 5.93–6.04 (m, 3H, H-3 & $OCH_2O$ signals overlapped), 6.25 (d, ∼0.32H, $^3J$ = 9.4, NH), 6.36 (d, ∼0.36H, $^3J$ = 10.7, NH), 6.47 (d, ∼0.22H, $^3J$ = 11.0, NH), 6.67–6.95 (m, 9H, HAr), 7.08 (d, ∼1.23H, $^3J$ = 8.3, HAr), 7.16 (d, ∼0.71H, $^3J$ = 8.3, HAr). LCMS, *m/z* (ES-API): 1080.3 $[2M+H]^+$, 540.8 $[M+H]^+$, 433.6 $[M\text{-}ArNH_2]^+$. MS (EI, 70 eV) *m/z* (*I*, %): 539 $[M]^+$(22), 280 (23), 135 [3,4-$(OCH_2O)$-$C_6H_3CH_2]^+$(100), 118 (24), 107 (14). Anal. Calcd for $C_{31}H_{29}N_3O_4S$: C 69.00; H 5.42; N 7.79. M = 539.66. Found: C 69.31; H 5.54; N 7.65.

*2-(1,3-Benzodioxol-5-ylmethyl)-7-(2-ethoxyphenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile **14b**, mixture of diastereomers*. Colorless crystals, yield was 35% (*i*-PrOH: MeCN= 3: 1). IR spectrum (nujol): 3330 (NH), 2190 (C≡N), 1685 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$), $\delta$ 1.31 (t, $^3J$ = 6.8, 3H, $OCH_2CH_3$), 1.42 (s, ∼1.8H, 2-$CH_3$), 1.49 (s, ∼1.2H, 2-$CH_3$), 2.11 (s, ∼1.8H, $ArCH_3$), 2.14 (s, ∼1.2H, $ArCH_3$), 2.39–2.44 (m, 1H, *cis*-H-6), 2.84–2.94 (m, 1H, 2-$CH_2$Ar), 3.05–3.12 (m, 1H, 2-$CH_2$Ar), 3.19–3.26 (m, 1H, *trans*-H-6), 4.01–4.06 (m, 2H, $OCH_2CH_3$), 4.12–4.19 (m, 1H, H-7), 5.93–6.05 (m, 3H, H-3 &$OCH_2O$ signals overlapped), 6.32 (d, ∼0.6H, $^3J$ = 10.9, NH), 6.43 (d, ∼0.4H, $^3J$ = 10.9, NH), 6.73–6.97 (m, 9H, H-Ar), 7.07 (d, 1H, $^3J$ = 7.3, H-Ar), 7.17–7.21 (m, 1H, H-Ar). $^{13}$C NMR (126 MHz, DMSO-$d_6$), $\delta$ 14.4, 19.8, 20.0, 20.03, 27.1, 33.0, 36.3, 40.4, 46.5, 60.9, 62.1, 63.2, 74.8, 76.8, 79.6, 80.7, 100.8, 100.9, 106.8, 107.8, 108.2, 109.9, 110.8, 111.8, 113.8, 114.4, 118.6, 120.4, 122.7, 123.7, 125.9, 126.3, 126.8, 126.9, 127.7, 128.6, 129.01, 129.04, 129.6, 130.4, 143.4, 143.7, 146.2, 146.3, 146.8, 147.2, 153.0, 153.7, 155.2, 165.6, 166.2. $^{13}$C NMR APT (126 MHz, DMSO-$d_6$), $\delta$ 14.4*, 19.8*, 19.96*, 20.0*, 27.1*, 33.0*, 36.3, 46.5, 60.9, 62.1, 63.2, 74.8*, 76.8*, 79.6, 80.7, 100.8, 107.8*, 108.2*, 109.9*, 110.8*, 111.8*, 113.8*, 114.8*, 118.5, 120.4*, 122.7*, 123.7*, 125.9, 126.3, 126.8*, 126.9*, 127.65, 128.6*, 129.0*, 129.6, 130.4, 143.4, 143.7, 146.2, 146.3, 146.8, 147.2, 153.0, 153.7, 155.2, 165.6, 166.2. *Signals with the opposite phase. LCMS, *m/z* (ES-API): 447.0 $[M\text{-}ArNH_2]^+$, 552.2 $[M-H]^-$. MS (EI, 70 eV) *m/z* (*I*, %): 553 $[M]^+$(12), 280

(12), 135 [3,4-($OCH_2O$)-$C_6H_3CH_2$]$^+$(100), 118 (23), 91 (12). Anal.Calcd for $C_{32}H_{31}N_3O_4S$: C, 69.42; H, 5.64; N, 7.59. M = 553.69 Found: C, 69.51; H, 5.71; N, 7.55.

*2-(1,3-Benzodioxol-5-ylmethyl)-7-(2-furyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile* ***14c****, mixture of diastereomers*. Sand-colored crystals, yield was 25% (*i*-PrOH: MeCN= 2: 1). IR spectrum (nujol): 3330 (NH), 2195 (C≡N), 1680 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$), $\delta$ 1.38 (s, ~2.7H, 2-$CH_3$), 1.50* (s, ~0.3H, c, 2-$CH_3$), 2.06–2.16 (m, 3H, $ArCH_3$); 2.56 (br.d, 1H, $^2J$ = 16.3, cis-H-6), 2.85 (dd, 1H, $^2J$ = 16.3, $^3J$ = 6.8, trans-H-6), 3.05 and 3.08 (both are d, each 1H, $^2J$ = 13.3, 2-$CH_2$Ar), 4.02–4.03 (m, 1H, H-7), 6.00–6.02 (m, 3H, signals of H-3 & $OCH_2O$ overlapped), 6.13–6.15 (m, 1H, furyl H-4), 6.23 (d, 1H, $^3J$ = 10.4, NH), 6.31–6.33 (m, 1H, furyl H-3), 6.70–6.76 (m, 3H, H Ar), 6.84–6.89 (m, 4H, H Ar), 7.47–7.49 (m, ~0.9H, furyl H-5), 7.60–7.62* (m, ~0.1H, furyl H-5). *The observed signals of minor diastereomers.$^{13}$CNMR (126 MHz, DMSO-$d_6$), $\delta$ 19.7, 20.0, 32.6, 34.9, 46.5, 61.1, 75.0, 78.3, 100.9, 105.8, 107.86, 110.5, 110.8, 113.8, 118.4, 123.8, 126.0, 129.1, 129.6, 142.7, 143.8, 146.2, 146.9, 153.1, 154.0, 165.2. $^{13}$CNMRAPT (126 MHz, DMSO-$d_6$), $\delta$ 19.7** (Me), 20.0** (Me), 32.6** (C-7), 34.9 (C-6), 46.5 ($CH_2$Ar), 61.1 ($OCH_2O$), 75.0** (C-3), 78.3 (C-8), 100.9 (C-2), 105.8** (HC-Ar), 107.8** (HC-Ar), 110.4** (HC-Ar), 110.8** (HC-Ar), 113.8** (HC-Ar), 118.4 (C≡N), 123.8** (HC-Ar), 125.9 (C-Ar), 129.1** (HC-Ar), 129.5 (C-Ar), 142.7** (furyl C-5), 143.7 (furyl C-2), 146.2 (C-Ar), 146.9 (C-Ar), 153.1 (C-8a or C-Ar), 153.9 (C-Ar or C-8a), 165.2 (C=O). **Signals with the opposite phase. LCMS, *m/z* (ES-API): 501.1 [M+H]$^+$, 393.0 [M-$ArNH_2$]$^+$, 498.0 [M-H]$^-$. MS (EI, 70 eV) *m/z* (*I*, %): 499 [M]+(18), 280 (18), 135 [3,4-($OCH_2O$)-$C_6H_3CH_2$]$^+$(100), 118 (21), 107 (14), 91 (12), 77 (10). Anal. Calcd for $C_{28}H_{25}N_3O_4S$: C 67.32; H 5.04; N 8.41. M = 499.59. Found: C, 67.53; H, 5.15; N, 8.40.

*2-(1,3-Benzodioxol-5-ylmethyl)-7-(4-bromophenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile* ***14d****, mixture of diastereomers*. The compound **14d** was obtained as yellow viscous oil in 27% yield after double recrystallization of crude product from *n*-BuOH. IR spectrum (nujol): 3330 (NH), 2190 (C≡N), 1680 (C=O) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ 1.40–1.53 (m, 3H, 2-$CH_3$), 2.10–2.16 (m, 3H, $ArCH_3$), 4.11–4.15 (m, 1H, H-7), 6.00–6.05 (m, 3H, H-3 & $OCH_2O$ overlapped), 6.25–6.28 (m, 1H, NH), 6.67–6.95 (m, 7H, HAr), 7.16–7.20 (m, 2H, HAr), 7.55–7.60 (m, 2H, HAr). Anal. Calcd for $C_{30}H_{26}BrN_3O_3S$: C 61.23; H 4.45; N 13.58. M = 588.53. Found: C, 61.44; H, 4.68; N, 13.44.

*2-(1,3-Benzodioxol-5-ylmethyl)-7-(4-benzyloxy-3-methoxyphenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile* ***14e****, mixture of diastereomers*. The compound **14e** was obtained as viscous oil in 25% yield after double recrystallization of crude product from *n*-BuOH. IR spectrum (nujol): 3330 (NH), 2195 (C≡N), 1680 (C=O cm$^{-1}$.$^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ 1.40–1.50 (m, 3H, 2-$CH_3$), 2.13–2.17 (m, 3H, $ArCH_3$), 3.72–3.75 (3H, m, OMe), 4.09–4.15 (m, 1H, H-7), 4.99–5.03 (m, 2H, Ph$C\underline{H}_2O$), 5.97–6.05 (m, 3H, H-3 & $OCH_2O$ overlapped), 6.25–6.30 (m, 1H, NH), 6.60–7.45 (m, 15H, HAr). Anal. Calcd for $C_{38}H_{35}N_3O_5S$: C 70.68; H 5.46; N 6.51. M = 645.78. Found: C, 70.49; H, 5.63; N, 6.48.

*X-ray studies of 2-(1,3-benzodioxol-5-ylmethyl)-7-(2-furyl)-2-methyl-3-[(4-methyl-phenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile* ***14c***. Single crystals of **14c** ($C_{28}H_{25}N_3O_4S$) were obtained by recrystallization from *i*-PrOH–MeCN mixture (2:1). X-ray diffraction studies were performed on a Bruker APEX II CCD diffractometer at 100 K. The structure was solved by charge flipping method (olex2.solve) and refined by the least squares technique using Olex2[40] software package and SHELXL 2014/7 program. Crystals of compound **14c** are monoclinic, $C_{28}H_{25}N_3O_4S$ (M = 499.57), space group $P2_1/c$ (No 14), $a$ = 10.099(6) Å, $b$ = 13.104(8) Å, $c$ = 18.303(10) Å, $\beta$ = 90.754(13)°, $V$ = 2422(2) Å$^3$, $Z$ = 4, $T$ = 100 K, $\mu$(MoK$\alpha$) = 0.175 mm$^{-1}$, $D_{calc}$ = 1.370 g/cm$^3$, 26667 reflections were collected (3.822° ≤ 2Θ ≤ 66.262°), of which 8871 were independent ($R_{int}$ = 0.0376, $R_{sigma}$ = 0.0479). The final probability factors were: $R_1$ = 0.0470 (I > 2$\sigma$(I)), w$R_2$ = 0.1196 (all reflections). The full crystallographic data has been placed at the Cambridge Crystallographic Data Center as deposit CCDC 1056696. Additional X-ray data collection parameters and selected bond lengths and angles are found in Tables S1–S8 (Supplemental Materials).

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