Synthesis of Substituted 3-(5-amino-[1,3,4]thiadiazol-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones

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An efficient two-step synthesis of novel 3-(5-amino-[1,3,4]thiadiazol-2-yl)-2*H*-pyrano[2,3-*c*]pyridine-2-ones was developed. In the first step, a new 2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide **5** was prepared by Knoevenagel condensation of pyridoxal hydrochloride with cyanoacetamide. In the second step, the reaction of carboxamide **5** with a series of N^4-substituted thiosemicarbazides yielded a library of 35 discrete compounds **8***{1-35}* in high yields. The intermolecular recyclization mechanism leading to these products is discussed.

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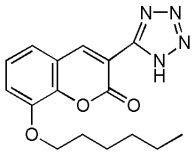
Introduction.

In continuation of our studies on the chemistry of substituted benzopyran-2-ones, we wish to report a general synthetic route to their novel 7-azaanalogs, the synthesis of a modest sized library of pyrano[2,3-*c*]pyridine-2-ones from pyridoxal and N^4-substituted thiosemicarbazides, and discuss possible mechanism of the intermolecular conversion. 3-Substituted 2*H*-benzopyran-2-one derivatives are known to possess a variety of biological activity. For instance, compounds **1** and **2** have been reported as mediator release inhibitors possessing antiallergic, antiarthritic [1] and antiasthmatic activities [2]. 2-Imino-derivatives of 3-substituted 2*H*-benzopyran-2-ones have been described as anti-inflammatory [3] and oncolytic [4] agents. These examples highlight the ongoing interest toward new benzopyran-2-one derivatives and have prompted us to explore synthetic route to their heterocycle-modified analogs, which can serve as a promising source of bioactive molecules.



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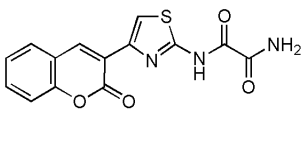

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Results and Discussion.

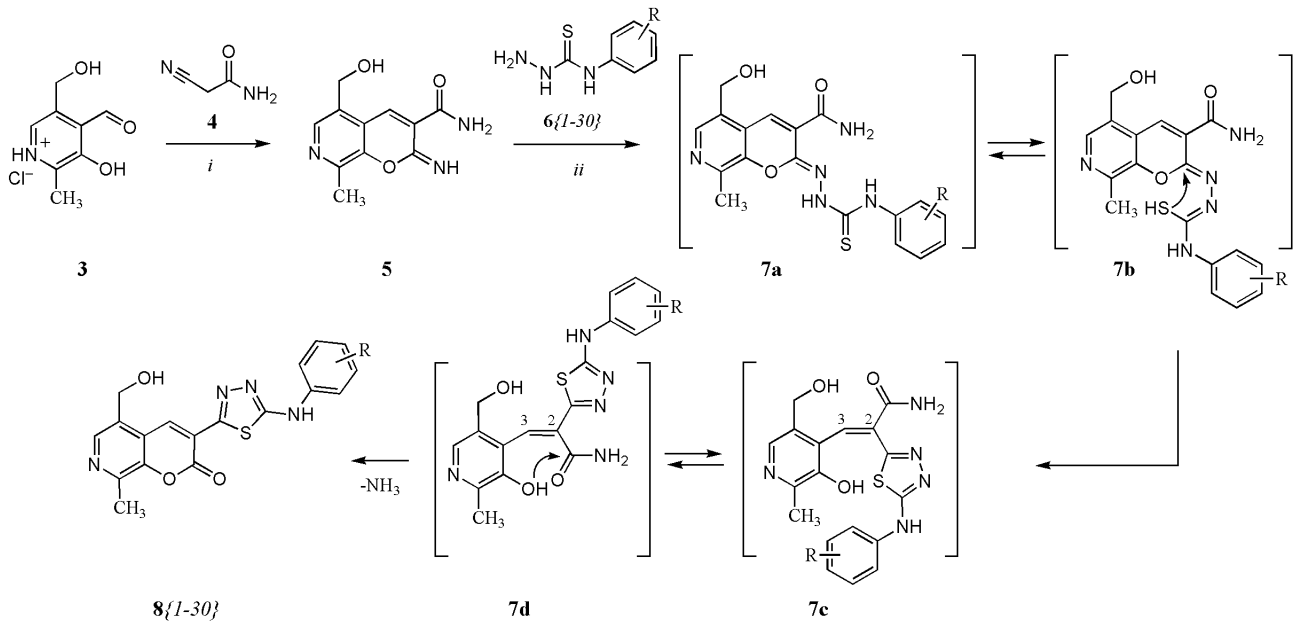
Knoevenagel condensation is a well-documented approach for the synthesis of 3-substituted coumarins [5]. However, there are only a few examples in which this method has been used for preparation of 3-substituted 7-azacoumarin derivatives [6]. Here, we report the use of the Knoevenagel reaction for the synthesis of 2*H*-pyrano[2,3-*c*]pyridine-3-carboxamides, which appear to be useful intermediates for diverse 3-heteroaryl-7-azacoumarins.

Recently, we have developed a novel synthetic approach to 3-substituted coumarins based on a rearrangement of 2-iminocoumarin-3-carboxamides under treatment with dinucleophilic agents as the key step [7-10]. We have obtained a series of 3-heteroaryl-2*H*-benzopyran-2-ones using acid-catalyzed intermolecular recyclization of the reactive intermediates produced by reaction of 2-imino-2*H*-1-benzopyran-3-carboxamides with *ortho*-substituted anilines [7], hydrazides of arylcarboxylic acids [8], anthranilic acids derivatives [9] and 2-aminothiophene derivatives [10]. The key benefits of our approach are high reaction yields, efficiency and synthetic convenience.

We recognized the efficacy of this recyclization conversion for the synthesis of different 3-substituted 2*H*-pyrano[2,3-*c*]pyridin-2-one derivatives. Accordingly, we envisaged that 2-imino-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide **5** and N^4-substituted thiosemicarbazides **6***{1-35}* would be suitable coupling partners for this transformation (Schemes 1 and 2).

Reaction of equimolar amounts of pyridoxal hydrochloride **3** and cyanoacetamide **4** in the presence of piperidine (2 equiv.) afforded carboxamide **5**. The reaction proceeded smoothly in absolute methanol, and the resulting product precipitated from the reaction mixture. Recrystallization from ethanol gave **5** as white crystals in 74% yield. The procedure is similar to that which we recently described for the synthesis of substituted 3-carboxamide-2*H*-benzopyran-2-imines [6-9], and can be recommended as an efficient synthetic approach to their heteroatom-containing analogs, which are useful synthetic intermediates for a variety of further transformations. Treatment of **5** with N^4-substituted thiosemicarbazides **6***{1-35}* in acetic acid at 40-45 °C furnished a library of novel 2*H*pyrano[2,3-*c*]pyridine-2-ones **8***{1-35}* in good yields. It can be suggested that, under the described conditions, the reaction proceeds *via* a series of species **7a-c** and involves a study of recyclization proposed in our recent work [10]. The intermediate **7a** represents a product of direct coupling of imine **5** with the NH_2-group of

Scheme 1

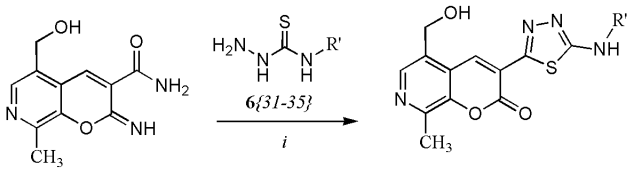


Reagents and conditions: (i) piperidine (2 equiv.), MeOH, 40-45 °C, 20 min (74%); (ii) AcOH, reflux, 20-30 min (39-93%). Substitutents R are given in Experimental Part.

the thiosemicarbazide **6**. Thione-thiol tautomeric conversion of **7a** leads to structure **7b**. The intermolecular nucleophilic attack of SH-group on the carbon atom of imino-group in the imidothiol **7b** is accompanied by opening of the iminolactone ring and formation of the 1,3,4-thiadiazole cycle in **7c**. *Cis-trans* isomerization (relative to the C2-C3 double bond) of the intermediate **7c** followed by secondary nucleophilic attack on the carbamoyl fragment in the intermediate **7d** restores the lactone cycle and affords the final compounds **8***{1-35}*. For reasons of clarity, Scheme 1 shows the reactions of carboxamide **5** with N^4-phenyl-substituted thiosemicarbazides, which constitute the major part of the studied transformations. However, a variety of differently substituted thiosemicarbazides can be used in this method. Scheme 2 shows the synthesis of five additional compounds **8***{31-35}* with R'-groups other than substituted phenyl.

The iminolactone ring opening is a well-documented transformation for 2-imino-2*H*benzopyran-3-carboxamides (Scheme 3) [11-14]. NMR spectral data of compounds of general formula **A** in dimethyl sulfoxide-d_6 solutions showed clearly the presence in solution not only of **A** but also of the two isomeric compounds **B** (s-*trans* and s-*cis*) which results from the opening of the pyran ring. Solution IR data also confirmed the presence of a nitrile band at 2260 cm^{-1}. It was observed that the preferred conformation for the C2-C3 bond (relative to OH) is s-*trans*. However, in solution the s-*cis* conformer is also present to a slight extent (ca. 5%), in equilibrium with s-*trans*, as evidenced by a very weak effect linking H-3 to H-6'.

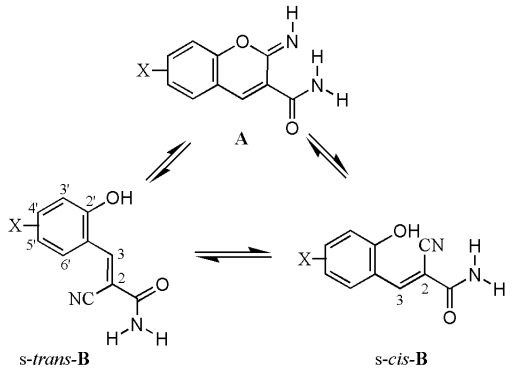
Scheme 2



8*{31}*: R' = 2-furylmethyl
8*{32}*: R' = ethyl
8*{33}*: R' = 2-tetrahydrofurylmethyl
8*{34}*: R' = allyl
8*{35}*: R' = phenethyl

Reagents and conditions: (i) AcOH, reflux, 20-30 min (34-76 %).

Scheme 3



The ring-unsubstituted compound **A** (X = H) underwent 35% ring-opening at 21 °C [12]. Isomerisation to this extent was evident immediately on dissolution (after 90 s), and at constant temperature there was no subsequent change in the percent isomerisation. Measurements at higher temperatures however showed that the extent of isomerisation was temperature-dependent, and that this dependence was reversible (prolonged heating at higher temperatures caused decomposition). These findings indicated that the two isomers, **A** and **B**, were in equilibrium in dimethyl sulfoxide. In other solvents (acetone-d_6 and deuteriochloroform), isomerisation did not occur, only the starting material **A** (X = H) being present.

A series of substituted compounds **A** (X ≠ H) displayed isomerism similar to **A** (X = H) in dimethyl sulfoxide [13]. The extent of a ring-opened form (measured after 24 h at 20 °C) was clearly related to the nature of the substituent and ranged from 0 to 86%. The position of the substituent group in the bicyclic compounds **A** was also significant. Thus, the 6-OMe (*para*-) and 8-OMe (*ortho*-) derivatives of **A** underwent 23 and 30% isomerisation, respectively, but the 7-OMe (*meta*-) derivative displayed 55% isomerisation. Apart from the 3-carbamoyl derivatives of **A**, the spectra of some other, related, 2-imino-2*H*-benzopyranes have also been examined. When the 3-carbamoyl group is replaced by a thiocarbamoyl group isomerisation to monocyclic compounds again takes place, and the degree of isomerisation follows a pattern very similar to that shown by the 3-carbamoyl compounds [14].

It is clear that 2-imino-2*H*-benzopyranes have a strong tendency to isomerise in dimethyl sulfoxide solution by ring-opening, and this should be borne in mind when analysing the spectral data for such compounds. The proposed mechanism of intermolecular transformations (Scheme 1) leading to compounds **8***{1-35}* is in full agreement with these experimental observations. Interestingly, we could not detect any ring-opening in DMSO-d_6 solution of compound **5** using conventional ^{1}H NMR measurements. The signals from the protons of the imino-group and from nonequivalent protons of the amido-group correspond to the ring-closed structure **A** indicate the presence of only the imine-form of compound **5** (Table 1).

It can be suggested that nucleophilic attack of the SH-group on the carbon atom of the imino-group in the imidothiol **7b** (Scheme 1) weakens the O1-C2 bond and favors opening of the iminolactone ring and formation of the 1,3,4-thiadiazole cycle. And, finally, the observed *cis-trans* isomerization relative to C2-C3 bond (conversion **7c**→**7d**) is related to the possibility of alternation of single and double bonds in these structures leading to isomeric forms in which the C2-C3 bond can freely rotate (Scheme 4).

Generally, the described reactions afforded very clean crystalline colored products. The colors ranged from yellow to orange. Isolated yields of **8***{1-35}* were generally high (>60%, up to 93%), except for a few cases.

The assignment of these structures was made on the basis of elemental analyses, IR-, ^{1}H NMR and mass-spectroscopy data. The IR spectra of pure products **8***{1-35}* indicated the presence of broadened O-H and N-H bands related to hydroxy and amide fragments, correspondingly, in the area of 3400-3300 cm^{-1}. Strong C=O bands at 1713-1759 cm^{-1} were also observed. Signals from the C=N fragments at 1632-1687 cm^{-1} were less expressed and usually were overlapped with signals from the aromatic C=C bonds.

^{1}H NMR spectra of compounds **8***{1-35}* showed characteristic signals from protons of the pyrano[2,3-*c*]pyridin-2-one heterocycle in the range of δ 8.78 – 9.11 (s, 1H, H-4) and δ 8.35 – 8.40 (s, 1H, H-6). All these spectra also contain resonances resulting from the methylene fragment (doublet at 4.80 – 4.90 ppm), hydroxyl (triplet at 5.45 – 5.52 ppm) and methyl group (singlet at 2.55 – 2.62 ppm). The proton of the secondary amino group was observed as

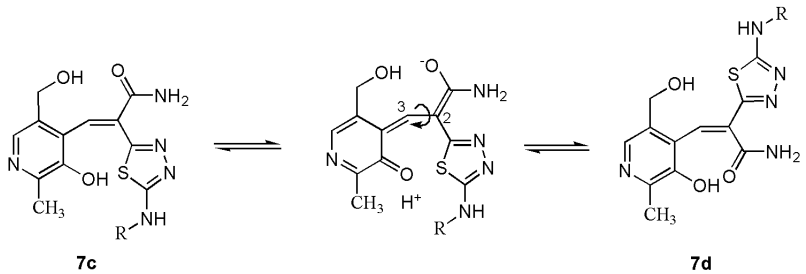
Table 1

Chemical Shifts (δ_H) of Imine, Amide and Hydroxyl Protons in the ^{1}H NMR Spectra in DMSO-d_6 [a]

Compound	=NH	NH	NH	2'-OH
5	9.04	7.70 (br. s.)	9.39 (br. s.)	no
A [b] (X = H)	8.90	7.81 (br. s.)	9.59 (br. s.)	no
B [b] (X = H)	no	7.7	7.8	10.44 (br. s.)

[a] Recorded at 20 °C (500 MHz); [b] Ref. [10].

Scheme 4



a broad singlet at 8.00 – 10.67 ppm. Mass-spectra of **8***{1-35}* revealed the presence of molecular ions and other large fragments, consistent with the assigned structures.

Conclusion.

We have shown that a novel 2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide **5** can be efficiently prepared by reaction of pyridoxal hydrochloride with cyanoacetamide. Upon treatment with N^4-substituted thiosemicarbazides, the carboxamide **5** can rearrange under acidic conditions by an intramolecular recyclization reaction leading to novel 3-heteroarylpyrano[2,3-*c*]pyridin-2-ones **8***{1-35}*. Considering the ease of preparation of the initial reactants, convenient synthesis and isolation of products, and the overall good chemical yields of these transformations, this route provides a new valuable entry to novel 7-azaanalogs of biologically active benzopyran-2-ones. The novel compounds represent valuable starting points for the development of compounds of biological interest. The use of compounds **8***{1-35}* in the search for novel bioactive agents is under investigation in the Chemical Diversity company and will be reported in a due course.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. IR spectra were recorded on Specord M80 spectrometers in KBr. ^{1}H NMR spectra were recorded on Varian Gemini-300 and Bruker DRX-500 spectrometers in DMSO-d_6 or DMSO-d_6 + CCl_4 (1:3) using TMS as an internal standard. Mass-spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer. Elemental analysis were within $\pm$ 0.4% of the theoretical value. $N^{(1)}$-Substituted thiosemicarbazides **6***{1-35}* were prepared from the corresponding dithiocarbamates using a previously described approach [14].

2-Imino-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide (**5**).

A solution of 10.18 g (50 mmol) of pyridoxal hydrochloride (**3**) and 4.2 g (50 mmol) of cyanoacetamide (**4**) in 100 ml of absolute methanol was heated to 40 – 45 °C. Distilled piperidine (1.0 ml, 100 mmol) was slowly added, and the resulting mixture was allowed to stand at 40 – 45 °C for 20 min. The formed precipitate was collected by filtration, washed by methanol and recrystallized from ethanol to afford (**5**) as a yellow crystalline solid. Yield 8.6 g (74%), mp 198–199 °C. ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H), 4.65 (d, 2H, J = 5.4 Hz), 5.30 (t, 1H, J = 5.2 Hz), 7.70 (s, 1H), 8.19 (s, 1H), 8.50 (s, 1H), 9.04 (s, 1H), 9.39 (s, 1H).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: H, 4.75; C 56.65; N 18.02. Found: H, 4.77; C 56.69; N 18.00.

General Procedure for the Reaction of 2-Imino-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide (**5**) with N-Substituted Thiosemicarbazides (**6***{1-35}*).

$N^{(4)}$-substituted thiosemicarbazide (**6***{1-35}*) (1 mmol) was dissolved at 30 – 40 °C in 3 ml of glacial acetic acid. A solution of 0.23 g (1 mmol) of carboxamide **5** in 3 ml of glacial acetic acid was added and the mixture was heated at reflux for 20 – 30 min. The reaction mixture was then cooled and allowed to stand at room temperature until a precipitate was formed. The precipitate was filtered out and recrystallized from the appropriate solvent, such as ethanol, dimethylformamide or its mixture, to afford the corresponding 3-(5-amino[1,3,4]thiadiazol-2-yl)-2*H*-pyrano[2,3-*c*]-pyridin-2-one (**8***{1-35}*) as a crystalline solid.

3-(5-*N*-Phenylamino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{1}*).

This compound was obtained in 70% yield as an orange solid, mp 328–330 °C; ir: 3404, 3333, 3106, 1708, 1685, 1604, 1554, 1497, 1443 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.82 (d, J = 7.4 Hz, 2H), 5.49 (t, J = 5.5 Hz, 1H), 7.03 (t, J = 6.8 Hz, 1H), 7.36 (t, J = 7.4 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 8.39 (s, 1H), 9.02 (s, 1H), 10.46 (br.s, 1H); ms: m/z 366 (M^+), 365, 190, 175, 91, 77.

Anal. Calcd. for $C_{18}H_{14}N_4O_3S$: C, 59.01; H, 3.85; N, 15.29. Found: C, 59.04; H, 3.86; N, 15.32.

3-(5-*N*-(2,4-Dimethoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{2}*).

This compound was obtained in 81% yield as a brownish solid, mp 238–240 °C; ir: 3404, 2940, 1730, 1686, 1612, 1544, 1459 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 4.81 (d, J = 5.2 Hz, 2H), 5.51 (t, J = 5.3 Hz, 1H), 6.58 (dd, J = 7.6 Hz, 1.8 Hz, 1H), 6.99 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 8.39 (s, 1H), 9.85 (s, 1H), 8.98 (s, 1H), 9.85 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.34; H, 4.27; N, 13.14.

3-(5-*N*-(2,5-Dimethoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{3}*).

This compound was obtained in 93% yield as an orange solid, mp 236–238 °C; ir: 3455, 3407, 2940, 1721, 1602, 1546, 1476, 1410 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 4.84 (d, J = 5.0 Hz, 2H), 5.52 (t, J = 5.3 Hz, 1H), 6.59 (dd, J = 7.8 Hz, 1.6 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H), 8.39 (s, 1H), 9.02 (s, 1H), 9.90 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.34; H, 4.28; N, 13.12.

3-(5-*N*-(2-Tolyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{4}*).

This compound was obtained in 55% yield as an orange solid, mp 294–296 °C; ir: 3399, 3350, 2927, 2857, 1711, 1595, 1552, 1492, 1446 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H), 2.60 (s, 3H), 4.84 (d, J = 5.4 Hz, 2H), 5.45 (t, J = 5.4 Hz, 1H), 7.05 – 7.30 (m, 3H), 7.75 (d, J = 7.9 Hz, 1H), 8.36 (s, 1H), 8.96 (s, 1H), 10.40 (br.s, 1H); ms: m/z 380 (M^+), 379, 365, 363, 349, 190, 105, 91.

Anal. Calcd. for $C_{19}H_{16}N_4O_3S$: C, 59.99; H, 4.24; N, 14.73. Found: C, 59.97; H, 4.25; N, 14.75.

3-(5-*N*-(3-Tolyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{5}*).

This compound was obtained in 60% yield as an orange solid, mp 314–316 °C; ir: 3361, 3317, 3124, 1685, 1654, 1602, 1570, 1498, 1450 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 2.60 (s, 3H), 4.85 (d, J = 4.3 Hz, 2H), 5.48 (t, J = 4.4 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.36 – 7.50 (m, 2H), 8.38 (s, 1H), 9.01 (s, 1H), 9.66 (br.s, 1H); ms: m/z 380 (M^+), 379, 363, 348, 190, 105, 91.

Anal. Calcd. for $C_{19}H_{16}N_4O_3S$: C, 59.99; H, 4.24; N, 14.73. Found: C, 59.98; H, 4.27; N, 14.72.

3-(5-*N*-(4-Fluorophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{6}*).

This compound was obtained in 45% yield as an orange solid, mp 330–332 °C; ir: 3410, 3327, 3109, 1707, 1688, 1617, 1563, 1492, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.81 (d, J = 5.1 Hz, 2H), 5.49 (t, J = 5.2 Hz, 1H), 7.13 – 7.30 (m, 2H), 7.55 – 7.73 (m, 2H), 8.38 (s, 1H), 9.00 (s, 1H), 10.48 (br.s, 1H); ms: m/z 384 (M^+), 383, 189, 109, 95.

Anal. Calcd. for $C_{18}H_{13}FN_4O_3S$: C, 56.24; H, 3.41; N, 14.58. Found: C, 56.22; H, 3.44; N, 14.60.

3-(5-*N*-(3-Chloro-4-fluorophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{6}*).

This compound was obtained in 40% yield as a yellow solid, mp 336–338 °C; ir: 3338, 3134, 2894, 1716, 1688, 1655, 1602, 1558, 1483 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.59 (s, 3H), 4.80 (d, J = 5.2 Hz, 2H), 5.48 (t, J = 5.1 Hz, 1H), 7.28 – 7.53 (m, 2H), 7.95 – 8.05 (m, 1H), 8.35 (s, 1H), 9.00 (s, 1H), 10.60 (br.s, 1H); ms: m/z 418 (M^+), 417, 400, 227, 191, 145, 130, 36.

Anal. Calcd. for C $C_{18}H_{12}ClFN_4O_3S$: C, 51.62; H, 2.89; N, 13.38. Found: C, 51.65; H, 2.91; N, 13.40.

3-(5-*N*-(2-Chlorophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{8}*).

This compound was obtained in 57% yield as a yellow solid, mp 335–336 °C; ir: 3420, 3311, 2921, 1713, 1687, 1599, 1546, 1481, 1440 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.80 (d, J = 5.3 Hz, 2H), 5.47 (t, J = 5.2 Hz, 1H), 7.14 (dt, J = 7.9 Hz, 1.8 Hz, 1H), 7.39 (dt, J = 7.7 Hz, 1.6 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 1.4 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.37 (s, 1H), 9.03 (s, 1H), 9.92 (br.s, 1H); ms: m/z 400 (M^+), 365, 191, 125, 111, 36.

Anal. Calcd. for $C_{18}H_{13}ClN_4O_3S$: C, 53.94; H, 3.27; N, 13.98. Found: C, 53.97; H, 3.25; N, 13.96.

3-(5-*N*-(2-Methoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**6***{9}*).

This compound was obtained in 67% yield as orange crystals, mp 306–308 °C; ir: 3270, 3035, 2827, 2712, 1722, 1688, 1603, 1545, 1492, 1460 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 3.88 (s, 3H), 4.81 (d, J = 5.0 Hz, 2H), 5.49 (t, J = 5.1 Hz, 1H), 6.92 – 7.01 (m, 2H), 7.06 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.39 (s, 1H), 8.98 (s, 1H), 9.81 (br.s, 1H); ms: m/z 396 (M^+), 395, 381, 365, 289, 191, 122, 108.

Anal. Calcd. for $C_{19}H_{16}N_4O_4S$: C, 57.57; H, 4.07; N, 14.13. Found: C, 57.59; H, 4.09; N, 14.15.

3-(5-*N*-(2,4-Dimethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{10}*).

This compound was obtained in 65% yield as orange crystals, mp 290–292 °C; ir: 3398, 3354, 2916, 1708, 1688, 1593, 1543, 1491 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H), 2.29 (s, 3H), 2.60 (s, 3H), 4.82 (d, J = 5.0 Hz, 2H), 5.52 (t, J = 5.1 Hz, 1H), 7.02 – 7.12 (m, 2H), 7.59 (d, J = 7.7 Hz, 1H), 8.39 (s, 1H), 8.99 (s, 1H), 9.68 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.91; H, 4.63; N, 14.17.

3-(5-*N*-(3,5-Dimethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{11}*).

This compound was obtained in 59% yield as red crystals, mp 338–340 °C; ^1H NMR (DMSO-d_6): δ 2.27 (s, 6H), 2.60 (s, 3H), 4.84 (d, J = 5.2 Hz, 2H), 5.51 (t, J = 5.3 Hz, 1H), 6.68 (s, 1H), 7.25 (s, 2H), 8.39 (s, 1H), 9.00 (s, 1H), 10.36 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.93; H, 4.64; N, 14.18.

3-(5-*N*-(2-Ethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{12}*).

This compound was obtained in 49% yield as orange crystals, mp 304–306 °C; ^1H NMR (DMSO-d_6): δ 1.12 (t, 3H), 2.60 (s, 3H), 2.69 (q, J = 7.3 Hz, 2H), 4.80 (d, J = 4.8 Hz, 2H), 5.50 (t, J = 5.1 Hz, 1H), 7.10 – 7.35 (m, 3H), 7.70 (d, J = 8.3 Hz, 1H), 8.38 (s, 1H), 8.97 (s, 1H), 9.72 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.94; H, 4.62; N, 14.19.

3-(5-*N*-(2,5-Dimethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{13}*).

This compound was obtained in 63% yield as a yellow solid, mp 284–286 °C; ir: 3399, 3333, 2921, 1721, 1700, 1588, 1554, 1482, 1410 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.22 (s, 3H), 2.29 (s, 3H), 2.60 (s, 3H), 4.82 (d, J = 4.9 Hz, 2H), 5.50 (t, J = 5.3 Hz, 1H), 6.91 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.60 (s, 1H), 8.36(s, 1H), 8.99 (s, 1H), 9.65 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.94; H, 4.62; N, 14.19.

3-(5-*N*-(3-Chloro-2-methylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{14}*).

This compound was obtained in 70% yield as an orange solid, mp 310–312 °C; ir: 3391, 3348, 2853, 1709, 1688, 1586, 1549, 1491, 1447 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H), 2.58 (s, 3H), 4.80 (d, J = 5.4 Hz, 2H), 5.50 (t, J = 5.2 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.78 (t, J = 7.3 Hz, 1H), 8.38 (s, 1H), 8.98 (s, 1H), 9.87 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{15}ClN_4O_3S$: C, 55.01; H, 3.64; N, 13.50. Found: C, 54.99; H, 3.67; N, 13.48.

3-(5-*N*-(2-Fluorophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{15}*).

This compound was obtained in 67% yield as yellow crystals, mp 334–335 °C; ir: 3399, 3342, 2873, 1701, 1686, 1620, 1544, 1498, 1452 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.81 (d, J = 5.0 Hz, 2H), 5.51 (t, J = 4.8 Hz, 1H), 7.01 – 7.68 (m, 3H), 8.29 (t, J = 7.9 Hz, 1H), 8.37 (s, 1H), 9.00 (s, 1H), 10.29 (br.s, 1H).

Anal. Calcd. for $C_{18}H_{13}FN_4O_3S$: C, 56.24; H, 3.41; N, 14.58. Found: C, 56.23; H, 3.43; N, 14.60.

3-(5-*N*-(3-Methoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{16}*).

This compound was obtained in 67% yield as an orange solid, mp 334–335 °C; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 3.78 (s, 3H), 4.82 (d, J = 5.2 Hz, 2H), 5.51 (t, J = 4.8 Hz, 1H), 6.60 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.05 – 7.40 (m, 3H), 8.39 (s, 1H), 9.00 (s, 1H), 10.50 (s, 1H).

Anal. Calcd. for $C_{19}H_{16}N_4O_4S$: C, 57.57; H, 4.07; N, 14.13. Found: C, 57.58; H, 4.08; N, 14.15.

3-(5-*N*-(4-Bromo-phenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{17}*).

This compound was obtained in 42% yield as an orange solid, mp 334 °C; ir: 3425, 3324, 2924, 1715, 1648, 1609, 1545, 1491, 1441 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.82 (d, J = 5.3 Hz, 2H), 5.50 (t, J = 5.5 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 8.38 (s, 1H), 9.01 (s, 1H), 10.60 (br.s, 1H).

Anal. Calcd. for $C_{18}H_{13}BrN_4O_3S$: C, 48.55; H, 2.94; N, 12.58. Found: C, 48.54; H, 2.98; N, 12.57.

3-(5-*N*-(3-Chloro-6-methylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{18}*).

This compound was obtained in 59% yield as yellow crystals, mp 318–320 °C; ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H), 2.61 (s, 3H), 4.84 (d, J = 4.3 Hz, 2H), 5.50 (t, J = 4.9 Hz, 1H), 7.06 (dd, J = 8.3 Hz, 1.9 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 8.18 (s, 1H), 8.39 (s, 1H), 9.04 (s, 1H), 9.70 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{15}ClN_4O_3S$: C, 55.01; H, 3.64; N, 13.50. Found: C, 54.98; H, 3.66; N, 13.49.

3-(5-*N*-(4-Biphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{19}*).

This compound was obtained in 45% yield as an orange solid, mp 326–327 °C; ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H), 4.82 (d, J = 4.7 Hz, 2H), 5.52 (t, J = 5.0 Hz, 1H), 7.30 – 7.45 (m, 3H), 7.62 – 7.73 (m, 6H), 8.38 (s, 1H), 9.03 (s, 1H), 10.67 (br.s, 1H).

Anal. Calcd. for $C_{24}H_{18}N_4O_3S$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.13; H, 4.13; N, 12.63.

3-(5-*N*-(4-Chlorophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{20}*).

This compound was obtained in 60% yield as a yellow solid, mp 338–340 °C; ir: 3427, 3333, 3093, 1715, 1649, 1610, 1549, 1491, 1448 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.84 (d, J = 5.4 Hz, 2H), 5.51 (t, J = 5.6 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 8.39 (s, 1H), 9.02 (s, 1H), 10.63 (br.s, 1H).

Anal. Calcd. for $C_{18}H_{13}ClN_4O_3S$: C, 53.94; H, 3.27; N, 13.98. Found: C, 53.96; H, 3.26; N, 13.96.

3-(5-*N*-(4-(4-Chlorophenyloxy)phenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{21}*).

This compound was obtained in 78% yield as a brown solid, mp 324–326 °C; ir: 3399, 3324, 3056, 1708, 1687, 1618, 1561, 1486, 1420 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H), 4.83 (d, J = 5.3 Hz, 2H), 5.51 (t, J = 5.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 7.0 Hz, 2H), 7.37 (d, J = 7.3 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 8.38 (s, 1H), 9.01 (s, 1H), 10.53 (br.s, 1H).

Anal. Calcd. for $C_{24}H_{17}ClN_4O_4S$: C, 58.48; H, 3.48; N, 11.37. Found: C, 58.49; H, 3.50; N, 11.40.

3-(5-*N*-(4-Ethoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{22}*).

This compound was obtained in 64% yield as a brown solid, mp 284–286 °C; ir: 3436, 3340, 2980, 1711, 1608, 1557, 1493 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (t, 3H), 2.60 (s, 3H), 4.01 (q, 2H), 4.83 (d, J = 5.7 Hz, 2H), 5.50 (t, J = 5.3 Hz, 1H), 6.93 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H), 8.37 (s, 1H), 8.98 (s, 1H), 10.30 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_4S$: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.56; H, 4.44; N, 13.66.

3-(5-*N*-(3-Methylthiophenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{23}*).

This compound was obtained in 53% yield as a yellow-brown solid, mp 302–303 °C; ir: 3399, 3326, 2918, 1706, 1684, 1592, 1550, 1491, 1447 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.61 (s, 3H), 3.00 (s, 3H), 4.85 (d, J = 5.4 Hz, 2H), 5.35 (t, J = 5.6 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 7.22 – 7.40 (m, 2H), 7.67 (s, 1H), 8.39 (s, 1H), 9.03 (s, 1H), 10.38 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{16}N_4O_3S_2$: C, 55.33; H, 3.91; N, 13.58. Found: C, 55.34; H, 3.92; N, 13.59.

3-(5-*N*-(2-Chloro-5-trifluoromethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{24}*).

This compound was obtained in 87% yield as yellow crystals, mp 316–318 °C; ir: 3399, 3316, 3039, 1708, 1687, 1603, 1560, 1485, 1439 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H), 4.88 (d, J = 6.1 Hz, 2H), 5.30 (t, J = 5.5 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 8.80 (s, 1H), 9.09 (s, 1H), 10.10 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{12}ClF_3N_4O_3S$: C, 48.68; H, 2.58; N, 11.95. Found: C, 48.70; H, 2.61; N, 11.97.

3-(5-*N*-(2,5-Diethoxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{25}*).

This compound was obtained in 67% yield as an orange solid, mp 272–273 °C; ir: 3399, 3279, 2965, 1716, 1596, 1543, 1491, 1448 cm^{-1}; ^1H NMR (DMSO-d_6 + CCl_4 (1:3)): δ 1.39 – 1.48 (m, 6H), 2.68 (s, 3H), 4.03 (q, 2H), 4.08 (q, J = 7.3 Hz, 2H), 4.85 (d, J = 4.6 Hz, 2H), 5.43 (t, J = 5.4 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H, H-4), 6.82 (d, J = 8.9 Hz, 1H, H-3), 8.09 (s, 1H, H-6), 8.35 (s, 1H), 9.11 (s, 1H), 9.54 (br.s, 1H).

Anal. Calcd. for $C_{22}H_{22}N_4O_5S$: C, 58.14; H, 4.88; N, 12.33. Found: C, 58.15; H, 4.90; N, 12.30.

3-(5-*N*-(3-Ethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{26}*).

This compound was obtained in 84% yield as a red solid, mp 318–320 °C; ir: 3428, 3247, 2827, 1730, 1621, 1571, 1498, 1439 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.22 (t, J = 7.3 Hz, 3H), 2.61 (s, 3H), 2.62 (m, 2H), 4.85 (d, J = 5.3 Hz, 2H), 5.54 (t, J = 5.8 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.53 (s, 1H), 8.40 (s, 1H), 9.04 (s, 1H), 10.50 (br.s, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.93; H, 4.62; N, 14.18.

3-(5-*N*-(4-Trifluoromethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{27}*).

This compound was obtained in 42% yield as a yellow solid, mp 342 °C; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.84 (d, J = 5.5

Hz, 2H), 5.52 (t, J = 5.2 Hz, 1H), 7.70 (d, J = 7.7 Hz, 2H), 7.85 (d, J = 6.9 Hz, 2H), 8.39 (s, 1H), 9.05 (s, 1H), 10.88 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{13}F_3N_4O_3S$: C, 52.53; H, 3.02; N, 13.12. Found: C, 52.55; H, 3.00; N, 13.12.

3-(5-*N*-(4-Phenyloxyphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{28}*).

This compound was obtained in 39% yield as a yellow solid, mp 287–288 °C; ^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3H), 4.84 (d, J = 5.8 Hz, 2H), 5.50 (t, J = 5.6 Hz, 1H), 6.97 – 7.13 (m, 5H), 7.36 (dt, J = 7.9 Hz, 1.4 Hz, 2H), 7.66 (dd, J = 8.0 Hz, 1.4 Hz, 2H), 8.38 (s, 1H), 9.04 (s, 1H).

Anal. Calcd. for $C_{24}H_{18}N_4O_4S$: C, 62.87; H, 3.96; N, 12.22. Found: C, 62.85; H, 3.98; N, 12.21.

3-(5-*N*-(3-Trifluoromethylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{29}*).

This compound was obtained in 62% yield as an orange solid, mp 323 °C; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.83 (d, J = 5.5 Hz, 2H), 5.50 (t, J = 5.3 Hz, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.20 (s, 1H), 8.39 (s, 1H), 9.04 (s, 1H), 10.80 (br.s, 1H).

Anal. Calcd. for $C_{19}H_{13}F_3N_4O_3S$: C, 52.53; H, 3.02; N, 13.12. Found: C, 52.54; H, 3.00; N, 13.13.

3-(5-*N*-(4-Isopropylphenyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{30}*).

This compound was obtained in 74% yield as yellow crystals, mp 324 °C; ^{1}H NMR (DMSO-d_6): δ 1.10 (d, 6H), 2.60 (s, 3H), 2.85 (m, 1H), 4.81 (d, J = 5.2 Hz, 2H), 5.50 (t, J = 5.4 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.3 Hz, 2H), 8.38 (s, 1H), 9.00 (s, 1H), 10.42 (br.s, 1H).

Anal. Calcd. for $C_{21}H_{20}N_4O_3S$: C, 61.75; H, 4.94; N, 13.72. Found: C, 61.77; H, 4.95; N, 13.74.

3-(5-*N*-(2-Furylmethyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{31}*).

This compound was obtained in 71% yield as a yellow solid, mp 274–276 °C; ir: 3334, 3244, 1695, 1656, 1588, 1543, 1492 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H), 4.52 (d, J = 5.0 Hz, 2H), 4.80 (d, J = 5.0 Hz, 2H), 5.45 (t, J = 6.0 Hz, 1H), 6.38 (m, 2H), 7.58 (s, 1H), 8.36 (s, 1H), 8.40 (t, J = 6.9 Hz, 1H), 8.91 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}N_4O_4S$: C, 55.13; H, 3.81; N, 15.13. Found: C, 53.16; H, 3.85; N, 15.11.

3-(5-*N*-Ethylamino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{32}*).

This compound was obtained in 34% yield as a yellow solid, mp 280–282 °C; ir: 3382, 3221, 2969, 2890, 1710, 1690, 1543, 1476, 1446 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.31 (t, J = 7.6 Hz, 3H), 2.60 (s, 3H), 3.35 (m, 2H), 4.80 (d, J = 5.3 Hz, 2H), 5.46 (t, J = 5.1 Hz, 1H), 8.00 (t, J = 7.8 Hz, 1H), 8.35 (s, 1H), 8.85 (s, 1H); ms: m/z 318 (M$^+$), 317, 303, 290, 190, 129, 44.

Anal. Calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52,86; H, 4.45; N, 17.57.

3-(5-*N*-(2-Tetrahydrofurylmethyl)amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*pyrano[2,3-*c*]pyridine-2-one (**8**{*33*}).

This compound was obtained in 76% yield as a yellow solid, mp 284–286 °C; ir: 3348, 3238, 2932, 2874, 1699, 1655, 1551, 1491, 1458 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.55 – 1.98 (m, 4H), 2.60 (s, 3H), 3.43 (m, 2H), 3.60 – 3.88 (m, 2H), 4.07 (m, 2H), 4.90 (d, J = 5.5 Hz, 2H), 5.45 (t, J = 5.0 Hz, 1H), 8.38 (s, 1H), 8.78 (s, 1H), 8.05 (t, J = 5.2 Hz, 1H); ms: m/z 374 (M$^+$), 304, 290, 274, 185, 101, 85, 71.

Anal. Calcd. for $C_{17}H_{18}N_4O_4S$: C, 54.53; H, 4.85; N, 14.96. Found: C, 54.55; H, 4.87; N, 14.93.

3-(5-*N*-Allylamino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{34}*).

This compound was obtained in 66% yield as a yellow solid, mp 278-280 °C; ir: 3340, 3294, 2894, 1719, 1688, 1578, 1528, 1490, 1458 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.80 (d, J = 5.2 Hz, 2H), 5.22 (m, 2H), 5.58 (t, J = 5.2 Hz, 1H), 5.94 (m, 1H), 8.37 (s, 1H), 8.91 (s, 1H), 8.17 (t, 1H); ms: m/z 330 (M$^+$), 329, 315, 303, 302, 290, 274, 189, 56, 41.

Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: C, 54.54; H, 4.27; N, 16.96. Found: C, 54.56; H, 4.29; N, 16.94.

3-(5-*N*-Phenethylamino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-2-one (**8***{35}*).

This compound was obtained in 63% yield as a light yellow solid, mp 268–270 °C; ir: 3336, 3252, 2897, 1694, 1589, 1535, 1492 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 2.95 (t, 2H), 3.65 (q, 2H), 4.81 (d, J = 5.0 Hz, 2H), 5.51 (t, J = 5.1 Hz, 1H), 7.18 – 7.34 (m, 5H), 8.39 (s, 1H), 8.92 (s, 1H), 8.16 (t, J = 8.7 Hz, 1H).

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.92; H, 4.62; N, 14.21.

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