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New Regio-selective Method of Combinatorial Synthesis of Substituted Thiophenes, Thieno[3,2-*b*]pyridines and other Heterocycles via Combination of "Domino"-type Reactions

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Graphical Abstract

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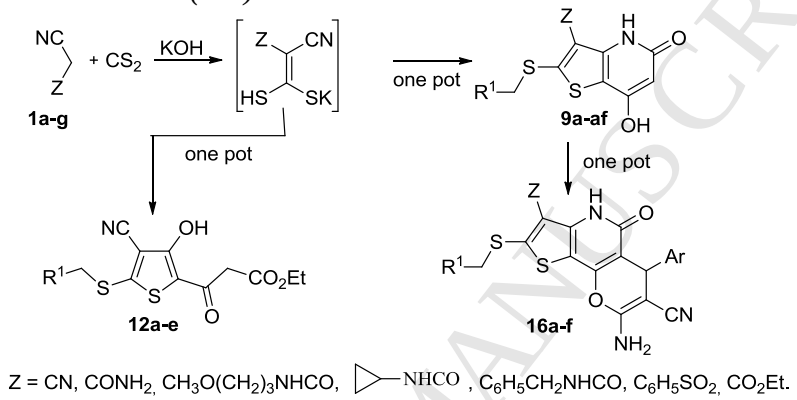

Z = CN, $CONH_2$, $CH_3O(CH_2)_3NHCO$, , $C_6H_5CH_2NHCO$, $C_6H_5SO_2$, CO_2Et.

Tetrahedron
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New Regio-selective Method of Combinatorial Synthesis of Substituted Thiophenes, Thieno[3,2-*b*]pyridines and other Heterocycles via Combination of "Domino"-type Reactions.

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ABSTRACT

We present a novel combinatorial multicomponent regio-selective approach towards the synthesis of thieno[3,2-*b*]pyridines and pyridine pyrans. The methodology is based on the "domino"-type reaction. The high regio-selectivity in this reaction is gained by the in-situ generation of the mono-potassium salt of 2-cyano-1-mercaptoethenethiolate. We also demonstrate, that the use of ethyl 2-cyanoacetate in this reaction as a CH-acid leads to the termination of the domino sequence at the Dieckmann condensation step and yields novel ethyl 3-(4-cyano-3-hydroxy-5-(alkylthio)thiophen-2-yl)-3-oxopropanoate.

1. Introduction

Substituted thieno[3,2-*b*]pyridines are pharmacologically important molecules with several types of biological activity. Previously, they were demonstrated as γ-aminobutyric acid ligands,[1] immune modulators,[1,2] inhibitors of calcium channels[1] and as herbicides.[1] Thiophenes, containing N-substituted amides in the three positions, have became an interest of several recent studies.[3] These molecules and their derivatives annulated with carbo- and heterocycles were shown as cannabinoid receptor ligands,[4] tumor growth inhibitors,[5] AMPA receptor modulators,[6] dihydroorthotetragenase inhibitors,[7] herbicides,[8] and mammalian hyperproliferative disorders agents.[9]

Previously, we explored the synthesis of thieno[3,2-*b*]pyridines using thiophene derivatives as primary scaffolds.[10] In another study, the thieno[3,2-*b*]pyridine structure was constructed from a pyridine derivative.[1] We also demonstrated a one-pot synthesis of thieno[3,2-*b*]pyridines directly from cyanodithioethylene salts with concomitant cyclization of both thiophen and pyridine rings. Using this methodology, we synthesized 7-hydroxy-5-oxo-2-(R-methylenthio)-4,5-dihydrothieno[3,2-*b*]pyridines from dipotassium 2-cyanoethene-1,1-ditiolathe and 4-chloroacetoacetic ester.[10] Similarly, a dipotassium N-cyanodithioimidocarbonate and 4-chloroacetoacetate were used in the domino reaction to prepare 7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones.[11] However, the yield of the synthesized compounds was moderate to low. It is known, that the dipotassium or disodium salts reacts with one equivalent of α-halogenated carbonyl compounds and give mixtures of S-mono- and S-,S-disubstituted unsaturated nitriles.[12] Moreover, for reaction mixtures of chloro-acetonitrile and disodium 2,2-dicyanoethylene-1,1-bis(thiolate) at any molar ratios the reaction always proceeds as two S_N2 and two Thorpe-Ziegler condensations and yields thienothiophenes.[12] This creates significant complications for the facile combinatorial synthesis of heterocyclic libraries.

2. Results and Discussion

Here, we demonstrate a novel combinatorial, multicomponent and highly regio-selective method for the preparation of thieno[3,2-*b*]pyridines **9** with combination of CH acids **1** (Figure 1) and alkylhalides **8** (Figure 2). The proposed methodology is unique and is based on the initial in-situ generation of the mono potassium salt of 2-cyano-1-mercaptoethenethiolates **3** directly from CH acids **1a-f**, carbondisulfide **2** and one equivalent of potassium hydroxide.

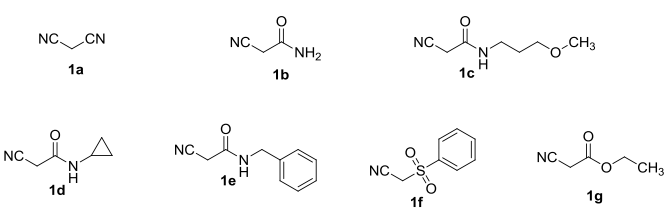

Figure 1. CH-acids **1a-g**.

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The following S_N2 reaction of salts **3** and 4-chloroacetoacetic ester **4** proceeds with high regio-selectivity at only one sulfur atom in contrast to the dipotassium salt reaction, which consumes both sulfur atoms.[12,13]

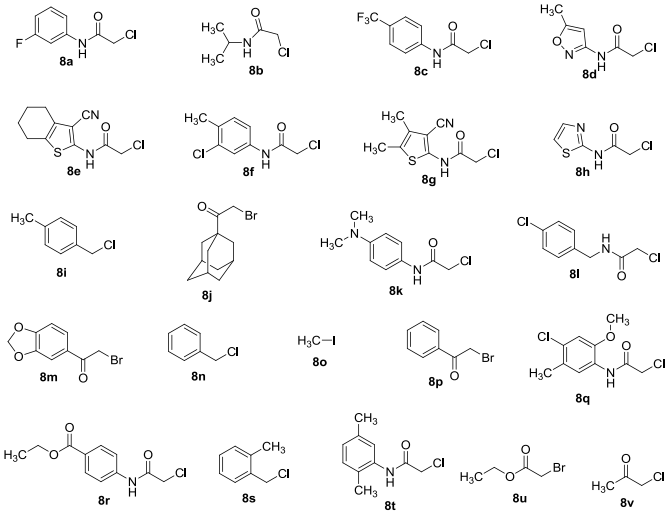
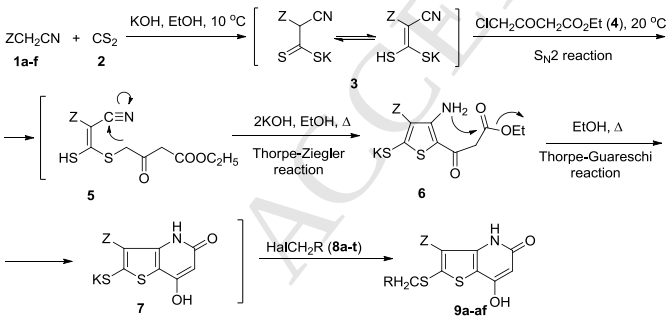


Figure 2. Alkylhalides **8a-v**.

The subsequent "domino"-type Thorpe-Ziegler and Thorpe-Guareschi reactions begin after the addition of two more equivalents of potassium hydroxide and conclude with the formation of potassium salt of thieno[3,2-*b*]pyridine **7** (Scheme 1). The solution of salt **7** is then divided into portions and reacted with alkylhalides **8a-t**. The remarkable regio-selectivity of each step ensures the high yields (58–88%) of final substituted thieno[3,2-*b*]pyridines **9a**–**af** in this five step multicomponent one-pot synthesis (Table 1).

Here for the first time, beside malonodinitrile (**1a**) and cyanoacetamide (**1b**), we used N-substituted cyanoacetamides: N-(3-methoxypropyl)- (**1c**), N-cyclopropyl- (**1d**), N-benzylcyanoacetamide (**1e**) and phenylsulfonyl acetonitrile (**1f**). These new CH-acids significantly expand the variety of synthetically available thieno[3,2-*b*]pyridines and provides access to molecules with pharmacologically important functional groups.

Scheme 1. Synthesis of thieno[3,2-*b*]pyridines **9a-af.**

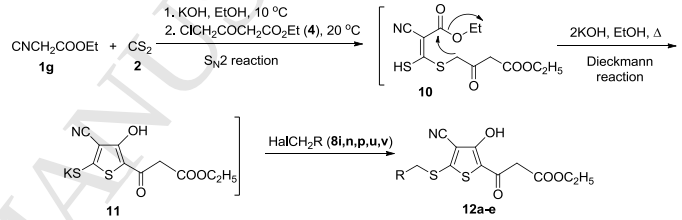


The structures of the prepared compounds were confirmed using NMR and IR analyses. The IR spectra of compounds **9a**–**af** contain characteristic absorption bands of the amide group and pyridine ring at 3360 – 3240 cm^{-1} and the absorption band of the carbonyl group at 1630 cm^{-1}. The IR spectra of phenylsulfonyl derivatives **9ac**–**af** contain signals of the SO_2R group at 1170 and 1130 cm^{-1}. ^1H NMR spectra of compounds **9a**–**af** show NH- and OH- proton peaks and a characteristic C(6)H peak at 5.77 – 6.08 ppm.

The reaction of cyanoacetic ester **1g** with carbon sulfide and α-halogengeminal compounds containing electron-withdrawing moieties lead to the formation of 4-amino-3-ethoxycarbonyl thiophenes.[14-19] However, the same reaction was also used to form 3-cyano-4-hydroxy thiophenes[20,21] or a mixture of the both isomers.[22] The reaction with 4-bromoacetoacetic ester yields a structure similar to the intermediate **6**.[17] However, under a relatively mild conditions (NaH, THF, room temperature) the subsequent cyclization is avoided. In contrast, we demonstrate that cyanoacetic ester (**1g**) shows different reactivity in the same reaction sequence, yielding substituted 4-hydroxythiophenes as the final products.

Compound **1g** reacts with carbon disulfide with the ester group, excluding the cyano group from the domino sequence all together (Scheme 2). Such difference in reactivity causes the intermediate **10** to undergo Dieckmann cyclization, as opposed to Thorpe-Ziegler condensation in intermediate **5**, and yields potassium salt **11** as a final product. The solution of salt **11** can be directly reacted with alkyl halides **8i,n,p,u,v** without isolation and purification. The resulting thiophenes **12a**–**e** represent a new class of previously unknown heterocyclic molecules.

Scheme 2. Synthesis of thiophenes **12a-e.**



The IR spectra of compounds **12a**–**e** contain characteristic absorption bands of cyano, carbonyl and ester groups. ^1H NMR spectra of **12a**–**e** contain proton signal of ethyl (1.16–1.17 and 4.08–4.09 ppm) and methylene (3.85–3.87 ppm) groups. The structures of thiophenes **12a**–**e** were also confirmed by HRMS spectroscopy.

Thieno[3,2-*b*]pyridines **9** contain several reactive groups and can be further modified via alkylation and cyclization reactions. As such, compounds **9q,u,w,z,ab** undergo three-component "domino"-type reaction (Knoevenagel condensation – Michal addition – hetero Thorpe-Ziegler condensation) when reacted with aromatic aldehydes **13a-c** (Figure 3) and malonodinitrile (**1a**) (Scheme 3).

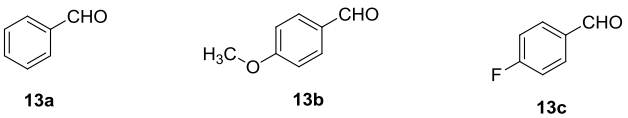


Figure 3. Aldehydes **13a-c**.

This multicomponent reaction yields pharmacologically important annulated pyrans **16**.[12,23]

Scheme 3. Synthesis of pyrans **16a-f.**

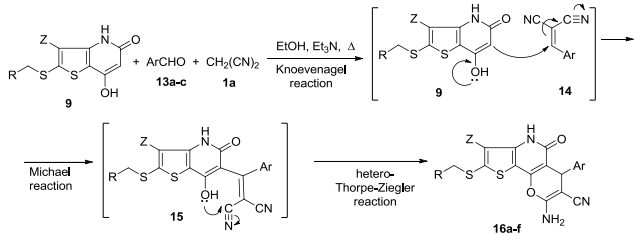
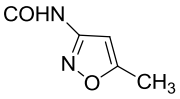
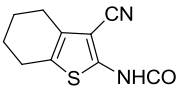
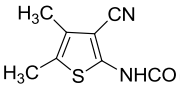
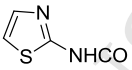
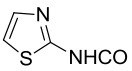
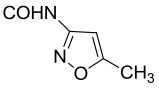
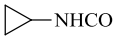
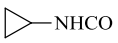
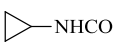
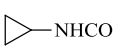
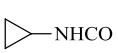


Table 1. Thieno[3,2-*b*]pyridines **9a-af**.

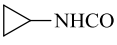
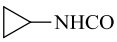
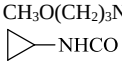
Entry	Product	Z	R	Yield, %
1	**9a**	CN	3-F-C_6H_4-NHCO	59 (43[10])
2	**9b**	CN	$(CH_3)_2$CH-NHCO	62 (46[10])
3	**9c**	CN	4-CF_3-C_6H_4-NHCO	58 (38[10])
4	**9d**	CN		65
5	**9e**	CN		73
6	**9f**	CN	3-Cl-4-CH_3-C_6H_3-NHCO	58
7	**9g**	CN		82
8	**9h**	CN		64
9	**9i**	$CONH_2$	4-CH_3-C_6H_4	88 (86[10])
10	**9j**	$CONH_2$	Ad[1]-CO	87 (86[10])
11	**9k**	$CONH_2$	4-$(CH_3)_2$N-C_6H_4-NHCO	70
12	**9l**	$CONH_2$	4-Cl-C_6H_4-CH_2NHCO	63
13	**9m**	$CONH_2$	$(CH_3)_2$CHNHCO	58
14	**9n**	$CONH_2$	3,4-OCH_2O-C_6H_3-CO	59
15	**9o**	$CONH_2$		60
16	**9p**	$CONH_2$		59
17	**9q**	$CH_3O(CH_2)_3NHCO$	C_6H_5	75
18	**9r**	$CH_3O(CH_2)_3NHCO$	H	72
19	**9s**	$CH_3O(CH_2)_3NHCO$	C_6H_5CO	83
20	**9t**	$CH_3O(CH_2)_3NHCO$	2-OCH_3-4-Cl-5-CH_3-C_6H_2-NHCO	61
21	**9u**	$CH_3O(CH_2)_3NHCO$	4-C_2H_5OOC-C_6H_4-NHCO	59
22	**9v**		2-CH_3-C_6H_4	75
23	**9w**		4-CH_3-C_6H_4	84
24	**9x**		2-OCH_3-4-Cl-5-CH_3-C_6H_2-NHCO	58
25	**9y**		C_6H_5CO	85
26	**9z**		H	86
27	**9aa**	$C_6H_5CH_2NHCO$	4-CH_3-C_6H_4	84

28	**9ab**	$C_6H_5CH_2NHCO$	H	76
29	**9ac**	$C_6H_5SO_2$	4-CH_3-C_6H_4	70
30	**9ad**	$C_6H_5SO_2$	C_6H_5	63
31	**9ae**	$C_6H_5SO_2$	C_6H_5CO	66
32	**9af**	$C_6H_5SO_2$	2,5-$(CH_3)_2$-C_6H_3-NHCO	60

Table 2. Thiophenes **12a-e**.

Entry	Product	R	Yield, %
1	**12a**	C_6H_5CO	58
2	**12b**	C_6H_5	50
3	**12c**	4-CH_3-C_6H_4	63
4	**12d**	C_2H_5OOC	72
5	**12e**	CH_3CO	54

Table 3. Pyrans **16a-f**.

Entry	Product	Z	R	Ar	Yield, %
1	**16a**	$CH_3O(CH_2)_3NHCO$	C_6H_5	C_6H_5	58
2	**16b**		H	C_6H_5	66
3	**16c**		H	4-CH_3O-C_6H_4	63
4	**16d**	$C_6H_5CH_2NHCO$	H	C_6H_5	80
5	**16e**	$CH_3O(CH_2)_3NHCO$	4-C_2H_5OOC-C_6H_4-NHCO	C_6H_5	73
6	**16f**		4-CH_3-C_6H_4	4-F-C_6H_4	76

The IR spectra of compounds **16a–f** contain absorption bands of the amine and amide groups at 3400–3200 cm^{-1}, the cyano group at 2200–2180 cm^{-1} and the carbonyl group at 1670 and 1630 cm^{-1}. ^1H NMR spectra of compounds **16a–f** contain characteristic singlet of the C(6) pyran ring proton at 4.40–4.59 ppm.

3. Conclusion

In conclusion, we demonstrated that complex tricyclic heterocycles can be prepared in 8 consecutive steps via two multicomponent reactions by cross-coupling two types of "domino" reaction: (**1**) S_N2 → Thorpe-Ziegler → Thorpe-Guareschi and (**2**) Knoevenagel → Michal → hetero Thorpe-Ziegler. The presented combinatorial methodology is highly flexible and permits the use of different CH acids **1a-f**, alkyl halides **8a-t** and aromatic aldehydes **13**. The use of cyanoacetic ester **1g** in this reaction changes the regio-selectivity of the initial cyclization and yields 4-cyano-3-hydroxythiophenes **12**.

4. Experimental Section

4.1. General

IR spectra were recorded on "Bruker Alpha" spectrometer in KBr pellets. NMR ^1H and ^{13}C analyses were performed on "Bruker AM300" (300.13 and 75.47 MHz) spectrometer in DMSO-d_6 solution. High resolution mass spectra were obtained on "micrOTOF" mass-spectrometer. All reagents and solvents were purchased from Sigma-Aldrich. N-Substituted cyanoacetamides **1**{3-5} were prepared from ethylcyanoacetate and corresponding amines using previously published method.[24]

4.2. General Experimental Procedure for 9a–af.

The corresponding CH-acid **1a-f** (25 mmol) was dissolved in a solution of potassium hydroxide (1.4 g, 25 mmol) in ethanol (50 ml) at 10 ºC. In several cases after addition of **1** a precipitate was formed, which did not have an effect on the reaction conditions or the final product. After stirring for 1 min carbon disulfide (1.5 ml, 25 mmol) was added to the resulting solution, and the reaction mixture was stirred for 20 mins. Water (10–15 ml) was added to the mixture to dissolve the resulting precipitate. Subsequently, ester **4** (3.4 ml, 25 mmol) in ethanol (20 ml) was added to the reaction mixture dropwise for 1 h, which was quenched with potassium hydroxide solution (2.8 g, 50 mmol) in ethanol (100 ml), after stirring for 10 min. The resulting reaction mixture was refluxed for 2.5 h. After cooling to room temperature, the solution was quenched with concentrated HBr (2.8 ml, 25 mmol), stirred for 30 min, and divided into five equal portions. Each portion was then reacted with the corresponding alkylhalide **8a-t** (5 mmol) under refluxing conditions for 1 min. After cooling the reaction to room temperature, the resulting precipitate was filtered off and rinsed on the filter to give pure thieno[3,2-b]pyridines **9a**–**af** in 58–88 % yield.

The analytical properties of compounds **9a-c,i,j** were identical to the previously reported literature data.[10]

4.2.1. *2-({3-Cyano-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)-N-(3-methyl-1,2-oxazol-5-yl)acetamide (**9d**).*

Yield: 1.18 g (65%); mp > 300 °C (des.).
IR (KBr): 3500, 3272, 3224, 3138, 2230, 1631 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3H, $\underline{CH_3}$), 4.16 (s, 2H, S$\underline{CH_2}$), 6.01 (s, 1H, $\underline{C(6)H}$), 6.60 (s, 1H, $\underline{CH}$), 11.23 (s, 1H, $\underline{NH}$), 11.82 (br s, 1H, $\underline{N(4)H}$). The protons of the OH group are subject to deutero exchange and were not resolved completely.

^{13}C NMR (75 MHz, DMSO-d6): δ = 11.9, 39.6, 93.3, 96.1, 105.7, 112.9, 114.2, 131.2, 151.9, 157.7, 160.2, 165.3, 165.5, 169.8.
Anal. Calcd for $C_{14}H_{10}N_4O_4S_2$: C, 46.40; H, 2.78; N, 15.46. Found: C, 46.67; H, 2.95; N, 15.79.

4.2.2. *N-(3-Cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-({3-cyano-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)acetamide (**9e**).*

Yield: 1.62 g (73%); mp > 300 °C.
IR (KBr): 3413, 3267, 3222, 3090, 2212, 1639 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.77 (m, 4H, CH_2-CH_2), 2.50 (m, 2H, CH_2 overlaped with DMSO), 2.60 (m, 2H, CH_2), 4.24 (br s, 2H, SCH_2), 6.03 (s, 1H, C(6)H), 11.23 (br s, 1H, NH), 11.67 (br s, 2H, N(4)H, OH).
^{13}C NMR (75 MHz, DMSO-d6): δ = 21.6, 22.5, 23.3, 23.4, 93.2, 93.5, 106.3, 112.9, 113.9, 127.8, 130.9, 135.9, 145.9, 149.8, 151.4, 160.3, 165.2, 165.3. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{19}H_{14}N_4O_3S_3$: C, 51.57; H, 3.19; N 12.66. Found: C, 51.28; H, 3.06; N 12.22.

4.2.3. *N-(3-Chloro-4-methylphenyl)-2-({3-cyano-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)acetamide (**9f**).*

Yield: 1.18 g (58%); mp 270-273 °C (des.).
IR (KBr): 3443, 3327, 3188, 3093, 2224, 1630 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 4.13 (s, 2H, SCH_2), 6.01 (s, 1H, C(6)H), 7.28 (d, J = 8.6 Hz, 2H, C_6H_3), 7.33 (d, J = 8.6 Hz, 2H, C_6H_3,), 7.73 (s, 1H, C_6H_3), 10.36 (s, 1H, NH), 11.38 (br s, 1H, N(4)H). The protons of the OH group are subject to deutero exchange and were not resolved completely.
^{13}C NMR (75 MHz, DMSO-d6): δ = 18.9, 40.2, 93.3, 105.5, 113.0, 114.1, 117.9, 119.2, 130.4, 131.2, 133.1, 137.6, 149.9, 152.3, 160.3, 165.2, 165.3.
Anal. Calcd for $C_{17}H_{12}ClN_3O_3S_2$: C, 50.31; H, 2.98; N, 10.35. Found: C, 50.58; H, 3.09; N, 10.62.

4.2.4. *N-(3-Cyano-4,5-dimethylthiophen-2-yl)-2-({3-cyano-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)acetamide (**9g**).*

Yield: 1.7 g (82%); mp 285-287 °C (des.).
IR (KBr): 3443, 3267, 3225, 3092, 2216, 1630 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 6.02 (s, 1H, C(6)H), 11.27 (br s, 1H, NH), 11.76 (br s, 2H, N(4)H, OH).
^{13}C NMR (75 MHz, DMSO-d6): δ = 12.4, 12.8, 93.1, 93.5, 106.3, 113.0, 113.9, 127.4, 130.3, 135.9, 145.9, 149.7, 151.1, 160.3, 165.1, 165.3. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{17}H_{12}N_4O_3S_3$: C, 49.02; H, 2.90; N, 13.45. Found: C, 48.73; H, 2.64; N, 13.18.

4.2.5. *2-({3-Cyano-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)-N-(1,3-thiazol-2-yl)acetamide (**9h**).*

Yield: 1.17 g (64%); mp 230-233 °C (des.).
IR (KBr): 3491, 3424, 3337, 3202, 3183, 2226, 1638 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.22 (s, 2H, SCH_2), 5.98 (s, 1H, C(1)H), 7.25 (d, J = 7.4 Hz, 1H, CH,), 7.49 (d, J = 7.4 Hz, 1H, CH,), 11.96 (br s, 2H, N(4)H, OH). The protons of the NH group are subject to deutero exchange and were not resolved completely.
^{13}C NMR (75 MHz, DMSO-d6): δ = 93.4, 106.2, 112.9, 113.9, 114.8, 137.7, 149.6, 151.2, 157.6, 160.9, 165.4, 165.5. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{13}H_8N_4O_3S_3$: C, 42.85; H, 2.21; N, 15.37. Found: C, 42.54; H, 2.04; N, 15.06.

4.2.6. *2-[({[4-(Dimethylamino)phenyl]carbamoyl}methyl)sulfanyl]-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9k**).*

Yield: 1.47 g (70%); mp > 300 °C (des.).
IR (KBr): 3422, 3327, 3263, 3185, 1641 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.84 (s, 6H, 2CH_3), 4.01 (s, 2H, SCH_2), 6.04 (s, 1H, C(6)H), 6.71 (d, J = 8.8 Hz, 2H, C_6H_4,), 7.41 (d, J = 8.8 Hz, 2H, C_6H_4,), 7.65 (br s, 1H, NH_2), 9.24 (br s, 1H, NH_2), 10.08 (s, 1H, NH), 10.78 (br s, 1H, OH), 11.67 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d6): δ = 40.4, 90.6, 112.2, 112.7, 120.6, 120.8, 128.6, 138.4, 147.1, 160.2, 163.8, 164.1, 164.6. The signal of CH_2S is overlapped with DMSO, the signal of C(9) is overlapped with Ar C(1).
Anal. Calcd for $C_{18}H_{18}N_4O_4S_2$: C, 51.66; H, 4.34; N, 13.39. Found: C, 51.38; H, 4.07; N, 13.12.

4.2.7. *2-[({[(4-Chlorophenyl)methyl]carbamoyl}methyl)sulfanyl]-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9l**).*

Yield: 1.34 g (63%); mp 296-299 °C.
IR (KBr): 3393, 3269, 3154, 3100, 1657 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.90 (s, 2H, SCH_2), 4.30 (d, J = 5.5 Hz, 2H, CH_2), 6.03 (s, 1H, C(6)H), 7.27 (d, J = 7.5 Hz, 2H, C_6H_4,), 7.33 (d, J = 7.5 Hz, 2H, C_6H_4,), 7.63 (br s, 1H, NH_2), 8.81 (t, J = 5.5 Hz, 1H, NH,), 9.22 (br s, 1H, NH_2), 10.78 (s, 1H, OH), 11.67 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d6): δ = 90.7, 112.2, 120.7, 120.8, 121.3, 127.2, 128.6, 128.7, 137.6, 160.2, 163.8, 164.1, 165.7. The signals of CH_2S and CH_2NH is overlapped with DMSO.
Anal. Calcd for $C_{17}H_{14}ClN_3O_4S_2$: C, 48.17; H, 3.33; N, 9.91. Found: C, 47.96; H, 3.14; N, 9.64.

4.2.8. *7-Hydroxy-5-oxo-2-({[(propan-2-yl)carbamoyl]methyl}sulfanyl)-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9m**).*

Yield: 1 g (58%); mp > 300 °C (des.).
IR (KBr): 3359, 3285, 3160, 3092, 1644 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.07 (d, J = 6.6 Hz, 6H, 2CH_3), 3.78 (s, 2H, SCH_2), 3.83 (m, 1H, CH), 6.01 (s, 1H, C(6)H), 7.63 (br s, 1H, NH_2), 8.15 (d, J = 7.3 Hz, 1H, NH,), 9.24 (br s, 1H, NH_2), 10.76 (br s, 1H, OH), 11.64 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.1, 38.1, 40.9, 90.8, 112.2, 121.1, 127.1, 150.4, 160.2, 163.7, 164.1, 165.5.
Anal. Calcd for $C_{13}H_{15}N_3O_4S_2$: C, 45.73; H, 4.43; N, 12.31. Found: C, 45.51; H, 4.23 N, 12.05.

4.2.9. *2-{[2-(2H-1,3-Benzodioxol-5-yl)-2-oxoethyl]sulfanyl}-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9n**).*

Yield: 1.19 g (59%); mp 265-268 °C.
IR (KBr): 3422, 3357, 3170, 3089, 1638 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.79 (s, 2H, SCH_2), 6.02 (s, 1H, C(6)H), 6.16 (s, 2H, OCH_2O), 7.09 (d, J = 8.1 Hz, 1H, C_6H_3), 7.55 (s, 1H, CH), 7.63 (br s, 1H, NH_2), 7.74 (d, J = 8.1 Hz, 1H, C_6H_3), 9.17 (br s, 1H, NH_2), 10.57 (br s, 1H, OH), 11.62 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.6, 90.6, 102.2, 107.7, 108.1, 112.1, 121.2, 125.1, 128.5, 129.8, 137.8, 147.9, 152.0, 160.2, 163.7, 164.1, 191.6.

Anal. Calcd for $C_{17}H_{12}N_2O_6S_2$: C, 50.49; H, 2.99; N, 6.93. Found: C, 50.72; H, 2.84; N, 6.72.

4.2.10. *7-Hydroxy-5-oxo-2-({[(1,3-thiazol-2-yl)carbamoyl]methyl}sulfanyl)-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9o**).*

Yield: 1.15 g (60%); mp 291-293 °C.
IR (KBr): 3438, 3172, 3139, 3089, 1636 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.18 (s, 2H, S$\underline{CH_2}$), 6.04 (s, 1H, C(6)$\underline{H}$), 7.25 (d, J = 3.5 Hz, 1H, $\underline{CH}$), 7.50 (d, J = 3.5 Hz, 1H, $\underline{CH}$), 7.68 (br s, 1H, $\underline{NH_2}$), 9.21 (br s, 1H, $\underline{NH_2}$), 10.81 (s, 1H, $\underline{OH}$), 11.70 (br s, 1H, N(4)$\underline{H}$), 12.51 (br s, 1H, $\underline{NH}$).
^{13}C NMR (75 MHz, DMSO-d6): δ = 93.6, 112.3, 113.8, 114.8, 137.7, 149.4, 151.2, 157.4, 160.9, 165.4, 165.5, 167.1 The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{13}H_{10}N_4O_4S_3$: C, 40.83; H, 2.64; N, 14.65. Found: C, 40.64; H, 2.48; N, 14.42.

4.2.11. *7-Hydroxy-2-({[(5-methyl-1,2-oxazol-3-yl)carbamoyl]methyl}sulfanyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9p**).*

Yield: 1.13 g (59%); mp > 300 °C.
IR (KBr): 3416, 3377, 3213, 3145, 3098, 1626 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.37 (s, 3H, $\underline{CH_3}$), 4.10 (s, 2H, S$\underline{CH_2}$), 6.03 (s, 1H, C(6)$\underline{H}$), 6.61 (s, 1H, $\underline{CH}$), 7.67 (br s, 1H, $\underline{NH_2}$), 9.23 (br s, 1H, $\underline{NH_2}$), 10.79 (s, 1H, $\underline{OH}$), 11.34 (br s, 1H, $\underline{NH}$), 11.70 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d6): δ = 12.1, 38.1, 90.8, 96.2, 112.2, 121.4, 151.0, 153.0, 157.9, 160.3, 163.9, 164.1, 166.1, 169.8.
Anal. Calcd for $C_{14}H_{12}N_4O_5S_2$: C, 44.20; H, 3.18; N, 14.73. Found: C, 44.48; H, 3.27; N, 14.95.

4.2.12. *2-(Benzylsulfanyl)-7-hydroxy-N-(3-methoxypropyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9q**).*

Yield: 1.52 g (75%); mp 197-200 °C.
IR (KBr): 3364, 3332, 1624 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.79 (m, 2H, $CH_2\underline{CH_2}CH_2OCH_3$), 3.24 (s, 3H, O$\underline{CH_3}$), 3.28-3.43 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$), 4.33 (s, 2H, S$\underline{CH_2}$), 6.03 (s, 1H, C(6)$\underline{H}$), 7.25-7.40 (m, 3H, $\underline{C_6H_5}$), 7.47 (m, 2H, $\underline{C_6H_5}$), 9.74 (br s, 1H, CO$\underline{NH}$), 10.79 (br s, 1H, $\underline{OH}$), 11.67 (s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.3, 35.6, 37.9, 57.9, 69.7, 90.8, 112.1, 120.4, 127.4, 127.8, 128.5, 129.1, 136.1, 148.5, 160.3, 162.4, 163.7.
Anal. Calcd for $C_{19}H_{20}N_2O_4S_2$: C, 56.42; H, 4.98; N, 6.93. Found: C, 56.19; H, 4.72; N, 6.64.

4.2.13. *7-Hydroxy-N-(3-methoxypropyl)-2-(methylsulfanyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9r**).*

Yield: 1.18 g (72%); mp 182-185 °C.
IR (KBr): 3336, 3268, 1628 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80 (m, 2H, $CH_2\underline{CH_2}CH_2OCH_3$), 2.56 (s, 3H, S$\underline{CH_3}$), 3.24 (s, 3H, O$\underline{CH_3}$), 3.28-3.43 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$), 6.04 (s, 1H, C(6)$\underline{H}$), 9.77 (br s, 1H, CO$\underline{NH}$), 10.74 (br s, 1H, $\underline{OH}$), 11.62 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.7, 29.4, 35.6, 57.9, 69.7, 90.3, 112.0, 120.3, 128.5, 147.8, 160.3, 162.5, 163.7.
Anal. Calcd for $C_{13}H_{16}N_2O_4S_2$: C, 47.54; H, 4.91; N, 8.53. Found: C, 47.29; H, 4.71; N, 8.32.

4.2.14. *7-Hydroxy-N-(3-methoxypropyl)-5-oxo-2-[(2-oxo-2-phenylethyl)sulfanyl]-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9s**).*

Yield: 1.79 g (83%); mp 175-177 °C.
IR (KBr): 3356, 3284, 1692, 1624 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81 (m, 2H, $CH_2\underline{CH_2}CH_2OCH_3$), 3.25 (s, 3H, O$\underline{CH_3}$), 3.30-3.43 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$), 4.89 (s, 2H, S$\underline{CH_2}$), 6.06 (s, 1H, C(6)$\underline{H}$), 7.58 (m, 2H, $\underline{C_6H_5}$), 7.70 (m, 1H, $\underline{C_6H_5}$), 8.08 (d, J = 7.6 Hz, 2H, $\underline{C_6H_5}$), 9.77 (br s, 1H, CO$\underline{NH}$), 10.76 (br s, 1H, $\underline{OH}$), 11.63 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.4, 35.7, 41.9, 57.9, 69.7, 90.9, 112.1, 121.3, 128.4, 128.8, 133.8, 135.3, 147.9, 160.3, 162.5, 163.7, 193.7. The signal of C(9) is overlapped with Aryl.
Anal. Calcd for $C_{20}H_{20}N_2O_5S_2$: C, 55.54; H, 4.66; N, 6.48. Found: C, 55.30; H, 4.42; N, 6.20.

4.2.15. *2-({[(4-Chloro-2-methoxy-5-methylphenyl)carbamoyl]methyl}sulfanyl)-7-hydroxy-N-(3-methoxypropyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9t**).*

Yield: 1.61 g (61%); mp 198-201 °C.
IR (KBr): 3296, 1684, 1628 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.82 (m, 2H, $CH_2\underline{CH_2}CH_2OCH_3$), 2.22 (s, 3H, $\underline{CH_3}$), 3.25 (s, 3H, O$\underline{CH_3}$), 3.30-3.42 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$), 3.83 (s, 3H, O$\underline{CH_3}$), 4.15 (s, 2H, S$\underline{CH_2}$), 6.08 (s, 1H, C(6)$\underline{H}$), 7.10 (s, 1H, $\underline{CH}$), 7.94 (s, 1H, $\underline{CH}$), 9.63 (s, 1H, $\underline{NH}$) 9.79 (br s, 1H, $\underline{NH}$), 10.82 (br s, 1H, $\underline{OH}$), 11.71 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.9, 29.3, 35.7, 56.2, 57.9, 69.7, 91.0, 111.9, 112.2, 121.4, 123.4, 123.6, 125.8, 126.6, 128.0, 148.4, 151.0, 160.3, 162.4, 163.7, 166.0. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{22}H_{24}ClN_3O_6S_2$: C, 50.23; H, 4.60; N, 7.99. Found: C, 50.48; H, 4.83; N, 8.25.

4.2.16. *Ethyl 4-[2-({7-hydroxy-3-[(3-methoxypropyl)carbamoyl]-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl}sulfanyl)acetamido]benzoate (**9u**).*

Yield: 1.54 g (59%); mp 268-271 °C.
IR (KBr): 3312, 3240, 1700, 1676, 1640, 1616 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.30 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$), 1.81 (m, 2H, $CH_2\underline{CH_2}CH_2OCH_3$), 3.25 (s, 3H, O$\underline{CH_3}$), 3.32-3.43 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$), 4.11 (s, 2H, S$\underline{CH_2}$), 4.28 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 6.04 (s, 1H, C(6)$\underline{H}$), 7.73 (d, J = 8.7 Hz, 2H, $\underline{C_6H_4}$), 7.93 (d, J = 8.7 Hz, 2H, $\underline{C_6H_4}$), 9.75 (br s, 1H, $\underline{NH}$), 10.58 (br s, 1H, $\underline{NH}$), 10.68 (br s, 1H, $\underline{OH}$), 11.67 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1, 29.4, 35.7, 57.9, 60.4, 69.7, 90.8, 112.1, 118.5, 121.3, 124.6, 130.3, 130.8, 143.0, 150.1, 160.3, 162.4, 163.7, 165.2, 166.2. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{23}H_{25}N_3O_7S_2$: C, 53.17; H, 4.85; N, 8.09. Found: C, 53.41; H, 4.88; N, 8.15.

4.2.17. *N-Cyclopropyl-7-hydroxy-2-{[(2-methylphenyl)methyl]sulfanyl}-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9v**).*

Yield: 1.45 g (75%); mp 133-135 °C.
IR (KBr): 3348, 3244, 1656, 1636 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.63 (m, 2H, $(\underline{CH_2})_2CH$), 0.73 (m, 2H, $(\underline{CH_2})_2CH$), 2.39 (s, 3H, $\underline{CH_3}$), 2.82 (m, 1H, $(CH_2)_2\underline{CH}$), 4.31 (s, 2H, S$\underline{CH_2}$), 6.03 (s, 1H, C(6)$\underline{H}$), 7.15-7.25 (m, 3H, $\underline{C_6H_4}$), 7.40 (d, J = 6.7 Hz, 1H, $\underline{CH}$), 9.68 (br s, 1H, $\underline{NH}$), 10.86 (br. s., 1H, $\underline{OH}$), 11.69 (br s, 1H, N(4)$\underline{H}$).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.2, 18.7, 22.2, 36.3, 90.9, 112.4, 120.8, 126.2, 127.9, 129.9, 130.4, 133.6, 136.9, 150.3, 160.4, 163.6, 163.8. The signal of C(9) is overlapped with aryl.

Anal. Calcd for $C_{19}H_{18}N_2O_3S_2$: C, 59.05; H, 4.69; N, 7.25. Found: C, 58.83; H, 4.48; N, 7.03.

4.2.18. *N-Cyclopropyl-7-hydroxy-2-{[(4-methylphenyl)methyl]sulfanyl}-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9w**).*

Yield: 1.62 g (84%); mp 145-147 °C.
IR (KBr): 3264, 1628 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.63 (m, 2H, $(CH_2)_2CH$), 0.73 (m, 2H, $(CH_2)_2CH$), 2.28 (s, 3H, CH_3), 2.82 (m, 1H, $(CH_2)_2CH$), 4.28 (s, 2H, SCH_2), 6.01 (s, 1H, C(6)H), 7.17 (d, *J* = 7.8 Hz, 2H, C_6H_4), 7.35 (d, *J* = 7.8 Hz, 2H, C_6H_4), 9.70 (br s, 1H, NH), 10.84 (br s, 1H, OH), 11.66 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.1, 20.7, 22.2, 37.6, 90.8, 112.2, 120.6, 129.0, 129.1, 132.9, 136.8, 150.4, 160.4, 163.6, 163.8. The signal of C(9) is overlapped with aryl.
Anal. Calcd for $C_{19}H_{18}N_2O_3S_2$: C, 59.05; H, 4.69; N, 7.25. Found: C, 59.31; H, 4.70; N, 7.27.

4.2.19. *2-({[(4-Chloro-2-methoxy-5-methylphenyl)carbamoyl]methyl}sulfanyl)-N-cyclopropyl-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9x**).*

Yield: 1.44 g (58%); mp 185-188 °C.
IR (KBr): 3340, 1628 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.64 (m, 2H, $(CH_2)_2CH$), 0.73 (m, 2H, $(CH_2)_2CH$), 2.22 (s, 3H, CH_3), 2.87 (m, 1H, $(CH_2)_2CH$), 3.83 (s, 3H, OCH_3), 4.16 (s, 2H, SCH_2), 6.07 (s, 1H, C(6)H), 7.09 (s, 1 H, C_6H_2), 7.94 (s, 1H, C_6H_2), 9.63 (s, 1H, NH), 9.70 (br s, 1H, NH), 10.81 (br s, 1H, OH), 11.77 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.1, 18.9, 22.1, 56.2, 90.8, 112.0, 112.3, 121.0, 123.4, 125.8, 126.6, 128.0, 128.6, 148.4, 152.1, 160.3, 163.5, 163.7, 166.0. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{21}H_{20}ClN_3O_5S_2$: C, 51.06; H, 4.08; N, 8.51. Found: C, 51.29; H, 4.15; N, 8.83.

4.2.20. *N-Cyclopropyl-7-hydroxy-5-oxo-2-[(2-oxo-2-phenylethyl)sulfanyl]-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9y**).*

Yield: 1.7 g (85%); mp 212-214 °C.
IR (KBr): 3308, 1688, 1644, 1620 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.60-0.80 (m, 4H, $(CH_2)_2CH$), 2.86 (m, 1H, $(CH_2)_2CH$), 4.89 (s, 2H, SCH_2), 6.02 (s, 1H, C(6)H), 7.55-7.75 (m, 3H, C_6H_5), 8.09 (d, *J* = 7.5 Hz, 2H, C_6H_5), 9.71 (br s, 1H, NH), 10.86 (br s, 1H, OH), 11.67 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.2, 22.2, 41.9, 90.8, 112.2, 121.0, 128.5, 128.9, 133.8, 135.0, 150.7, 160.3, 163.7, 163.8, 193.7.
Anal. Calcd for $C_{19}H_{16}N_2O_4S_2$: C, 56.98; H, 4.03; N, 7.00. Found: C, 56.72; H, 3.87; N, 6.65.

4.2.21. *N-Cyclopropyl-7-hydroxy-2-(methylsulfanyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9z**).*

Yield: 1.27 g (86%); mp 257-259 °C.
IR (KBr): 3356, 3260, 1632, 1616 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58-0.78 (m, 4H, $(CH_2)_2CH$), 2.55 (m, 2H, SCH_3), 2.84 (m, 1H, $(CH_2)_2CH$), 6.01 (s, 1H, C(6)H), 9.71 (br s, 1H, NH), 10.84 (br s, 1H, OH), 11.67 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.2, 16.7, 22.1, 90.3, 112.1, 120.0, 127.9, 151.2, 160.3, 163.6, 163.7.

Anal. Calcd for $C_{12}H_{12}N_2O_3S_2$: C, 48.63; H, 4.08; N, 9,45. Found: C, 48.36; H, 3.85; N, 9,29.

4.2.22. *N-Benzyl-7-hydroxy-2-{[(4-methylphenyl)methyl]sulfanyl}-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9aa**).*

Yield: 1.84 g (84%); mp 140-143 °C.
IR (KBr): 3352, 3284, 1616 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3 H, CH_3), 4.29 (s, 2H, SCH_2), 4.55 (d, *J* = 6.2 Hz, 2H, $C_6H_5CH_2NH$,), 6.08 (s, 1H, C(6)H), 7.15-7.40 (m, 9H, Ar), 10.36 (br s, 1H, NH), 10.85 (br s, 1H, OH), 11.75 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.7, 37.6, 41.7, 90.7, 112.1, 120.4, 126.7, 127.1, 128.0, 128.3, 129.0, 129.1, 132.8, 136.7, 139.7, 151.7, 160.4, 162.6, 163.7.
Anal. Calcd for $C_{23}H_{20}N_2O_3S_2$: C, 63.28; H, 4.62; N, 6.42. Found: C, 62.97; H, 4.45; N, 6.26.

4.2.23. *N-Benzyl-7-hydroxy-2-(methylsulfanyl)-5-oxo-4H,5H-thieno[3,2-b]pyridine-3-carboxamide (**9ab**).*

Yield: 1.32 g (76%); mp 272-275 °C.
IR (KBr): 3312, 3284, 1636, 1620 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.58 (s, 3 H, SCH_3), 4.56 (d, *J* = 6.2 Hz, 2H, $C_6H_5CH_2NH$), 6.06 (s, 1H, C(6)H), 7.20-7.35 (m, 5H, C_6H_5), 10.36 (br s, 1H, NH), 10.81 (br s, 1H, OH), 11.68 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.7, 41.6, 90.2, 112.1, 119.9, 126.6, 127.0, 128.0, 128.3, 139.7, 149.9, 160.3, 162.6, 163.7.
Anal. Calcd for $C_{16}H_{14}N_2O_3S_2$: C, 55.47; H, 4.07; N, 8.09. Found: C, 55.72; H, 3.84; N, 7.75.

4.2.24. *3-(Benzenesulfonyl)-7-hydroxy-2-{[(4-methylphenyl)methyl]sulfanyl}-4H,5H-thieno[3,2-b]pyridin-5-one (**9ac**).*

Yield: 1.56 g (70%); mp 252-255 °C.
IR (KBr): 3348, 1632, 1172, 1136 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 4.40 (s, 2H, SCH_2), 5.77 (s, 1H, C(6)H), 7.12 (d, *J* = 7.7 Hz, 2H, C_6H_4), 7.27 (d, *J* = 7.7 Hz, 2H, C_6H_4), 7.62 (m, 2H, C_6H_5), 7.74 (t, *J* = 7.2 Hz, 1H, C_6H_5), 8.13 (d, *J* = 7.7 Hz, 2H, C_6H_5), 11.84 (br s, 1 H, N(4)H). The protons of the OH group are subject to deutero exchange and were not resolved completely.
^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.6, 38.1, 94.0, 122.1, 126.0, 127.1, 128.4, 128.9, 129.1, 129.3, 131.8, 134.2, 137.1, 140.3, 152.6, 160.2, 163.3.
Anal. Calcd for $C_{21}H_{17}NO_4S_3$: C, 56.86; H, 3.86; N, 3.16. Found: C, 57.09; H, 3.72; N, 3.31.

4.2.25. *3-(Benzenesulfonyl)-2-(benzylsulfanyl)-7-hydroxy-4H,5H-thieno[3,2-b]pyridin-5-one (**9ad**).*

Yield: 1.25 g (63%); mp 148-150 °C.
IR (KBr): 3344, 1616, 1172, 1136 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.45 (s, 2H, SCH_2), 5.77 (s, 1H, C(6)H), 7.2-7.45 (m, 5H, C_6H_5), 7.62 (m, 2H, C_6H_5), 7.74 (m, 1H, C_6H_5), 8.14 (d, *J* = 7.7 Hz, 2H, C_6H_5), 9.76 (br s, 1H, OH), 11.89 (br s, 1 H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 38.3, 94.0, 126.0, 127.1, 127.7, 128.6, 129.0, 129.2, 129.4, 134.2, 135.0, 140.3, 152.4, 160.2, 163.4.
Anal. Calcd for $C_{20}H_{15}NO_4S_3$: C, 55.92; H, 3.52; N, 3.26. Found: C, 56.23; H, 3.32; N, 3.17.

4.2.26. *3-(Benzenesulfonyl)-7-hydroxy-2-[(2-oxo-2-phenylethyl)sulfanyl]-4H,5H-thieno[3,2-b]pyridin-5-one (**9ae**).*

Yield: 1.51 g (66%); mp 225-228 °C.
IR (KBr): 3352, 1676, 1632, 1172, 1136 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.11 (s, 2H, SCH$_2$), 5.78 (s, 1H, C(6)H), 7.5-7.8 (m, 6H, C$_6$H$_5$, C$_6$H$_5$), 8.05 (d, *J* = 7.5 Hz, 2H, C$_6$H$_5$), 8.19 (d, *J* = 7.7 Hz, 2H, C$_6$H$_5$), 9.86 (br s, 1H, OH), 11.82 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 43.1, 93.8, 110.6, 122.4, 127.1, 128.5, 128.9, 129.4, 129.6, 134.1, 134.3, 134.9, 140.5, 152.7, 160.2, 163.6, 192.7.
Anal. Calcd for $C_{21}H_{15}NO_5S_3$: C, 55.13; H, 3.30; N, 3.06. Found: C, 55.38; H, 3.12; N, 3.18.

4.2.27. *2-{[3-(Benzenesulfonyl)-7-hydroxy-5-oxo-4H,5H-thieno[3,2-b]pyridin-2-yl]sulfanyl}-N-(2,5-dimethylphenyl)acetamide (**9af**).*

Yield: 1.51 g (60%); mp 242-245 °C.
IR (KBr): 3360, 3256, 1648, 1168, 1132 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 4.26 (s, 2H, SCH$_2$), 5.83 (s, 1H, C(6)H), 6.90 (d, *J* = 7.7 Hz, 1H, C$_6$H$_3$), 7.08 (d, *J* = 7.7 Hz, 1H, C$_6$H$_3$), 7.21 (s, 1H, C$_6$H$_3$), 7.61 (m, 2H, C$_6$H$_5$), 7.72 (t, *J* = 7.2 Hz, 1H, C$_6$H$_5$), 8.20 (d, *J* = 7.7 Hz, 2H, C$_6$H$_5$), 9.71 (s, 1H, NH), 11.84 (br s, 1 H, N(4)H). The protons of the OH group are subject to deutero exchange and were not resolved completely.
^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 17.3, 20.5, 38.9, 93.8, 110.6, 121.9, 125.2, 126.2, 127.1, 128.4, 129.4, 129.6, 130.2, 134.3, 135.1, 135.5, 140.5, 152.9, 160.2, 163.6, 164.8.
Anal. Calcd for $C_{23}H_{20}N_2O_5S_3$: C, 55.18; H, 4.03; N, 5.60. Found: C, 54.86; H, 3.85; N, 5.51.

4.3. General Experimental Procedure for 12a–e. The procedure of synthesis of thiophenes **12** is same as for **9**, starting from ethylcyanoacetate (**1g**).

4.3.1. *Ethyl 3-{4-cyano-3-hydroxy-5-[(2-oxo-2-phenylethyl)sulfanyl]thiophen-2-yl}-3-oxopropanoate (**12a**).*

Yield: 1.13 g (58%); mp 154-156 °C.
IR (KBr): 3435, 2221, 1742, 1677 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, *J* = 7.1 Hz, 3H, CH$_3$), 3.86 (s, 2H, COCH$_2$CO), 4.09 (q, *J* = 7.1 Hz, 2H, CH$_2$CH$_3$), 5.17 (s, 2H, SCH$_2$), 7.58 (m, 2H, C$_6$H$_5$), 7.72 (t, *J* = 7.3 Hz, 1H, C$_6$H$_5$), 8.06 (d, *J* = 7.4 Hz, 2H, C$_6$H$_5$). The protons of the OH group are subject to deutero exchange and were not resolved completely.
^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0, 42.9, 46.6, 60.5, 102.1, 112.2, 119.0, 128.6, 128.9, 134.1, 134.7, 158.2, 159.3, 167.4, 183.1, 192.4.
HRMS (ESI): m/z calcd for $C_{18}H_{16}NO_5S_2$ [M + H]$^+$: 390.0470, found: 390.0464.

4.3.2. *Ethyl 3-[5-(benzylsulfanyl)-4-cyano-3-hydroxythiophen-2-yl]-3-oxopropanoate (**12b**).*

Yield: 0.91 g (50%); mp 73-75 °C.
IR (KBr): 3430, 2226, 1720, 1686 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 7.1 Hz, 3H, CH$_2$CH$_3$), 3.85 (s, 2 H, COCH$_2$CO), 4.08 (q, *J* = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.50 (s, 2H, SCH$_2$), 7.25-7.5 (m, 5H, C$_6$H$_5$), 8.09 (br s, 1H, OH).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.8, 37.8, 46.6, 60.5, 101.8, 112.2, 118.9, 127.4, 127.8, 128.5, 138.4, 158.3, 159.4, 167.3, 183.1.
HRMS (ESI): m/z calcd for $C_{17}H_{16}NO_4S_2$ [M + H]$^+$: 362.0521, found: 362.0515.

4.3.3. *Ethyl 3-(4-cyano-3-hydroxy-5-{[(4-methylphenyl)methyl]sulfanyl}thiophen-2-yl)-3-oxopropanoate (**12c**).*

Yield: 1.19 g (63%); mp 80-82 °C.
IR (KBr): 3422, 2228, 1717, 1681 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, *J* = 7.1 Hz, 3H, CH$_2$CH$_3$), 2.28 (s, 3H, CH$_3$), 3.85 (s, 2H, COCH$_2$CO), 4.08 (q, *J* = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.46 (s, 2H, SCH$_2$), 7.16 (d, *J* = 7.7 Hz, 2H, C$_6$H$_4$), 7.32 (d, *J* = 7.7 Hz, 2H, C$_6$H$_4$), 8.12 (br s, 1H, OH).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.9, 20.7, 37.9, 46.6, 60.5, 101.9, 112.2, 119.0, 128.9, 129.2, 131.9, 137.3, 158.2, 159.3, 167.3, 183.1.
HRMS (ESI): m/z calcd for $C_{18}H_{18}NO_4S_2$ [M + H]$^+$: 376.0677, found: 376.0672.

4.3.4. *Ethyl 3-{4-cyano-5-[(2-ethoxy-2-oxoethyl)sulfanyl]-3-hydroxythiophen-2-yl}-3-oxopropanoate (**12d**).*

Yield: 1.29 g (72%); mp 82-84 °C.
IR (KBr): 3438, 2228, 1725, 1691 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.10-1.25 (m, 6H, 2 CH$_3$), 3.87 (s, 2H, COCH$_2$CO), 4.05-4.20 (m, 4H, 2 CH$_2$CH$_3$), 4.24 (s, 2H, SCH$_2$), 7.30 (br s, 1H, OH).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.9, 14.0, 36.2, 46.7, 60.6, 61.8, 103.1, 112.1, 119.5, 157.0, 159.2, 167.3, 167.4, 183.3.
HRMS (ESI): m/z calcd for $C_{14}H_{16}NO_6S_2$ [M + H]$^+$: 358.0419, found: 358.0414.

4.3.5. *Ethyl 3-{4-cyano-3-hydroxy-5-[(2-oxopropyl)sulfanyl]thiophen-2-yl}-3-oxopropanoate (**12e**).*

Yield: 0.89 g (54%); mp 97-99 °C.
IR (KBr): 3432, 2229, 1722, 1686 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, *J* = 7.1 Hz, 3H, CH$_2$CH$_3$), 2.27 (s, 3 H, CH$_3$CO), 3.86 (s, 2H, COCH$_2$CO), 4.09 (q, *J* = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.47 (s, 2H, SCH$_2$), 6.91 (br s, 1H, OH).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0, 28.5, 45.1, 46.5, 60.5, 102.1, 112.2, 118.6, 158.2, 159.7, 167.4, 182.9, 200.8.
HRMS (ESI): m/z calcd for $C_{13}H_{14}NO_5S_2$ [M + H]$^+$: 328.0313, found: 328.0308.

4.4. General Experimental Procedure for Pyrans 16a-f. The solution of dioxipyridines **9** (0.9 mmol), malonodinitrile (**1a**) (0.06 g, 0.9 mmol), aldehydes **13** (0.9 mmol) and Et$_3$N (0.015 g, 0.15 mmol) in 8 ml of EtOH was refluxed for 30 min, then cooled to room temperature and the precipitate filtered off to obtain pyrans **16a-f.**

4.4.1. *8-Amino-2-(benzylthio)-7-cyano-N-(3-methoxypropyl)-5-oxo-6-phenyl-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridine-3-carboxamide (**16a**).*

Yield: 0.29 g (58%); mp 158-160 °C.
IR (KBr): 3372, 3290, 3204, 2196, 1668, 1624 cm^{-1}.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.76 (m, 2H, CH$_2$CH$_2$CH$_2$OCH$_3$), 3.20 (s, 3H, OCH$_3$), 3.27-3.45 (m, 4H, CH$_2$CH$_2$CH$_2$OCH$_3$), 4.36 (s, 2H, SCH$_2$), 4.54 (s, 1H, C(6)H), 7.05-7.5 (m., 12H, 2 C$_6$H$_5$, NH$_2$), 9.35 (br s, 1 H, CONH), 11.61 (br s, 1 H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.5, 36.0, 36.6, 57.9, 58.3, 69.8, 101.3, 109.6, 119.6, 120.2, 127.0, 127.4, 127.6, 127.8,

128.3, 128.5, 129.0, 135.9, 144.4, 150.2, 155.2, 158.2, 160.4, 162.3. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{29}H_{26}N_4O_4S_2$: C, 62.35; H, 4.69; N, 10.03. Found: C, 62.04; H, 4.83; N, 10.34.

4.4.2. *8-Amino-7-cyano-N-cyclopropyl-2-(methylthio)-5-oxo-6-phenyl-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridine-3-carboxamide* ***(16b)***.

Yield: 0.27 g (66%); mp 302-304 °C.
IR (KBr): 3376, 3256, 3188, 2188, 1660, 1620 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 0.55-0.71 (m, 4H, $(CH_2)_2CH$), 2.62 (s, 3H, SCH_3), 2.84 (m, 1H, $(CH_2)_2CH$), 4.57 (s, 1H, C(6)H), 7.15-7.35 (m, 7 H, C_6H_5, NH_2), 9.41 (br s, 1H, CONH), 11.64 (s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.9, 16.9, 22.2, 36.5, 58.2, 101.1, 109.8, 119.6, 123.4, 126.7, 127.4, 127.9, 128.3, 138.3, 144.5, 150.3, 158.5, 160.2, 163.1.
Anal. Calcd for $C_{22}H_{18}N_4O_3S_2$: C, 58.65; H, 4.03; N, 12.44. Found: C, 58.91; H, 3.86; N, 12.23.

4.4.3. *8-Amino-7-cyano-N-cyclopropyl-6-(4-methoxyphenyl)-2-(methylthio)-5-oxo-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridine-3-carboxamide* ***(16c)***.

Yield: 0.27 g (63%); mp 275-277 °C.
IR (KBr): 3376, 3324, 3272, 3184, 2200, 1668, 1628 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 0.55-0.75 (m, 4H, $(CH_2)_2CH$), 2.62 (s, 3H, SCH_3), 2.84 (m, 1H, $(CH_2)_2CH$), 3.70 (s, 3H, OCH_3), 4.52 (s, 1H, C(6)H), 6.84 (d, *J* = 6.2 Hz, 2H, C_6H_4), 7.08 (d, *J* = 6.2 Hz, 2H, C_6H_4), 7.20 (s, 2H, NH_2), 9.40 (br s, 1H, CONH), 11.62 (br s, 1 H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.9, 16.9, 22.2, 35.7, 55.0, 58.5, 100.8, 110.2, 113.7, 119.7, 119.9, 128.5, 136.6, 150.1, 158.1, 158.4, 160.2, 163.2, 163.7. The signal of C(2) is overlapped with Aryl.
Anal. Calcd for $C_{23}H_{20}N_4O_4S_2$: C, 57.48; H, 4.19; N, 11.66. Found: C, 57.19; H, 4.02; N, 11.89.

4.4.4. *8-Amino-N-benzyl-7-cyano-2-(methylthio)-5-oxo-6-phenyl-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridine-3-carboxamide* ***(16d)***.

Yield: 0.36 g (80%); mp 279-281 °C.
IR (KBr): 3544, 3480, 3312, 2180, 1656, 1628 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, SCH_3), 4.45-4.60 (m, 3H, C(6)H, CH_2), 7.12-7.35 (m, 12H, 2 C_6H_5, NH_2), 10.07 (br s, 1H, CONH), 11.61 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.0, 36.5, 41.7, 58.3, 100.0, 110.0, 119.6, 126.6, 126.7, 127.0, 127.4, 128.3, 128.4, 130.4, 139.5, 144.5, 150.4, 152.3, 158.5, 160.3, 162.2. The signal of C(13) is overlapped with Aryl.
Anal. Calcd for $C_{26}H_{20}N_4O_3S_2$: C, 62.38; H, 4.03; N, 11.19. Found: C, 62.07; H, 3.84; N, 11.36.

4.4.5. *Ethyl 4-({[(8-amino-7-cyano-3-{[(3-methoxypropyl)amino]carbonyl}-5-oxo-6-phenyl-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridin-2-yl)thio]acetyl}amino)benzoate* ***(16e)***.

Yield: 0.44 g (73%); mp 289-291 °C.
IR (KBr): 3456, 3308, 3276, 3200, 2200, 1700, 1672, 1628 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 6.2 Hz, 3H, CH_2CH_3), 1.79 (m, 2H, $CH_2CH_2CH_2OCH_3$), 3.21 (s, 3H, OCH_3), 3.25-3.45 (m, 4H, $CH_2CH_2CH_2OCH_3$), 4.14 (s, 2H, SCH_2), 4.28 (q, *J* = 6.2 Hz, 2H, CH_2CH_3), 4.56 (s, 1H, C(6)H), 7.15-7.35 (m, 5H, C_6H_5), 7.73 (d, *J* = 8.4 Hz, 2H, C_6H_4), 7.94 (d, *J* = 8.4 Hz, 2H, C_6H_4), 9.49 (br s, 1H, CONH), 10.70 (br s, 1H, CONH), 11.63 (br s, 1 H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.2, 29.2, 36.0, 36.5, 57.9, 58.3, 60.4, 69.7, 102.4, 111.8, 118.6, 119.6, 124.6, 126.7, 127.4, 128.3, 130.3, 143.0, 144.4, 150.3, 153.8, 158.5, 160.3, 161.8, 165.2, 166.2. The signal of CH_2S is overlapped with DMSO.
Anal. Calcd for $C_{33}H_{31}N_5O_7S_2$: C, 58.83; H, 4.64; N, 10,39. Found: C, 58.54; H, 4.42; N, 10,18.

4.4.6. *8-Amino-7-cyano-N-cyclopropyl-6-(4-fluorophenyl)-2-[(4-methylbenzyl)thio]-5-oxo-4,6-dihydro-5H-pyrano[2,3-d]thieno[3,2-b]pyridine-3-carboxamide* ***(16f)***.

Yield: 0.38 g (76%); mp 276-278 °C.
IR (KBr): 3380, 3305, 3184, 2196, 1664, 1628 cm^{-1}.
^1H NMR (300 MHz, DMSO-d_6): δ = 0.53-0.75 (m, 4H, $(CH_2)_2CH$), 2.29 (s, 3H, CH_3), 2.83 (m, 1H, $(CH_2)_2CH$), 4.31 (s, 2H, SCH_2), 4.59 (s, 1H, C(6)H), 7.05-7.4 (m, 10H, 2 C_6H_4, NH_2), 9.37 (br s, 1H, CONH), 11.68 (br s, 1H, N(4)H).
^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.9, 20.7, 22.3, 35.9, 37.7, 58.1, 100.7, 110.0, 114.9, 115.1, 119.5, 126.6, 128.9, 129.1, 129.4, 129.5, 132.6, 136.9, 140.7, 150.1, 154.2, 158.4, 159.4, 160.3, 162.6, 163.0. The signal of C(2) is overlapped with Aryl.
Anal. Calcd for $C_{29}H_{23}FN_4O_3S_2$: C, 62.35; H, 4.15; N, 10.03. Found: C, 62.14; H, 3.94; N, 9.78.

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