

Metal free, one pot synthesis of tetracyclic fused scaffolds benzothiazine-pyranopyridines

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ABSTRACT

In this study, we present a highly efficient multicomponent domino reaction for synthesizing benzothiazine-pyranopyridine derivatives, achieving moderate to high yields. This metal-free, one-pot process involves the reaction between N-Alkyl 1,2-benzothiazinone 1,1-dioxide, benzaldehyde, and malononitrile dimer. The mechanism progresses through sequential condensation, followed by domino cyclization, to afford a fused tetracyclic scaffold. The resulting structure integrates benzothiazine and pyranopyridine moieties, featuring two free amine groups that provide valuable sites for further functionalization.

1. Introduction

One of the most significant challenges in modern synthetic organic chemistry, which is essential for preparing natural products, pharmaceuticals, diagnostics, and agrochemicals, is enhancing efficiency while minimizing toxic reagents, reducing waste, and ensuring responsible resource management. The development and application of domino reactions, involving consecutive bond-forming steps, addresses these goals by efficiently synthesizing complex molecules from simple substrates [1]. Generating molecular complexity and diversity from common starting materials while considering economic and environmental factors remains a central focus for academic and industrial chemists [2]. In this context, domino reactions stand out due to their atom economy and eco-friendly nature, enabling the rapid and efficient construction of complex structures with minimal waste while bypassing labor-intensive and costly synthetic routes. These reactions also demonstrate excellent chemo- and regio-selectivity, enhancing their utility [3] (see Fig. 1).

Cyclic sulfonamides (sultams), particularly benzosultams, have attracted considerable attention in various industries, including the pharmaceutical and agricultural sectors [4,5]. These compounds exhibit remarkable bioactivity, such as antibacterial properties [6,7], anticancer effects [8], and enzyme inhibition, including Calpain I and MMP-2 [9,10]. The 1,2-benzothiazine 1,1-dioxide (benzosultam) core is

foundational to many biologically active molecules and forms the basis of several well-known non-steroidal anti-inflammatory drugs (NSAIDs), such as piroxicam, meloxicam, and droxicam [11]. Derivatives of 1,2-benzothiazine 1,1-dioxide have demonstrated a range of biological activities, including anticancer, antidiabetic, and antimicrobial effects [12]. Moreover, 1,2-benzothiazinone 1,1-dioxide serves as a crucial precursor for the synthesis of various benzothiazine derivatives [13–15].

Similarly, the pyranopyridine scaffold is biologically relevant, being present in a variety of small molecules with significant bioactivities, including anticancer [16], antibiotic [17], and antimycobacterial properties [18]. This attention has fuelled efforts to synthesize and evaluate these bicyclic compounds. For instance, Eman R. Kotb et al. synthesized a series of 2-aminopyranopyridines exhibiting anticancer activity in different cell lines [16]. A notable example of bioactive pyranopyridines is MBX2319, which has demonstrated potency against *P. aeruginosa* by selectively permeabilizing the outer membrane [19]. MBX2319's activity is specifically effective against the RND-type pumps of *P. aeruginosa* [17] Fig. 2.

Molecular hybridization is one of the most promising strategies for developing new scaffolds that serve as multitarget drug candidates [20]. This approach integrates two or more bioactive fragments into a single molecule, combining their pharmacological properties and enhancing therapeutic potential [21]. In pursuing such complex scaffolds,

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multicomponent reactions (MCRs) have become invaluable tools, offering an efficient pathway for synthesizing diverse molecular frameworks [22,23]. These reactions are advantageous due to their ability to generate structurally complex compounds in a single step, minimizing both time and resource consumption. Leveraging the benefits of MCRs, we employed a multicomponent domino reaction to synthesize a novel class of compounds featuring benzothiazine and pyranopyridine skeletons. This strategy enables the rapid assembly of multifunctional molecules and opens new avenues for scaffold diversification and optimization in drug discovery.

2. Result and discussion

Given these considerations, we aimed to design a three-component reaction to synthesize pyranopyridine fused to benzothiazine via a domino process. While 1,2-benzothiazinone 1,1-dioxide was a crucial starting material, its limited availability and the requirement for an N-protected form led us to utilize its commercially available precursor, saccharin, successfully adapted for the multicomponent reaction [24]. To address this challenge, we proposed performing the Gabriel-Colman rearrangement on saccharin [25,26]. Before hydrolyzing the product to obtain N-methyl or N-benzyl 1,2-benzothiazinone 1,1-dioxide, we ensured the nitrogen of the intermediate would be protected.

As shown in Scheme 1, the reaction began with sodium saccharin (1) and methyl chloroacetate (2), yielding methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl) acetate (3) without a base. Methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl) acetate was then subjected to standard Gabriel-Colman rearrangement conditions, producing methyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (4). Treatment of this intermediate with dimethyl sulfate or benzyl chloride afforded methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (5a) and benzyl 4-hydroxy-2-benzyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (5b), respectively. The final step involved acidic hydrolysis, yielding the desired compounds 6a and 6b.

The other essential component for the multicomponent domino reaction was 2-amino-1,1,3-propanetricarbonitrile (malononitrile dimer). This compound is critical in forming the pyranopyridine moiety in the final product through the domino process. It has been reported as a precursor for synthesizing various molecules with similar frameworks,

which have been evaluated for their biological activities [27–29]. Anderson et al. synthesized a series of benzopyranopyridines as MK-2 inhibitors using this same starting material [30]. We synthesized the malononitrile dimer in the lab through a one-step process from malononitrile in a potassium hydroxide solution with absolute ethanol.

With all the necessary components in hand, we proceeded with a test reaction to evaluate the feasibility of the proposed approach. Initially, N-methyl 1,2-benzothiazinone 1,1-dioxide was reacted with benzaldehyde in the presence of base to produce the α,β -unsaturated intermediate. This intermediate was purified, fully characterized, and subsequently utilized as the starting material for the second reaction. In this step, the intermediate was reacted with 2-amino-1,1,3-propanetricarbonitrile, yielding the final product.

The next phase was to investigate whether the reaction could proceed to completion in a single pot. All three components—N-methyl 1,2-benzothiazinone 1,1-dioxide, benzaldehyde, and 2-amino-1,1,3-propanetricarbonitrile—were combined in a flask with *i*-Pr₂NEt as the base. To our delight, the reaction proceeded efficiently, affording the final product a higher overall yield than the stepwise approach. This outcome highlights the efficiency of the multicomponent domino process, which facilitated the formation of the desired product in higher yields while eliminating the need for intermediate purification.

To optimize the reaction conditions, 4-fluorobenzaldehyde, N-methyl 1,2-benzothiazinone 1,1-dioxide, benzaldehyde, and 2-amino-1,1,3-propanetricarbonitrile were selected as the model substrates (Table 1). Various bases were evaluated to enhance the yield, with the best results obtained using *i*-Pr₂NEt (Table 1, entries 1–5). Additionally, increasing the temperature and employing a reflux system reduced the reaction time from 72 h to 24 h, achieving complete conversion of the starting materials.

The solvent screening was also performed, and as anticipated, the highest yield percentage was observed with a protic solvent, stabilizing the charged intermediates. Notably, the final product precipitated as a solid in Ethanol, the solvent of choice. This feature not only simplifies the method by eliminating the need for further purification but also drives the reaction to completion, making the process more economical.

With the optimized conditions in hand, we explored the scope of the reaction by testing a variety of benzaldehydes (Table 2). Notably, almost all aldehydes led to the formation of the desired product in moderate to

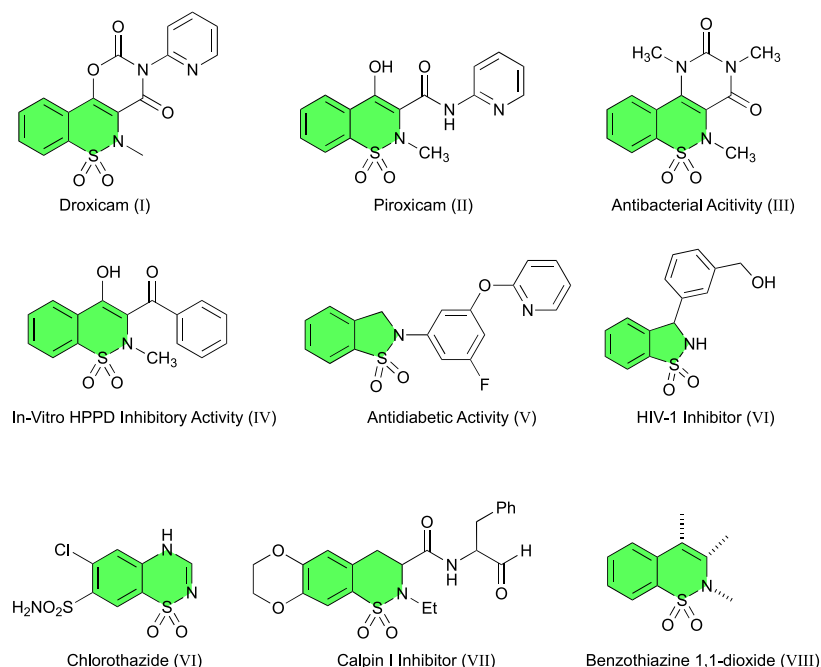


Fig. 1. Selected examples of biologically active sultam-containing compounds.

good yields, regardless of their electronic nature. Both electron-withdrawing and electron-donating aldehydes proved to be compatible with the reaction, demonstrating its broad substrate tolerance. To assess the scalability of the method, reaction **9b** was performed on a five mmol scale, yielding approximately 69 % of the product. This result demonstrates the robustness and practicality of the approach for larger-scale synthesis.

The proposed mechanism for synthesizing compound **9a** is illustrated in Scheme 2. The process begins with deprotonating N-methyl 1,2-benzothiazinone 1,1-dioxide (**6a**) by N,N-diisopropylethylamine, generating a stabilized enolate due to resonance with the adjacent amine. This enolate undergoes condensation with benzaldehyde (**7a**), resulting in the formation of an α,β -unsaturated intermediate (**I**). The subsequent step involves a 1,4-Michael addition with deprotonated 2-amino-1,1,3-propanetricarbonitrile (**8**), initiating a domino process and the intermediate (**II**) will be formed. The oxygen anion formed from the enolate attacks the carbon of the nearest nitrile group, creating a pyran ring with an acetimidate-like backbone (**III**). This intermediate facilitates the next step in the domino sequence, forming an aromatic pyridine ring and completing the reaction. To validate the proposed mechanism and gain further insights into the reaction pathway, we previously isolated and characterized the intermediate product formed between benzothiazinone (**6**) and benzaldehyde (**7**). This intermediate was then subjected to a subsequent reaction with 2-amino-1,1,3-propanetricarbonitrile (**8**), allowing us to investigate its reactivity and confirm the progression of the proposed mechanism.

All the synthesized structures are characterized by IR, Mass spectroscopy, ^1H , and ^{13}C NMR spectroscopy. Finally, the structure of compound **9a** was also confirmed by single-crystal X-ray analysis (Fig. 3) (CCDC 2419559).

3. Conclusion

In conclusion, we have successfully developed a domino multicomponent reaction utilizing N-methyl 1,2-benzothiazinone 1,1-dioxide (**6** (a–b)), benzaldehyde (**7** (a–j)), and 2-amino-1,1,3-propanetricarbonitrile (malononitrile dimer) (**8**) to construct complex scaffolds containing both benzothiazine and pyranopyridine moieties. The reaction conditions were optimized to enable a one-pot procedure, eliminating the need for extensive purification, as the product precipitates selectively in the chosen solvent. This methodology efficiently generates a library of structurally diverse and unprecedented pyranopyridine derivatives.

The resulting products incorporate three bioactive fragments pyranopyridine, benzothiazine, and substituted pyridine, alongside functional groups, including two amines and one cyano group, which are amenable to further functionalization and structural modifications. These features enhance their potential as valuable products for synthesizing multi-substituted pyranopyridine-fused structures. Given the biological relevance of these functional groups, it is anticipated that the synthesized compounds will hold significant promise for applications in

medicinal chemistry and drug discovery.

4. Experimental

4.1. General information

All solvents and reagents used in this study were obtained from Merck, Alfa Aesar, and Fluka Chemical Companies and were used as received, without further purification. Reaction progress was monitored by Thin-Layer Chromatography (TLC) using pre-coated silica gel 60 (F254) aluminium sheets and visualized under UV light (254 nm). Melting points were determined using an Electrothermal-9100 apparatus. Fourier transform infrared (FT-IR) spectra were recorded as KBr pellets on an ABB FT-IR (FTLA 2000) spectrophotometer. Nuclear magnetic resonance (NMR) spectra (^1H and ^{13}C) were obtained on a Bruker Advance DRX instrument, with ^1H NMR recorded at 500 MHz and ^{13}C NMR at 126 MHz. The chemical shifts for ^1H NMR spectra are reported in parts per million (δ) relative to tetramethylsilane (TMS) as the internal standard, with multiplicities indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) are reported in Hertz (Hz) alongside integration values. ^{13}C NMR data were recorded in DMSO- d_6 solvent with TMS as the internal reference, reporting δ in ppm and J in Hz.

4.2. Procedure for synthesis of 2-methyl-2H-1,2-benzothiazin-4-(3H)-one 1,1-dioxide **6a** [31–33]

Methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (5.385 g, 20 mmol) was suspended in acetic acid (55 ml). A solution of hydrochloric acid (20 ml HCl (conc.)) and water (5 ml) was added, and the reaction mixture was heated to 110 °C in an oil bath. After 24 h, an additional solution of hydrochloric acid (20 ml HCl (conc.)) and water (5 ml) was added, and the reaction mixture was heated to 110 °C for an additional 2 days. The mixture was then cooled and poured into 110 ml of ice-cooled water. The resulting precipitate was filtered, washed with water (3 times), and dried. Yield 6.816 g (71 %), white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.00 (dd, J = 8.0, 1.3, 1H, ArH), 7.84–7.75 (m, 2H, ArH), 7.70 (td, J = 7.3, 1.8, 1H, ArH), 4.34 (s, 2H), 2.89 (s, 3H), ^{13}C NMR (126 MHz, CDCl_3) δ 189.69, 137.88, 135.49, 133.16, 129.01, 128.04, 125.06, 60.77, 38.21.

4.3. Procedure for synthesis of 2-benzyl-2,3-dihydro-4H-benzo [1,2]thiazin-4-one 1,1-dioxide **6b**

Methyl 2-benzyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (5.385 g, 20 mmol) was suspended in acetic acid (70 ml). A solution of hydrochloric acid (20 mL HCl (conc.)) and water (5 ml) was added, and the reaction mixture was heated to 110 °C in an oil bath. After 24 h, an additional solution of hydrochloric acid (20 ml HCl (conc.)) and water (5 ml) was added, and the reaction was heated to 110 °C for an additional 4 days. The mixture was then cooled and poured

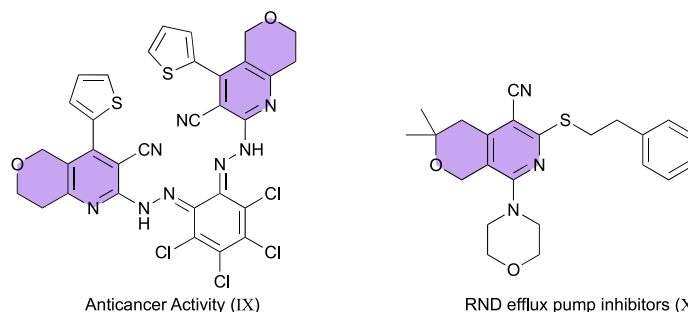
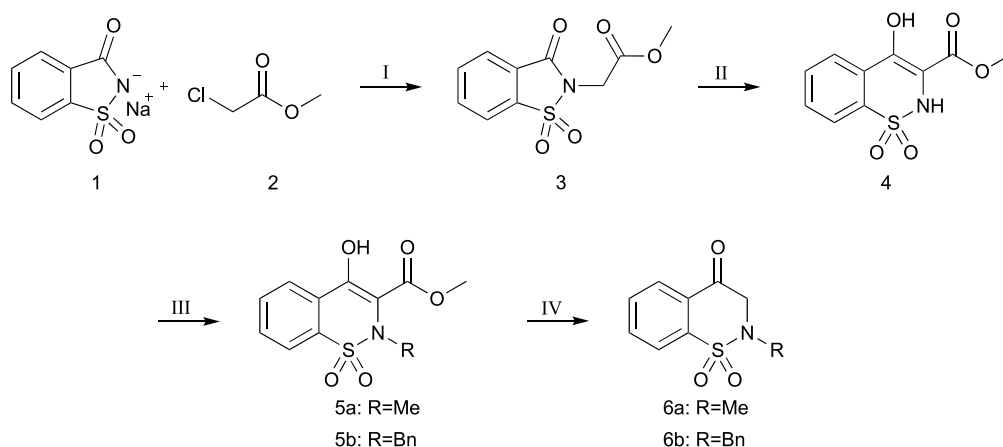


Fig. 2. Selected examples of biologically active pyranopyridine containing compounds.

**Scheme 1.** Synthesis of 1,2-benzothiazinone 1,1-dioxide.

Reaction Condition: I. DMF, 110 °C; II. NaOMe/MeOH, 55 °C; III. Me₂SO₄, aq, K₂CO₃, DMF, r.t. (R = Me); PhCH₂Cl, K₂CO₃, DMF, r.t. (R=Bn); IV. Conc. HCl, Acetic acid, 110 °C.

Table 1

Screening and optimization reaction condition for synthesis of **9**^{b,c}.

Entry	Solvent	Base	Temp. (°C)	Time (hr)	Yield (%) ^a
1	EtOH	i-Pr ₂ NEt	85	24	69
2	EtOH	Et ₃ N	85	24	56
3	EtOH	DABCO	85	24	35
4	EtOH	(CH ₂) ₅ NH	85	24	33
5	EtOH	O(CH ₂ CH ₂) ₂ NH	85	24	20
6	MeOH	KOH	75	24	0
7	MeOH	K ₂ CO ₃	75	24	0
8	MeOH	i-Pr ₂ NEt	75	24	59
9	EtOH	i-Pr ₂ NEt	r.t.	72	20
10	EtOH	i-Pr ₂ NEt	r.t.	72	35
11	MeOH	i-Pr ₂ NEt	r.t.	72	35
12	DCM	i-Pr ₂ NEt	r.t.	72	15
13	MeCN	i-Pr ₂ NEt	r.t.	72	Trace
14	DMF	i-Pr ₂ NEt	r.t.	72	Trace

^a Isolated yield based on **6a**.

^b 1 mmol base was added.

^c All reactions were carried out with **6a** (1 mmol), **7b** (4-Fluorobenzaldehyde) (1 mmol), and **8** (1 mmol) in the presence of base (2 mmol) in solvent (10 ml) at different temperature.

into 120 ml of ice-cooled water. The resulting precipitate was filtered, washed with water (3 times), and recrystallized from ethanol. Yield 6.073 g (48 %), white solid, ¹H NMR (500 MHz, CDCl₃) δ 7.94 (dd, *J* = 7.8, 1.3, 1H, ArH), 7.91–7.85 (m, 1H, ArH), 7.79 (td, *J* = 7.6, 1.3, 1H, ArH), 7.24 (m, 5H, ArH), 4.38 (s, 2H), 4.29 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 189.62, 139.65, 139.60, 135.11, 133.52, 132.94, 129.33, 129.02, 128.86, 128.55, 128.43, 128.09, 124.43, 57.01, 54.40.

4.4. General procedure for synthesis of compound **9** (a-m)

A mixture of benzothiazinone **6**(a-b) (1 mmol), malononitrile dimer (1 mmol), and benzaldehyde **7**(a-j) (1 mmol) was suspended in Ethanol (10 ml). i-Pr₂NEt (2 mmol) was then added, and the reaction mixture was refluxed (85 °C) in an oil bath for 24 h. The resulting precipitate was filtered, washed three times with ethanol (5 ml), and dried under vacuum. For reactions involving nitrobenzaldehyde, 1 mmol of i-Pr₂NEt was used, while the reaction with 2-chloroquinoline-3-carbaldehyde was stirred at room temperature for 48 h.

8,10-diamino-6-methyl-7-(p-tolyl)-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9a). Yield 160 mg (36 %), off white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.88–7.79 (m, 3H, H Ar), 7.69 (t, *J* = 7.5, 1H, H Ar), 7.23 (d, *J* = 7.8, 2H, H Ar), 7.09 (d, *J* = 7.8, 2H, H Ar), 6.61 (s, 2H, NH₂), 6.52 (s,

2H, NH₂), 5.19 (s, 1H, CH), 3.04 (s, 3H, CH₃), 2.23 (s, 3H, CH₃). ¹³C NMR (126 MHz, DMSO-d₆) δ 159.65, 157.96, 156.86, 138.45, 136.25, 134.89, 132.84, 131.26, 129.87, 129.00, 127.70, 126.91, 123.56, 122.93, 122.24, 116.19, 90.26, 71.14, 35.97, 33.27, 20.64. HRMS (ESI) *m/z* calculated for C₂₃H₁₉N₅O₃S⁺ [M+H]⁺: 446.1281; found: 446.1274.

8,10-diamino-7-(4-fluorophenyl)-6-methyl-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9b). Yield 310 mg (69 %), off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.88–7.79 (m, 3H), 7.69 (t, *J* = 7.5, 1H, H Ar), 7.38 (dd, *J* = 8.6, 5.3, 2H, H Ar), 7.12 (t, *J* = 8.7, 2H, H Ar), 6.62 (s, 2H, NH₂), 6.55 (s, 2H, NH₂), 5.25 (s, 1H, CH), 3.05 (s, 3H, CH₃). ¹³C NMR (126 MHz, DMSO-d₆) δ 162.18, 160.25, 159.78, 158.01, 156.95, 137.49, 135.28, 132.88, 131.41, 130.06, 129.75, 129.69, 126.79, 123.22, 123.08, 122.36, 116.17, 115.23, 115.06, 89.87, 71.20, 35.52, 33.47. HRMS (ESI) *m/z* calculated for C₂₂H₁₆FN₅O₃S⁺ [M+H]⁺: 450.1030; found: 450.1039.

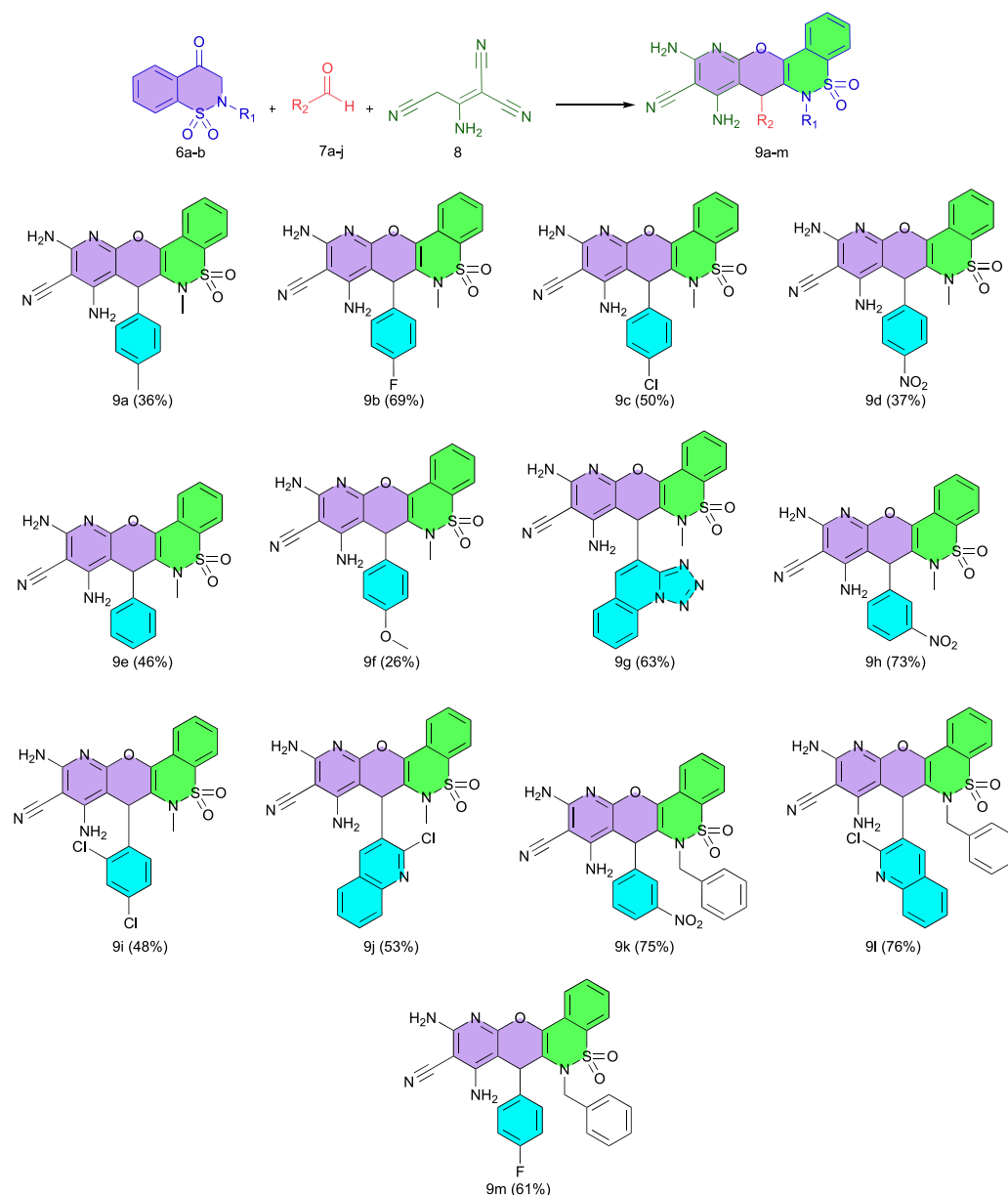
8,10-diamino-7-(4-chlorophenyl)-6-methyl-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9c). Yield 233 mg (50 %), off white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.84 (q, *J* = 8.2 Hz, 4H, H Ar), 7.69 (t, *J* = 7.3 Hz, 1H, H Ar), 7.36 (d, *J* = 3.3 Hz, 4H, H Ar), 6.66 (s, 2H, NH₂), 6.56 (s, 2H, NH₂), 5.25 (s, 1H, CH), 3.05 (s, 3H, CH₃). ¹³C NMR (126 MHz, DMSO-d₆) δ 159.74, 157.94, 156.89, 140.16, 135.40, 132.82, 131.71, 131.38, 130.05, 129.57, 128.29, 126.67, 123.03, 122.84, 122.31, 116.06, 89.50, 71.15, 35.59, 33.46. HRMS (ESI) *m/z* calculated for C₂₂H₁₆ClN₅O₃S⁺ [M+H]⁺: 466.0735; found: 466.6694.

8,10-diamino-6-methyl-7-(4-nitrophenyl)-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9d). Yield 176 mg (37 %), pale yellow solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.19 (d, *J* = 8.2, 2H, H Ar), 7.84 (m, 3H, H Ar), 7.71 (t, *J* = 7.5, 1H, H Ar), 7.61 (d, *J* = 8.3, 2H, H Ar), 6.72 (s, 2H, NH₂), 6.62 (s, 2H, NH₂), 5.43 (s, 1H, CH), 3.07 (s, 3H, CH₃). ¹³C NMR (126 MHz, DMSO-d₆) δ 159.99, 158.07, 157.08, 148.66, 146.61, 136.15, 132.98, 131.59, 130.40, 129.16, 126.59, 123.59, 123.26, 122.53, 122.12, 116.03, 88.84, 71.28, 36.08, 33.79. HRMS (ESI) *m/z* calculated for C₂₂H₁₆N₆O₅S⁺ [M+H]⁺: 477.0975; found: 477.0980.

8,10-diamino-6-methyl-7-phenyl-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9e). Yield 198 mg (46 %), pale yellow solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.87 (d, *J* = 7.7 Hz, 1H, H Ar), 7.82 (q, *J* = 6.2 Hz, 2H, H Ar), 7.68 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H, H Ar), 7.29 (q, *J* = 6.2 Hz, 2H, H Ar), 7.21 (t, *J* = 7.0 Hz, 1H, H Ar), 6.61 (s, 2H, NH₂), 6.54 (s, 2H, NH₂), 5.25 (s, 1H, CH), 3.06 (s, 3H, CH₃). ¹³C NMR (126 MHz, DMSO-d₆) δ 162.29, 159.71, 158.06, 156.90, 141.37, 135.10, 132.84, 131.28, 129.92, 128.40, 127.78, 127.17, 126.85, 123.46, 122.98,

Table 2

The scope and yields of the synthesized benzothiazine-pyranopyridine derivatives.



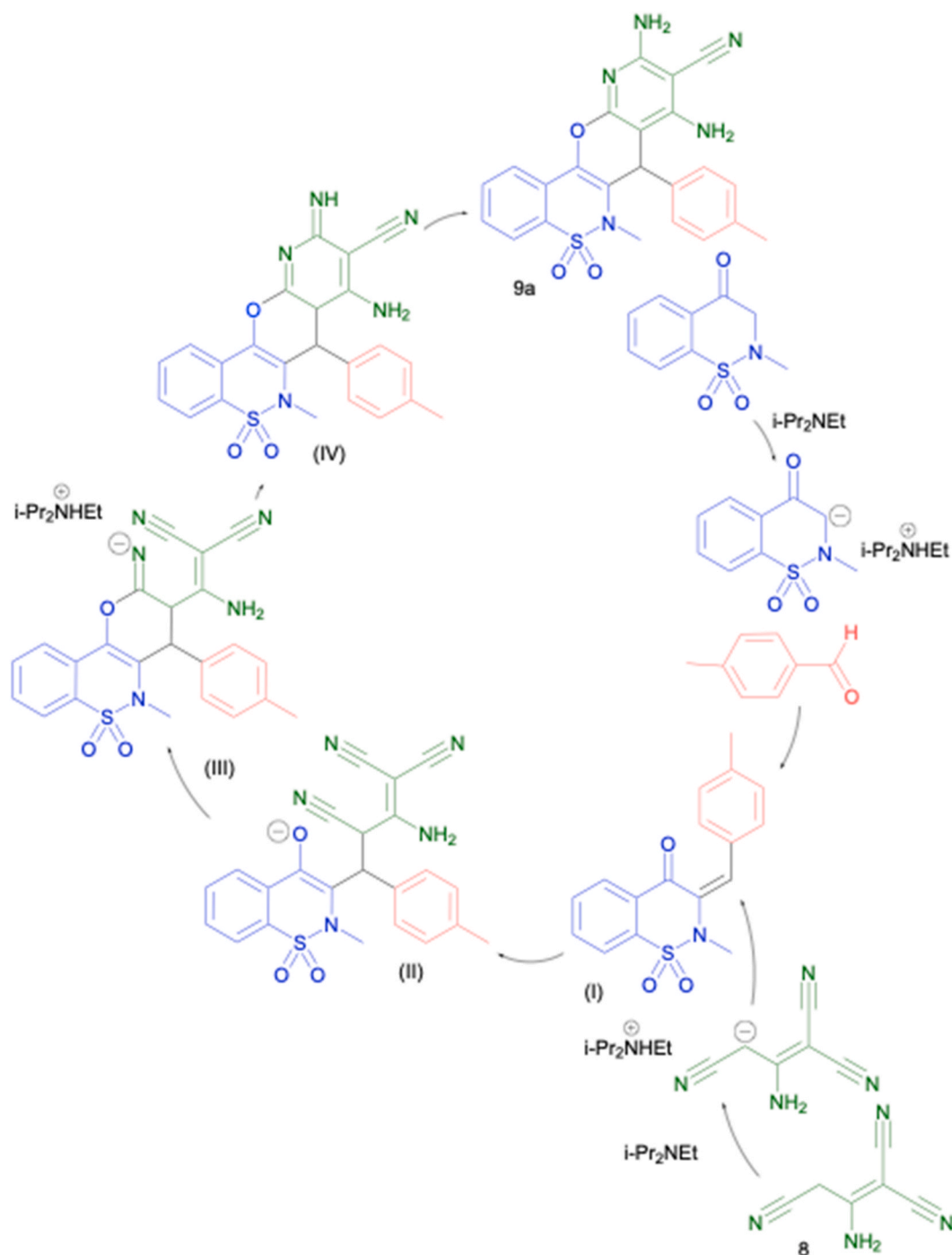
122.27, 116.20, 90.12, 71.17, 36.32, 33.38. HRMS (ESI) m/z calculated for $C_{22}H_{17}N_5O_3S^+$ $[M+H]^+$: 432.1124; found: 432.1124.

8,10-diamino-7-(4-methoxyphenyl)-6-methyl-6H,7H-benzo[e]pyrido[3',2':5,6]pyrano[3,2-c][1,2]thiazine-9-carbonitrile 5,5-dioxide (9f). Yield 120 mg (26 %), off white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 7.83 (m, 3H, H Ar), 7.72–7.65 (m, 1H, H Ar), 7.26 (d, J = 8.4, 2H, H Ar), 6.85 (d, J = 8.4, 2H, H Ar), 6.60 (s, 2H, NH₂), 6.52 (s, 2H, NH₂), 5.17 (s, 1H, CH), 3.69 (s, 3H, OCH₃), 3.04 (s, 3H, CH₃). ^{13}C NMR (126 MHz, DMSO- d_6) δ 159.62, 158.26, 157.91, 156.85, 134.76, 133.40, 132.82, 131.24, 129.84, 128.87, 126.91, 123.64, 122.92, 122.22, 116.21, 113.78, 90.35, 71.13, 54.94, 35.52, 33.23. HRMS (ESI) m/z calculated for $C_{23}H_{19}N_5O_4S^+$ $[M+H]^+$: 462.1230; found: 462.1231.

8,10-diamino-6-methyl-7-(tetrazolo[1,5-a]quinolin-4-yl)-6H,7H-benzo[e]pyrido[3',2':5,6]pyrano[3,2-c][1,2]thiazine-9-carbonitrile 5,5-dioxide (9g). Yield 329 mg (63 %), off white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.57 (d, J = 8.4, 1H, H Ar), 8.44 (s, 1H, H_{Ar}), 8.23 (d, J = 8.0, 1H, H Ar), 7.93 (t, J = 8.5, 2H, H Ar), 7.85 (t, J =

7.7, 1H), 7.79 (t, J = 7.7, 1H, H Ar), 7.75 (d, J = 7.6, 1H, H Ar), 7.70 (t, J = 7.5, 1H, H Ar), 6.69 (s, 2H, NH₂), 6.45 (s, 2H, NH₂), 5.76 (s, 1H, CH), 3.08 (s, 3H, CH₃). ^{13}C NMR (126 MHz, DMSO- d_6) δ 160.00, 158.48, 157.27, 146.52, 137.78, 132.99, 132.16, 131.96, 131.41, 130.58, 129.67, 129.46, 128.38, 126.66, 124.73, 123.64, 123.41, 122.71, 118.88, 116.14, 116.10, 86.96, 71.21, 34.74, 34.10. HRMS (ESI) m/z calculated for $C_{25}H_{17}N_9O_3S^+$ $[M+H]^+$: 524.1247; found: 524.1248.

8,10-diamino-6-methyl-7-(3-nitrophenyl)-6H,7H-benzo[e]pyrido[3',2':5,6]pyrano[3,2-c][1,2]thiazine-9-carbonitrile 5,5-dioxide (9h). Yield 347 mg (73 %), pale yellow solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.29 (s, 1H, H Ar), 8.11 (d, J = 8.2, 1H, H Ar), 7.84 (m, 3H, H Ar), 7.73 (d, J = 8.0, 2H, H Ar), 7.61 (t, J = 7.9, 1H, H Ar), 6.69 (s, 2H, NH₂), 6.65 (s, 2H, NH₂), 5.42 (s, 1H, CH), 3.06 (s, 3H, CH₃). ^{13}C NMR (126 MHz, DMSO- d_6) δ 159.98, 158.03, 157.08, 147.57, 143.37, 136.17, 134.58, 133.04, 131.64, 130.45, 130.14, 126.59, 123.32, 122.56, 122.38, 122.29, 116.03, 89.03, 71.29, 35.89, 33.77. HRMS (ESI) m/z calculated for $C_{22}H_{16}N_6O_5S^+$ $[M+H]^+$: 477.0975; found: 477.0967.



Scheme 2. Proposed mechanism for synthesis of 9a.

8,10-diamino-7-(2,4-dichlorophenyl)-6-methyl-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9i). Yield 240 mg (48 %), off white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.89–7.79 (m, 3H, H Ar), 7.77–7.69 (m, 1H, H Ar), 7.55 (d, $J = 2.2$, 1H, H Ar), 7.51 (d, $J = 8.3$, 1H, H Ar), 7.41 (dd, $J = 8.5$, 2.3, 1H, H Ar), 6.71 (s, 2H, NH_2), 6.05 (s, 2H, NH_2), 5.49 (s, 1H, CH), 2.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 159.88, 158.02, 156.96, 137.05, 136.63, 133.53, 133.05, 132.92, 132.82, 131.95, 130.61, 129.41, 127.77, 126.53, 123.53, 122.93, 120.34, 115.91, 88.41, 71.57, 35.49, 34.47. HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{15}\text{Cl}_2\text{N}_5\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$: 500.0345; found: 500.0336.

8,10-diamino-7-(2-chloroquinolin-3-yl)-6-methyl-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile

5,5-dioxide (9j). Yield 274 mg (53 %), off white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.61 (s, 1H, H Ar), 8.03 (d, $J = 8.2$, 1H, H Ar), 7.94 (d, $J = 8.5$, 1H, H Ar), 7.91–7.78 (m, 4H, H Ar), 7.73 (t, $J = 7.5$, 1H, H Ar), 7.65 (t, $J = 7.6$, 1H, H Ar), 6.76 (s, 2H, NH_2), 6.14 (s, 2H, NH_2), 5.65 (s, 1H, CH), 3.02 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 159.96, 158.20, 157.04, 148.96, 146.22, 140.37, 137.51, 133.12, 132.01, 131.06, 130.74, 128.09, 127.53, 127.45, 126.84, 126.55, 123.65, 123.05, 119.98, 115.89, 88.03, 71.66, 36.08, 34.62. HRMS (ESI) m/z calculated for $\text{C}_{25}\text{H}_{17}\text{ClN}_6\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$: 517.0844; found: 517.0839.

8,10-diamino-6-benzyl-7-(3-nitrophenyl)-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9k). Yield 414 mg (75 %), pale yellow solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.33 (s, 1H, H Ar), 8.12 (dd, $J = 8.2$, 2.4, 1H, H Ar), 7.77 (d,

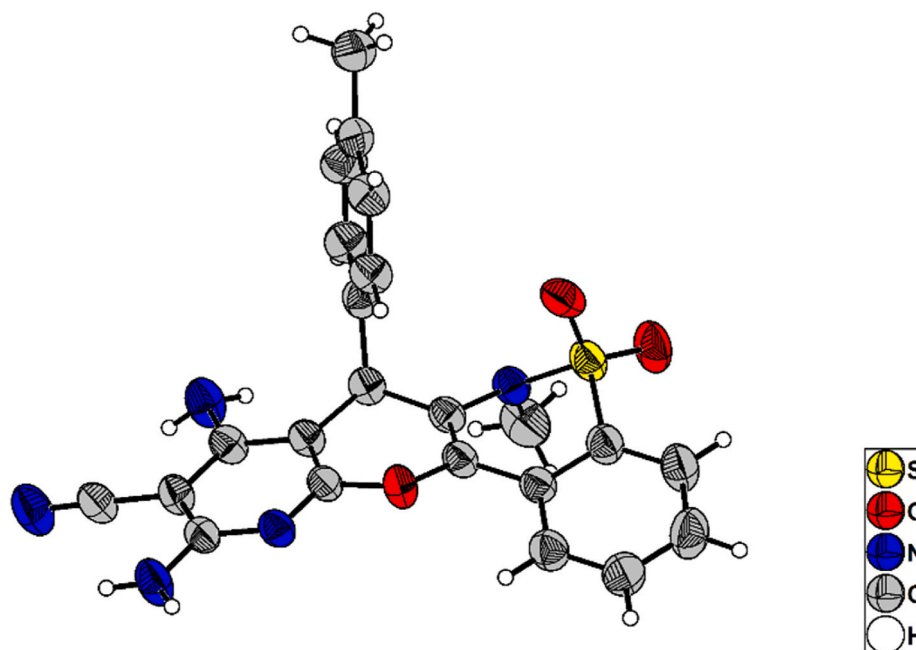


Fig. 3. ORTEP structure of compound 9a.

$J = 7.6$, 1H, H Ar), 7.71 (dd, $J = 18.2$, 7.9, 2H, H Ar), 7.68–7.58 (m, 3H, H Ar), 7.08–6.94 (m, 5H, H Ar), 6.74 (d, $J = 10.8$, 4H, NH₂), 5.58 (s, 1H, CH), 4.97 (d, $J = 15.8$, 1H, CH₂), 4.81 (d, $J = 15.8$, 1H, CH₂). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.97, 158.01, 157.13, 147.51, 143.21, 138.01, 134.56, 133.91, 133.44, 132.67, 130.37, 130.14, 127.90, 127.85, 126.25, 123.12, 122.40, 122.33, 121.82, 119.64, 116.01, 88.58, 71.32, 49.59, 35.39. HRMS (ESI) m/z calculated for C₂₈H₂₀N₆O₅S⁺ [M+H]⁺: 553.1288; found: 553.1289.

8,10-diamino-6-benzyl-7-(2-chloroquinolin-3-yl)-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9l). Yield 450 mg (76 %), off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.64 (s, 1H, H Ar), 8.01 (d, $J = 8.2$, 1H, H Ar), 7.95 (d, $J = 8.5$, 1H, H Ar), 7.82 (t, $J = 7.7$, 1H, H Ar), 7.66 (m, 4H, H Ar), 7.57 (d, $J = 7.8$, 1H, H Ar), 7.02 (m, 5H, H Ar), 6.73 (s, 2H, NH₂), 6.26 (s, 2H, NH₂), 5.81 (s, 1H, CH), 4.88–4.77 (m, 2H, CH₂). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.99, 158.26, 157.20, 148.98, 146.20, 140.38, 139.40, 134.16, 133.22, 132.53, 131.04, 130.38, 128.51, 128.09, 127.87, 127.67, 127.54, 127.47, 126.70, 126.31, 123.30, 122.05, 116.59, 115.93, 87.47, 71.76, 50.33, 35.91. HRMS (ESI) m/z calculated for C₃₁H₂₁ClN₆O₃S⁺ [M+H]⁺: 593.1157; found: 593.1152.

8,10-diamino-6-benzyl-7-(4-fluorophenyl)-6H,7H-benzo [e] pyrido [3',2':5,6] pyrano [3,2-c] [1,2] thiazine-9-carbonitrile 5,5-dioxide (9m). Yield 320 mg (61 %), off white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.75 (d, $J = 7.6$, 1H, H Ar), 7.68 (t, $J = 7.6$, 1H, H Ar), 7.65–7.57 (m, 2H, H Ar), 7.38 (dd, $J = 8.5$, 5.4, 2H, H Ar), 7.13 (t, $J = 8.7$, 2H, H Ar), 7.01 (m, 5H, H Ar), 6.62 (d, $J = 6.0$, 4H, NH₂), 5.39 (s, 1H, CH), 4.96 (d, $J = 15.8$, 1H, CH₂), 4.84 (d, $J = 16.0$, 1H, CH₂). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 162.20, 160.27, 159.79, 158.08, 157.05, 137.31, 134.07, 133.28, 132.52, 130.04, 129.72, 129.66, 127.94, 127.88, 127.82, 126.45, 122.93, 121.68, 120.57, 116.17, 115.18, 115.01, 89.33, 71.21, 49.27, 34.92. HRMS (ESI) m/z calculated for C₂₈H₂₀FN₆O₃S⁺ [M+H]⁺: 526.1343; found: 526.1353.

CCRediT authorship contribution statement

Mohtasham Molaie: Methodology. **Sorour Ramezanzpour:** Supervision. **Hassan Seyrani:** Writing – original draft, Methodology. **Alireza Abbasi:** Formal analysis. **Hamidreza Bijanzadeh:** Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.2025.134888>.

Data availability

No data was used for the research described in the article.

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