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SYNTHESIS OF *(E)*-5-(3,4-DIMETHOXYBENZYLIDENE)-3-METHYL-6,7-DIHYDROPYRROLO[*1,2-a*]THIENO[*3,2-d*]PYRIMIDIN-9(*5H*)-ONE

Annotation

(*E*)-5-(3,4-Dimethoxybenzylidene)-3-methyl-6,7-dihydropyrrolo[*1,2-a*]thieno[*3,2-d*]pyrimidin-9(5*H*)-one (**AR-109**) was synthesized in two steps from ethyl 3-amino-5-bromobenzo[*b*]thiophene-2-carboxylate (**AT-2**). ^{1}H and ^{13}C NMR, HRMS confirmed the structure. Increased reaction temperature and duration significantly improved yield. These derivatives hold promise for pharmaceutical and material applications.

Key words: cancer, catalyst, cyclization, drug design, thieno[2,3-*d*]pyrimidine, Williamson ether synthesis,

(E)-5-(3,4-DIMETOKSIBENZILIDEN)-3-METIL-6,7-DIGIDROPIRROLO[*1,2-a*]TIENO[*3,2-d*]PIRIMIDIN-9(*5H*)-ON SINTEZI

Annotatsiya

(E)-5-(3,4-dimetoksibenziliden)-3-metil-6,7-digidropirrolo[*1,2-a*]tiyeno[*3,2-d*]pirimidin-9(*5H*)-on (**AR-109**) ikki bosqichda, etil 3-amino-5-bromobenzo[*b*]tiofen-2-karboksilat (**AT-2**) asosida sintez qilindi. ^{1}H va ^{13}C YaMR, YuAMS orqali tuzilma to‘liq tasdiqlandi. Reaksiya harorati va davomiyligini oshirish hosildorlikni sezilarli yaxshiladi. Ushbu hosilalar farmatsevtika va materialshunoslikda istiqbolli hisoblanadi.

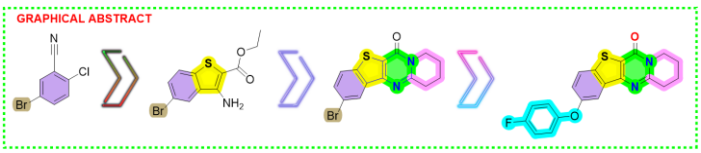
Kalit so‘zlar: dori dizayni, katalizator, saraton, siklizatsiya, tieno[3,2-*d*]pirimidin, Uilyamson efir sintezi.

СИНТЕЗ *(E)*-5-(3,4-ДИМЕТОКСИБЕНЗИЛИДЕН)-3-МЕТИЛ-6,7-ДИГИДРОПИРРОЛО[*1,2-a*]ТИЕНО[*3,2-d*]ПИРИМИДИН-9(*5H*)-ОНА

Аннотация

(*E*)-5-(3,4-диметоксибензилиден)-3-метил-6,7-дигидропирроло[*1,2-a*]тиено[*3,2-d*]пиримидин-9(*5H*)-он (**AR-109**) был синтезирован в два этапа из этил-3-амино-5-бромобензо[*b*]тиофен-2-карбоксилата (**AT-2**). Структура подтверждена ^{1}H и ^{13}C ЯМР, ВТМС. Повышение температуры и времени реакции значительно увеличило выход. Эти производные перспективны для фармацевтики и материаловедения..

Ключевые слова: катализатор, циклизация, дизайн лекарств, рак, синтез простых эфиров по Вильямсону, тиено[*3,2-d*]пиримидин.



Introduction. Cancer represents a highly intricate and heterogeneous pathology, hallmarked by dysregulated cellular proliferation, invasive potential, and metastatic dissemination. Despite decades of intensive research, it persists as a predominant contributor to global mortality[1]. Recent breakthroughs in oncogenomics, precision therapeutics, and individualized treatment paradigms have markedly enhanced clinical outcomes. This dissertation seeks to elucidate the most recent advancements in cancer biology and therapeutic innovation, with a particular focus on the convergence of systems biology, computational oncology, and state-of-the-art molecular engineering in shaping next-generation treatment modalities.

The emergence of molecularly targeted therapeutics has yielded substantial survival benefits for patients harboring oncogenic driver mutations. Small-molecule inhibitors targeting EGFR, ALK, and BRAF mutations have exhibited profound efficacy in non-small cell lung carcinoma and melanoma[2]. Meanwhile, CRISPR-Cas9 genome editing and RNA-targeted therapeutics are pioneering novel avenues in precision oncology, enabling genetic reprogramming at an unparalleled level of specificity.

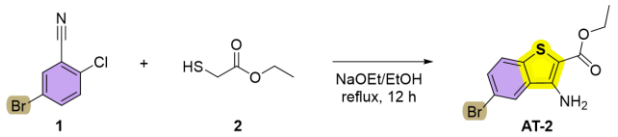
Despite remarkable breakthroughs, formidable challenges persist in overcoming therapeutic resistance, tumor plasticity, and disparities in treatment accessibility. Ongoing research in gene-editing technologies (CRISPR-based modalities), combinatorial therapeutic regimens, synthetic biology, and next-generation pharmacotherapeutics holds immense promise for the future of oncology. Additionally, emerging frontiers such as oncolytic virotherapy, microbiome-modulated cancer therapeutics, and quantum dot-based imaging are poised to redefine cancer diagnostics and therapeutics, ushering in a new era of precision medicine.

Literature review. Vitiligo is a dermatological disorder characterized by the progressive depletion of melanocytes within the epidermis, leading to localized hypopigmentation[3]. This condition can affect any anatomical site housing melanocytes, thereby inducing both functional impairments and structural abnormalities in the affected dermal regions. Although the precise etiology remains an area of active investigation, multiple mechanistic hypotheses have been proposed to explain the pathogenesis of vitiligo[4]. The prevailing theory suggests that the disorder arises from melanocyte destruction coupled with dysregulated melanin biosynthesis[5].

Various pharmacological interventions are currently employed in vitiligo therapy, including topical corticosteroids, calcineurin inhibitors, vitamin D_3 analogs, and psoralens[6]. Among these, psoralens (furocoumarins) have been extensively explored due to their ability to intercalate into DNA and induce photoreactivity under ultraviolet (UV) exposure. Clinically relevant examples include 8-methoxypsoralen[7], 5-methoxypsoralen[8], and 4,5,8-trimethylpsoralen[9]. These molecular scaffolds exhibit potent photosensitizing properties, facilitating their therapeutic utility when activated by long-wave UV radiation. However, despite their efficacy, psoralen-based photochemotherapy is associated with notable drawbacks, such as genotoxicity and an elevated risk of photocarcinogenesis[10].

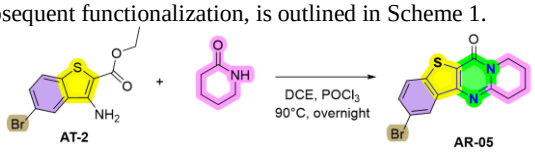
Thieno[*2,3-d*]pyrimidine represents a privileged scaffold with broad pharmacological potential, exhibiting antibacterial and antineoplastic properties, among other bioactivities[11]. Notably, its core framework bears structural similarity to that of psoralen, prompting the hypothesis that thienopyrimidines may exhibit comparable melanogenic activity. Our recent synthetic endeavors resulted in the development of 18 novel sulfonamide-functionalized tricyclic thieno[*2,3-d*]pyrimidin-4-one derivatives, several of which displayed over 1.5-fold greater potency than 8-MOP in preliminary biological evaluations[7]. Encouraged by these findings, the present study details the design and synthesis of 51 new amide derivatives of tricyclic thienopyrimidines and investigates their potential as melanogenesis modulators in murine B16 cell assays.

Research methodology. The thienopyrimidine scaffold has multiple reactive centers, making it highly versatile for modifications. However, tri- and tetracyclic derivatives remain underexplored. Our research expands the synthetic scope of tetracyclic thienopyrimidines by developing novel, strategically functionalized derivatives. We synthesized a tetracyclic thieno[*3,2-d*]pyrimidine system incorporating aromatic and aliphatic rings. Further diversification was achieved via regioselective ether bond formation for precise derivatization.



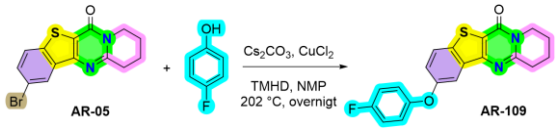
Scheme 1. Reaction reagent and synthesis condition for AT-2.

The synthesis of ethyl 3-amino-5-bromobenzo[*b*]thiophene-2-carboxylate (**AT-2**) was initiated by the cyclization of 5-bromo-2-chlorobenzonitrile (**1**). This transformation proceeded through a nucleophilic substitution mechanism, followed by intramolecular cyclization, driven by the reaction with ethyl 2-mercaptoacetate under alkaline conditions in ethanol. The stepwise formation of this key intermediate, crucial for subsequent functionalization, is outlined in Scheme 1.



Scheme 2. Reaction reagent and condition for forming AR-05.

In the next stage, **AT-2** underwent acid-catalyzed cyclization with piperidin-2-one under extended reflux, forming the tetracyclic **AR-05** (Scheme 2). Optimized conditions ensured efficient ring closure. The reaction proceeded via nucleophilic substitution (S_N), displacing bromine to form an R–O–R bond through Williamson ether synthesis. AR-05 then underwent modification, yielding **AR-109** within the tetracyclic thienopyrimidine core (Scheme 3), involving alkoxide-mediated ether bond formation.



Scheme 3. Reaction reagent and condition for forming AR-27.

The table below presents the optimization of the Wallinson reaction under varying reaction conditions, systematically evaluating the impact of key parameters, including the catalyst, solvent, temperature, base, reaction duration, and yield.

Table 1.

Entry	*Catalyst*	*Solvent*	*Base*	*Temperature (°C)*	*Time*	*Yield (%)*	*Remarks*
1	$CuCl_2$	NMP	Cs_2CO_3	180	12 h	65	Standard conditions
2	CuCl	NMP	Cs_2CO_3	180	12 h	72	Improved catalyst
3	$Cu(OAc)_2$	DMF	Cs_2CO_3	200	12 h	58	Effect of solvent
4	$CuCl_2$	NMP	K_2CO_3	180	12 h	60	Effect of base
5	$CuCl_2$	NMP	Cs_2CO_3	190	12 h	75	Increased temperature
6	$CuCl_2$	NMP	Cs_2CO_3	190	24 h	78	Extended reaction time
7	$CuCl_2$	Toluene	Cs_2CO_3	190	12 h	40	Less efficient solvent
8	$CuCl_2$	NMP	Na_2CO_3	190	12 h	55	Weaker base
9	$CuCl_2$	NMP	Cs_2CO_3	202	12 h	80	Optimal conditions
10	**$CuCl_2$**	**NMP**	**Cs_2CO_3**	**202**	**24 h**	**83**	**Highest yield**

Structural analysis of key intermediates and final products was performed using ^{1}H- and ^{13}C-NMR (VARIAN 400 MHz) with detailed peak assignment and spin-spin coupling evaluation to confirm regioselectivity and reaction completion. HRMS (SCIEX QTRAP 6500+, ESI) provided precise mass determination and isotopic analysis, ensuring molecular formula validation and structural integrity.

Analysis and results. The precursor materials were obtained commercially and used without purification. Anhydrous solvents, including ethanol, toluene, ethyl acetate, and 1,2-dichloroethane, prevented moisture interference. Reaction progress was monitored via TLC on $HSGF_{254}$ silica plates, with chromatograms visualized under UV (254/365 nm) or iodine staining. TMS served as the internal reference for ^{1}H- and ^{13}C-NMR (VARIAN 400 MHz). HRMS (QTRAP® 6500+) confirmed molecular composition and structural integrity.

*1.1.1. Procedure for the preparation of ethyl 3-amino-5-bromobenzo[b]thiophene-2-carboxylate (**AT-2**).*

A 35 mL high-pressure reaction vessel was charged with ethanol (8 mL), followed by the addition of sodium ethanolate (164 mg, 2.4 mmol). The mixture was stirred at 0°C using a magnetic stirrer until complete dissolution of the base was achieved. Subsequently, ethyl 2-mercaptoacetate (288 mg, 2.4 mmol) was introduced, followed by the sequential addition of 5-bromo-2-chlorobenzonitrile (433 mg, 2.0 mmol). The resulting reaction mixture was subjected to heating at 90°C in a glycerol bath under continuous stirring for 12 hours. Reaction progress was monitored via thin-layer chromatography (TLC). Upon completion, the cyclized product, ethyl 3-amino-5-bromobenzo[*b*]thiophene-2-carboxylate, was purified using **AT-2** column chromatography with a petroleum ether/ethyl acetate (5:1) eluent system, yielding a product with an R_f value of 0.7. The reaction afforded 363.8 mg of a light white solid, corresponding to a 60.63% yield. The melting point of the compound was found to be 115-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 1.8, 0.6 Hz, 1H), 7.62 – 7.49 (m, 2H), 5.80 (s, 2H), 4.36 (qd, *J* = 7.1, 0.5 Hz, 2H), 1.39 (td, *J* = 7.1, 0.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.37, 147.29, 138.64, 133.23, 131.29, 124.97, 124.28, 117.91, 101.27, 60.87, 14.70. HRMS (ESI) calcd for $C_{11}H_{10}BrNO_2S$ [M+H]+ 299.9688 and 301.9668, found 299.9688 (5.82 %) and 301.9667 (6.12%).

*1.1.2. Procedure for the preparation of 2-bromo-8,9,10,11-tetrahydro-6H-benzo[4,5]thieno[3,2-d]pyrido[1,2-a]pyrimidin-6-one (**AR-05**).*

A 50 mL high-pressure reaction vessel was charged with 10 mL of anhydrous dichloroethane (DCE), followed by the dissolution of **AT-2** (300 mg, 1 mmol) under continuous stirring. Piperidin-2-one (119 mg, 1.2 mmol) was then introduced into the reaction medium. Subsequently, phosphoryl trichloride ($POCl_3$, 0.50 mL) was carefully added dropwise over 20 minutes under controlled conditions to ensure gradual reactivity. The reaction mixture was then subjected to thermal activation at 90°C in a glycerol bath and maintained under these conditions overnight, with periodic monitoring via thin-layer chromatography (TLC). Upon completion, the crude product was purified through column chromatography using a petroleum ether/ethyl acetate (1:1) solvent system, affording the target compound, 2-bromo-8,9,10,11-tetrahydro-6H-benzo[4,5]thieno[*3,2-d*]pyrido[*1,2-a*]pyrimidin-6-one (**AR-05**), with an R_f value of 0.60. The final product was obtained as a light white solid (259.2 mg) in 77.33% yield, exhibiting a melting point of 220–221°C. ^{1}H NMR (400 MHz, Pyridine-d 5) δ 8.62 (d, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.1 Hz, 1H), 4.00 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H), 1.77 – 1.63 (m, 4H). ^{13}C NMR (100 MHz, Pyridine-d 5) δ 158.99, 158.45, 151.58, 140.69, 137.26, 132.33, 127.12, 126.10, 122.42, 119.83, 43.30, 32.30, 22.40, 19.73. HRMS (ESI) calcd for $C_{14}H_{11}BrN_2OS$ [M+H]+ 334.9849 and 336.9828, found 334.9847 (93.54 %) and 336.9819 (100%).

*1.1.3. 2-(4-fluorophenoxy)-8,9,10,11-tetrahydro-6H-benzo[4,5]thieno[3,2-d]pyrido[1,2-a]pyrimidin-6-one (**AR-109**).*

A 50 mL volumetric flask was charged with 4 mL of N-methyl-2-pyrrolidone (NMP) as the solvent, followed by the addition of 12 mg of $CuCl_2$ as the catalyst and 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as the coordinating ligand. To establish an alkaline reaction medium, 326 mg of cesium carbonate (Cs_2CO_3) was introduced, after which 77 mg of the **AR-05** intermediate was added, ensuring thorough mixing. Subsequently, 40 mg of 4-fluorophenol was incorporated as the nucleophilic coupling partner. The reaction mixture was then purged with argon to eliminate residual oxygen and moisture. The assembled reaction system was maintained under continuous stirring at 202 °C 24 h. Progress was monitored via thin-layer chromatography (TLC), confirming the completion of the transformation. Upon reaction termination, purification via column chromatography furnished 50.11 mg of the target compound **AR-109** as a brown solid. The compound exhibited an R_f value of 0.60 in a 1:1 petroleum ether/ethyl acetate solvent system, and its melting point was determined to be 187–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.77 (m, 2H), 7.29 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.15 – 6.93 (m, 4H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H), 2.09 – 1.91 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.14 (d, *J* = 242.1 Hz), 159.07, 157.18, 156.04, 153.29 (d, *J* = 2.6 Hz), 136.41, 135.90, 124.81, 122.34, 121.52, 120.69 (d, *J* = 8.3 Hz), 116.66 (d, *J* = 23.6 Hz), 112.10, 42.77, 31.89, 29.90, 22.22, 19.45. HRMS (ESI) calcd for $C_{20}H_{15}N_2O_2S$ [M+H]+ 367.0911, found 367.0906.

Conclusion. A novel halogenated tetracyclic thieno[3,2-d]pyrimidine scaffold was constructed via sequential dual cyclization. Functionalization through Williamson ether synthesis expanded its chemical space. Optimization showed the highest yield with $CuCl_2$ catalyst, NMP solvent, Cs_2CO_3 base, at 202 °C for 24 h, with increased temperature and time enhancing yield. Ether linkages with pharmacophore-bearing aromatic alcohols significantly boosted bioactivity. These structurally refined compounds hold promise as therapeutic agents.

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