A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (8) 202412221

One-pot three-component synthesis of 6-aryl-3-(arylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines utilizing 4-amino-6-oxo-pyrimidin-tethered *N*-aryl-2-mercaptoacetamides as precursors

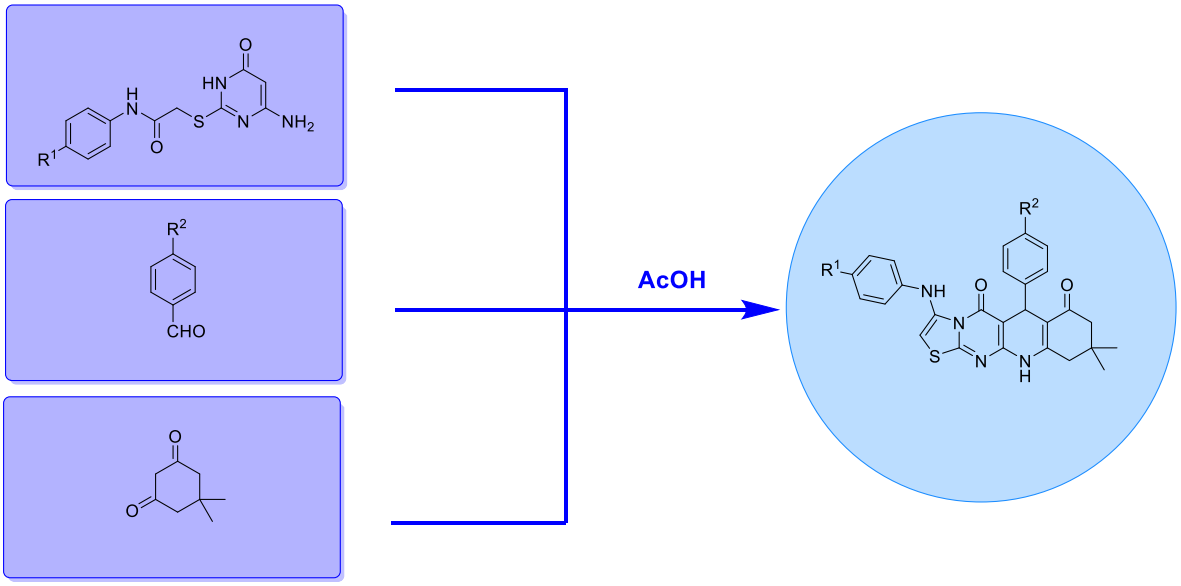
Rania Samy Omar, Amr M. Abdelmoniem, Ahmed H. M. Elwahy,* and Ismail A. Abdelhamid*

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
Email: aelwahy@hotmail.com; aelwahy@cu.edu.eg; ismail_shafy@yahoo.com; ismail_shafy@cu.edu.eg

Received 05-12-2024 **Accepted Manuscript** 07-04-2024 **Published on line** 07-27-2024

Abstract

New thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines were synthesized in good yields using a three-component Hantzsch reaction comprising the appropriate aldehyde and one mole each of 6-aminothiouracil and 5,5-dimethyl-1,3-cyclohexanedione. The identical compounds might also be generated by alkylating the relevant 5-aryl-2-thioxopyrimido[4,5-*b*]quinoline-4,6-diones with the matching 2-chloro-*N*-arylacetamide. A feasible mechanistic approach to the production of the target products was proposed.



Keywords: Thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines, Hantzsch reaction, alkylation

Cite as *Arkivoc* **2024** (8) 202412221
DOI: https://doi.org/10.24820/ark.5550190.p012.221

Introduction

Multicomponent reactions (MCRs) are an intriguing synthetic method because they provide atom economy, selectivity, effectiveness, reliability, and quick access to synthetic organic molecules[1–11]. One of the most popular multi-component approaches for the synthesis of 1,4-dihydropyridines is the Hantzsch reaction, which displays a variety of biological and pharmacological properties, including anticancer[12], anti-inflammatory[13] antiviral[14], antituberculosis[15], anticonvulsant[16], and anti-Alzheimer activity[17].

Furthermore, nitrogen-containing heterocycles have emerged as important structural units for chemical and medical scientists in recent years. Among them, quinolines were shown to have a broad spectrum of biological actions, including antihypertensive, antibacterial, antituberculosis, anti-asthmatic, anticancer, antimalarial, and anti-inflammatory characteristics[18–23]. Moreover, pyrimidines [24–27] and pyridines [28–32] are crucial heterocycles with noteworthy biological characteristics.

Furthermore, pyrimidoquinolines have been found to display substantial biological properties as antimicrobial[33–35], antioxidant[34], anticancer[36–39], anti-inflammatory[34,35], analgesic[35,40] and antimalarial[19] activities.

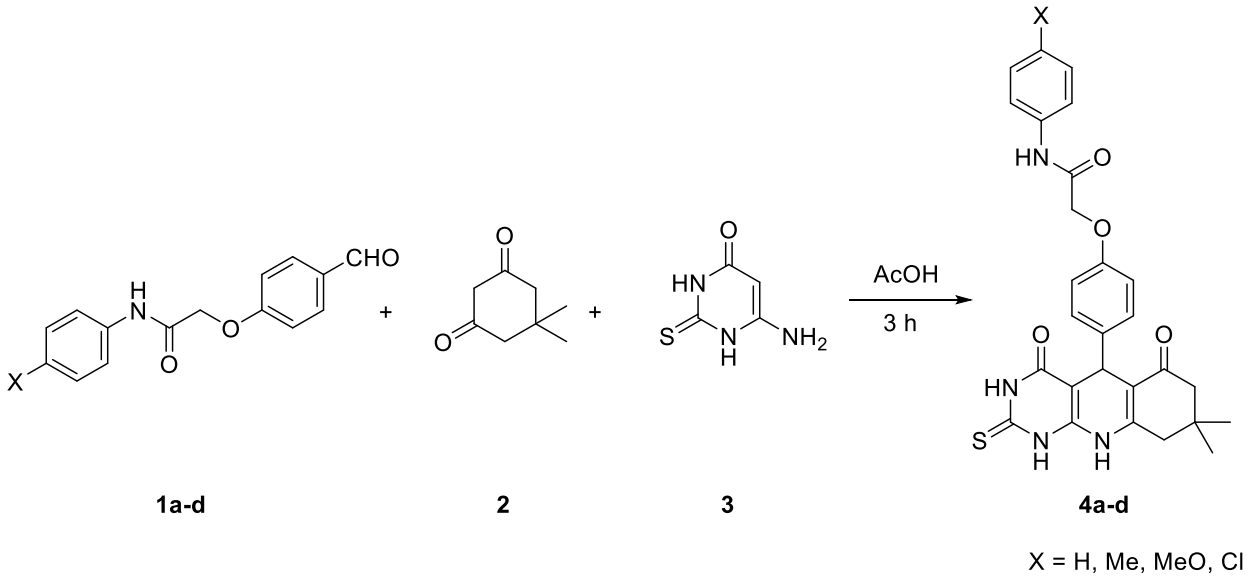
It has been demonstrated that thiazoles possess antifungal, antibacterial, analgesic, anti-inflammatory, antiprotozoal, antiviral, antioxidant, anticancer, and antidiabetic properties [41,42].

Besides, to address the problem of drug resistance, the idea of hybrid pharmaceuticals has provided a new drug design technique that combines two or more drugs with intrinsic action in one agent[43–52]. Molecular hybridization (MH) is regarded as a strong method for the synthesis of molecules with more than one structural unit with enhanced bioactivities[53].

In consideration of these improvements and our continuous endeavor to explore the synthesis of heterocycles,[50,54–58] we present the design and synthesis of 6-aryl-3-(arylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines as novel hybrid molecules.

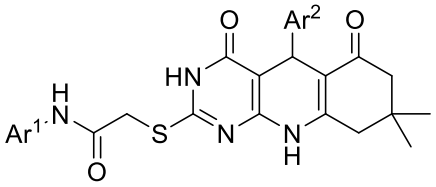
Results and Discussion

Recently, we reported the synthesis of pyrimido[4,5-*b*]quinolines **4a-d** in which phenoxy-*N*-arylacetamide is linked to the position five of the pyrimido[4,5-*b*]quinoline system in 67-93% yield *via* a three-component reaction of aldehydes **1a-d** with two moles of both 6-aminouracil **3** and 5,5-dimethyl-1,3-cyclohexanedione **2** in acetic acid at reflux (Scheme 1).[59]



Scheme 1. Synthesis of pyrimido[4,5-*b*]quinolines **4a-d.**

In continuation of this work, we attempted to synthesize novel pyrimido[4,5-*b*]quinolines **5** in which *N*-arylacetamide is linked to position two of the pyrimido[4,5-*b*]quinoline system *via* thioether linkage (Figure 1).



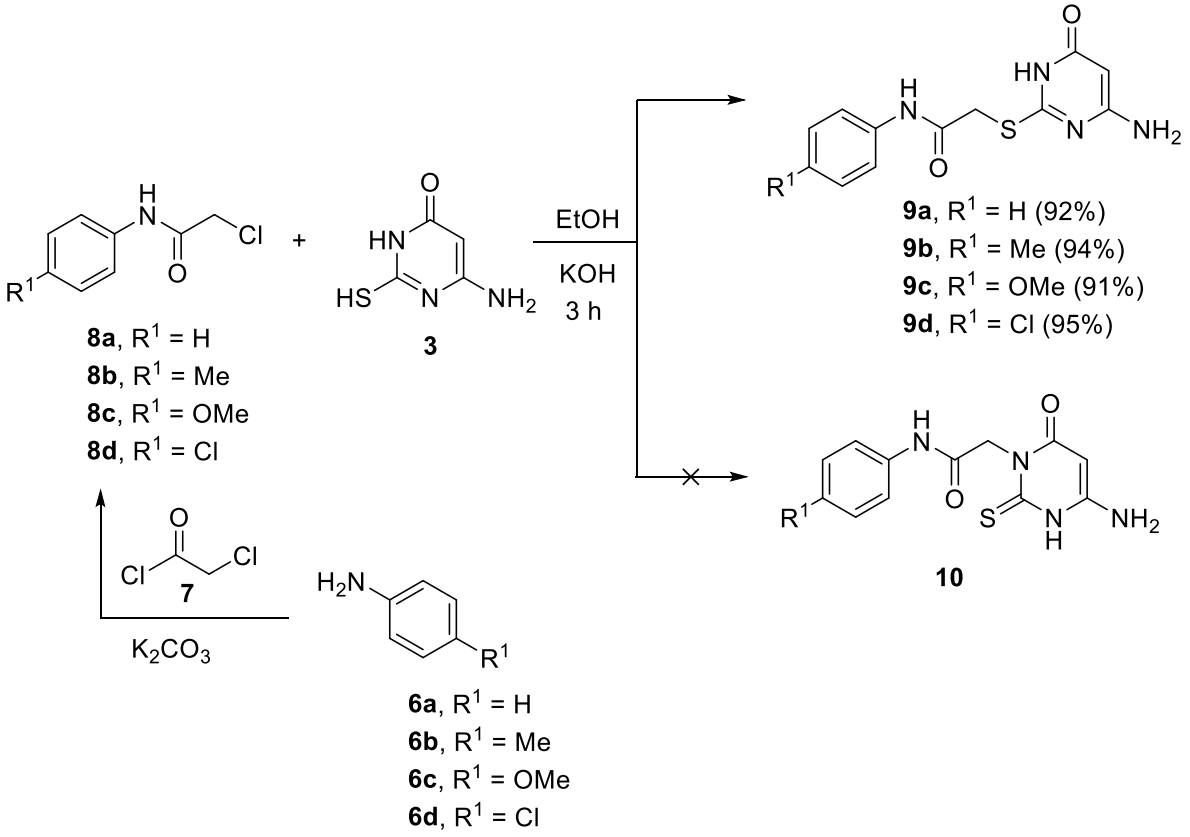
5

Figure 1. Structure of pyrimido[4,5-*b*]quinolines **5** linked to *N*-arylacetamide *via* thioether linkage.

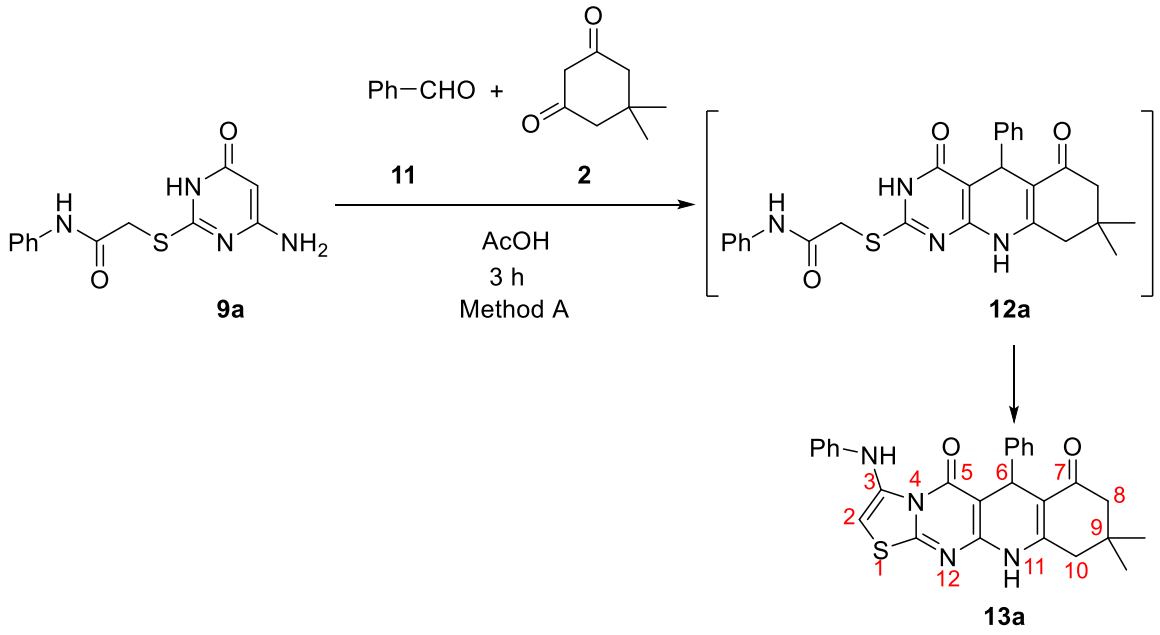
For this purpose, the 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamides **9** have been chosen as precursors to our target compounds. They are prepared through the direct *S*-alkylation reaction of 6-aminothiouracil **3** with the 2-chloro-*N*-arylacetamides **8** in the presence of anhydrous KOH (Scheme 2). NMR spectroscopy and theoretical studies of related compounds rule out the other potential *N*-alkylated product **10**[60]. Furthermore, the methylene carbon was detected at δ 34.5 ppm in the ^{13}C NMR spectrum of **9b**, implying that the methylene carbons are bound to sulfur. Additionally, it showed that there was no C=S signal[61], which is very strong evidence for the alkylation of sulfur.

Upon establishing the chemical structure of **9**, their reactivity towards the activated double bond in the Michael addition process has been examined. Consequently, the intermediate Michael addition product, 2-((5-phenyl-octahydropyrimido[4,5-*b*]quinolin-2-yl)thio)-*N*-phenylacetamide **12a** was produced by reacting one equivalent of **9a** with the mole equivalents of both benzaldehyde **11** and dimedone **2**. Under the effect of reaction conditions, compound **12a** cyclized directly to give 6-phenyl-3-(phenylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline **13a** in 86% yield (Method A, Scheme 3). The formation of **13a** rather than **12a** is strongly evidenced based on mass spectrometry that indicated the loss of a water molecule

(*m/z* 468). In addition, ^{1}H NMR of **13a** indicated the absence of -SCH_2- group at *δ* 3.0-4.0 ppm and the appearance of singlet at 7.98 ppm for H-2.

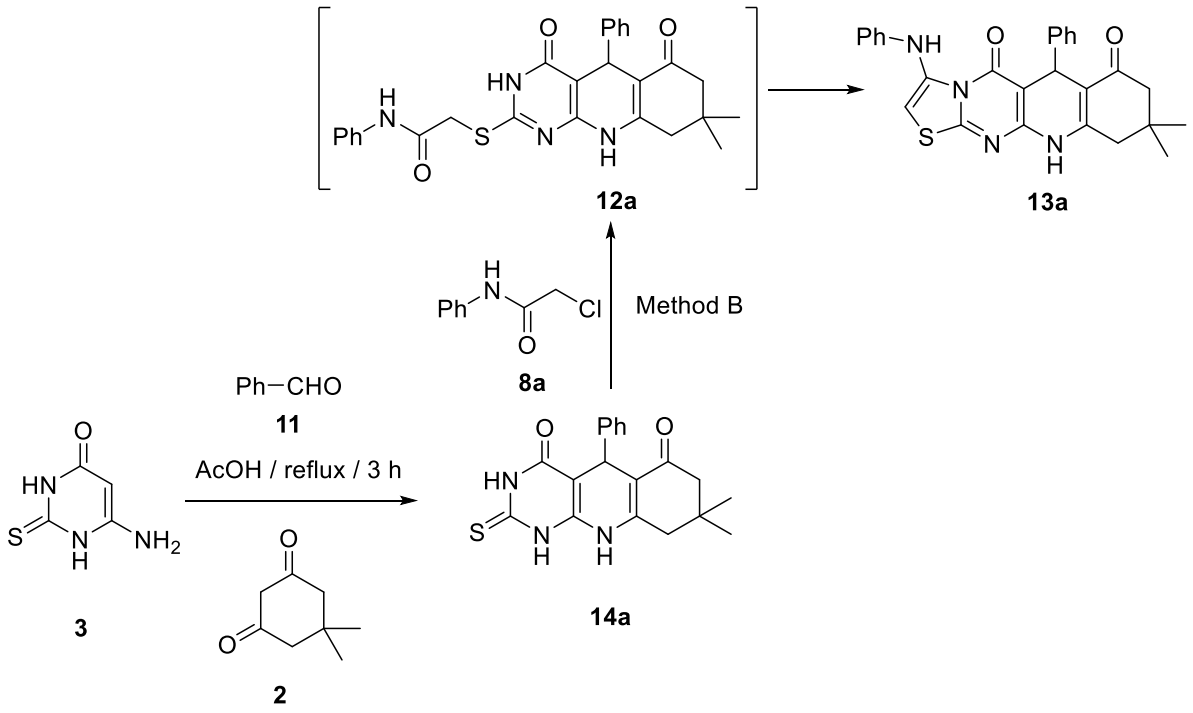


Scheme 2. Synthesis of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamides **5a-d.**



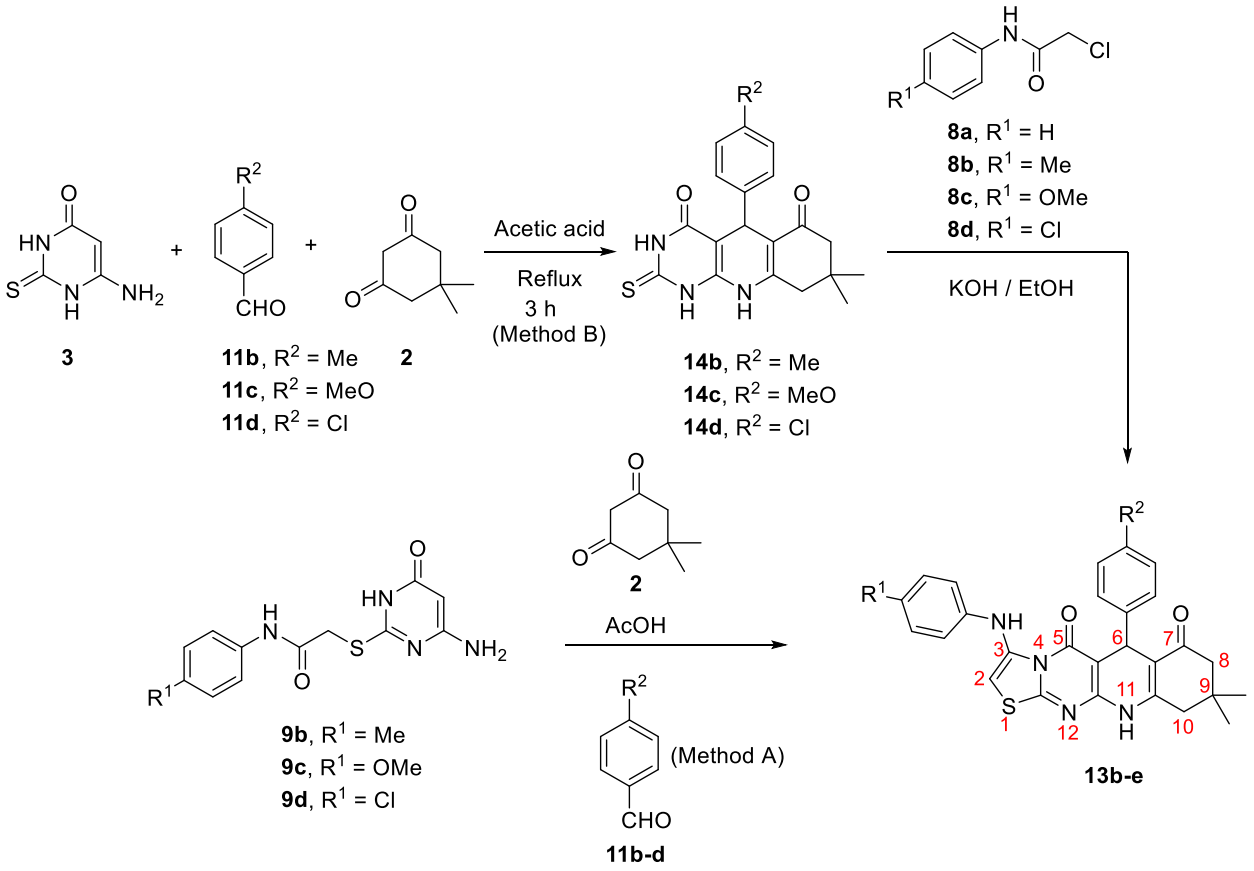
Scheme 3. A three-component synthesis of 6-phenyl-3-(phenylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline **13a.**

The same product **13a** could be alternatively produced in 84% yield *via* the alkylation of the initially formed 5-phenyl-2-thioxopyrimido[4,5-*b*]quinoline-4,6-dione **14a**[62,63] with the mole equivalent of 2-chloro-*N*-phenylacetamide **8a** in the presence of KOH (Method B, Scheme 4). Compound **14a** was produced *via* the interaction of 6-amino-2-thioxopyrimidin-4-one **3** with benzaldehyde **11** and dimedone **2** in refluxing acetic acid.[56,62,63]



Scheme 4. Synthesis of **13a** *via* the alkylation of 2-thioxopyrimido[4,5-*b*]quinoline **14a.**[62,63]

Motivated by these results, the synthetic scope of this reaction has been broadened to prepare some 6-aryl-3-(arylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines **13b-e** with different substituents at positions 3 and 6 *via* either the reaction of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamides **9b-d** with one equivalent of both substituted arylaldehydes **11b-d** and dimedone **2** (Method A) or the direct alkylation reaction of 5-aryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-diones **14b-d**[56] with 2-chloro-*N*-arylacetamides **8a-d** (Method B) (Scheme 5, Table 1).



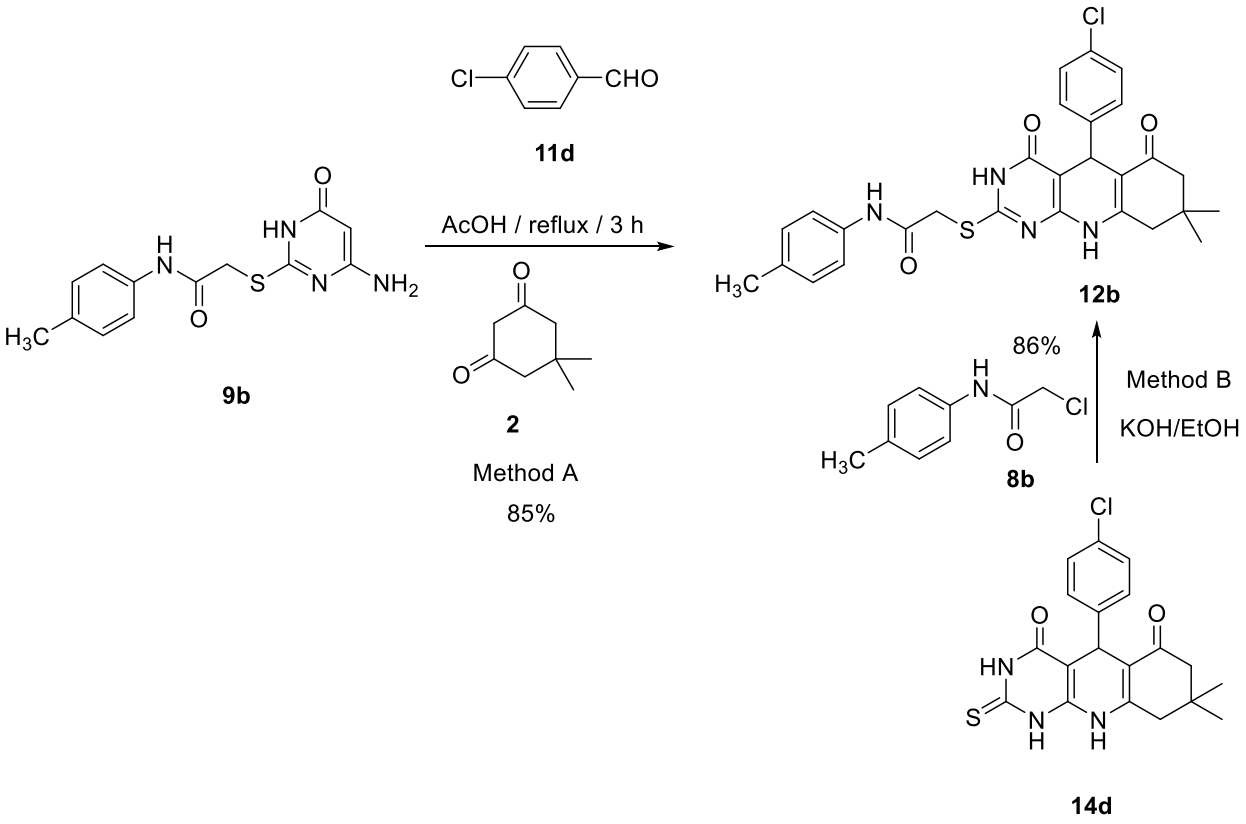
Scheme 5. Synthesis of 5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines **13b-e.**

Table 1. % yield of compounds **13b-e**

Compound	R^1	R^2	Yield (%) Method A	Method B
13b	H	OCH3	84	80
13c	CH3	CH3	89	83
13d	OCH3	OCH3	83	80
13e	Cl	H	82	78

The constitutions of compounds **13** were approved based on spectral data. The mass spectrometry of compound **13c** as a representative example showed a molecular ion peak at *m/z* 498 as a base peak corresponding to the removal of a water molecule. ^{1}H NMR of **13c** indicated the presence of three singlets at 0.93, 1.03, and 2.20 for three methyl groups. Besides it featured two singlets at 4.91 and 7.94 for the respective H6 and H2. Moreover, H8 and H10 appeared as multiplets in the region 2.01–2.25 and 2.45–2.54 ppm. ^{1}H NMR indicated the aromatic protons as four doublets at 7.00, 7.11, 7.37, and 7.56 ppm. The two broad singlets at 10.24 and 11.09 ppm were assigned to two NH groups.

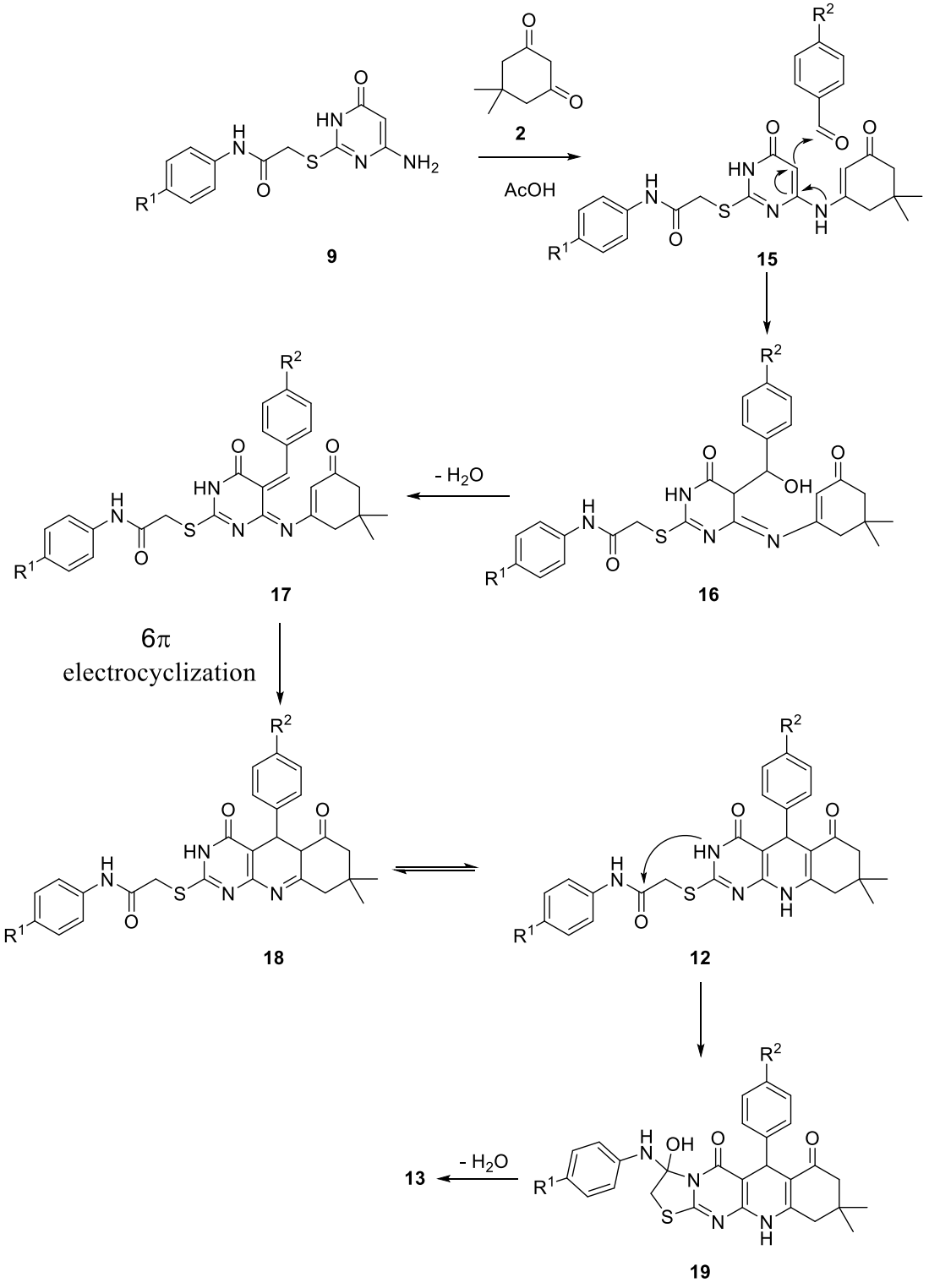
It is worth mentioning that octahydropyrimido[4,5-*b*]quinolin-2-ylthio-*N*-(*p*-tolyl)acetamide **12b** could be obtained as the sole product in 85% yield when **9b** reacted with aldehyde **11d** and dimedone **2** in acetic acid at reflux. The same product was obtained in 86% yield by the alkylation reaction of 5-aryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-dione **14d**[56] with 2-chloro-*N*-arylacetamide **8b** in ethanolic KOH (Scheme 6).



Scheme 6. Synthesis of 5-aryl-octahydropyrimido[4,5-*b*]quinoline **12b.**

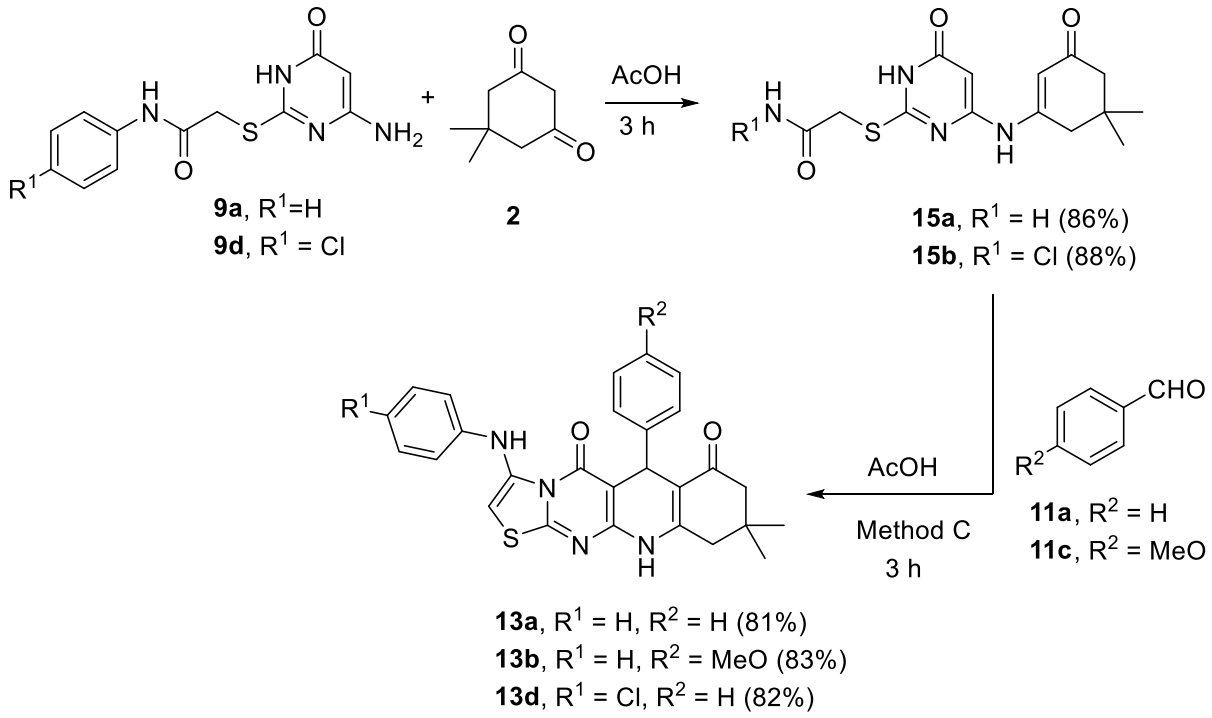
The constitution of compound **12b** was confirmed based on spectral data. The mass spectrometry showed a molecular ion peak at *m/z* 536 as a base peak. ^{1}H NMR indicated the presence of three singlets at 0.89, 1.01, and 2.27 for three methyl groups. Besides it featured two singlets at 3.98 and 4.86 for the respective -SCH_2- and H5. Moreover, H7 and H9 appeared as multiplets in the region 1.96–2.25 and 2.33–2.47 ppm. ^{1}H NMR indicated the aromatic protons as a multiplet at δ 7.16–7.25 in addition to two doublets at 7.56, and 7.94. The two broad singlets at 9.80 and 12.57 ppm were assigned to three NH groups.

Scheme 7 depicts a hypothesized reaction pathway for producing **13**. In the presence of acid catalyst, 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamide **9** condensed with dimedone **2**, resulting in the formation of the cyclic enaminones **15**, that undergo nucleophilic addition to the corresponding aldehydes **11** to give the intermediates **16**. Subsequent water elimination produces triene **17**. Intermediate **17** undergoes 6π electrocyclization to afford **18** which tautomerizes to create product **12**. Nucleophilic addition of ring-NH of **12** to the carbonyl group of arylacetamide side-chain affords intermediate **19**. Elimination of water leads to the final isolable products **13**.



Scheme 7. Mechanistic pathway for the formation of 6-aryl-3-(arylamino)-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines **13.**

The effective isolation of **12b** provides evidence for the process mentioned above. Furthermore, in support of this approach, we isolated the cyclic enaminones **15a** and **15b** by reacting **9a** and **9b** directly with dimedone **2** in acetic acid at reflux for two hours. The reaction of **15** with aldehydes **11a** and **11c** in acetic acid produced **13a**, **13b**, and **13d** in 81-83% yield (Scheme 8).



Scheme 8. Stepwise synthesis of compounds **13**.

Conclusions

We developed efficient methods for producing new thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinolines *via* a multi-component reaction or an S-alkylation reaction. The products' structures were validated using spectrum data and elemental studies. This reaction has several benefits, including gentle reaction conditions, high yields, and easy access to starting materials. This technique gives beneficial access to new compounds with expected biological activity.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 as solvent on Varian Gemini NMR spectrometer at 300 MHz and 75 MHz, respectively, using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

General procedure for the synthesis of compounds 9a-d. To a mixture of 2-chloro-*N*-arylacetamide derivatives **8a-d** (10 mmol), 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**3**) (1.43 g, 10 mmol), and potassium hydroxide (0.56 g, 10 mmol) in absolute EtOH (20 mL). The solution is heated at reflux for 3 h. The excess solvent was removed under reduced pressure and the collected residue was recrystallized from EtOH/dioxane (5:1, v/v).

2-((4-Amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-phenylacetamide (9a). Colorless crystals (2.54 g, 92%). Mp 264 ºC. IR (KBr) υ 3475, 3336, 3255, 3194 (2NH and NH_2), 1675 (C=O), 1650 (C=O) cm^{-1}. ^{1}H NMR (300 MHz,

DMSO-d_6): δ 3.94 (s, 2H, S-CH_2), 5.03 (s, 1H, =C-*H*), 6.53 (s, 2H, NH_2), 7.01 – 7.61 (m, 5H, Ar-*H*), 10.26 (s, 1H, N*H*), 11.20 (s, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 276 $[M]^+$. Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.14; H, 4.35; N, 20.22.

2-((4-Amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(*p*-tolyl)acetamide (9b). Colorless crystals (2.73 g, 94%). Mp 258-260 ºC; IR (KBr) υ 3487, 3339, 3278, 3194 (2NH and NH_2), 1674 (C=O), 1654 (C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 3.94 (s, 2H, S-CH_2), 5.04 (s, 1H, =C-*H*), 6.55 (s, 2H, NH_2), 7.09 (d, *J* 8.1 Hz, 2H, Ar-*H*), 7.48 (d, *J* 8.1 Hz, 2H, Ar-*H*), 10.16 (s, 1H, N*H*), 11.54 (s, 1H, N*H*) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4, 34.5, 81.4, 119.3, 129.1, 132.4, 136.4, 163.0, 163.8, 165.2, 166.4 ppm. MS (EI, 70 eV): *m/z* (%) 290 $[M]^+$. Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.78; H, 4.86; N, 19.30. Found: C, 53.74; H, 4.80; N, 19.31.

2-((4-Amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(4-methoxyphenyl)acetamide (9c). Gray crystals (2.78 g, 91%). Mp 242-244 ºC. IR (KBr) υ 3481, 3398, 3270, 3188 (2NH and NH_2), 1672 (C=O), 1653 (C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.90 (s, 2H, S-CH_2), 5.03 (s, 1H, =C-*H*), 6.50 (s, 2H, NH_2), 6.86 (d, *J* 9.0 Hz, 2H, Ar-*H*), 7.49 (d, *J* 9.0 Hz, 2H, Ar-*H*), 10.16 (s, 1H, N*H*), 11.04 (s, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 306 $[M]^+$. Anal. Calcd for $C_{13}H_{14}N_4O_3S$: C, 50.97; H, 4.61; N, 18.29 Found: C, 50.90; H, 4.55; N, 18.21.

2-((4-Amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(4-chlorophenyl)acetamide (9d). Colorless crystals (2.95 g, 95%). Mp 254 – 256 ºC. IR (KBr) υ 3480, 3394, 3248, 3165 (2NH and NH_2), 1673 (C=O), 1660 (C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 2H, S-CH_2), 5.03 (s, 1H, =C-*H*), 6.37 (s, 2H, NH_2), 7.32 (d, *J* 8.9 Hz, 2H, Ar-*H*), 7.63 (d, *J* 8.9 Hz, 2H, Ar-*H*), 10.74 (s, 1H, N*H*), 11.70 (s, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 312 $[M+2]^+$, 310 $[M]^+$. Anal. Calcd for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03 Found: C, 46.35; H, 3.50; N, 18.02.

General procedure for synthesis of compounds 12b and 13a-e

Method A. A mixture of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamide **9a-d** (1 mmol), dimedone (**2**) (0.14 g, 1 mmol), and aromatic aldehyde **11a-d** (1 mmol) was heated at reflux for 3 h in glacial acetic acid (20 mL). The solvent was removed under reduced pressure and the collected residue was recrystallized from EtOH/dioxane (5:1, v/v).

Method B. A mixture of 5-arylhexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,7*H*)-dione derivatives **14a-d** (1 mmol), 2-chloro-*N*-arylacetamide derivatives **8a-d** (1 mmol), potassium hydroxide (0.06 g, 1 mmol) was heated at reflux in absolute ethanol (30 mL) for 3 h. The excess solvent was removed under reduced pressure. The obtained residue was treated with aq. HCl (1 *N*, 20 mL) and washed thoroughly with distilled water. After being dried in air, the crude solid was purified by recrystallization from EtOH/dioxane (5:1, v/v).

Method C. (for compounds **13a**, **13b,** and **13e**): A mixture of enamine **15a,d** (1 mmol) and aromatic aldehydes **11a,b** (1 mmol) was heated at reflux in glacial AcOH for 3 h. The solvent was removed under reduced pressure and the collected residue was recrystallized from EtOH/dioxane (5:1, v/v).

2-((5-(4-Chlorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-*b*]quinolin-2-yl)thio)-*N*-(*p*-tolyl)acetamide (12b). Colorless crystals (method A: 0.45 g, 85%; method B: 0.46 g, 86%). Mp 194-196 ºC; IR (KBr) υ 3478, 3392, 3302 (3NH), 1772, 1681, 1676 (3C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.96 – 2.25 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.33 – 2.47 (m, 2H, CH_2), 3.98 (s, 2H, S-CH_2), 4.86 (s, 1H, *H*-5), 7.16 – 7.25 (m, 4H, Ar-*H*), 7.56 (d, *J* 8.5 Hz, 2H, Ar-*H*), 7.94 (d, *J* 8.5 Hz, 2H, 2H, Ar-*H*), 9.80 (s, 1H, N*H*), 12.57 (br, 2H, 2N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 536 $[M+2]^+$, 534 $[M]^+$. Anal. Calcd for $C_{28}H_{27}ClN_4O_3S$: C, 62.85; H, 5.09; N, 10.47. Found: C, 62.78; H, 5.03; N, 10.44.

9,9-Dimethyl-6-phenyl-3-(phenylamino)-6,9,10,11-tetrahydro-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline-5,7(8*H*)-dione (13a). Colorless crystals (method A: 0.40 g, 86%; method B: 0.39 g, 84%; method C: 0.38 g, 81%). Mp >300 ºC. IR (KBr) υ 3478, 3362 (2NH), 1715, 1671 (2C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.02 – 2.24 (m, 2H, CH_2), 2.42 – 2.55 (m, 2H, CH_2), 4.97 (s, 1H, *H*-6), 7.18 – 7.26 (m, 5H, Ar-*H*), 7.48 – 7.59 (m, 3H, Ar-*H*), 7.67 (d, *J* 7.7 Hz, 2H, Ar-*H*), 7.98 (s, 1H, *H*-2), 10.32 (s, 1H, N*H*),

11.45 (br, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 468 $[M]^+$. Anal. Calcd for $C_{27}H_{24}N_4O_2S$: C, 69.21; H, 5.16; N, 11.96. Found: C, 69.16; H, 5.06; N, 11.88.

6-(4-Methoxyphenyl)-9,9-dimethyl-3-(phenylamino)-6,9,10,11-tetrahydro-5*H*-thiazolo[3',2':1,2]pyrimido [4,5-*b*]quinoline-5,7(8*H*)-dione (13b). Colorless crystals (method A: 0.42 g, 84%; method B: 0.40 g, 80%; method C: 0.41 g, 83%). Mp >300 ºC. IR (KBr) υ 3478, 3362 (2NH), 1715, 1671 (2C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 – 2.23 (m, 2H, CH_2), 2.45 – 2.53 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.89 (s, 1H, *H*-6), 6.76 (d, *J* 8.3 Hz, 2H, Ar-*H*), 7.10 – 7.14 (m, 5H, Ar-*H*), 7.63 (d, *J* 8.5 Hz, 2H, Ar-*H*), 7.92 (s, 1H, *H*-2), 10.23 (s, 1H, N*H*), 11.07 (br, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 498 $[M]^+$. Anal. Calcd for $C_{28}H_{26}N_4O_3S$: C, 67.45; H, 5.26; N, 11.24. Found: C, 67.40; H, 5.16; N, 11.17.

9,9-Dimethyl-6-(*p*-tolyl)-3-(*p*-tolylamino)-6,9,10,11-tetrahydro-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline-5,7(8*H*)-dione (13c). Colorless crystals (method A: 0.44 g, 89%; method B: 0.41 g, 83%). Mp >300 ºC. IR (KBr) υ 3476, 3361 (2NH), 1722, 1676 (2C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.01 – 2.25 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.37 (s, 3H), 2.45 – 2.54 (m, 2H, CH_2), 4.91 (s, 1H, *H*-6), 7.00 (d, *J* 7.8 Hz, 2H, Ar-*H*), 7.11 (d, *J* 7.7 Hz, 2H, Ar-*H*), 7.37 (d, *J* 7.9 Hz, 2H, Ar-*H*), 7.56 (d, *J* 7.9 Hz, 2H, Ar-*H*), 7.94 (s, 1H, *H*-2), 10.24 (s, 1H, N*H*), 11.09 (br, 1H, N*H*).ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6, 21.2, 26.7, 29.0, 32.2, 33.6, 38.8, 50.2, 98.0, 110.4, 118.1, 127.7, 128.4, 130.1, 130.5, 134.9, 135.1, 141.5, 143.1, 149.9, 150.6, 157.4, 158.5, 162.5, 194.3 ppm. MS (EI, 70 eV): *m/z* (%) 496 $[M]^+$. Anal. Calcd for $C_{29}H_{28}N_4O_2S$: C, 70.14; H, 5.68; N, 11.28. Found: C, 70.05; H, 5.60; N, 11.24.

6-(4-Methoxyphenyl)-3-((4-Methoxyphenyl)amino)-9,9-dimethyl-6,9,10,11-tetrahydro-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline-5,7(8*H*)-dione (13d). Colorless crystals (method A: 0.44 g, 83%; method B: 0.42 g, 80%). Mp >300 ºC. IR (KBr) υ 3483, 3355 (2NH), 1724, 1677 (2C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.01 – 2.23 (m, 2H, CH_2), 2.46 – 2.53 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.90 (s, 1H, *H*-6), 6.74 – 6.76 (m, 2H, Ar-*H*), 7.09 – 7.15 (m, 4H, Ar-*H*), 7.63 (d, *J* 9.2 Hz, 2H, Ar-*H*), 7.93 (s, 1H, *H*-2), 10.25 (s, 1H, N*H*), 12.25 (br, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 528 $[M]^+$. Anal. Calcd for $C_{29}H_{28}N_4O_4S$: C, 65.89; H, 5.34; N, 10.60. Found: C, 65.83; H, 5.30; N, 10.53.

3-((4-Chlorophenyl)amino)-9,9-dimethyl-6-phenyl-6,9,10,11-tetrahydro-5*H*-thiazolo[3',2':1,2]pyrimido[4,5-*b*]quinoline-5,7(8*H*)-dione (13e). Colorless crystals (method A: 0.41 g, 82%; method B: 0.39 g, 78%; method C: 0.41 g, 82%). Mp >300 ºC. IR (KBr) υ 3481, 3360 (2NH), 1721, 1680 (2C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.02 – 2.24 (m, 2H, CH_2), 2.42 – 2.55 (m, 2H, CH_2), 4.96 (s, 1H, *H*-6), 7.18 – 7.26 (m, 4H, Ar-*H*), 7.51 – 7.59 (m, 3H, Ar-*H*), 7.67 (d, *J* 8.2 Hz, 2H, Ar-*H*), 7.97 (s, 1H, *H*-2), 10.32 (s, 1H, N*H*), 11.03 (br, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 504 $[M+2]^+$, 502 $[M]^+$. Anal. Calcd for $C_{27}H_{23}ClN_4O_2S$: C, 64.47; H, 4.61; N, 11.14. Found: C, 64.36; H, 4.52; N, 11.07.

General procedure for the synthesis of compounds 15a,b. A mixture of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-arylacetamide **9a,d** (1 mmol), dimedone (**2**) (0.14 g, 1 mmol) was heated at reflux in glacial AcOH (20 mL) for 3 h. The solvent was removed under reduced pressure and the remaining residue was recrystallized from EtOH/dioxane (5:1, v/v).

2-((4-((5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)amino)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-phenylacetamide (15a). Colorless crystals (0.34 g, 86%). Mp >300 ºC. IR (KBr) υ 3481, 3360, 3291 (3NH), 1721, 1680, 1665 (3C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.97 – 2.20 (m, 2H, CH_2), 2.44 – 2.48 (m, 2H, CH_2), 3.87 (s, 2H, S-CH_2), 4.87 (s, 1H, *H*-2'), 6.43 (s, 1H, *H*-5), 7.16 – 7.25 (m, 5H, Ar-*H*), 9.79 (s, 1H, N*H*), 10.78 (br, 1H, 1N*H*), 11.28 (br, 1H, 1N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 398 $[M]^+$. Anal. Calcd for $C_{20}H_{22}N_4O_3S$: C, 60.28; H, 5.57; N, 14.06. Found: C, 60.21; H, 5.55; N, 14.09.

***N*-(4-Chlorophenyl)-2-((4-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)acetamide (15b).** Colorless crystals (0.38 g, 88%). Mp >300 ºC. IR (KBr) υ 3475, 3365, 3298 (3NH), 1724,

1681, 1666 (3C=O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.02 – 2.24 (m, 2H, CH_2), 2.42 – 2.55 (m, 2H, CH_2), 4.96 (s, 1H, *H*-6), 7.18 – 7.26 (m, 4H, Ar-*H*), 7.51 – 7.59 (m, 3H, Ar-*H*), 7.67 (d, *J* 8.2 Hz, 2H, Ar-*H*), 7.97 (s, 1H, *H*-2), 10.32 (s, 1H, N*H*), 11.03 (br, 1H, N*H*) ppm. MS (EI, 70 eV): *m/z* (%) 434 $[M+2]^+$, 432 $[M]^+$. Anal. Calcd for $C_{20}H_{21}ClN_4O_3S$: C, 55.49; H, 4.89; N, 12.94. Found: C, 55.44; H, 4.81; N, 12.90.

Supplementary Material

Spectral data including copies of ^1H and ^{13}C NMR spectra of new compounds are given in the supplementary material associated with this manuscript.

References

1. Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193. https://doi.org/10.1021/cr100108k
2. Isambert, N.; Duque, M. del M. S.; Plaquevent, J.-C.; Génisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347–1357. https://doi.org/10.1039/C0CS00013B
3. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71*, 1413–1418. https://doi.org/10.1016/j.tet.2015.01.026
4. Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549. https://doi.org/10.1021/cr2003954
5. Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135. https://doi.org/10.1021/cr100233r
6. Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948–4962. https://doi.org/10.1039/c3cs35505e
7. Chen, M. N.; Mo, L. P.; Cui, Z. S.; Zhang, Z. H. *Current Opinion in Green and Sustainable Chemistry*. Elsevier B.V. February 1, 2019, pp 27–37. https://doi.org/10.1016/j.cogsc.2018.08.009
8. Zhang, M.; Liu, Y. H.; Shang, Z. R.; Hu, H. C.; Zhang, Z. H. *Catal. Commun.* **2017**, *88*, 39–44. https://doi.org/10.1016/j.catcom.2016.09.028
9. Tabibi, T.; Esmaeili, A. A. *Mol. Divers.* **2023**, *27*, 477–486. https://doi.org/10.1007/s11030-022-10439-z
10. Abdelwahab, R. E.; Ragheb, M. A.; Elwahy, A. H. M.; Abdelhamid, I. A.; Abdelmoniem, A. M. *J. Mol. Struct.* **2024**, *1307*, 137946. https://doi.org/10.1016/j.molstruc.2024.137946
11. WalyEldeen, A. A.; Sabet, S.; El-Shorbagy, H. M.; Abdelhamid, I. A.; Ibrahim, S. A. *Chem. Biol. Interact.* **2023**, *369*, 110297. https://doi.org/10.1016/j.cbi.2022.110297
12. Safak, C.; Simsek, R. *Mini Rev. Med. Chem.* **2006**, *6*, 747–755. https://doi.org/10.2174/138955706777698606
13. Murthy, Y. L. N.; Rajack, A.; Ramji, M. T.; Babu, J. J.; Praveen, C.; Lakshmic, K. A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6016–6023. https://doi.org/10.1016/j.bmcl.2012.05.003

14. Wollmann, J.; Baumert, C.; Erlenkamp, G.; Sippl, W.; Hilgeroth, A. *ChemBioChem* **2008**, *9*, 874–878. https://doi.org/10.1002/cbic.200700646
15. Wachter, G. A.; Davis, M. C.; Martin, A. R.; Franzblau, S. G. *J. Med. Chem.* **1998**, *41*, 2436–2438. https://doi.org/10.1021/jm9708745
16. Tusell, J. M.; Barro´n, S.; Serratosa, J. *Brain Res.* **1993**, *622*, 99–104. https://doi.org/10.1016/0006-8993(93)90807-Y
17. Choi, S. J.; Cho, J. H.; Im, I.; Lee, S. D.; Jang, J. Y.; Oh, Y. M.; Jung, Y. K.; Jeon, E. S.; Kim, Y. C. *Eur. J. Med. Chem.* **2010**, *45*, 2578–2590. https://doi.org/10.1016/j.ejmech.2010.02.046
18. Carosati, E.; Mannhold, R.; Wahl, P.; Hansen, J. B.; Fremming, T.; Zamora, I.; Cianchetta, G.; Baroni, M. *J. Med. Chem.* **2007**, *50*, 2117–2126. https://doi.org/10.1021/jm061440p
19. Joshi, A. A.; Viswanathan, C. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613–2617. https://doi.org/10.1016/j.bmcl.2006.02.038
20. Muruganantham, N.; Sivakumar, R.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Biol. Pharm. Bull.* **2004**, *27*, 1683–1687. https://doi.org/10.1248/bpb.27.1683
21. Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14*, 4600–4609. https://doi.org/10.1016/j.bmc.2006.02.020
22. Ridley, R. G. *Nature* **2002**, *415*, 686–693. https://doi.org/10.1038/415686a
23. Tsotinis, A.; Vlachou, M.; Zouroudis, S.; Jeney, A.; Timár, F.; Thurston, D. E.; Roussakis, C. *Lett. Drug Des. Discov.* **2005**, *2*, 189–192. https://doi.org/10.2174/1570180053765075
24. Xie, F.; Zhao, H.; Zhao, L.; Lou, L.; Hu, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 275–278. https://doi.org/10.1016/j.bmcl.2008.09.067
25. Pathak, V.; Maurya, H. K.; Sharma, S.; Srivastava, K. K.; Gupta, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2892–2896. https://doi.org/10.1016/j.bmcl.2014.04.094
26. Abdelgawad, M. A.; Bakr, R. B.; Azouz, A. A. *Bioorg. Chem.* **2018**, *77*, 339–348. https://doi.org/10.1016/j.bioorg.2018.01.028
27. Diab, H. M.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M. *Arkivoc* **2021**, *2021*, 329–377. https://doi.org/10.24820/ark.5550190.p011.474
28. Kolocouris, A.; Dimas, K.; Pannecouque, C.; Witvrouw, M.; Foscolos, G. B.; Stamatiou, G.; Fytas, G.; Zoidis, G.; Kolocouris, N.; Andrei, G.; Snoeck, R.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 723–727. https://doi.org/10.1016/S0960-894X(01)00838-1
29. Quintela, J.; Peinador, C.; Botana, L.; Estévez, M.; Riguera, R. *Bioorg. Med. Chem.* **1997**, *5*, 1543–1553. https://doi.org/10.1016/S0968-0896(97)00108-9
30. Girgis, A. S.; Hosni, H. M.; Ahmed-Farag, I. S. *Zeitschrift für Naturforsch. B* **2003**, *58*, 678–685. https://doi.org/10.1515/znb-2003-0712
31. Amr, A. E.; Abdulla, M. M. *Bioorg. Med. Chem.* **2006**, *14*, 4341–4352. https://doi.org/10.1016/j.bmc.2006.02.045
32. Son, J.-K.; Zhao, L.-X.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, T. C.; Jeong, B.-S.; Lee, C.-S.;

Lee, E.-S. *Eur. J. Med. Chem.* **2008**, *43*, 675–682.
https://doi.org/10.1016/j.ejmech.2007.05.002
33. Selvi, S. T.; Nadaraj, V.; Mohan, S.; Sasi, R.; Hema, M. *Bioorg. Med. Chem.* **2006**, *14*, 3896–3903.
https://doi.org/10.1016/j.bmc.2006.01.048
34. El-Gazzar, A. B. A.; Hafez, H. N.; Nawwar, G. A. M. *Eur. J. Med. Chem.* **2009**, *44*, 1427–1436.
https://doi.org/10.1016/j.ejmech.2008.09.030
35. Rajanarendar, E.; Reddy, M. N.; Krishna, S. R.; Murthy, K. R.; Reddy, Y. N.; Rajam, M. V. *Eur. J. Med. Chem.* **2012**, *55*, 273–283.
https://doi.org/10.1016/j.ejmech.2012.07.029
36. Cordeu, L.; Cubedo, E.; Bandrés, E.; Rebollo, A.; Sáenz, X.; Chozas, H.; Domínguez, M. V.; Echeverría, M.; Mendivil, B.; Sanmartin, C.; Palop, J. A. *Bioorg. Med. Chem.* **2007**, *15*, 1659–1669.
https://doi.org/10.1016/j.bmc.2006.12.010
37. Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Noaman, E.; Ghorab, M. M. *Eur. J. Med. Chem.* **2010**, *45*, 738–744.
https://doi.org/10.1016/j.ejmech.2009.11.021
38. Insuasty, B.; Becerra, D.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J. *J. Heterocycl. Chem.* **2013**, *50*, 506–512.
https://doi.org/10.1002/jhet.1510
39. Ghorab, M. M.; Ragab, F.; Heiba, H. I.; Arafa, R. K.; El-Hossary, E. M. *Eur. J. Med. Chem.* **2010**, *45*, 3677–3684.
https://doi.org/10.1016/j.ejmech.2010.05.014
40. El-Gazzar, A. R. B. A.; El-Enany, M. M.; Mahmoud, M. N. *Bioorg. Med. Chem.* **2008**, *16*, 3261–3273.
https://doi.org/10.1016/j.bmc.2007.12.012
41. Alizadeh, S. R.; Hashemi, S. M. *Medicinal Chemistry Research*. Springer 2021, pp 771–806.
https://doi.org/10.1007/s00044-020-02686-2
42. Petrou, A.; Fesatidou, M.; Geronikaki, A. *Molecules* **2021**, *26*, 3166.
https://doi.org/10.3390/molecules26113166
43. Muregi, F. W.; Ishih, A. *Drug Dev. Res.* **2009**, *71*, 20–32.
https://doi.org/10.1002/ddr.20345
44. Singh, K.; Kaur, H.; Smith, P.; De Kock, C.; Chibale, K.; Balzarini, J. *J. Med. Chem.* **2014**, *57*, 435–448.
https://doi.org/10.1021/jm4014778
45. Elwahy, A. H. M.; Hammad, H. F.; Ibrahim, N. S.; Al-Shamiri, H. A. S.; Darweesh, A. F.; Abdelhamid, I. A. *J. Mol. Struct.* **2024**, *1307*, 137965.
https://doi.org/10.1016/j.molstruc.2024.137965
46. Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M.; Ragheb, M. A.; Alqahtani, A. sultan; Zaki, M. E. A.; Algethami, F. K.; Mahmoud, H. K. *Heliyon* **2024**, *10*, e31082.
https://doi.org/10.1016/j.heliyon.2024.e31082
47. Abdullah, A. H.; Ibrahim, N. S.; Algethami, F. K.; Elwahy, A. H. M.; Abdelhamid, I. A.; Salem, M. E. *J. Mol. Struct.* **2024**, *1302*, 137506.
https://doi.org/10.1016/j.molstruc.2024.137506
48. Ragheb, M. A.; Mohamed, F. G.; Diab, H. M.; Ragab, M. S.; Emara, M.; Elwahy, A. H. M.; Abdelhamid, I. A.; Soliman, M. H. *Chem. Biodivers.* **2024**, *21*, e202301341.
https://doi.org/10.1002/cbdv.202301341
49. Saleh, F. M.; Hassaneen, H. M.; Abdelhamid, I. A.; Mohamed Teleb, M. A. *Tetrahedron Lett.* **2024**, *137*,

154957.
https://doi.org/10.1016/j.tetlet.2024.154957
50. Salem, M. E.; Abdullah, A. H.; Zaki, M. E. A.; Abdelhamid, I. A.; Elwahy, A. H. M. *ACS Omega* **2024**, *9*, 10146–10159.
https://doi.org/10.1021/acsomega.3c06653
51. Elwahy, A. H. M.; Shaaban, M. R.; Abdelhamid, I. A. *Adv. Heterocycl. Chem.* **2024**, *143*, 227–276.
https://doi.org/10.1016/bs.aihch.2023.11.003
52. Elwahy, A. H. M.; Ginidi, A. R. S.; Shaaban, M. R.; Mohamed, A. H.; Gaber, H. M.; Ibrahim, L. I.; Farag, A. M.; Salem, M. E. *Arkivoc* **2024**, *2024*, 202412181.
https://doi.org/10.24820/ark.5550190.p012.181
53. Claudio Viegas-Junior; Eliezer J. Barreiro; Carlos Alberto Manssour Fraga. *Curr. Med. Chem.* **2007**, *14*, 1829–1852.
https://doi.org/10.2174/092986707781058805
54. Abdelmoniem, A. M.; Abdella, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Arkivoc* **2020**, *2020*, 136–149.
https://doi.org/10.24820/ark.5550190.p011.357
55. Abdelmoniem, A. M.; Ghozlan, S. A. S.; Butenschön, H.; Abdelmoniem, D. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Arkivoc* **2019**, *2019*, 163–177.
https://doi.org/10.24820/ark.5550190.p010.875
56. Diab, H. M.; Salem, M. E.; Elwahy, A. H. M.; Abdelhamid, I. A. *Synth. Commun.* **2021**, *51*, 2001–2015.
https://doi.org/10.24820/ark.5550190.p011.474
57. Abdelhamid, I. A.; Diab, H. M.; Mahmoud, N. E.; Elwahy, A. H. M.; Fares, I. M. Z. *Arkivoc* **2024**, *2024*, 202412209.
https://doi.org/10.24820/ark.5550190.p012.209
58. Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2016**, *53*, 1113–1120.
https://doi.org/10.1002/jhet.2373
59. Diab, H. M.; Elwahy, A. H. M.; Ragheb, M. A.; Abdelhamid, I. A.; Mahmoud, H. K. *J. Mol. Struct.* **2023**, *1287*, 135721.
https://doi.org/10.1016/j.molstruc.2023.135721
60. Abd El-Fatah, N. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. *Tetrahedron* **2017**, *73*, 1436–1450.
https://doi.org/10.1016/j.tet.2017.01.047
61. El Ashry, E. S. H.; El Tamany, E. S. H.; El Fattah, M. E. D. A.; Boraei, A. T. A.; Abd El-Nabi, H. M. *Eur. J. Med. Chem.* **2013**, *66*, 106–113.
https://doi.org/10.1016/j.ejmech.2013.04.047
62. Crepaldi, P.; Cacciari, B.; Bonache, M. C.; Spalluto, G.; Varani, K.; Borea, P. A.; Kügelgen, I. von; Hoffmann, K.; Pugliano, M.; Razzari, C.; Cattaneo, M. *Bioorg. Med. Chem.* **2009**, *17*, 4612–4621.
https://doi.org/10.1016/j.bmc.2009.04.061
63. Cheng, C. C.; Lewis, L. R. *J. Heterocycl. Chem.* **1964**, *1*, 260–262.
https://doi.org/10.1002/jhet.5570010512