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Article

Synthesis of Novel Pyrimido[4,5-*b*] Quinolines Containing Benzyloxy and 1,2,3-Triazole Moieties by DABCO as a Basic Catalyst

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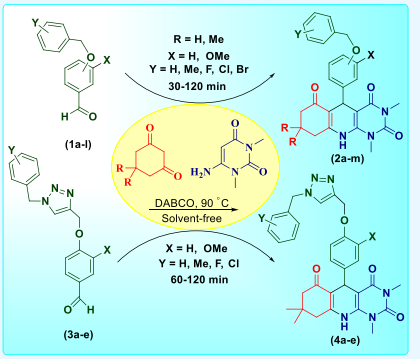
ABSTRACT: DABCO was used as a basic and inexpensive catalyst for the synthesis of some new benzyloxy pyrimido[4,5-*b*]quinoline derivatives and 1,2,3- triazole-fused pyrimido[4,5-*b*]quinolines by the one-pot multi-component reaction of various benzyloxy benzaldehydes or benzylic −1,2,3-triazol-4-yl-methoxy benzaldehydes with dimedone and 6-amino-1,3-dimethyluracil at 90 °C under the solvent-free condition.



1. INTRODUCTION

The compounds containing quinoline and pyrimidine or both of them in their structure including pyrimido[4,5-*b*]quinolines are important in pharmaceutical chemistry due to significant biological activities[1] such as antitumor,[2] antihistaminic,[3] anti-inflammatory,[4] anticancer,[5] antimicrobial,[6] and antimalarial properties.[7] Moreover, some compounds containing pyrimidine in their structure, have been used as inhibitors of AbI kinase and PTP1B[8,9] and applied as an antimicrobial agent.[10] Some compounds with quinoline in their structure have biological activities such as DNA binding[11] and DNA intercalating carrier.[12] Uracil derivatives are used in drug discovery with a wide range of biological activities and synthetic accessibility.[13] Antiviral, antitumor,[14] herbicidal, insecticidal, and bactericidal properties are other activities which reported for these compounds.[13]

An important strategy for the preparation of pyrimido[4,5-*b*]quinolines, which complies with green chemistry protocols, is the one-pot multi-component condensation reaction of dimedone, 6-amino-1,3-dimethyluracil and aldehydes.[1] Nowadays, multi-component reactions are one of the most important synthetic protocols in organic chemistry due to shortening the production path of the target product and saving on the consumption of raw materials and solvents without the need to separate the intermediates produced during the reaction. Decrease of the reaction time, increase the yield of the product, and high atomic economy are some other advantages of this protocol.[15−22]

According to the importance of the mentioned pyrimido-[4,5-*b*]quinolines, various catalysts were reported for the multi-component synthesis of pyrimido[4,5-*b*]quinolines such as [TSSECM],[1] SBA-15/PrN$(CH_2PO_3H_2)_2$,[23] [H_2-DABCO]-$[ClO_4]_2$,[24] nano-[Fe_3O_4@SiO_2/*N*-propyl-1-(thiophen-2-yl)-ethanimine][$ZnCl_2$],[25] nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$]-$[H_2PO_4]$,[26] Fe_3O_4@Cellulose sulfuric acid,[27] *N*,*N*-diethyl-*N*-sulfoethanaminium chloride,[28] [bmim]Br,[29] glycolic acid-supported cobalt ferrite,[30] nanocrystalline MgO,[31] $[C_4(DABCO)_2]\cdot 2OH$,[32] and agar-entrapped sulfonated DABCO.[33] However, most of the proposed methods are performed by acidic and expensive catalysts. A suitable basic catalyst for the synthesis of these valuable compounds has not yet been proposed.

Diazabicyclo [2.2.2] octane (DABCO) was recently used as a homogeneous and efficient organic catalyst in some organic synthesis. Inexpensiveness, non-toxicity, and commercially available are some important advantages of this organic catalyst.[34] Previously, DABCO was reported as a catalyst for the preparation of some important organic compounds such as xanthene derivatives,[34] 3-oxo-3H-benzo[*a*]pyrano[2,3-*c*] phenazine-1-carboxylates,[35] densely functionalized cyclohexanones,[36] unsymmetrical coumarins,[37] 3,3-disubstituted oxindoles and spirooxindoles,[38] heteroaryl-substituted benzenes,[39] highly substituted cyclopentenes,[40] 5-aryl-pyrimido[4,5-*b*]-quinoline-diones,[41] pyrano[3,2-*a*]phenazine derivatives,[42]

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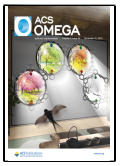

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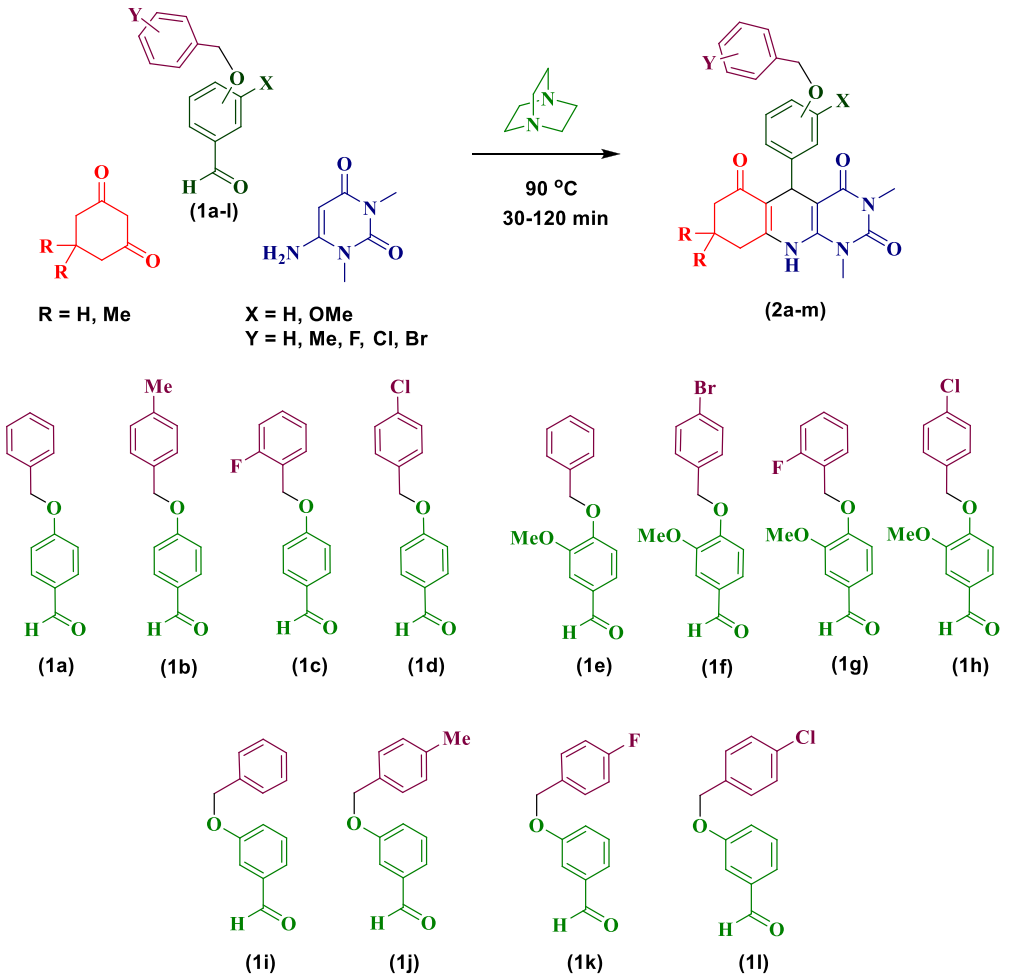
Scheme 1. Preparation of Pyrimido[4,5-*b*]quinolines



highly substituted imidazoles,[43] polysubstituted phthalimides and piperidines,[44] and bis-spiro pyranopyrazole.[45]

Herein, in the presented work, we have introduced DABCO as a homogeneous and efficient organic catalyst for the synthesis of some pyrimido[4,5-*b*]quinoline derivatives and 1,2,3-triazole derivatives of pyrimido[4,5-*b*]quinoline as new products at 90 °C under solvent-free conditions (Schemes 1 and 2).

2. RESULTS AND DISCUSSION

At first, to find the best reaction condition for the synthesis of pyrimido[4,5-*b*]quinoline derivatives, the reaction of 4-(4-chlorobenzyloxy)benzaldehyde with dimedone and 6-amino-1,3-dimethyluracil was considered as a model reaction. The effect of temperature changes from room temperature up to 110 °C, various solvents and various bases such as DABCO and HMTA were tested on the model reaction (Table 1). Also, the model reaction was studied under solvent-free condition in comparison with solvent media. The acidic media was also tested in this reaction. For this purpose, acetic acid and para toluene sulfonic acid as a common acidic catalyst were tested on the model reaction which did not have a better result (Table 1). As it is displayed from Table 1, it is indicated that the best result was obtained using 25 mol % of DABCO as a catalyst at 90 °C under the solvent-free condition.

After the optimization of the reaction condition, various substituted benzyloxy benzaldehydes, which prepared by the reaction of 4-hydroxybenzaldehyde with benzyl halide derivatives in the presence of a base,[46] were reacted with dimedone and 6-amino-1,3-dimethyluracil to obtain different pyrimido[4,5-*b*]quinolines as new products (Scheme 3).

In a mechanism which is supported by the previous literature,[23−33] dimedone converts into the enol form by the tautomerization and then DABCO attracted one proton from the hydroxyl group to obtain 5,5-dimethyl-3-oxocyclohex-1-enolate. In the next step, the prepared enolate attacked to aldehyde which is activated by protonated DABCO and lost a molecule of water to generate (**I**) as an intermediate. 6-Amino-1,3-dimethyluracil reacts with intermediate (**I**) as a Michael acceptor to furnish (**II**). Finally, by intramolecular nucleophilic attack in (**II**), with the removal of one molecule of water and tautomerization, the desired product is prepared (Scheme 4).

In the next part of our investigation, we have prepared 1,2,3-triazole-fused pyrimido[4,5-*b*]quinolines as new compounds from two different paths. In the first method, 4-hydroxybenzaldehyde was reacted with propargyl bromide in the presence of potassium carbonate to give 4-(prop-2-ynyloxy)-benzaldehyde and then added to a mixture of sodium azide and benzyl halide derivative in dimethylformamide (DMF) as a solvent in the presence of copper(**II**)sulfate, ascorbic acid, triethylamine, and water to prepare 4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]benzaldehyde and other derivatives (**3a**−

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Scheme 2. Preparation of 1,2,3-Triazole Derivatives of Pyrimido[4,5-*b*]quinolines

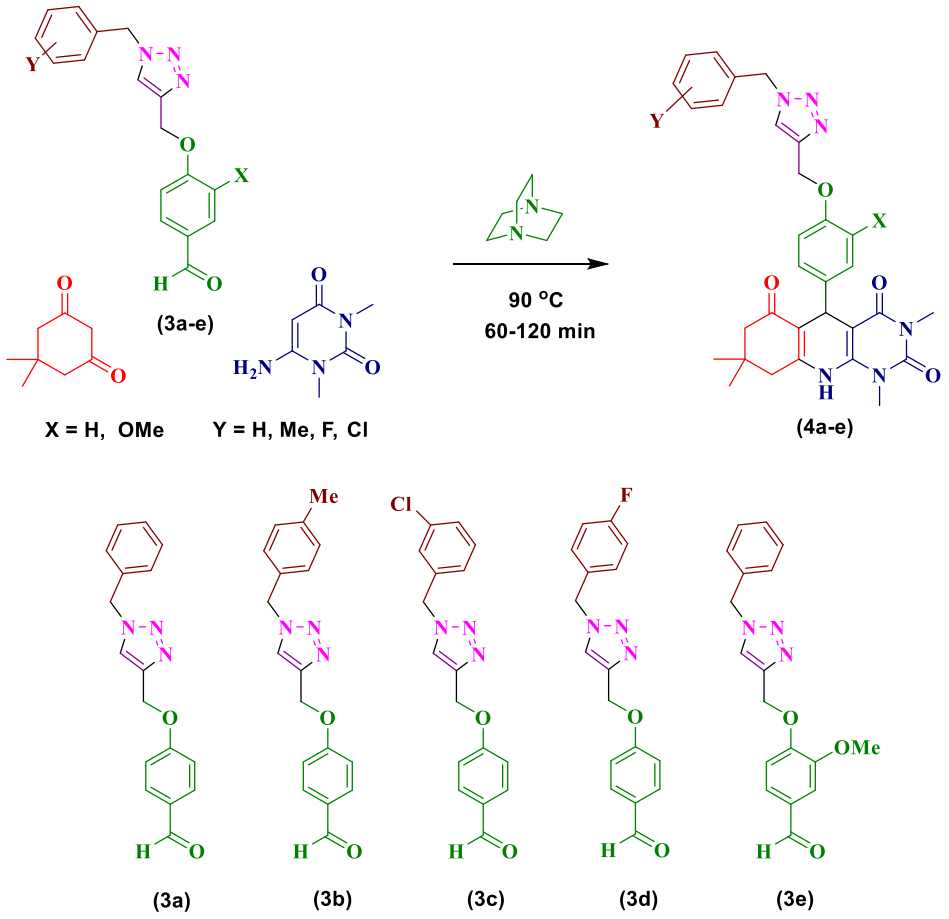

Table 1. Effect of Temperatures, Solvents, and Various Catalysts on the Reaction of 4-(4-Chlorobenzyloxy)benzaldehyde with Dimedone and 6-Amino-1,3-dimethyluracil

entry	solvent	catalyst (mol %)	temp. (°C)	time (h)	yield[a] (%)
1			110 °C	12	N.R.
2	H_2O		reflux	12	N.R.
3	EtOH		reflux	12	N.R.
4	H_2O	DABCO (25)	r.t.	4	N.R.
5	H_2O	DABCO (25)	reflux	4	18
6	H_2O/EtOH(1:1)	DABCO (25)	reflux	4	51
7	EtOH	DABCO (25)	r.t.	4	33
8	EtOH	DABCO (25)	reflux	4	68
9		DABCO (10)	90 °C	2	71
10		**DABCO (25)**	**90 °C**	**1**	**95**
11		DABCO (40)	90 °C	1	95
12		DABCO (25)	110 °C	2	97
13		HMTA (25)	90 °C	4	26
14	EtOH	HMTA (25)	reflux	2	TRACE
15	EtOH/H_2O(1:1)	HMTA (25)	reflux	2	TRACE
16		P-TSA (25)	90 °C	1	43
17		acetic acid (25)	90 °C	1	48

[a]Isolated yield.

e). Finally, by the reaction of aldehyde **3a−e** with dimedone and 6-amino-1,3-dimethyluracil in the presence of DABCO as a catalyst at 90 °C under the solvent-free condition, the expected products (**4a−e**) were prepared (Scheme 2). In another method, 4-(prop-2-ynyloxy)benzaldehyde was prepared by the mentioned procedure and reacted separately with dimedone and 6-amino-1,3-dimethyluracil in the presence of DABCO as a catalyst at 90 °C to give (**6a−b**). In the next step, by the click reaction of compounds **6a−b** with sodium azide and benzyl halide derivatives in DMF as a solvent in the presence of copper(**II**)sulfate, ascorbic acid, triethylamine, and water compounds **4a−e** were synthesized as click products (Schemes 5 and 6). It should be mentioned that the yield of the expected products (**4a−e**) in this method is lower than in comparison to the first method.

One of the effective methods for the azide−alkyne cycloaddition is using of copper(**I**) as a catalyst. In the presented method, Cu(**I**) is generated by the reaction of copper(**II**)sulfate and sodium ascorbate.[47] Moreover, the excess amount of sodium ascorbate, due to converting Cu(**II**) into Cu(**I**), prevents the oxidative homo coupling reaction. The triple bond is reacted with Cu(**I**) to give copper acetylide and another copper atom connects to the π bond by coordination. By the addition of benzyl azide to active copper acetylide, a six-membered ring of copper metallacycle with low stability is generated. The copper atom in the six-membered ring acts as a stabilizing donor ligand. Ring contraction of the metallacycle ring and then protonolysis process give the desired triazole product (Scheme 7).[48]

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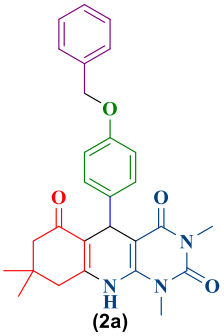
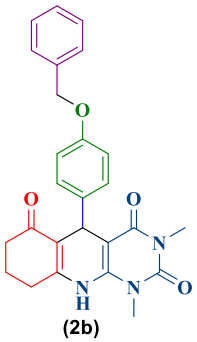
Scheme 3. Structure of Benzyloxy Pyrimido[4,5-*b*]quinoline Derivatives



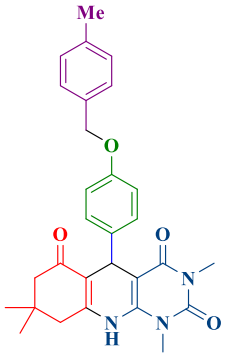
(2a)

[Time: 60 min, Yield: 84%]
mp: 295-299 °C



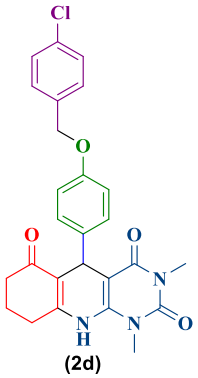
(2b)

[Time: 30 min, Yield: 90%]
mp: 193-195 °C



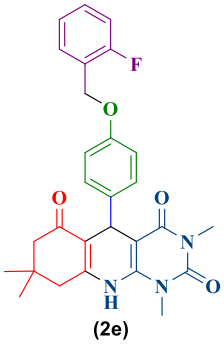
(2c)

[Time: 20 min, Yield: 95%]
mp: 290-294 °C



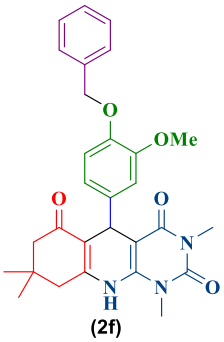
(2d)

[Time: 40 min, Yield: 84%]
mp: 257-260 °C



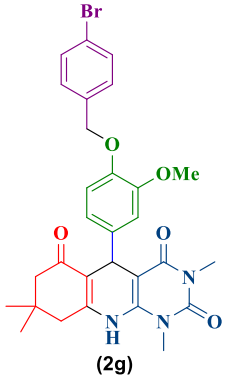
(2e)

[Time: 60 min, Yield: 93%]
mp: 299-303 °C



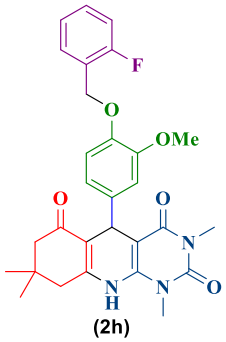
(2f)

[Time: 40 min, Yield: 45%]
mp: 255-259 °C



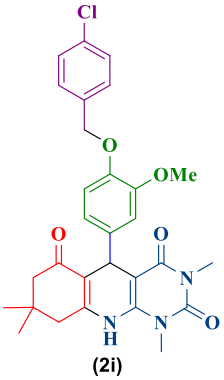
(2g)

[Time: 45 min, Yield: 81%]
mp: 217-220 °C



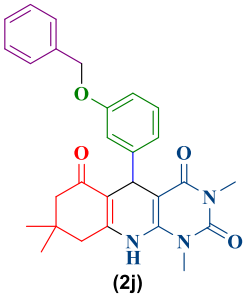
(2h)

[Time: 60 min, Yield: 90%]
mp: 264-266 °C



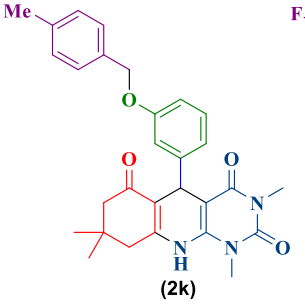
(2i)

[Time: 80 min, Yield: 65%]
mp: 239-242 °C



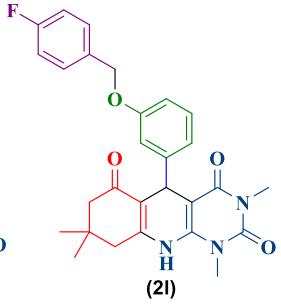
(2j)

[Time: 60 min, Yield: 78%]
mp: 296-298 °C



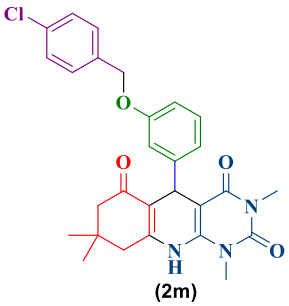
(2k)

[Time: 60 min, Yield: 90%]
mp: 293-296 °C



(2l)

[Time: 30 min, Yield: 92%]
mp: 304-306 °C



(2m)

[Time: 60 min, Yield: 95%]
mp: 297-300 °C

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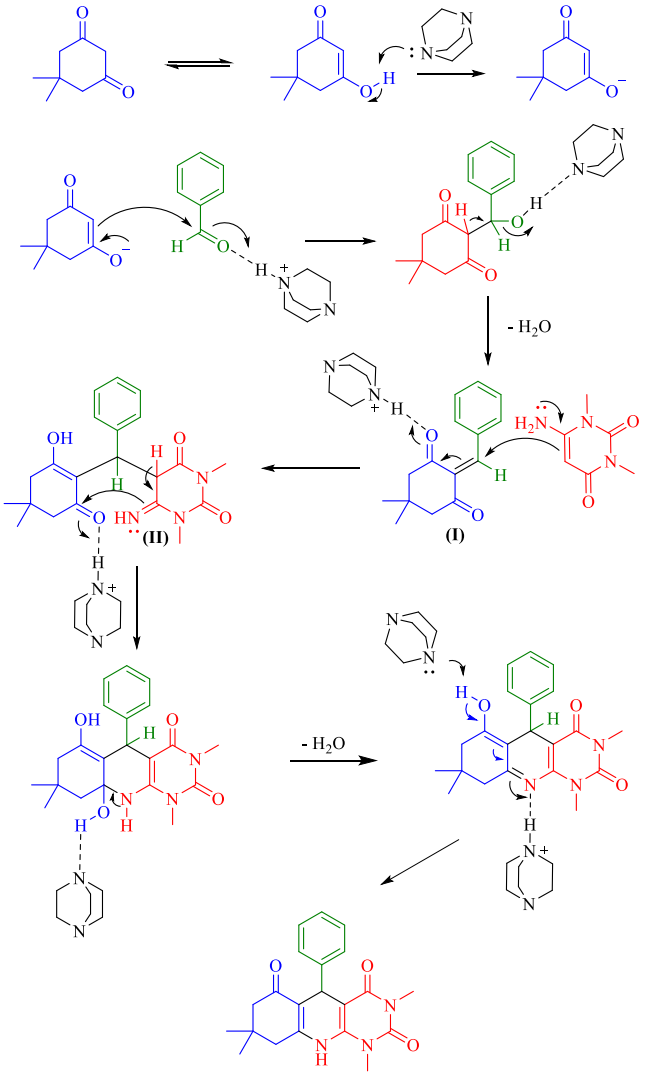
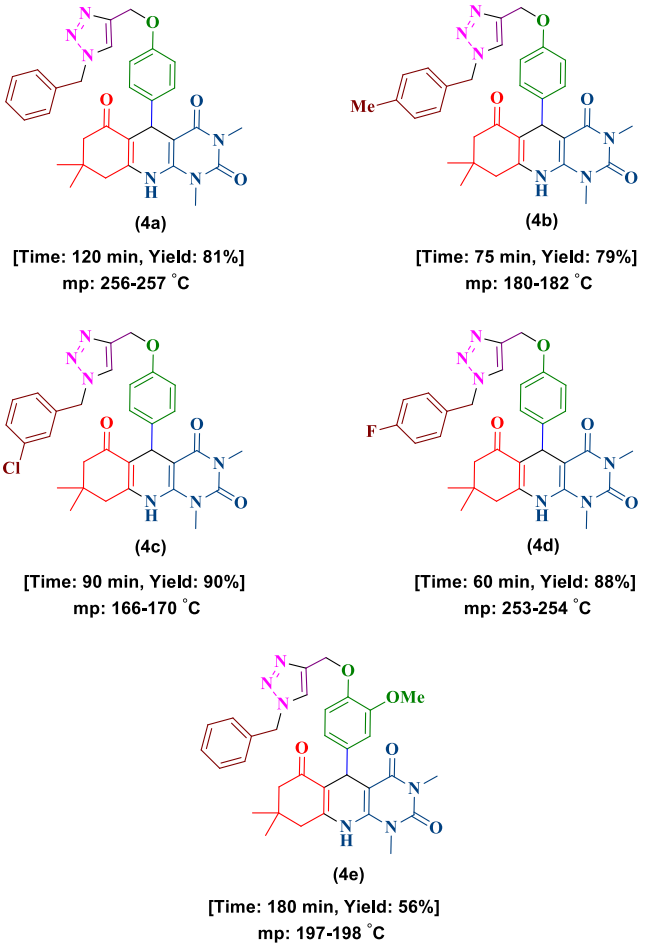
Scheme 4. Proposed Mechanism for the Preparation of Pyrimido[4,5-*b*]quinolines Catalyzed by DABCO



3. CONCLUSIONS

In conclusion, some new benzyloxy pyrimido[4,5-*b*]quinoline derivatives and 1,2,3- triazole-fused pyrimido[4,5-*b*]quinolines were synthesized by the one-pot multi-component reaction of various aryl aldehydes with dimedone and 6-amino-1,3-dimethyluracil using DABCO as a cheap and basic catalyst at 90 °C under the solvent-free condition.

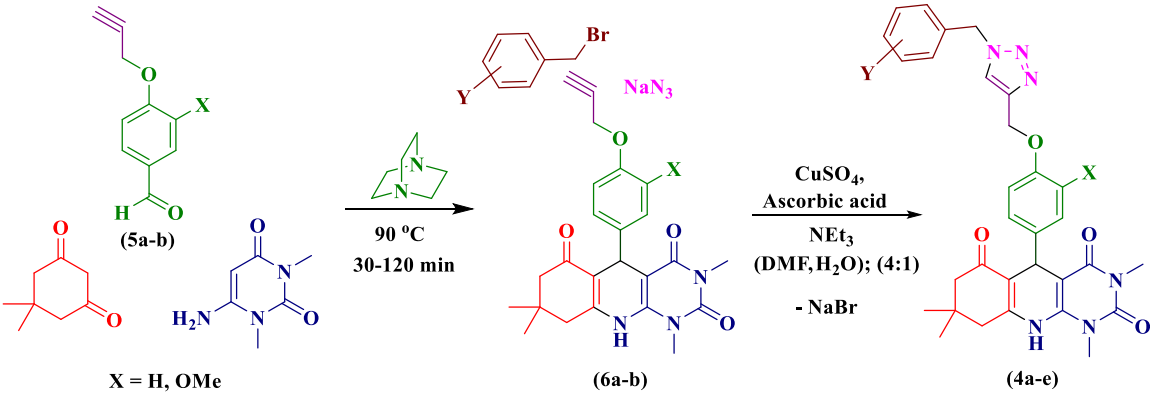
Scheme 6. Structure of 1,2,3-Triazole-Fused Pyrimido[4,5-*b*]quinoline Derivatives



4. EXPERIMENTAL SECTION

4.1. Procedure for the Preparation of Benzyloxy Benzaldehydes. In a round-bottomed flask which is connected to a reflux condenser, a mixture of various hydroxyl benzaldehyde (1 mmol), various benzyl halide (1.3 mmol), potassium carbonate (1.5 mmol), and DMF (4 mL) as a solvent was stirred at room temperature for 4−6 h. After the

Scheme 5. Preparation of 1,2,3-Triazole-Fused Pyrimido[4,5-*b*]quinolines



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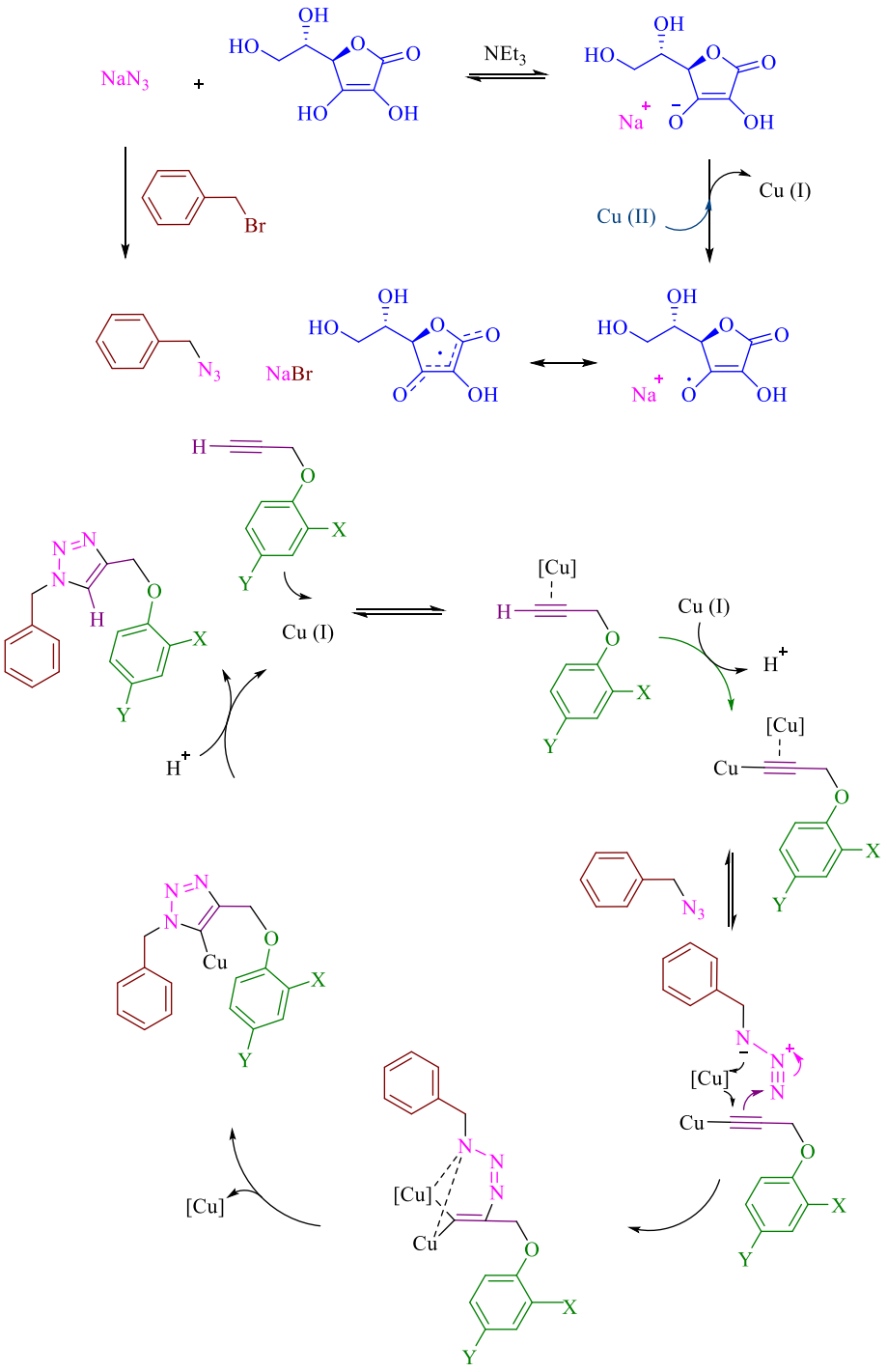
Scheme 7. Proposed Mechanism for the Click Synthesis of 1,2,3-Triazole-Fused Pyrimido[4,5-*b*]quinolines



completion of the reaction as considered by thin-layer chromatography (TLC) (solvent: ethyl acetate and n-hexane (2/8)), cold water (10 mL) was added to the reaction mixture to precipitate the product and then separated by simple filtration. Note: for the purification of aldehydes **1f** and **1j**, there is no precipitate by adding cold water and the products were extracted by ethyl acetate.

4.2. Procedure for the Preparation of Benzylic −1,2,3-Triazol-4-yl-methoxy Benzaldehydes. Hydroxybenzaldehyde derivative (1 mmol), propargyl bromide (1.2 mmol), potassium carbonate (1.5 mmol), and DMF (4 mL) as a solvent were added in a round-bottomed flask, which is connected to a reflux condenser, and stirred at room temperature. After the completion of the reaction as monitored by TLC (solvent/ethyl acetate/hexane 2:8), cold water (10 mL) was added to the reaction mixture to precipitate propargyloxy benzaldehyde derivative and separated by simple filtration. In the next step, sodium azide (3 mmol, 0.2 g), various benzyl halide (2.5 mmol), and DMF (4 mL) were added in a round-bottomed flask which is connected to a reflux condenser and stirred at room temperature for 1 h and then the prepared propargyloxy benzaldehyde derivative (1 mmol), $CuSO_4{\cdot}5H_2O$ (0.25 mmol), ascorbic acid (0.25 mmol), NEt_3 (0.2 mL), and water (1 mL) were added to the reaction

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mixture and stirred at room temperature for 24 h. After this time and completion of the reaction as monitored by TLC, cold water (50 mL), ammonia (25%) (1 mL), and ethyl acetate (50 mL) were added to the reaction mixture. Finally, the organic phase was decanted, dried by sodium sulfate, and ethyl acetate was removed to purify the expected aldehyde (**3a**−**e**).

4.3. Procedure for the Preparation of Pyrimido[4,5-*b*]quinolines. In a round-bottomed flask which is connected to a reflux condenser, a mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol, 0.14 g), 6-amino-1,3-dimethyluracil (1 mmol, 0.155 g), and DABCO (25 mol %) as a catalyst was added and stirred at 90 °C under solvent-free condition. After the completion of the reaction as monitored by TLC, the reaction mixture was washed with aqueous ethanol (ethanol/H_2O; 20:80%) (10 mL) to remove DABCO, and finally, the desired product was purified by washing with acetone. Note: compounds **2g** and **2i** were purified by washing with ethyl acetate.

4.4. Spectral Data of Compounds. *4.4.1. 5-(4-(Benzyloxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**2a**).* IR (KBr, cm^{-1}): 735, 1154, 1208, 1241, 1289, 1378, 1490, 1507, 1607, 1644, 1664, 1695, 2875, 2960, 3083, 3200; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.20 Hz, 1H), 2.58 (d, J = 8.30 Hz, 2H), 3.10 (s, 3H), 3.46 (s, 3H), 4.83 (s, 1H), 5.02 (s, 2H), 6.83 (d, J = 8.20, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.32−7.44 (m, 5H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 27.0, 28.1, 29.5, 30.6, 32.6, 33.3, 50.5, 69.5, 90.8, 112.3, 114.3, 128.1, 128.2, 128.8, 129.0, 137.7, 139.3, 144.1, 149.7, 151.0, 157.0, 161.1, 195.0; MS: m/z = 471.3.

*4.4.2. 5-(4-(Benzyloxy)phenyl)-1,3-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**2b**).* IR (KBr, cm^{-1}): 1013, 1171, 1198, 1240, 1380, 1506, 1636, 1661, 1701, 2948, 3083, 3222, 3287; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 1.78−1.84 (m, 1H), 1.93−2.00 (m, 1H), 2.23−2.28 (m, 2H), 2.56−2.62 (m, 1H), 2.75−7.79 (m, 1H), 3.11 (s, 3H), 3.46 (s, 3H), 4.88 (s, 1H), 5.03 (s, 2H), 6.82 (d, J = 8.70 Hz, 2H), 7.14 (d, J = 8.70 Hz, 2H), 7.45 (s, 5H), 9.08 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 21.2, 27.0, 28.1, 30.6, 33.0, 37.1, 68.7, 90.7, 113.3, 114.4, 128.9, 129.0, 129.8, 132.7, 136.8, 139.7, 151.0, 156.8, 161.2, 195.2; MS: m/z = 443.3.

*4.4.3. 1,3,8,8-Tetramethyl-5-(4-((4-methylbenzyl)oxy)-phenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2c**).* IR (KBr, cm^{-1}): 797, 1155, 1208, 1287, 1376, 1490, 1507, 1606, 1644, 1663, 1695, 2892, 2958, 3083, 3191; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.22 (d, J = 16.20 Hz, 1H), 2.30 (s, 3H), 2.57 (d, J = 9.00 Hz, 2H), 3.10 (s, 3H), 3.46 (s, 3H), 4.83 (s, 1H), 4.97 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.12−7.19 (m, 4H), 7.30 (d, J = 8.00 Hz, 2H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 21.2, 26.9, 28.1, 29.5, 30.6, 32.5, 33.3, 50.5, 69.4, 90.8, 112.3, 114.3, 128.1, 129.0, 129.4, 134.7, 137.4, 139.3, 144.1, 149.7, 151.0, 157.0, 161.1, 195.0; MS: m/z = 485.4.

*4.4.4. 5-(4-((4-Chlorobenzyl)oxy)phenyl)-1,3-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2d**).* IR (KBr, cm^{-1}): 759, 829, 947, 1013, 1046, 1172, 1199, 1224, 1355, 1379, 1505, 1661, 1700, 2948, 3070, 3221, 3288; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 1.81−1.86 (m, 1H), 1.94−2.00 (m, 1H), 2.23−2.28 (m, 2H), 2.59−2.64 (m, 1H), 2.74−7.83 (m, 1H), 3.11 (s, 3H), 3.46 (s, 3H), 4.89 (s, 1H), 5.00 (s, 2H), 6.82 (d, J = 8.7 Hz, 2H), 7.14−7.23 (m, 4H), 7.43−7.50 (m, 2H), 9.07 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 21.2, 26.9, 28.1, 30.6, 33.1, 37.1, 68.8, 90.8, 113.4, 114.4, 115.5, 115.8, 129.0, 130.3, 134.0, 139.6, 144.0, 151.0, 151.8, 156.9, 161.2, 195.3; MS: m/z = 477.4.

*4.4.5. 5-(4-((2-Fluorobenzyl)oxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2e**).* IR (KBr, cm^{-1}): 760, 1208, 1241, 1377, 1490, 1508, 1608, 1644, 1663, 1695, 2897, 2960, 3085, 3205; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.06 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.10 Hz, 1H), 2.58 (d, J = 6.00 Hz, 2H), 3.10 (s, 3H), 3.46 (s, 3H), 4.84 (s, 1H), 5.06 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 6.00 Hz, 2H), 7.21−7.28 (m, 2H), 7.39−7.46 (m, 1H), 7.53 (t, J = 6.80 Hz, 1.8 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.5, 30.6, 32.6, 33.3, 50.5, 63.8, 90.7, 112.3, 114.2, 115.7, 115.9, 124.5, 125.0, 129.1, 130.7, 131.1, 131.1, 139.6, 144.1, 149.7, 151.0, 156.8, 161.1, 195.0; MS: m/z = 489.3.

*4.4.6. 5-(4-(Benzyloxy)-3-methoxyphenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2f**).* IR (KBr, cm^{-1}): 740, 1033, 1140, 1207, 1235, 1267, 1377, 1511, 1605, 1643, 1661, 1695, 2899, 2959, 3077, 3187; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.95 (s, 3H), 1.06 (s, 3H), 2.07 (d, J = 16.1 Hz, 1H), 2.24 (d, J = 16.1 Hz, 1H), 2.59 (d, J = 10.0 Hz, 2H), 3.46 (s, 3H), 3.12 (s, 3H), 3.72 (s, 3H), 4.85 (s, 1H), 5.00 (s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.92−6.80 (m, 2H), 7.44−7.31 (m, 5H), 9.05 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.6, 30.6, 32.5, 33.6, 50.6, 55.9, 70.3, 90.7, 112.1, 112.7, 113.5, 119.8, 128.1, 128.2, 128.8, 137.8, 140.0, 144.3, 146.6, 148.8, 151.0, 161.2, 195.0; MS: m/z = 501.4.

*4.4.7. 5-(4-((4-Bromobenzyl)oxy)-3-methoxyphenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-Trione (**2g**).* IR (KBr, cm^{-1}): 701, 804, 1035, 1140, 1208, 1230, 1372, 1509, 1616, 1645, 1665, 1698, 2902, 2958, 3082, 3197; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.94 (s, 3H), 1.06 (s, 3H), 2.07 (d, J = 16.20 Hz, 1H), 2.24 (d, J = 16.20 Hz, 1H), 2.58 (d, J = 8.1 Hz, 2H), 3.11 (s, 3H), 3.45 (s, 3H), 3.71 (s, 3H), 4.84 (s, 1H), 4.99 (s, 2H), 6.68 (d, J = 8.30 Hz, 1H), 6.82 (d, J = 8.30 Hz, 1H), 6.87 (d, J = 2.00 Hz, 1H), 7.37 (d, J = 8.40 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 9.02 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.8, 28.1, 29.6, 30.6, 32.5, 33.6, 50.5, 55.9, 69.5, 90.7, 112.1, 112.7, 113.6, 119.8, 121.3, 130.2, 131.7, 137.3, 140.1, 144.1, 146.3, 148.8, 150.0, 151.0, 161.2, 195.2; MS: m/z = 580.4.

*4.4.8. 5-(4-((2-Fluorobenzyl)oxy)-3-methoxyphenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione (**2h**).* IR (KBr, cm^{-1}): 767, 1033, 1148, 1208, 1235, 1270, 1377, 1508, 1607, 1643, 1661, 1694, 2898, 2958, 3084, 3195; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.95 (s, 3H), 1.07 (s, 3H), 2.08 (d, J = 16.2 Hz, 2H), 2.25 (d, J = 16.60 Hz, 2H), 3.12 (s, 3H), 3.46 (s, 3H), 3.70 (s, 3H), 4.85 (s, 1H), 5.04 (s, 2H), 6.69−6.72 (m, 1H), 6.88−6.91 (m, 2H), 7.22−7.28 (m, 2H), 7.41−7.44 (m, 1H), 7.51−7.55 (m, 1H), 9.02 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9.28.1, 29.6, 30.6, 32.5, 33.6, 50.5, 55.8, 64.5, 90.7, 112.1, 112.7, 113.4, 115.6, 115.9, 119.9, 124.4, 125.0, 130.7, 130.8, 131.2, 140.3, 144.1, 146.4, 148.8, 151.0, 161.2, 195.1; MS: m/z = 519.4.

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*4.4.9. 5-(4-((4-Chlorobenzyl)oxy)-3-methoxyphenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione (**2i**).* IR (KBr, cm^{-1}): 751, 809, 1035, 1140, 1209, 1245, 1378, 1418, 1508, 1609, 1645, 1664, 1697, 2958, 3086, 3195, 3274; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.94 (s, 1H), 1.06 (s, 1H), 2.07 (d, J = 18.0 Hz, 1H), 2.24 (d, J = 18.0 Hz, 1H), 2.58 (d, J = 6.8 Hz, 2H), 3.11 (s, 3H), 3.45 (s, 3H), 3.71 (s, 3H), 4.84 (s, 1H), 5.00 (s, 2H), 6.68 (d, J = 7.70 Hz, 1H), 6.82 (d, J = 8.30 Hz, 1H), 6.87 (s, 1H), 7.43−7.44 (m, 4H), 9.03 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.6, 30.6, 32.5, 33.6, 50.5, 55.9, 69.6, 90.7, 112.2, 112.8, 113.7, 119.8, 128.8, 129.8, 132.7, 136.9, 140.2, 144.1, 146.4, 148.8, 149.9, 151.0, 161.2, 195.0; MS: m/z = 535.5.

*4.4.10. 5-(3-(Benzyloxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2j**).* IR (KBr, cm^{-1}): 732, 1039, 1208, 1256, 1380, 1497, 1592, 1613, 1638, 1664, 1697, 2892, 2951, 3060, 3096, 3235, 3289; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.92 (s, 3H), 1.05 (s, 3H), 2.06 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.20 Hz, 1H), 2.58 (d, J = 8.50 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.87 (s, 1H), 5.02 (s, 2H), 6.75−6.85 (m, 3H), 7.11 (t, J = 7.80 Hz, 1H), 7.33−7.44 (m, 5H), 9.02 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 27.0, 28.1, 29.4, 30.6, 32.6, 34.1, 50.5, 69.5, 90.4, 112.0, 112.1, 115.0, 120.7, 128.1, 128.2, 128.8, 129.1, 137.6, 144.2, 148.3, 150.0, 151.0, 158.4, 161.1, 195.0; MS: m/z = 471.1.

*4.4.11. 1,3,8,8-Tetramethyl-5-(3-((4-methylbenzyl)oxy)-phenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2k**).* IR (KBr, cm^{-1}): 489, 802, 1042, 1152, 1208, 1260, 1377, 1508, 1608, 1645, 1697, 2872, 2899, 2958, 3086, 3195, 3268; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 2.05 (d, J = 15.00 Hz, 1H), 1.05 (s, 3H), 2.22 (d, J = 15.00 Hz, 1H), 2.32 (s, 3H), 2.57 (d, J = 15.00 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.86 (s, 1H), 4.96 (s, 2H), 6.72−6.84 (m, 3H), 7.10 (t, J = 7.80 Hz, 1H), 7.19 (d, J = 7.90 Hz, 2H), 7.31 (d, J = 8.00 Hz, 2H), 9.06 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 21.2, 26.9, 28.1, 29.4, 30.6, 32.5, 34.1, 44.8, 50.5, 69.3, 90.4, 112.0, 112.2, 115.0, 120.6, 128.2, 129.1, 129.4, 134.5, 137.4, 144.3, 148.2, 150.1, 151.0, 158.5, 161.1, 195.0; MS: m/z = 485.4.

*4.4.12. 5-(3-((4-Fluorobenzyl)oxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2l**).* IR (KBr, cm^{-1}): 810, 1047, 1151, 1208, 1258, 1376, 1490, 1645, 1664, 1696, 2874, 2895, 2961, 3086, 3198, 3268; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.90 (s, 3H), 1.05 (s, 3H), 2.03 (d, J = 15.00 Hz, 1H), 2.22 (d, J = 15.00 Hz, 1H), 2.56 (d, J = 6.00 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.87 (s, 1H), 5.02 (s, 2H), 6.73−6.85 (m, 3H), 7.11 (t, J = 7.80 Hz, 1H), 7.46 (s, 4H), 9.05 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.4, 30.6, 32.5, 34.1, 45.4, 50.5, 68.6, 90.4, 111.9, 112.2, 115.0, 120.8, 128.8, 129.1, 129.9, 132.8, 136.7, 144.4, 148.3, 150.3, 151.0, 158.2, 161.2, 195.1; MS: m/z = 489.3.

*4.4.13. 5-(3-((4-Chlorobenzyl)oxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**2m**).* IR (KBr, cm^{-1}): 1153, 1208, 1222, 1288, 1377, 1490, 1509, 1610, 1664, 1697, 2898, 2959, 3078, 3192; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 15.00 Hz, 1H), 2.22 (d, J = 15.00 Hz, 1H), 2.57 (d, J = 9.00 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.87 (s, 1H), 5.00 (s, 2H), 6.74−6.85 (m, 3H), 7.12 (t, J = 7.80 Hz, 1H), 7.19−7.25 (m, 2H), 7.46−7.51 (m, 2H), 9.03 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.4, 30.6, 32.6, 34.1, 44.5, 50.5, 68.7, 90.4, 112.1, 115.0, 115.5, 115.8, 120.8, 129.1, 130.3, 130.4, 133.8, 144.2, 148.3, 150.1, 151.0, 158.3, 161.1, 195.0; MS: m/z = 505.3.

*4.4.14. 5-(4-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)-phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido-[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**4a**).* IR (KBr, cm^{-1}): 1173, 1210, 1240, 1354, 1378, 1504, 1608, 1642, 1662, 1696, 2072, 2961, 3202, 3268; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 9.00 (s, 1H), 8.27 (s, 1H), 7.40−7.32 (m, 5H), 7.13 (m, 2H), 6.84 (d, J = 8.60 Hz, 2H), 5.61 (s, 2H), 5.05 (s, 2H), 4.83 (s, 1H), 3.45 (s, 3H), 3.10 (s, 3H), 2.56 (d, J = 7.30 Hz, 2H), 2.22 (d, J = 16.10 Hz, 1H), 2.04 (d, J = 16.10 Hz, 1H), 1.05 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (76 MHz, DMSO) δ_{ppm}: 28.1, 28.5, 30.3, 32.3, 39.0, 39.3, 39.6, 39.8, 40.1, 40.4, 40.7, 47.7, 53.3, 61.4, 86.2, 108.2, 113.8, 122.8, 125.1, 128.4, 128.6, 129.2, 129.2, 131.3, 136.4, 143.6, 151.2, 152.2, 157.5, 167.2, 196.1; MS: m/z = 552.1.

*4.4.15. 1,3,8,8-Tetramethyl-5-(4-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**4b**).* IR (KBr, cm^{-1}): 549, 754, 827, 1049, 1107, 1245, 1282, 1363, 1409, 1513, 1546, 1612, 1672, 1719, 2869, 2957, 3086, 3136; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.90 (s, 3H). 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.20 Hz, 1H), 2.29 (s, 3H), 2.58 (d, J = 8.4 0 Hz, 2H), 3.10 (s, 3H), 3.46 (s, 3H), 4.84 (s, 1H), 5.04 (s, 2H), 5.55 (s, 2H), 6.84 (d, J = 8.30 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.21 (m, 4H), 8.22 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 21.1, 26.9, 28.1, 29.5, 30.6, 32.6, 33.3, 50.5, 53.1, 61.4, 90.8, 112.3, 114.3, 124.8, 128.5, 129.1, 129.8, 133.7, 137.9, 139.4, 143.6, 144.1, 149.8, 151.0, 156.8, 161.1, 195.0; MS: m/z = 566.4.

*4.4.16. 5-(4-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)-methoxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**4c**).* IR (KBr, cm^{-1}): 751, 961, 1050, 1210, 1289, 1378, 1506, 1609, 1643, 1663, 1697, 2872, 2958, 3211; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.20 Hz, 1H), 2.58 (d, J = 8.60 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.84 (s, 1H), 5.07 (s, 2H), 5.64 (s, 2H), 6.85 (d, J = 8.70 Hz, 2H), 7.14 (d, J = 8.70 Hz, 2H), 7.28 (m, 1H), 7.39−7.45 (m, 3H), 8.31 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.5, 30.6, 32.5, 33.3, 50.5, 52.5, 61.4, 90.7, 112.3, 114.2, 125.1, 127.1, 128.3, 128.6, 129.0, 131.2, 133.7, 138.8, 139.5, 143.7, 144.1, 149.7, 151.0, 156.7, 161.1, 195.0; MS: m/z = 588.3.

*4.4.17. 5-(4-((1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)-methoxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**4d**).* IR (KBr, cm^{-1}): 787, 843, 1050, 1147, 1210, 1289, 1379, 1508, 1638, 1659, 1699, 2958, 3083, 3225, 3291; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.23 (d, J = 16.10 Hz, 1H), 2.58 (d, J = 6.00 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 4.84 (s, 1H), 5.06 (s, 2H), 5.60 (s, 2H), 6.85 (d, J = 8.50 Hz, 2H), 7.14 (d, J = 8.30 Hz, 2H), 7.17−7.26 (m, 2H), 7.41 (m, 2H), 8.27 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.5, 30.6, 32.5, 33.3, 52.5, 61.4, 90.7, 112.3, 114.2, 115.9, 116.2, 124.9, 129.0, 130.7, 130.8, 132.7, 132.8, 139.5, 143.7, 144.1, 149.7, 151.0, 156.7, 161.1, 195.0; MS: m/z = 570.1.

4.4.18. 5-(4-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1,3,8,8-tetramethyl-5,8,9,10-

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*tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (**4e**)*. IR (KBr, cm^{-1}): 756, 1033, 1052, 1105, 1145, 1220, 1252, 1359, 1412, 1458, 1514, 1554, 1677, 1705, 1725, 2875, 2961, 3146; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.94 (s, 3H), 1.06 (s, 3H), 2.08 (d, J = 16.00 Hz, 1H), 2.24 (d, J = 16.20 Hz, 1H), 2.59 (d, J = 8.60 Hz, 2H), 3.12 (s, 3H), 3.46 (s, 3H), 3.67 (s, 3H), 4.84 (s, 1H), 5.03 (s, 2H), 5.61 (s, 2H), 6.69 (d, J = 8.30, 1H), 6.86 (s, 1H), 6.93 (d, J = 8.30 Hz, 1H), 7.29−7.43 (m, 5H), 8.25 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28.1, 29.6, 30.6, 32.5, 33.5, 50.5, 53.2, 55.76, 61.1, 90.7, 112.1, 112.5, 113.5, 119.7, 125.1, 128.4, 128.6, 129.2, 136.5, 140.1, 144.1, 146.2, 148.75, 150.0, 151.0, 161.2, 195.1; MS: m/z = 582.1.

*4.4.19. 1,3,8,8-Tetramethyl-5-(4-(prop-2-yn-1-yloxy)-phenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-(1H,3H,7H)-trione (**6a**)*. IR (KBr, cm^{-1}): 696, 845, 1029, 1209, 1225, 1378, 1491, 1506, 1603, 1644, 1663, 1698, 2124, 2875, 2902, 2968, 3086, 3212, 3267; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.91 (s, 3H), 1.05 (s, 3H), 2.05 (d, J = 16.10 Hz, 1H), 2.22 (d, J = 16.20 Hz, 1H), 2.58 (d, J = 9.70 Hz, 2H), 3.11 (s, 3H), 3.46 (s, 3H), 3.54 (t, J = 2.40 Hz, 1H), 4.72 (d, J = 2.50 Hz, 2H), 4.84 (s, 1H), 6.80 (d, J = 8.70 Hz, 2H), 7.15 (d, J = 8.80 Hz, 2H), 9.00 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 27.0, 28.1, 29.5, 30.6, 32.6, 33.4, 50.5, 55.6, 78.5, 80.0, 90.7, 12.2, 114.4, 129.0, 139.9, 144.2, 151.0, 155.8, 161.1, 195.0; MS: m/z = 419.3.

*4.4.20. 5-(3-Methoxy-4-(prop-2-yn-1-yloxy)phenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione (**6b**)*. IR (KBr, cm^{-1}): 1266, 1209, 1379, 1505, 1639, 1662, 1699, 2124, 2875, 2958, 3100, 3231, 3294, 3312; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 0.95 (s, 3H), 1.06 (s, 3H), 2.08 (d, J = 16.20 Hz, 1H), 2.24 (d, J = 16.20 Hz, 1H), 2.59 (d, J = 10.10 Hz, 2H), 3.12 (s, 3H), 3.46 (s, 3H), 3.52 (t, J = 2.30 Hz, 1H), 3.70 (s, 3H), 4.69 (d, J = 2.40, 2H), 4.85 (s, 1H), 6.70 (d, J = 8.30, 1H), 6.83−6.88 (m, 2H), 9.01 (s, 1H); ^{13}C NMR (76 MHz, DMSO-d_6) δ_{ppm}: 26.9, 28., 29.61, 30.6, 32.5, 33.6, 50.5, 55.8, 56.4, 78.5, 80.0, 90.7, 112.1, 112.6, 114.1, 119.6, 120.1, 140.7, 144.1, 145.2, 148.9, 150.1, 151.0, 161.2, 195.1; MS: m/z = 449.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05896.

Spectral data of all compounds and copies of FT-IR, NMR, and mass spectra (PDF)

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Notes

The authors declare no competing financial interest.

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