

RESEARCH ARTICLE

Efficient and environmentally benign synthetic protocol for the synthesis of structurally diverse annulated pyridopyrimidines

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Structurally diverse annulated pyridopyrimidines have been synthesized by an efficient and environmentally benign synthetic protocol involving catalyzed four-component reaction of 2-aminobenzothiazoles with thiophene-2-carbaldehyde and carbonyl compounds in ethanol. Mild reaction conditions, operational simplicity, and structural diversity with excellent yields are some special attractions of the present protocol.

Keywords: 2-aminobenzothiazoles; *p*-TSA; multicomponent reaction; pyridopyrimidines; pyrimidoquinolines

1. Introduction

Multicomponent reactions (MCRs) have emerged as one of the most powerful techniques with robust efficiency to assemble structurally diverse medicinally privileged heterocyclic scaffolds in a single molecule for the synthesis of bioactive compounds with structural skeleton of natural products and combinatorial libraries of drug-like molecules (1–4). Environmental and economically positive implications, the inherent convergence, and high productive nature of MCRs along with their exploratory and molecular complexity and diversity generating power make them very attractive to access complex structures in a single procedural step from simple building blocks with promising pharmaceutical and biological activities (5–8).

Pyridopyrimidines have been described as potent inhibitors of tyrosine kinase (9), dihydrofolate reductase (10), adenosine kinase (11) and also specific inhibitors of cyclin-dependent kinase (12) and cholecystokinin receptor subtype-1 (CCK1R) (13). Pyridopyrimidines (14–16) are the bioisosters of purine bases and associated with diverse immunopharmacological activities such as analgesic (17), anti-inflammatory (18), antiallergic (19), antiplatelet aggregatory (20), antihistaminic (21), and antitumor (22). Moreover, pyridopyrimidine analogs constitute a novel class of active drugs, e.g., PDGF, EGFR, DMFR, P38 MAP kinase (23), P13 kinase (24), and proapoptotic agents (25) (Figure 1).

The heterocyclic compounds incorporating pyrimidoquinoline scaffold have also been reported to show a wide range of pharmacological activities such as antimicrobial, antifungal, anticancer, antiviral, analgesic, anti-inflammatory, etc. (26). Pyrimidoquinolines, such as 5-deazaflavins {pyrimido[4,5-*b*]quinoline-2,4 (3*H*,10*H*)-diones} and 2-deoxy-2-phenyl-5-deazaflavins {2-phenylpyrimido [4,5-*b*]quinolin-4(10*H*)-ones}, exhibit anti-HIV and antitumor activities (27, 28) as these are selective inhibitors of protein kinase C (PKC) which inhibit growth of cancer cell lines such as A 431 cells and HT 1080 cells (29).

In the present research work, in view of biological importance of pyridopyrimidine scaffold and our continuing interest in the synthesis of therapeutically interesting fused heterocycles incorporating privileged heterocyclic systems (30–32), we have combined the potentials of MCRs with ecocompatibility to present synthetic protocol for the synthesis of drug-like small heterocyclic molecules of structural diversity with promising biological activities. The present synthetic protocol involves multicomponent domino reaction of 2-aminobenzothiazoles, thiophene-2-carbaldehyde, and carbonyl compounds in ethanol under organocatalysis of environmentally benign, economically viable, recyclable, and reusable solid acid catalyst *p*-toluenesulphonic acid (*p*-TSA).

2. Results and discussion

In the present work, chromenopyridopyrimidines, pyranopyridopyrimidines, indenopyridopyrimidines,

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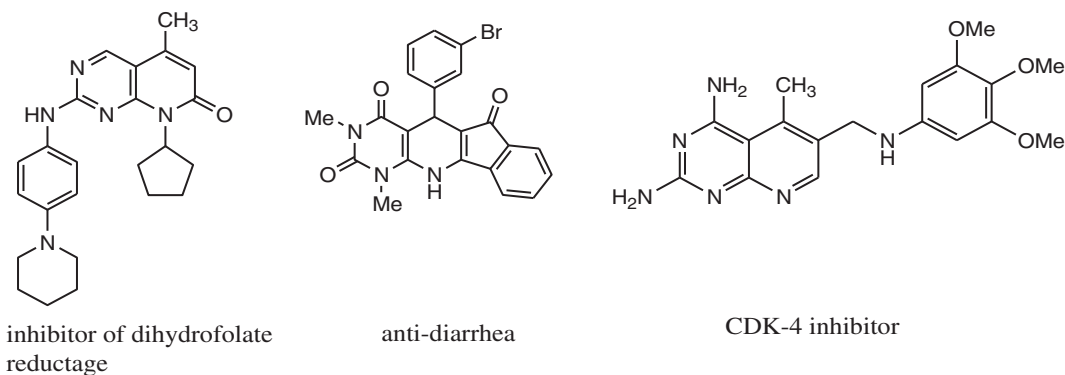


Figure 1. Some drugs with pyridopyrimidine framework.

pyrimidoquinolines, and benzo[*h*]pyrimidoquinolines have been synthesized by an efficient and environmentally benign synthetic protocol involving *p*-TSA catalyzed four-component domino reaction of 2-aminobenzothiazoles with thiophene-2-carbaldehyde and carbonyl compounds. Initially, we selected four-component domino reaction of 2-aminobenzothiazole with thiophene-2-carbaldehyde, 4-hydroxy-6-methylpyran-2-one, and 1,3-dimethylbarbituric acid as a simple model reaction to establish the feasibility of the synthetic strategy and to optimize the reaction conditions (Scheme 1) (Table 1).

The model reaction was also performed using water as a solvent with catalytic amount of sulfamic acid/*p*-TSA, but the yield of the product was not satisfactory (Table 1, Entry 1 and 2). The model reaction was also performed in ethanol as solvent without using any catalyst. It was observed that product yield was not good and the reaction required longer time in completion. Then triethyl amine was also screened for this model reaction using ethanol as solvent. However, the yield of product was not satisfactory and required comparatively more time for completion (Table 1, Entry 4). The reaction was carried out in the presence of sulphamic acid-ethanol and a comparatively better yield of the product was obtained (Table 1, Entry 5). But it was observed that when the model reaction was performed in the presence of *p*-TSA as a catalyst using ethanol as a

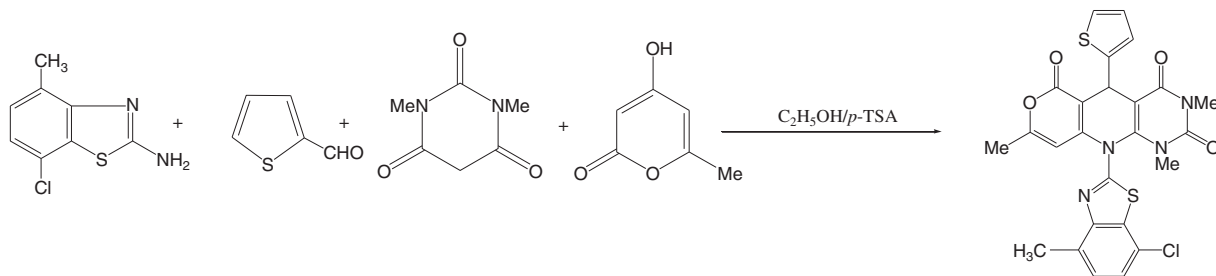
solvent, the product yield was excellent with shorter reaction time (Table 1, Entry 6). Therefore, on the basis of evaluation of reaction conditions, in view of solvent and time, the best results were obtained when the reaction was performed using ethanol as solvent and *p*-TSA as a catalyst.

In continuation of our efforts, the recyclability of *p*-TSA was also examined. It was found that, the catalytic activity of *p*-TSA decrease with subsequent reusability runs and could be reused four times without the noticeable loss of activity (Figure 2).

The present synthetic strategy was extended for the preparation of pyranopyridopyrimidines, chromenopyridopyrimidines, indenopyridopyrimidines, pyrimidoquinolines, benzo[*h*]pyrimidoquinolines, and the products were obtained in excellent yields with high purity.

The schematic presentation of six series of structurally diverse heterocycles with fused heterosystems is presented in Scheme 2. The reaction mechanism is presented in Scheme 3.

In the proposed mechanism, it can be seen that there are two possible pathways for the synthesis of final product. The intermediate can react with 2-aminobenzothiazole to form the final product (path A), or this intermediate can undergo intramolecular dehydrative cyclization and then reacts subsequently with 2-aminobenzothiazole to produce final product (path B).



Scheme 1. Model reaction.

Table 1. Influence of solvents and catalysts for the synthesis of heterocyclic compounds.

Entry	Solvent	Conditions	Catalyst	Time	Yield ^a (%)
1	H ₂ O	reflux	sulfamic acid	1.5 hrs	65
2	H ₂ O	reflux	<i>p</i> -toluenesulfonic acid	50 min	68
3	C ₂ H ₅ OH	reflux	without catalyst	>10 hrs	45
4	C ₂ H ₅ OH	reflux	triethyl amine	4 hrs	<65
5	C ₂ H ₅ OH	reflux	sulfamic acid	50 min	86
6	C ₂ H ₅ OH	reflux	<i>p</i> -toluenesulfonic acid	15 min	92

Note: Reaction conditions: 2-aminobenzothiazole (1.0 mmol), thiophene-2-carbaldehyde (1.0 mmol), 1,3-dimethylbarbituric acid (1.0 mmol), pyrone (1.0 mmol), ethanol/water (5 mL) with 0.1 mmol catalyst, stirred and refluxed.

^aIsolated yield of the pure compound.

3. Conclusion

In conclusion, we have presented an efficient and convenient environmentally benign synthetic protocol to synthesize structurally diverse heterocyclic compounds incorporating medicinally privileged heterocyclic systems. The present synthetic method offers several advantages such as environmentally benign nature of the procedure, excellent yields, shorter reaction time, simpler work-up, and use of recoverable and recyclable, nontoxic, inexpensive, and easily available catalyst. The present synthetic strategy will be useful in therapeutical and medicinal fields not only from an academic point of view but from an industrial viewpoint also.

4. Experimental section

4.1. Materials and methods

The melting points of all the synthesized compounds were determined by an electric melting point apparatus and are uncorrected. Thiophene-2-carbaldehyde and carbonyl compounds used in the synthesis of complex heterocycles were purchased from commercial sources and were used as such. 2-Aminobenzothiazoles were prepared according to the method reported. The purity of all the synthesized compounds was checked by thin layer chromatography (TLC).

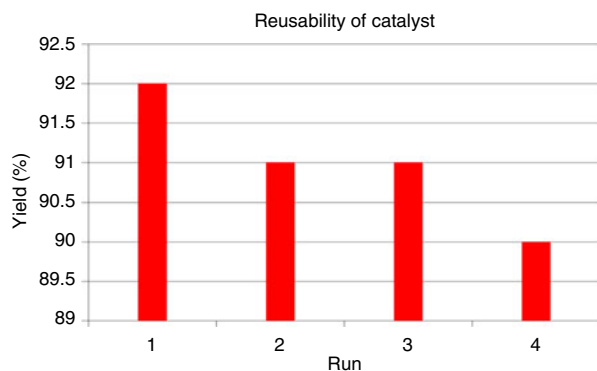


Figure 2. Reusability of catalyst.

Infrared (IR) spectra were recorded on Shimadzu 8400S FTIR spectrometer. ¹H NMR and ¹³C NMR were recorded on Bruker NMR spectrometer at 300 and 75 MHz, respectively. Analytical and spectral data of the synthesized heterocycles are also included.

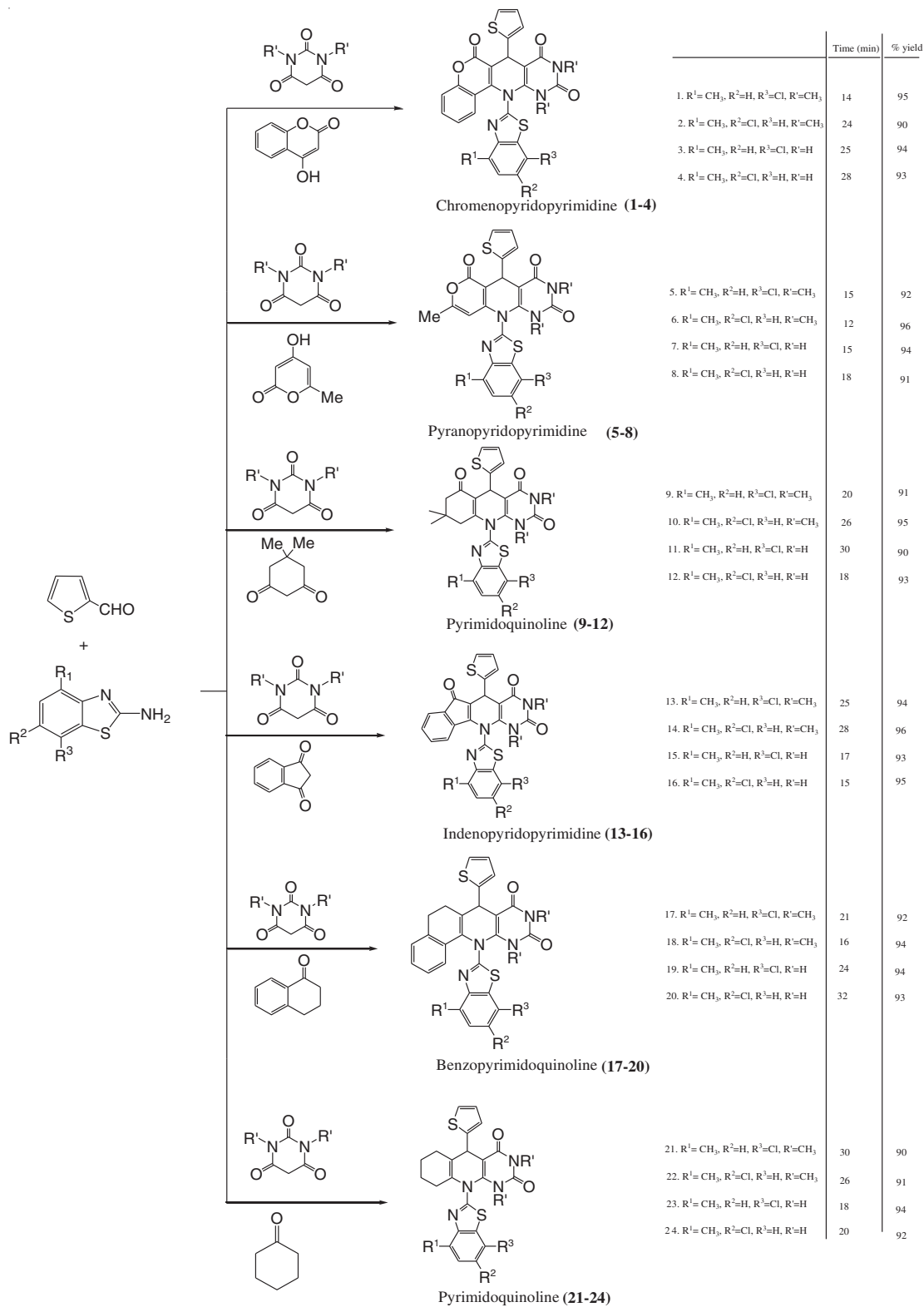
4.2. General procedure

A mixture of thiophene-2-carbaldehyde (1 mmol), carbonyl compound (1 mmol each), 2-aminobenzothiazole (1 mmol), and *p*-TSA (0.1 mmol) in ethanol (5 ml) was stirred magnetically at 80°C for 12–32 min. The progress of the reaction was monitored by TLC and by the change in the color of reaction mixture. After completion of the reaction, the reaction mixture was cooled to room temperature, and the precipitate formed was isolated by filtration. The precipitate was washed well with water. The *p*-TSA remaining in water was recovered from the filtrate by evaporation of water. Solid product then dried and finally recrystallized from ethanol to obtain pure product.

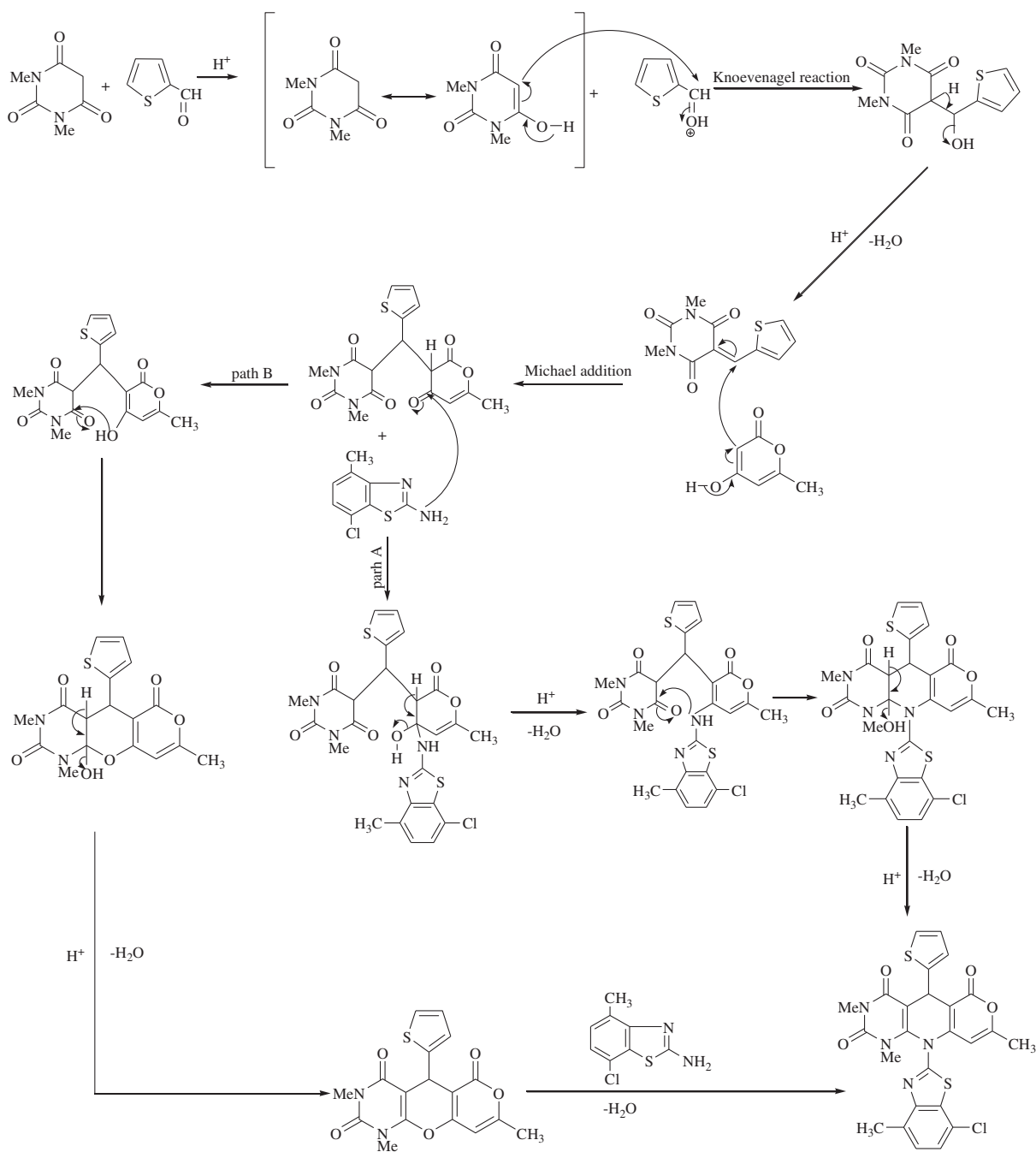
4.3. Compound names and spectral details

1) **1,3-dimethyl-12-(7-chloro-4-methyl benzothiazol-2-yl)-5-(2-thienyl)-5H-chromeno[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 205–207°C, IR(KBr) cm⁻¹: 1705, 1630–1670, 3010–3040. ¹H NMR (300 MHz, CDCl₃, DMSO-d₆) δ(ppm): 2.40 (3H, s, CH₃), 3.09 (3H, s, CH₃), 3.45 (3H, s, CH₃), 4.74(1H, s), 7.68–7.90 (9H, m, H-Ar). ¹³C NMR(DMSO-d₆) δ(ppm): 18.2, 35.2, 40.3, 40.8, 78.8, 96.4, 121.3, 122.9, 123.6, 125.1, 125.3, 126.2, 126.5, 126.8, 127.8, 128.1, 128.5, 139.5, 146.5, 150.1, 150.4, 150.8, 152.6, 156.8, 158.5, 172.6, 180.2. Anal. calcd. (%) for C₂₈H₁₉ClN₄O₄S₂ (574.05): C(58.48), H(3.33), N(9.74); found: C(58.32), H(3.16), N(9.58).

2) **1,3-dimethyl-12-(6-chloro-4-methyl benzothiazol-2-yl)-5-(2-thienyl)-5H-chromeno[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 210–212°C, IR(KBr) cm⁻¹: 1705, 1630–1670, 3010–3040. ¹H NMR (300 MHz,



Scheme 2. Synthesized compounds.



Scheme 3. Plausible mechanism.

CDCl₃, DMSO-d₆) δ (ppm): 2.40 (3H, s, CH₃), 3.09 (3H, s, CH₃), 3.45 (3H, s, CH₃), 4.74(1H, s), 7.68–7.90 (9H, m, H-Ar). ¹³C NMR(DMSO-d₆) δ (ppm): 18.2, 35.2, 40.3, 40.8, 78.8, 96.4, 121.3, 122.9, 123.6, 125.1, 125.3, 126.2, 126.5, 126.8, 127.8, 128.1, 128.5, 139.5, 146.5, 150.1, 150.4, 150.8, 152.6, 156.8, 158.5, 172.6, 180.2. Anal. calcd. (%) for C₂₈H₁₉ClN₄O₄S₂ (574.05): C(58.48), H(3.33), N(9.74); found: C(58.45), H(3.21), N(9.57).

3) **12-(7-chloro-4-methyl benzothiazo-2-yl)-5-(2-thienyl)-5H-chromeno[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 222–224°C, IR (KBr) cm⁻¹: 1705, 1632–1672, 3010–3050, 3290–3300. ¹H NMR (300 MHz, CDCl₃, DMSO-d₆) δ (ppm): 2.46(s, 3H), 4.76 (s, 1H), 7.27–7.44(9H, m, H-Ar), 9.45(s, 1H, NH), 10.46(s, 1H, NH), ¹³C NMR(DMSO-d₆) δ (ppm): 18.6, 35.6, 78.9, 97.2, 121.3, 122.9, 123.4, 125.2, 125.3, 126.2, 126.5, 126.9, 127.8, 128.2, 128.5,

140.5, 145.5, 150.1, 150.1, 150.7, 152.6, 155.8, 158.5, 174.2, 180.2. Anal. calcd. (%) for $C_{26}H_{15}ClN_4O_4S_2$ (546.02): C(57.09), H(2.76), N(10.24); found: C(56.92), H(2.54), N(10.05).

4) **12-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-chromeno[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 228–230°C, IR (KBr) cm^{-1} : 1705, 1632–1672, 3010–3050, 3290–3300. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.46(s, 3H, CH_3), 4.76 (s, 1H), 7.27–7.44 (9H, m, H–Ar), 9.45(s, 1H, NH), 10.46(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 18.6, 35.6, 78.9, 97.2, 121.3, 122.9, 123.4, 125.2, 125.3, 126.2, 126.5, 126.9, 127.8, 128.2, 128.5, 140.5, 145.5, 150.1, 150.1, 150.7, 152.6, 155.8, 158.5, 174.2, 180.2. Anal. calcd. (%) for $C_{26}H_{15}ClN_4O_4S_2$ (546.02): C(57.09), H(2.76), N(10.24); found: C(56.91), H(2.58), N(10.11).

5) **1,3,8-trimethyl-10-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-pyrano[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 215–217°C, IR(KBr) cm^{-1} : 1700, 1635–1672, 3010–3045. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.41(3H, s, CH_3), 2.64 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.45 (3H, s, CH_3), 4.69 (s,1H), 6.85–7.55 (6H, m, H–Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 17.9, 21.6, 35.1, 40.2, 40.6, 78.5, 100.5, 101.6, 122.3, 123.7, 124.9, 125.3, 125.8, 126.4, 128.1, 129.4, 138.7, 145.3, 148.9, 150.3, 153.6, 156.8, 158.3, 173.5, 180.9. Anal. calcd. (%) for $C_{25}H_{19}ClN_4O_4S_2$ (538.05): C(55.71), H(3.55), N(10.39); found: C(55.59), H(3.41), N(10.22).

6) **1,3,8-trimethyl-10-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-pyrano[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 214–216°C, IR(KBr) cm^{-1} : 1700, 1635–1672, 3010–3045. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.40 (3H, s, CH_3), 2.64 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.45 (3H, s, CH_3), 4.69 (s,1H), 6.85–7.55 (6H, m, H–Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 17.9, 21.6, 35.1, 40.2, 40.6, 78.5, 100.5, 101.6, 122.3, 123.7, 124.9, 125.3, 125.8, 126.4, 128.1, 129.4, 138.7, 145.3, 148.9, 150.3, 153.6, 156.8, 158.3, 173.5, 180.9. Anal. calcd. (%) for $C_{25}H_{19}ClN_4O_4S_2$ (538.05): C(55.71), H(3.55), N(10.39); found: C(55.61), H(3.42), N(10.22).

7) **8-methyl-10-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-pyrano[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 240–242°C, IR(KBr) cm^{-1} : 1700, 1635–1675, 3010–3045, 3295–3310. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.45(s, 3H, CH_3), 2.65(s, 3H, CH_3), 4.62 (s, 1H), 6.80–7.60 (6H, m, H–Ar), 9.30(s, 1H, NH), 10.56(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.8, 22.4, 36.1, 77.2, 101.5, 102.1, 121.8, 123.2, 124.2, 125.3, 125.9, 126.2, 128.1, 129.3, 139.1, 144.8, 148.2, 150.1, 154.6, 156.3, 157.8, 174.5, 181.1. Anal. calcd. (%) for

$C_{23}H_{15}ClN_4O_4S_2$ (510.02): C(54.06), H(2.96), N(10.96); found: C(53.92), H(2.78), N(10.83).

8) **8-methyl-10-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-pyrano[4,3-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 248–250°C, IR(KBr) cm^{-1} : 1700, 1635–1675, 3010–3045, 3295–3310. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.45 (s,3H, CH_3), 2.65 (s, 3H, CH_3), 4.62 (s, 1H), 6.80–7.60 (6H, m, H–Ar), 9.30(s, 1H, NH), 10.56(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.8, 22.4, 36.1, 77.2, 101.5, 102.1, 121.8, 123.2, 124.2, 125.3, 125.9, 126.2, 128.1, 129.3, 139.1, 144.8, 148.2, 150.1, 154.6, 156.3, 157.8, 174.5, 181.1. Anal. calcd. (%) for $C_{23}H_{15}ClN_4O_4S_2$ (510.02): C(54.06), H(2.96), N(10.96); found: C(53.89), H(2.77), N(10.84).

9) **1,3,8,8-tetramethyl-10-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-7,8-dihydro-5H,9H-pyrimido[4,5-b]quinoline-2,4,6-trione**. M.p. 228–230°C, IR (KBr) cm^{-1} : 1630–1660, 1700, 3050–3070. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.06–2.14(2H, m, CH_2), 2.41 (3H, s, CH_3), 2.45–2.61 (2H, m, CH_2), 3.11 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.65 (s, 1H), 6.86–7.43 (5H, m, H–Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.8, 18.1, 28.1, 28.6, 35.3, 40.1, 40.3, 48.6, 51.3, 79.5, 107.3, 122.3, 123.9, 124.9, 125.3, 125.8, 126.3, 127.5, 129.6, 138.5, 146.3, 150.6, 153.1, 155.2, 157.3, 175.3, 190.2. Anal. calcd. (%) for $C_{27}H_{25}ClN_4O_3S_2$ (552.11): C(58.63), H(4.56), N(10.13); found: C(58.51), H(4.42), N(10.01).

10) **1,3,8,8-tetramethyl-10-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-7,8-dihydro-5H,9H-pyrimido[4,5-b]quinoline-2,4,6-trione**. M.p. 233–235°C, IR(KBr) cm^{-1} : 1630–1660, 1700, 3050–3070. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.06–2.14(2H, m, CH_2), 2.41 (3H, s, CH_3), 2.45–2.61 (2H, m, CH_2), 3.11 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.65 (s,1H), 6.86–7.43 (5H, m, H–Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.8, 18.1, 28.1, 28.5, 35.3, 40.1, 40.3, 48.6, 51.3, 79.5, 107.3, 122.3, 123.9, 124.9, 125.3, 125.8, 126.3, 127.5, 129.6, 138.5, 146.3, 150.6, 153.1, 155.2, 157.3, 175.3, 190.2. Anal. calcd. (%) for $C_{27}H_{25}ClN_4O_3S_2$ (552.11): C(58.63), H(4.56), N(10.13); found: C(58.44), H(4.42), N(10.02).

11) **8,8-dimethyl-10-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-7,8-dihydro-5H,9H-pyrimido[4,5-b]quinoline-2,4,6(1H,3H)-trione**. M.p. 203–205°C, IR (KBr) cm^{-1} : 1631–1665, 1700, 3060–3070, 3285–3300. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 0.97 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.06–2.14(2H, m, CH_2), 2.41 (3H, s, CH_3), 2.45–2.61 (2H, m, CH_2), 4.75 (s, 1H), 6.86–7.43 (5H, m, H–Ar), 9.45 (s, 1H, NH), 10.85 (s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.6, 17.1, 28.2, 28.8, 35.1, 49.2, 51.2, 78.5, 106.7, 121.4,

122.9, 124.2, 125.1, 125.7, 126.2, 128.3, 130.2, 140.1, 145.4, 150.1, 153.6, 156.2, 156.9, 174.6, 189.2. Anal. calcd. (%) for $C_{25}H_{21}ClN_4O_3S_2$ (524.07): C(57.19), H(4.03), N(10.67); found: C(56.96), H(3.88), N(10.51).

12) **8,8-dimethyl-10-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-7,8-dihydro-5H,9H-pyrimido[4,5-b]quinoline-2,4,6(1H,3H)-trione**. M.p. 212–214°C, IR (KBr) cm^{-1} : 1631–1665, 1700, 3060–3070, 3285–3300. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 0.97 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.06–2.14 (2H, m, CH_2), 2.41 (3H, s, CH_3), 2.45–2.61 (2H, m, CH_2), 4.75 (s, 1H), 6.86–7.43 (5H, m, H-Ar), 9.45(s, 1H, NH), 10.85(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.8, 17.1, 28.1, 28.9, 35.1, 49.2, 51.2, 78.5, 106.7, 121.4, 122.9, 124.2, 125.1, 125.7, 126.2, 128.3, 130.2, 140.1, 145.4, 150.1, 153.6, 156.2, 156.9, 174.6, 189.2. Anal. calcd. (%) for $C_{25}H_{21}ClN_4O_3S_2$ (524.07): C(57.19), H(4.03), N(10.67); found: C(57.03), H(3.92), N(3.89).

13) **1,3-dimethyl-11-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-indeno[1,2-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 251–253°C, IR(KBr) cm^{-1} : 1630–1665, 1701, 3020–3050. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.46 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.64 (s, 1H), 7.68–7.90 (9H, m, H-Ar), ^{13}C NMR(DMSO- d_6) δ (ppm): 16.9, 35.4, 39.8, 40.1, 78.2, 101.6, 122.8, 123.6, 124.9, 125.3, 125.6, 126.1, 126.5, 126.9, 128.3, 129.6, 130.1, 134.5, 137.1, 140.2, 146.4, 150.3, 153.6, 155.2, 156.3, 174.9, 187.6. Anal. calcd. (%) for $C_{28}H_{19}ClN_4O_3S_2$ (558.06): C(60.15), H(3.43), N(10.02); found: C(60.01), H(3.25), N(9.86).

14) **1,3-dimethyl-11-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-indeno[1,2-b]pyrido[2,3-d]pyrimidine-2,4,6-trione**. M.p. 245–247°C, IR(KBr) cm^{-1} : 1630–1665, 1701, 3020–3050. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.46 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.64 (s, 1H), 7.68–7.90 (9H, m, H-Ar), ^{13}C NMR(DMSO- d_6) δ (ppm): 16.9, 35.4, 39.8, 40.1, 78.2, 101.6, 122.8, 123.6, 124.9, 125.3, 125.6, 126.1, 126.5, 126.9, 128.3, 129.6, 130.1, 134.5, 137.1, 140.2, 146.4, 150.3, 153.6, 155.2, 156.3, 174.9, 187.6. Anal. calcd. (%) for $C_{28}H_{19}ClN_4O_3S_2$ (558.06): C(60.15), H(3.43), N(10.02); found: C(60.02), H(3.27), N(9.91).

15) **11-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-indeno[1,2-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 240–242°C, IR(KBr) cm^{-1} : 1634–1670, 1701, 3020–3050, 3290–3300. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.44 (3H, s, CH_3), 4.74 (s, 1H), 7.68–7.90 (9H, m, H-Ar), 9.60(s, 1H, NH), 10.80(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 17.6, 34.9, 77.2, 102.6, 120.8, 122.5, 124.6, 124.8, 125.7, 126.1, 126.5, 127.2, 128.5, 129.8, 130.8, 135.3, 136.3, 140.6, 145.4, 150.2, 152.9, 155.2, 156.7,

174.5, 187.9. Anal. calcd. (%) for $C_{26}H_{17}ClN_4O_3S_2$ (532.04): C(58.59), H(3.21), N(10.51); found: C(58.44), H(3.16), N(10.42).

16) **11-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-5H-indeno[1,2-b]pyrido[2,3-d]pyrimidine-2,4,6(1H,3H)-trione**. M.p. 253–255°C, IR(KBr) cm^{-1} : 1634–1670, 1701, 3020–3050, 3290–3300. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.44 (3H, s, CH_3), 4.74 (s, 1H), 7.68–7.90 (9H, m, H-Ar), 9.60(s, 1H, NH), 10.80(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 17.6, 34.9, 77.2, 102.6, 120.8, 122.5, 124.6, 124.8, 125.7, 126.1, 126.5, 127.2, 128.5, 129.8, 130.8, 135.3, 136.3, 140.6, 145.4, 150.2, 152.9, 155.2, 156.7, 174.5, 187.9. Anal. calcd. (%) for $C_{26}H_{17}ClN_4O_3S_2$ (532.04): C(58.59), H(3.21), N(10.51); found: C(58.41), H(3.16), N(10.39).

17) **1,3-dimethyl-12-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-6,7-dihydro-5H-benzo[h]pyrimido[4,5-b]quinoline-2,4-dione**. M.p. 224–226°C, IR(KBr) cm^{-1} : 1630–1670, 2900–2950, 3010–3050. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.07–2.35 (m, 4H); 2.45(s, 3H, CH_3), 3.08 (3H, s, CH_3), 3.54 (3H, s, CH_3), 4.68 (s, 1H), 7.36–7.52(m, 9H, H-Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 18.5, 28.9, 29.6, 35.6, 40.2, 40.5, 78.9, 104.6, 122.7, 123.6, 124.9, 125.1, 125.6, 126.5, 126.9, 127.2, 128.3, 130.2, 130.8, 133.6, 137.9, 138.9, 150.6, 153.6, 155.9, 156.1. Anal. calcd. (%) for $C_{29}H_{23}ClN_4O_2S_2$ (558.10): C(62.30), H(4.15), N(10.02); found: C(62.15), H(3.98), N(9.87).

18) **1,3-dimethyl-12-(6-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-6,7-dihydro-5H-benzo[h]pyrimido[4,5-b]quinoline-2,4-dione**. M.p. 231–233°C, IR(KBr) cm^{-1} : 1630–1670, 2900–2950, 3010–3050. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.07–2.35 (m, 4H), 2.46 (s, 3H, CH_3), 3.08 (3H, s, CH_3), 3.54 (3H, s, CH_3), 4.68 (s, 1H), 7.36–7.52(m, 9H, H-Ar). ^{13}C NMR(DMSO- d_6) δ (ppm): 18.5, 28.9, 29.6, 35.6, 40.2, 40.5, 78.9, 104.6, 122.7, 123.6, 124.9, 125.1, 125.6, 126.5, 126.9, 127.2, 128.3, 130.2, 130.8, 133.6, 137.9, 138.9, 150.6, 153.6, 155.9, 156.1. Anal. calcd. (%) for $C_{29}H_{23}ClN_4O_2S_2$ (558.10): C(62.30), H(4.15), N(10.02); found: C(62.17), H(4.03), N(9.91).

19) **12-(7-chloro-4-methyl benzothiazolo-2-yl)-5-(2-thienyl)-6,7-dihydro-5H-benzo[h]pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione**. M.p. 220–222°C, IR(KBr) cm^{-1} : 1635–1672, 2920–2950, 3015–3090, 3280–3295. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.04–2.38 (m, 4H), 2.45(s, 3H, CH_3), 4.72 (s, 1H), 7.22–7.48(m, 9H, H-Ar), 9.87(s, 1H, NH), 11.02(s, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 18.1, 29.3, 30.1, 35.8, 78.3, 103.5, 122.4, 123.6, 124.2, 124.7, 125.3, 126.1, 126.8, 127.6, 128.3, 129.6, 130.8, 134.6, 137.6, 139.6, 150.3, 153.5, 155.9, 156.6. Anal. calcd.

(%) for $C_{27}H_{19}ClN_4O_2S_2$ (530.06): C(61.07), H(3.60), N(10.55); found: C(60.77), H(3.44), N(10.38).

20) **12-(6-chloro-4-methyl benzothiazol-2-yl)-5-(2-thienyl)-6,7-dihydro-5H-benzoh[pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione**. M.p. 215–217°C, IR(KBr) cm^{-1} : 1635–1672, 2920–2950, 3015–3090, 3280–3295. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.04–2.38 (*m*, 4H), 2.45 (*s*, 3H, CH_3), 4.72 (*s*, 1H), 7.22–7.48(*m*, 9H, H–Ar), 9.87(*s*, 1H, NH), 11.02(*s*, 1H, NH). ^{13}C NMR(DMSO- d_6) δ (ppm): 18.1, 29.3, 30.1, 35.8, 78.3, 103.5, 122.4, 123.6, 124.2, 124.7, 125.3, 126.1, 126.8, 127.6, 128.3, 129.6, 130.8, 134.6, 137.6, 139.6, 150.3, 153.5, 155.9, 156.6. Anal. calcd. (%) for $C_{27}H_{19}ClN_4O_2S_2$ (530.06): C(61.07), H(3.60), N(10.55); found: C(60.85), H(3.45), N(10.41).

21) **1,3-dimethyl-10-(7-chloro-4-methyl benzothiazol-2-yl)-5-(2-thienyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]quinoline-2,4-dione**. M.p. 207–209°C, IR(KBr) cm^{-1} : 1630, 1670, 2900–2980, 3012–3048. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6): 2.16–2.54 (*m*, 8H); 2.42(*s*, 3H), 3.11 (3H, *s*, CH_3), 3.44 (3H, *s*, CH_3), 4.72 (*s*, 1H), 7.31–7.60 (*m*, 5H). ^{13}C NMR(DMSO- d_6): 16.9, 28.3, 28.4, 29.6, 32.1, 35.3, 40.1, 40.5, 79.7, 110.8, 122.8, 123.5, 125.4, 125.8, 126.1, 126.6, 127.9, 129.5, 135.1, 138.6, 150.6, 153.2, 155.1, 156.3. Anal. calcd. (%) for $C_{25}H_{23}ClN_4O_2S_2$ (510.10): C(58.75), H(4.54), N(10.96); found: C(58.63), H(4.41), N(10.77).

22) **1,3-dimethyl-10-(6-chloro-4-methyl benzothiazol-2-yl)-5-(2-thienyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]quinoline-2,4-dione**. M.p. 219–221°C, IR(KBr) cm^{-1} : 1630, 1670, 2900–2980, 3012–3048. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.16–2.54 (*m*, 8H); 2.42(*s*, 3H), 3.11 (3H, *s*, CH_3), 3.44 (3H, *s*, CH_3), 4.72 (*s*, 1H), 7.31–7.60 (*m*, 5H). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.9, 28.3, 28.4, 29.6, 32.1, 35.3, 40.1, 40.5, 79.7, 110.8, 122.8, 123.5, 125.4, 125.8, 126.1, 126.6, 127.9, 129.5, 135.1, 138.6, 150.6, 153.2, 155.1, 156.3. Anal. calcd. (%) for $C_{25}H_{23}ClN_4O_2S_2$ (510.10): C(58.75), H(4.54), N(10.96); found: C(58.61), H(4.41), N(10.83).

23) **10-(7-chloro-4-methylbenzothiazol-2-yl)-5-(2-thienyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione**. M.p. 228–230°C, IR(KBr) cm^{-1} : 1634, 1671, 2915–2950, 3020–3090, 3282–3298. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.13–2.53 (*m*, 8H), 2.46(*s*, 3H), 4.72 (*s*, 1H), 7.42–7.76 (*m*, 5H), 9.88(*s*, 1H), 10.85(*s*, 1H). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.5, 28.1, 27.8, 29.6, 31.7, 35.8, 79.2, 111.6, 122.3, 123.4, 125.1, 125.6, 126.1, 126.6, 127.8, 130.2, 134.7, 138.2, 150.1, 153.2, 155.2, 156.6. Anal. calcd. (%) for $C_{23}H_{19}ClN_4O_2S_2$ (482.06): C(57.19), H(3.96), N(11.60); found: C(57.02), H(3.78), N(11.48).

24) **10-(6-chloro-4-methylbenzothiazol-2-yl)-5-(2-thienyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]quinoline-2,4(1H,3H)-dione**. M.p. 216–218°C, IR(KBr) cm^{-1} :

1634, 1671, 2915–2950, 3020–3090, 3282–3298. 1H NMR (300 MHz, $CDCl_3$, DMSO- d_6) δ (ppm): 2.13–2.53 (*m*, 8H), 2.46(*s*, 3H), 4.72 (*s*, 1H), 7.42–7.76 (*m*, 5H), 9.88(*s*, 1H), 10.85(*s*, 1H). ^{13}C NMR(DMSO- d_6) δ (ppm): 16.5, 28.1, 27.8, 29.6, 31.7, 35.8, 79.2, 111.6, 122.3, 123.4, 125.1, 125.6, 126.1, 126.6, 127.8, 130.2, 134.7, 138.2, 150.1, 153.2, 155.2, 156.6. Anal. calcd. (%) for $C_{23}H_{19}ClN_4O_2S_2$ (482.06): C(57.19), H(3.96), N(11.60); found: C(57.01), H(3.77), N(11.49).

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References

- (1) (a) Toure, B.B.; Hall, D.G. *Chem. Rev.* **2009**, *109*, 4439; (b) Jang, B.; Shi, F.; Tu, S.-T. *Curr. Org. Chem.* **2010**, *14*, 357; (c) Bannwarth, W.; Felder, E., Eds. *Combinatorial Chemistry: A Practical Approach*; Wiley-VCH: Weinheim, 2000; pp 209–237. doi:10.1002/cr800296p.
- (2) (a) Chen, X.H.; Xu, X.Y.; Liu, H.; Cun, L.F.; Gong, L.Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802; (b) Jiang, B.; Tu, S.J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. doi:10.1021/ja065267y.
- (3) Ruijter, E.; Orru, R.V.A. *Drug Discov. Today: Technol.* **2013**, *10* (1), e15. doi:10.1016/j.ddtec.2012.10.012.
- (4) Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. doi:10.1021/cr100233r.
- (5) (a) Tietze, L.F.; Brasche, G.; Gericke, K.M., Eds. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, **2006**; (b) Powner, M.W.; Sutherland, J.D.; Szostak, J.W. *J. Am. Chem. Soc.* **2010**, *132*, 16677.
- (6) (a) Marson, C.M. *Chem. Soc. Rev.* **2012**, *41* (23), 7712; (b) Graaff, C.D.; Ruijter, E.; Orru, R.V.A. *Chem. Soc. Rev.* **2012**, *41*, 3969. doi:10.1039/c2cs35183h.
- (7) (a) Wan, J.-P.; Liu, Y. *RSC Adv.* **2012**, *2*, 9763; (b) Dandapani, S.; Marcaurelle, L.A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362. doi:10.1039/c2ra21406g.
- (8) (a) Houck, J.E.B.; Younai, A.; Shaw, J.T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371; (b) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**, ISBN 3-527-30806-7. doi:10.1016/j.cbpa.2010.03.003.
- (9) Klutchko, S.R.; Zhou, H.; Winters, R.T.; Tran, T.P.; Bridges, A.J.; Althaus, I.W.; Amato, D.M.; Elliott, W. L.; Ellis, P.A.; Meade, M.A.; Roberts, B.J.; Fry, D.W.; Gonzales, A.J.; Harvey, P.J.; Nelson, J.M.; Sherwood, V.; Han, H.K.; Pace, G.; Smaill, J.B.; Denny, W.A.; Showalter, H.D. *J. Med. Chem.* **2006**, *49*, 1475. doi:10.1021/jm050936o.

- (10) Smaill, J.B.; Palmer, B.D.; Rewcastle, G.W.; Denny, W.A.; McNamara, D.J.; Dobrusin, E.M.; Bridges, A.J.; Zhou, H.; Showalter, H.D.; Winters, R.T.; Leopold, W. R.; Fry, D.W.; Nelson, J.M.; Slintak, V.; Elliott, W.L.; Roberts, B.J.; Vincent, P.W.; Patmore, S.J. *J. Med. Chem.* **1999**, *42*, 1803. doi:10.1021/jm9806603.
- (11) (a) Palmer, B.D.; Smaill, J.F.; Rewcastle, G.W.; Dobrusin, E.M.; Kraker, A.; Moore, C.W.; Steinkempff, R.W.; Denny, W.A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1931; (b) Perner, R.J.; Lee, C.H.; Gu, Y.-G.; Didomenico, S.; Baybut, E.K.; Alexander, K.M.; Kohlhaas, H.L.; Jarvis, M.F.; Kowaluk, E.L.; Bhagawat, S.S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2803. doi:10.1016/j.bmcl.2005.01.079.
- (12) (a) Vander Wel, S.N.; Harvey, P.J.; McNamara, D.J.; Repine, J.T.; Keller, P.R.; Quin, J.; Booth, R.J.; Elliott, W.L.; Dobrusin, E.M.; Fry, D.W.; Toogood, P.L. *J. Med. Chem.* **2005**, *48*, 2371; (b) Zhang, J.; Yang, P.L.; Gray, N.S. *Nat. Rev. Cancer* **2009**, *9*, 28. doi:10.1021/jm049355+.
- (13) Martinez, M.M.; Bartolomé-Nebreda, J.M.; Gómez-Monterrey, I.; González-Muñiz, R.; García-López, M. T.; Ballaz, S.; Barber, A.; Fortuño, A.; Río, J.D.; Herranz, R. *J. Med. Chem.* **1997**, *40*, 3402. doi:10.1021/jm9703247.
- (14) Guiles, J.W.; Toro1, A.; Ochsner, U.A.; Bullard, J.M. *Org. Med. Chem. Lett.* **2012**, *2*, 5; (b) Nemati, F.; Saecdirad, R. *Chin. Chem. Lett.* **2013**, *24*, 370; (c) Sarma, R.; Sarmah, M.M.; Prajapati, D. *J. Org. Chem.* **2012**, *77*, 2018. doi:10.1186/2191-2858-2-5.
- (15) (a) Rajesh, S.M.; Kumar, R.S.; Libertsen, L.A.; Perumal, S.; Yogeewari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3012; (b) Riadi, Y.; Massip, S.; Leger, J.-M.; Jarry, C.; Lazar, S.; Guillaumet, G. *Tetrahedron* **2012**, *68*, 5018. doi:10.1016/j.bmcl.2011.03.045.
- (16) (a) Sarmah, M.M.; Sarma, R.; Prajapati, D.; Hu, W. *Tetrahedron Lett.* **2013**, *54*, 267; (b) Font, M.; González, A.; Palop, J.A.; Sanmartín, C. *Eur. J. Med. Chem.* **2011**, *46*, 3887. doi:10.1016/j.tetlet.2012.11.018.
- (17) Kowaluk, E.A.; Mikusa, J.; Wismer, C.T.; Zhu, C.Z.; Schweitzer, E.; Lynch, J.J.; Lee, C.H.; Jiang, M.; Bhagwat, S.S.; Gomtsyan, A.; Mckie, J.; Cox, B.F.; Polakowski, J.; Reinhart, G.; Williams, M.; Jarvis, M. F. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1165.
- (18) Gyires, K.; Furst, S.; Miklya, I.; Budavari, I.; Knoll, J. *Drugs Exp. Clin. Res.* **1985**, *11*, 493.
- (19) Connor, D.T.; Sorenson, D.T.; Cetenko, W.A.; Kerbleski, J.J.; Tinney, F.J. *J. Med. Chem.* **1984**, *27*, 528. doi:10.1021/jm00370a016.
- (20) Hou, G.; Gravier, D.; Casadebaig, F.; Dupin, J.P.; Bernard, H.; Biosseau, M. *Pharmazie*, **1995**, *50*, 719.
- (21) Suhagia, B.N.; Chhabria, M.T.; Makwana, A.G. *J. Enzyme Inhib. Med. Chem.* **2006**, *21*, 681. doi:10.1080/14756360600851104.
- (22) (a) Rostom, S.A.F.; Hassan, G.S.; El-Subbagh, H.I. *Arch. Der. Pharm.* **2009**, *342*, 584; (b) Molina, P.; Aller, E.; Lorenzo, A.; Lopez-Cremades, P.; Rioja, I.; Ubeda, A.; Terencio, M.C.; Alcaraz, M.J. *J. Med. Chem.* **2001**, *44*, 1011. doi:10.1002/ardp.200900062.
- (23) Natarajan, S.R.; Wisnoski, D.D.; Singh, S.B.; Stelmach, J.E.; O'Neill, E.A.; Schwartz, C.D.; Thompson, C.M.; Fitzgerald, C.E.; O'Keefe, S.J.; Kumar, S.; Hop, C.E.C.A.; Zaller, D.M.; Schmatz, D.M.; Doherty, J.B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 273. doi:10.1016/S0960-894X(02)00876-4.
- (24) Hayakawa, M.; Kaizawa, H.; Moritomo, H.; Koizumi, T.; Ohishi, T.; Okada, M.; Ohta, M.; Tsukamoto, S.I.; Parker, P.; Workman, P.; Waterfield, M. *Bioorg. Med. Chem.* **2006**, *14*, 6847. doi:10.1016/j.bmc.2006.06.046.
- (25) Font, M.; González, A.; Palop, J.A.; Sanmartín, C. *Eur. J. Med. Chem.* **2011**, *46*, 3887. doi:10.1016/j.ejmech.2011.05.060.
- (26) (a) Zoorob, H.H.; Zahab, M.M.A.; Abdel-Mogib, M.; Ismail, M.A. *Tetrahedron* **1996**, *52*, 10147; (b) Basolo, L.; Beccalli, E.M.; Borsini, E.; Broggin, G. *Tetrahedron* **2009**, *65*, 3486; (c) Agarwal, P.K.; Sharma, S.K.; Sawant, D.; Kundu, B. *Tetrahedron* **2009**, *65*, 1153; (d) Ismaili, L.; Nadaradjane, A.; Nicod, L.; Guyon, C.; Xicluna, A.; Robert, J.F.; Refouvet, B. *Eur. J. Med. Chem.* **2008**, *43*, 1270; (e) Wentland, M.P.; Carlson, J. A.; Dorff, P.H.; Aldous, S.C.; Perni, R.B.; Young, D. C.; Woods, M.G.; Kingsley, S.D.; Ryan, K.A.; Rosi, D.; Drozd, M.L.; Dutko, F.J. *J. Med. Chem.* **1995**, *38*, 2541. doi:10.1016/0040-4020(96)00537-6.
- (27) (a) Alqasoumi, S.I.; Al-Taweel, A.M.; Alafeefy, A.M.; Noaman, E.; Ghorab, M.M. *Eur. J. Med. Chem.* **2010**, *45*, 738; (b) Vásquez, D.; Rodríguez, J.A.; Theoduloz, C.; Verrax, J.; Calderon, P.B.; Valderrama, J.A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5060. doi:10.1016/j.ejmech.2009.11.021.
- (28) (a) Metwally, K.; Pratsinis, H.; Kletsas, D. *Eur. J. Med. Chem.* **2007**, *42*, 344; (b) Dorjsuren, D.; Burnette, A.; Gray, G.N.; Chen, X.; Zhu, W.; Roberts, P.E.; Currens, M.J.; Shoemaker, R.H.; Ricciardi, R.P.; Sei, S. *Antiviral Res.* **2006**, *69*, 9. doi:10.1016/j.ejmech.2006.10.008.
- (29) Nagamatsu, T.; Yoneda, F.; Kawashima, Y.; Yamagishi, T.; Ikeya, H. The 6th Annual Meeting of Division of Medicinal Chemistry, **1987**, Tsukuba, Japan, Book Abstract, pp 148–149.
- (30) (a) Arya, A.K.; Kumar, M. *Mol. Divers* **2011**, *15*, 781; (b) Arya, A.K.; Gupta, S.K.; Kumar, M. *Tetrahedron Lett.* **2012**, *53*, 6035; (c) Kumar, M.; Sharma, K.; Arya, A.K. *Tetrahedron Lett.* **2012**, *53*, 4604; (d) Arya, A.K.; Kumar, M. *Green Chem.* **2011**, *13*, 1332; (e) Khandelwal, S.; Rajawat, A.; Kumar, M. *Curr. Bioactive Compounds* **2013**, *9*, 203–210; (f) Kumar, M.; Sharma, K.; Sharma, D.K.; Arya, A.K. *Tetrahedron Lett.* **2013**, *54*, 878. doi:10.1007/s11030-011-9309-2.
- (31) Kumar, M.; Sharma, K.; Samarth, R.M.; Kumar, A. *Eur. J. Med. Chem.* **2010**, *45*, 4467. doi:10.1016/j.ejmech.2010.07.006.
- (32) (a) Gupta, R.R.; Kumar, M. Synthesis, Reactions and Properties of Phenothiazines. In *Phenothiazines and 1,4-Benzothiazines, Chemical and Biomedical Aspect*: Gupta, R.R., Ed.; Elsevier: Amsterdam, **1998**; pp 1–161; (b) Rathore, B.S.; Kumar, M. *Bioorg. Med. Chem.* **2006**, *14*, 5678; (c) Rathore, B.S.; Gupta, V.; Gupta, R. R.; Kumar, M. *Heteroatom Chem.* **2007**, *18*, 81.