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Mild and efficient synthesis of benzothiazolopyrimidine derivatives *via* CuAAC/ring cleavage/cyclization reaction†

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An operationally mild and efficient synthesis of benzothiazolopyrimidine is achieved by a three-component reaction of 2-aminebenzo[*d*]thiazoles, sulfonyl azides and terminal ynones. This cascade process involved a CuAAC/ring cleavage/cyclization reaction. Particularly, most of the benzothiazolopyrimidine derivatives could be isolated by filtration without further purification.

Introduction

Benzothiazolopyrimidine derivatives are well established as privileged scaffolds which are commonly encountered in many pharmacologically active molecules that may be good drug candidates.[1–7] Most of the benzothiazolopyrimidines possess various biological activities like inhibition of SHP2 (Fig. 1, I),[2] anticancer agent (II),[3] antitumor activity (III),[4] analgesic (IV),[5] and nucleoside transporter (V).[6] Also, some benzothiazolopyrimidine derivatives are commercially available as chiral catalysts (VI).[7] Therefore, the development of novel methods for the synthesis of these benzothiazolopyrimidine is important in the field of synthetic organic and pharmaceutical chemistry.

Numerous synthetic methods for the preparation of benzothiazolopyrimidines reported in the literature involve three major strategies: (a) intramolecular cyclization reaction with amino alcohol substrates under reflux conditions (Scheme 1a);[8] (b) [4 + 2] cycloaddition of 2-benzothiazolimines and alkenes or other unsaturated compounds (Scheme 1b);[9] (c) a one-pot acylation–cyclization of 2-aminobenzothiazole with α,β-unsaturated acid chlorides (Scheme 1c).[10] Each of these methods has considerable merit, including synthesis of stereoselective benzothiazolopyrimidine derivatives and polysubstituted products. However, there synthetic utility is impaired by the requirement of multistep synthesis, high temperatures and complex purification. Under this background, the development of operationally mild multicomponent one-pot synthetic strategies for the preparation of benzothiazolopyrimidines still remains highly desirable.

Since reported by Chang's group,[11] copper-catalyzed sulfonyl azide–alkyne cycloaddition/ring cleavage (CuAAC/ring cleavage

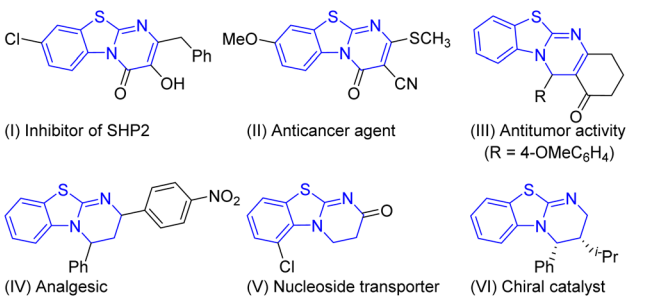
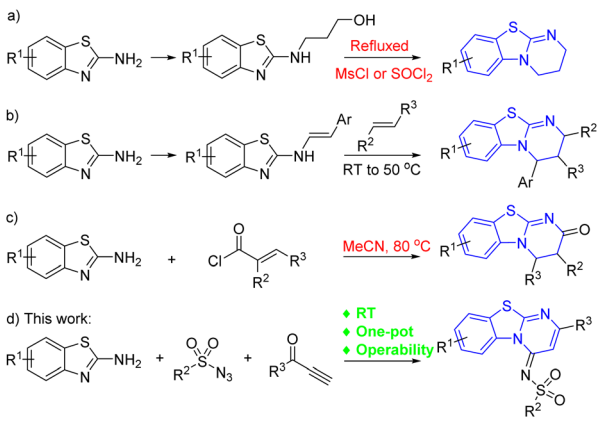


Fig. 1 Benzothiazolopyrimidines drug candidates and chiral catalyst.



Scheme 1 Synthesis of benzothiazolopyrimidine derivatives by (a) intramolecular cyclization reaction, (b) [4+2] cycloaddition, (c) acylation–cyclization, (d) this work, CuAAC/ring cleavage/cyclization reaction.

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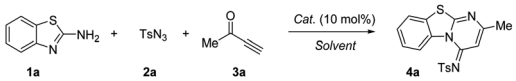
reaction) has been recognized as a mild multicomponent reaction and high efficient method for the synthesis of various N-heterocyclic compounds, which was applied to the structural modification of natural products, drugs or biological macromolecules.[12] Our group has also applied the CuAAC/ring cleavage reaction to the construction of pyridines, fused heterocycles, coumarins, indoles and other N-heterocyclic compounds.[13] Accordingly, we here describe a mild and efficient synthesis of benzothiazolopyrimidine derivatives *via* CuAAC/ring cleavage reaction (Scheme 1d). This protocol encompasses stirring a three-component reaction of 2-aminebenzo[*d*]thiazoles, sulfonyl azides and terminal ynones.

Results and discussion

Our investigations began with an examination of the synthesis of (*Z*)-4-methyl-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo [3,2-*a*] pyrimidin-4-ylidene)benzenesulfonamide **4a** by using 2-aminobenzothiazole **1a**, TsN_3 **2a** and 3-butyn-2-one **3a** (Table 1).

The solvent screening revealed that by using CuI as the catalysts, EtOH and MeCN delivering product **4a** in highest yield (93%) (Table 1, entries 1–10). Since EtOH is less toxic and cheaper than MeCN, the optimal solvent was determined to be EtOH. Encouraged by this promising result, variety of catalysts were screened. Among the copper catalysts used, both Cu^{I} or Cu^{II} catalysts exhibited high catalytic reactivity while AgTFA failed to produce the desired product (Table 1, entries 11–17). Lastly, the effect of temperature was evaluated (Table 1, entries 18–20). The results revealed room temperature is the best. Considering atomic economy, reaction rate and efficiency, the optimal reaction conditions have been defined to be Table 1, entry 9.

Table 1 Optimization of catalytic conditions[a]



1a 2a 3a 4a

Entry	Cat.	Solvent	Yield[b] (%) **4a**
1	CuI	$CHCl_3$	75
2	CuI	DCE	85
3	CuI	Toluene	70
4	CuI	MeCN	93
5	CuI	THF	60
6	CuI	1,4-Dioxane	51
7	CuI	DMSO	81
8	CuI	DMA	78
9	**CuI**	**EtOH**	**93**
10	CuI	Acetone	68
11	CuCl	EtOH	90
12	CuBr	EtOH	83
13	$CuBr_2$	EtOH	80
14	$Cu(OAc)_2$	EtOH	90
15	$Cu(OTf)_2$	EtOH	80
16	$Cu(acac)_2$	EtOH	85
17	AgTFA	EtOH	n.d.[c]
18	CuI	EtOH	93[d]
19	CuI	EtOH	90[e]
20	CuI	EtOH	87[f]

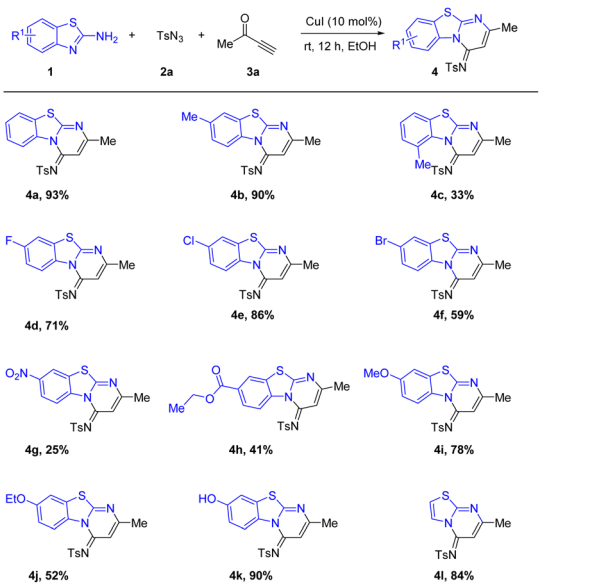
[a] Reaction conditions: **1a** (0.5 mmol), cat. (10 mol%) in the solvent (3 mL) was added **2a** (1.5 equiv.) and **3a** (1.5 equiv.) stirring at room temperature for 12 h. [b] Isolated yields. [c] n.d. = not detected the target product. [d] The reaction temperature was 40 °C. [e] The temperature was 60 °C. [f] The temperature was 100 °C.

Under the optimized conditions (Table 1, entry 9), we performed a substrates screening using a series of 2-aminobenzothiazoles. Agreeably, as shown in Table 2, various 2-Aminobenzothiazoles with either electron-donating groups (–Me, –OMe, –OEt, –OH) or electron-withdrawing groups (–F, –Cl, –Br, $-NO_2$ $-COOCH_2CH_3$) exhibited good functional-group tolerance to produced the desired products (**4a**–**4k**). It is worth noting that the yield of **4c** is relatively low due to the influence of steric effect, while the yield of **4g** is the lowest with the influence of the strong pull electron effect. Gratifyingly, 2-aminothiazole proceeded smoothly in this transformation, which generated **4l** in decent yield. However, 2-aminobenzothiazole bearing electron-withdrawing group (–CN) gave a complex reaction system and difficult to isolate the desired product.

Next, the scope and limitation of substrates sulfonyl azides **2** were tested (Table 3). It is noteworthy that the substrates sulfonyl azides showed slight influence on this reaction. With R^3 changed by aliphatic or aromatic substituents, such as phenyl, –(4-C_6H_5), –(4-ClC_6H_4), –(4-BrC_6H_4), –(4-$OMeC_6H_4$), –(4-$NO_2C_6H_4$), –Me, –Pr, *etc.*, the reaction could smoothly give the anticipated products (**4m**–**4x**) in comparable yields of 76–97%.

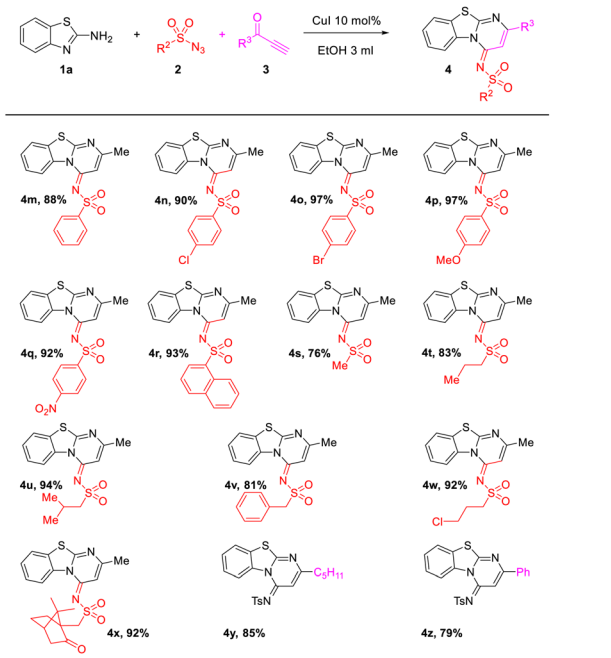
Products **4a**–**4z** are stable towards purification under conventional conditions. Nevertheless, *N*-sulfonyl benzothiazolo-pyrimidine **4a** could undergo hydrolysis and converted into imine **5a** under forcing conditions (Scheme 2).

Table 2 Substrate scope of the amines **1**[a]



[a] Reaction conditions: **1** (0.5 mmol), CuI (10 mol%) in EtOH (3 mL) was added **2a** (1.5 equiv.) and **3a** (1.5 equiv.) stirring at room temperature for 12 h.

Table 3 Substrate scope of the sulfonyl azides 2[a]



[a] Reaction conditions: **1a** (0.5 mmol), CuI (10 mol%) in the solvent (3 mL) was added **2** (1.5 equiv.) and **3** (1.5 equiv.) stirring at room temperature for 12 h.

Scheme 2 Hydrolysis of *N*-sulfonyl benzothiazolopyrimidine **4a**.

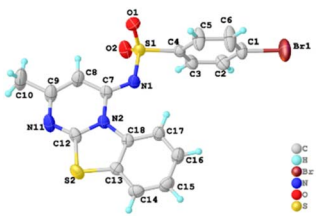
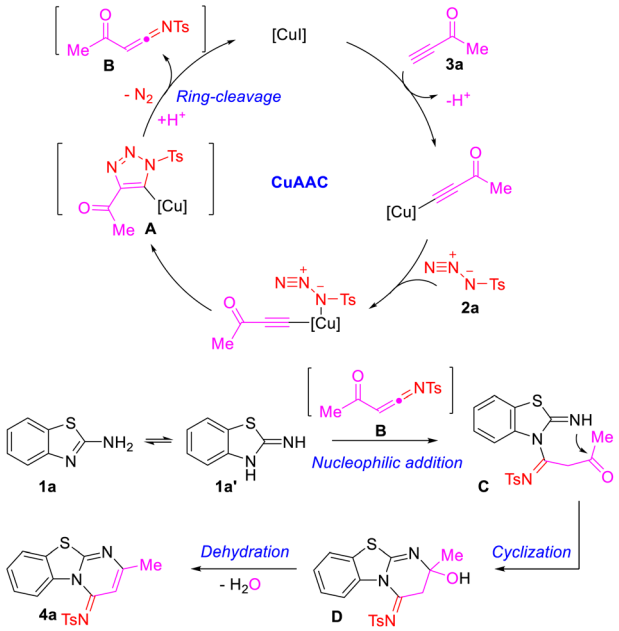


Fig. 2 Single-crystal X-ray analysis of **4o** (CCDC 2270393).

None of the product imidazo[1,2-*a*]pyridines **4a–4z** have been reported previously, which were subject to full spectroscopic characterization in the experimental section and the derived data were in complete accord with the assigned structures. The structure of **4o** was confirmed by single-crystal X-ray analysis (Fig. 2).

A possible reaction pathway for the formation of benzothiazolopyrimidine (**4a**) from precursors **1a**, **2a** and **3a** is shown in Scheme 3. As described in the literature,[12,13] the substrates **2a** and **3a** reacted in the presence of the copper(I) catalyst to form



Scheme 3 Plausible reaction mechanism.

the metallated triazole **A** through the CuAAC pathway. Then, the complex **A** underwent a ring-cleavage rearrangement, leading to a highly active intermediate *N*-sulfonyl α-acylketenimine **B**. The species **B** was captured by **1a** *via* nucleophilic addition to generate the intermediate **C**, which delivered the intermediate **D** by intramolecular cyclization, and generated the final product **4a** after dehydration.

Conclusions

We have developed an operationally mild and high efficient reaction for preparing benzothiazolopyrimidines by a three-component reaction of 2-aminebenzo[*d*]thiazoles, sulfonyl azides and terminal ynones. From a mechanistic perspective, the cascade process involved a CuAAC/ring cleavage/cyclization reaction. This methodology appears quite flexible and offers a capacity to generate forms of the title products that will be particularly useful in drug development studies.

Experimental

General

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at ambient temperatures on a 400 MHz Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are presented as δ values relative to TMS and ^{1}H–^{1}H coupling constants (J values) are given in Hz. IR spectra were recorded on a BUCHI IRAffinity-1S spectrometer while HRMS measurements were carried out on a Bruker micrOTOF-Q II spectrometer. Melting points were determined on a BUCHI melting point M-565 apparatus and are uncorrected.

Preparation and characterizations of compounds 4a–4z

(*Z*)-4-Methyl-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin -4-ylidene)benzenesulfonamide (4a). To a solution of CuI (9.5 mg, 0.05 mmol) and 2-aminobenzothiazole (**1a**, 75.0 mg, 0.5 mmol) in EtOH (3 mL) was added TsN_3 (**2a**, 147.9 mg, 0.75 mmol), and 3-butyn-2-one (**3a**, 51.1 mg, 0.75 mmol). After stirring at room temperature for 12 h (TLC monitoring), the reaction mixture was directly centrifuged after the end of the reaction. The centrifuged solid was washed twice with EtOH : H_2O = 2 : 1 to obtain product **4a** (171.6 mg, 93%) as a white solid, mp 252–254 °C (R_f = 0.37 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, J = 10.4 Hz, 1H), 7.94 (d, J = 5.6 Hz, 2H), 7.70 (d, J = 10.0 Hz, 1H), 7.45–7.53 (m, 2H), 7.40 (s, 1H), 7.30 (d, J = 5.6 Hz, 2H), 2.44 (d, J = 14.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.5, 156.2, 142.8, 140.0, 136.0, 129.5 (2C), 128.0, 127.4, 126.7 (2C), 124.6, 122.7, 122.0, 104.8, 24.2, 21.7; IR ν 2920, 1609, 1493, 1450, 1402, 1283, 1140, 1088, 984, 812, 793, 756, 692 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{16}N_3O_2S_2^+$, $[M + H]^+$ 370.0679; found 370.0672.

The products **4b–4z** were prepared by the similar procedure.

(*Z*)-*N*-(2,8-Dimethyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4b). 172.4 mg (90%), yellow solid, mp 256–258 °C (R_f = 0.44 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 10.0 Hz, 2H), 7.49 (s, 1H), 7.39 (s, 1H), 7.29 (t, J = 11.4 Hz, 3H), 2.46 (d, J = 4.4 Hz, 6H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.5, 156.0, 142.7, 140.1, 138.6, 133.9, 129.5 (2C), 128.5, 126.7 (2C), 124.7, 122.3, 122.0, 104.8, 24.2, 21.7, 21.5; IR ν 2924, 1599, 1493, 1277, 1142, 1086, 982, 822, 810, 789, 733, 700, 671 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{19}H_{18}O_2N_3S_2^+$, $[M + H]^+$ 384.0835; found 384.0827.

(*Z*)-*N*-(2,6-Dimethyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4c). 63.2 mg (33%), white solid, mp 172–199 °C (R_f = 0.37 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 6.8 Hz, 1H), 7.37 (t, J = 6.4 Hz, 2H), 7.26 (d, J = 4.4 Hz, 3H), 2.49 (s, 3H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 162.3, 157.0, 143.0, 139.6, 134.2, 132.8, 131.3, 129.4 (2C), 127.8, 126.9 (2C), 125.5, 119.4, 104.5 25.6, 23.8, 21.7; IR ν 2926, 1597, 1487, 1398, 1298, 1283, 1146, 1086, 978, 810, 787, 739, 706, 664 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{19}H_{18}O_2N_3S_2^+$, $[M + H]^+$ 384.0835; found 384.0828.

(*Z*)-*N*-(8-Fluoro-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4d). 137.4 mg (71%), white solid, mp 191–242 °C (R_f = 0.26 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (t, J = 5.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.41 (s, 2H), 7.31 (d, J = 6.8 Hz, 2H), 7.18 (t, J = 9.2 Hz, 1H), 2.44 (d, J = 13.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.20 (d, J = 250.1 Hz, 1C), 161.17, 155.9, 142.9, 139.9, 132.4 (d, J = 2.4 Hz, 1C), 129.6 (2C), 126.7 (2C), 126.4 (d, J = 10.3 Hz, 1C), 124.3 (d, J = 8.4 Hz, 1C), 115.1 (d, J = 22.9 Hz, 1C), 109.1 (d, J = 27.0 Hz, 1C), 105.0, 24.2, 21.7; IR ν 2920, 2851, 1595, 1491, 1460, 1400, 1148, 1088, 984, 854, 806, 789, 664 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{15}O_2N_3FS_2^+$, $[M + H]^+$ 388.0584; found 388.0579.

(*Z*)-*N*-(8-Chloro-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4e). 173.3 mg (86%), yellow solid, mp 261–262 °C (R_f = 0.51 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.42 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 2.44 (d, J = 13.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.0, 156.0, 143.0, 139.8, 134.5, 134.0, 129.6 (2C), 127.8, 126.7 (2C), 126.2, 123.5, 121.7, 105.0, 24.3, 21.7; IR ν 2924, 1597, 1495, 1395, 1312, 1150, 1092, 982, 824, 808, 791, 675, 664 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{15}O_2N_3ClS_2^+$, $[M + H]^+$ 404.0289; found 404.0284.

(*Z*)-*N*-(8-Bromo-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4f). 131.9 mg (59%), white solid, mp 269–270 °C (R_f = 0.32 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 9.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.82 (s, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.42 (s, 1H), 7.31 (d, J = 5.6 Hz, 2H), 2.45 (d, J = 12.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.9, 156.0, 143.0, 139.9, 134.9, 130.6, 129.6 (2C), 126.7 (2C), 126.5, 124.6, 123.7, 121.6, 105.1, 24.3, 21.7; IR ν 1597, 1487, 1474, 1391, 1362, 1302, 1287, 1144, 1086, 982, 814, 791, 664 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{15}O_2N_3BrS_2^+$, $[M + H]^+$ 447.9784; found 447.9778.

(*Z*)-4-Methyl-*N*-(2-methyl-8-nitro-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)benzenesulfonamide (4g). 51.8 mg (25%), yellow solid, mp 253–255 °C (R_f = 0.46 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, J = 9.6 Hz, 1H), 8.60 (s, 1H), 8.31 (d, J = 10.4 Hz, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.50 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 2.48 (d, J = 17.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.3, 156.1, 146.2, 143.4, 139.7, 139.6, 129.8 (2C), 126.7 (2C), 126.2, 122.9, 122.7, 117.7, 105.4, 24.4, 21.7; IR ν 2920, 1694, 1597, 1539, 1504, 1458, 1337, 1315, 1152, 1090, 669 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{15}O_4N_4S_2^+$, $[M + H]^+$ 415.0529; found 415.0522.

Ethyl(*Z*)-2-methyl-4-(tosylimino)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-8-carboxylate (4h). 90.4 mg (41%), yellow solid, mp 135–209 °C (R_f = 0.35 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, J = 9.2 Hz, 1H), 8.39 (s, 1H), 8.11 (d, J = 11.6 Hz, 1H), 7.94 (d, J = 10.8 Hz, 2H), 7.45 (s, 1H), 7.33 (d, J = 8.0 Hz, 2H), 4.40–4.46 (m, 2H), 2.46 (d, J = 13.6 Hz, 6H), 1.42 (t, J = 9.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.3, 161.7, 156.2, 143.0, 139.9, 138.8, 130.0, 129.6 (2C), 128.6, 126.7 (2C), 125.0, 123.4, 122.3, 105.1, 62.0, 24.3, 21.7, 14.4; IR ν 2924, 1717, 1605, 1493, 1458, 1395, 1268, 1150, 1087, 984, 785, 762, 692 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{21}H_{20}O_4N_3S_2^+$, $[M + H]^+$ 442.0890; found 442.0883.

(*Z*)-*N*-(8-Methoxy-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4i). 155.6 mg (78%), yellow solid, mp 248–250 °C (R_f = 0.25 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, J = 9.6 Hz, 1H), 7.94 (d, J = 9.6 Hz, 2H), 7.37 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.16 (s, 1H), 6.99 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H), 2.43 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.1, 159.1, 155.8, 142.7, 140.2, 129.8, 129.5 (2C), 126.7

(2C), 126.3, 123.8, 114.3, 106.1, 104.8, 56.0, 24.2, 21.7; IR ν 2926, 1612, 1503, 1493, 1271, 1140, 1090, 1022, 984, 831, 737, 702, 673 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{19}H_{18}O_3N_3S_2^+$ $[M + H]^+$ 400.0784; found 400.0778.

(*Z*)-*N*-(8-Ethoxy-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4j). 107.4 mg (52%), white solid, mp 261–263 °C ($R_f = 0.24$ in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, $J = 13.2$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 2H), 7.36 (s, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.14 (s, 1H), 6.97 (d, $J = 11.2$ Hz, 1H), 4.06–4.12 (m, 2H), 2.43 (d, $J = 6.8$ Hz, 6H), 1.45 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 161.1, 158.5, 155.7, 142.7, 140.1, 129.6, 129.5 (2C), 126.7 (2C), 126.2, 123.7, 114.7, 106.6, 104.7, 64.4, 24.2, 21.7, 14.8; IR ν 1603, 1497, 1288, 1184, 1144, 1094, 982, 941, 829, 816, 665, cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{20}H_{20}O_3N_3S_2^+$ $[M + H]^+$ 414.0941; found 414.0933.

(*Z*)-*N*-(8-Hydroxy-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-4-ylidene)-4-methylbenzenesulfonamide (4k). 173.3 mg (90%), white solid, mp 255–257 °C ($R_f = 0.31$ in 2 : 1 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.98 (d, $J = 9.6$ Hz, 1H), 7.82 (d, $J = 6.8$ Hz, 2H),7.36 (d, $J = 8.4$ Hz, 3H), 7.11 (s, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 2.35 (d, $J = 10.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.7, 157.2, 155.4, 142.7, 139.9, 129.8 (2C), 128.4, 126.7, 126.5 (2C), 122.8, 115.0, 108.8, 103.5, 23.8, 21.2; IR ν 3277, 2926, 1618, 1503, 1452, 1261, 1130, 1090, 1063, 988, 845, 835, 704, 687 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{16}O_3N_3S_2^+$ $[M + H]^+$ 386.0628; found 386.0621.

(*Z*)-4-Methyl-*N*-(7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ylidene)benzenesulfonamide (4l). 140.0 mg (84%), white solid, mp 93–122 °C ($R_f = 0.22$ in 1 : 1 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (t, $J = 4.2$ Hz, 1H), 7.96 (d, $J = 7.2$ Hz, 2H), 7.35 (s, 3H), 7.26 (t, $J = 4.0$ Hz, 1H), 2.54 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.0, 153.4, 142.7, 139.9, 129.4 (2C), 126.7 (2C), 123.3, 113.3, 102.4, 24.8, 21.6; IR ν 2920, 1587, 1456, 1412, 1279, 1140, 1083, 1045, 1003, 937, 822, 787, 706, 664 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{14}H_{14}O_2N_3S_2^+$ $[M + H]^+$ 320.0522; found 320.0516.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)benzenesulfonamide (4m). 156.2 mg (88%), white solid, mp 258–260 °C ($R_f = 0.33$ in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, $J = 12.0$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.42–7.54 (m, 6H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.6, 156.3, 142.9, 136.0, 132.2, 129.0 (2C), 128.0, 127.4, 126.7 (2C), 124.7, 122.7, 122.0, 104.9, 24.3; IR ν 2924, 1605, 1503, 1495, 1452, 1287, 1144, 1088, 984, 814, 758, 694 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{17}H_{14}O_2N_3S_2^+$ $[M + H]^+$ 356.0522; found 356.0517.

(*E*)-4-Chloro-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-4-ylidene)benzenesulfonamide (4n). 175.1 mg (90%), yellow solid, mp 216–220 °C ($R_f = 0.20$ in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, $J = 8.8$ Hz, 1H), 7.99 (d, $J = 4.8$ Hz, 2H), 7.72 (d, $J = 10.8$ Hz, 1H), 7.48–7.55 (m, 4H), 7.40 (s, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.6, 156.3, 141.5, 138.5, 136.0, 129.2 (2C), 128.2 (2C), 128.1, 127.5, 124.8, 122.6, 122.1, 104.9, 24.3; IR ν 1607, 1491, 1454, 1400, 1292, 1140, 1088, 984, 812, 756, 683 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{17}H_{13}O_2N_3ClS_2^+$ $[M + H]^+$ 390.0132; found 390.0126.

(*E*)-4-Bromo-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-4-ylidene)benzenesulfonamide (4o). 210.0 mg (97%), yellow solid, mp 179–242 °C ($R_f = 0.24$ in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, $J = 5.6$ Hz, 1H), 7.92 (d, $J = 9.2$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 9.2$ Hz, 2H), 7.47–7.56 (m, 2H), 7.40 (s, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.7, 156.3, 142.0, 135.9, 132.2 (2C), 128.3 (2C), 128.2, 127.5, 127.0, 124.8, 122.6, 122.1, 104.9, 24.3; IR ν 3088, 1605, 1491, 1452, 1402, 1292, 1136, 1086, 982, 812, 756, 739, 677 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{17}H_{13}O_2N_3BrS_2^+$ $[M + H]^+$ 435.9607; found 435.9598.

(*E*)-4-Methoxy-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-4-ylidene)benzenesulfonamide (4p). 186.8 mg (97%), white solid, mp 185–205 °C ($R_f = 0.25$ in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, $J = 11.2$ Hz, 1H), 7.99 (d, $J = 10.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.46–7.54 (m, 2H), 7.41 (s, 1H), 6.98 (d, $J = 10.4$ Hz, 2H), 3.87 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.6, 161.6, 156.2, 136.1, 134.9, 128.7 (2C), 128.0, 127.4, 124.7, 122.7, 122.0, 114.1 (2C), 104.8, 55.7, 24.3; IR ν 1595, 1487, 1443, 1406, 1285, 1250, 1140, 1086, 1026, 984, 812, 758, 669 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{16}O_3N_3S_2^+$ $[M + H]^+$ 386.0628; found 386.0622.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-4-nitrobenzenesulfonamide (4q). 184.0 mg (92%), yellow solid, mp 257–259 °C ($R_f = 0.32$ in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, $J = 10.4$ Hz, 1H), 8.37 (d, $J = 9.6$ Hz, 2H), 8.25 (d, $J = 7.2$ Hz, 2H), 7.75 (d, $J = 5.2$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 8.6$ Hz, 1H), 7.44 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.8, 156.4, 149.9, 148.6, 135.8, 128.4, 128.0 (2C), 127.6, 124.9, 124.3 (2C), 122.5, 122.3, 104.9, 24.4; IR ν 2922, 1557, 1522, 1493, 1342, 1146, 1090, 984, 818, 764, 739, 685 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{17}H_{13}O_4N_4S_2^+$ $[M + H]^+$ 401.0373; found 401.0366.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)naphthalene-1-sulfonamide (4r). 188.4 mg (93%), white solid, mp 171–212 °C ($R_f = 0.27$ in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, $J = 11.6$ Hz, 1H), 8.63 (s, 1H), 8.05 (d, $J = 11.6$ Hz, 1H), 7.98 (t, $J = 8.2$ Hz, 2H), 7.90 (d, $J = 7.2$ Hz, 1H), 7.70 (d, $J = 11.2$ Hz, 1H), 7.60 (s, 2H), 7.42–7.52 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.6, 156.3, 139.8, 136.0, 134.8, 132.3, 129.4, 129.3, 128.5, 128.0 (2C), 127.4 (2C), 127.3, 124.7, 122.74, 122.68, 122.0, 104.9, 24.3; IR ν 1607, 1495, 1452, 1404, 1285, 1144, 1124, 1074, 986, 860, 806, 748, 691 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{21}H_{16}O_2N_3S_2^+$ $[M + H]^+$ 406.0679; found 406.0671.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)methanesulfonamide (4s). 111.4 mg (76%), yellow solid, mp 133–223 °C ($R_f = 0.14$ in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, $J = 5.2$ Hz, 1H), 7.74 (d, $J = 3.2$ Hz, 1H), 7.55 (d, $J = 3.6$ Hz, 2H), 7.35 (s, 1H), 3.22 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9,

161.5, 156.3, 136.0, 128.0, 127.2, 124.7, 122.3, 122.2, 105.1, 42.9, 24.2; IR ν 2922, 1605, 1503, 1493, 1454, 1277, 1252, 1115, 1063, 982, 953, 824, 761, 660 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{12}H_{12}O_2N_3S_2^+$ $[M + H]^+$ 294.0366; found 294.0359.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)propane-1-sulfonamide (4t). 133.2 mg (83%), white solid, mp 120–128 °C (R_f = 0.34 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, J = 4.4 Hz, 1H), 7.73 (d, J = 4.0 Hz, 1H), 7.55 (d, J = 3.6 Hz, 2H), 7.40 (s, 1H), 3.25 (t, J = 8.0 Hz, 2H), 2.46 (s, 3H), 2.00–2.07 (m, 2H), 1.14 (t, J = 9.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 161.5, 156.5, 136.1, 127.9, 127.1, 124.7, 122.2 (2C), 105.3, 56.8, 24.2, 17.6, 13.3; IR ν 2967, 1603, 1493, 1452, 1406, 1275, 1250, 1115, 1059, 984, 820, 758, 669 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{14}H_{16}O_2N_3S_2^+$ $[M + H]^+$ 322.0679; found 322.0674.

(*E*)-2-Methyl-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)propane-1-sulfonamide (4u). 157.5 mg (94%), yellow solid, mp 127–145 °C (R_f = 0.43 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 4.0 Hz, 1H), 7.55 (d, J = 4.0 Hz, 2H), 7.40 (s, 1H), 3.20 (s, 2H), 2.46 (s, 4H), 1.19 (d, J = 5.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 161.5, 156.4, 136.1, 127.9, 127.1, 124.7, 122.3, 122.2, 105.2, 62.7, 25.1, 24.2, 23.0 (2C); IR ν 2922, 1605, 1495, 1450, 1402, 1369, 1283, 1113, 982, 835, 814, 758, 667 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{15}H_{18}O_2N_3S_2^+$ $[M + H]^+$ 336.0835; found 336.0828.

(*E*)-*N*-(2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)-1-phenylmethanesulfonamide (4v). 149.5 mg (81%), white solid, mp 188–222 °C (R_f = 0.36 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 28.0 Hz, 5H), 7.30 (s, 3H), 4.46 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 161.4, 156.9, 135.8, 134.5, 132.3, 131.0, 130.0, 129.1, 128.8, 128.0, 127.2, 124.6, 122.5, 122.1, 105.1, 60.6, 24.1; IR ν 2924, 1603, 1493, 1400, 1256, 1152, 1099, 982, 824, 756, 704, 677 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{18}H_{16}O_2N_3S_2^+$ $[M + H]^+$ 370.0679; found 370.0681.

(*E*)-3-Chloro-*N*-(2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)propane-1-sulfonamide (4w). 163.3 mg (92%), white solid, mp 107–120 °C (R_f = 0.25 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, J = 4.8 Hz, 1H), 7.74 (t, J = 4.4 Hz, 1H), 7.56 (d, J = 5.2 Hz, 2H), 7.37 (s, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.46 (t, J = 6.0 Hz, 2H), 2.48 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.6, 156.6, 136.0, 128.1, 127.4, 124.7, 122.3, 122.2, 105.3, 52.1, 43.4, 27.4, 24.2; IR ν 1601, 1491, 1452, 1445, 1406, 1281, 1250, 1111, 1061, 984, 820, 758, 669 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{14}H_{15}O_2N_3ClS_2^+$, $[M + H]^+$ 356.0289; found 356.0283.

1-((1*R*,4*S*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-((*E*)-2-methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)methanesulfonamide (4x). 197.4 mg (92%), white solid, mp 202–240 °C (R_f = 0.29 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, J = 10.8 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.56 (m, 2H), 7.47 (s, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.14 (d, J = 14.8 Hz, 1H), 2.76 (t, J = 14.8 Hz, 1H), 2.48 (s, 3H), 2.39 (d, J = 18.4 Hz, 1H), 2.02–2.11 (m, 2H), 1.92 (d, J = 18.8 Hz, 1H), 1.72–1.79 (m, 1H), 1.40 (t, J = 11.0 Hz, 1H), 1.18 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 162.9, 161.5, 156.7, 136.0, 128.0, 127.4, 124.6, 122.8, 122.0, 105.3, 58.6, 50.4, 48.3, 42.9, 42.7, 27.2, 24.7, 24.2, 20.2, 20.0; IR ν 2953, 1740, 1611, 1503, 1456, 1398, 1281, 1121, 1053, 986, 818, 752, 683 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{21}H_{24}O_3N_3S_2^+$, $[M + H]^+$ 430.1254; found 430.1246.

(*Z*)-4-Methyl-*N*-(2-pentyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)benzenesulfonamide (4y). 180.7 mg (85%), white solid, mp 174–181 °C (R_f = 0.40 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, J = 6.8 Hz, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 6.8 Hz, 1H), 7.50 (m, 2H), 7.37 (s, 1H), 7.30 (d, J = 7.6 Hz, 2H), 2.66 (t, J = 8.6 Hz, 2H), 2.42 (s, 3H), 1.71 (s, 2H), 1.34 (s, 4H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 161.6, 156.5, 142.8, 140.0, 136.1, 129.5 (2C), 127.9, 127.4, 126.8 (2C), 124.7, 122.8, 122.0, 104.2, 37.8, 31.5, 28.0, 22.5, 21.7, 14.1; IR ν 2926, 1601, 1493, 1450, 1404, 1279, 1146, 1086, 1047, 810, 752, 669 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{22}H_{24}O_2N_3S_2^+$, $[M + H]^+$ 426.1305; found 426.1297.

(*Z*)-4-Methyl-*N*-(2-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ylidene)benzenesulfonamide (4z). 170.3 mg (79%), white solid, mp 258–259 °C (R_f = 0.24 in 1 : 6 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, J = 3.6 Hz, 1H), 8.09 (s, 2H), 7.98 (s, 3H), 7.72 (s, 1H), 7.51 (s, 5H), 7.32 (d, J = 6.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 159.2, 156.8, 142.9, 140.1, 136.0, 135.1, 131.9, 129.6 (2C), 129.1 (2C), 128.0 (3C), 127.5, 126.8 (2C), 125.0, 122.8, 122.0, 101.0, 21.7; IR ν 2922, 1589, 1483, 1443, 1396, 1310, 1279, 1261, 1144, 1080, 818, 750, 660 cm^{-1}; HRMS (ESI-TOF) (m/z). Calcd for $C_{23}H_{18}O_2N_3S_2^+$, $[M + H]^+$ 432.0835; found 432.0830.

2-Methyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-imine (5a). 84.9 mg (79%), white solid, mp 141–178 °C (R_f = 0.31 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 6.4 Hz, 1H), 7.45 (t, J = 9.0 Hz, 1H), 7.38 (t, J = 8.6 Hz, 1H), 6.95 (s, 1H), 5.97 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 159.3, 153.9, 137.3, 126.6, 126.0, 123.9, 121.4, 121.0, 107.7, 23.0; IR ν 2922, 2853, 2205, 1636, 1524, 1456, 1271, 1182, 976, 748, 698 cm^{-1}.

All NMR spectra please see ESI Section 3.†

Conflicts of interest

There are no conflicts to declare.

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