Regioselective Sulfonylation and N- to O-Sulfonyl Migration of Quinazolin-4(3H)-ones and Analogous Thienopyrimidin-4(3H)-ones

Matthias D. Mertens,[†] Markus Pietsch,^{†,§} Gregor Schnakenburg,[‡] and Michael Gütschow^{*,†}

[†]Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany [‡]Institute of Inorganic Chemistry, University of Bonn, Gerhard-Domagk-Strasse 1, D-53121 Bonn, Germany

Supporting Information

ABSTRACT: The sulfonylation of quinazolin-4(3*H*)-ones and related tetrahydrobenzothieno[2,3-d]pyrimidin-4(3*H*)ones with mesyl, tosyl, and *p*-cyanobenzenesulfonyl chloride was studied. A hydrogen substituent at 2-position directed the sulfonyl group to the N-3 position, while alkylsulfanyl or amino substituents led to sulfonylation of the carbonyl oxygen. The latter effect was attributed to steric influence and the positive mesomeric effect of the 2-substituent. An access to *N*sulfonylated 2-substituted regioisomers was established. An



unexpected 1,3-sulfonyl migration was observed and further analyzed. This process occurred as an intramolecular *N*- to *O*-shift as verified by kinetic and crossover experiments.

INTRODUCTION

Nucleophilic displacement reactions of sulfonamides and sulfonates are characterized by competitive reaction pathways and have been the subject of numerous mechanistic studies and synthetic applications. The underlying mechanistic variations are known to depend on the nucleophile, the solvent, and explicitly, the substrate, i.e., the structure of the parent sulfonic acid and the amine or alcohol/phenol portion, respectively.¹ Sulfonamides composed of basic amines are notably stable to alkaline hydrolysis and other conditions, whereas sulfonamides of less basic amines are easier to cleave due to their improved nucleofugality. Alternatively, arenesulfonamides can undergo a nucleophilic aromatic substitution at the ipso-carbon of the electron-poor aromatic ring (Chart 1, A; nucleophilic attacks are indicated by arrows) as utilized in nosyl protecting groups.² In common nucleophilic substitutions of alkyl sulfonates, the sulfonate anion serves as leaving group. In aryl sulfonates (Chart 1, B), nucleophilic displacement reactions take place at

Chart 1. Possible Sites for Nucleophilic Attack at Arenesulfonamides, Aryl Sulfonates, N-(Sulfonyloxy)imides, and Fused 3-(Arylsulfonyl)pyrimidin-4(3H)-ones



the SO₂ center by S–O bond scission,^{3,4} and a competing C–O bond cleavage occurs to release the sulfonate anion from a Meisenheimer-type intermediate.¹

N-Unsubstituted O-sulfonyl hydroxamic acids are substrates for the Lossen rearrangement, whereas N-substituted derivates behave differently in the presence of nucleophiles. By concomitant loss of the sulfonyl group, amides or lactams with the newly introduced substituent in α -position are formed.⁵ In N-(sulfonyloxy)imides (Chart 1, C), the typical reaction is initiated by the nucleophilic attack at the carbonyl carbon followed by the expulsion of the sulfonate,^{6,7} but a nucleophilic displacement at the sulfonate sulfur is also possible.⁸ Moreover, α -sulfonyl carbanions of alkanesulfonates or -sulfonamides can attack electrophilic sites to undergo intramolecular or intermolecular coupling reactions.⁹ Thus, in heterocyclic chemistry, different sulfonyl transfer reactions may have to be considered, for example, for the targeted preparation of N- or O-sulfonylated lactams and their utilization for subsequent chemical transformations.

In this study, we examined sulfonylation reactions of quinazolin-4(3*H*)-ones and related thieno[2,3-*d*]pyrimidin-4(3*H*)-ones. While the regioselectivity of alkylation of such systems has been investigated,^{10,11} corresponding reports on sulfonylation of fused pyrimidinones are lacking. The products, i.e., *N*- or *O*-sulfonylated heterocycles, possess biological activities and represent attractive intermediates for diverse transformations. Fused pyrimidin-4(3*H*)-ones, e.g., unsubstituted in the 2-position and bearing an arylsulfonyl substituent at N-3, are susceptible to nucleophilic attack at four positions (Chart 1, D).¹²

Received: July 2, 2013



© XXXX American Chemical Society

Table 1. Preparation of N- and O-Sulfonylated Fused Pyrimidines 11-14

Entry Substrate SO ₂ R ² Yield (%) Entry Substrate SO ₂ R ² Yield (%) 1 $f = \int_{1}^{1} \int_{0}^{1} \int_{0}^{1} H$ Ts 73 (11a) 16 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 30 (14b) 2 1 SO ₂ C ₆ H ₄ -4-CN 55 (11b) 17 6 SO ₂ C ₆ H ₄ -4-CN 31 (14i) 3 1 Ms 58 (11c) 18 6 Ms 47 (14j) 4 1 SO ₂ C ₆ H ₇ -2,4,6-i-Pr 52 (11d) 19 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 41 (13k) 5 $\int_{0}^{2} \int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 74 (12a) 19 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 41 (13k) 6 2 SO ₂ C ₆ H ₂ -2,4,6-i-Pr 61 (14d) 21 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 66 (14k) 8 2 SO ₂ C ₆ H ₂ -2,4,6-i-Pr 61 (14d) 21 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 66 (14k) 9 $\int_{0}^{1} \int_{0}^{1} H^{H}$ Ts 83 (13e) 22 8 SO ₂ C ₆ H ₄ -4-CN		$\underbrace{\bigcup_{O}}^{N} \underset{O}{\overset{V}{\underset{O}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset$			$ \begin{array}{c} & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & $			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Entry	Substrate	SO_2R^2	Yield (%)	Entry	Substrate	SO_2R^2	Yield (%)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1		Ts	73 (11a)	16	6	Ts	30 (14h)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2	1	SO ₂ C ₆ H ₄ -4-CN	55 (11b)	17	6	SO ₂ C ₆ H ₄ -4-CN	31 (14i)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3	1	Ms	58 (11c)	18	6	Ms	47 (14 j)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4	1	SO ₂ C ₆ H ₂ -2,4,6- <i>i</i> -Pr	52 (11d)				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	5		Ts	74 (12a)	19	NH 7 O	Ts	41 (13k)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6	2	SO ₂ C ₆ H ₄ -4-CN	72 (12b)	20	7	SO ₂ C ₆ H ₄ -4-CN	50 (13l)
8 2 $SO_2C_6H_2-2,4,6-i-Pr$ 61 (14d) 9 4 Ts 83 (13e) 10 3 $SO_2C_6H_4-4-CN$ 71 (13f) 11 4 $SO_2C_6H_4-4-CN$ 71 (13f) 12 4 $SO_2C_6H_4-4-CN$ 76 (14f) 13 4 Ms 56 (14g) 26 Me Me $SO_2C_6H_4-4-CN$ 76 (14f) 14 $\int_{-K}^{-K} MH$ Ts 64 (13h)	7	2	Ms	40 (12c)	21	S N N	Ts	66 (14k)
9 $\int_{3} \left(\int_{0}^{N_{H}} \int_{NH}^{N_{H}} \right)^{NH} T_{S}$ $R_{3} (13e)$ 22 8 $SO_{2}C_{6}H_{4}-4-CN$ 79 (14) 10 3 $SO_{2}C_{6}H_{4}-4-CN$ 71 (13f) 11 $\int_{0}^{S} \int_{0}^{N_{H}} \int_{NH}^{N_{H}} T_{S}$ 69 (14e) 24 $\int_{9} \int_{0}^{M_{H}} \int_{NH}^{M_{H}} T_{S}$ 67 (13n) 12 4 $SO_{2}C_{6}H_{4}-4-CN$ 76 (14f) 13 4 Ms 56 (14g) 26 $\int_{10}^{N_{H}} \int_{NH}^{M_{H}} T_{S}$ 68 (14n) 14 $\int_{0}^{N_{H}} \int_{NH}^{N_{S}Bn} T_{S}$ 68 (14n)	8	2	SO ₂ C ₆ H ₂ -2,4,6- <i>i</i> -Pr	61 (14d)		8 O		· · ·
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9	3 O	Ts	83 (13e)	22	8	SO ₂ C ₆ H ₄ -4-CN	79 (14I)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10	3	SO ₂ C ₆ H ₄ -4-CN	71 (13f)	23	8 Me	Ms	68 (14m)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	11	S N SM	e Ts	69 (14e)	24	9 ON NH	Ts	67 (13n)
13 4 Ms $56 (14g)$ 26 $S \downarrow N \downarrow N_B n$ Ts $68 (14n)$ 14 14 Ts $64 (13h)$	12	4	SO ₂ C ₆ H ₄ -4-CN	76 (14f)	25	9	SO ₂ C ₆ H ₄ -4-CN	51 (13 0)
$14 \qquad \qquad 10 \qquad 10 \qquad 0$	13	4	Ms	56 (14g)	26		Ts	68 (14n)
5 $\overset{\parallel}{\rm O}$ 27 10 SO ₂ C ₆ H ₄ -4-CN 74 (140)	14	5 O SBn	Ts	64 (1 3h)	27	10 Ö	SO ₂ C ₆ H ₄ -4-CN	74 (14o)
15 5 SO ₂ C ₆ H ₄ -4-CN 34 (13i) 28 10 Ms 56 (14p)	15	5	SO ₂ C ₆ H ₄ -4-CN	34 (13i)	28	10	Ms	56 (14 p)

Quinazoline-2,4-diones with aromatic sulfonyl groups at position N-3 were identified as inhibitors of the serine protease chymase. Their interaction with the target enzyme was assumed to involve a nucleophilic attack of the active-site serine at the C-4 carbonyl followed by ring-opening.¹³ In addition, related compounds are useful in heterocyclic syntheses. For example, N-3 tosyl-substituted quinazolin-4(3H)-one undergoes a ringopening-recyclization reaction with primary alkylamines to afford 3-alkylquinazolin-4(3H)-ones upon loss of tosyl amide.¹⁴ Inosines bearing aromatic sulfonyl groups at position N-1

(corresponding to N-3 in pyrimidin-4(3H)-ones) have been studied in detail with respect to their reactivity toward primary aliphatic amines. An initial attack at C-2 and alternate ring closure reactions of the ring-open intermediates yield various types of products.¹⁵

O-Sulfonylated fused pyrimidin-4(3H)-ones have attracted attention as versatile electrophilic intermediates. For example, activation of quinazolin-4(3H)-ones with tosyl chloride generates a sulfonate structure, which is subsequently replaced with thiols or amines.¹⁶ Arylsulfonyloxy groups were

introduced at C-6 of purines (corresponding to position C-4 in pyrimidines) and successfully used for the preparation of corresponding amines, *O*-alkyl or *O*-aryl ethers.^{17,18} Furthermore, 6-arylsulfonyloxy purines are valuable building blocks for Pd-catalyzed cross-couplings. Such derivatives of 2'-deoxyguanosine or guanosine were shown to undergo Suzuki-Miyaura reactions with arylboronic acids,¹⁹ and were employed as halogen surrogates in Stille-type reactions with vinyltributyl-stannane.²⁰ Similarly, 4-arylsulfonyloxy derivatives of uridines and thymidines were successfully utilized in C–C coupling reactions.^{21,22}

RESULTS AND DISCUSSION

As initial part of this study, we investigated the regioselectivity of the sulfonylation of a series of representative fused pyrimidin-4-ones (1–10). Three sulfonyl chlorides, i.e., mesyl, tosyl, and *p*-cyanobenzenesulfonyl chloride, were reacted with 1–10 in dichloromethane in the presence of DIPEA (*N*,*N*diisopropylethylamine) and DMAP (4-dimethylaminopyridine) at room temperature (Table 1, all entries except of entries 4 and 8), and the main products of these transformations were isolated. On the one hand, *N*-sulfonylated compounds (11a–c and 12a–c) were obtained in good yields from quinazoline 1 and thienopyrimidine 2, bearing no substitutent at position 2 ($R^1 = H$). On the other hand, starting materials 3–10 with various substituents R^1 in position 2 gave exclusively the corresponding *O*-sulfonylated products.

A steric influence of the sulfonylating reagent was studied by treating 1 and 2 with the sterically demanding 2,4,6-triisopropylbenzenesulfonyl chloride (Table 1, entries 4 and 8). This reagent has frequently been used for *O*-sulfonylations of related lactams.^{4,22-24} The reaction of the quinazolinone 1 afforded the *N*-sulfonylated product 11d, whereas the thienopyrimidinone 2 gave the *O*-sulfonylated product 14d.

A strong impact of the substituent at position 2 on the outcome of the sulfonylation was observed. A hydrogen substituent with the lowest steric hindrance for an electrophilic attack at the adjacent N-3 position allowed for the sulfonylation of the lactam nitrogen. The only exception (entry 8) was the formation of 14d from 2,4,6-triisopropylbenzenesulfonyl chloride and the thienopyrimidinone 2. The quinazolinone 1 gave exclusively 3-sulfonylated products, even with 2,4,6triisopropylbenzenesulfonyl chloride (entry 4). The different behavior of 1 and 2 might be attributed to an increased electron density of the carbonyl oxygen in 2 due to the anellated thiophene ring.²⁵ The larger 2-substituents (i.e., methylsulfanyl, benzylsulfanyl, morpholino, N-benzyl-N-methylamino) directed the sulfonyl group to the carbonyl oxygen. In addition to the steric influence, the positive mesomeric effect of these substituents, connected to carbon C-2 via S or N atoms, is expected to contribute to O-sulfonylation. Such substituents can donate their lone pair for resonance, which leads to an increased electron density at the oxygen (Chart 2).¹⁰

Chart 2. Mesomeric Effect of the 2-Substituent (X = N-Alk, S) in Fused Pyrimidin-4(3H)-ones



With the exception of 2,4,6-triisopropylbenzenesulfonyl chloride, the nature of the reagent, i.e., aliphatic (mesyl), electron-rich aromatic (tosyl), or electron-deficient aromatic (p-cyanobenzenesulfonyl chloride), did not influence the regioselectivity of the reaction.

The structures of the two types of products were elucidated on the basis of ¹H and ¹³C NMR spectra and confirmed by Xray diffraction analyses, both for two representative Nsulfonylated derivatives (**11d** and **12b**; see the Supporting Information, Figures S1 and S2) and for seven O-sulfonylated derivatives **14d**, **13e**, **14e**, **14f**, **14g**, **14k**, and **14o** (see the Supporting Information, Figures S3–9). Comparison of the ¹³C NMR resonances of the N- and O-isomers revealed diagnostic differences (see below).

Our results are in accordance with the reported *N*sulfonylation of quinazolin-4(3*H*)-one **1**.^{14,26} Analogously, reaction of inosine derivatives with 2,4-dinitrobenzenesulfonyl chloride or *ortho*-nosyl chloride only gave *N*-sulfonylated products.^{12,15} Mixtures of *N*- and *O*-sulfonylated products were formed in reactions of hypoxanthine nucleosides with 2,4,6-triisopropylbenzenesulfonyl chloride,¹⁸ whereas 2-isobutyrylamino and 2-(dimethylamino)methyleneamino hypoxanthines and as well as 2-amino, 2-tritylamino, acetylamino and 2benzoylamino guanosines furnished *O*-sulfonylated compounds when reacted with aromatic sulfonyl chlorides.^{4,23} Reactions of thymidines and uridines with aromatic sulfonyl chlorides resulted in 4-sulfonyloxy products.^{21,22,24}

For the exemplary preparation of the 2-substituted *N*-sulfonyl compounds, which were not accessible via direct sulfonylation of pyrimidinones 3-10, we followed another synthetic strategy. It includes, similar to the preparation of 3-arylsulfonylquinazoline-2,4-diones,¹³ the attachment of the sulfonyl group to the terminal nitrogen of an isothiourea moiety prior to cyclization (Scheme 1). Starting from 2-nitrobenzoic acid (15), the corresponding *tert*-butyl ester was

Scheme 1. Synthesis of the N-Sulfonylated Quinazoline 11e^a



^aReagents and conditions: (a) (i) $(COCl)_2$, cat. DMF, CH_2Cl_2 , 2 h; (ii) *t*-BuOH, cat. ZnCl₂, pyridine, 12 h; (b) H_2 , Pd/C (10%), EtOH, 3 days; (c) $CSCl_2$, Et₃N, EtOAc, -78 °C to rt, 12 h; (d) TsNH₂, K₂CO₃, acetone, reflux, 20 h; (e) MeI, EtOH, NaOH_(aq), 2 h; (f) TFA, 2 h; (g) CDI, THF, 1 h.

prepared with oxalyl chloride and a catalytic amount of DMF. followed by the treatment with tert-butyl alcohol in the presence of pyridine and ZnCl₂. The resulting ester 16 was hydrogenated using Pd/C to give the tert-butyl ester of anthranilic acid (17). Upon treatment with thiophosgene, 17 was converted to the isothiocyanate 18. Reaction with ptoluenesulfonamide in the presence of potassium carbonate yielded the corresponding sulfonylthiourea 19, which was Smethylated to give 20. Cleavage of the ester group with trifluoroacetic acid produced the benzoic acid derivative 21. While 2-thioureidobenzoic acids are readily accessible in their open-chain structure, in particular if an electron withdrawing group is placed at the terminal nitrogen,²⁷ benzoic acids with an adjacent isothioureido group have not been described so far. Compound 21 was cyclized by activating the carboxylic acid with CDI to yield the desired N-tosylated product 11e.

In order to receive further pairs of isomeric *N*- and *O*-sulfonated compounds, in addition to the quinazolines **11e** and **13e**, a subseries of *N*-sulfonylated tetrahydrobenzothienopyrimidines was prepared. For this purpose, the established synthetic route was transferred to the thiophene scaffold (Scheme 2). Isothiocyanate **22** was synthesized²⁸ and

Scheme 2. Synthesis of N-Sulfonylated Thieno [2,3-d] pyrimidines 12e-h,j^a



"Reagents and conditions: (a) $R^2SO_2NH_2$, K_2CO_3 , acetone, reflux, 20 h ($R^2 = C_6H_4$ -4-Me or C_6H_4 -4-CN) or NaH, DMF, 60 °C, 1 h ($R^2 = Me$); (b) $R^{1}I/Br$, EtOH, NaOH_(aq), 2 h; (c) TFA, 2 h; (d) (COCl)₂, cat. DMF, CH₂Cl₂, 1 h.

subsequently reacted with different sulfonamides. In the case of the less acidic methanesulfonamide, sodium hydride was applied as base according to a literature report.²⁹ S-Alkylation yielded compounds **26**, whose *tert*-butyl esters were cleaved.³⁰ The resulting 2-isothioureidothiophene-3-carboxylic acids **27** underwent cyclocondensation with oxalyl chloride to give the final *N*-sulfonyl compounds **12e**, **12f**, **12g**, **12h**, and **12j**. The molecular structure of **12e** is shown in the Supporting Information (Figure S10).

Oxalyl chloride was not applicable for the cyclization of the benzoic acid derivative 21 (Scheme 1) as, instead of 11e, the corresponding desulfonylated quinazolinone 3 (for structure, see Table 1) and tosyl chloride were isolated. These products originate from the nucleophilic attack of chloride at the sulfur atom of 11e. The different behavior reflects the decreased electron density of the quinazolinone in comparison to the thienopyrimidinone scaffold. This finding indicates the ability of N-3 sulfonylated fused pyrimidines to act as sulfonyl donors.

In their ¹³C NMR spectra, the three downfield signals were found to be indicative to distinguish between the substrates of the sulfonylation reaction, the N-sulfonylated products 11 and 12 and the isomeric O-sulfonylated products 13 and 14. For example, in the case of the N-sulfonyl quinazoline 11e, the three downfield carbon shifts (146.1, 154.2, 161.2 ppm for C-2, C-4 and C-8a) appeared at higher field than in 3 (149.2, 155.2, 163.1 ppm for C-2, C-4 and C-8a). On the contrary, the signals for the O-sulfonylated quinazoline 13e were shifted downfield (153.3, 160.9, 166.9 ppm for C-2, C-4 and C-8a) in comparison to the substrate 3. For the thienopyrimidine series, similar shift differences were noticed. The N-sulfonylated thienopyrimidines 12e, 12f, 12g, 12h, and 12j showed resonances (~155, ~157, \sim 160 ppm for C-2, C-4, C-9a) similar to or at higher field than the unsulfonylated compounds 4 and 6 (~155, ~158, ~163 ppm for C-2, C-4, C-9a). A notable downfield shift occurred for two of the three downfield carbon signals as a result of the Osulfonylation of 4 and 6 to 14e, 14f, 14g, 14h, and 14j (~156, ~165, ~171 ppm for C-2, C-4, and C-9a). The corresponding signals for 2-unsubstituted, O-sulfonylated 14d appeared at 151.2. 157.8. and 170.1 ppm.

When inspecting different cyclization conditions, 27e (Scheme 2) was also treated with boiling acetic anhydride. Instead of 12e, we obtained the isomeric O-sulfonylated product 14e (for structure, see Table 1) suggesting that an unexpected migration of the sulfonyl group from the nitrogen atom to the carbonyl oxygen might have occurred.³³ To proof this hypothesis, compound 12e was heated in acetonitrile and the course of the reaction was monitored by HPLC (Figure 1, see also the Supporting Information, Figure S11). The separation of both regioisomers was accomplished using an isocratic elution. Indeed, 12e was completely converted to 14e and side products were only formed to minor extent. The reaction followed a first-order kinetics and the analysis of the migration process by nonlinear regression using the equation for exponential decay gave a first-order rate constant of 0.0041 \pm 0.0001 min⁻¹. These data confirm the postulated sulforyl transfer to the thermodynamically more stable O-sulfonylated isomer and are also in agreement with the results of the direct sulfonylation as outlined in Table 1. However, the educts which are unsubstituted at 2-position, i.e., 1 and 2, behaved differently and were predominately sulfonylated at the nitrogen N-3. When 12a was heated in acetonitrile over 24 h, it remained unchanged. Thus, an N- to O-transfer did not occur, which indicates that in this case the N-sulfonylated products represent the thermodynamically favored isomers.

Further kinetic experiments were performed to shed light on the observed N- to O-sulfonyl migration. We repeated the experiment in the presence of 0.2 equiv of the unsulfonylated thienopyrimidine 4. Under the assumption of an intermolecular sulfonyl shift,³⁴ 4 might act as sulfonyl acceptor and 12e as donor. The additive 4 would then lead to an accelerated sulfonyl transfer. However, we obtained the same first-order rate constant as before (see the Supporting Information, Figure



Figure 1. (A) N- to O-sulfonyl migration to convert 12e into 14e. Compound 12e (1 mM) was heated in acetonitrile at 81 °C, and the reaction mixture was subjected to HPLC analysis. (B) Chromatograms after 0 min (bottom), 175 min (middle), and 630 min (top). Retention times of 12e and 14e were 22.7 and 25.4 min, respectively. (C) Relative concentrations of 12e, determined as the ratio of the AUC of the substrate to the sum of the AUCs of substrate and product, were plotted versus reaction time. Nonlinear regression using the equation for exponential decay gave a first-order rate constant of $0.0041 \pm 0.0001 \text{ min}^{-1}$.

S12). The kinetic analysis of the crossover migration reaction in the presence of 0.2 equiv of the unsulfonylated quinazoline **3** as additive is illustrated in Figure 2. This time, a sulfonyl transfer from the thienopyrimidine **12e** to **3** would lead to the formation of the crossover product, i.e., the O-sulfonylated quinazoline **13e**. This possible product, available by direct sulfonylation (Table 1), was employed as reference for the HPLC analysis. However, no additional product peak was observed and **13e** was not formed. Again, the depletion of **12e** was only accompanied by the formation of **14e** and the rate constant was similar to the previous experiments. It could be concluded from these findings that the unsulfonylated heterocycles do not function as intermediates in the sulfonyl transfer. We therefore postulate an intramolecular 1,3-sulfonyl migration as the underlying mechanism.



Figure 2. (A) Sulfonyl migration in the presence of a potential sulfonyl acceptor. Compounds 12e (1 mM) and 3 (0.2 mM) were heated in acetonitrile at 81 °C and the reaction mixture was subjected to HPLC analysis. The *O*-sulfonylated product 14e was exclusively formed. An intermolecular sulfonyl migration, i.e., the conversion of 3 into 13e, did not occur. (B) Chromatograms of the reaction mixture after 0 min (bottom) and 495 min (middle), chromatogram of 13e (top). Retention times were as follows: 20.6 min (12e), 2.07 min (3), 22.3 min (14e), and 8.22 min (13e). (C) Relative concentrations of 12e were plotted versus reaction time and the first-order rate constant of $0.0045 \pm 0.0001 \text{ min}^{-1}$ was obtained as described in Figure 1.

There are several literature reports on sulfonyl shifts.^{35,36} For example, similar *N*- to *O*-sulfonyl shifts in pyridinones have been observed (Chart 3, A).³⁷ In addition to such 1,3-migrations, the aromatization of 6-hydroxy-1-tosyl-1,6-dihydro-2*H*-pyrid-3-ones and a subsequent tosyl transfer gave 3-pyridyl tosylates (Chart 3, B). This 1,4-sulfonyl migration was assumed to proceed as intramolecular reaction.³⁸

Featured Article

Chart 3. 1,3- and 1,4-Sulfonyl Migrations in Pyridinones



Further 1,3-sulfonyl shifts have been described which occur as N- to C-migrations. 3-Tosyl-4-vinylidene-2-oxazolidinones undergo an intramolecular migration of the sulfonyl group from N to C α that can be promoted by enol ethers or silanes. The reactions are proposed to pass through intermediate fourmembered sulfurane oxides.³⁹ Such cyclic intermediates resemble the 1,2-oxathietan-4-one-type transition states in the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides.⁴⁰ An aza-Claisen-1,3-sulfonyl shift was reported when N-allyl-Nsulfonyl ynamides were heated in toluene for several hours and α -sulfonyl carbonitriles were formed.⁴¹ N-Alkynyl-N-sulfonyl hydroxylamines are precursors for 3-pyrrolidinones whereby the Au^I-catalyzed cyclization is accompanied by a N- to Ctransfer.⁴² AuBr₃-catalyzed syntheses of 3- and 6-sulfonylindoles were reported, with the former reactions being intramolecular 1,3-sulfonyl migrations.⁴³ However, recently published AlCl₃-assisted transformations of N-sulfonyl to 7-sulfonyl indoles were found to be nonconcerted processes involving N-S cleavage and subsequent C-7 sulfonylation as could be demonstrated by a crossover experiment.⁴⁴

In summary, the regioselectivity of sulfonylation reactions of quinazolin-4(3H)-ones and tetrahydrobenzothieno[2,3-d]-pyrimidin-4(3H)-ones was found to depend on the respective 2-substituent. 2-Unsubstituted substrates afforded predominately N-sulfonylated products, whereas methylsulfanyl, benzylsulfanyl, morpholino and N-benzyl-N-methylamino substituents directed the sulfonyl group to the carbonyl oxygen. A synthetic access to the corresponding N-sulfonylated isomers was demonstrated, which relies on the attachment of the sulfonyl group to the nitrogen atom prior to the ring closure. We observed an N- to O-sulfonyl migration which was, although unexpected to occur, in agreement with the regioselectivity of the direct sulfonylations. Most likely, this sulfonyl shift proceeded as an intramolecular event.

EXPERIMENTAL SECTION

General Experimental Methods. Thin-layer chromatography was carried out on aluminum sheets, silica gel 60 F₂₅₄. Detection was performed with UV light at 254 nm. Preparative column chromatography was performed on silica gel 60 (70-230 mesh). Petroleum ether used was a mixture of alkanes boiling between 40 and 60 °C, according to the supplier's declaration. Melting points are uncorrected. $^1\rm H$ NMR and $^{13}\rm C$ NMR spectra were recorded at 500 and 125 MHz, unless stated otherwise. NMR spectra were recorded in CDCl₃ or DMSO- d_{6} , and chemical shifts δ are given in ppm referring to the signal center using the solvent peaks for reference: CDCl₃ 7.26/ 77.0 ppm and DMSO-d₆ 2.49/39.7 ppm. In addition, HSQC and HMBC spectra of representative compounds were measured. HRMS (EI or ESI) spectra were recorded on a micrOTOF-Q spectrometer. LC-DAD chromatograms and ESI-MS spectra were recorded on an HPLC system with mass spectrometer. Elemental analyses were performed for C, H, and N. HPLC was carried out with a UV detector $(\lambda = 220 \text{ nm})$ on a 5 μ C18 column, 110A, 250 \times 4.60 mm, 5 μ m.

Elution was performed with an isocratic mixture of $\rm H_2O$ and acetonitrile (45:55). A flow rate of 2.0 mL/min was applied. Compounds $1,^{45}$ $2,^{46}$ $3,^{47}$ $4,^{31}$ and 5^{47} were prepared as described.

Quinazolin-4(3H)-one (1). A mixture of 2-aminobenzoic acid (10.0 g, 73 mmol) and formamide (15 mL) was refluxed for 4 h. After the mixture was cooled to room temperature, water (200 mL) was added and the precipitate was filtered off. The crude product was recrystallized from acetonitrile (100 mL) to yield 1 as a white solid (8.44 g, 79%): mp 213–214 °C (lit.⁴⁵ mp 215 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.51 (ddd, 1H, ³*J* = 7.6 Hz, ³*J* = 7.6 Hz, ⁴*J* = 1.3 Hz), 7.65 (d, 1H, ³*J* = 7.9 Hz), 7.80 (ddd, 1H, ³*J* = 7.9 Hz, ⁴*J* = 1.3 Hz), 12.20 (s, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 122.8, 126.0, 126.9, 127.3, 134.4, 145.5, 148.9, 160.9. The material's identity was confirmed by comparison with ¹H NMR and ¹³C NMR literature data.⁴⁸

5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (2). A mixture of ethyl 2-amino-5,6,7,8-tetrahydrobenzo[b]thiophene-3-carboxylate (2.25 g, 10 mmol) and formamide (60 mL) was refluxed for 2 h, then left to cool to room temperature overnight. The precipitated solid was filtered off, washed with water (50 mL), dried, and recrystallized from EtOH (60 mL) to yield 2 as brown crystals (1.32 g, 64%): mp 269–270 °C (lit.⁴⁶ mp 259 °C); ¹H NMR (500 MHz, DMSO- d_6) δ 1.71–1.81 (m, 4H), 2.71–2.73 (m, 2H), 2.84–2.87 (m, 2H), 7.97 (s, 1H), 12.23 (br s, 1H); ¹³C NMR (125 MHz, DMSO- d_6) δ 21.9, 22.6, 24.6, 25.5, 122.8, 131.0, 132.2, 145.0, 157.8, 162.6. Anal. Calcd for C₁₀H₁₀N₂OS: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.23; H, 4.86; N, 13.72.

2-(Methylsulfanyl)quinazolin-4(3H)-one (**3**). 2-Thioxo-2,3-dihydroquinazolin-4(1H)-one (2.23 g, 12.5 mmol) and NaOH (0.55 g, 13.75 mmol) were dissolved in water (62.5 mL). Methyl iodide (0.86 mL, 13.75 mmol) was added dropwise, and the solution was stirred for 3 h at room temperature. The resulting precipitate was filtered off and washed with water (20 mL) to yield 3 as a pale brown solid (1.66 g, 69%): mp 209–210 °C (lit.⁴⁷ mp 210–211 °C); ¹H NMR (500 MHz, CDCl₃) δ 2.68 (s, 3H), 7.38 (ddd, 1H, ³J = 7.4 Hz, ³J = 7.5 Hz, ⁴J = 0.9 Hz), 7.60 (d, 1H, ³J = 7.9 Hz), 7.70 (ddd, 1H, ³J = 7.1 Hz, ³J = 8.4 Hz, ⁴J = 1.6 Hz), 8.24 (dd, 1H, ³J = 8.0 Hz, ⁴J = 1.3 Hz), 11.05 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 13.4, 119.8, 125.8, 126.4, 126.7, 134.9, 149.2, 155.2, 163.1. Anal. Calcd for C₉H₈N₂OS·0.2H₂O C, 55.20; H, 4.32; N, 14.30. Found: C, 55.17, H, 4.07; N, 14.28.

2-(Methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4). Ethyl 2-(3-benzoylthioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (18.0 g, 46.2 mmol) was heated under reflux for 2 h in a mixture of EtOH (230 mL) and 1 N NaOH (115 mL). After being cooled to room temperature, the solution was filtered and diluted with EtOH (30 mL) and 1 N NaOH (230 mL). Methyl iodide (4.8 mL, 77 mmol) was added dropwise, and the mixture was stirred for an additional 2 h. A solid was obtained, filtered off, and washed with water (80 mL) to yield 3-methyl-2-(methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (0.64 g, 5%). The filtrate was acidified with 2 N HCl to precipitate 4 as a white solid (10.9 g, 90%): mp 255–257 °C (lit.³¹ mp 251–255 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.67–1.82 (br m, 4H), 2.49 (s, 3H), 2.66-2.68 (m, 2H), 2.79-2.81 (m, 2H), 12.50 (s, 1H); 13 C NMR (125 MHz, DMSO- d_6) δ 13.0, 21.9, 22.6, 24.4, 25.3, 119.0, 130.2, 130.7, 156.5, 158.2, 162.8. The material's identity was confirmed by comparison with ¹H NMR literature data.⁴

2-(Benzylsulfanyl)quinazolin-4(3H)-one (5). 2-Thioxo-2,3-dihydroquinazolin-4(1H)-one (1.78 g, 10 mmol) was dissolved in EtOH (75 mL) and 1 N NaOH (20 mL). Benzyl bromide (1.31 mL, 11 mmol) was added dropwise, and the solution was stirred for 3 h at room temperature. The mixture was diluted with water (70 mL) and acidified with 2 N HCl to pH ~3. The resulting precipitate was filtered off and washed with water (20 mL) to yield 5 as a white solid (2.14 g, 80%): mp 213-215 °C (lit.⁴⁷ mp 212–213 °C); ¹H NMR (500 MHz, CDCl₃) δ 4.54 (s, 2H), 7.25–7.32 (m, 3H), 7.39 (ddd, 1H, ³J = 7.4 Hz, ³J = 7.6 Hz, ⁴J = 1.0 Hz), 7.44 (m, 2H), 7.62 (d, 1H, ³J = 8.2 Hz), 7.72 (ddd, 1H, ³J = 7.7 Hz, ³J = 7.8 Hz, ⁴J = 1.6 Hz), 8.20 (dd, 1H, ³J = 7.9 Hz, ⁴J = 1.6 Hz), 9.95 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 35.0, 120.0, 125.9, 126.4, 126.8, 127.7, 128.6, 129.2, 134.9, 136.5, 149.0, 154.1, 162.9. Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.12; H, 4.46; N, 10.22.

2-(Benzylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (6). Ethyl 2-(3-benzoylthioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (2.33 g, 6.0 mmol) was heated under reflux for 2 h in EtOH (30 mL) and 1 N NaOH (15 mL). After being cooled to room temperature, the solution was filtered and diluted with EtOH (10 mL) and 1 N NaOH (30 mL). Benzyl bromide (1.2 mL, 10 mmol) was added dropwise, and the mixture was stirred for 2 h. The solution was filtered off, and the filtrate was acidified with 2 N HCl to precipitate 6 as a white solid (2.33 g, 93%): mp 225–228 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 1.70–1.81 (m, 4H), 2.68–2.82 (m, 4H), 4.41 (s, 2H), 7.23–7.26 (m, 1H), 7.28–7.41 (m, 4H), 12.53 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 21.9, 22.6, 24.5, 25.3, 33.9, 119.3, 127.5, 128.6, 129.2, 130.5, 130.8, 137.0, 155.3, 158.2, 162.6. Anal. Calcd for C₁₇H₁₆N₂OS₂: C, 62.16; H, 4,91; N, 8.53. Found: C, 61.97; H, 5.07; N, 8.34.

2-(Morpholin-4-yl)quinazolin-4(3H)-one (7). 2-(Methylsulfanyl)quinazolin-4(3H)-one (3) (0.96 g, 5.0 mmol) was heated in morpholine (20 g, 20 mL, 230 mmol) in a sealed glass reactor at 160 °C overnight. After being cooled to room temperature, the solution was diluted with water (80 mL) and acidified with 2 N HCl to pH ~2. The aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (50 mL) and dried with anhydrous Na2SO4. After evaporation, the residue was recrystallized from EtOH/EtOAc (50 mL, 1:1) to yield 7 as white needles (0.61 g, 53%): mp 247–250 °C (lit.⁵⁰ mp 245–248.5 °C); ¹H NMR (500 MHz, DMSO-d₆) δ 3.59 (m, 4H), 3.65-3.67 (m, 4H), 7.14-7.17 (m, 1H), 7.28-7.29 (m, 1H), 7.57-7.60 (m, 1H), 7.90-7.91 (m, 1H), 11.34 (br s, 1H); ¹³C NMR (125 MHz, DMSO- d_6) δ 45.4, 65.8, 117.4, 122.5, 125.1, 126.0, 134.5, 150.4, 151.1, 163.1. Anal. Calcd for C12H13N3O2: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.31; H, 5.56; N, 18.18.

2-(Morpholin-4-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (8). 2-(Methylsulfonyl)-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (28) (0.20 g, 0.7 mmol) was heated in morpholine (5.0 g, 5 mL, 57 mmol) in a sealed glass reactor at 160 °C for 18.5 h. After the mixture was cooled to room temperature, the resulting precipitate was filtered off and washed with water (10 mL) to yield 8 as a pale gray solid (0.14 g, 69%): mp >350 °C (lit.⁵¹ mp 330 °C); ¹H NMR (500 MHz, DMSO- d_6) δ 1.68–1.80 (m, 4H), 2.59–2.62 (m, 2H), 2.75–2.78 (m, 2H), 3.51–3.53 (m, 4H), 3.61–3.64 (m, 4H), 10.95 (br s, 1H); ¹³C NMR (125 MHz, DMSO- d_6) δ 22.0, 22.9, 24.4, 25.4, 45.4, 65.7, 114.2, 126.1, 130.1, 152.0, 159.3, 165.8. Anal. Calcd for C₁₄H₁₇N₃O₂S·0.5H₂O: C, 55.98; H, 6.04; N, 13.99. Found: C, 56.03; H, 5.76; N, 13.89.

2-(*N*-Benzyl-*N*-methylamino)quinazolin-4(3*H*)-one (**9**). 2-(Methylsulfanyl)quinazolin-4(3*H*)-one (**3**) (0.96 g, 5.0 mmol) was heated in *N*-benzyl-*N*-methylamine (18.8 g, 20 mL, 155 mmol) in a sealed glass reactor at 180 °C overnight. After the mixture was cooled to room temperature, the precipitated solid was filtered off and recrystallized from EtOH (60 mL) to yield **9** as white needles (0.53 g, 40%): mp 199–200 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.20 (s, 3H), 4.91 (s, 2H), 7.07–7.10 (m, 1H), 7.24–7.31 (m, 5H), 7.38 (d, 1H, ³*J* = 8.2 Hz), 7.54–7.57 (m, 1H), 7.95 (d, 1H, ³*J* = 7.0 Hz), 10.83 (br s, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 35.3, 52.9, 116.4, 122.1, 124.9, 126.3, 127.46, 127.52, 128.7, 134.8, 137.0, 150.6, 151.2, 165.0; HRMS-ESI *m*/*z* [M + Na]⁺ calcd for C₁₆H₁₅N₃ONa 288.1107, found 288.1106.

2-(*N*-Benzyl-*N*-methylamino)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (10). 2-(Methylsulfonyl)-5,6,7,8tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (28) (0.20 g, 0.7 mmol) was heated in *N*-benzyl-*N*-methylamine (6.6 g, 7 mL, 54 mmol) in a sealed glass reactor at 200 °C for 52 h. After being cooled to room temperature, the mixture was poured on ice–water (150 mL) and neutralized with 8 N HCl. The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL). The organic layer was washed with 2 N CH₃COOH (50 mL) and brine (100 mL) and dried with anhydrous Na₂SO₄. After evaporation, the residue was suspended in MeOH (30 mL) and filtered off to yield 5a as white needles (0.12 g, 53%): mp 250–253 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.68–1.79 (m, 4H), 2.58–2.60 (m, 2H), 2.75–2.78 (m, 2H), 3.01 (s, 3H), 4.77 (s, 2H), 7.19–7.34 (m, 5H), 10.93 (br s, 1H); ¹³C NMR (125 MHz, DMSO- d_6) δ 22.17, 22.9, 24.3, 25.5, 35.8, 52.2, 113.4, 125.1, 127.2, 127.3, 128.7, 130.1, 137.5, 152.0, 159.2, 166.4; HRMS-EI m/z [M]⁺ calcd for C₁₈H₁₉N₃OS 325.1243, found 325.1245.

2-(Methylsulfonyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (28). Method A: 2-(Methylsulfanyl)-5,6,7,8tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4) (0.51 g, 2.0 mmol) was stirred for 5 h at 45 °C in AcOH/H2O2 (10 mL/8 mL, 30%). The precipitate was filtered off and washed with water (60 mL) to yield the product as a white solid (0.20 g, 35%). Method B: 2-(Methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4) (1.26 g, 5.0 mmol) was suspended in acetone (50 mL) and cooled to 0 °C. m-CPBA (70%, 2.70 g, 11 mmol) was added over 30 min. The mixture was stirred for 24 h at room temperature. After evaporation in vacuo, the residue was dissolved in H_2O (70 mL) and 2 N NaOH (15 mL). The solution was acidified with 2 N HCl to pH \sim 5. The precipitate was filtered off and washed with water (25 mL) to yield 28 as a white solid (0.45 g, 32%): mp 246-249 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.82-1.91 (m, 4H), 2.80-2.83 (m, 2H), 3.01-3.04 (m, 2H), 3.32 (s, 3H), 10.38 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) *δ* 22.0, 22.7, 25.3, 25.5, 40.4, 124.7, 132.5, 138.8, 149.0, 156.7, 160.1. Anal. Calcd for C₁₁H₁₂N₂O₃S₂ × 0.2 H₂O: C, 45.88; H, 4.34; N, 9.73. Found: C, 45.92; H, 4.42; N, 9.81.

General Prodecure for Sulfonylation. DIPEA (*N*,*N*-diisopropylethylamine, 1.2 equiv) and the sulfonyl chloride (1.2 equiv, unless stated otherwise) were added to a suspension of the appropriate substrate (1–10) and a catalytic amount of DMAP (4-dimethylaminopyridine) in CH₂Cl₂. The mixture was stirred at room temperature, and a solution was obtained. After evaporation in vacuo, the residue was recrystallized from MeOH or purified by column chromatography to yield compounds 11–14. The compounds are listed in the order of their appearance in Table 1.

3-(4-Methylbenzenesulfonyl)quinazolin-4(3H)-one (11a). Compound 1 (0.29 g, 2.0 mmol), DMAP (20 mg), DIPEA (0.31 g, 2.4 mmol), and 4-methylbenzenesulfonyl chloride (0.46 g, 2.4 mmol) were reacted in CH₂Cl₂ (10 mL) for 2 h. The crude product was recrystallized from MeOH to yield 11a as white crystals (0.51 g, 73%): mp 184–187° (lit.²⁶ mp 185–188 °C); ¹H NMR (500 MHz, CDCl₃) δ 2.43 (s, 3H), 7.37 (d, 2H, ³J = 8.2 Hz), 7.46 (ddd, 1H, ³J = 7.1 Hz, ³J = 8.0 Hz, ⁴J = 1.3 Hz), 7.70 (dd, 1H, ³J = 8.2 Hz, ⁴J = 0.6 Hz), 7.74–7.77 (m, 1H), 8.04–8.06 (d, 2H, ³J = 8.5 Hz), 8.15–8.17 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.8, 122.0, 127.2, 128.0, 128.3, 129.8, 133.4, 135.6, 140.4, 146.7, 146.7, 158.6. Anal. Calcd for C₁₅H₁₂N₂O₃S C, 59.99; H, 4.03; N, 9.33. Found: C, 59.97; H, 4.14; N, 9.15.

4-((4-Oxoquinazolin-3(4H)-yl)sulfonyl)benzonitrile (11b). Compound 1 (0.15 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 1 h. The crude product was recrystallized from MeOH to yield 11b as a white solid (0.17 g, 55%): mp 200–202 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.50 (ddd, 1H, ³*J* = 7.6 Hz, ³*J* = 7.6 Hz, ⁴*J* = 1.3 Hz), 7.72 (d, 1H, ³*J* = 7.6 Hz), 7.80 (ddd, 1H, ³*J* = 8.0 Hz, ³*J* = 7.6 Hz, ⁴*J* = 1.3 Hz), 7.86–7.88 (d, 2H, ³*J* = 8.8 Hz), 8.13–8.15 (dd, 1H, ³*J* = 8.0 Hz, ⁴*J* = 1.3 Hz), 8.29–8.31 (d, 2H, ³*J* = 8.8 Hz), 8.72 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 116.7, 118.8, 121.6, 127.2, 128.2, 128.8, 130.4, 132.8, 136.1, 139.5, 140.5, 146.5, 158.5. Anal. Calcd for C₁₅H₉N₃O₃S: C, 57.87; H, 2.91; N, 13.50. Found: C, 57.90; H, 2.96; N, 13.16.

3-(Methylsulfonyl)quinazolin-4(3H)-one (11c). Compound 1 (0.73 g, 5.0 mmol), DMAP (40 mg), DIPEA (0.78 g, 6.0 mmol), and methanesulfonyl chloride (0.69 g, 6.0 mmol) were reacted in CH₂Cl₂ (30 mL) for 7 h. The product was purified by column chromatography using petroleum ether/EtOAc (1:1) to yield 11c as a white powder (0.65 g, 58%): mp 146–149 °C; ¹H NMR (500 MHz, CDCl₃) δ 3.65 (s, 3H), 7.54–7.58 (m, 1H), 7.73–7.75 (m, 1H), 7.81–7.85 (m, 1H), 8.29–8.31 (m, 1H), 8.55 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 42.6, 121.7, 127.3, 128.2, 128.6, 136.0, 139.7, 146.8, 159.7. Anal. Calcd for C₉H₈N₂O₃S: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.33; H, 3.73; N, 12.28.

3-(2,4,6-Triisopropylbenzenesulfonyl)quinazolin-4(3H)-one (11d). Compound 1 (0.15 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (0.36 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 1 h. The crude product was recrystallized from MeOH to yield 11d as colorless crystals (0.22 g, 52%): mp 157–159 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.12 (d, 12H, ³J = 6.7 Hz), 1.20 (d, 6H, ³J = 6.9 Hz), 2.95 (sept, 1H), 4.03 (sept, 2H), 7.34 (s, 2H), 7.58–7.62 (m, 1H), 7.78–7.80 (m, 1H), 7.91–7.95 (m, 1H), 8.08–8.09 (m, 1H), 8.92 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 2.3.3, 24.1, 29.0, 33.6, 121.2, 124.5, 126.8, 128.0, 129.0, 130.1, 136.5, 140.3, 146.3, 151.2, 155.5, 158.6; HRMS-ESI *m*/*z* [M + Na]⁺ calcd for C₂₃H₂₈N₂NaO₃S 435.1713, found 435.1715.

3-(4-Methylbenzenesulfonyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (12a). Compound 2 (0.21 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4methylbenzenesulfonyl chloride (0.23 g, 1.2 mmol) were reacted in CH₂Cl₂ (7.5 mL) for 3 h. The crude product was recrystallized from MeOH to yield 12a as white crystals (0.27 g, 74%): mp 166–167 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.66–1.76 (m, 4H), 2.41 (s, 3H), 2.70–2.73 (m, 4H), 7.49 (d, 2H, ³J = 7.9 Hz), 8.03 (d, 2H, ³J = 8.5 Hz), 8.75 (s, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 21.4, 21.6, 22.3, 24.6, 25.2, 122.0, 129.5, 130.0, 131.7, 133.3, 135.5, 141.6, 146.7, 154.3, 160.9. Anal. Calcd for C₁₇H₁₆N₂O₃S₂: C, 56.65; H, 4.47; N, 7.77. Found: C,56.44; H, 4.57; N, 7.72.

4-((4-Oxo-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-3(4H)-yl)sulfonyl)benzonitrile (12b). Compound 2 (0.41 g, 2.0 mmol), DMAP (20 mg), DIPEA (0.31 g, 2.4 mmol), and 4cyanobenzenesulfonyl chloride (0.48 g, 2.4 mmol) were reacted in CH₂Cl₂ (7.5 mL) for 30 min. A solid precipitated, which was filtered off and washed with CH₂Cl₂ (5 mL). The filtrate was evaporated in vacuo, and the combined material was recrystallized from MeOH/ CH₂Cl₂ (9:1) to yield 12b as pale yellow crystals (0.53 g, 72%): mp 206–211 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 1.66–1.77 (m, 4H), 2.69–2.75 (m, 4H), 8.18 (d, 2H, ³J = 8.8 Hz), 8.34 (d, 2H, ³J = 8.8 Hz), 8.73 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 21.6, 22.3, 24.6, 25.2, 117.4, 117.6, 121.9, 130.1, 131.7, 133.6, 135.7, 140.3, 141.5, 154.3, 161.0. Anal. Calcd for C₁₇H₁₃N₃O₃S₂: C, 54.97; H, 3.53; N, 11.31. Found: C, 54.71; H, 3.70; N, 11.20.

3-(Methylsulfonyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (12c). Compound 2 (0.21 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.31 g, 2.4 mmol), and methanesulfonyl chloride (0.27 g, 2.4 mmol) were reacted in CH₂Cl₂ (7.5 mL) for 1 h. The crude product was recrystallized from MeOH to yield 12c as a brown solid (0.11 g, 40%): mp 152–155 °C; ¹H NMR (500 MHz, DMSO d_6) δ 1.75–1.83 (m, 4H), 2.77–2.79 (m, 2H), 2.86–2.89 (m, 2H), 3.80 (s, 3H), 8.44 (s, 1H); ¹³C NMR (125 MHz, DMSO- d_6) δ 21.8, 22.4, 24.7, 25.3, 42.1, 122.1, 131.8, 135.3, 141.6, 155.5, 161.2; HRMS-EI m/z [M]⁺ calcd for C₁₁H₁₂N₂O₃S₂ 284.0284, found 284.0290.

5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 2,4,6-Triisopropylbenzenesulfonate (14d). Compound 2 (0.21 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 2,4,6triisopropylbenzenesulfonyl chloride (0.36 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 1 h. The crude product was recrystallized from MeOH to yield 14d as colorless crystals (0.29 g, 61%): mp 135–137 °C; ¹H NMR (600 MHz, CDCl₃) δ 1.24 (d, 18H, ³J = 5.7 Hz), 1.89–1.92 (m, 4H), 2.84–2.86 (m, 2H), 2.92 (sept, 1H, ³J = 7.0 Hz), 3.00–3.01 (m, 2H), 4.28 (sept, 2H, ³J = 6.8 Hz), 7.19 (s, 2H), 8.43 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 22.1, 22.7, 23.5, 24.5, 25.4, 25.7, 120.3, 123.9, 126.3, 131.5, 138.4, 150.8, 151.2, 154.3, 157.8, 170.1; HRMS-ESI *m*/z [M + Na]⁺ calcd for C₂₅H₃₂N₂NaO₃S₂ 473.1927, found 473.1932.

2-(Methylsulfanyl)quinazolin-4-yl 4-Methylbenzenesulfonate (**13e**). Compound 3 (0.19 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-methylbenzenesulfonyl chloride (0.23 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 30 min. The crude product was recrystallized from EtOH to yield **13e** as pale yellow crystals (0.28 g, 83%): mp 146–148 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.45 (s, 3H), 2.54 (s, 3H), 7.37 (d, 2H, ³J = 7.9 Hz), 7.47 (ddd, 1H, ³J = 6.6 Hz, ³J = 8.4 Hz, ⁴J = 1.3 Hz), 7.76–7.78 (m, 2H), 8.03–8.05 (m, 1H), 8.06–8.08 (d, 2H, ³J = 8.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 14.2,

21.8, 113.6, 123.5, 126.6, 129.57, 129.59, 133.5, 135.0, 146.0, 153.3, 160.9, 166.9, one signal was not detected; HRMS-ESI m/z [M + Na]⁺ calcd for C₁₆H₁₄N₂O₃S₂Na 369.0338, found 369.0330.

2-(*Methylsulfanyl*)*quinazolin-4-yl* 4-*Cyanobenzenesulfonate* (**13f**). Compound **3** (0.19 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 1 h. The product was purified by column chromatography using petroleum ether/EtOAc (4:3) to yield **13f** as a white solid (0.25 g, 71%): mp 122–124 °C, ¹H NMR (500 MHz, CDCl₃) δ 2.55 (s, 3H), 7.50–7.53 (m, 1H), 7.80–7.86 (m, 2H), 7.88–7.90 (d, 2H, ³J = 8.9 Hz), 8.04–8.06 (m, 1H), 8.33 (d, 2H, ³J = 8.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 14.1, 113.3, 117.0, 118.3, 123.3, 126.8, 126.9, 130.3, 132.6, 135.4, 140.8, 153.5, 160.5, 166.6; HRMS-ESI *m*/*z* [M + Na]⁺ calcd for C₁₆H₁₁N₃O₃S₂Na 380.0134, found 380.0136.

2-(Methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Methylbenzenesulfonate (**14e**). Compound 4 (0.25 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4methylbenzenesulfonyl chloride (0.23 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 1.5 h. The crude product was recrystallized from EtOH to yield **14e** as yellow crystals (0.28 g, 69%): mp 123–124 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.83–1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.75–2.79 (m, 2H), 2.91–2.94 (m, 2H) 7.36 (d, 2H, ³J = 7.85 Hz), 7.99 (d, 2H, ³J = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 14.1, 21.7, 22.1, 22.7, 25.2, 25.5, 116.9, 126.1, 129.1, 129.6, 134.2, 135.7, 145.6, 156.5, 165.2, 171.4. Anal. Calcd for C₁₈H₁₈N₂O₃S₃: C, 53.18; H, 4.46; N, 6.89. Found: C, 53.02; H, 4.35; N, 6.83.

2-(Methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Cyanobenzenesulfonate (14f). Compound 4 (0.51 g, 2.0 mmol), DMAP (20 mg), DIPEA (0.31 g, 2.4 mmol), and 4cyanobenzenesulfonyl chloride (0.48 g, 2.4 mmol) were reacted in CH₂Cl₂ (10 mL) for 30 min. The crude product was recrystallized from MeOH to yield 14f as yellow crystals (0.64 g, 76%): mp 162– 165 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.81–1.86 (m, 4H), 2.31 (s, 3H), 2.81–2.85 (m, 4H), 8.22 (d, 2H, ³J = 8.9 Hz), 8.30 (d, 2H, ³J = 8.9 Hz); ¹³C NMR (125 MHz, DMSO- d_6) δ 13.6, 21.6, 22.3, 24.8, 25.1, 116.5, 117.4, 117.5, 125.6, 129.4, 133.9, 136.7, 140.5, 155.8, 164.9, 171.2. Anal. Calcd for C₁₈H₁₅N₃O₃S₃: C, 51.78; H, 3.62; N, 10.06. Found: C, 51.61; H, 3.75; N, 9.91.

2-(Methylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl Methanesulfonate (**14g**). Compound 4 (0.25 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and methanesulfonyl chloride (0.14 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 1.5 h. The crude product was recrystallized from MeOH to yield **14g** as brown crystals (0.11 g, 56%): mp 152–155 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.83–1.84 (m, 4H), 2.59 (s, 3H), 2.81–2.84 (m, 4H), 3.79 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 14.1, 21.6, 22.3, 24.9, 25.1, 41.8, 116.6, 125.8, 136.2, 156.4, 165.1, 171.0. Anal. Calcd for C₁₂H₁₄N₂O₃S₃: C, 43.63; H, 4.27; N, 8.48. Found: C, 43.37; H, 4.41; N, 8.38.

2-(Benzylsulfanyl)quinazolin-4-yl 4-Methylbenzenesulfonate (13h). Compound 5 (0.40 g, 1.5 mmol), DMAP (15 mg), DIPEA (0.23 g, 1.8 mmol), and 4-methylbenzenesulfonyl chloride (0.34 g, 1.8 mmol) were reacted in CH₂Cl₂ (7.5 mL) for 2 h. The product was purified by column chromatography using petroleum ether/EtOAc (6:1) to yield 13h as a white solid (0.41 g, 64%): mp 105–107 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.41 (s, 3H), 4.39 (s, 2H), 7.22–7.34 (m, 5H), 7.40–7.42 (m, 2H), 7.47–7.50 (m, 1H), 7.78–7.82 (m, 2H), 8.04–8.06 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 21.7, 35.4, 113.8, 123.6, 126.6, 126.7, 127.3, 128.5, 129.1, 129.5, 129.6, 133.5, 135.1, 137.2, 146.0, 153.2, 161.0, 166.0. Anal. Calcd for C₂₂H₁₈N₂O₃S₂: C, 62.54; H, 4.29; N, 6.63. Found: C, 62.58; H, 4.16; N, 6.41.

2-(Benzylsulfanyl)quinazolin-4-yl 4-Cyanobenzenesulfonate (13i). Compound 5 (0.27 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (16 mL) for 1 h. The crude product was recrystallized from MeOH to yield 13i as a light green solid (0.15 g, 34%): mp 145–148 °C; ¹H NMR (500 MHz, CDCl₃) δ 4.41 (s, 2H), 7.24–7.25 (m, 1H), 7.29–7.32 (m, 2H), 7.41–7.42 (m, 2H), 7.51–7.54 (m, 1H), 7.83–7.86 (m, 4H), 8.05–8.06 (m, 1H), 8.29 (d, 2H, ${}^{3}J$ = 8.5 Hz); 13 C NMR (125 MHz, CDCl₃) δ 35.3, 113.4, 116.9, 118.2, 123.3, 126.8, 127.0, 127.4, 128.6, 129.1, 130.2, 132.6, 135.5, 136.9, 140.7, 153.3, 160.7, 165.6. Anal. Calcd for C₂₂H₁₅N₃O₃S₂: C, 60.95; H, 3.49; N, 9.69. Found: C, 60.87; H, 3.56; N, 9.61.

2-(Benzylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Methylbenzenesulfonate (14h). Compound 6 (0.22 g, 0.7 mmol), DMAP (10 mg), DIPEA (0.12 g, 0.9 mmol), and 4methylbenzenesulfonyl chloride (0.17 g, 0.9 mmol) were reacted in CH₂Cl₂ (5 mL) for 2 h. The crude product was recrystallized from MeOH to yield 14h as pale yellow crystals (0.10 g, 30%): mp 149– 153 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.85–1.91 (m, 4H), 2.37 (s, 3H), 2.77–2.79 (m, 2H), 2.93–2.95 (m, 2H), 4.19 (s, 2H), 7.21–7.32 (m, 7H), 7.97 (d, 2H, ³J = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.7, 22.1, 22.8, 25.3, 25.6, 35.4, 117.3, 126.2, 127.3, 128.5, 129.06, 129.09, 129.64, 134.3, 136.0, 137.0, 145.7, 156.6, 164.3, 171.5. Anal. Calcd for C₂₄H₂₂N₂O₃S₃: C, 59.73; H, 4.59; N, 5.80. Found: C, 60.00; H, 4.59; N, 5.79.

2-(Benzylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Cyanobenzenesulfonate (14i). Compound 6 (0.31 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 30 min. The crude product was recrystallized from MeOH to yield 14i as pale yellow crystals (0.15 g, 31%): mp 174–177 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.88–1.91 (m, 4H), 2.79–2.81 (m, 2H), 2.92–2.94 (m, 2H), 4.25 (s, 2H), 7.23–7.34 (m, 5H), 7.78– 7.80 (m, 2H), 8.19–8.22 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.1, 22.7, 25.2, 25.6, 35.3, 117.0, 118.0, 126.0, 127.5, 128.6, 129.0, 129.8, 132.6, 136.7, 136.8, 141.4, 156.2, 164.2, 171.8. Anal. Calcd for C₂₄H₁₉N₃O₃S₃: C, 58.40; H, 3.88; N, 8.51. Found: C, 58.23; H, 3.94; N, 8.20.

2-(Benzylsulfanyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl Methanesulfonate (**14***j*). Compound **6** (0.63 g, 2.0 mmol), DMAP (20 mg), DIPEA (0.31 g, 2.4 mmol), and methanesulfonyl chloride (0.27 g, 2.4 mmol) were reacted in CH₂Cl₂ (10 mL) for 1 h. The product was purified by column chromatography using CH₂Cl₂ to yield **14***j* as a pale brown solid (0.38 g, 47%): mp 184–186 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.84–1.91 (m, 4H), 2.79–2.81 (m, 2H), 2.90–2.93 (m, 2H), 3.50 (s, 3H), 4.45 (s, 2H), 7.22–7.31 (m, 4H), 7.41–7.43 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.1, 22.7, 25.2, 25.6, 35.7, 41.9, 117.6, 126.2, 127.4, 128.6, 128.9, 136.5, 136.8, 156.6, 164.3, 171.9; HRMS-EI *m*/*z* [M]⁺ calcd for C₁₈H₁₈N₂O₃S₃ 406.0475, found 406.0480.

2-(Morpholin-4-yl)quinazolin-4-yl 4-Methylbenzenesulfonate (**13k**). Compound 7 (0.23 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-methylbenzenesulfonyl chloride (0.23 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 2 h. The crude product was recrystallized from *n*-hexane/EtOAc (2:1) to yield **13k** as pale green crystals (0.16 g, 41%): mp 133–136 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.44 (s, 3H), 3.68–3.71 (m, 8H), 7.17–7.20 (m, 1H), 7.35 (d, 2H, ³J = 8.5 Hz), 7.50 (br d, 1H, ³J = 8.5 Hz), 7.62–7.66 (m, 1H), 7.86 (dd, 1H, ³J = 8.2 Hz, ⁴J = 1.3 Hz), 7.95 (d, 2H, ³J = 8.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.7, 44.5, 66.7, 110.7, 123.1, 123.5, 125.3, 128.5, 129.7, 134.3, 135.0, 145.6, 154.9, 157.1, 162.3. Anal. Calcd for C₁₉H₁₉N₃O₄S: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.15; H, 4.82; N, 10.82.

2-(Morpholin-4-yl)quinazolin-4-yl 4-Cyanobenzenesulfonate (13). Compound 7 (0.23 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 2 h. The crude product was recrystallized from MeOH (60 mL) to yield 13I as green crystals (0.20 g, 50%): mp 143–146 °C; ¹H NMR (500 MHz, CDCl₃) δ 3.68–3.69 (m, 8H), 7.21–7.24 (m, 1H), 7.52 (d, 1H, ³*J* = 8.6 Hz), 7.66–7.69 (m, 1H), 7.82–7.84 (m, 1H), 7.88 (d, 2H, ³*J* = 8.5 Hz), 8.20 (d, 2H, ³*J* = 8.6 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 44.5, 66.6, 110.4, 116.7, 118.0, 123.2, 123.5, 125.6, 129.0, 132.9, 135.4, 141.5, 155.2, 157.0, 162.1; HRMS-EI *m*/*z* [M]⁺ calcd for C₁₉H₁₆N₄O₄S 396.0887, found 396.0892.

2-(Morpholin-4-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Methylbenzenesulfonate (14k). Compound 8 (0.15 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.08 g, 0.6 mmol), and 4methylbenzenesulfonyl chloride (0.12 g, 0.6 mmol) were reacted in CH₂Cl₂ (5 mL) for 3 h. The crude product was recrystallized from MeOH to yield **14k** as white crystals (0.15 g, 66%): mp 207–211 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.77–1.83 (m, 4H), 2.43 (s, 3H), 2.68–2.71 (m, 2H), 2.75–2.79 (m, 2H), 3.41 (m, 4H), 3.53–3.55 (m, 4H), 7.50 (d, 2H, ³J = 8.2 Hz), 7.92 (d, 2H, ³J = 8.6 Hz); ¹³C NMR (125 MHz, DMSO- d_6) δ 21.3, 21.8, 22.6, 24.8, 24.9, 44.4, 65.8, 111.4, 125.3, 128.4, 130.2, 130.9, 134.0, 145.9, 157.0, 157.2, 172.7. Anal. Calcd for C₂₁H₂₃N₃O₄S₂: C, 56.61; H, 5.20; N, 9.43. Found: C, 56.44; H, 5.38; N, 9.34.

2-(Morpholin-4-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Cyanobenzenesulfonate (14l). Compound 8 (0.15 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.08 g, 0.6 mmol), and 4cyanobenzenesulfonyl chloride (0.12 g, 0.6 mmol) were reacted in CH₂Cl₂ (6 mL) for 1 h. The crude product was recrystallized from MeOH to yield 14l as white crystals (0.18 g, 79%): mp 231–232 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.80–1.92 (m, 4H), 2.69–2.71 (m, 2H), 2.81–2.83 (m, 2H), 3.50 (m, 4H), 3.63–3.65 (m, 4H), 7.86 (d, 2H, ³J = 8.6 Hz), 8.15 (d, 2H, ³J = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 22.2, 22.9, 25.2, 25.3, 44.6, 66.5, 112.1, 116.8, 117.7, 125.4, 129.0, 132.0, 132.7, 142.1, 157.0, 157.1, 173.4. Anal. Calcd for C₂₁H₂₀N₄O₄S₂: C, 55.25; H, 4.42; N, 12.27. Found: C, 55.15; H, 4.42; N, 12.31.

2-(Morpholin-4-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl Methanesulfonate (14m). Compound 8 (0.15 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.16 g, 1.2 mmol), and methanesulfonyl chloride (0.14 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 4 h. The crude product was recrystallized from MeOH to yield 14m as white solid (0.16 g, 68%): mp 178–180 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.77–1.83 (m, 4H), 2.69–2.75 (m, 4H), 3.68 (s, 8H), 3.74 (s, 3H); ¹³C NMR (125 MHz, DMSO- d_6) δ 21.8, 22.6, 24.8, 24.9, 41.6, 44.6, 65.9, 111.5, 125.4, 130.9, 157.3, 157.6, 172.6; HRMS-EI m/z [M]⁺ calcd for C₁₅H₁₉N₃O₄S₂ 369.0812, found 369.0818.

2-(*N*-Benzyl-*N*-methylamino)quinazolin-4-yl 4-Methylbenzenesulfonate (**13n**). Compound **9** (0.27 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-methylbenzenesulfonyl chloride (0.23 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 2 h. The crude product was recrystallized from MeOH to yield **13n** as pale green crystals (0.28 g, 67%): mp 80–82 °C, ¹H NMR (500 MHz, CDCl₃) δ 2.29 (br s, 3H), 3.06 (br s, 3H), 4.76 (br s, 2H), 7.12–7.20 (m, 5H), 7.25–7.30 (m, 3H), 7.52 (d, 1H, ³J = 8.2 Hz), 7.64 (ddd, 1H, ³J = 8.4 Hz, ³J = 7.1 Hz, ⁴J = 1.3 Hz), 7.85–7.93 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 34.8, 52.5, 110.5, 122.6, 123.6, 125.3, 127.1, 127.4, 128.3, 128.5, 129.6, 134.3, 134.8, 138.0, 145.2, 155.1, 157.9, 162.3; HRMS-ESI *m*/*z* [M + H]⁺ calcd for C₂₃H₂₂N₃O₃S 420.1376, found 420.1370.

2-(*N*-Benzyl-*N*-methylamino)quinazolin-4-yl 4-Cyanobenzenesulfonate (**13o**). Compound **9** (0.27 g, 1.0 mmol), DMAP (10 mg), DIPEA (0.16 g, 1.2 mmol), and 4-cyanobenzenesulfonyl chloride (0.24 g, 1.2 mmol) were reacted in CH₂Cl₂ (10 mL) for 1 h. The crude product was recrystallized from MeOH to yield **13o** as light green crystals (0.22 g, 51%): mp 122–127 °C, ¹H NMR (500 MHz, CDCl₃) δ 3.09 (br s, 3H), 4.64 (br s, 2H), 7.03 (m, 2H), 7.21–7.49 (m, 6H), 7.56 (d, 1H, ³J = 8.6 Hz), 7.68 (ddd, 1H, ³J = 7.7 Hz, ³J = 7.9 Hz, ⁴J = 1.3 Hz), 7.91–7.99 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 35.0, 52.5, 110.2, 116.8, 117.5, 123.0, 123.3, 125.5, 126.7, 127.6, 128.6, 128.8, 132.7, 135.3, 137.6, 141.5, 155.4, 157.7, 162.2. Anal. Calcd for C₂₃H₁₈N₄O₃S: C, 64.17; H, 4.21; N, 13.01. Found: C, 63.85; H, 4.27; 12.92.

2-(*N*-Benzyl-*N*-methylamino)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Methylbenzenesulfonate (14n). Compound 10 (0.16 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.08 g, 0.6 mmol), and 4-methylbenzenesulfonyl chloride (0.12 g, 0.6 mmol) were reacted in CH₂Cl₂ (5 mL) for 3 h. The crude product was recrystallized from MeOH to yield 14n as white crystals (0.17 g, 68%): mp 87–90 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.83–1.88 (m, 4H), 2.28 (s, 3H), 2.68–2.71 (m, 2H), 2.88–2.90 (m, 2H), 2.94 (s, 3H), 4.61 (br s, 2H), 7.07–7.08 (m, 4H), 7.23–7.27 (m, 3H), 7.80–7.82 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 22.3, 23.0, 25.3, 25.4, 34.8, 52.6, 111.5, 125.8, 127.1, 127.3, 128.3, 128.5, 129.5, 130.3, 135.1, 138.0, 144.9, 157.5, 158.3, 173.3. Anal. Calcd for $C_{25}H_{25}N_3O_3S_2$: C, 62.61; H, 5.25; 8.76. Found: C, 62.30; H, 5.47; N, 8.61.

2-(*N*-Benzyl-*N*-methylamino)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl 4-Cyanobenzenesulfonate (**14o**). Compound **10** (0.16 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.08 g, 0.6 mmol), and 4-cyanobenzenesulfonyl chloride (0.12 g, 0.6 mmol) were reacted in CH₂Cl₂ (7 mL) for 1 h. The crude product was recrystallized from MeOH to yield **14o** as white crystals (0.17 g, 74%): mp 167–170 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.83–1.91 (m, 4H), 2.71–2.73 (m, 2H), 2.88–2.89 (m, 2H), 2.99 (br s, 3H), 4.52 (br s, 2H), 7.01 (m, 2H), 7.30–7.45 (m, 5H), 7.96 (m, 2H); ¹³C NMR (125 MHz, DMSO- d_6) δ 22.3, 23.0, 25.3, 25.3, 35.1, 52.6, 111.6, 116.9, 117.3, 125.5, 126.7, 127.5, 128.6, 128.8, 131.4, 132.6, 137.4, 142.0, 157.2, 157.8, 173.4. Anal. Calcd for C₂₅H₂₂N₄O₃S₂: C, 61.20; H, 4.52; N, 11.42. Found: C, 60.86; H, 4.58; N, 11.11.

2-(*N*-Benzyl-*N*-methylamino)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl Methanesulfonate (14p). Compound 10 (0.16 g, 0.5 mmol), DMAP (5 mg), DIPEA (0.16 g, 1.2 mmol), and methanesulfonyl chloride (0.14 g, 1.2 mmol) were reacted in CH₂Cl₂ (5 mL) for 3 h. The crude product was recrystallized from MeOH to yield 14p as white crystals (0.12 g, 56%): mp 149–150 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 1.76–1.83 (m, 4H), 2.69–2.75 (m, 4H), 3.12 (s, 3H), 3.62 (br s, 3H), 4.86 (s, 2H), 7.24–7.33 (m, 5H); ¹³C NMR (125 MHz, DMSO-d₆) δ 21.8, 22.6, 24.8, 25.0, 35.4, 41.5, 52.3, 110.9, 125.4, 127.2, 127.2, 128.7, 130.3, 137.9, 157.3, 158.0, 172.8; HRMS-EI m/z [M]⁺ calcd for C₁₉H₂₁N₃O₃S₂ 403.1019, found 403.1020.

tert-Butyl 2-Nitrobenzoate (16). 2-Nitrobenzoic acid (15) (11.7 g, 70 mmol) was suspended in CH₂Cl₂ (105 mL) and oxalyl chloride (7.0 mL, 70 mmol), and four drops of DMF were added. The suspension was stirred until a solution was obtained, and after evaporation, tert-butyl alcohol (52.5 mL), pyridine (52.5 mL), and a catalytic amount of ZnCl₂ (50 mg) were added to the residue. The mixture was stirred for 12 h and cold 1N HCl solution (250 mL) was added. The product was extracted with EtOAc (3×200 mL), and the organic layer was dried with anhydrous Na2SO4 and evaporated to obtain 16⁵² as a pale green oil (13.8 g, 88%): ¹H NMR (500 MHz, CDCl₃) δ 1.54 (s, 9H), 7.56 (ddd, 1H, ³J = 7.9 Hz, ³J = 7.6 Hz, ⁴J = 1.6 Hz), 7.61 (ddd, 1H, ${}^{3}J$ = 7.2 Hz, ${}^{3}J$ = 7.6 Hz, ${}^{4}J$ = 1.3 Hz), 7.70 (dd, 1H, ${}^{3}J = 7.7$ Hz, ${}^{4}J = 1.6$ Hz), 7.81 (dd, 1H, ${}^{3}J = 8.0$ Hz, ${}^{4}J = 1.3$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ 27.7, 83.7, 123.5, 128.9, 129.8, 131.2, 132.6, 148.4, 164.2. The material's identity was confirmed by comparison with ¹H NMR and ¹³C NMR literature data.⁵³

tert-Butyl 2-Aminobenzoate (17). A suspension of tert-butyl 2nitrobenzoate (16) (12.4 g, 55.5 mmol) and Pd/C (1.2 g) in EtOH (100 mL) was hydrogenated using hydrogen gas at approximately 2 atm. Upon completion, the catalyst was filtered off and the filtrate evaporated in vacuo. Compound 17^{54} was obtained as a colorless oil (9.05 g, 84%): ¹H NMR (500 MHz, CDCl₃) δ 1.57 (s, 9H), 5.67 (br s, 2H), 6.59–6.62 (m, 2H), 7.20–7.23 (m, 1H), 7.79–7.80 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 28.3, 80.5, 112.5, 116.1, 116.6, 131.4, 133.5, 150.3, 167.6. (C₁₁H₁₅NO₂); LC-MS (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220–400 nm), 100% purity, m/z = 194.26 ([M + H]⁺).

tert-Butyl 2-Isothiocyanatobenzoate (18). Thiophosgene (2.7 g, 23.0 mmol) was dissolved in EtOAc (90 mL) and cooled to -78 °C. Triethylamine (4.6 g, 46.0 mmol) dissolved in EtOAc (60 mL) was added dropwise over 30 min. The resulting suspension was stirred vigorously for 15 min, and tert-butyl 2-aminobenzoate (17) (4.0 g, 21 mmol) in EtOAc (70 mL) was added over 30 min. The obtained solution was stirred for 20 h at room temperature, subsequently diluted with EtOAc (200 mL), and washed sequentially with water (2 × 200 mL) and brine (200 mL). The organic layer was dried with anhydrous Na₂SO₄ and evaporated in vacuo to yield 18 as a brown oil, which solidified upon cooling to -20 °C (4.47 g, 83%): ¹H NMR (500 MHz, CDCl₃) δ 1.61 (s, 9H) 7.27–7.30 (m, 2H) 7.43–7.46 (m, 1H), 7.86–7.88 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 28.2, 82.5, 126.8, 128.0, 128.4, 129.7, 131.4, 132.5, 134.2, 163.2; HRMS-EI *m*/*z* [M]⁺ calcd for C₁₂H₁₃NO₂S 235.0662, found 235.0668. (C₁₂H₁₃NO₂S).

tert-Butyl 2-(3-(4-Methylbenzenesulfonyl)thioureido)benzoate (19). 4-Methylbenzenesulfonamide (1.71 g, 10 mmol) and potassium carbonate (1.80 g, 10 mmol) were added to a solution of tert-butyl 2isothiocyanatobenzoate (18) (2.35 g, 10 mmol) in anhydrous acetone (100 mL), and the mixture was refluxed for 20 h. After evaporation, the residue was dissolved in a mixture of water (70 mL) and EtOH (35 mL) and acidified with 2 N HCl. A precipitate was filtered off and washed with water (20 mL) to afford 19 (0.90 g, 24%) as a pale brown solid: mp 134–136 °C; ¹H NMR (500 MHz, CDCl₂) δ 1.61 (s, 9H), 2.42 (s, 3H), 7.19–7.22 (m, 1H), 7.31 (d, 2H, ${}^{3}I = 8.2$ Hz), 7.42–7.45 (m, 1H), 7.88 (d, 2H, ${}^{3}J = 8.5$ Hz), 7.92–7.94 (m, 1H), 8.14–8.16 (m, 1H), 11.60 (br s, 1H), one signal (NH) was not detected; ¹³C NMR (125 MHz, CDCl₃) δ 21.7, 28.2, 82.9, 122.8, 124.9, 125.5, 127.6, 130.0, 130.8, 132.2, 135.6, 139.1, 145.3, 166.0, 177.1. Anal. Calcd for C₁₉H₂₂N₂O₄S₂: C, 56.14; H, 5.45; N, 6.89. Found: C, 55.75; H, 5.46; N, 6.50.

(Z)-tert-Butyl 2-((4-Methylbenzenesulfonamido)(methylsulfanyl)methyleneamino)benzoate (20). tert-Butyl 2-(3-(4methylbenzenesulfonyl)thioureido)benzoate (19) (1.27 g, 3.15 mmol) was dissolved in EtOH (30 mL), and 1 N NaOH (6 mL) and methyl iodide (0.64 mL, 4.5 mmol) were added dropwise. The mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to pH ~3, the mixture was stored at -20 °C for 2 h to obtain 20 as white needles (0.83 g, 55%): mp 85–87 °C, ¹H NMR (500 MHz, CDCl₃) δ 1.58 (s, 9H), 2.39 (s, 3H), 2.51 (s, 3H), 7.17– 7.20 (m, 1H), 7.26 (d, 2H, ³J = 7.9 Hz), 7.43–7.47 (m, 1H), 7.89 (d, 2H, ³J = 8.2 Hz), 7.91–7.92 (m, 1H), 8.09–8.10 (m, 1H), 11.06 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 15.1, 21.5, 28.1, 83.1, 121.8, 124.4, 125.2, 126.8, 129.2, 131.1, 133.2, 138.8, 139.4, 142.7, 165.1, 166.8. Anal. Calcd for C₂₀H₂₄N₂O₄S₂·0.2H₂O: C, 56.63; H, 5.80; N, 6.60. Found: C, 56.52; H, 5.78; N, 6.72..

(Z)-2-((4-Methylbenzenesulfonamido)(methylsulfanyl)methyleneamino)benzoic Acid (21). (Z)-tert-Butyl 2-((4methylbenzenesulfonamido)(methylsulfanyl)methyleneamino)benzoate (20) (0.50 g, 1.2 mmol) was dissolved in a mixture of CH_2Cl_2 (14 mL) and trifluoroacetic acid (7 mL), and the solution was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was suspended in EtOAc (10 mL) and the insoluble material was filtered off to yield 21 (0.42 g, 96%) as a white solid: mp 174-176 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 2.37 (s, 3H), 2.56 (s, 3H), 7.31 (ddd, 1H, ${}^{3}J$ = 7.9 Hz, ${}^{3}J$ = 7.5 Hz, ${}^{3}J$ = 1.3 Hz), 7.37 (d, 2H, ${}^{3}J$ = 7.9 Hz), 7.61 (ddd, 1H, ${}^{3}J$ = 8.5 Hz, ${}^{3}J$ = 7.1 Hz, ${}^{4}J$ = 1.6 Hz), 7.76 (d, 2H, ${}^{3}J = 8.2$ Hz), 8.00 (dd, 1H, ${}^{3}J = 7.9$ Hz, ${}^{4}J = 1.6$ Hz), 8.10 (d, 1H, ${}^{3}J =$ 8.2 Hz), 11.09 (s, 1H), 13.79 (br s, 1H); ¹³C NMR: (125 MHz, DMSO-*d*₆) *δ* 14.7, 21.1, 120.9, 123.9, 125.5, 126.5, 129.5, 131.3, 133.7, 138.9, 139.5, 142.7, 164.8, 168.9. Anal. Calcd for C16H16N2O4S2: C, 52.73; H, 4.43; N, 7.69. Found: C, 52.52; H, 4.40; N, 7.60.

3-(4-Methylbenzenesulfonyl)-2-(methylsulfanyl)quinazolin-4(3H)-one (11e). (Z)-2-((4-Methylbenzenesulfonamido)-(methylsulfanyl)methyleneamino)benzoic acid (21) (0.18 g, 0.5 mmol) was dissolved in THF (10 mL) and 1,1'-carbonyldiimidazole (0.1 g, 0.6 mmol) was added. The mixture was stirred for 1 h at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/EtOAc (2:1) to yield **11e** as a white solid (0.13 g, 78%): mp 122–127 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.43 (s, 3H), 2.57 (s, 3H), 7.30 (ddd, 1H, ³J = 7.7 Hz, ³J = 7.6 Hz, ⁴J = 1.0 Hz), 7.35 (d, 2H, ³J = 8.5 Hz), 7.48 (d, 1H, ³J = 8.2 Hz), 7.66 (ddd, 1H, ³J = 7.6 Hz, ³J = 7.4 Hz, ⁴J = 1.6 Hz), 8.02 (dd, 1H, ³J = 8.0 Hz, ⁴J = 1.6 Hz), 8.16 (d, 2H, ³J = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 16.8, 21.8, 119.6, 126,2, 126.5, 127.2, 129.3, 129.5, 135.5, 135.6, 145.4, 146.1, 154.2, 161.2; HRMS-ESI *m*/*z* [M + Na]⁺ calcd for C₁₆H₁₄N₂O₃S₂Na 369.0338, found 369.0336.

tert-Butyl 2-Isothiocyanato-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (22). A mixture prepared from thiophosgene (8.0 g, 70 mmol), CaCO₃ (7.0 g, 70 mmol), CH₂Cl₂ (35 mL), and H₂O (70 mL) was stirred at 0 °C, and a solution of tert-butyl 2amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate²⁷ (17.7 g, 70 mmol) in CH₂Cl₂ (120 mL) was added dropwise over a period of 40 min. The mixture was stirred overnight at room temperature. The organic layer was washed with water, dried using anhydrous Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using petroleum ether/EtOAc (9:1) to obtain **22** as a yellow solid (15.6 g, 75%): mp 89 °C (lit.²⁸ mp 79–80 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.52 (s, 9H), 1.67–1.76 (m, 4H), 2.62–2.66 (m, 4H). Anal. Calcd for C₁₄H₁₇NO₂S₂: C, 56.92; H, 5.80; N, 4.74. Found: C, 56.64; H, 5.58; N; 4.71.

tert-Butvl 2-(3-(4-Methylbenzenesulfonyl)thioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (23). 4-Methylbenzenesulfonamide (1.71 g, 10 mmol) and potassium carbonate (1.80 g, 10 mmol) were added to a solution of tert-butyl 2-isothiocyanato-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (22) (2.95 g, 10 mmol) in anhydrous acetone (140 mL), and the reaction mixture was refluxed for 20 h. After evaporation, the residue was dissolved in a mixture of water (140 mL) and EtOH (100 mL) and acidified with 2 N HCl. A precipitate was filtered off and washed with water (20 mL) to yield 23 (4.42 g, 95%) as a pale yellow solid: mp 176-180 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.62 (s, 9H), 1.73–1.77 (m, 4H), 2.39 (s, 3H), 2.59– 2.61 (m, 2H), 2.73-2.75 (m, 2H), 7.26-7.28 (m, 2H), 7.91-7.93 (m, 2H), 8.10 (s, 1H), 13.15 (br s, 1H); 13 C NMR (125 MHz, CDCl₃) δ 21.7, 22.8, 22.9, 24.3, 26.5, 28.4, 82.5, 117.3, 127.8, 128.2, 130.0, 131.4, 135.2, 145.4, 146.9, 165.6, 171.8. Anal. Calcd for C₂₁H₂₆N₂O₄S₃: C₂ 54.05; H, 5.62; N, 6.00. Found: C, 54.37; H, 5.56; N, 6.12.

tert-Butyl 2-(3-(4-Cyanobenzenesulfonyl)thioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (24). 4-Cyanobenzenesulfonamide (0.64 g, 3.5 mmol) and potassium carbonate (0.46 g, 3.5 mmol) were added to a solution of tert-butyl 2-isothiocyanato-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (22) (1.03 g, 3.5 mmol) in anhydrous acetone (40 mL), and the mixture was refluxed for 20 h. After evaporation, the residue was dissolved in a mixture of water (60 mL) and EtOH (90 mL) and acidified with 2 N HCl. A precipitate was filtered off and washed with water (20 mL) to provide 24 (1.27 g, 76%) as a yellow solid: mp 164-167 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.61 (s, 9H), 1.74–1.77 (m, 4H), 2.60–2.62 (m, 2H), 2.72-2.74 (m, 2H), 7.78-7.80 (m, 2H), 8.17-8.19 (m, 2H), 8.31 (br s, 1H), 13.18 (s, 1H); 13 C NMR (125 MHz, CDCl₃) δ 22.79, 22.79, 24.4, 26.5, 28.4, 82.8, 116.9, 117.3, 117.8, 128.5, 128.6, 131.6, 133.1, 142.3, 146.6, 165.9, 170.7. Anal. Calcd for C₂₁H₂₃N₃O₄S₃: C, 52.81; H, 4.85; N, 8.80. Found: C, 52.45; H, 4.87; N, 8.57.

tert-Butyl 2-(3-(Methylsulfonyl)thioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (25). Methanesulfonamide (0.52 g, 5.5 mmol) and sodium hydride (0.22 g, 5.5 mmol, 70% oil dispersion) were dissolved in anhydrous DMF (15 mL) and stirred for 15 min. tert-Butyl 2-isothiocyanato-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (22) (1.47 g, 5.0 mmol) was added, and the mixture was stirred at 60 °C for 1 h. After evaporation in vacuo, the residue was dissolved in water (20 mL) and EtOH (10 mL) and acidified with 6 N HCl to provide a precipitate that was collected by suction filtration to yield 25 (1.93 g, 99%) as a white solid: mp 159-162 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.56 (s, 9H), 1.73-1.79(m, 4H), 2.63-2.65 (m, 2H), 2.72-2.75 (m, 2H), 3.33 (s, 3H), 8.09 (s, 1H), 13.02 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 22.84, 22.84, 24.4, 26.5, 28.3, 41.5, 82.7, 117.3, 128.3, 131.5, 146.7, 166.0, 171.8. Anal. Calcd for C15H22N2O4S3: C, 46.13; H, 5.68; N, 7.17. Found: C, 46.22; H, 5.97; N, 6.96.

(Z)-tert-Butyl 2-((4-Methylbenzenesulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26e**). tert-Butyl 2-(3-(4-methylbenzenesulfonyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**23**) (1.45 g, 3.0 mmol) was dissolved in a mixture of EtOH (30 mL) and 1 N NaOH (6 mL). Methyl iodide (0.64 g, 4.5 mmol) was added dropwise, and the mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to pH ~3, a precipitate was filtered off to obtain **26e** as a white solid (1.31 g, 91%): mp 209–213 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.53 (s, 9H), 1.71–1.77 (m, 4H), 2.38 (s, 3H), 2.59–2.61 (m, 5H), 2.68–2.70 (m, 2H), 7.24–7.25 (m, 2H), 7.88–7.89 (m, 2H), 12.05 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 15.0, 21.5, 22.81, 22.84, 24.4, 26.5, 28.3, 82.5, 114.3, 127.2, 129.1, 129.1, 131.0, 139.0, 142.7, 146.5, 159.8, 166.8. Anal. Calcd for C₂₂H₂₈N₂O₄S₃ × 0.1 H₂O: C, 54.77; H, 5.89; N, 5.81. Found: C, 54.42; H, 5.92; N, 5.76. (Z)-tert-Butyl 2-((4-Cyanobenzenesulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26f**). tert-Butyl 2-(3-(4-cyanobenzenesulfonyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**24**) (1.05 g, 2.2 mmol) was dissolved in a mixture of EtOH (20 mL) and 2 N NaOH (2.2 mL). Methyl iodide (0.47 g, 3.3 mmol) was added dropwise, and the mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to pH ~3, a precipitate was filtered off to obtain **26f** as a pale yellow solid (1.00 g, 92%): mp 194–196 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.54 (s, 9H), 1.73–1.77 (m, 4H), 2.58–2.60 (m, 2H), 2.65 (s, 3H), 2.68–2.71 (m, 2H), 7.75–7.76 (m, 2H), 8.10–8.12 (m, 2H), 12.26 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 15.1, 22.73, 22.77, 24.4, 26.5, 28.3, 82.9, 114.9, 115.7, 117.7, 127.8, 129.6, 131.3, 132.4, 145.8, 146.0, 160.7, 166.8. Anal. Calcd for C₂₂H₂₅N₃O₄S₃: C, 53.74; H, 5.13; N, 8.55. Found: C, 53.59; H, 5.15; N, 8.43.

(Z)-tert-Butyl 2-((Methylsulfonyl)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26g**). tert-Butyl 2-(3-(methylsulfonyl)thioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (**25**) (1.56 g, 4.0 mmol) was dissolved in a mixture of EtOH (30 mL) and 2 N NaOH (4 mL). Methyl iodide (0.85 g, 6 mmol) was added dropwise, and the mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to pH ~3, a precipitate was filtered off to obtain **26g** as a white solid (1.27 g, 78%): mp 135–138 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.56 (s, 9H), 1.73–1.79 (m, 4H), 2.61–2.63 (m, 2H), 2.67 (s, 3H), 2.71–2.73 (m, 2H), 3.14 (s, 3H), 12.07 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 15.1, 22.79, 22.84, 24.4, 26.5, 28.3, 42.4, 82.6, 114.3, 128.7, 131.1, 146.3, 159.2, 166.8; HRMS-EI *m*/*z* [M]⁺ calcd for C₁₆H₂₄N₂O₄S₃: 404.0893, found: 404.0898.

(Z)-tert-Butyl 2-((4-Methylbenzenesulfonamido)(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (26h). tert-Butyl 2-(3-(4-methylbenzenesulfonyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (23) (0.7 g, 1.5 mmol) was dissolved in a mixture of EtOH (20 mL) and 1 N NaOH (3 mL). Benzyl bromide (0.38 g, 2.25 mmol) was added dropwise, and the mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to $pH \sim 3$, a precipitate was filtered off to obtain 26h as a white solid (0.58 g, 70%): mp 152-155 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.53 (s, 9H), 1.71–1.77 (m, 4H), 2.40 (s, 3H), 2.58–2.60 (m, 2H), 2.68–2.70 (m, 2H), 4.34 (s, 2H), 7.23–7.32 (m, 7H), 7.87 (d, 2H, ${}^{3}J$ = 8.2 Hz), 12.08 (br s, 1H); ${}^{13}C$ NMR (125 MHz, CDCl₃) δ 21.5, 22.79, 22.82, 24.4, 26.5, 28.3, 36.6, 82.5, 127.3, 128.1, 128.8, 129.1, 129.3, 131.1, 133.2, 138.9, 142.7, 146.2, 158.6, 158.8, 166.5. Anal. Calcd for C₂₈H₃₂N₂O₄S₃ × 1.0 H₂O: C, 58.51; H, 5.96; N, 4.87. Found: C, 58.69; H, 5.63; N, 4.90.

(Z)-tert-Butyl 2-((Methylsulfonamido(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (26j). tert-Butyl 2-(3-(methylsulfonyl)thioureido)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylate (25) (0.39 g, 1 mmol) was dissolved in a mixture of EtOH (10 mL) and 1 N NaOH (2 mL). Benzyl bromide (0.26 g, 1.5 mmol) was added dropwise, and the mixture was stirred for 2 h at room temperature. After acidification with 2 N HCl to pH \sim 3, a precipitate was filtered off to afford 26j as a white solid (0.38 g, 80%): mp 178-181 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.55 (s, 9H, 1.73-1.79 (m, 4H), 2.61-2.63 (m, 2H), 2.70-2.73 (m, 2H), 3.12 (s, 3H), 4.42 (s, 2H), 7.26-7.33 (m, 3H), 7.42-7.44 (m, 2H), 12.09 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 22.78, 22.83, 24.4, 26.5, 28.3, 36.8, 42.4, 82.6, 128.3, 128.9, 129.0, 129.4, 131.3, 133.0, 146.1, 158.1, 166.6, one carbon signal was not observed; HRMS-EI m/z [M]⁺ calcd for C₂₂H₂₈N₂O₄S₃ 480.1206, found 480.1215.

(Z)-2-((4-Methylbenzenesulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetra-hydrobenzo[b]thiophene-3-carboxylic Acid (**27e**). (Z)-tert-Butyl 2-((4-methylbenzene-sulfonamido)-(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26e**) (0.30 g, 0.62 mmol) was dissolved in CH₂Cl₂ (7 mL) and trifluoroacetic acid (3.5 mL), and the mixture was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was suspended in EtOAc (10 mL) and filtered off to yield **27e** as a light-brown solid (0.22 g, 84%): mp 225–226 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 1.67–1.73 (m, 4H), 2.36 (s, 3H), 2.58–2.61 (m, 2H), 2.65 (s, 3H), 2.69–2.71 (m, 2H), 7.37 (d, 2H, ${}^{3}J$ = 8.2 Hz), 7.75 (d, 2H, ${}^{3}J$ = 8.2 Hz), 12.12 (s, 1H), one signal (CO₂H) was not detected; 13 C NMR: (125 MHz, DMSO- d_6) δ 14.4, 21.1, 22.3, 22.6, 23.8, 25.8, 113.9, 126.7, 128.4, 129.5, 131.4, 139.0, 142.9, 145.7, 160.5, 167.9; LC-MS (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220–400 nm), 98% purity, *m*/*z* = 425.18 ([M + H]⁺). Anal. Calcd for C₁₈H₂₀N₂O₄S₃·0.3H₂O: C, 50.28; H, 4.83; N, 6.52. Found: C, 50.08; H, 4.88; N, 6.23.

(*Z*)-2-((4-Cyanobenzenesulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (**27f**). (*Z*)-tert-Butyl 2-((4-cyanobenzene-sulfonamido)-(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**26f**) (0.73 g, 1.5 mmol) was dissolved in CH₂Cl₂ (15 mL) and trifluoroacetic acid (7.5 mL), and the mixture was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was suspended in EtOAc (10 mL) and filtered off to yield **27f** as a light-brown solid (0.56 g, 85%): mp 211–214 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.65–1.73 (m, 4H), 2.58–2.61 (m, 2H), 2.67 (s, 3H) 2.69–2.71 (m, 2H), 8.01–8.03 (m, 2H), 8.05–8.06 (m, 2H), 12.31 (s, 1H), one signal (CO₂H) was not detected; ¹³C NMR (125 MHz, DMSO-*d*₆) δ 1.4.5, 22.2, 22.5, 23.8, 25.8, 114.4, 115.0, 117.9, 127.4, 128.8, 131.6, 133.3, 145.4, 145.8, 161.6, 167.8; HRMS-ESI *m*/*z* [M – H]⁻ calcd for C₁₈H₁₆N₃O₄S₃ 434.0308, found 434.0314.

(*Z*)-2-(*Methylsulfonamido*(*methylsulfanyl*)*methyleneamino*)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (**27g**). (*Z*)tert-Butyl 2-((methylsulfonyl)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**26g**) (0.81 g, 2.0 mmol) was dissolved in CH₂Cl₂ (20 mL) and trifluoroacetic acid (10 mL), and the mixture was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was suspended in EtOAc (10 mL) and filtered off to obtain **27g** as a white solid (0.67 g, 96%): mp 213-215 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.68–1.75 (m, 4H), 2.61– 2.63 (m, 2H), 2.70 (s, 3H), 2.71–2.73 (m, 2H), 3.08 (s, 3H), 12.03 (s, 1H), one signal (CO₂H) was not detected; ¹³C NMR: (125 MHz, DMSO-*d*₆) δ 14.4, 22.3, 22.6, 23.8, 25.9, 42.2, 113.5, 128.1, 131.4, 146.0, 159.5, 168.0. Anal. Calcd for C₁₂H₁₆N₂O₄S₃: C, 41.36; H, 4.63; N, 8.04. Found: C, 41.61; H, 4.80; N, 7.72.

(Z)-2-((4-Methylbenzenesulfonamido)(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic Acid (27h). (Z)-tert-Butyl 2-((4-methylbenzenesulfonamido)-(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (26h) (0.45 g, 0.8 mmol) was dissolved in CH₂Cl₂ (8 mL) and trifluoroacetic acid (4 mL), and the mixture was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was suspended in EtOAc (10 mL) and filtered off to yield 27h as a white solid (0.29 g, 59%): mp 204–207 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 1.69–1.72 (m, 4H), 2.38 (s, 3H), 2.58–2.59 (m, 2H), 2.70–2.71 (m, 2H), 4.50 (s, 2H), 7.28–7.30 (m, 5H), 7.37 (d, 2H, ³) = 7.9 Hz), 7.73 (d, 2H, ${}^{3}J$ = 8.2 Hz), 12.26 (br s, 1H), one signal (CO₂H) was not detected; ¹³C NMR (125 MHz, DMSO- d_6) δ 21.1, 22.3, 22.6, 23.8, 25.8, 35.6, 114.1, 126.8, 128.1, 128.7, 128.9, 129.2, 129.5, 131.6, 133.9, 138.8, 142.9, 145.5, 158.8, 167.9. Anal. Calcd for C₂₄H₂₄N₂O₄S₃: C, 57.58; H, 4.83; N, 5.60. Found: C, 57.42; H, 4.61; N, 5.39.

(*Z*)-2-((Methylsulfonamido)(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic Acid (**27***j*). (*Z*)tert-Butyl 2-((methylsulfonamido)(benzyl-sulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**26***j*) (0.3 g, 0.63 mmol) was dissolved in CH₂Cl₂ (6 mL) and trifluoroacetic acid (3 mL), and the mixture was stirred for 2 h at room temperature. After evaporation in vacuo, the residue was recrystallized from EtOAc (30 mL) to obtain **27***j* as white crystals (0.24 g, 90%): mp 202–204 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.69–1.75 (m, 4H), 2.62–2.64 (m, 2H), 2.72–2.74 (m, 2H), 3.08 (s, 3H), 4.56 (s, 2H), 7.30–7.39 (m, 3H), 7.47–7.48 (m, 2H), 12.17 (br s, 1H), one signal (CO₂H) was not detected; ¹³C NMR (125 MHz, DMSO-*d*₆) δ 22.3, 22.6, 23.9, 25.9, 35.7, 42.2, 113.9, 128.2, 128.4, 129.0, 129.4, 131.6, 133.9, 145.8, 157.9, 167.9; HRMS-EI *m*/*z* [M – H₂O]⁺ calcd for C₁₈H₁₈N₂O₃S₃ 406.0474, found 406.0483; LC-MS (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), 97% purity, m/z = 425.17 ([M + H]⁺).

3-(4-Methylbenzenesulfonyl)-2-(methylsulfanyl)-5.6.7.8tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (12e). To a suspension of (Z)-2-((4-methylbenzenesulfonamido)-(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (27e) (0.21 g, 0.5 mmol) in CH₂Cl₂ (5 mL) were added three drops of DMF and oxalyl chloride (0.05 mL, 0.5 mmol). The mixture was stirred for 45 min at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/EtOAc (2:1) to yield 12e as a white solid (0.15 g, 74%): mp 195-197 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.70–1.75 (m, 2H), 1.77–1.82 (m, 2H), 2.43 (s, 3H), 2.51 (s, 3H), 2.65–2.68 (m, 2H), 2.78–2.80 (m, 2H), 7.32–7.34 (m, 2H), 8.11-8.12 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 17.1, 21.8, 22.0, 22.8, 25.0, 25.3, 118.9, 129.2, 129.4, 131.9, 132.9, 135.8, 145.9, 155.3, 157.4, 160.5; HRMS-EI *m/z* [M]⁺ calcd for C₁₈H₁₈N₂O₃S₃ 406.0475, found 406.0482.

4-((2-(Methylsulfanyl)-4-oxo-5,6,7,8-tetrahydrobenzo[4,5]thieno-[2,3-d]pyrimidin-3(4H)-yl)sulfonyl)benzonitrile (12f). To a suspension of (Z)-2-((4-cyanobenzenesulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (27f) (0.22 g, 0.5 mmol) in CH₂Cl₂ (5 mL) were added three drops of DMF and oxalyl chloride (0.05 mL, 0.5 mmol). A solution was obtained and the mixture was stirred for 45 min at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/EtOAc (9:1) to yield 12f as a white solid (0.12 g, 56%): mp 136-143 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.71–1.75 (m, 2H), 1.78–1.83 (m, 2H), 2.54 (s, 3H), 2.66–2.69 (m, 2H), 2.74–2.76 (m, 2H), 7.83 (d, 2H, ${}^{3}J$ = 8.9 Hz), 8.32 (d, 2H, ${}^{3}J$ = 8.8 Hz); ${}^{13}C$ NMR (125 MHz, CDCl₃) δ 17.0, 21.9, 22.7, 25.0, 25.3, 117.0, 118.0, 118.6, 129.6, 131.9, 132.5, 133.7, 142.9, 154.9, 157.1, 160.6; HRMS-EI m/z [M]⁺ calcd for C18H15N2O2S2: 417.0271, found: 417.0277.

3-(Methylsulfonyl)-2-(methylsulfanyl)-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-d]-pyrimidin-4(3H)-one (12g). To a suspension of (Z)-2-((methylsulfonamido)(methylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylic acid (27g) (0.21 g, 0.5 mmol) in CH₂Cl₂ (5 mL) were added three drops of DMF and oxalyl chloride (0.05 mL, 0.5 mmol). The mixture was stirred for 45 min at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/ EtOAc (9:1) to yield 12g as a white solid (0.13 g, 78%): mp 147–150 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.77–1.87 (m, 4H), 2.48 (s, 3H), 2.70–2.73 (m, 2H), 2.87–2.90 (m, 2H), 3.65 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 16.9, 22.0, 22.8, 25.0, 25.3, 44.5, 118.7, 131.95, 133.4, 155.0, 158.5, 160.8. Anal. Calcd for C₁₂H₁₄N₂O₃S₃: C, 43.62; H, 4.27; N, 8.48. Found: C, 43.68; H, 4.86; N, 7.91.

3-(4-Methylbenzenesulfonyl)-2-(benzylsulfanyl)-5,6,7,8tetrahydrobenzo[4,5]thieno[2,3-d]-pyrimidin-4(3H)-one (12h). To a suspension of (*Z*)-2-((4-methylbenzenesulfonamido)(benzylsulfanyl)methyleneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (27h) (0.21 g, 0.5 mmol) in CH₂Cl₂ (5 mL) were added three drops of DMF and oxalyl chloride (0.05 mL, 0.5 mmol). The mixture was stirred for 45 min at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/EtOAc (2:1) to yield 12h as a white solid (0.14 g, 59%): mp 195–197 °C, ¹H NMR (500 MHz, CDCl₃) δ 1.70–1.75 (m, 2H), 1.77–1.82 (m, 2H), 2.42 (s, 3H), 2.66–2.69 (m, 2H), 2.77– 2.79 (m, 2H), 4.33 (s, 2H), 7.22–7.35 (m, 5H), 7.41 (d, 2H, ${}^{3}J = 8,5$ Hz), 8.08 (d, 2H, ${}^{3}J$ = 8,5 Hz); ${}^{13}C$ NMR (125 MHz, CDCl₃) δ 21.8, 22.0, 22.8, 25.0, 25.3, 38.5, 119.1, 127.48, 127.48, 128.5, 129.2, 129.4, 129.6, 132.0, 133.1, 135.6, 145.9, 154.0, 157.3, 160.2; HRMS-ESI m/z $[M + Na]^+$ calcd for $C_{24}H_{22}N_2O_3S_3Na$ 505.0685, found 505.0678.

2-(Benzylsulfanyl)-3-(methylsulfonyl)-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (12j). To a suspension of (Z)-2-((methylsulfonamido)(benzylsulfanyl)methyleneamino)-4,5,6,7tetrahydrobenzo[b]thiophene-3-carboxylic acid (27j) (0.20 g, 0.47 mmol) in CH_2Cl_2 (5 mL) were added three drops of DMF and oxalyl chloride (0.05 mL, 0.5 mmol). The mixture was stirred for 30 min at room temperature. After evaporation in vacuo, the residue was purified by flash column chromatography using petroleum ether/EtOAc (4:1 to 2:1) to yield **12j** as a white solid (0.15 g, 78%): mp 148–151 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.77–1.88 (m, 4H), 2.71–2.74 (m, 2H), 2.87–2.90 (m, 2H), 3.62 (s, 3H), 4.30 (s, 2H), 7.23–7.25 (m, 1H), 7.27–7.30 (m, 2H), 7.37–7.38 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.1, 22.8, 25.1, 25.3, 38.3, 44.5, 119.0, 127.6, 128.5, 129.7, 132.0, 133.6, 135.7, 153.6, 158.4, 160.5. Anal. Calcd for C₁₈H₁₈N₂O₃S₃: C, 53.18; H, 4.46; N, 6.89. Found: C, 52.78; H, 4.80; N, 6.52.

HPLC Analysis of the Sulfonyl Migration. A mixture of compound **12e** (13.2 mg, 0.032 mmol) and anhydrous acetonitrile (32 mL) was refluxed under argon atmosphere. Without interrupting the heating, aliquots of 200 μ L were collected via a syringe through a rubber septum. After 2 min, these aliquots were directly subjected to the HPLC. The chromatograms were analyzed to determine relative concentrations under the assumption of equal extinction coefficients for **12e** and **14e** at 220 nm. The first-order rate constant of the exponential decay was determined by nonlinear regression using the program GraFit v5.0 (Erithacus Software, Horley, U.K.). Similarly, the reaction of compound **12e** (13.2 mg, 0.032 mmol) in acetonitrile (32 mL) in the presence of compound **3** (1.23 mg, 0.0064 mmol) and the reaction of **12e** (13.2 mg, 0.032 mmol) in acetonitrile (32 mL) in the presence of compound **4** (1.64 mg, 0.0064 mmol) were analyzed.

ASSOCIATED CONTENT

Supporting Information

X-ray crystal structures (CIF), additional analytical data to sulfonyl migration, and ¹H NMR, ¹³C NMR, HSQC, and HMBC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: guetschow@uni-bonn.de.

Present Address

[§]Department of Pharmacology, University of Cologne, Gleueler Strasse 24, D-50931 Cologne, Germany.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

G.S. thanks Prof. A. C. Filippou for support. We thank Marion Schneider for performing LC/MS analyses and Sabine Terhart-Krabbe and Annette Reiner for recording NMR spectra.

REFERENCES

(1) Choi, J. H.; Lee, B. C.; Lee, H. W.; Lee, I. J. Org. Chem. 2002, 67, 1277–1281.

(2) Kan, T.; Fukuyama, T. Chem. Commun. 2004, 353-359.

(3) (a) Pregel, M. J.; Buncel, E. J. Org. Chem. 1991, 56, 5583-5588.
(b) Tarkka, R. M.; Park, W. K.; Liu, P.; Buncel, E.; Hoz, S. J. Chem. Soc., Perkin Trans. 2 1994, 2439-2444. (c) Hoz, S.; Liu, P.; Buncel, E. Chem. Commun. 1996, 995-996. (d) Sach, N. W.; Richter, D. T.; Cripps, S.; Tran-Dubé, M.; Zhu, H.; Huang, B.; Sutton, S. C. Org. Lett. 2012, 14, 3886-3889.

(4) Štimac, A.; Muhič, D.; Kobe, J. Nucleosides Nucleotides 1994, 13, 625–636.

(5) (a) Gasparski, C. M.; Teng, M.; Miller, M. J. J. Am. Chem. Soc. 1992, 114, 2741–2743. (b) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. J. Am. Chem. Soc. 1992, 114, 6262–6263. (c) Durham, T. B.; Miller, M. J. J. Org. Chem. 2003, 68, 27–34.

(6) (a) Bauer, L.; Exner, O. Angew. Chem., Int. Ed. Engl. 1974, 13, 376–384.
(b) Gütschow, M. J. Org. Chem. 1999, 64, 5109–5115.
(c) Cal, M.; Jaremko, M.; Jaremko, Ł.; Stefanowicz, P. Amino Acids 2013, 44, 1085–1091.

(7) The subsequent Lossen rearrangement to isocyanates gives rise to further inter- and intramolecular transformations and has also been applied for the design of enzyme-activated inhibitors of serine proteases, see: (a) Groutas, W. G.; Stanga, M. A.; Brubaker, M. J. J. Am. Chem. Soc. **1989**, *111*, 1931–1932. (b) Neumann, U.; Gütschow, M. J. Biol. Chem. **1994**, *269*, 21561–21567. (c) Martyn, D. C.; Moore, M. I.; Abell, A. D. Curr. Pharm. Des. **1999**, *5*, 405–415.

(8) Chapman, T. M.; Freedman, E. A. J. Org. Chem. 1973, 38, 3908–3911.

(9) For carbanion-mediated sulfonate (or sulfonamide) intermolecular (or intramolecular) couplings (or cyclizations), i.e., CSIC reactions, see: Postel, D.; Van Nhien, A. N.; Marco, J. L. *Eur. J. Org. Chem.* **2003**, 3713–3726.

(10) Hori, M.; Ohtaka, H. Chem. Pharm. Bull. 1993, 41, 1114–1117.
(11) (a) Burbuliene, M. M.; Mazeikaite, R.; Vainilavicius, P. J. Heterocycl. Chem. 2008, 45, 607–610. (b) Dzhavakhishvili, S. G.; Gorobets, N. Yu.; Shishkina, S. V.; Shishkin, O. V.; Desenko, S. M.; Groth, U. M. J. Comb. Chem. 2009, 11, 508–514.

(12) Terrazas, M.; Ariza, X.; Vilarrasa, J. Org. Lett. 2005, 7, 2477–2479.

(13) Fukami, H.; Imajo, S.; Ito, A.; Kakutani, S.; Shibata, H.; Sumida, M.; Tanaka, T.; Niwata, S.; Saitoh, M.; Kiso, Y.; Miyazaki, M.; Okunishi, H.; Urata, H.; Arakawa, K. *Drug. Des. Discov.* **2000**, *17*, 69–84.

(14) Špulák, M.; Novák, Z.; Palát, K.; Kuneš, J.; Pourová, J.; Pour, M. *Tetrahedron* **2013**, *69*, 1705–1711.

(15) Terrazas, M.; Ariza, X.; Farràs, J.; Vilarrasa, J. Chem. Commun. 2005, 3968–3970.

(16) (a) Peng, Y.; Qiu, G.; Yang, Q.; Yuan, J.; Deng, Z. *Synthesis* **2012**, *44*, 1237–1246. (b) Lockman, J. W.; Klimova, Y.; Anderson, M. B.; Willardsen, J. A. *Synth. Commun.* **2012**, *42*, 1715–1723.

(17) Lakshman, M. K.; Ngassa, F. N.; Keeler, J. C.; Dinh, Y. Q.; Hilmer, J. H.; Russon, L. M. Org. Lett. **2000**, *2*, 927–930.

(18) (a) Seela, F.; Herdering, W.; Kehne, A. Helv. Chim. Acta **1987**, 70, 1649–1660. (b) Sarfati, S. R.; Kansal, Y. K. Tetrahedron **1988**, 44, 6267–6372. (c) Kiselyov, A. S.; Steinbrecher, T.; Harvey, R. G. J. Org. Chem. **1995**, 60, 6129–6134. (d) Brossette, T.; Klein, E.; Créminon, C.; Grassi, J.; Mioskowski, C.; Lebeau, L. Tetrahedron **2001**, 57, 8129–8143. (e) Buff, M. C. R.; Schäfer, F.; Wulffen, B.; Müller, J.; Pötzsch, B.; Heckel, A.; Mayer, G. Nucleic Acids Res. **2010**, 38, 2111–2118.

(19) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. Org. Lett. **2002**, *4*, 1479–1482.

(20) (a) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron Lett.* **1995**, *36*, 421–424. (b) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron* **1997**, *9*, 3035–3044.

(21) Kang, S. B.; De Clercq, E.; Lakshman, M. K. J. Org. Chem. 2007, 72, 5724–5730.

(22) Hennecke, U.; Kuch, D.; Carell, T. Synthesis 2007, 929-935.

(23) (a) Daskalov, H. P.; Sekine, M.; Tsujiaki, H. *Tetrahedron Lett.* **1980**, 21, 3899–3902. (b) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, 22, 2253–2256. (c) Belyakov, S.; Ikaunieks, M.; Madre, M. *Acta Crystallogr.* **2005**, *E61*, 03452–03454.

(24) Höbartner, C.; Micura, R. J. Am. Chem. Soc. 2004, 126, 1141– 1149.

(25) This assumption is supported by the following finding. Reactions of thienopyrimidinones 4 and 6 with mesyl chloride gave the O-sulfonylated products 14g and 14j, whereas mixtures of the N-and O-isomers were obtained in reactions of quinazolinones 3 and 5 with mesyl chloride.

(26) Bunnett, J. F.; Bassett, J. Y. J. Org. Chem. 1962, 27, 3714-3715.
(27) (a) Kavalek, J.; Kotyk, M.; El Bahaie, S.; Sterba, V. Collect. Czech. Chem. Commun. 1981, 46, 246-255. (b) Leistner, S.; Gütschow, M.; Stach, J. Arch. Pharm. (Weinheim, Ger.) 1990, 323, 857-861.
(c) Neumann, U.; Gütschow, M. Bioorg. Chem. 1995, 23, 72-88.
(d) Nilsson, J.; Gidlöf, R.; Østergaard Nielsen, E.; Liljefors, T.; Nielsen, M.; Sterner, O. Bioorg. Med. Chem. 2011, 19, 111-121.

(28) Gütschow, M.; Neumann, U. J. Med. Chem. 1998, 41, 1729–1740.

The Journal of Organic Chemistry

(29) Zhang, J.; Shi, Y. Tetrahedron Lett. 2000, 41, 8075-8078.

(30) Corresponding ethyl esters are not suited for the preparation of **12** for the following reasons. They did not cyclize after S-alkylation under basic condition (see refs 31 and 32 for comparison). Under conditions of saponification, the isothioureido moiety was affected; reaction of the corresponding ethyl ester of **26e** with sodium hydroxide (1 N, in 50% EtOH) under reflux for 3 h yielded the corresponding 2-(3-tosylureido)thiophene-3-carboxylic acid.

(31) Leistner, S.; Gütschow, M.; Wagner, G. Arch. Pharm. (Weinheim, Ger.) 1989, 322, 227–230.

(32) Gütschow, M.; Powers, J. C. J. Org. Chem. 2001, 66, 4723-4727.
(33) In contrast, the long-known Chapman rearrangement proceeds as O- to N-transfer. For example, see: (a) Westby, T. R.; Barfknecht, C. F. J. Med. Chem. 1973, 16, 40-43. (b) Schöllkopf, U.; Driessler, F. Liebigs Ann. Chem. 1975, 1521-1530. (c) Kaczor, A.; Proniewicz, L. M.; Almeida, R.; Gómez-Zavaglia, A.; Cristiano, M. L. S.; Matos Beja, A. M.; Ramos Silva, M.; Fausto, R. J. Mol. Struct. 2008, 892, 343-352.

(34) The transfer of the tosyl group from the N atom of **12e** to an unspecific acceptor might produce traces of **4** whose O atom might then accept the tosyl group to form **14e**.

(35) For example, 1,3-sulfonyl shifts are known to proceed as C- to C-transfers in allylic systems; see: (a) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. Tetrahedron Lett. 1982, 23, 2269-2272.
(b) Braverman, S.; Cherkinsky, M.; Raj, P. Sulfur Rep. 1999, 22, 49-84.

(36) For an O- to O-1,4-tosyl shift, see: Zagorevskii, V. A.; Kirsanova, Z. D. Khim. Geterots. Soedin. **1970**, 6, 309–310.

(37) (a) Fujita, R.; Wantabe, K.; Ikeura, W.; Ohtake, Y.; Hongo, A.; Harigaya, Y.; Matsuzaki, H. *Tetrahedron* 2001, *57*, 8841–8850.
(b) Hiroya, K.; Jouka, R.; Katoh, O.; Sakuma, T.; Anzai, M.; Sakamoto, T. *ARKIVOC* 2003, 232–247. (c) Teyssot, M. L.; Lormier, A. T.; Chataigner, I.; Piettre, S. R. *J. Org. Chem.* 2007, *72*, 2364–2373.
(d) Chou, S. S. P.; Wang, H. C.; Chen, P. W.; Yang, C. H. *Tetrahedron* 2008, *64*, 5291–5297. (e) Kipassa, N. T.; Okamura, A.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* 2008, *10*, 815–816.

(38) (a) Hodgson, R.; Majid, T.; Nelson, A. J. Chem. Soc., Perkin Trans. 1 2002, 1631–1643. (b) Hodgson, R.; Kennedy, A.; Nelson, A.; Perry, A. Synlett 2007, 7, 1043–1046.

(39) Kimura, M.; Horino, Y.; Mori, M.; Tamaru, Y. Chem.-Eur. J. 2007, 13, 9686-9702.

(40) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. J. Am. Chem. Soc. **1984**, 106, 139–143.

(41) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. J. Org. Chem. **2011**, 76, 5092– 5103.

(42) Yeom, H. S.; So, E.; Shin, S. Chem.-Eur. J. 2011, 17, 1764-1767.

(43) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. Angew. Chem., Int. Ed. Engl. 2007, 46, 2284–2287.

(44) Prasad, B.; Adepu, R.; Sandra, S.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Misra, P.; Pal, M. *Chem. Commun.* **2012**, 48, 10434–10436.

(45) LeMahieu, R. A.; Carson, M.; Nason, W. C.; Parrish, D. R.; Welton, A. F.; Baruth, H. W.; Yaremko, B. J. Med. Chem. **1983**, 26, 420–425.

(46) Ried, W.; Gieße, R. Liebigs Ann. Chem. 1968, 713, 143-148.

(47) Yun, L. M.; Yangibaev, S.; Shakhidoyatov, Kh. M.; Alekseeva, V. A.; Vyunov, K. A. *Khim. Geterotsikl. Soedin.* **1987**, *2*, 254–256.

(48) Chakrabarty, M.; Batabyal, A.; Morales-Ríos, M. S.; Joseph-Nathan, P. Monatsh. Chem. 1995, 126, 789-794.

(49) Abu Zied, Kh. Phosphorous, Sulfur Relat. Elem. 2007, 182, 2179–2191.

(50) Hori, M.; Iemura, R.; Hara, H.; Ozaki, A.; Sukamoto, T.; Ohtaka, H. *Chem. Pharm. Bull.* **1990**, 38, 1286–1291.

(51) Sauter, F.; Deinhammer, W. Monatsh. Chem. 1974, 105, 558-562.

(52) Li, J.; Wakefield, B. D.; Ruble, J. C.; Stiff, C. M.; Romero, D. L.; Marotti, K. R.; Sweeney, M. T.; Zurenko, G. E.; Rohrer, D. C.; Thorarensen, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2347–2350.

- (53) McNulty, J.; Nair, J. J.; Robertson, A. Org. Lett. 2007, 9, 4575–4578.
- (54) Chauhan, J.; Fletcher, S. Tetrahedron Lett. 2012, 53, 4951-4954.