Highly Stereoselective Formal Synthesis of Rosuvastatin and Pitavastatin Through Julia–Kocienski Olefination Using the Lactonized Statin Side-Chain Precursor

Jan Fabris,[a,b] Zdenko Časar,*[b,c,d] Ivana Gazić Smilović,[b] Martin Črnugelj[b]

[a] Cadonic Consultancy Services, LL.C., Cesta na postajo 74, 1351 Brezovica pri Ljubljani, Slovenia

[b] Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, API Development, Organic Synthesis Department, Kolodvorska 27, 1234 Mengeš, Slovenia

[c] Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

[d] Sandoz GmbH, Global Portfolio Management API, Biochemiestrasse 10, 6250 Kundl, Austria
Fax +43(5338)200418; E-mail: zdenko.casar@sandoz.com

Received: 13.03.2014; Accepted after revision: 24.04.2014

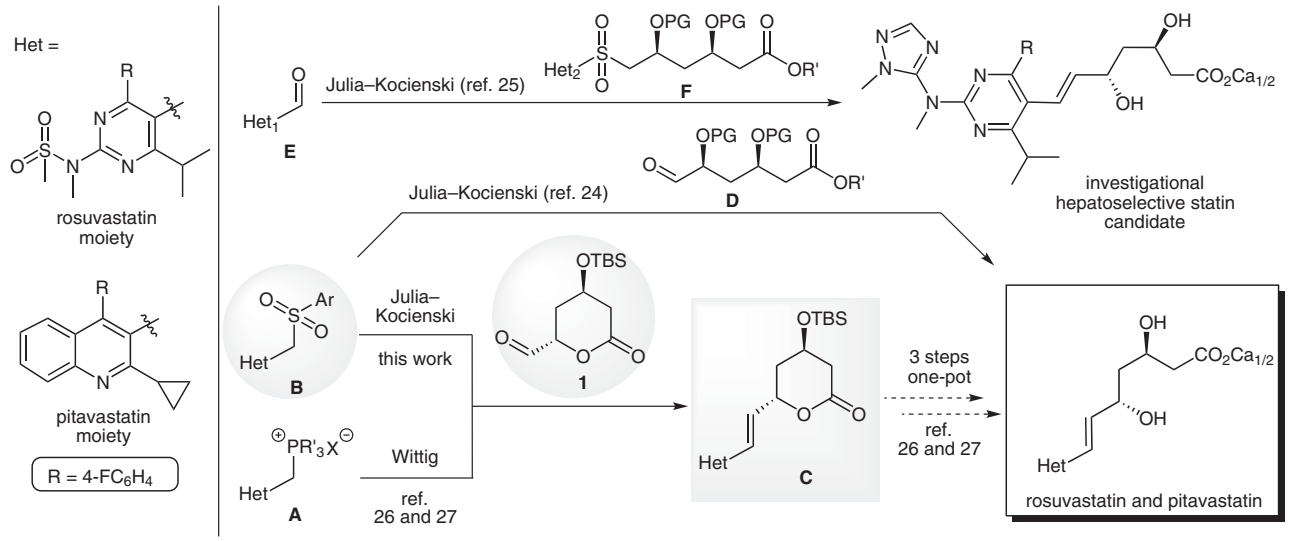
Abstract: An expedient and simple synthetic approach to pitavastatin and rosuvastatin final intermediates is described. The presented approach consists of completely stereoselective Julia–Kocienski olefination step (*E*/*Z* up to 300:1) between lactonized statin side-chain precursor and sulfone derivative of the corresponding pyrimidine and quinoline heterocyclic cores. The desired *O*-TBS protected statin lactones were isolated in 66–71% yield and high >97% purity (HPLC).

Key words: stereoselective synthesis, olefination, heterocycles, sulfones, lactones, aldehydes, drugs

Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (EC 1.1.1.88),[1] known as statins, are one of the most pronounced success stories in modern medicine.[2] This is due to their unique ability to efficiently inhibit the HMG-CoA reductase, the rate-controlling enzyme of the mevalonate metabolic pathway that produces cholesterol.[3] Consequently, remarkable cholesterol-lowering effect is achieved, which renders statins the most effective hypolipidemic drugs available.[4] Moreover, this therapeutic group of compounds demonstrated enormous potential for structural refinement as evidenced by rapid evolution from pioneering discovery of natural derivatives such as compactin (mevastatin) by Endo et al.[5] and lovastatin by Alberts et al.[6] to semisynthetic compounds represented by simvastatin[7] and pravastatin[8] to fully synthetic derivatives. The latter are frequently addressed also as super-statins[9,10] and consist of a heterocyclic core attached to the chiral 3,5-dihydroxyhept-6-enoic or -heptanoic acid side-chain residue, which remains as the key pharmacophore from its naturally derived ancestors. Nowadays, the group of super-statins that has received and maintained the marketing authorization by regulatory authorities on different territories, consists of fluvastatin,[11] atorvastatin,[12] rosuvastatin,[13] and pitavastatin.[14] Although all four compounds share some common structural features, there are specific structural particularities associated with each of them. While fluvastatin is the only racemic compound in the class, atorvastatin contains a fully saturated chiral side-chain motive. The two compounds that are both optically pure and contain the C=C spacer with *E*-geometry between the heterocyclic core and the chiral side chain are rosuvastatin and pitavastatin (Scheme 1). Nevertheless, both compounds differ significantly with respect to the key substituents on the heterocyclic core, which provides unique structural features. Namely, pitavastatin is the only super-statin, which has a cyclopropyl moiety attached to the heterocyclic core instead of the isopropyl group, while rosuvastatin is the only group member that contains a polar sulfonamide substituent (Scheme 1). These structural particularities give some unique properties to both compounds in terms of activity for rosuvastatin[15] as well as metabolism and tolerability in combination with other drugs in the case of pitavastatin.[16] Therefore, both compounds are interesting synthetic targets. Indeed, many synthetic approaches have been devised to both rosuvastatin[9,17] and pitavastatin.[9,18,19] The most frequently applied are, due to their technical simplicity and cost competitiveness, associated with Wittig reaction employing phosphonium salts **A** (Scheme 1) or Horner–Wadsworth–Emmons (HWE) olefination using other phosphorous functionalized heterocyclic precursors.[13,20,21] Nevertheless, both Wittig and HWE olefinations are not completely stereoselective and give rise to the undesirable *Z*-stereoisomer, which represents a tedious to remove impurity in these drugs.

An interesting alternative method for the assembly of rosuvastatin and pitavastatin could be the well established Julia–Kocienski olefination[22,23] (Scheme 1). Interestingly, reports on Julia–Kocienski olefination strategy to super-statins are much less frequent and are addressed mostly in the patent literature employing sulfones **B** and dually protected open statin side-chain precursor **D**. Moreover, these reports provide poor scientific insights and characterization details.[24] The only scientific report on Julia–Kocienski olefination related to statin chemistry on investigational drug candidate employs the inverse coupling partners: the aldehyde **E** of the corresponding heterocyclic precursor and sulfone derivative of the dually protected open statin side-chain derivative **F** (Scheme 1). This approach provided initial stereoselectivities of 15:1 for *E*-olefin, which

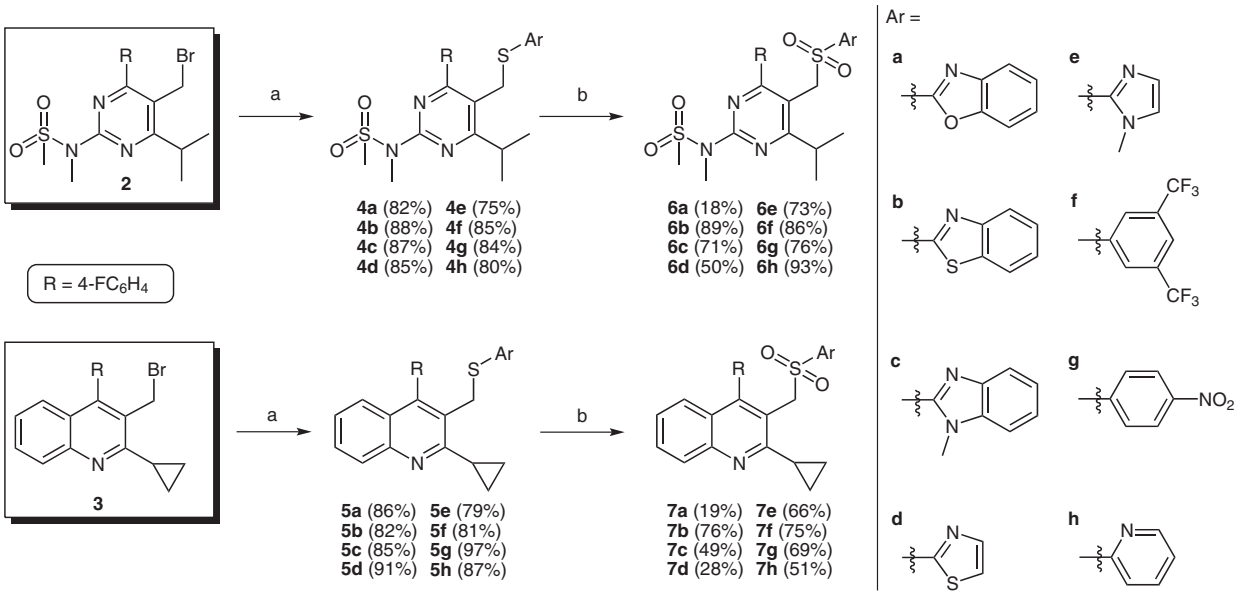
SYNTHESIS 2014, 46, 2333–2346
Advanced online publication: 12.06.2014
DOI: 10.1055/s-0033-1338648; Art ID: st-2014-t0180-op



Scheme 1 Synthetic strategy towards rosuvastatin and pitavastatin described in this and previous related work

dramatically increased to >100:1 in favor of *E*-isomer when the reaction mixture was 'aged' after reagents addition at noncryogenic temperatures.[25] Based on the above mentioned shortcomings of other routes to super-statins and our recent success in the first successful assembly of rosuvastatin[26] and pitavastatin[27] via lactonized statin side-chain precursor **1**[28] employing the Wittig reaction, we were prompted to consider the assembly of rosuvastatin and pitavastatin via Julia–Kocienski olefination employing lactone **1**. This would also enable us to verify, if the suboptimal stereoselectivity of our Wittig approach with lactone **1**, where an *E*/*Z* ratio between 7:1 and 12:1 was achieved,[26,27] could be improved. Therefore, in this paper we present a detailed study on the formal synthesis of pitavastatin and rosuvastatin via highly stereoselective Julia–Kocienski olefination of the lactonized statin side-chain derivative **1** and sulfone derivatives **B** of the corresponding pyrimidine and quinoline heterocyclic cores to produce known *O*-TBS-protected super-statin lactones **C**. These are easily transformed to rosuvastatin and pitavastatin in a three-step/one-pot sequence in high yields (Scheme 1).[26,27]

Our first goal was to prepare diverse array of sulfone heterocyclic precursors **6** and **7**, through a two-step reaction pathway, which would allow us a relevant screening for the best performing Julia–Kocienski olefination partners (Scheme 2). In the first reaction step, the sulfide heterocyclic precursors **4** and **5** were prepared via the reaction be-



Scheme 2 Synthesis of various sulfide heterocyclic precursors **4a**–**h** and **5a**–**h** and sulfone heterocyclic precursors **6a**–**h** and **7a**–**h**. *Reagents and conditions*: (a) ArSH (1.2 equiv), NaOH (1.5 equiv), MeOH or MeOH–THF (2:1), r.t., 18 h; (b) *m*CPBA (5 equiv), THF, r.t., 17 h. Compounds **4b**, **5b**, **6b**, and **7b** were prepared according to the published procedures with comparable yields.[24e]

tween the heterocyclic alkyl bromide **2**[26d] or **3**[27a] and various aromatic and heterocyclic thiols at room temperature, where NaOH was used as a base and methanol as a solvent. When pyrimidine alkyl bromide **2** was used, THF was also added to the mixture to achieve better solubility. After the workup and recrystallization, the desired products **4** and **5** were obtained in good to excellent yields (75–97%).

Trying to find a general procedure for sulfide oxidation, three different reaction conditions were tested on the prepared sulfides **4** and **5**: $KMnO_4$ in AcOH–acetonitrile,[24e,29] $NaIO_4/RuCl_3 \cdot H_2O$ in acetonitrile–H_2O,[30] and *m*-chloroperoxybenzoic acid (*m*CPBA) in THF.[24e,31] In most cases, the latter oxidizing agent gave the cleanest reaction with generally good outcomes for desired products **6** and **7**. All of the sulfides **4** and **5** were therefore oxidized with *m*CPBA and the major product **6** and **7** was isolated via trituration and/or column chromatography in good to high yields (49–93%) except for **6a**, **7a**, and **7d** where low yields were attained. The known compounds **4b**, **5b**, **6b**, and **7b** were prepared according to the patent literature in similar yields.[24e]

The oxidation of sulfides with *m*CPBA was monitored with LC-MS, which enabled us to study the reaction progress. In most cases, as the starting material was slowly oxidized, the firstly formed intermediate had a molar mass 16 units higher (M + 16) than the starting sulfide, which indicated that this compound could probably be a sulfoxide derivative. Further oxidation of this first intermediate gave the next one, which exhibited the desired molar mass of a sulfone (M + 32). Still, there was also another minor side-product with a molar mass that was 48 units higher (M + 48) than the starting compound. Because all the starting sulfides **4** and **5** possess at least one nitrogen atom within the structure, which is capable of being oxidized, the formation of *N*-oxides could not be excluded. Therefore, after oxidation of sulfides **4** or **5** to sulfones **6** or **7**, there is also a possibility of over-oxidation of the desired sulfone, which would produce an unwanted sulfone *N*-oxide (see Figure S1 in the Supporting Information for structure description). With only that information in hand, a reverse order of previously mentioned oxidations could also be possible (from the formation of *N*-oxide to sulfoxide and sulfone), which would imply that the product with desired molar mass would contain the unwanted *N*-oxide functional group. Various spectroscopy techniques, including IR, NMR, and MS/MS, were required to distinguish between the above mentioned functional groups and to provide insight into step-by-step oxidation reactions of sulfides **4** and **5**.

Therefore, the IR spectroscopy seemed to be an appropriate method, because every functional group of our interest has its representative infrared absorption bands.[32] IR spectra of all synthesized compounds **6** and **7** with desired molar mass exhibit the absorption bands in the ranges, typical for sulfones, and lack the strong band, characteristic for sulfoxides. Unfortunately, presence of *N*-oxides cannot be proved with IR spectroscopy solely, because a band, typical for C–N stretch of amines, also lies in the same wavenumber range.

To further prove the presence of sulfone functional group we resorted to MS/MS analysis. Fragmentation behavior of compound **7c** was investigated with atmospheric pressure chemical ionization mass spectrometry in the positive ion mode. Mass spectrum displayed a peak at m/z = 408 corresponding to the elimination of SO_2 molecule via rearrangement[33] from the protonated starting compound at m/z = 472. The elimination of SO_2 molecule obviously confirmed the presence of sulfone functional group in **7c**. The m/z = 276 ion resulted from the further loss of *N*-methylbenzimidazole fragment (proposed fragmentation pathways of **7c** and its mass spectrum are both presented in Scheme S1 in the Supporting Information).

Finally, when preparing compound **7d** according to the discussed procedure, we also managed to isolate the over-oxidized product **7d′** (see Figure S1 in the Supporting Information for structure description). Molar mass for **7d′** was 16 units higher than for **7d**. Comparison of ^{1}H NMR spectra between **7d** and **7d′** revealed, that the main difference lies in the chemical shifts of CH of cyclopropyl group (2.50 ppm for **7d** and 1.94 ppm for **7d′**) and H-8 of quinoline (7.98 ppm for **7d** and 8.76 ppm for **7d′**). Further, ^{1}H–^{15}N heteronuclear correlations in HMBC NMR spectra showed that in both cases chemical shift of the thiazole nitrogen remains unchanged (334 ppm). However, there is a significant chemical shift difference between the quinoline nitrogen atoms (297 ppm for **7d** and 282 ppm for **7d′**). These results clearly indicate that compound **7d′** contains sulfone as well as the *N*-oxide functional group, whereas **7d** lacks the latter one. Therefore, when sulfides are oxidized, they form sulfones in the first place and the corresponding *N*-oxides only due to the over-oxidation. At this point we were sure, that all of the newly synthesized compounds **6** and **7** have the desired structure and so were ready for the screening of the Julia–Kocienski olefination.

In order to set proper reaction conditions for screening of the Julia–Kocienski olefination with novel sulfone heterocyclic precursors (**6** and **7**) and lactonized statin side-chain precursor **1**, the reaction conditions according to the already published procedure for the olefination with precursor **D** were first tried.[24e] The THF solution of compound **7b** and aldehyde **1** (prepared from its hydrate form **1′**, see the Experimental Section) was first cooled to –30 °C, then potassium *tert*-butoxide was added and the mixture was left to stir for half an hour. Then, the reaction mixture was warmed to room temperature and stirred for another hour. After quench and workup, HPLC analysis of the crude product surprisingly showed very low ratio of desired product (*E*)-**9** to starting sulfone **7b** (1:7) and many side products (see Scheme S2 in the Supporting Information for reaction description). Under exact conditions we repeated the reaction with compound **6b** and gained practically the same result.

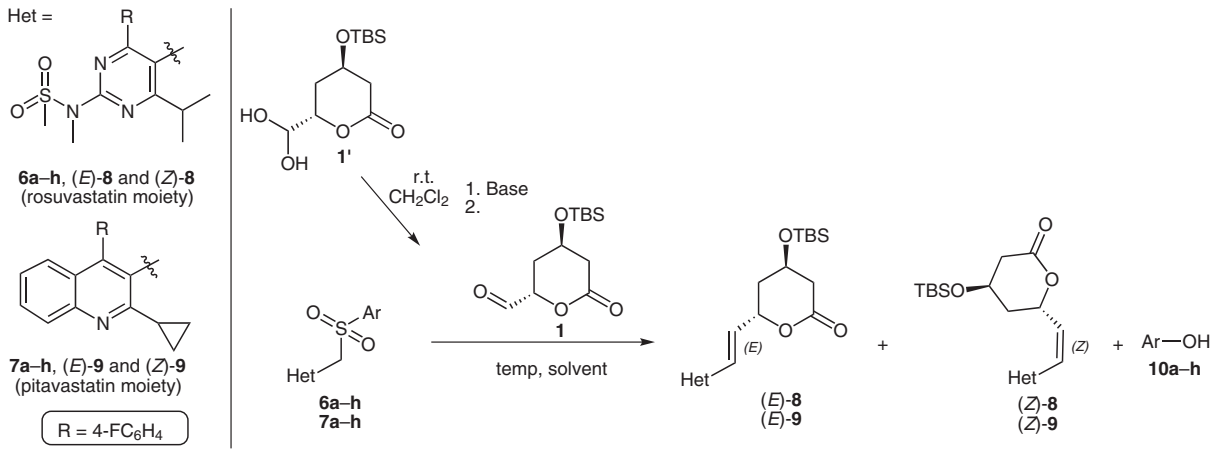
Due to the fact that we were unable to apply the reaction conditions according to the above mentioned procedure, it was decided to perform a preliminary Julia–Kocienski olefination between compound **6b** and benzaldehyde as a model substrate at lower temperatures (from –20 to –80 °C) using sodium hexamethyldisilazide (NaHMDS) as a base. A THF solution of **6b** was cooled and then the base was added to form red-orange colored solution. After five minutes, a solution of benzaldehyde (1.2 equiv) in THF was rapidly added under vigorous stirring. The loss of color of the solution was immediate. After quench and workup, ^{1}H NMR and HPLC analyses of the crude products showed a large ratio of desired product to starting sulfone (as high as 17:1) with only minor side products being present. Encouraged by these results, we decided to perform the Julia–Kocienski olefination screening over sulfones **6** and **7** according to our preliminary procedure (Scheme 3). All of the screening reactions took place at –60 °C, NaHMDS was used as a base, and the lactonized statin side-chain precursor **1** as the coupling partner. The crude reaction products of the screening were analyzed by ^{1}H NMR spectroscopy to gain data on conversion and yield. The results of the screening are summarized in Table 1.

Table 1 Screening of the Olefination Step Between Aldehyde **1** and Sulfone Heterocyclic Precursors **6a–h** and **7a–h**

Entry[a]	**6** or **7**	Conversion (%)[b]	(*E*)-**8** or (*E*)-**9** Yield (%)[b,c]
1	**6a**	90	41
2	**6b**	81	64
3	**6c**	56	19
4	**6d**	36	9
5	**6e**	27	nd
6	**6f**	28	nd
7	**6g**	72	nd
8	**6h**	51	5
9	**7a**	86	45
10	**7b**	83	63
11	**7c**	53	33
12	**7d**	65	11
13	**7e**	60	nd
14	**7f**	62	nd
15	**7g**	54	nd
16	**7h**	37	nd

[a] All reactions were performed in THF on a 0.2 mmol scale and at –60 °C with 1.1 equiv of NaHMDS and 1.2 equiv of aldehyde **1** (see Experimental Section).
[b] Conversions and yields are set by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.
[c] The difference between the yields and conversions goes on the expense of formed unidentified side-products. nd: not determined.

At the first glance, Table 1 reveals that results for rosuvastatin and pitavastatin substrates are very comparable with each other. In both cases, benzothiazole substrates **6b** and **7b** gave the best result with 64% and 63% yield, respectively (Table 1, entries 2 and 10). In addition, there were only three major compounds in the crude mixture: desired product (*E*)-**8** or (*E*)-**9**, starting sulfone **6** or **7** and the stoichiometric by-products **10a–h** (generally written as ArOH, for exact structure of aryl moieties see Scheme 2). Interestingly, all three pairs of the uncondensed ring heterocyclic sulfones **6d**,**e**,**h** and **7d**,**e**,**h** (entries 4, 5, 8, 12, 13, and 16) gave very poor results as well as both pairs of the electron-poor aromatic sulfones **6f**,**g** and **7f**,**g** (entries 6, 7, 14, and 15). In all ten mentioned cases, the yield was never higher than 11%. On the other hand, both pairs of the condensed heterocyclic sulfones gave considerably higher yields (entries 1, 3, 9, and 11). Compounds **6c** and **7c** gave 19% and 33% yield, whereas **6a** and **7a** gave 41% and 45% yield, respectively. Results of the screening revealed that Julia–Kocienski olefination gave better results



Scheme 3 Study of the olefination step between aldehyde **1** and sulfone heterocyclic precursors **6a–h** and **7a–h**. Structures of aryl substituents (Ar) in compounds **10a–h** are the same as shown in Scheme 2.

when sulfones with sterically more hindered substituents are used. Besides, using substrates with trifluoromethyl (**6f** and **7f**) and nitro (**6g** and **7g**), substituents on the benzene ring gave similarly poor results as when using substrates with the pyridyl functional group **6h** and **7h**. For that, it seems that electronic effects of the substituents have no significant influence on the reaction outcome. With the hit result in hand, we next tried to optimize the reaction conditions in order to improve the reaction yield and to find the optimal method to purify our desired products (*E*)-**8** and (*E*)-**9**.

Because the reaction between both of the benzothiazole sulfones **6b** and **7b** and aldehyde **1** gave almost no considerable side products except the by-product **10b**, we decided to analyze crude reaction mixtures of optimization reactions with HPLC analysis (Table 2). Reactions for each entry in Table 2 were performed with **6b** and **7b** in parallel, which gave the corresponding results for (*E*)-**8**, (*Z*)-**8**, **6b** and (*E*)-**9**, (*Z*)-**9**, **7b**, respectively. Analytical standards of compounds (*Z*)-**8** and (*Z*)-**9** were prepared in accordance with the already published procedures.[26,27] Again, all results for pitavastatin and rosuvastatin derivatives are very comparable with each other. Our first attempt to improve the reaction yield was with the variation of the temperature (Table 2, entries 1 and 2), which gave comparable or slightly worse results, so the temperature was kept constant at –60 °C for further experiments (HPLC analysis of crude reaction mixtures from entries 2 and 10 in Table 1 showed that (*E*)-**8**/**6b** = 79:21 and (*E*)-**9**/**7b** = 68:32, respectively). Next, a small scale-up from 0.2 mmol to 0.4 mmol was performed with the same volumes of solvents (concentrations were therefore two-fold higher) in order to make handling with such small amounts of compounds easier. Because the results were slightly improved (entry 3), the reactions were continued on a 0.4 mmol scale. Then we tried to vary some other bases, but unfortunately all performed less successful (entries 4 and 5). Lithium hexamethyldisilazide (LiHMDS) gave lower yield, whereas potassium hexamethyldisilazide (KHMDS) gave comparable yield, but many undesirable side products as well. Variation of the solvent also gave poorer results, for example, using dimethoxyethane gave lower product/reactant ratio, whereas with diethyl ether almost complete starting material was recovered. Since in all cases there was some starting material left in the crude reaction mixture, we thought that basic sulfonyl carbanion could as well abstract the α-carbonyl proton from the excess aldehyde **1** to form the starting sulfone compound again. Therefore, we tried first to lower the amount of aldehyde **1** and second to lower the amounts of both aldehyde **1** and base (entries 6 and 7). In both cases, the results were worse, suggesting that excess aldehyde **1** does not have any major contribution to the starting material recovery. Trying to enhance the sulfonyl carbanion formation, we next raised the excess of the base from 1.1 equivalents to 1.3 equivalents (entry 8). The results showed significantly higher product/reactant ratio. There were 7% and 18% higher yields of compounds (*E*)-**8** and (*E*)-**9**, respectively (than in entry 3). Furthermore, the experiment was performed with 1.5 equivalents of aldehyde **1** and 1.3 equivalents of base (entry 9), but the overall outcome was slightly worse. Finally, using even a higher excess of the base (1.5 equiv), only poorer result was obtained (entry 10).

Table 2 Optimization of Reaction Conditions for the Olefination Step Between Aldehyde **1** and Sulfone Heterocyclic Precursors **6b** and **7b**

Entry[a]	**1** (equiv)	Base (equiv)	Temp (°C)	(*E*)-**8** (%)[b]	(*Z*)-**8** (%)[b]	**6b** (%)[b]	(*E*)-**8**/**6b**[c]	(*E*)-**9** (%)[b]	(*Z*)-**9** (%)[b]	**7b** (%)[b]	(*E*)-**9**/**7b**[c]
1[d]	1.2	NaHMDS (1.1)	–70	45	0.36	36	71:29	45	0.02	27	72:28
2[d]	1.2	NaHMDS (1.1)	–50	45	0.44	31	74:26	29	0.02	57	44:56
3	1.2	NaHMDS (1.1)	–60	53	0.62	27	79:21	53	nd	26	76:24
4	1.2	LiHMDS (1.1)	–60	35	0.34	57	54:46	21	0.07	72	30:70
5	1.2	KHMDS (1.1)	–60	51	0.33	13	88:12	47	nd	6	93:7
6	0.9	NaHMDS (1.1)	–60	40	0.18	36	68:32	34	0.05	35	60:40
7	0.9	NaHMDS (1.0)	–60	38	0.16	47	61:39	39	nd	37	61:39
8	1.2	NaHMDS (1.3)	–60	60	0.45	18	86:14	71	0.23	12	90:10
9	1.5	NaHMDS (1.3)	–60	66	0.53	22	85:15	66	0.14	16	86:14
10	1.2	NaHMDS (1.5)	–60	54	0.50	24	81:19	71	0.24	18	86:14

[a] Reactions were run on a 0.4 mmol scale. For details, see the Experimental Section.
[b] Yields, set by HPLC analysis of the crude products, are given as the area percentage of the peaks, where no response factors were taken in account, due to unidentified minor side products. The sum of the products is lower than 100% owing to the presence of unidentified minor side products. Standards for (*Z*)-**8** and (*Z*)-**9** were prepared according to the literature data.[26,27] nd: not determined.
[c] Product to reactant ratios are set by HPLC analysis of the crude reaction mixtures. The values are calculated taking response factors into account and are normalized to 100.
[d] Reactions were run on a 0.2 mmol scale.

The best result was hence obtained on a 0.4 mmol scale at –60 °C using 1.3 equivalents of the base, 1.2 equivalents of aldehyde **1**, and THF as a solvent. Both of the hit results (Table 2, entry 8,) gave practically complete stereoselective reactions, where (*E*)-**8**/(*Z*)-**8** is >130:1 and (*E*)-**9**/(*Z*)-**9** is >300:1. Having determined the best reaction conditions, the scale up of the reaction was attempted at a 1.0 mmol scale, where the molar ratio for all compounds involved in the reaction remained the same. Completing the reactions, NMR analyses of the crude reaction mixtures showed that 71% and 78% yield was obtained for (*E*)-**8** and (*E*)-**9**, respectively, whereas HPLC analyses revealed that no other impurity was on the higher level than 2 area%. Compounds (*E*)-**8** and (*E*)-**9** were purified via column chromatography to give 66% and 71% isolated yield, respectively. According to HPLC analysis, the purity of both desired compounds was >97%.

To conclude, we have presented in depth study on the preparation of sulfides **4** and **5** and sulfones **6** and **7**. Furthermore, a practical and simple synthetic approach, via Julia–Kocienski olefination, was developed towards *O*-TBS protected pitavastatin and rosuvastatin lactones (*E*)-**8** and (*E*)-**9** which are known to be easily converted into the corresponding drugs.[26,27] For the first time, the Julia–Kocienski olefination step between the lactonized statin side-chain precursor **1** and the sulfone substrate is described. Extending the scope of olefinations towards super-statins using the lactonized aldehyde **1**, allowed us straightforward comparison between Wittig and Julia–Kocienski approach. Whereas Wittig route[26,27] utilizes high yield single step preparation of the phosphorous precursors from the same starting compounds **2** and **3** and facilitates the olefination at reasonably higher temperature, the main advantage of the Julia–Kocienski method is associated with complete stereoselectivity of the olefination step with almost none of the other side products. Gratifyingly, both methods provide very good and comparable yields of the olefination step. Nevertheless, due to the more favorable impurity profile of the Julia–Kocienski olefination reaction, this approach seems to be better suited for larger scale production of rosuvastatin and pitavastatin.

Reagents and solvents were acquired from commercial sources and were used without further purification. Reactions were monitored by using analytical TLC plates (Merck; silica gel 60 F254, 0.25 mm), and compounds were visualized with UV radiation. Silica gel grade 60 (70–230 mesh, Merck) was used for column chromatography. HPLC analysis were performed with MeCN–H_2O as the mobile phase (MeCN gradient 5–90%) on a Waters 2695 instrument with photodiode array detector and a Waters X Bridge (150 × 4.6 mm, 3.5 μm) column. LC-MS analyses were performed on Agilent 1200 instrument with diode array detector and a YMC-Triart C18 (100 × 2.0 mm I.D., S-1.9 μm, 12 nm) column. Mass spectra were obtained with a Bruker HCT esquire ion trap with atmospheric pressure chemical ionization. All the NMR spectra were recorded with a Bruker Avance III 500 MHz spectrometer at 25 °C. ^{1}H NMR spectra were obtained at 500 MHz, ^{13}C NMR spectra were obtained at 125 MHz. Chemical shifts are reported in ppm relative to the peak of the residual nondeuterated solvent, $CDCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). The coupling constants (*J*) are given in Hertz. Melting points were determined with a Mettler Toledo DSC822e apparatus (heating rate 10 °C/min) and are referred to as onset values and peak values. IR spectra were recorded on a Thermo Nicolet Nexus FTIR spectrometer; only noteworthy absorptions are listed. High-resolution mass spectra were obtained with a VG-Analytical AutospecQ instrument and a Q-TOF Premier instrument. All reactions involving air or moisture-sensitive reagents were performed under N_2 in oven-dried glassware by using syringe/septum cap techniques.

Sulfide Heterocyclic Precursors; General Procedure

Aq 1 M NaOH (9 mL, 1.5 equiv) was added to a stirred MeOH (20 mL) solution of the appropriate aromatic thiol (7.2 mmol, 1.2 equiv). The solution was stirred at r.t. for 15 min and then the heterocyclic alkyl bromide **2** or **3** (6 mmol, 1 equiv) was added. When rosuvastatin moiety bromides **2** were used, THF (10 mL) was also added to the mixture to improve solubility. After 18 h, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (50 mL), and washed with H_2O (100 mL). The aqueous phase was additionally extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was recrystallized and the isolated product was dried in vacuum overnight at 60 °C below 50 mbar to give the pure sulfide heterocyclic precursor **4** or **5** in 75–97% yield.

***N*-{5-[(Benzo[*d*]oxazol-2-ylthio)methyl]-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl}-*N*-methylmethanesulfonamide (4a)**

Prepared according to the general procedure; recrystallized from MeOH–THF (3:1) to give a brown crystalline product after drying; yield: 2.38 g (82%); mp 147.7 °C (onset), 149.5 °C (peak).

IR (KBr): 3439, 2964, 2929, 2870, 1553, 1504, 1455, 1376, 1337, 1150, 1140, 956, 741, 575, 509 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34–1.41 (m, 6 H), 3.49–3.56 (m, 4 H), 3.58 (s, 3 H), 4.60 (s, 2 H), 7.12–7.18 (m, 2 H), 7.25–7.35 (m, 2 H), 7.43–7.48 (m, 1 H), 7.57–7.62 (m, 1 H), 7.69–7.76 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 30.8, 31.9, 33.3, 42.6, 110.2, 115.9 (d, *J* = 21.8 Hz), 116.0, 118.6, 124.5, 124.7, 130.9 (d, *J* = 8.4 Hz), 133.8 (d, *J* = 3.2 Hz), 141.7, 151.9, 158.2, 163.1, 163.7 (d, *J* = 250.3 Hz), 166.9, 177.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}FN_4O_3S_2$: 487.1268; found: 487.1264.

***N*-{5-[(Benzo[*d*]thiazol-2-ylthio)methyl]-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl}-*N*-methylmethanesulfonamide (4b)**

Prepared according to the procedure described in the literature with comparable yield;[24e] mp 134.3 °C (onset), 137.9 °C (peak) (Lit.[24e] 132–135 °C).

IR (KBr): 3432, 2969, 2929, 2869, 1605, 1554, 1510, 1455, 1430, 1380, 1330, 1215, 1162, 967, 913, 843, 774, 749, 707, 618, 565, 511 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32–1.39 (m, 6 H), 3.48–3.56 (m, 4 H), 3.58 (s, 3 H), 4.64 (s, 2 H), 7.09–7.16 (m, 2 H), 7.30–7.35 (m, 1 H), 7.40–7.46 (m, 1 H), 7.70–7.76 (m, 2 H), 7.76–7.80 (m, 1 H), 7.82–7.86 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 31.8, 31.9, 33.2, 42.6, 115.7 (d, *J* = 21.7 Hz), 116.6, 121.2, 121.7, 124.7, 126.4, 130.9 (d, *J* = 8.5 Hz), 133.9 (d, *J* = 3.1 Hz), 135.2, 153.0, 158.1, 163.6 (d, *J* = 250.1 Hz), 164.8, 166.6, 177.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}FN_4O_2S_3$: 503.1040; found: 503.1038.

***N*-{4-(4-Fluorophenyl)-6-isopropyl-5-[(1-methyl-1*H*-benzo[*d*]imidazol-2-ylthio)methyl]pyrimidin-2-yl}-*N*-methylmethanesulfonamide (4c)**

Prepared according to the general procedure; recrystallized from MeOH–THF (3:1) to give a white crystalline product after drying; yield: 2.60 g (87%); mp 153.6 °C (onset), 155.1 °C (peak).

IR (KBr): 3434, 2967, 2925, 2870, 1550, 1374, 1150, 956, 743, 574 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35–1.40 (m, 6 H), 3.53–3.58 (m, 4 H), 3.60 (s, 3 H), 3.70 (s, 3 H), 4.66 (s, 2 H), 7.10–7.16 (m, 2 H), 7.24–7.33 (m, 3 H), 7.64–7.69 (m, 1 H), 7.69–7.75 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 30.2, 31.0, 31.8, 33.3, 42.7, 108.8, 115.8 (d, *J* = 21.7 Hz), 116.9, 118.4, 122.2, 122.4, 130.9 (d, *J* = 8.3 Hz), 134.0 (d, *J* = 2.5 Hz), 136.8, 143.4, 150.7, 158.1, 163.6 (d, *J* = 250.0 Hz), 166.7, 177.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}FN_5O_2S_2$: 500.1585; found: 500.1578.

_N_-{4-(4-Fluorophenyl)-6-isopropyl-5-[(thiazol-2-ylthio)methyl]pyrimidin-2-yl}-_N_-methylmethanesulfonamide (4d)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give an off-white crystalline product after drying; yield: 2.32 g (85%); mp 97.2 °C (onset), 101.3 °C (peak).

IR (KBr): 3433, 3096, 2976, 2957, 2925, 1548, 1512, 1377, 1148, 968, 912, 774, 522 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 6 H), 3.47–3.56 (m, 4 H), 3.59 (s, 3 H), 4.49 (s, 2 H), 7.13–7.19 (m, 2 H), 7.29 (d, *J* = 3.4 Hz, 1 H), 7.69 (d, *J* = 3.4 Hz, 1 H), 7.73–7.78 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 31.8, 32.8, 33.2, 42.6, 115.7 (d, *J* = 21.7 Hz), 116.9, 119.7, 131.0 (d, *J* = 8.4 Hz), 133.9 (d, *J* = 2.8 Hz), 143.0, 158.0, 162.7, 163.6 (d, *J* = 250.0 Hz), 166.5, 177.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}FN_4O_2S_3$: 453.0883; found: 453.0885.

_N_-{4-(4-Fluorophenyl)-6-isopropyl-5-[(1-methyl-1_H_-imidazol-2-ylthio)methyl]pyrimidin-2-yl}-_N_-methylmethanesulfonamide (4e)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a white crystalline product after drying; yield: 2.01 g (75%); mp 153.4 °C (onset), 155.6 °C (peak).

IR (KBr): 3432, 2994, 2971, 1551, 1377, 1334, 1232, 1152, 971, 956, 864, 779 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.36 (m, 6 H), 3.45–3.57 (m, 10 H), 4.26 (s, 2 H), 6.92 (d, *J* = 1.3 Hz, 1 H), 7.00 (d, *J* = 1.3 Hz, 1 H), 7.07–7.16 (m, 2 H), 7.61–7.71 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 31.6, 32.4, 33.1, 33.1, 42.4, 115.4 (d, *J* = 21.7 Hz), 117.6, 122.7, 129.6, 130.7 (d, *J* = 8.4 Hz), 133.9 (d, *J* = 2.6 Hz), 139.9, 157.6, 163.3 (d, *J* = 249.7 Hz), 166.1, 177.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}FN_5O_2S$: 450.1428; found: 450.1421.

_N_-(5-{[(3,5-Bis(trifluoromethyl)phenylthio]methyl}-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-_N_-methylmethanesulfonamide (4f)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a white crystalline product after drying; yield: 2.96 g (85%); mp 169.8 °C (onset), 171.3 °C (peak).

IR (KBr): 3441, 2979, 2936, 1554, 1381, 1355, 1277, 1120, 966, 818, 771, 682 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.6 Hz, 6 H), 3.46 (sept, *J* = 6.6 Hz, 1 H), 3.53 (s, 3 H), 3.58 (s, 3 H), 4.21 (s, 2 H), 7.10–7.17 (m, 2 H), 7.60–7.64 (m, 2 H), 7.67–7.75 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 32.0, 32.2, 33.3, 42.6, 115.8 (d, *J* = 21.7 Hz), 116.5, 120.3, 123.0 (q, *J* = 273.0 Hz), 128.3, 130.8 (d, *J* = 8.4 Hz), 132.6 (q, *J* = 33.6 Hz), 133.9 (d, *J* = 2.8 Hz), 139.7, 158.2, 163.7 (d, *J* = 250.8 Hz), 166.5, 177.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}F_7N_3O_2S_2$: 582.1114; found: 582.1111.

_N_-{4-(4-Fluorophenyl)-6-isopropyl-5-[(4-nitrophenylthio)methyl]pyrimidin-2-yl}-_N_-methylmethanesulfonamide (4g)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a yellow crystalline product after drying; yield: 2.46 g (84%); mp 203.7 °C (onset), 205.7 °C (peak).

IR (KBr): 3439, 2966, 2927, 1546, 1510, 1377, 1338, 1228, 1157, 853, 777, 740 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.6 Hz, 6 H), 3.46 (sept, *J* = 6.6 Hz, 1 H), 3.52 (s, 3 H), 3.58 (s, 3 H), 4.20 (s, 2 H), 7.10–7.17 (m, 2 H), 7.29–7.34 (m, 2 H), 7.73–7.79 (m, 2 H), 8.12–8.17 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 31.2, 31.9, 33.3, 42.7, 115.8 (d, *J* = 21.7 Hz), 116.1, 124.3, 126.6, 130.9 (d, *J* = 8.4 Hz), 133.9 (d, *J* = 2.8 Hz), 145.7, 146.3, 158.2, 163.8 (d, *J* = 250.6 Hz), 166.4, 177.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{24}FN_4O_4S_2$: 491.1218; found: 491.1215.

_N_-{4-(4-Fluorophenyl)-6-isopropyl-5-[(pyridin-2-ylthio)methyl]pyrimidin-2-yl}-_N_-methylmethanesulfonamide (4h)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a white crystalline product after drying; yield: 2.14 g (80%); mp 129.0 °C (onset), 132.4 °C (peak).

IR (KBr): 3440, 2975, 2934, 1550, 1511, 1383, 1220, 1152, 957, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.37 (m, 6 H), 3.45–3.55 (m, 4 H), 3.57 (s, 3 H), 4.41 (s, 2 H), 7.00–7.07 (m, 1 H), 7.07–7.15 (m, 2 H), 7.15–7.23 (m, 1 H), 7.49–7.57 (m, 1 H), 7.72–7.80 (m, 2 H), 8.36–8.42 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 28.5, 31.7, 33.3, 42.6, 115.5 (d, *J* = 21.6 Hz), 118.1, 120.0, 122.0, 131.1 (d, *J* = 8.4 Hz), 134.3 (d, *J* = 2.7 Hz), 136.3, 149.7, 157.8, 158.1, 163.6 (d, *J* = 249.6 Hz), 166.3, 177.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}FN_4O_2S_2$: 447.1319; found: 447.1320.

2-({[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}thio)benzo[*d*]oxazole (5a)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a green crystalline product after drying; yield: 2.20 g (86%); mp 160.6 °C (onset), 162.3 °C (peak).

IR (KBr): 3396, 3058, 3000, 2948, 2852, 1604, 1577, 1514, 1493, 1452, 1239, 1213, 1122, 1090, 920, 765, 743, 603, 558 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.09–1.16 (m, 2 H), 1.38–1.44 (m, 2 H), 2.48–2.56 (m, 1 H), 4.74 (s, 2 H), 7.16–7.23 (m, 2 H), 7.23–7.38 (m, 6 H), 7.41–7.45 (m, 1 H), 7.57–7.61 (m, 1 H), 7.62–7.68 (m, 1 H), 7.98–8.03 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 15.1, 32.5, 110.1, 115.8 (d, *J* = 21.6 Hz), 118.5, 124.2, 124.5, 124.7, 125.9, 126.4, 129.1, 129.6, 131.1 (d, *J* = 8.1 Hz), 132.0 (d, *J* = 2.7 Hz), 141.9, 147.4, 147.7, 151.9, 161.7, 162.8 (d, *J* = 248.1 Hz), 164.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calculated for $C_{26}H_{20}FN_2OS$: 427.1275; found: 427.1269.

2-({[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}thio)benzo[*d*]thiazole (5b)

Prepared according to the procedure described in the literature with comparable yield;[24e] mp 147.3 °C (onset), 149.6 °C (peak) (Lit.[24e] 122–124 °C).

IR (KBr): 3433, 3062, 3039, 2997, 1606, 1512, 1491, 1462, 1430, 1217, 1160, 1058, 987, 921, 839, 765, 729, 558 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.07–1.17 (m, 2 H), 1.37–1.48 (m, 2 H), 2.50–2.59 (m, 1 H), 4.81 (s, 2 H), 7.15–7.22 (m, 2 H), 7.26–

7.38 (m, 5 H), 7.41–7.47 (m, 1 H), 7.62–7.68 (m, 1 H), 7.74–7.78 (m, 1 H), 7.83–7.88 (m, 1 H), 8.00–8.05 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.1, 15.1, 33.5, 115.7 (d, *J* = 21.6 Hz), 121.1, 121.6, 124.5, 125.3, 125.8, 126.2, 126.4, 126.4, 129.1, 129.4, 131.1 (d, *J* = 7.9 Hz), 132.1 (d, *J* = 2.7 Hz), 135.3, 147.3, 147.4, 153.1, 161.8, 162.7 (d, *J* = 247.6 Hz), 166.0.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{20}FN_2S_2$: 443.1046; found: 443.1044.

2-Cyclopropyl-4-(4-fluorophenyl)-3-[(1-methyl-1*H*-benzo[*d*]imidazol-2-ylthio)methyl]quinoline (5c)

Prepared according to the general procedure; recrystallized from MeCN–THF (2:1) to give a white crystalline product after drying; yield: 2.25 g (85%); mp 162.1 °C (onset), 163.7 °C (peak).

IR (KBr): 3437, 3054, 3010, 2933, 1512, 1492, 1445, 1420, 1279, 1215, 924, 738, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04–1.11 (m, 2 H), 1.36–1.43 (m, 2 H), 2.50–2.58 (m, 1 H), 3.62 (s, 3 H), 4.76 (s, 2 H), 7.12–7.19 (m, 2 H), 7.20–7.37 (m, 7 H), 7.60–7.70 (m, 2 H), 7.98–8.02 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3, 15.0, 30.1, 32.8, 108.7, 115.7 (d, *J* = 21.5 Hz), 118.4, 122.1, 122.2, 125.5, 125.7, 126.4, 129.0, 129.4, 131.2 (d, *J* = 7.8 Hz), 132.2 (d, *J* = 1.8 Hz), 136.7, 143.4, 147.3, 147.3, 151.5, 162.1, 162.7 (d, *J* = 247.7 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{23}FN_3S$: 440.1591; found: 440.1593.

2-({[(2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}thio)thiazole (5d)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:1) to give a dark red crystalline product after drying; yield: 2.14 g (91%); mp 140.5 °C (onset), 143.1 °C (peak).

IR (KBr): 3432, 3067, 3015, 1603, 1551, 1491, 1388, 1219, 1017, 927, 770, 712, 596, 559 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09–1.15 (m, 2 H), 1.38–1.45 (m, 2 H), 2.50–2.59 (m, 1 H), 4.64 (s, 2 H), 7.17–7.26 (m, 3 H), 7.26–7.30 (m, 1 H), 7.30–7.38 (m, 3 H), 7.61–7.69 (m, 2 H), 7.99–8.04 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0, 14.9, 34.4, 115.5 (d, *J* = 21.5 Hz), 119.2, 125.4, 125.6, 126.2, 126.2, 128.9, 129.2, 131.0 (d, *J* = 8.0 Hz), 131.9 (d, *J* = 3.0 Hz), 142.7, 147.0, 147.1, 161.6, 162.5 (d, *J* = 247.6 Hz), 163.8.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}FN_2S_2$: 393.0890; found: 393.0888.

2-Cyclopropyl-4-(4-fluorophenyl)-3-[(1-methyl-1*H*-imidazol-2-ylthio)methyl]quinoline (5e)

Prepared according to the general procedure; CH_2Cl_2–hexane (1:2) to give a brown crystalline product after drying; yield: 1.85 g (79%); mp 127.3 °C (onset), 129.6 °C (peak).

IR (KBr): 3429, 3066, 2999, 2961, 1513, 1493, 1280, 1221, 1159, 841, 765, 729, 604, 559 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01–1.10 (m, 2 H), 1.28–1.37 (m, 2 H), 2.44–2.53 (m, 1 H), 3.33 (s, 3 H), 4.32 (s, 2 H), 6.86 (d, *J* = 1.2 Hz, 1 H), 7.01 (d, *J* = 1.2 Hz, 1 H), 7.12–7.21 (m, 5 H), 7.23–7.29 (m, 1 H), 7.52–7.58 (m, 1 H), 7.90–7.95 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 14.7, 33.1, 34.5, 115.4 (d, *J* = 21.5 Hz), 122.6, 125.5, 126.1, 126.2, 126.3, 128.8, 129.0, 129.6, 131.0 (d, *J* = 7.9 Hz), 132.1 (d, *J* = 2.9 Hz), 140.4, 146.5, 146.9, 161.8, 162.4 (d, *J* = 247.6 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}FN_3S$: 390.1428; found: 390.1435.

3-{[3,5-Bis(trifluoromethyl)phenyl)thio]methyl}-2-cyclopropyl-4-(4-fluorophenyl)quinoline (5f)

Prepared according to the general procedure; recrystallized from CH_2Cl_2–hexane (1:10) to give a brown crystalline product after drying; yield: 2.53 g (81%); mp 146.8 °C (onset), 148.5 °C (peak).

IR (KBr): 3436, 3068, 3052, 1515, 1493, 1355, 1275, 1187, 1131, 844, 771, 680 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.22 (m, 2 H), 1.42–1.52 (m, 2 H), 2.48–2.58 (m, 1 H), 4.38 (s, 2 H), 7.19–7.27 (m, 2 H), 7.28–7.35 (m, 3 H), 7.36–7.42 (m, 1 H), 7.60–7.65 (m, 2 H), 7.65–7.71 (m, 1 H), 7.71–7.74 (m, 1 H), 8.02–8.08 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 15.1, 34.3, 115.8 (d, *J* = 21.6 Hz), 120.0, 123.1 (q, *J* = 273.1 Hz), 125.2, 125.9, 126.4, 126.4, 128.7, 129.1, 129.5, 131.2 (d, *J* = 7.9 Hz), 132.1 (d, *J* = 3.0 Hz), 132.3 (q, *J* = 33.4 Hz), 140.6, 147.2, 147.4, 161.5, 162.8 (d, *J* = 248.5 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{19}F_7NS$: 522.1121; found: 522.1123.

2-Cyclopropyl-4-(4-fluorophenyl)-3-{[(4-nitrophenyl)thio]methyl}quinoline (5g)

Prepared according to the general procedure; recrystallized from MeCN to give a yellow crystalline product after drying; yield: 2.51 g (97%); mp 167.4 °C (onset), 169.6 °C (peak).

IR (KBr): 3433, 3103, 3014, 3061, 1575, 1507, 1335, 1224, 1092, 925, 838, 770, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.16 (m, 2 H), 1.39–1.45 (m, 2 H), 2.45–2.53 (m, 1 H), 4.35 (s, 2 H), 7.19–7.25 (m, 2 H), 7.25–7.31 (m, 3 H), 7.34–7.40 (m, 3 H), 7.64–7.70 (m, 1 H), 8.00–8.04 (m, 1 H), 8.10–8.16 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.1, 15.0, 32.9, 115.7 (d, *J* = 21.5 Hz), 124.1, 124.6, 124.7, 125.9, 126.4, 126.5, 129.1, 129.5, 131.1 (d, *J* = 7.8 Hz), 132.0 (d, *J* = 3.0 Hz), 145.4, 147.3, 147.3, 147.5, 161.6, 162.8 (d, *J* = 248.3 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{20}FN_2O_2S$: 431.1224; found: 431.1217.

2-Cyclopropyl-4-(4-fluorophenyl)-3-[(pyridin-2-ylthio)methyl]quinoline (5h)

Prepared according to the general procedure; recrystallized from MeOH–THF (1:1) to give a white crystalline product after drying; yield: 2.02 g (87%); mp 168.3 °C (onset), 169.6 °C (peak).

IR (KBr): 3426, 3039, 3002, 2953, 1578, 1515, 1493, 1451, 1412, 1220, 1122, 926, 767, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02–1.12 (m, 2 H), 1.34–1.47 (m, 2 H), 2.50–2.60 (m, 1 H), 4.60 (s, 2 H), 6.96–7.03 (m, 1 H), 7.10–7.25 (m, 3 H), 7.25–7.40 (m, 4 H), 7.44–7.52 (m, 1 H), 7.59–7.68 (m, 1 H), 7.97–8.06 (m, 1 H), 8.34–8.43 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0, 15.0, 30.0, 115.5 (d, *J* = 21.5 Hz), 119.6, 121.8, 125.6, 126.2, 126.5, 126.9, 129.0, 129.0, 131.3 (d, *J* = 8.0 Hz), 132.5 (d, *J* = 2.9 Hz), 136.0, 146.8, 147.0, 149.5, 158.8, 162.1, 162.6 (d, *J* = 247.1 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{20}FN_2S$: 387.1326; found: 387.1327.

Sulfone Heterocyclic Precursors; General Procedure

*m*CPBA (77%, 2.24 g, 10 mmol, 5 equiv) was added to a THF (25 mL) solution of a sulfide heterocyclic precursor **4** or **5** (2 mmol, 1 equiv) and left to stir at r.t. for 17 h. After quenching the reaction with sat. aq $Na_2S_2O_3$ (25 mL), THF was evaporated. EtOAc (50 mL) was added to the residue and the aqueous phase was separated. The organic phase was washed with H_2O (25 mL), sat. aq $NaHCO_3$ (2 × 25 mL), and brine (25 mL), respectively. The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo to give an impure solid or oily residue. Subsequent purification by recrystallization or silica gel column chromatography provided pure products

6 or **7**, which were dried in vacuum overnight at 60 °C below 50 mbar.

***N*-{5-[(Benzo[*d*]oxazol-2-ylsulfonyl)methyl]-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl}-*N*-methylmethanesulfonamide (6a)**

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) and recrystallized from MeOH to provide a yellow crystalline product after drying; yield: 184 mg (18%); mp 161.8 °C (onset), 168.0 °C (peak).

IR (KBr): 3431, 2974, 2960, 2870, 1607, 1548, 1511, 1377, 1349, 1154, 1124, 968, 798, 746, 704, 575, 524, 509 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.43 (m, 6 H), 3.48 (s, 3 H), 3.50–3.57 (m, 4 H), 5.08 (s, 2 H), 6.79–6.89 (m, 2 H), 7.24–7.30 (m, 2 H), 7.50–7.62 (m, 3 H), 7.80–7.85 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 32.9, 33.3, 42.6, 53.6, 108.7, 112.1, 115.7 (d, *J* = 21.8 Hz), 122.4, 126.6, 129.1, 130.6 (d, *J* = 8.4 Hz), 133.1 (d, *J* = 2.8 Hz), 139.6, 151.3, 157.6, 158.6, 163.2 (d, *J* = 250.5 Hz), 167.9, 179.0.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}FN_4O_5S_2$: 519.1167; found: 519.1162.

***N*-{5-[(Benzo[*d*]thiazol-2-ylsulfonyl)methyl]-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl}-*N*-methylmethanesulfonamide (6b)**

Prepared according to procedure described in the literature with comparable yield;[24e] mp 187.4 °C (onset), 189.0 °C (peak) (Lit.[24e] 189–190 °C).

IR (KBr): 3425, 3038, 3005, 2971, 2930, 2872, 1606, 1550, 1511, 1433, 1402, 1373, 1339, 1331, 1227, 1154, 1124, 1066, 969, 908, 853, 836, 775, 758, 604, 563, 506 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.31–1.42 (m, 6 H), 3.47 (s, 3 H), 3.54 (s, 3 H), 3.55–3.62 (m, 1 H), 5.06 (s, 2 H), 6.75–6.82 (m, 2 H), 7.20–7.26 (m, 2 H), 7.58–7.67 (m, 2 H), 7.94–7.98 (m, 1 H), 8.04–8.09 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.8, 33.2, 42.5, 53.5, 109.5, 115.5 (d, *J* = 21.8 Hz), 122.3, 125.7, 127.9, 128.4, 130.6 (d, *J* = 8.4 Hz), 133.2 (d, *J* = 2.3 Hz), 137.3, 152.6, 158.4, 163.1 (d, *J* = 250.1 Hz), 164.9, 167.7.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}FN_4O_4S_3$: 535.0938; found: 535.0939.

***N*-(4-(4-Fluorophenyl)-6-isopropyl-5-{[(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)sulfonyl]methyl}pyrimidin-2-yl)-*N*-methylmethanesulfonamide (6c)**

Prepared according to the general procedure. The crude reaction mixture was triturated with Et_2O to provide a white crystalline product after drying; yield: 755 mg (71%); mp 141.7 °C (onset), 146.2 °C (peak).

IR (KBr): 3435, 2971, 2932, 1608, 1547, 1513, 1442, 1377, 1338, 1333, 1156, 1132, 964, 910, 744, 564 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25–1.45 (m, 6 H), 3.47 (s, 3 H), 3.50–3.64 (m, 4 H), 3.72 (s, 3 H), 5.15 (s, 2 H), 6.77–6.88 (m, 2 H), 7.16–7.29 (m, 2 H), 7.32–7.43 (m, 2 H), 7.43–7.52 (m, 1 H), 7.69–7.80 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 31.3, 32.8, 33.2, 42.6, 53.2, 109.0, 110.7, 115.5 (d, *J* = 21.8 Hz), 121.9, 124.3, 126.4, 130.6 (d, *J* = 8.4 Hz), 133.3 (d, *J* = 2.2 Hz), 136.3, 140.9, 146.5, 158.5, 163.2 (d, *J* = 250.2 Hz), 168.0, 179.2.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}FN_5O_4S_2$: 532.1483; found: 532.1479.

***N*-{4-(4-Fluorophenyl)-6-isopropyl-5-[(thiazol-2-ylsulfonyl)methyl]pyrimidin-2-yl}-*N*-methylmethanesulfonamide (6d)**

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) and triturated with Et_2O to provide a white crystalline product after drying; yield: 484 mg (50%); mp 141.7 °C (onset), 145.6 °C (peak).

IR (KBr): 3440, 2967, 2943, 1604, 1552, 1510, 1380, 1332, 1225, 1161, 1130, 957, 913, 772, 765, 540 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.40 (m, 6 H), 3.49 (s, 3 H), 3.51–3.58 (m, 4 H), 4.94 (s, 2 H), 7.06–7.14 (m, 2 H), 7.41–7.48 (m, 2 H), 7.71 (d, *J* = 3.0 Hz, 1 H), 7.92 (d, *J* = 3.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.8, 33.3, 42.6, 53.6, 109.5, 115.8 (d, *J* = 21.7 Hz), 126.9, 131.0 (d, *J* = 8.4 Hz), 133.6 (d, *J* = 2.6 Hz), 145.5, 158.5, 163.4 (d, *J* = 250.1 Hz), 165.0, 168.3, 178.8.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{22}FN_4O_4S_3$: 485.0782; found: 485.0782.

***N*-(4-(4-Fluorophenyl)-6-isopropyl-5-{[(1-methyl-1*H*-imidazol-2-yl)sulfonyl]methyl}pyrimidin-2-yl)-*N*-methylmethanesulfonamide (6e)**

Prepared according to the general procedure, but on a 1.50 mmol scale (the molar ratio of all compounds involved in the reaction remained the same). The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:1) to provide a white crystalline product after drying; yield: 527 mg (73%); mp 183.8 °C (onset), 185.3 °C (peak).

IR (KBr): 3434, 2964, 2937, 1604, 1548, 1509, 1379, 1327, 1224, 1124, 974, 959, 836, 761, 618, 528 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.27–1.36 (m, 6 H), 3.49 (s, 3 H), 3.50–3.53 (m, 1 H), 3.54 (s, 3 H), 3.59 (s, 3 H), 4.95 (s, 2 H), 6.93 (d, *J* = 0.9 Hz, 1 H), 7.03 (d, *J* = 0.9 Hz, 1 H), 7.07–7.13 (m, 2 H), 7.40–7.45 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.7, 33.3, 34.9, 42.6, 53.3, 109.4, 115.7 (d, *J* = 21.7 Hz), 126.3, 129.7, 131.0 (d, *J* = 8.4 Hz), 133.8 (d, *J* = 2.7 Hz), 141.3, 158.4, 163.4 (d, *J* = 250.1 Hz), 168.3, 178.9.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{25}FN_5O_4S_2$: 482.1327; found: 482.1320.

***N*-[5-({[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}methyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (6f)**

Prepared according to the general procedure. The crude reaction mixture was triturated with Et_2O to provide a white crystalline product after drying; yield: 1054 mg (86%); mp 218.1 °C (onset), 219.2 °C (peak).

IR (KBr): 3433, 3085, 3055, 2960, 1556, 1516, 1340, 1284, 1156, 1134, 964, 908, 841, 776, 582 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.48 (m, 6 H), 3.49 (s, 3 H), 3.52–3.61 (m, 4 H), 4.74 (s, 2 H), 6.97–7.05 (m, 2 H), 7.13–7.22 (m, 2 H), 7.80–7.89 (m, 2 H), 8.04–8.12 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.9, 33.3, 42.6, 54.6, 109.5, 116.0 (d, *J* = 21.9 Hz), 122.2 (q, *J* = 273.6 Hz), 127.8, 128.5, 130.5 (d, *J* = 8.3 Hz), 133.3, 133.4 (q, *J* = 34.9 Hz), 141.8, 158.6, 163.4 (d, *J* = 252.0 Hz), 167.7, 178.8.

HRMS-ESI: *m*/*z* $[M - H]^-$ calcd for $C_{24}H_{21}F_7N_3O_4S_2$: 612.0867; found: 612.0857.

***N*-(4-(4-Fluorophenyl)-6-isopropyl-5-{[(4-nitrophenyl)sulfonyl]methyl}pyrimidin-2-yl)-*N*-methylmethanesulfonamide (6g)**

Prepared according to the general procedure. The crude reaction mixture was triturated with Et_2O to provide a bright yellow crystalline product after drying; yield: 794 mg (76%); mp 191.0 and 201.2 °C (onset), 196.6 and 203.5 °C (peak).

IR (KBr): 3435, 3112, 2963, 1606, 1534, 1376, 1227, 1157, 967, 611 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.28–1.46 (m, 6 H), 3.48 (s, 3 H), 3.52–3.60 (m, 4 H), 4.71 (s, 2 H), 6.97–7.07 (m, 2 H), 7.16–7.24 (m, 2 H), 7.57–7.67 (m, 2 H), 8.16–8.25 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.9, 33.3, 42.7, 54.3, 109.5, 115.8 (d, *J* = 21.7 Hz), 124.5, 129.6, 130.8 (d, *J* = 8.3 Hz), 133.5 (d, *J* = 2.7 Hz), 144.3, 151.1, 158.5, 163.3 (d, *J* = 251.4 Hz), 167.4, 178.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{24}FN_4O_6S_2$: 523.1116; found: 523.1111.

_N_-{4-(4-Fluorophenyl)-6-isopropyl-5-[(pyridin-2-ylsulfonyl)methyl]pyrimidin-2-yl}-_N_-methylmethanesulfonamide (6h)

Prepared according to the general procedure. The crude reaction mixture was triturated with Et_2O to provide a white crystalline product after drying; yield: 889 mg (93%); mp 178.5 °C (onset), 180.7 °C (peak).

IR (KBr): 3436, 3085, 2970, 2932, 1606, 1550, 1510, 1378, 1337, 1230, 1167, 1153, 977, 607 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.5 Hz, 6 H), 3.48 (s, 3 H), 3.54 (s, 3 H), 3.59 (sept, *J* = 6.5 Hz, 1 H), 4.92 (s, 2 H), 7.00–7.09 (m, 2 H), 7.37–7.44 (m, 2 H), 7.48–7.53 (m, 1 H), 7.82–7.91 (m, 2 H), 8.50–8.56 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 32.7, 33.2, 42.6, 50.4, 110.2, 115.6 (d, *J* = 21.7 Hz), 122.4, 127.7, 131.0 (d, *J* = 8.4 Hz), 133.9, 138.3, 150.4, 157.2, 158.3, 163.2 (d, *J* = 249.7 Hz), 167.9, 178.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}FN_4O_4S_2$: 479.1218; found: 479.1220.

2-({[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}sulfonyl)benzo[*d*]oxazole (7a)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) and triturated with Et_2O to provide white crystalline product after drying; yield: 174 mg (19%); mp 173.1 °C (onset), 174.8 °C (peak).

IR (KBr): 3438, 3095, 3007, 2991, 1604, 1515, 1492, 1447, 1342, 1227, 1145, 1125, 799, 765, 627, 603 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.95–1.11 (m, 2 H), 1.21–1.41 (m, 2 H), 2.44–2.56 (m, 1 H), 5.21 (s, 2 H), 6.91–7.09 (m, 2 H), 7.15–7.24 (m, 3 H), 7.28–7.37 (m, 1 H), 7.48–7.56 (m, 1 H), 7.56–7.63 (m, 2 H), 7.63–7.71 (m, 1 H), 7.81–7.89 (m, 1 H), 7.94–8.04 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6, 15.7, 56.3, 112.1, 115.7 (d, *J* = 21.6 Hz), 117.3, 122.4, 126.1, 126.4, 126.5, 126.6, 128.9, 129.2, 130.4, 131.5 (br s), 139.6, 147.9, 149.9, 151.2, 158.6, 162.0, 162.7 (d, *J* = 248.6 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{20}FN_2O_3S$: 459.1173; found: 459.1169.

2-({[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}sulfonyl)benzo[*d*]thiazole (7b)

Prepared according to procedure described in the literature with comparable yield;[24e] mp 160.9 °C (onset), 162.9 °C (peak) (Lit.[24e] 159–161 °C).

IR (KBr): 3434, 3074, 3017, 2998, 2929, 1603, 1513, 1492, 1469, 1398, 1332, 1314, 1225, 1160, 1141, 1124, 1023, 920, 869, 840, 767, 730, 707, 601, 556, 521, 506, 490 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.98–1.10 (m, 2 H), 1.21–1.43 (br s, 2 H), 2.53–2.63 (m, 1 H), 5.22 (s, 2 H), 6.88–7.03 (m, 2 H), 7.12–7.21 (m, 3 H), 7.27–7.35 (m, 1 H), 7.55–7.61 (m, 1 H), 7.61–7.69 (m, 2 H), 7.92–8.02 (m, 2 H), 8.09–8.15 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 15.7, 56.0, 115.5 (d, *J* = 21.6 Hz), 118.0, 122.3, 125.5, 125.9, 126.3, 126.6, 127.8, 128.2, 129.1, 130.1, 131.5 (br s), 137.0, 147.7, 149.6, 152.6, 162.2, 162.5 (d, *J* = 248.3 Hz), 166.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{20}FN_2O_2S_2$: 475.0945; found: 475.0944.

2-Cyclopropyl-4-(4-fluorophenyl)-3-{[(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)sulfonyl]methyl}quinoline (7c)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to provide a bright yellow crystalline product after drying; yield: 462 mg (49%); mp 198.2 °C (onset), 199.3 °C (peak).

IR (KBr): 3434, 2924, 1513, 1334, 1229, 1162, 1130, 816, 759, 744, 630, 582 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 2 H), 1.18–1.35 (m, 2 H), 2.42–2.52 (m, 1 H), 3.75 (s, 3 H), 5.32 (s, 2 H), 6.97–7.09 (m, 2 H), 7.15–7.24 (m, 3 H), 7.29–7.36 (m, 1 H), 7.35–7.44 (m, 2 H), 7.45–7.52 (m, 1 H), 7.62–7.70 (m, 1 H), 7.78–7.85 (m, 1 H), 7.95–8.03 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 15.4, 31.5, 55.8, 110.6, 115.6 (d, *J* = 21.6 Hz), 117.6, 122.0, 124.3, 126.0, 126.3, 126.4, 126.6, 129.2, 130.2, 131.7 (d, *J* = 2.9 Hz), 131.7 (br s), 136.4, 140.9, 147.8, 150.1, 162.4, 162.7 (d, *J* = 248.4 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{23}FN_3O_2S$: 472.1490; found: 472.1488.

2-({[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl}sulfonyl)thiazole (7d)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to provide a white crystalline product after drying; yield: 237 mg (28%); mp 182.3 °C (onset), 183.5 °C (peak).

IR (KBr): 3447, 3083, 1604, 1513, 1492, 1330, 1222, 1147, 1053, 922, 838, 767, 744, 712, 656, 597 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.02–1.10 (m, 2 H), 1.21–1.38 (m, 2 H), 2.45–2.53 (m, 1 H), 5.08 (s, 2 H), 7.13–7.28 (m, 5 H), 7.30–7.35 (m, 1 H), 7.62–7.68 (m, 1 H), 7.70 (d, *J* = 3.0 Hz, 1 H), 7.97 (d, *J* = 3.0 Hz, 1 H), 7.98–7.99 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 15.6, 56.2, 115.7 (d, *J* = 21.5 Hz), 118.0, 126.0, 126.5, 126.6, 126.7, 129.1, 130.2, 131.7 (d, *J* = 2.9 Hz), 131.7 (br s), 145.3, 147.8, 149.9, 162.1, 162.7 (d, *J* = 248.1 Hz), 166.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}FN_2O_2S_2$: 425.0788; found: 425.0781.

2-Cyclopropyl-4-(4-fluorophenyl)-3-[(thiazol-2-ylsulfonyl)methyl]quinoline 1-Oxide (7d′)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to provide a bright yellow product after drying; yield: 238 mg (27%); mp 200.1 °C (onset), 203.5 °C (peak).

IR (KBr): 3425, 3115, 2960, 1599, 1508, 1381, 1364, 1323, 1219, 1176, 1143, 1063, 841, 763, 705, 556 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92–1.07 (m, 2 H), 1.27–1.37 (m, 2 H), 1.89–1.99 (m, 1 H), 5.11 (s, 2 H), 7.10–7.30 (m, 5 H), 7.43–7.50 (m, 1 H), 7.68–7.75 (m, 2 H), 7.91–7.97 (m, 1 H), 8.73–8.79 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.7, 11.8, 56.1, 115.8 (d, *J* = 21.6 Hz), 121.3, 127.0, 127.4, 128.5, 128.6, 130.7 (d, *J* = 3.0 Hz), 131.1, 132.3 (br s), 139.3, 141.6, 145.3, 147.8, 162.8 (d, *J* = 249.1 Hz), 165.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}FN_2O_3S_2$: 441.0737; found: 441.0742.

2-Cyclopropyl-4-(4-fluorophenyl)-3-{[(1-methyl-1*H*-imidazol-2-yl)sulfonyl]methyl}quinoline (7e)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:1) and triturated with Et_2O to provide a white crystalline product after drying; yield: 556 mg (66%); mp 167.6 °C (onset), 169.4 C (peak).

IR (KBr): 3433, 3141, 2936, 1604, 1513, 1492, 1325, 1243, 1157, 922, 776, 720, 601, 490 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.98–1.10 (m, 2 H), 1.15–1.44 (m, 2 H), 2.35–2.48 (m, 1 H), 3.57 (s, 3 H), 5.10 (s, 2 H), 6.91–7.02 (m, 1 H), 7.10–7.16 (m, 1 H), 7.16–7.30 (m, 5 H), 7.32–7.40 (m, 1 H), 7.62–7.72 (m, 1 H), 7.95–8.04 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6, 15.2, 34.9, 56.0, 115.5 (d, *J* = 21.5 Hz), 117.9, 126.0, 126.2, 126.4, 126.6, 129.0, 129.5, 130.1, 131.8 (d, *J* = 2.8 Hz), 131.8 (br s), 142.3, 147.7, 150.1, 162.2, 162.7 (d, *J* = 248.2 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}FN_3O_2S$: 422.1333; found: 422.1332.

3-({[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}methyl)-2-cyclopropyl-4-(4-fluorophenyl)quinoline (7f)

Prepared according to the general procedure. The crude reaction mixture was triturated with Et_2O to provide a white crystalline product after drying; yield: 830 mg (75%); mp 163.5 °C (onset), 164.5 °C (peak).

IR (KBr): 3433, 1513, 1494, 1360, 1340, 1276, 1151, 1107, 910, 843, 767, 681, 587 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.00–1.18 (m, 2 H), 1.18–1.50 (m, 2 H), 2.47–2.60 (m, 1 H), 4.82 (s, 2 H), 7.10–7.25 (m, 5 H), 7.31–7.39 (m, 1 H), 7.64–7.72 (m, 1 H), 7.92–8.05 (m, 3 H), 8.08–8.15 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.9, 15.7, 57.7, 115.9 (d, *J* = 21.6 Hz), 117.8, 122.3 (q, *J* = 273.3 Hz), 126.2, 126.5, 127.5, 128.6, 129.3, 130.4, 131.7 (br s), 131.7, 133.4 (q, *J* = 34.5 Hz), 143.0, 148.0, 149.7, 161.8, 162.8 (d, *J* = 250.1 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{19}F_7NO_2S$: 554.1019; found: 554.1017.

2-Cyclopropyl-4-(4-fluorophenyl)-3-{[(4-nitrophenyl)sulfonyl]methyl}quinoline (7g)

Compound was prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to provide a white crystalline product after drying; yield: 638 mg (69%); mp 180.5 °C (onset), 182.6 °C (peak).

IR (KBr): 3436, 2924, 1606, 1533, 1349, 1306, 1159, 1144, 1084, 924, 855, 872, 765 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.98–1.09 (m, 2 H), 1.17–1.39 (m, 2 H), 2.44–2.52 (m, 1 H), 4.79 (s, 2 H), 7.13–7.23 (m, 5 H), 7.31–7.37 (m, 1 H), 7.64–7.70 (m, 1 H), 7.74–7.79 (m, 2 H), 7.96–8.01 (m, 1 H), 8.26–8.32 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.9, 15.7, 57.3, 115.8 (d, *J* = 21.5 Hz), 117.9, 124.5, 126.2, 126.3, 126.6, 129.2, 129.8, 130.3, 131.7 (d, *J* = 3.1 Hz), 131.8 (br s), 145.6, 147.8, 149.7, 151.0, 161.8, 162.7 (d, *J* = 249.1 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{20}FN_2O_4S$: 463.1122; found: 463.1122.

2-Cyclopropyl-4-(4-fluorophenyl)-3-[(pyridin-2-ylsulfonyl)methyl]quinoline (7h)

Prepared according to the general procedure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:4) to provide a white crystalline product after drying; yield: 426 mg (51%); mp 152.3 °C (onset), 153.4 °C (peak).

IR (KBr): 3434, 3049, 2991, 1512, 1493, 1306, 1222, 1145, 1110, 923, 840, 764, 592 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.99–1.09 (m, 2 H), 1.23–1.39 (m, 2 H), 2.53–2.64 (m, 1 H), 5.07 (s, 2 H), 7.04–7.13 (m, 2 H), 7.12–7.24 (m, 3 H), 7.27–7.34 (m, 1 H), 7.47–7.54 (m, 1 H), 7.58–7.66 (m, 1 H), 7.82–7.92 (m, 2 H), 7.93–8.00 (m, 1 H), 8.56–8.64 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6, 15.7, 53.1, 115.5 (d, *J* = 21.5 Hz), 119.0, 122.2, 125.8, 126.5, 126.5, 127.5, 129.1, 129.9, 131.7 (br s), 131.9, 138.2, 147.6, 149.3, 150.3, 158.1, 162.4, 162.5 (d, *J* = 247.7 Hz).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{20}FN_2O_2S$: 419.1224; found: 419.1228.

Screening of the Olefination Step Between Aldehyde 1 and Sulfone-Derivatized Heterocyclic Precursors 6 and 7

A solution of **1′** (66 mg, 0.24 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (10 mL) was stirred at r.t. for 2 h. Then, it was warmed to 50 °C and purged with N_2 to remove the mixture of CH_2Cl_2 and released H_2O. THF (5 mL) was then added to the resulting residue to form an anhydrous solution of pure aldehyde **1**. A three-necked reaction flask containing the sulfone heterocyclic precursor (0.2 mmol, 1 equiv) was dried at 85 °C under vacuum for 2 h and then cooled to r.t. under N_2. Sulfone **6** or **7** was dissolved in anhydrous THF (10 mL) and the flask was cooled in a cryostated EtOH bath to –60 °C. A solution of 1 M NaHMDS in THF (220 μL, 0.22 mmol, 1.1 equiv) was then added to the mixture to form a colored solution. After 5 min, the formerly prepared solution of aldehyde **1** was rapidly added to the reaction mixture with vigorous stirring. The reaction was completed within few seconds, which was indicated by loss of color. Sat. aq NH_4Cl (5 mL) was added to the mixture, which was then slowly warmed to r.t. THF was evaporated under reduced pressure and EtOAc (50 mL) was added to the residue. The organic phase was washed with H_2O (25 mL) and sat. aq $NaHCO_3$ (25 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction product was analyzed with HPLC and ^1H NMR spectroscopy. Results of these reactions are gathered in Table 1.

Optimization of the Olefination Step Between Sulfone Precursors 6b and 7b with Aldehyde 1

A solution of **1′** (0.90–1.50 equiv) in anhydrous CH_2Cl_2 (10 mL) was stirred at r.t. for 2 h. Then, it was warmed to 50 °C and purged with N_2 to remove the mixture of CH_2Cl_2 and released H_2O. Solvent (5 mL) was then added to the resulting residue to form an anhydrous solution of pure aldehyde **1**. A three-necked reaction flask containing the sulfone precursor **6b** or **7b** (1 equiv) was dried at 85 °C under vacuum for 2 h and then cooled to r.t. under N_2. Sulfone **6b** or **7b** was dissolved in anhydrous solvent (10 mL) and the flask was cooled in a cryostated EtOH bath to –50, –60, or –70 °C. A solution of base (1.1–1.5 equiv) was then added to the mixture to form a colored solution. After 5 min, the formerly prepared solution of aldehyde **1** was rapidly added to the reaction mixture with vigorous stirring. The reaction was completed within few seconds, which was indicated by loss of color. Sat. aq NH_4Cl (5 mL) was added to the reaction mixture, which was then slowly warmed to r.t. The solvent was evaporated under reduced pressure and EtOAc (50 mL) was added to the residue. The organic phase was washed with H_2O (25 mL) and sat. aq $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude reaction product was analyzed with HPLC [**6b**, t_R = 22.8 min; **7b**, t_R = 25.0 min; (*E*)-**8**, t_R = 27.0 min; (*Z*)-**8**, t_R = 25.5 min; (*E*)-**9**, t_R = 34.0 min; (*Z*)-**9**, t_R = 33.5 min; ArOH t_R = 14.5 min]. Results of these reactions are collected in Table 2 (see also the discussion part for the solvents used).

The Final Preparative Process of the Olefination Between Benzothiazole Sulfone Precursors 6b and 7b with Aldehyde 1 on a 1 mmol scale; General Procedure

A solution of **1′** (0.330 g, 1.20 mmol, 1.20 equiv) in anhydrous CH_2Cl_2 (25 mL) was stirred at r.t. for 2 h. Then it was warmed to

50 °C and purged with N_2 to remove the mixture of CH_2Cl_2 and released H_2O. THF (12.5 mL) was then added to the resulting residue to form an anhydrous solution of pure aldehyde **1**. A three-necked reaction flask containing compound **6b** or **7b** (1 mmol, 1 equiv) was dried at 85 °C under vacuum for 2 h and then cooled to r.t. under N_2. Sulfone **6b** or **7b** was dissolved in anhydrous THF (25 mL) and the flask was cooled in a cryostated EtOH bath to –60 °C. A solution of 1 M NaHMDS in THF (1.30 mL, 1.30 mmol, 1.30 equiv) was then added to the mixture to form a colored solution. After 5 min the formerly prepared solution of aldehyde **1** was rapidly added to the reaction mixture with vigorous stirring. The reaction was completed within few seconds, which was indicated by the loss of color. Sat. aq NH_4Cl (15 mL) was added to the mixture, which was then slowly warmed to r.t. THF was evaporated under reduced pressure and EtOAc (50 mL) was added to the residue. The organic phase was washed with H_2O (50 mL) and sat. aq $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated in vacuo.

_N_-(5-{(_E_)-2-[(2_S_,4_R_)-4-(_tert_-Butyldimethylsilyloxy)-6-oxotetrahydro-2_H_-pyran-2-yl]vinyl}-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-_N_-methylmethanesulfonamide [(_E_)-8)]

Synthesized according to the above described preparative general procedure. The desired product was purified by silica gel column chromatography (Et_2O–methylcyclohexane, 1:3) to provide a white amorphous solid after drying at 60 °C below 50 mbar; yield: 381 mg (66%); HPLC purity: 97.1 area%.

IR (KBr): 3443, 3071, 2957, 2929, 2855, 1731, 1547, 1511, 1442, 1383, 1234, 1156, 1076, 968, 839, 777, 615, 564 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.27 (d, *J* = 6.7 Hz, 6 H), 1.51–1.83 (m, 2 H), 2.53–2.68 (m, 2 H), 3.34 (sept, *J* = 6.7 Hz, 1 H), 3.51 (s, 3 H), 3.58 (s, 3 H), 4.23–4.33 (m, 1 H), 5.12–5.25 (m, 1 H), 5.49 (dd, *J* = 16.1, 5.8 Hz, 1 H), 6.70 (dd, *J* = 16.1, 1.3 Hz, 1 H), 7.03–7.17 (m, 2 H), 7.55–7.70 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.90, –4.82, 18.0, 21.6, 21.7, 25.7, 32.3, 33.1, 36.4, 39.4, 42.5, 63.3, 75.4, 115.1 (d, *J* = 21.7 Hz), 120.6, 125.5, 132.1 (d, *J* = 8.4 Hz), 134.3 (d, *J* = 3.3 Hz), 134.8, 157.6, 163.3 (d, *J* = 250 Hz), 163.7, 169.6, 175.0.

HRMS-ESI (+): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{41}FN_3O_5SSi$: 578.2520; found: 578.2540.

(4_R_,6_S_)-4-[(_tert_-Butyldimethylsilyl)oxy]-6-{(_E_)-2-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]vinyl}tetrahydro-2_H_-pyran-2-one [(_E_)-9]

Synthesized according to the above described preparative general procedure. The desired product was purified by silica gel column chromatography (MTBE–methylcyclohexane, 1:5) to provide a white crystalline solid after drying at 60 °C below 50 mbar; yield: 369 mg (71%); mp 157.0 °C (onset) and 159.3 °C (peak) [Lit.[27a] 157.2 °C (onset) and 159.2 °C (peak)]; HPLC purity: 98.4 area%.

IR (KBr): 3440, 3065, 3003, 2950, 2926, 2895, 2855, 1741, 1606, 1516, 1492, 1344, 1252, 1241, 1222, 1163, 1074, 1046, 930, 847, 837, 775, 767 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9 H), 0.99–1.06 (m, 2 H), 1.29–1.36 (m, 2 H), 1.48 (ddd, *J* = 2.6, 11.2, 13.9 Hz, 1 H), 1.56–1.63 (m, 1 H), 2.35–2.43 (m, 1 H), 2.49–2.60 (m, 2 H), 4.20–4.26 (m, 1 H), 5.07–5.15 (m, 1 H), 5.63 (dd, *J* = 6.6, 16.2 Hz, 1 H), 6.65 (dd, *J* = 1.2, 16.2 Hz, 1 H), 7.11–7.22 (m, 4 H), 7.29 (ddd, *J* = 1.2, 6.7, 8.2 Hz, 1 H), 7.34 (dd, *J* = 1.1, 8.4 Hz, 1 H), 7.57 (ddd, *J* = 1.5, 6.7, 8.3 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.7 (d, *J* = 10.7 Hz), 10.6 (d, *J* = 5.4 Hz), 16.0, 18.1, 25.8, 36.8, 39.4, 63.5, 76.1, 115.5 (dd, *J* = 11.4 Hz, *J* = 21.4 Hz), 125.7, 126.0, 126.2, 128.4, 128.8, 129.1, 129.1, 132.0 (dd, *J* = 7.8 Hz, *J* = 43.5 Hz), 133.4 (d, *J* = 3.2 Hz), 135.1, 144.7, 147.2, 160.7, 162.4 (d, *J* = 247.4 Hz), 170.0.

HRMS-ESI (+): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{37}FNO_3Si$: 518.2521; found: 518.2519.

Acknowledgment

L. Kolenc, T. Tome, S. Borišek, and M. Borišek are acknowledged for assistance in some analytical work. D. Orkič is gratefully acknowledged for support on LC-MS and MS-MS analyses as well as Dr. D. Urankar (University of Ljubljana) for HRMS analysis, and Prof. J. Košmrlj (University of Ljubljana) for valuable discussions. The authors thank Lek Pharmaceuticals d.d. and EN-FIST Centre of Excellence for support of this project. J. Fabris thanks Public Agency for Technology of the Republic of Slovenia (TIA) for a young researcher fellowship (MR-10/75). Operation part was financed by the European Union, European Social Fund.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

References

(1) (a) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160. (b) Singh, N.; Tamariz, J.; Chamorro, G.; Medina-Franco, J. L. *Mini-Rev. Med. Chem.* **2009**, *9*, 1272. (c) Haines, B. E.; Wiest, O.; Stauffacher, C. V. *Acc. Chem. Res.* **2013**, *46*, 2416.
(2) (a) Kidd, J. *Nat. Rev. Drug Discovery* **2006**, *5*, 813. (b) Endo, A. *Nat. Med.* **2008**, *14*, 1050.
(3) Tobert, J. A. *Nat. Rev. Drug Discovery* **2003**, *2*, 517.
(4) (a) Davidson, M. H.; Robinson, J. G. *Expert Opin. Pharmacother.* **2006**, *7*, 1701. (b) Reiner, Ž. *Nat. Rev. Cardiol.* **2013**, *10*, 453.
(5) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31. (c) Endo, A. *J. Lipid Res.* **1992**, *33*, 1569. (d) Endo, A.; Hasumi, K. *Nat. Prod. Rep.* **1993**, *10*, 541.
(6) Also known as mevinolin, with a brand name of Mevacor® (Merck & Co). For selected literature, see: (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852. (b) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.
(7) Also known as velostatin, with a brand name of Zocor® (Merck & Co). For selected literature, see: Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849.
(8) FDA approved in 1996, also known as eptastatin with a brand name of Pravachol® (Bristol–Myers Squibb). For selected literature, see: Tsujita, Y.; Kuroda, M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, I.; Tanaka, M.; Masuda, H.; Tarumi, C.; Watanabe, Y. *Biochim. Biophys. Acta* **1986**, *877*, 50.
(9) (a) Časar, Z. *Curr. Org. Chem.* **2010**, *14*, 816. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
(10) McPherson, P. A. C. *Mini-Rev. Med. Chem.* **2012**, *12*, 1250.
(11) FDA approved in 1993, with a brand name of Lescol® (Novartis Pharma AG). For selected literature, see: Fuenfschilling, P. C.; Pascale, H.; Mutz, J.-P. *Org. Process Res. Dev.* **2007**, *11*, 13; and references cited therein.
(12) FDA approved in 1996, with a brand name of Lipitor® [Pfizer (Parke–Davis)]. For selected literature, see: Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.;

Sliskovic, D. R.; Stratton, C. D.; Wilson, M. *J. Med. Chem.* **1991**, *34*, 357.
(13) FDA approved in 2003, with a brand name of Crestor® (AstraZeneca). For selected literature, see: Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Sea, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437.
(14) The last super-statin group member pitavstatin with a brand name of Livalo® (Kowa Company, Ltd.) was launched in Japan in 2003 and approved by FDA in 2009 and entered the US market in 2010. For selected literature, see: Watson, K. E. *Rev. Cardiovas. Med.* **2010**, *11*, 26.
(15) Soran, H.; Durrington, P. *Expert Opin. Pharmacother.* **2008**, *9*, 2145.
(16) (a) Kajinami, K.; Mabuchi, H.; Saito, Y. *Expert Opin. Invest. Drugs* **2000**, *9*, 2653. (b) Iglestas, P.; Díez, J. J. *Expert Opin. Invest. Drugs* **2003**, *12*, 1777. (c) Scharnagl, H.; März, W. *Curr. Top. Med. Chem.* **2005**, *5*, 233. (d) Mukhtar, R. Y. A.; Reid, J.; Reckless, J. P. D. *Int. J. Clin. Pract.* **2005**, *59*, 239. (e) Hayashi, T.; Yokote, K.; Saito, Y.; Iguchi, A. *Expert Opin. Pharmacother.* **2007**, *8*, 2315. (f) Wensel, T. M.; Waldrop, B. A.; Wensel, B. *Ann. Pharmacother.* **2010**, *44*, 507. (g) Ahmad, H.; Cheng-Lai, A. *Cardiol. Rev.* **2010**, *18*, 264. (h) Gotto, A. M. Jr.; Moon, J. *Expert Rev. Cardiovasc. Ther.* **2010**, *8*, 1079. (i) Ohbayashi, H. *Drugs Today* **2010**, *46*, 765. (j) Baker, W. L.; Datta, R. *Adv. Ther.* **2011**, *28*, 13. (k) Kawai, Y.; Sato-Ishida, R.; Motoyama, A.; Kouji, K. *Drug Des. Devel. Ther.* **2011**, *5*, 283. (l) Yee, L. L.; Wright, E. A. *Clin. Ther.* **2011**, *33*, 1023. (m) Corsini, A.; Ceska, R. *Curr. Med. Res. Opin.* **2011**, *27*, 1551.
(17) (a) Balanov, A.; Shenkar, N.; Niddam-Hildesheim, V. US Patent Appl. US 2007167625 A1, **2007**; *Chem. Abstr.* **2007**, *147*, 166109. (b) Radl, S.; Stach, J.; Klvana, R.; Jirman, J. PCT Patent Appl. WO 2007000121 A1, **2007**; *Chem. Abstr.* **2007**, *146*, 121983. (c) Patel, D. J.; Kumar, R.; Dwivedi, S. P. D. PCT Patent Appl. WO 2007099561 A1, **2007**; *Chem. Abstr.* **2007**, *147*, 322770. (d) Žličar, M. PCT Patent Appl. WO 2007017117, **2007**; *Chem. Abstr.* **2007**, *146*, 251655. (e) Andrushko, N.; Andrushko, V.; König, G.; Spannenberg, A.; Börner, A. *Eur. J. Org. Chem.* **2008**, 847.
(18) For reviews on synthesis of pitavastatin, see: (a) Miyachi, N.; Suzuki, M.; Ohara, Y.; Hiyama, T. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 186. (b) Sorbera, L. A.; Leeson, P. A.; Castaner, J. *Drugs Fut.* **1998**, *23*, 847.
(19) For the non-Wittig and non-HWE synthesis of pitavastatin, see: (a) Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 201. (b) Takahashi, K.; Minami, T.; Ohara, Y.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8263. (c) Miyachi, N.; Yanagawa, Y.; Iwasaki, H.; Ohara, Y.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8267. (d) Takahashi, K.; Minami, T.; Ohara, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2649. (e) Hiyama, T.; Minami, T.; Takahashi, K.; Miyachi, N.; Ohara, Y. PCT Patent Int. Appl. WO 9406746, **1994**; *Chem. Abstr.* **1994**, *122*, 105264. (f) Suzuki, M.; Yanagawa, Y.; Iwasaki, H.; Kanda, H.; Yanagihara, K.; Matsumoto, H.; Ohara, Y.; Yazaki, Y.; Sakoda, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2977. (g) Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Kitahara, M.; Sakashita, M.; Sakoda, R. *Bioorg. Med. Chem.* **2001**, *9*, 2727. (h) Chen, G.-P.; Kapa, P. K.; Loeser, E. M.; Beutler, U.; Zaugg, W.; Girgis, M. J. PCT Patent Appl. WO 2003064382, **2003**; *Chem. Abstr.* **2003**, *139*, 164712. (i) Manne, S. R.; Bairy, K. R.; Chepyala, K. R.; Muppa, K. K.; Srinivasan, R. T.; Sajja, E.; Maramreddy, S. R. *Orient. J. Chem.* **2007**, *23*, 559.
(20) (a) Minami, T.; Hiyama, T. *Tetrahedron Lett.* **1992**, *33*, 7525. (b) Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513. (c) Hiyama, T.; Minami, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 364. (d) Hiyama, T.; Minami, T.; Yanagawa, Y.; Ohara, Y. PCT Patent Int. Appl. WO 9511898, **1995**; *Chem. Abstr.* **1995**, *123*, 313782.
(21) Acemoglu, M.; Brodbeck, A.; Garcia, A.; Grimler, D.; Hassel, M.; Riss, B.; Schreiber, R. *Helv. Chim. Acta* **2007**, *90*, 1069.
(22) For reviews on Julia–Kocienski olefination, see: (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163. (c) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831. (d) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, 5939.
(23) For representative papers and mechanistic discussions on Julia–Kocienski olefination, see: (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (c) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149. (d) Mirk, D.; Grassot, J.-M.; Zhu, J. *Synlett* **2006**, 1255. (e) Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* **2006**, *71*, 2009. (f) Pospišil, J. *Tetrahedron Lett.* **2011**, *52*, 2348. (g) Robiette, R.; Pospíšil, J. *Eur. J. Org. Chem.* **2013**, 836. (h) Habib, S.; Larnaud, F.; Pfund, E.; Lequeux, T.; Fenet, B.; Goekjian, P. G.; Gueyrard, D. *Eur. J. Org. Chem.* **2013**, 1872. (i) Hafner, A.; Fischer, T. S.; Bräse, S. *Eur. J. Org. Chem.* **2013**, 7996.
(24) For patent literature related to the synthesis of statins via Julia–Kocienski olefination with aldehyde type dually protected open side-chain derivatives **D**, see: (a) Ju, H.; Joung, S.-S.; Yi, H.-J.; Khoo, J.-H.; Lim, J.-C.; Kim, J.-G. PCT Patent Appl. WO 2012002741, **2012**; *Chem. Abstr.* **2012**, *156*, 122219. (b) Pandya, V. P.; Richhariya, S.; Divya, P.; Meeran, H. N. P. N.; Tewari, N. PCT Patent Appl. WO 2011132172, **2011**; *Chem. Abstr.* **2011**, *155*, 589162. (c) Reddy, M. S.; Rajan, S. T.; Reddy, M. S. PCT Patent Appl. WO 2011083495, **2011**; *Chem. Abstr.* **2011**, *155*, 182074. (d) Reddy, M. S.; Rajan, S. T.; Reddy, M. S. PCT Patent Appl. WO 2011086584, **2011**; *Chem. Abstr.* **2011**, *155*, 182078. (e) Kim, H. S.; Kim, W. J.; Kim, H. C.; Sim, J. Y.; Cho, S. M.; Byun, E. Y.; Jeon, J. Y.; Lee, Y. J.; Suh, K. H.; Lee, G. S. PCT Patent Appl. WO 2010077062, **2010**; *Chem. Abstr.* **2010**, *153*, 174956. (f) Kim, H. S.; Kim, H.; Sim, J. Y.; Cho, S. M.; Kim, W. J.; Suh, K. H.; Lee, G. S. PCT Patent Appl. WO 2010098583, **2010**; *Chem. Abstr.* **2010**, *153*, 334077. (g) Anegondi, S. P.; Rajmahendra, S.; Joseph, J.; Srinivas, P. V. PCT Patent Appl. WO 2010023678, **2010**; *Chem. Abstr.* **2010**, *152*, 287413. (h) Reddy, M. S.; Rajan, S. T.; Reddy, M. S. PCT Patent Appl. WO 2008044243, **2008**; *Chem. Abstr.* **2008**, *148*, 471771. (i) Reddy, M. S.; Rajan, S. T.; Reddy, M. S. PCT Patent Appl. WO 2007125547, **2007**; *Chem. Abstr.* **2007**, *147*, 522015. (j) Brodfuehrer, P. R.; Sattelberg, T. R. Sr.; Kant, J.; Qian, X. PCT Patent Appl. WO 2002098854, **2002**; *Chem. Abstr.* **2002**, *138*, 24717.
(25) Hobson, L. A.; Akiti, O.; Deshmukh, S. S.; Harper, S.; Katipally, K.; Chiajen, J.; Livingston, R. C.; Lo, E.; Miller, M. M.; Ramakrishnan, S.; Shen, L.; Spink, J.; Tummala, S.; Wei, C.; Yamamoto, K.; Young, J.; Parsons, R. L. *Org. Process Res. Dev.* **2010**, *14*, 44.
(26) (a) Časar, Z. PCT Patent Int. Appl. WO 2007039287, **2007**; *Chem. Abstr.* **2007**, *146*, 421841. (b) Časar, Z.; Steinbücher, M.; Košmrlj, J. *J. Org. Chem.* **2010**, *75*, 6681. (c) McLaughlin, M.; Garci Rubio, S.; Wilson, I.; Delaney, P.; Zhao, W.; Zlota, A.; Laird, T. *Org. Process Res. Dev.* **2010**, *14*, 1276. (d) Šterk, D.; Časar, Z.; Jukič, M.; Košmrlj, J. *Tetrahedron* **2012**, *68*, 2155. (e) Šterk, D.; Jukič, M.;

Časar, Z. *Org. Process Res. Dev.* **2013**, *17*, 145. (f) Fabris, J.; Makuc, D.; Časar, Z.; Plavec, J. *Tetrahedron* **2013**, *69*, 6262.
(27) (a) Fabris, J.; Gazić Smilović, I.; Časar, Z. *Synthesis* **2012**, *44*, 1700. (b) Makuc, D.; Fabris, J.; Časar, Z.; Plavec, J. *Molecules* **2013**, *18*, 13283.
(28) (a) Časar, Z. *Synlett* **2008**, 2036. (b) Časar, Z.; Košmrlj, J. *Synlett* **2009**, 1144. (c) Cluzeau, J.; Časar, Z.; Mrak, P.; Ošlaj, M.; Kopitar, G. PCT Patent Int. Appl. WO 2009092702, **2009**; *Chem. Abstr.* **2009**, *151*, 218948 (d) Časar, Z.; Tramšek, M.; Goršek, A. *Acta Chim. Slov.* **2010**, *57*, 66. (e) Troiani, V.; Cluzeau, J.; Časar, Z. *Org. Process Res. Dev.* **2011**, *15*, 622. (f) Ošlaj, M.; Cluzeau, J.; Orkić, D.; Kopitar, G.; Mrak, P.; Časar, Z. *PLoS One* **2013**, *8*, e62250. (g) Turner, K. *Org. Process Res. Dev.* **2013**, *17*, 893.
(29) El-Azab, A. S.; Al-Omar, M. A.; Abdel-Aziz, A. A.; Abdel-Aziz, N. I.; El-Sayed, M. A.; Aleisa, A. M.; Sayed-Ahmed, M. M.; Abdel-Hamid, S. G. *Eur. J. Med. Chem.* **2010**, *45*, 4188.
(30) Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089.
(31) Ringger, D. H.; Chen, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 4686.
(32) (a) Klemm, L. H.; Mathur, S. B.; Zell, R.; Merrill, R. E. *J. Heterocycl. Chem.* **1971**, *8*, 931. (b) Sulfoxides have a band between 1040 and 1050 cm^{-1}, sulfones exhibit a symmetrical stretch between 1165 and 1170 cm^{-1} and an asymmetrical stretch between 1300 and 1330 cm^{-1}, whereas *N*-oxides show a band between 1210 and 1265 cm^{-1}.
(33) Sun, M.; Dai, W.; Liu, D. Q. *J. Mass Spectrom.* **2008**, *43*, 383.

