Synthesis T. Glachet et al. Paper

Late-Stage Sulfoximination: Improved Synthesis of the Anticancer Drug Candidate Atuveciclib

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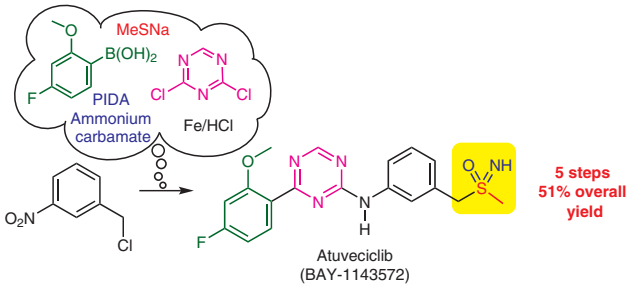

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Abstract An efficient synthesis of racemic atuveciclib was accomplished in five steps with an excellent 51% overall yield, using cheap reagents and mild reaction conditions. The key sulfoximination reaction was realized during the last step of the synthesis from the corresponding sulfide.

Key words atuveciclib, sulfoxide, sulfoximine, sulfanenitrile, palladium, cross-coupling

Despite the early discovery of methionine sulfoximine (MSO, Figure 1) in the 1950's,[1] as a potent inhibitor of glutamine synthetase, sulfoximines appeared only recently in the life sciences.[2] Only one drug containing a sulfoximine group, sulfoxaflor (insecticide) was marketed in 2013.[3] At the moment, few compounds (Figure 1) are evaluated in clinical trials (phase 2) for cancer treatment (kinase inhibitors), like AZD6738,[4] roniciclib (BAY 1000394),[5] and atuveciclib (BAY 1143572).[6]

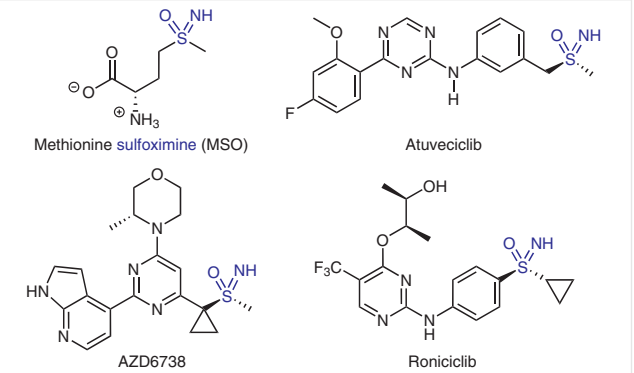
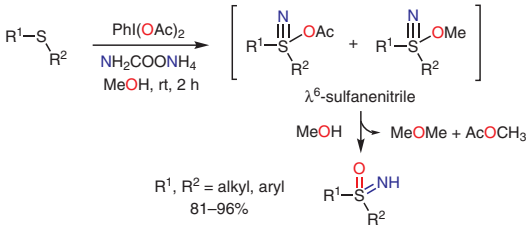


Figure 1 Structure of bioactive sulfoximines

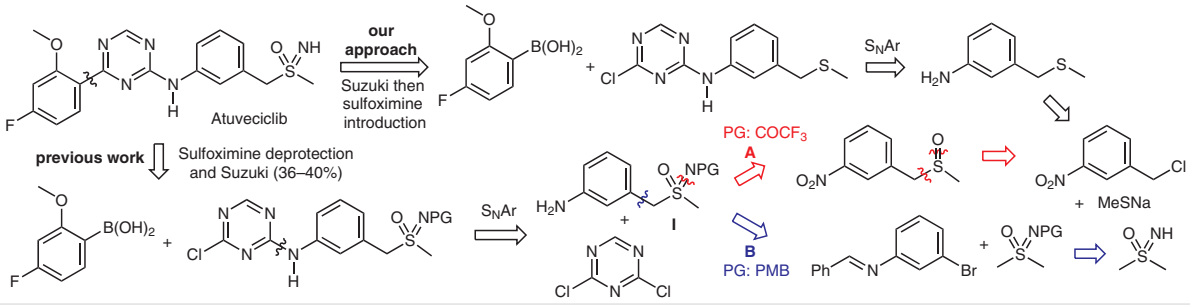
Sulfoximines are mainly used as a bioisosteres of carboxylic acids,[7] amidines,[8] alcohols,[9] sulfones,[10] sulfonamides,[5,11] sulfoxides, or piperazines.[12] The sulfoximine moiety continues to flourish since it often exhibits favorable physicochemical properties, for example,[13] metabolic stability, high aqueous solubility, high passive permeability, minor decomposition in acidic or basic conditions, and lipophilicity comparable to sulfones or amides. Further applications of sulfoximines in drug discovery are facilitated by the recent development of safer synthetic methods, especially from sulfoxides[14] and sulfides.[15]

In this context, we recently developed an efficient synthesis of sulfoximines from sulfides using phenyliodine diacetate (PIDA) and ammonium carbamate (AC).[15c,16] In this method, we highlighted the importance of methanol, the solvent of this reaction, which also reacts as a nucleophile with λ⁶-sulfanenitrile intermediates to afford the corresponding NH-sulfoximine (Scheme 1). Considering that this reaction is highly tolerant to a large number of functional groups and N-heterocycles,[17] we reasoned that it could be applied to the late-stage sulfoximination of atuveciclib.



Scheme 1 Reactive intermediates during the synthesis of NH-sulfoximines

Atuveciclib is the first potent and highly selective PTEFb[18]/CDK9 inhibitor (positive transcription elongation factor b) to enter clinical trials, making it a promising new



Scheme 2 Retrosynthetic pathways of atuveciclib

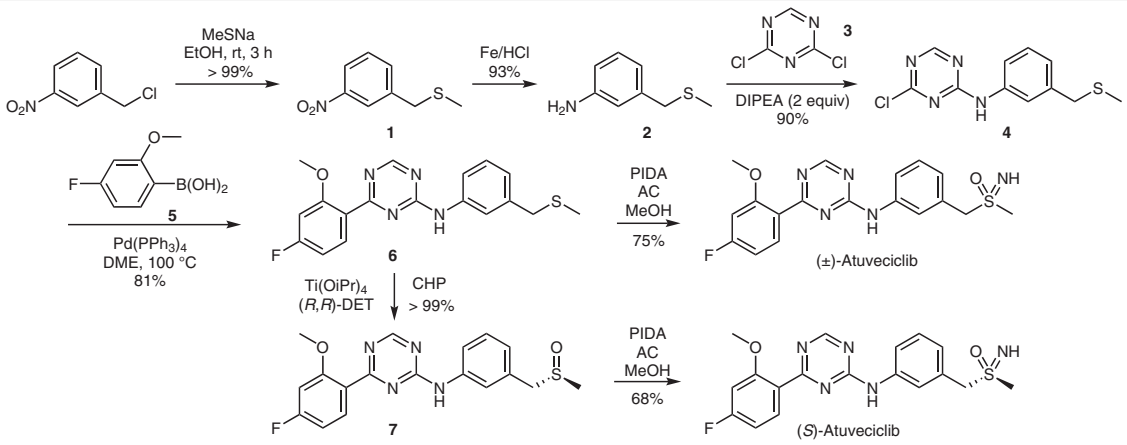
approach in cancer therapy. Lücking's group described two synthetic strategies (Scheme 2) with 9 steps (**A**, 16.8% overall yield)[19] or 6 steps (**B**, 13.9% overall yield).[20] Both syntheses rely on the aromatic substitution reaction with 2,4-dichloro-1,2,3-triazine and a Suzuki cross-coupling reaction with a boronic acid. However, amine **I** is either obtained through Bolm's rhodium-catalyzed imination[21] of sulfoxide (approach **A**, red disconnection), or through an original palladium-catalyzed direct α-arylation (approach **B**, blue disconnection) developed by the same group.[20] In both syntheses, the Suzuki cross-coupling reaction afforded low yields (36 and 40%).

We reasoned that the sulfoximine function could be responsible for this low reactivity due to palladium-catalyst poisoning and therefore propose a late-stage sulfoximination approach (Scheme 2).[22]

Our synthesis started (Scheme 3) with the S_N2 reaction of sodium methanethiolate on commercially available benzyl chloride leading to thioether **1** in quantitative yield (no purification). Next, the nitro group was reduced and, instead of using titanium(III) chloride as described by Lücking, a less toxic and inexpensive Fe/HCl mixture was used. Aniline **2** was thus obtained in 93% yield and was pure enough to be used directly in the next step.[23] It should be noted that when the reduction was performed in the presence of Sn/HCl, it proved to be unsuccessful.[24] Next, the nucleophilic aromatic substitution with 2,4-dichloro-1,3,5-triazine (**3**) gave thioether **4** in 90% yield after purification on silica gel. The Suzuki cross-coupling on commercial boronic acid **5** was then performed using tetrakis(triphenylphosphine)palladium in DME at 100 °C. To our delight, the desired tricyclic compound **6** was obtained in a satisfactory 81% yield.[25] However, surprisingly no reaction occurred when 2,4-dichloro-1,3,5-triazine (**3**) and boronic acid **5** were mixed under the same conditions.[26]

Finally, the last step consisted of the sulfoximination reaction that was performed using our previously described conditions:[15c] PIDA (2.1 equiv), AC (1.5 equiv) in methanol at room temperature. After 30 minutes, complete conversion was observed and atuveciclib was obtained in 75% yield on gram scale after purification on silica gel. Hence, the whole synthetic sequence consisted of only 5 steps with an excellent 51% overall yield, which competes favorably with the previous Lücking's syntheses (6 or 9 steps with 13.8 or 16.8% overall yield, respectively).

Moreover, our strategy is also applicable to asymmetric synthesis of atuveciclib. Indeed, thioether **6** could be easily transformed into the corresponding enantioenriched sulfoxide **7**.[27] Asymmetric oxidation was performed using Kagan's conditions, a titanium-mediated oxidation with cu-



Scheme 3 Racemic and asymmetric synthesis of atuveciclib

mene hydroperoxide (CHP) in the presence of diethyl (*R*,*R*)-tartrate[28] and sulfoxide **7** was isolated in quantitative yield. Then, the imination reaction into the corresponding atuveciclib was achieved using Bull's metal-free conditions[14] in 68% yield and with only 19.8% ee.[29] Due to the fact that the sulfoximination occurs stereospecifically with retention of configuration, this low enantiomeric excess originates from a weakly asymmetric sulfoxidation step.[30]

In conclusion, we have described a short and efficient racemic synthesis of clinical anticancer drug atuveciclib with an excellent 51% overall yield, using commercially available starting material, cheap reagents and featuring a late-stage sulfoximination. The proof of concept for asymmetric synthesis was also demonstrated and would need to be improved.[31] Hence, we believe that the late-stage sulfoximination approach can be applied to various other molecules provided that the corresponding sulfide is available.

^{1}H NMR spectra were recorded at 400 MHz or 500 MHz and ^{13}C NMR spectra were recorded at 101 MHz or 125 MHz on a Bruker DRX400 or Bruker Avance III 500 spectrometer. ^{19}F NMR spectra were recorded at 470.5 MHz on a Bruker Avance III 500 spectrometer. IR spectra were recorded on a PerkinElmer ATR-spectrum one spectrometer. The high-resolution mass spectrometry (HRMS) analyses were performed using a Xevo G2-XS QTof Waters mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. HPLC separations were achieved with Waters Alliance system, using Chiralpak IC column. Melting points were determined using a Gallen-Kamp melting point apparatus. Compounds **1**, **2**, and atuveciclib were previously described, and their spectroscopic data are in agreement with those reported in the literature.[6,20]

1-[(Methylsulfanyl)methyl]-3-nitrobenzene (1)

Sodium methanethiolate (3.5 g, 49.5 mmol) was added in three portions to a stirred solution of 1-(chloromethyl)-3-nitrobenzene (5.0 g, 29.1 mmol) in EtOH (60 mL) at –15 °C. The cold bath was removed and the solution was stirred at r.t. for 3 h. The reaction mixture was diluted with brine and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 5.33 g (>99%) of thioether **1** as a yellow oil, which was used without purification in the next step; R_f = 0.9 (pentane/EtOAc, 70:30).

IR (ATR): 1522, 1350 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H, ArH), 8.11 (d, *J* = 8.0 Hz, 1 H, ArH), 7.66 (d, *J* = 8.0 Hz, 1 H, ArH), 7.50 (t, *J* = 8.0 Hz, 1 H, ArH), 3.75 (s, 2 H, ArCH_2S), 2.01 (s, 3 H, SCH_3).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 148.4 (C_q), 140.6 (C_q), 134.9 (C_{Ar}), 129.4 (C_{Ar}), 123.7 (C_{Ar}), 122.1 (C_{Ar}), 37.8 (CH_2), 15.0 (CH_3).

HRMS (ESI-QTOF): *m*/*z* [M]$^+$ calcd for $C_8H_9NO_2S$: 183.0354; found: 183.0351.

3-[(Methylsulfanyl)methyl]aniline (2)

Iron powder (3.27 g, 54.6 mmol) and few drops of concd HCl were added to a stirred solution of nitrobenzene **1** (1.00 g, 5.46 mmol) in EtOH/H_2O (4:1, 15 mL) at r.t. The mixture was stirred for 3 h at reflux. After filtration through Celite 545, the residue was washed with EtOH. Then, the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 0.776 g (93%) of aniline **2** as a brown oil, which was used without purification in the next step; R_f = 0.7 (pentane/EtOAc, 70:30).

IR (ATR): 3349, 2913, 1618, 1602, 1589 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.09 (t, *J* = 7.9 Hz, 1 H, ArH), 6.70–6.66 (m, 2 H, ArH), 6.59–6.56 (m, 1 H, ArH), 3.59 (s, 2 H, ArCH_2S), 2.00 (s, 3 H, SCH_3).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 148.6 (C_q), 138.3 (C_q), 128.3 (C_{Ar}), 118.2 (C_{Ar}), 114.4 (C_{Ar}), 112.8 (C_{Ar}), 37.3 (CH_2), 14.0 (CH_3).

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}NS$: 154.0690; found: 154.0690.

4-Chloro-*N*-{3-[(methylsulfanyl)methyl]phenyl}-1,3,5-triazin-2-amine (4)

2,4-Dichloro-1,3,5-triazine (**3**; 840 mg, 5.6 mmol) was dissolved in THF/*i*-PrOH (1:1, 25.5 mL) and the solution was cooled to 0 °C. Then, DIPEA (1.8 mL, 10.2 mmol) and a solution containing aniline **2** (805 mg, 5.1 mmol) in THF/*i*-PrOH (1:1, 25.5 mL) were added sequentially. The resulting solution was stirred at 0 °C for 30 min. Volatiles were removed under reduced pressure and the crude mixture was purified by column chromatography (pentane/EtOAc, 70:30) to afford 1.217 g (90%) of product **4** as a yellow solid; mp 124.7–125.4 °C; R_f = 0.6 (pentane/EtOAc, 70:30).

IR (ATR): 3090, 2953, 1543, 1512, 1488, 1377, 1013, 796 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.57–8.51 (m, 1 H, HetArH), 7.60–7.47 (m, 3 H, ArH and NH), 7.34 (t, *J* = 7.8 Hz, 1 H, ArH), 7.13 (d, *J* = 7.8 Hz, 1 H, ArH), 3.69 (s, 2 H, ArCH_2S), 2.03 (s, 3 H, SCH_3).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 167.7 (C_{HetAr}), 166.9 (C_q), 164.1 (C_q), 139.7 (C_q), 136.6 (C_q), 129.3 (C_{Ar}), 125.9 (C_{Ar}), 121.6 (C_{Ar}), 120.0 (C_{Ar}), 38.2 (CH_2), 15.0 (CH_3).

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd $C_{11}H_{12}{}^{35}ClN_4S$: 267.0471; found: 267.0472.

4-(4-Fluoro-2-methoxyphenyl)-*N*-{3-[(methylsulfanyl)methyl]phenyl}-1,3,5-triazin-2-amine (6)

A degassed mixture containing chloride **4** (267 mg, 1 mmol), 4-fluoro-2-methoxyphenylboronic acid (**5**; 255 mg, 1.5 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), and aq 2 M K_2CO_3 (1.0 mL, 2 mmol) in 1,2-DME (6 mL) was heated under N_2 atmosphere at 100 °C for 90 min in a sealed tube. After cooling, the mixture was diluted with EtOAc and washed with brine. The organic phase was dried ($MgSO_4$), filtered, and the volatiles were removed under reduced pressure. The crude mixture was purified by column chromatography (pentane/EtOAc, 70:30) to give 290 mg (81%) of compound **6** as a yellow solid; mp 101.5–104.5 °C; R_f = 0.3 (pentane/EtOAc, 70:30).

IR (ATR): 3285, 2911, 1616, 1550, 1420, 1237, 798 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.83 (br s, 1 H, HetArH), 7.99–7.60 (m, 4 H, ArH and NH), 7.31 (t, *J* = 7.8 Hz, 1 H, ArH), 7.06 (d, *J* = 7.8 Hz, 1 H, ArH), 6.78–6.74 (m, 2 H, ArH), 3.93 (br s, 3 H, ArOCH_3), 3.68 (s, 2 H, ArCH_2S), 2.01 (s, 3 H, SCH_3).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 171.4 (C_q), 166.3 (C_{HetAr}), 165.6 (d, *J* = 208.8 Hz, C_q), 163.6 (C_q), 160.5 (C_q), 139.5 (C_q), 138.0 (C_q), 133.5 (C_q), 129.2 (C_{Ar}), 124.8 (C_{Ar}), 122.0 (C_{Ar}), 120.9 (C_{Ar}), 119.3 (C_{Ar}), 107.7 (d, *J* = 21 Hz, C_{Ar}), 100.3 (d, *J* = 25.5 Hz, C_{Ar}), 56.4 (CH_3), 38.4 (CH_2), 15.0 (CH_3).

^{19}F NMR ($CDCl_3$, 470.5 MHz): δ = –105.5 (m, 1 F).

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd $C_{18}H_{18}FN_4OS$: 357.1185; found: 357.1187.

(*rac*)-4-(4-Fluoro-2-methoxyphenyl)-*N*-{3-[(*S*-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine [(±)-Atuveciclib]

To a flask containing a stir bar was added successively, sulfide **6** (1.019 g, 2.86 mmol), ammonium carbamate (335 mg, 4.29 mmol), and MeOH (15 mL). PIDA (1.936 g, 6.01 mmol) was added in one portion and the reaction mixture was stirred at r.t. for 30 min (open flask to the atmosphere). The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 0.825 g (75%) of atuveciclib as an off-white solid with spectral data identical with those described;[6,20] mp 167–168 °C; R_f = 0.3 (CH_2Cl_2/MeOH, 95:5).

IR (ATR): 3258, 2923, 1546, 1420, 1279, 1194, 1025, 1006, 955, 803 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.78 (br s, 1 H, HetArH), 8.16–7.73 (m, 4 H, ArH and ArN*H*Ar), 7.38 (t, *J* = 7.8 Hz, 1 H, ArH), 7.13 (d, *J* = 7.8 Hz, 1 H, ArH), 6.78–6.73 (m, 2 H, ArH), 4.40 and 4.27 (AB system, J_{AB} = 13.0 Hz, 2 H, ArC*H*$_2$S), 3.91 (br s, 3 H, ArOC*H*$_3$), 2.96 (s, 3 H, SCH$_3$).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ = 172.0 (C_q), 166.3 (C_q), 165.7 (d, *J* = 250.1 Hz, C_q), 163.6 (C_q), 160.4 (C_q), 138.7 (C_q), 133.9 (C_{HetAr}), 129.7 (C_q), 129.4 (C_{Ar}), 126.3 (C_{Ar}), 122.9 (C_{Ar}), 122.0 (d, *J* = 2.9 Hz, C_{Ar}), 121.1 (C_{Ar}), 107.7 (d, *J* = 21 Hz, C_{Ar}), 100.3 (d, *J* = 25.5 Hz, C_{Ar}), 64.0 (CH_2), 56.4 (CH_3), 41.6 (CH_3).

^{19}F NMR ($CDCl_3$, 470.5 MHz): δ = –105.2 (m, 1 F).

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd $C_{18}H_{19}FN_5O_2S$: 388.1243; found: 388.1245.

4-(4-Fluoro-2-methoxyphenyl)-*N*-{3-[(*S*-methylsulfinyl)methyl]phenyl}-1,3,5-triazin-2-amine (7)

Diethyl (*R*,*R*)-tartrate (82.5 mg, 0.4 mmol), Ti(O*i*-Pr)$_4$ (56.8 mg, 0.2 mmol), and three drops of H_2O were added to a suspension of **6** (71.3 mg, 0.2 mmol) in toluene (3 mL) at 54 °C. The mixture was stirred for 1 h at 54 °C, the temperature was then adjusted to 30 °C, and subsequently DIPEA (26 mg, 0.2 mmol) and cumene hydroperoxide (84% in cumene, 61 mg, 0.4 mol) were added. The solution was extracted with NH_4OH (28% of NH_3, 3 × 20 mL). Subsequently, Et_2O (20 mL) was added to the combined aqueous extracts. Then the pH of the aqueous phase was adjusted to **7** with AcOH, the layers were separated, and the aqueous layer was extracted with an additional portion of Et_2O (20 mL). To the combined organic solutions was added aq 1 M NaOH (100 mL) and the solution was left to stir for 1 h. After separation, the organic phase was dried ($MgSO_4$), filtered, and the volatiles were removed under reduced pressure. The crude was purified by column chromatography (CH_2Cl_2/MeOH, 95:5) to give the 74.5 mg (>99%) of sulfoxide **7** as a yellow solid; mp 51.1–54.1 °C; R_f = 0.4 (CH_2Cl_2/MeOH, 95:5).

IR (ATR): 3259, 3095, 2964, 1544, 1419, 1399, 1279, 1156, 1026, 955, 831, 803 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.81 (br s, 1 H, HetArH), 7.94–7.63 (m, 4 H, ArH and ArN*H*Ar), 7.36 (t, *J* = 7.9 Hz, 1 H, ArH), 7.03 (d, *J* = 7.9 Hz, 1 H, ArH), 6.79–6.74 (m, 2 H, ArH), 4.05 and 3.94 (AB system, J_{AB} = 14.0 Hz, 2 H, ArCH$_2$S), 3.92 (br s, 3 H, ArOC*H*$_3$), 2.49 (s, 3 H, SCH$_3$).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 166.0 (d, *J* = 254.1 Hz, Cq), 165.8 (C_q), 163.4 (C_q), 160.4 (C_q), 138.6 (C_q), 134.0 (C_{HetAr}), 130.6 (C_q), 129.7 (C_{Ar}), 125.6 (C_{Ar}), 122.0 (C_{Ar}), 121.9 (C_{Ar}), 120.6 (C_{Ar}), 107.7 (d, *J* = 22 Hz, C_{Ar}), 100.3 (d, *J* = 25.2 Hz, C_{Ar}), 60.2 (CH_2), 56.4 (CH_3), 37.4 (CH_3).

^{19}F NMR (470.5 MHz, $CDCl_3$): δ = –105.2 (m, 1 F).

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}FN_4O_2S$: 373.1134; found: 373.1135.

(*S*)-4-(4-Fluoro-2-methoxyphenyl)-*N*-{3-[(*S*-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine [(*S*)-Atuveciclib]

To a flask was added successively sulfoxide **7** (74.5 mg, 0.2 mmol), ammonium carbamate (21.9 mg, 0.28 mmol), and MeOH (1 mL). PIDA (67.6 mg, 0.21 mmol) was added in one portion and the reaction mixture was stirred at r.t. for 30 min (flask open to the atmosphere). After completion, the solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 53 mg (68%) of atuveciclib as an off-white solid; mp 167–168 °C.

An ee of 19.8% was determined by HPLC [Chiralpak IC column, 1:1 heptane/*i*-PrOH, λ = 275 nm, t_R = 30.6 min (*S*) and t_R = 37.5 min (*R*)].

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610316.

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(31) Currently, (*R*)-atuveciclib is obtained via chiral preparative HPLC separation. See reference 19.