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Microwave-assisted diastereoselective two-step three-component synthesis for rapid access to drug-like libraries of substituted 3-amino-β-lactams

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ABSTRACT

Large, diverse compound libraries are an essential requisite in target-based drug development. In this work, a robust microwave-assisted synthesis for the diastereoselective generation of 3-saccharinyl-*trans*-β-lactams is reported. The method is optimised for combinatorial library synthesis in which decoration of the scaffold is varied on both the β-lactam and the saccharine moiety. Within the European Lead Factory (ELF) consortium, a library of 263 compounds was efficiently produced using the developed methodology.

1. Introduction

The identification of lead compounds in drug discovery relies heavily on high throughput screening of large collections of compounds to a biological target for a desired effect. Structural diversity in these collections is mainly limited to planar scaffolds. 3D-complexity, which has been proven to be an important element in drug discovery,[1] is mainly enhanced by combining a planar core with substituents.[2] While there is an increasing trend in the development of scaffolds that contain more 3D elements, the synthetic tractability of these scaffolds diminishes.

Within the European Lead Factory (ELF) consortium,[3–5] we aim to develop libraries of lead-like compounds that have a high molecular complexity and that are synthesized from easily accessible building blocks in a minimum number of steps. In this work, we present a scaffold that consists of a saccharine moiety that is connected to a β-lactam via its amide-nitrogen atom (**4**, Scheme 1A) and that can be synthesized in a single step.[6] The β-lactam core is a frequently found structural motif in antibiotics[7] targeting the cell wall synthesis by blocking the action of transpeptidases[8–10] and it is useful as a building block in organic chemistry.[11] Saccharine has, next to being an artificial sweetener, also found application in medicinal chemistry. For example as inhibitor for tumour-associated carbonic anhydrase IX and XII,[12,13] inhibitor for interferon-mediated inflammation[14] and as antidiarrheal agents by activation of the μ opioid receptor.[15] Thereby, the combination of these two functionalities renders a chemical entity with great biological potential.

The perpendicular orientation of the two ring systems, together with the substituents that we aim to introduce on the sp^3 backbone of the β-lactam provide the non-planar elements in this scaffold. For functionalization, three diversification points are envisioned on the scaffold. R^1 is envisioned as proton or nitro-group, of which the latter can be reduced to the amine **4c** and subsequently be acylated to increase the diversity (**4d**, Scheme 1A). The two remaining diversity points are R^2 and R^3 that are introduced by choosing the appropriate imine.

Several syntheses are known for β-lactams of which the Staudinger reaction, in which an *in-situ* formed ketene is reacted with an imine, is the most frequently used (Scheme 1B).[16] Usually acid chlorides are used as ketene precursors in the Staudinger reaction.[17] However, these reactive species are less suitable for use in parallel synthesis. Therefore we envisioned *in-situ* activation of **1** to intermediate **3** using Mukaiyama's salt as a more convenient approach.[18] Although the synthesis of the proposed scaffold using the Staudinger reaction using Mukaiyama's salt has been described

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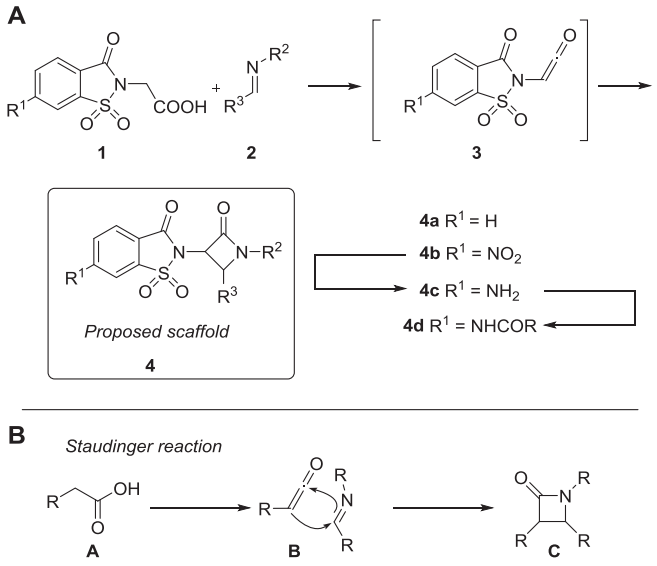


Scheme 1. (A) General scheme for the Staudinger reaction; (B) approach for the synthesis of scaffold 4.

before,[6] the scope of the reaction has not been thoroughly examined. Moreover, due to the fact that a stepwise addition of reagents is required, this method is impractical for use in the combinatorial synthesis of a large number of analogues.

In this report we present the optimisation of the reported procedure for the combinatorial synthesis of tri-substituted β-lactams, expand the scope of the reaction and show its applicability by producing a 263 compound library using the optimised method.

2. Results and discussion

We started with the synthesis of saccharinylacetic acid **1a** by reacting potassium saccharine **5a** and bromoacetic acid **6** neat for 4 h at 110 °C to afford **1a** in 85% yield (Scheme 2A). Unfortunately, the potassium salt of 6-nitrosaccharine **5b** was unreactive under the same conditions. We therefore resorted to a two-step synthesis in which **5b** is reacted with methyl bromoacetate **7** at 70 °C in DMF for 4 h after which the crude methyl ester is hydrolysed in concentrated HCl to yield **1b** in 55% yield over two steps without the need for purification (Scheme 2B).

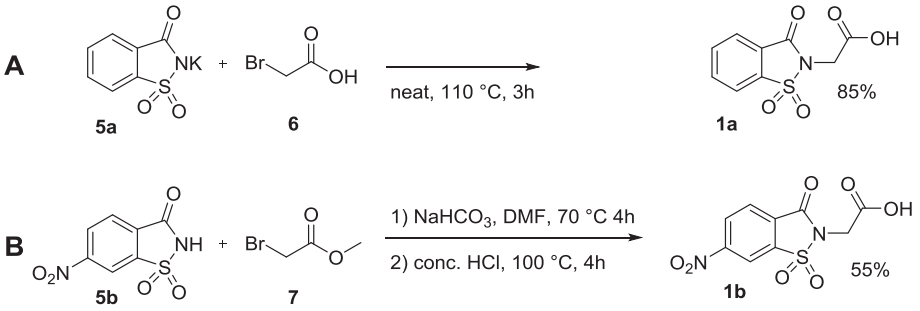
For optimisation of the Staudinger reaction, we selected saccharinyl acetic acid **1a** and imine **2a** as benchmark substrates. In the initial experiment we reacted **1a** with Mukaiyama's salt **10** in CH_2Cl_2 for 8 h at reflux, followed by the addition of imine **2a** and Et_3N which was refluxed for 16 h. This afforded the desired β-lactam **11a** in 85% yield with excellent diastereoselectivity (*cis*/*trans* < 5:95) according to ^1H NMR analysis of the crude reaction mixture (Table 1, entry 1).[19] Refluxing **1a**, **2a**, and **10** in CH_2Cl_2 with Et_3N as base for 16 h was equally effective since **11a** was obtained in a comparable yield (82%) and diastereoselectivity (*cis*/*trans* < 5:95, entry 2).

Unfortunately, amide **12** was quantatively obtained when benzaldehyde **9** and aniline **8** were used in a one-pot reaction instead of using imine **2a**, (entry 3). This can be explained by the fact that imine formation is slow compared to the acid activation and amide formation between the amine and the activated acid. Consequently, this necessitates the use of pre-formed imines in the reaction. The reaction time was reduced dramatically from 16 h to 10 min using a microwave. The reaction of **1a** and **2a** in a microwave at 100 °C for 30 or 10 min afforded **11a** in 87% and 86% yield respectively, selectively *trans* (entries 4–5).

With optimised conditions (Table 1, entry 5) established, we explored the scope of the reaction with acetic acid **1a** (R^1 = H) and a variety of imines **2b**–**2j** (Table 2). Electron withdrawing as well as electron donating aromatic rings on the R^2- and R^3-position afforded the products in selectively *trans* configuration **11b**–**11h** in moderate yields after preparative HPLC/MS[20] (30–50%; Table 2, entries 1–7). However, the reactions of aliphatic imines **2i** and **2j**, derived from neohexanal and *n*-hexanal, resulted in mixtures of unidentified products (entries 8 and 9). While R^3 is thus limited to aromatic rings, the reaction with imines derived from isopropylamine afforded the desired products **11k**–**11m** in reasonable yields (63–32%), but not with full diastereoselectivity (*cis*/*trans* 15:85–33:67, entries 10–12).[21] The reactions with 4-aminomethylpyridine and β-alanine derived imines **2n** and **2o** further emphasise the fact that *N*-aliphatic imines are more challenging substrates because the reaction with **2n** did not afford any product and with imine **2o** product **11o** is obtained in only a minimal yield of 8% (entries 13 and 14). Finally, 6-nitrosaccharinyl acetic acid **2b** could be used without difficulties in the reaction with imines **2c** and **2b** affording **11p** and **11q** in acceptable yields of 58 and 61% respectively as single diastereomers (entries 15 and 16).

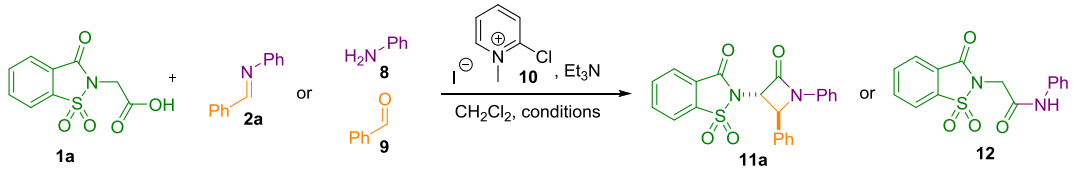
Having established the scope of the reaction for R^2 and R^3, we were also interested to see if it would be possible to use substituted acetic acids other than **1**. Phthaloyl glycine **13** and theophylline-7-acetic acid **14** proved good substrates for the reaction and gave access to **18** and **19** respectively in good yields (89 and 65%) with full diastereoselectivity (Table 3, entries 1 and 2). Imidazol-4-acetic acid **15** and indomethacine **16** on the other hand, failed to react and resulted in mixtures of unidentified products (entries 3 and 4). To investigate whether this is caused by the less electron withdrawing properties of the aromatic systems connected to the acetic acid part, we tested the moderately electron poor *p*-nitrophenyl acetic acid **17** (entry 5). Indeed this acetic acid did not afford the product and consequently more electron poor acetic acids are required.

We next turned our attention to modification of the nitro group of compounds **11p** and **11q** (Scheme 3). Reduction to the amine



Scheme 2. Synthesis of saccharine acetic acids **1a** and **1b**.

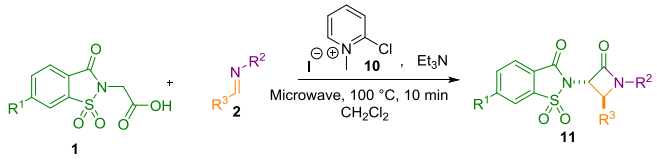
Table 1
Optimisation of the conditions for the benchmark reaction.

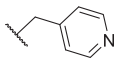
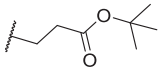


Entry	Imine or amine/aldehyde	Conditions	d.r. (*cis*/*trans*)[a]	Yield **11a** (%)[b]	Yield **12** (%)[b]
1	**2a**	**1a** & **10** reflux 8 h, then **2a** and Et_3N	<5:95	85	–
2	**2a**	Reflux 16 h	<5:95	82	–
3	**8** & **9**	Reflux 16 h	–	–	Quant.
4	**2a**	100 °C, microwave, 30 min	<5:95	87	–
5	**2a**	100 °C, microwave, 10 min	<5:95	86	–

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Yield of isolated product.

Table 2
Investigation of the reaction scope for the imine.



Entry	Acetic acid	R^1	Imine	R^2	R^3	d.r.[a]	Yield (%)[b]	Product
1	**1a**	H	**2b**	4-BrC_6H_4	4-$OMeC_6H_4$	<5:95	42	**11b**
2	**1a**	H	**2c**	4-BrC_6H_4	4-MeC_6H_4	<5:95	50	**11c**
3	**1a**	H	**2d**	4-BrC_6H_4	3-$NO_2C_6H_4$	<5:95	25	**11d**
4	**1a**	H	**2e**	3-$OMeC_6H_4$	4-$OMeC_6H_4$	<5:95	40	**11e**
5	**1a**	H	**2f**	3-$OMeC_6H_4$	4-MeC_6H_4	<5:95	40	**11f**
6	**1a**	H	**2g**	3-$OMeC_6H_4$	3-$NO_2C_6H_4$	<5:95	30	**11g**
7	**1a**	H	**2h**	Phenyl	2-Pyrrole	<5:95	35	**11h**
8	**1a**	H	**2i**	4-BrC_6H_4	Neohexyl	–	–	**11i**
9	**1a**	H	**2j**	3-$OMeC_6H_4$	*n*-Hexyl	–	–	**11j**
10	**1a**	H	**2k**	*i*-Propyl	4-$OMeC_6H_4$	15:85	63	**11k**
11	**1a**	H	**2l**	*i*-Propyl	4-MeC_6H_4	33:67	32	**11l**
12	**1a**	H	**2m**	*i*-Propyl	3-$NO_2C_6H_4$	15:85	51	**11m**
13	**1a**	H	**2n**		4-MeC_6H_4	–	–	**11n**
14	**1a**	H	**2o**		4-MeC_6H_4	<5:95	8	**11o**
15	**1b**	NO_2	**2c**	4-BrC_6H_4	4-MeC_6H_4	<5:95	58	**11p**
16	**1b**	NO_2	**2b**	4-BrC_6H_4	4-$OMeC_6H_4$	<5:95	61	**11q**

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Yield of isolated product.

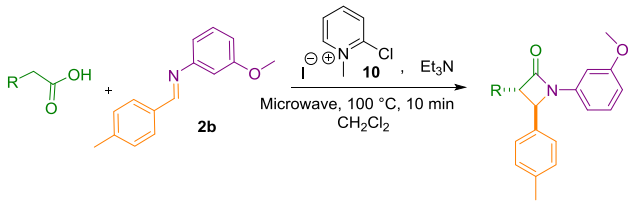
and subsequent amidation using acid chlorides can further increase the diversity potential of the scaffold. Reduction of **11p** and **11q** was quantitatively achieved by treatment with iron in acetic acid for 3 h at room temperature to afford **23a** and **23b**. The acylated amines **24a** and **24b** were obtained in good yields when the amines **23** were treated with acetyl chloride and sodium bicarbonate in THF, illustrating the applicability of the functionalization.

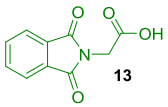
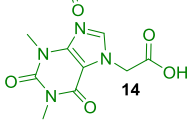
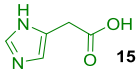
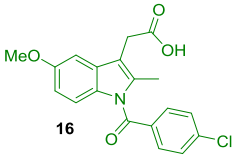
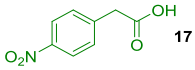
With the chemistry established, we enumerated a library of 349 compounds with an average cLog*P* of 3.6 and average molecular weight of 502 (Chart 1).[22] For production of the library, large batches of saccharinyl acetic acids **1a** (187 mmol, 45.0 g) and **1b** (143 mmol, 41.6 g) were prepared using the same methods as during optimisation. Subsequently, the appropriate imines (**2**) were pre-formed and reacted with **1a**, **10** and Et_3N in CH_2Cl_2.[23] After purification of the final products by preparative LC/MS, 263 compounds were isolated with a purity over 85% (LC/MS), which corresponds to a success rate of 75%. These compounds were added to the Joint European Compound Library.

3. Conclusions

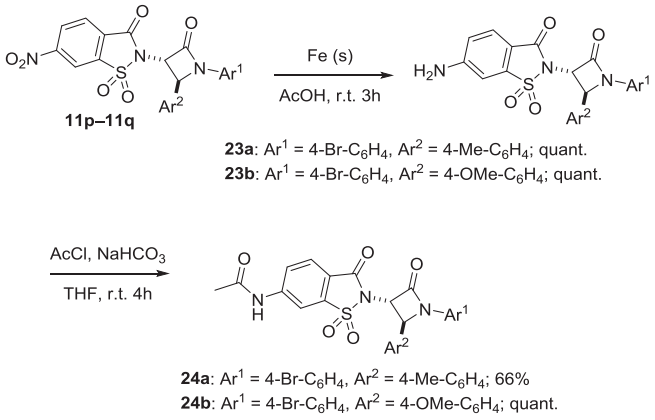
In conclusion, we have developed a rapid, efficient microwave-assisted synthesis of 3-amino-β-lactams, suitable for the combinatorial synthesis of 3-saccharinyl-β-lactams starting from substituted acetic acids. The resulting 3-amino-β-lactams were isolated in reasonable yields and excellent diastereoselectivity using a range of different imines and substituted acetic acids. We have shown the application of the obtained β-lactams in follow-up

Table 3
Investigation of the reaction scope for the acetic acid.



Entry	Acetic acid	d.r. (*cis*/*trans*)[a]	Yield (%)[b]	Product
1	 **13**	<5:95	89	**18**
2	 **14**	<5:95	65	**19**
3	 **15**	–	–	**20**
4	 **16**	–	–	**21**
5	 **17**	–	–	**22**

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Yield of isolated product.



Scheme 3. Functionalisation of the saccharine moiety (R^1).

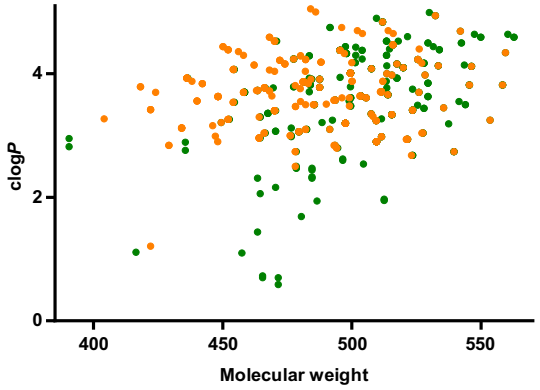


Chart 1. Physiochemical properties plot (MW *vs.* cLog*P*) for the library compounds: green dots 349 enumerated compounds; orange dots 263 produced compounds.

chemistry, and the developed methodology was used to produce a 263 compound library.

4. Experimental

4.1. General experimental details

All commercially available reagents and solvents were used as purchased. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (75.00 MHz for 13C) using the residual solvent as internal standard (1H: δ 7.26 ppm, 13C{1H}: δ 77.00 ppm for CDCl3), Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet) and m (multiplet) or combinations thereof. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Waters Xevo G2 XS QTOF instrument in positive ion mode (capillary potential of 3000 V). Flash chromatography was performed on Grace Davisil Silica Gel (particle size 40–63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm) unless mentioned otherwise. Microwave reactions were performed in a Biotage Initiator$^+$ using the corresponding microwave vials.

Reversed phase preparative HPLC/MS was carried out on a Waters AutoPurification system equipped with a Waters 2998 pho-

todiode array detector, Waters 3100 mass detector and a Waters 2767 sample manager using preparative Waters X-bridge C_{18} μm (30 mm × 150 mm or 19 mm × 150 mm) column using water acetonitrile mixtures containing 0.1% TFA.

4.2. Synthetic procedures

4.2.1. General procedures

General procedure A, synthesis of the imines. To a vial containing toluene were added aldehyde (1.0 equiv) and amine (1.0 equiv) followed by $MgSO_4$. The mixture was allowed to be stirred overnight after which it was filtered and evaporated to dryness. The imines were used in the cycloaddition without further purification.

General procedure B, cycloaddition. A microwave vial was charged with dichloromethane the appropriate imine (1.0 equiv), saccharinyl acetic acid (1.0 equiv), Mukaiyama's salt (1.05 equiv) and triethylamine (2 equiv). The mixture was heated for 10 min in the microwave at 100 °C. After the reaction, the mixture was concentrated *in vacuo* and purified on a preparative LCMS. Waters X-Bridge 30 mm × 150 mm C_{18} column; gradient, CH_3CN:H_2O (0.1% TFA). Fractions containing the product were automatically collected based on observed mass and UV-signal after which they were lyophilized to obtain the pure products.

General procedure C, nitro reduction. A roundbottomed flask was charged with the required nitro saccharinyl β-lactam that was dissolved in glacial acetic acid. Next iron (10 equiv) was added and the suspension was stirred for 3 h at room temperature. After completion of the reaction (TLC) the mixture was diluted with ethyl acetate and neutralized with saturated $NaHCO_3$ solution. The water layer was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure D, Library production. In an 8 mL screw cap vial a solution of amine (0.1 mmol, 1 equiv) and aldehyde (0.1 mmol, 1 equiv) in dry toluene (1 mL) was prepared. Subsequently $MgSO_4$ (approx. 100 mg) was added. The resulting mixtures were stirred overnight. The mixtures were filtered and the filtrate was concentrated to afford the imines. The imine was used in the next step immediately without purification. To the imines was added 2 mL of a stock solution containing the appropriate saccharinylacetic acid in CH_2Cl_2 (0.05 mM ≡ 0.1 mmol, 1 equiv). Subsequently, 2-chloro-1-methylpyridin-1-ium iodide (Mukaiyama's salt) (0.105 mmol, 1.05 equiv) and triethylamine (0.22 mmol, 2.2 equiv) were added. The resulting mixtures were overnight heated at 45 °C in closed vials. The mixtures were washed with water (1 mL) after which the organic layers were evaporated. The crude mixtures were purified by preparative HPLC (acetonitrile/water mixtures containing 0.1% TFA). The product containing fractions were lyophilized to afford the pure products.

4.2.2. Saccharine acetic acid (**1a**)

Potassium saccharine (4.0 g, 18 mmol, 1 equiv) was mixed with bromoacetic acid (4.52 g, 32 mmol, 1.8 equiv) and heated till the compounds melted (~110 °C). The molten mixture was then stirred for 3 h. Water was added and the mixture was filtered to yield saccharine acetic acid (**1a**) as a white crystalline solid (3.7 g, 85%). ^{1}H NMR (300 MHz, DMSO) δ (ppm) = 13.33 (bs, 1H), 8.38–8.33 (m, 1H), 8.20–7.86 (m, 3H), 4.49 (s, 2H).

4.2.3. 6-Nitrosaccharine acetic acid (**1b**)

6-Nitrosaccharine (3.5 g, 11 mmol) was dissolved in DMF (6 mL). Sodium bicarbonate (1.84 g, 21.9 mmol) was added and the mixture stirred for 30 min after which methyl bromoacetate (1.29 mL, 13.2 mmol) was slowly added to the solution that was then heated to 70 °C for 4 h. The mixture was poured in water (25 mL) and the precipitate was filtered. The crude 6-nitrosaccharine acetic acid methyl ester was suspended in HCl (30 mL, 37% in water) and heated to 100 °C for 4 h after which the hydrolysis was complete. After cooling to r.t., the mixture was diluted with water and the precipitated carboxylic acid was filtered to yield (**1b**) as a Bordeaux-reddish solid (1.81 g, 55%). ^{1}H NMR (300 MHz, DMSO) δ (ppm) = 13.44 (bs, 1H), 9.32 (d, *J* = 1.8 Hz, 1H), 8.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 4.56 (s, 2H).

4.2.4. (E)-N-(4-Bromophenyl)-1-(p-tolyl)methanimine (**2b**)

2b was synthesized according to general procedure A from 4-methylbenzaldehyde and 4-bromoaniline to yield a brownish crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.31 (s, 1H), 7.82–7.74 (m, 2H), 7.54–7.45 (m, 2H), 7.33–7.26 (m, 2H), 7.13–7.00 (m, 2H), 2.43 (s, 3H).

4.2.5. (E)-N-(4-Bromophenyl)-1-(4-methoxyphenyl)methanimine (**2c**)

2c was synthesized according to general procedure A from 4-methoxybenzaldehyde and 4-bromoaniline to yield a yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.35 (s, 1H), 7.90–7.77 (m, 2H), 7.53–7.44 (m, 2H), 7.12–7.03 (m, 2H), 7.02–6.94 (m, 2H), 3.88 (s, 3H).

4.2.6. (E)-N-(4-Bromophenyl)-1-(3-nitrophenyl)methanimine (**2d**)

2d was synthesized according to general procedure A from 3-nitro benzaldehyde and 4-bromoaniline to yield a yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.79–8.71 (m, 1H), 8.53 (s, 1H), 8.34 (ddd, *J* = 8.1, 2.3, 1.1 Hz, 1H), 8.24 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.67 (t, *J* = 8.1 Hz, 1H), 7.60–7.49 (m, 2H), 7.19–7.08 (m 2H).

4.2.7. (E)-N-(3-Methoxyphenyl)-1-(4-methoxyphenyl)methanimine (**2e**)

2e was synthesized according to general procedure A from 4-methoxy benzaldehyde and 3-methoxyaniline to yield a pale yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.39 (s, 1H), 7.91–7.80 (m, 2H), 7.34–7.11 (m, 3H), 7.04–6.93 (m, 2H), 6.82–7.71 (m, 3H), 3.88 (s, 3H), 3.84 (s, 3H).

4.2.8. (E)-N-(3-methoxyphenyl)-1-(p-tolyl)methanimine (**2f**)

2f was synthesized according to general procedure A from 4-methyl benzaldehyde and 3-methoxyaniline to yield a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.42 (s, 1H), 7.84–7.73 (m, 2H), 7.34–7.21 (m, 3H), 6.84–6.72 (m, 3H), 3.84 (s, 3H), 2.42 (s, 3H).

4.2.9. (E)-N-(3-methoxyphenyl)-1-(3-nitrophenyl)methanimine (**2g**)

2g was synthesized according to general procedure A from 3-nitro benzaldehyde and 3-methoxyaniline to yield a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.75 (t, *J* = 1.9 Hz, 1H), 8.55 (s, 1H), 8.33 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.25 (dt, *J* = 7.7, 1.2 Hz, 2H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.88–6.75 (m, 2H), 3.86 (s, 3H).

4.2.10. (E)-1-Phenyl-N-(1H-pyrrol-2-yl)methanimine (**2h**)

2h was synthesized according to general procedure A from benzaldehyde and 2-aminopyrrole to yield a Bordeaux reddish crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.91 (bs, 1H), 8.27 (d, *J* = 0.6 Hz, 1H), 7.44–7.33 (m, 2H), 7.24–7.15 (m, 3H), 6.90–6.85 (m, 1H), 6.69 (dd, *J* = 3.6, 1.4 Hz, 1H), 6.29 (dd, *J* = 3.6, 2.6 Hz, 1H).

4.2.11. (E)-N-Isopropyl-1-(4-methoxyphenyl)methanimine (**2k**)

2k was synthesized according to general procedure A from 4-methoxybenzaldehyde and isopropyl amine to yield a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.16 (s, 1H), 7.64–7.56 (m, 2H), 6.90–6.81 (m, 2H), 3.77 (s, 3H), 3.43 (dhept, *J* = 6.3, 0.6 Hz, 1H), 1.18 (d, *J* = 6.3 Hz, 6H).

*4.2.12. (E)-N-Isopropyl-1-(p-tolyl)methanimine (**2l**)*

2l was synthesized according to general procedure A from 4-methyl benzaldehyde and isopropyl amine to yield a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.27 (s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.9, 2H), 3.61 (dhept, J = 6.3, 0.6 Hz, 1H), 2.37 (3H), 1.25 (d, J = 6.3 Hz, 6H).

*4.2.13. (E)-N-Isopropyl-1-(3-nitrophenyl)methanimine (**2m**)*

2m was synthesized according to general procedure A from 2-nitrobenzaldehyde and isopropyl amine to yield a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.58–8.54 (m, 1H), 8.37 (s, 1H), 8.25 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 8.08 (dt, J = 7.7, 1.3 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 3.61 (dhept, J = 6.3, 0.6 Hz, 1H), 1.28 (d, J = 6.3 Hz, 6H).

*4.2.14. Trans-2-(-2-oxo-1,4-diphenylazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11a**)*

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2a** (37.6 mg, 0.21 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.42 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11a** (0.18 mmol, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.96–7.89 (m, 1H), 7.83–7.67 (m, 3H), 7.30–7.05 (m, 9H), 7.00–6.90 (m, 1H), 5.33 (d, J = 2.7 Hz, 1H), 4.87 (d, J = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.76 (Cq), 158.35 (Cq), 137.57 (Cq), 136.94 (Cq), 135.32 (CH), 135.17 (Cq), 134.72 (CH), 129.44 (2×CH), 129.24 (CH), 129.15 (2×CH), 126.64 (Cq), 125.98 (2×CH), 125.55 (CH), 124.70 (CH), 121.25 (CH), 117.65 (2×CH), 63.04 (CH), 61.03 (CH). HRMS ESI (3000 V): calculated for $C_{22}H_{13}N_2O_4S$ ($M+H^+$) 405.0909, found 405.0911.

*4.2.15. Trans-2-(1-(4-bromophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11b**)*

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2b** (60.2 mg, 0.21 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.42 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11b** (0.09 mmol, 42%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.04 (m, 1H), 7.98–7.83 (m, 3H), 7.43–7.34 (m, 2H), 7.33–7.19 (m, 4H), 6.97–6.88 (m, 2H), 5.38 (d, J = 2.6 Hz, 1H), 4.98 (d, J = 2.6 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.42 (Cq), 159.89 (Cq), 158.37 (Cq), 137.61 (Cq), 135.98 (Cq), 135.35 (CH), 134.74 (CH), 132.17 (2×CH), 127.34 (2×CH), 126.64 (Cq), 126.50 (Cq), 125.57 (CH), 121.28 (CH), 119.22 (2×CH), 117.51 (Cq), 114.97 (2×CH), 62.41 (CH), 60.96 (CH), 55.35 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{19}N_2O_5SBr$ ($M+H^+$) 513.0120, found 513.0114.

*4.2.16. Trans-2-(2-(4-methoxyphenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl) benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11c**)*

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2c** (28.4 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11c** (0.05 mmol, 50%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.03 (m, 2H), 7.98–7.83 (m, 3H), 7.43–7.34 (m, 2H), 7.28–7.17, (m, 6H), 5.39 (d J = 2.7 Hz 1H), 4.99 (d, J = 2.7 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.85 (Cq), 158.37 (Cq), 139.45 (Cq), 137.62 (Cq), 135.99 (Cq), 135.35 (CH), 134.74 (CH), 132.17 (2×CH), 130.22 (2×CH), 126.63 (Cq), 125.89 (2×CH), 125.57 (CH), 121.28 (CH), 119.20 (2×CH), 117.50 (Cq), 63.34 (CH), 61.14 (CH), 21.24 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{18}N_2O_4SBr$ ($M+H^+$) 497.0171, found 497.0168.

*4.2.17. Trans-2-(1-(4-bromophenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11d**)*

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2d** (63 mg, 0.21 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.46 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11d** (0.05 mmol, 25%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.30–8.25 (m, 2H), 8.12–8.06 (m, 1H), 7.99–7.87 (m, 3H), 7.75–7.59 (m, 2H), 7.46–7.39 (m, 2H), 7.23–7.16 (m, 2H), 5.51 (d, J = 2.7 Hz, 1H), 5.01 (d, J = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.10 (C_q), 158.44 (Cq), 148.99 (Cq), 137.49 (Cq), 137.15 (Cq), 135.62 (CH), 135.38 (Cq), 132.51 (2×CH), 131.65 (CH), 130.87 (CH), 126.44 (Cq), 125.72 (CH), 124.46 (CH), 124.46 (CH), 121.45 (CH), 121.33 (CH), 119.03 (2×CH), 118.15 (Cq), 63.08 (CH), 60.31 (CH). HRMS ESI (3000 V): calculated for $C_{22}H_{15}N_3O_6SBr$ ($M+H^+$) 527.9865, found 527.9845.

*4.2.18. Trans-2-(1-(3-methoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11e**)*

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2e** (50 mg, 0.21 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.46 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11e** (0.084 mmol, 40%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.02 (m, 2H), 7.99–7.80 (m, 3H), 7.36–7.26 (m, 2H), 7.16 (t, J = 8.2 Hz, 1H), 7.05 (t, J = 2.2 Hz, 1H), 6.98–6.88 (m, 2H), 6.81 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.65 (ddd, J = 8.4, 2.5, 0.8 Hz, 1H), 5.39 (d, J = 2.6 Hz), 5.39 (d, J = 2.6 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 159.10 (Cq), 158.44 (Cq), 148.99 (Cq), 137.49 (Cq), 137.15 (Cq), 135.62 (CH), 135.38 (Cq), 132.51 (2×CH), 131.65 (CH), 130.87 (CH), 126.44 (Cq), 125.72 (CH), 124.46 (CH), 124.46 (CH), 121.45 (CH), 121.33 (CH), 119.03 (2×CH), 118.15 (Cq), 63.08 (CH), 60.31 (CH), 55.32 (CH_3), 55.27 (CH_3). HRMS ESI (3000 V): calculated for $C_{22}H_{15}N_3O_6SBr$ ($M+H^+$) 527.9865, found 527.9845. HRMS ESI (3000 V): calculated for $C_{24}H_{21}N_2O_6S$ ($M+H^+$) 465.1120, found 465.1166.

*4.2.19. Trans-2-(1-(3-methoxyphenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl) benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11f**)*

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2f** (47 mg, 0.21 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.46 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11f** (0.84 mmol, 40%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.02 (m, 2H), 7.97–7.81 (m, 3H), 7.32–7.10 (m, 5H), 7.07 (t, J = 2.2 Hz, 1H), 6.80 (ddd, J = 8.0, 1.9, 0.8 Hz, 1H), 6.65 (ddd, J = 8.3, 2.5, 0.8 Hz, 1H), 5.40 (d, J = 2.6 Hz), 1H), 4.98 (d, J = 2.7 Hz, 1H), 3.75 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.12 (Cq), 159.93 (Cq), 158.33 (Cq), 139.16 (Cq), 138.09 (Cq), 137.61 (Cq), 135.28 (CH), 134.68 (CH), 132.15 (CH), 130.10 (2×CH), 129.90 (CH), 126.67 (Cq), 125.90 (2×CH), 125.53 (CH), 121.23 (CH), 110.67 (CH), 109.81 (CH), 103.62 (CH), 63.12 (CH), 61.13 (CH), 55.27 (CH3), 21.22 (CH_3). HRMS ESI (3000 V): calculated for $C_{24}H_{21}N_2O_5S$ ($M+H^+$) 449.1171, found 465.1165.

*4.2.20. Trans-2-(1-(3-methoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11g**)*

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2g** (26.6 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11g**

(0.03 mmol, 30%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.32–8.25 (m, 2H), 8.13–8.06 (m, 1H), 8.00–7.85 (m, 3H), 7.73 (dt, J = 7.7, 1.2 Hz, 1H), 7.62 (dt, J = 7.8, 0.5 Hz, 1H), 7.19 (t, J = 8.2 Hz, 1H), 7.03 (t, J = 2.2 Hz, 1H), 6.75–6.66 (m, 2H), 5.52 (d, J = 2.6 Hz, 1H), 4.99 (d, J = 2.7 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.35 (Cq), 159.14 (Cq), 158.39 (Cq), 148.93 (Cq), 137.61 (Cq), 137.50 (Cq), 137.47 (Cq), 135.54 (CH), 134.89 (CH), 131.75 (CH), 130.72 (CH), 130.22 (CH), 126.51 (Cq), 125.68 (CH), 124.28 (CH), 121.41 (CH), 121.31 (CH), 110.97 (CH), 109.53 (CH), 103.79 (CH), 62.84 (CH), 60.31 (CH), 55.37 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{18}N_3O_7SBr$ ($M+H^+$) 480.0865, found 480.0868.

4.2.21. Trans-2-(2-oxo-1-phenyl-4-(1H-pyrrol-2-yl)azetidin-3-yl) benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11h**)

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2h** (17.6 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11h** (0.035 mmol, 35%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.11–8.04 (m, 1H), 8.01–7.80 (m, 3H), 7.24–7.10 (m, 3H), 6.86–6.68 (m, 3H), 6.56 (t, J = 3.2 Hz, 1H), 6.29–6.25 (m, 1H), 5.54–4.49 (m, 1H), 5.09 (d, J = 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 163.11, (Cq), 158.82 (Cq), 145.50 (Cq), 137.70 (Cq), 129.47 (2×CH), 125.67 (CH), 121.39 (CH), 119.60 (CH), 119.54 (CH), 114.39 (2×CH), 113.00 (CH), 107.42 (CH), 60.86 (CH), 52.56 (CH). HRMS ESI (3000 V): calculated for $C_{20}H_{16}N_3O_4S$ ($M+H^+$) 394.0862, found 394.0861.

4.2.22. Trans-2-(1-isopropyl-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11k**)

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2k** (18.4 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11k** (0.063 mmol, 63%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.04 (m, 1H), 7.95–7.81 (m, 3H), 7.35–7.28 (m, 2H), 6.99–6.90 (m, 2H), 4.98 (d, J = 2.4 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 3.92–3.75 M, 1H), 3.83 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.74 (Cq), 160.22 (Cq), 158.46 (Cq), 137.61 (Cq), 135.11 (CH), 134.58 (CH), 128.51 (Cq), 127.86 (2×CH), 125.37 (CH), 121.16 (CH), 114.55 (2×CH), 62.42 (CH), 58.96 (CH), 55.34 (CH_3), 45.87 (CH), 20.80 (CH_3), 20.08 (CH_3). HRMS ESI (3000 V): calculated for $C_{20}H_{21}N_2O_5$-SNa ($M+Na^+$) 423.1002, found 423.0991.

4.2.23. Trans-2-(1-isopropyl-2-oxo-4-(p-tolyl)azetidin-3-yl)benzo[d] isothiazol-3(2H)-one 1,1-dioxide (**11l**)

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2 l** (16.7 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11l** (0.032 mmol, 32%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.10–8.03 (m, 1H), 7.94–7.80 (m, 3H), 7.34–7.18 (m, 4H), 5.00 (d, J = 2.4 Hz, 1H), 4.83 (d, J = 2.4 Hz, 1H), 3.83 (sept, J = 6.8 Hz, 1H), 2.37 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.95 (Cq), 158.46 (Cq), 139.11 (Cq), 137.59 (Cq), 135.12 (CH), 134.58 (CH), 133.53 (Cq), 129.84 (2×CH), 126.81 (Cq), 126.48 (2×CH), 125.37 (CH), 121.15 (CH), 62.30 (CH), 59.26 (CH), 46.01 (CH_3), 21.22 (CH), 20.77 (CH_3), 20.06 (CH_3). HRMS ESI (3000 V): calculated for $C_{20}H_{21}N_2O_4S$ ($M+H^+$) 385.1213, found 385.1222.

4.2.24. Trans-2-(1-isopropyl-2-(4-nitrophenyl)-4-oxoazetidin-3-yl) benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11m**)

According to general procedure B, saccharinylacetic acid **1a** (25.0 mg, 0.10 mmol) was reacted with: imine **2m** (19.9 mg, 0.10 mmol), Mukaiyama's salt (27.8 mg, 0.11 mmol) and triethylamine (32 μL, 0.23 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11m** (0.051 mmol, 51%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.12–8.06 (m, 1H), 7.97–7.84 (m, 3H), 7.77 (dt, J = 7.8, 1.3 Hz, 1H), 7.65 (dt, J = 7.9, 0.3 Hz, 1H), 5.12 (d, J = 2.4 Hz, 1H), 4.81 (d, J = 2.4 Hz, 1H), 3.89 (sept, J = 6.8 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.17 (d J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 162.40 (Cq), 158.49 (Cq), 148.78 (Cq), 139.39 (Cq), 137.52 (Cq), 135.37 (CH), 134.78 (CH), 132.23 (CH), 130.46 (CH), 126.64 (Cq), 125.53 (CH), 124.17 (CH), 121.62 (CH), 121.31 (CH), 62.42 (CH), 58.52 (CH), 46.44 (CH), 20.84 (CH_3), 20.18 (CH_3). HRMS ESI (3000 V): calculated for $C_{19}H_{18}N_3O_6S$ ($M+H^+$) 416.0916, found 416.0932.

4.2.25. tert-Butyl trans-3-(3-(1,1-dioxido-3-oxobenzo[d]isothiazol-2 (3H)-yl)-2-oxo-4-(p-tolyl)azetidin-1-yl)propanoate (**11o**)

According to general procedure B, saccharinylacetic acid **1a** (50.0 mg, 0.21 mmol) was reacted with: imine **2o** (53.8 mg, 0.22 mmol), Mukaiyama's salt (55.6 mg, 0.22 mmol) and triethylamine (64 μL, 0.46 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Preparative LCMS purification afforded **11o** (0.015 mmol, 8%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.14–8.01 (m, 1H), 7.98–7.80 (m, 3H), 7.24 (s, 4H), 5.02 (d, J = 2.4 Hz, 1H) 4.85 (d, J = 2.4 Hz, 1H), 3.82 (ddd, J = 13.9, 7.6, 5.9 Hz, 1H), 3.30–3.16 (m, 1H), 2.78–2.51 (m, 2H), 2.38 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.21 (Cq), 162.91 (Cq), 158.34 (Cq), 139.21 (Cq), 137.62 (Cq), 135.14 (CH), 134.59 (CH), 132.19 (Cq), 129.99 (2×CH), 126.82 (Cq), 126.35 (2×CH), 125.40 (CH), 121.19 (CH), 81.09 (Cq), 63.10 (CH), 61.01 (CH), 37.04 (CH_2), 33.31 (CH_2), 28.01 (3×CH_3), 21.24 (CH_3). HRMS ESI (3000 V): calculated for $C_{24}H_{26}N_2O_6SNa$ ($M+Na^+$) 493.1409, found 493.1429.

4.2.26. Trans-2-(1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)-6-nitrobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11p**)

According to general procedure B, 6-nitroaccharinylacetic acid **2b** (71.55 mg, 0.25 mmol) was reacted with: imine **2c** (68.5 mg, 0.25 mmol), Mukaiyama's salt (70.3 mg, 0.27 mmol) and triethylamine (77 μL, 0.55 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Column chromatography (heptane:EtOAc/99:1 → 1:1) afforded **11p** (0.15 mmol, 61%) as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ (ppm) = 8.78 (dd, J = 1.9, 0.5 Hz, 1H), 8.70 (dd, J = 8.4, 1.9 Hz, 1H), 8.27 (dd, J = 8.3, 0.5 Hz, 1H), 7.44 (m, 2H), 7.28–7.16 (m, 6H), 5.39 (d, J = 2.6 Hz, 1H), 5.01 (d, J = 2.6 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, d_6-DMSO) δ (ppm) = 158.96 (Cq), 156.35 (Cq), 151.81 (Cq), 139.74 (Cq), 138.79 (Cq), 135.75 (Cq), 132.25 (2×CH), 131.21 (Cq), 130.88 (Cq), 130.33 (2×CH), 129.74 (CH), 127.20 (CH), 125.86 (2×CH), 119.19 (2×CH), 117.77 (Cq), 117.37 (CH), 63.52 (CH), 60.31 (CH), 21.26 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{17}N_3O_{6S}Br$ ($M+H^+$) 542.0021, found 542.0007.

4.2.27. Trans-2-(1-(4-bromophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-6-nitrobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (**11q**)

According to general procedure B, 6-nitrosaccharinylacetic acid **1b** (400 mg, 1.4 mmol) was reacted with: imine **2b** (405 mg, 1.4 mmol), Mukaiyama's salt (375 mg, 1.5 mmol) and triethylamine (0.43 mL, 3.1 mmol) in CH_2Cl_2 (10 mL) under microwave irradiation (100 °C, 10 min). Column chromatography (heptane: EtOAc/4:1 → 2:1) afforded **11q** (0.854 mmol, 61%) as a pale yellow

solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ (ppm) = 9.37 (d, J = 1.9 Hz, 1H), 8.76 (dd, J = 8.4, 2.0 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.60–7.42 (m, 4H), 7.24–7.14 (m, 2H), 7.02–6.91 (m, 2H), 5.61 (d, J = 2.7 Hz, 1H), 5.39 (d, J = 2.7 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.68 (Cq), 160.19 (Cq), 157.30 (Cq), 152.47 (Cq), 138.02 (Cq), 136.35 (Cq), 132.70 (2×CH), 131.07 (Cq), 131.05 (CH), 129.03 (2×CH), 127.49 (CH), 127.07 (Cq), 119.67 (2×CH), 119.04 (CH), 116.81 (Cq), 114.81 (2×CH), 62.61 (CH), 60.07 (CH), 55.64 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{17}N_3O_7SBr$ (M+H$^+$) 557.9971, found 557.9968.

4.2.28. Trans-2-(1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl) isoindoline-1,3-dione (**18**)

According to general procedure B, phthaloyl glycine **13** (51.3 mg, 0.25 mmol) was reacted with: imine **2b** (68.5 mg, 0.25 mmol), Mukaiyama's salt (70.3 mg, 0.27 mmol) and triethylamine (77 µL, 0.55 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Column chromatography (heptane:EtOAc/99:1 → 1:1) afforded **18** (0.15 mmol, 58%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.93–7.84 (m, 2H), 7.82–7.73 (m, 2H), 7.43–7.34 (m, 2H), 7.28–7.17 (m, 6H), 5.32 (d, J = 2.7 Hz, 1H), 5.27 (d, J = 2.7 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 166.74 (Cq), 162.09 (Cq), 139.32 (Cq), 136.14 (Cq), 134.61 (2×CH), 132.23 (Cq), 132.11 (2×CH), 131.64 (Cq), 130.16 (2×CH), 126.05 (2×CH), 123.84 (2×CH), 119.12 (2×CH), 119.12 (2×CH), 117.24 Cq), 62.97 (CH), 61.28 (CH), 21.23 (CH_3). HRMS ESI (3000 V): calculated for $C_{24}H_{18}N_2O_3Br$ (M+H$^+$) 461.0501, found 461.0486.

4.2.29. 1,3-Dimethyl-7-trans-(1-(3-nitrophenyl)-2-oxo-4-(p-tolyl) azetidin-3-yl)-3,7-dihydro-1H-purine-2,6-dione (**19**)

According to general procedure B, theophylline-7-acetic acid **14** (29.8 mg, 0.125 mmol) was reacted with: imine **2b** (34.3 mg, 0.12 mmol), Mukaiyama's salt (35.1 mg, 0.14 mmol) and triethylamine (39 µL, 0.28 mmol) in CH_2Cl_2 under microwave irradiation (100 °C, 10 min). Column chromatography (heptane:EtOAc/4:1 → 0:100) afforded **19** (0.078 mmol, 65%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.66 (s, 1H), 7.45–7.37 (m, 2H), 7.32–7.20 (m, 6H), 5.48 (d, J = 2.7 Hz, 1H), 5.31 (d, J = 2.7 Hz, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 160.49 (Cq), 154.61 (Cq), 151.45 (Cq), 149.56 (Cq), 141.3 (CH, *not observed in APT; determined from HSQC spectrum*), 139.78 (Cq), 132.25 (2×CH), 131.33 (Cq), 130.26 (2×CH), 126.21 (2×CH) 119.44 (2×CH), 117.80 (Cq), 70.12 (CH), 64.32 (CH), 29.93 (CH_3), 28.29 (CH_3), 21.26 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{21}N_5O_3Br$ (M+H$^+$) 494.0828, found 494.0838.

4.2.30. Trans-6-amino-2-(1-(4-bromophenyl)-2-oxo-4-(p-tolyl) azetidin-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**23a**)

Lactam **11p** (50 mg, 0.090 mmol) was dissolved in glacial acetic acid (1 mL) followed by the addition of powdered iron (0.51 mg, 0.92 mmol). The mixture was stirred for 3 h after which the reaction was complete (TLC). The mixture was filtered over Celite, diluted in EtOAc and washed with saturated $NaHCO_3$ till no more CO_2 evolved. The organic layer was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. This afforded **23a** (0.85 mmol, 92%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.44 (d, J = 8.4 Hz, 1H), 7.32–7.23 (m, 2H), 7.17–7.05 (m, 6H), 6.79–6.70 (m, 2H), 5.29 (d, J = 2.6 Hz, 1H), 4.84 (bs, 2H), 4.80 (d J = 2.7 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 161.35 (Cq), 158.73 (Cq), 153.61 (Cq), 139.56 (Cq), 139.35 (Cq), 135.89 (Cq), 132.17 (2×CH), 131.66 (Cq), 130.17 (Cq), 126.96 (CH), 125.86 (2×CH), 119.24 (2×CH), 119.00 (CH), 117.56 (Cq), 114.00 (Cq), 104.92 (CH), 63.06 (CH), 31.22 (CH), 21.23 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{19}N_3O_4SBr$ (M+H$^+$) 512.280, found 512.0294.

4.2.31. Trans-N-(2-(1-(4-bromophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)acetamide (**23b**)

Lactam **11q** (200 mg, 0.36 mmol) was dissolved in glacial acetic acid (3 mL) followed by the addition of powdered iron (200 mg, 3.6 mmol). The mixture was stirred for 1 h after which the reaction was complete (TLC). The mixture was filtered over Celite, diluted in EtOAc and washed with saturated $NaHCO_3$ till no more CO_2 evolved. The organic layer was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. This afforded **23b** (0.35 mmol, 99%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.44–7.04 (m, 7H), 6.89–6.60 (m 4H), 5.32 (d, J = 1.6 Hz, 1H), 5.02 (bs, 2H), 4.83 (d, J = 1.9 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 161.57 (Cq), 160.26 (Cq), 158.75 (Cq), 153.86 (Cq), 139.52 (Cq), 135.72 (Cq), 132.11 (2×CH), 127.28 (2×CH), 126.78 (CH), 119.21 (2×CH), 118.88 (CH), 117.55 (Cq), 114.83 (2×CH), 113.37 (Cq), 104.82 (CH), 62.97 (CH), 60.97 (CH), 55.27 (CH_3). HRMS ESI (3000 V): calculated for $C_{23}H_{19}N_3O_5SBr$ (M+H$^+$) 528.0229, found 528.0221.

4.2.32. Trans-N-(2-(1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)acetamide (**24a**)

Lactam **23a** (21 mg, 0.04 mmol) and sodium bicarbonate (8.6 mg, 0.10 mmol) were dissolved in THF (1.0 mL). Then acetyl chloride (3.5 µL, 0.05 mmol) was added and the mixture was stirred for 16 h after which the reaction was complete (TLC). The volatiles were evaporated and suspended in EtOAc (2 mL). The organic layer was washed with 1 M HCl, brine, dried over Na_2SO_4 and evaporated. Column chromatography (heptane:EtOAc/99:1 → 25:75) afforded **24a** (0.027 mmol, 66%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.03 (s, 1H), 8.70 (d, J = 1.7 Hz, 1H), 7.60–7.31 (m, 4H), 7.30–7.16 (m, 6H), 5.54 (d, J = 2.7 Hz, 1H), 5.00 (d, J = 2.7 Hz, 1H), 2.36 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.46 (Cq), 162.18 (Cq), 157.86 (Cq), 145.47 (Cq), 139.74 (Cq), 138.48 (Cq), 135.38 (Cq), 132.36 (2×CH), 131.00 (Cq), 125.92 (CH), 125.85 (2×CH), 123.68 (CH), 119.50 (2×CH), 118.27 (Cq), 111.24 (CH), 62.78 (CH), 60.82 (CH), 24.63 (CH_3), 21.24 (CH_3). HRMS ESI (3000 V): calculated for $C_{25}H_{21}N_3O_5SBr$ (M+H$^+$) 554.0380, found 554.0362.

4.2.33. Trans-N-(2-(1-(4-bromophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)acetamide (**24b**)

Lactam **23b** (66.1 mg, 0.13 mmol) and sodium bicarbonate (26.2 mg, 0.31 mmol) were dissolved in THF (1.5 mL). Then acetyl chloride (11 µL, 0.15 mmol) was added and the mixture was stirred for 3 h after which the reaction was complete (TLC). The volatiles were evaporated and suspended in EtOAc (5 mL). The organic layer was washed with 1 M HCl, brine, dried over Na_2SO_4 and evaporated. This yielded **24b** (0.12 mmol, 95%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.04 (s, 1H), 8.71 (d, J = 1.7 Hz, 1H), 7.53–7.40 (m, 3H), 7.39–7.20 (m, 5H), 6.98–6.88 (m, 2H), 5.53 (d, J = 2.6 Hz, 1H), 5.00 (d, J = 2.7 Hz, 1H), 3.81 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.51 (Cq), 162.28 (Cq), 160.60 (Cq), 157.89 (Cq), 145.50 (Cq), 138.49 (Cq), 138.49 (Cq), 135.38 (Cq), 132.40 2×CH), 127.37 (2×CH), 125.95 (CH), 125.81 (Cq), 123.71 (CH), 119.56 (2×CH), 118.33 (Cq), 115.10 (2×CH), 111.28 (CH), 62.86 (CH), 60.68 (CH), 55.42 (CH_3), 24.69 (CH_3). HRMS ESI (3000 V): calculated for $C_{25}H_{22}N_3O_6SBr$ (M+H$^+$) 570.0334, found 570.0318.

Author contributions

All authors have approved the final version of the manuscript.

Conflicts of interest

None.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmc.2017.11.014.

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19. The stereochemistry of the lactam rings were assigned by comparing the coupling constants of H-3 and H-4 ($J_{3,4}$ > 4.0 Hz) for the *cis* stereoisomer and ($J_{3,4}$ < 3.0 Hz) for the *trans* stereoisomer.
20. The yields are determined from the pure products after preparative HPLC (see Experimental section for details). Since a part of the product is lost during these purifications, the yields are lower than the products that are isolated by FC-chromatography.
21. The *cis* and *trans* diastereoisomers are separable using preparative LC/MS.
22. Chemaxon Calculator (cxcalc) was used to calculate the cLog*P* values, calculator 16.7.1800, 2017, Chemaxon (http://www.chemaxon.com).
23. For practical reasons, conventional heating in closed vials at 45 °C was applied for 16 h instead of microwave heating.