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3-Aminopropylazetidines: facile synthesis and application for medicinal chemical purposes

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Dedicated to Prof. György Keglevich on the occasion of his 65th birthday

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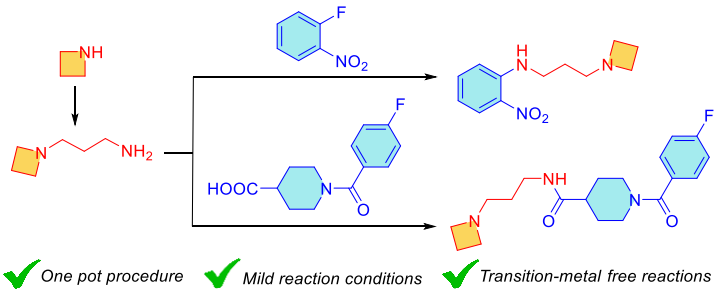
Abstract

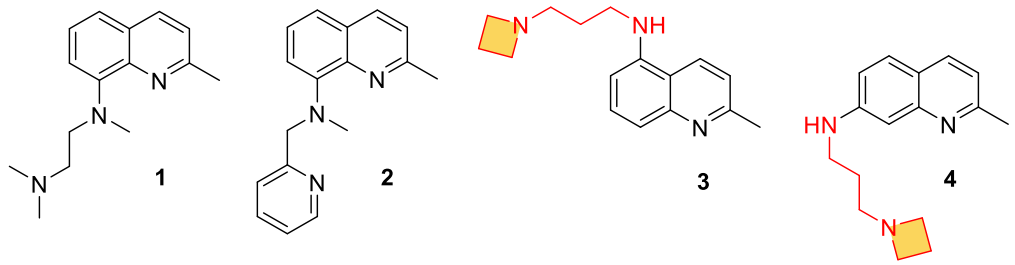
The 3-(azetidin-1-yl)propan-1-amine moiety is present in various potentially pharmacologically-active molecules and can be of interest also for the design of metal-complexing agents. In the present study, a new, one-pot protocol using mild conditions has been developed for the straightforward synthesis of various drug-like *N*-aminopropyl scaffolds. The process combines azetidine dimerization with a subsequent functionalization such as alkylation or amide formation. Analyzing more in detail the first step, the conditions (concentration, catalyst, solvent, temperature) affecting azetidine ring opening and controlled dimerization were investigated.



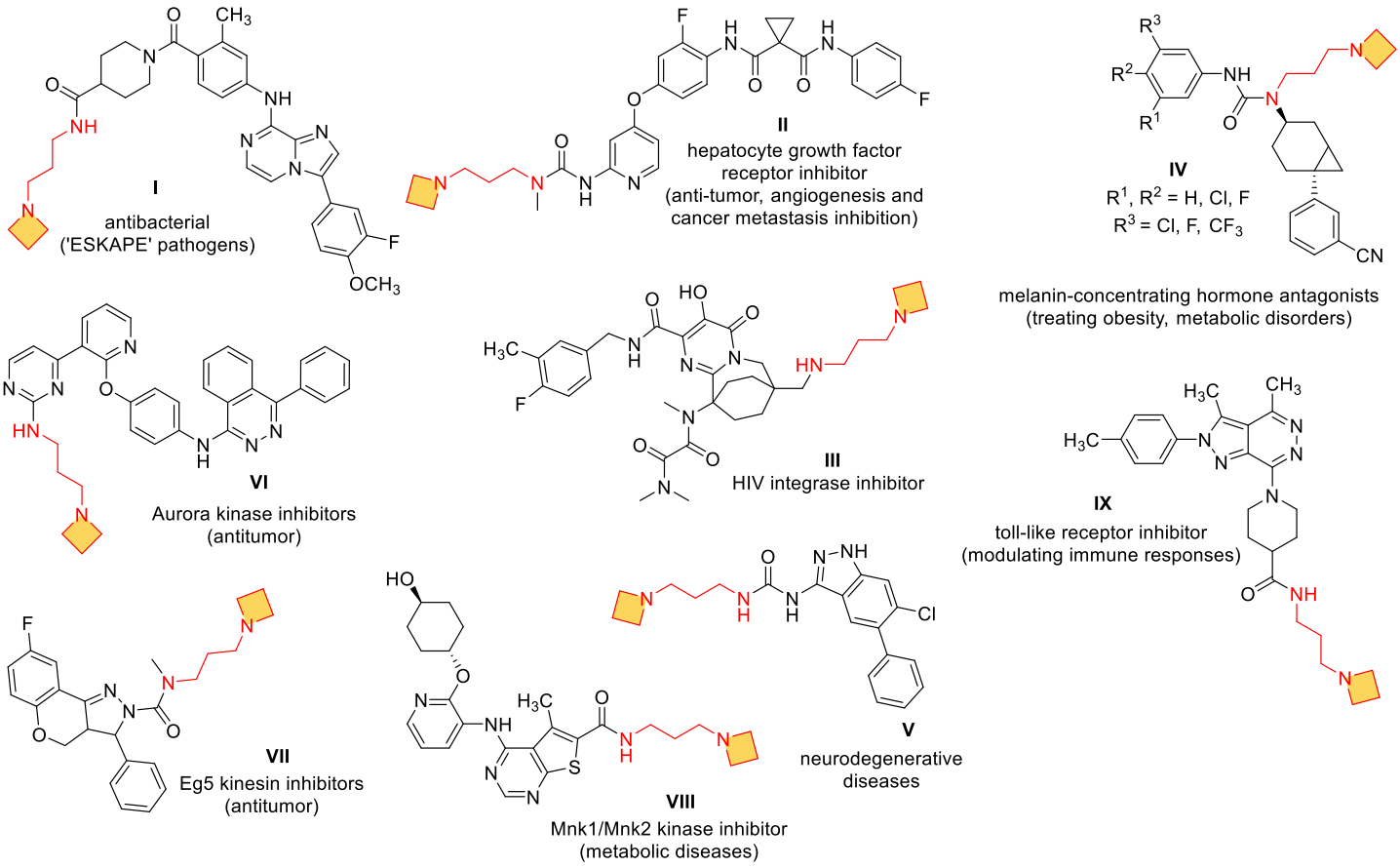
Keywords: Azetidine, aminopropylation, dimerization, ring opening, amine scaffolds, saturated nitrogen heterocycles, acid catalysis, one-pot reaction

Introduction

In the course of our ongoing studies on fluorescent dyes and fluorescent turn-on probes for various metal ions,[1–4] we were interested in the synthesis of novel chemical tools with an aminoquinoline heterocycle as the metal-complexing scaffold (Scheme 1). Out of the various amine side chains, the 3-(azetidin-1-yl)propan-1-amine moiety is used in a number of potentially pharmacologically-active molecules, described mainly in the medicinal chemistry patent literature. Some illustrative examples (**I**-**IX**) are compiled in Scheme 2 with their studied pharmacological effects.[5–13]



Scheme 1. Selected examples of aminoquinoline derivatives used for the synthesis of metal sensors[4].

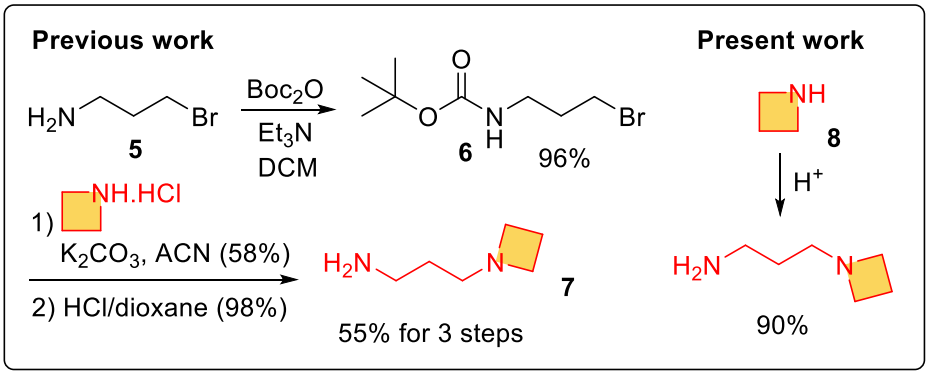


Scheme 2. Examples of the 3-(Azetidin-1-yl)propan-1-amine moiety in medicinal chemistry.

From a broader perspective, four-membered saturated aza-heterocycles are present in a wide variety of natural products and drug molecules, such as in the widely used β-lactams, azetidin-2-one antibiotics. Recently,

saturated building blocks are becoming more prevalent in medicinal chemistry.[14] Compared to their 5- and 6-membered analogues, however, azetidines or substituted azetidines are synthetically more challenging targets.[15–22] Many synthetic approaches are based on the energetically less favorable intramolecular C-C or C-N cyclisation of appropriately functionalized linear precursors. Further approaches include the reduction of azetidin-2-ones, intermolecular 2+2 cycloadditions and ring expansion of aziridines.[23] Functionalized azetidines (*e.g.*, spirocyclic derivatives) could be obtained starting from azabicyclo[1.1.0]butanes (ABBs) via various strain-release transformations.[24]

Logically, the 3-(azetidin-1-yl)propan-1-amine (**7**) moiety could be obtained by alkylating azetidine (**8**), although literature precedents are scarce (Scheme 3).[25] A straightforward preparation starts with Boc-protection of (3-bromopropyl)amine (**5**) (1 mmol typically costing 7.5-37 USD),[26,27] followed by azetidine alkylation and deprotection under acidic conditions.[25] Compound **7** is available also from a limited number of commercial sources, however, at less affordable prices (1 mmol typically costing 60-140 USD).[27] The formation of compound **7** can be observed upon prolonged storing (> 6 months) of azetidine as well.



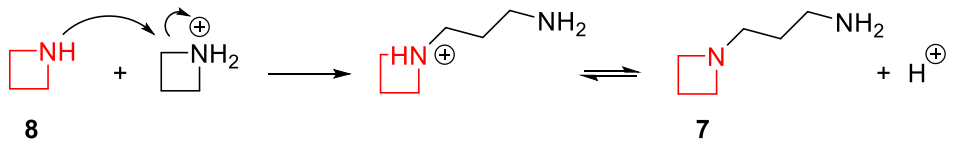
Scheme 3. Synthesis of 3-(azetidin-1-yl)propan-1-amine (**7**).

Inspired by the interest of medicinal chemistry in carbo- and heterocycles decorated with this moiety, we planned to exploit a different, straightforward access to compound **7** and its derivatives, based on the dimerization of the more readily available azetidine (1 mmol typically costing 2-3.5 USD).[27] On the one hand, a systematic study of the reaction conditions and the scope of the dimerization was carried out, backed up by theoretical considerations. On the other hand, we aimed to test a practical and scalable one-pot procedure for the sequential preparation and functionalization of compound **7**, where the dimerization step is followed by a further derivatization to yield various heterocyclic scaffolds.

Results and Discussion

The ring opening of aziridines (N–C σ-bond cleavage), which have a highly strained three-membered ring, is a well-known reaction widely used in synthesis.[28] Azetidines, with a four-membered ring, are less strained, and studies of their ring openings are less numerous (the calculated aziridine *vs* azetidine strain energy is 114.2 kJ/mol *vs* 105.4 kJ/mol).[29,30] Aziridine and azetidine ring openings are of considerable interest for polymer synthesis, giving rise to various linear or branched polyamines via different mechanisms, with potential applications in several fields, *e.g.*, CO_2 adsorption and antimicrobial coatings.[31] Particularly, but not exclusively, the dimerization of azetidine, *i.e.*, formation of **7** has been described in polymerization studies. Causey *et al.*

identified compound **7** as a side product formed during the hydrogenation of *N*-benzhydrylazetidine in various organic solvents and subsequent distillation of the azetidine product, besides the formation of additional azetidine oligomers (**7** was not isolated).[32] Studying the cationic polymerization of azetidine (neat or in MeOH, 80 °C, catalytic $HClO_4$), Schacht and Goethals observed the formation of **7** as the first step in the polymerization proceeding from this dimer. In this case, **7** was isolated by preparative gas chromatography and characterized with MS and ^{1}H NMR. Regarding the mechanism of the dimerization, first a protonation of azetidine by the acid catalyst was suggested, followed by a nucleophilic attack on the protonated species by another azetidine molecule. From the protonated dimer form, proton transfer to a more basic azetidine molecule keeps the reaction proceeding to full conversion (Scheme 4). Rate constants with different acid-initiator concentrations were determined in MeOH at 70 °C by gas chromatography, and further polymerization from the dimer was studied.[33] 3-(Azetidin-1-yl)propan-1-amine (**7**) formation from azetidine and subsequent ring-opening polymerization were addressed more recently by Sarazen and Jones as well, calculating the degree of polymerization using ^{1}H NMR (**7** was not isolated).[34]



Scheme 4. Formation of 3-(azetidin-1-yl)propan-1-amine (**7**) via acid-catalyzed dimerization according to Schacht and Goethals (adapted from Sarazen and Jones).[33,34]

Formation of the dimer as an intermediary step of the thermally-induced (80 °C) polymerization of an azetidine-$ZnCl_2$ complex and azetidine + catalytic HCl was observed by Cherchenko and Abubakirov.[35] In the framework of their studies on catalytic alkyl-exchange reactions of secondary amines, Murahashi *et al*. described the quantitative formation of **7** from azetidine with palladium black catalysis (neat, 140 °C), presumably *via* a reactive azetine intermediate, and extended the method to the preparation of triamines using azetidine as a source of the 3-aminopropyl group. In this case **7** was isolated by distillation.[36] The most detailed experimental and theoretical investigation of nucleophilic ring openings of azetidine, in comparison with aziridine, and oxygen heterocycles oxirane and oxetane, was disclosed by Sharikov et al.[37] The presence of proton donors was found to be essential for the process, and a study of the kinetic parameters showed a correlation between the reactivity of the amine nucleophiles used and their basicity. Ring openings were studied with various primary and secondary amines (azetidine, ammonia, ethylene diamine, piperazine, morpholine, piperidine, propylamine, diethylamine, *tert*-butylamine, hydrazine and ethanolamine), using GC-MS monitoring and structure elucidation based on mass-fragmentation patterns (**7** was not isolated).

For synthetic purposes, we were interested in the selective formation of the dimer 3-(azetidin-1-yl)propan-1-amine (**7**) product, *i.e*., avoiding further polymerization. Therefore, we set out to do a brief study on the effect of the following factors: i) temperature, ii) reaction time, iii) solvent, iv) type and ratio of the initiator, v) concentration - using ^{1}H NMR spectroscopy to monitor the process. Assessing, first, solutions of azetidine in various deuterated solvents (DMSO-d_6, D_2O, CD_3OD, DMSO-d_6/D_2O 9/1) without a proton donor present, compound **7** was formed typically only in trace amounts (4-6%) after stirring for 96 h at rt, whereas azetidine remained intact in $CDCl_3$ (Supplementary material, Figures S8, S14, S17, S24). Mild heating (50°C) in the above solvents increased the product ratio (10-30% after 96 h) depending on the nature of the solvent, however, the reaction remained slow, as could be expected given the importance of the protonation step. As acid initiator for

further studies, we opted for a strong organic acid: trifluoroacetic acid (TFA, used in 0.5 eq). Apart from $CDCl_3$, where mainly precipitation of the protonated species occurred, and acetone-d_6 among the other solvents studied, in the presence of TFA, a considerable amount of the dimer product was obtained already at rt, and reasonable reaction rates were observed upon heating (50 °C) (Fig.1.). These results were in good agreement with the tendencies observed from calculations. The possible effect of water was assessed by running the reaction both in anhydrous DMSO-d_6 and in a 9/1 mixture of DMSO-d_6/D_2O. Of note, in the latter mixture as well as in CD_3CN, besides the 3-(azetidin-1-yl)propan-1-amine (**7**) product formation, side reactions also occurred upon heating. DMSO-d_6 provided a slightly slower, but cleaner reaction profile; therefore, it became our solvent of choice for further experiments and developing the one-pot synthetic protocol. However, for isolating **7**, the more volatile CH_3CN could be a reasonable alternative as well (Experimental section). Modifying the amount of the acid initiator, 1.0 eq TFA led to trace amounts of compound **7**, whereas, in the presence of catalytic (0.1 eq) TFA, side reactions increased (Fig.2.). Running the experiments at 0.5 - 1.0 M azetidine concentration led mainly to compound **7** formation, whereas at 5.0 M, peaks belonging to further products became more prevalent in the ^1H NMR spectra, presumably due to polymerization (Supplementary material, Figure S36).

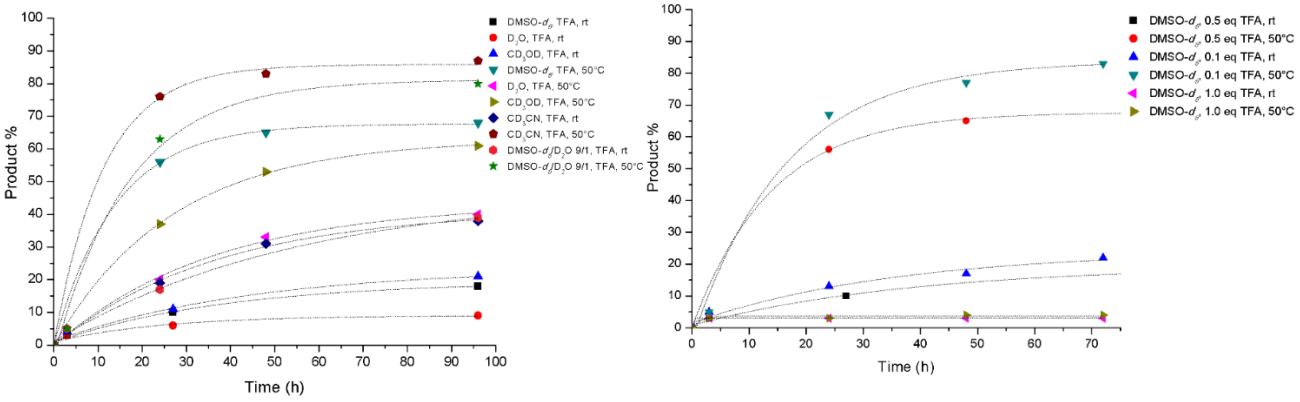


Figure 1. Azetidine dimerization: *left:* in the presence of TFA (0.5 eq.) in various solvents; *right*: in the presence of varying amounts of TFA initiator and varying temperature.

Since it has been described in the literature that the thermal ring cleavage of azetidine proceeds in the presence of $ZnCl_2$, we assessed the effect of a small set of Lewis acids in catalytic amounts (Table 1), finding similar outcomes as those observed with the TFA initiator. For operational reasons (reaction under non-inert conditions, homogenous reaction mixture), and a slightly cleaner outcome however, TFA initiator was used for the synthetic experiments.

Table 1. The effect of Lewis acid catalysts on azetidine dimerization.

Entry	Temperature (°C)	Catalyst	Yield (%)*
1	rt	$Yb(OTf)_3$	8
2	50	$Yb(OTf)_3$	57
3	rt	$Gd(OTf)_3$	19
4	50	$Gd(OTf)_3$	46
5	rt	$AlCl_3$	13
6	50	$AlCl_3$	78
7	rt	$BF_3.OEt_2$	22
8	50	$BF_3.OEt_2$	69
10	50	LiCl	16
12	50	$ZnCl_2$	31

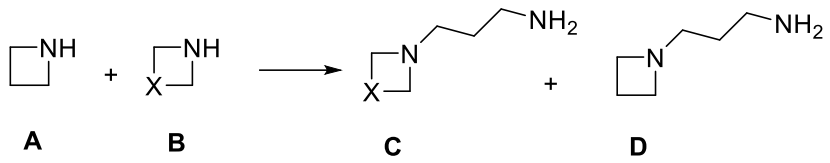
Reaction conditions: 20 µL azetidine in 0.6 mL DMSO-d_6, catalyst (0.01 eq), stirring for 72 h at the indicated temperature

*Composition of the product in the reaction mixture determined by ^{1}H NMR

As typically longer reaction times were needed for full conversion, we considered using microwave heating, as it is has been often found to lead to shortened reaction times due to a more efficient heating profile.[38] Moreover, DMSO as a high MW absorbing solvent is an ideal choice also for this direction. Increasing the temperature to 100°C led to decomposition besides product formation, whereas at 75°C, in addition to a faster reaction (77% product after 4 h), side products' formation was less pronounced (Supplementary material, Figure S47-49).

We investigated whether the reaction could be extended to larger rings. According to literature observations, the ring opening (N–C σ bond cleavage) is feasible for the 3- and 4-membered rings, but not for larger, sterically less strained homologues (Supplementary material, Figures S50, S54, S57, S60, S64, S66).[37] This reactivity pattern was confirmed also by our NMR monitoring experiments (50°C, 72 h – no dimerization observed for 5-8 membered cyclic amines). In the reaction of azetidine with other secondary amines (monocyclic - 5- to 8-membered rings - or benzo-fused), however, an aminopropylation could be expected under mild conditions (TFA initiator, DMSO, 50°C). In each case studied, the aminopropylation (*i.e.*, formation of **C** products) was accompanied by azetidine dimerization as well (Table 2, Supplementary material, Figures S51-69). The formation of **7** could not be ruled out, even using a higher excess (3.0 eq) of the amine partner. For synthetic purposes, a fractional distillation step could be integrated, if necessary, before further functionalization. In the present study, the aminopropylated derivatives listed in Table 2 were not isolated. Alternatively, to rule out the reaction of azetidine with itself, ring opening of an N-substituted derivative, 1-diphenylmethylazetidine, was tested in the presence of pyrrolidine, piperidine and their benzo-condensed analogues. This reaction, followed by the cleavage of the diphenylmethyl protecting group, could offer a selective alternative for the aminopropylation step. Product formation was observed only in the case of the latter entry, albeit affording a modest (15-20%) conversion following even longer reaction times (7 days) (Supplementary material, Figure S74). No further optimization of this reaction was done.

Table 2. Aminopropylation of cyclic amines

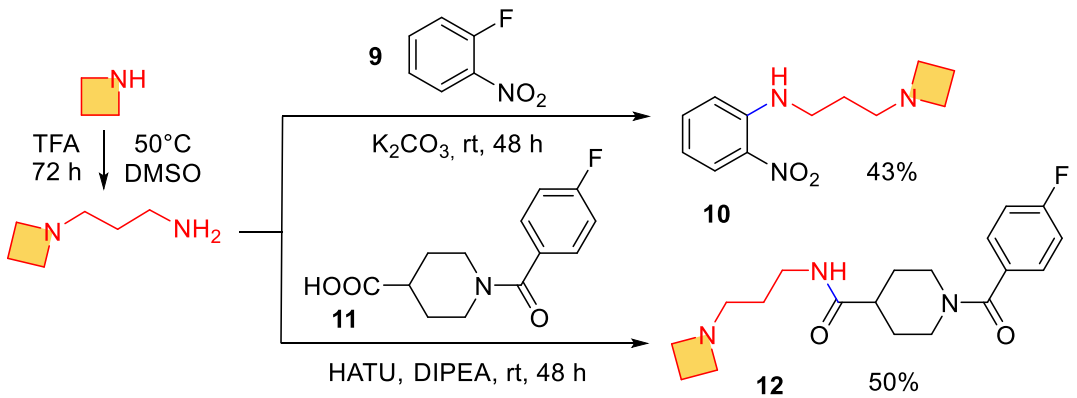


Entry	Reagent B	% A*	% B*	% C*	% D*
1	pyrrolidine (1.0 eq)	4	50	33	13
2	pyrrolidine (3.0 eq)	1	71	25	3
3	piperidine (1.0 eq)	4	50	29	17
4	piperidine (3.0 eq)	2	73	21	4
5	morpholine (1.0 eq)	5	52	26	17
6	morpholine (3.0 eq)	2	75	18	4
7	*N*-methylpiperazine (1.0 eq)	6	49	33	12
8	*N*-methylpiperazine (3.0 eq)	2	68	25	5
9	4-methylpiperidine (1.0 eq)	10	49	27	14
10	hexahydroazepine (1.0 eq)	5	56	22	17
11	octahydroazocine (1.0 eq)	7	56	14	23
12	1,2,3,4-tetrahydroisoquinoline	4	67	20	9
13	isoindoline	8	49	27	16

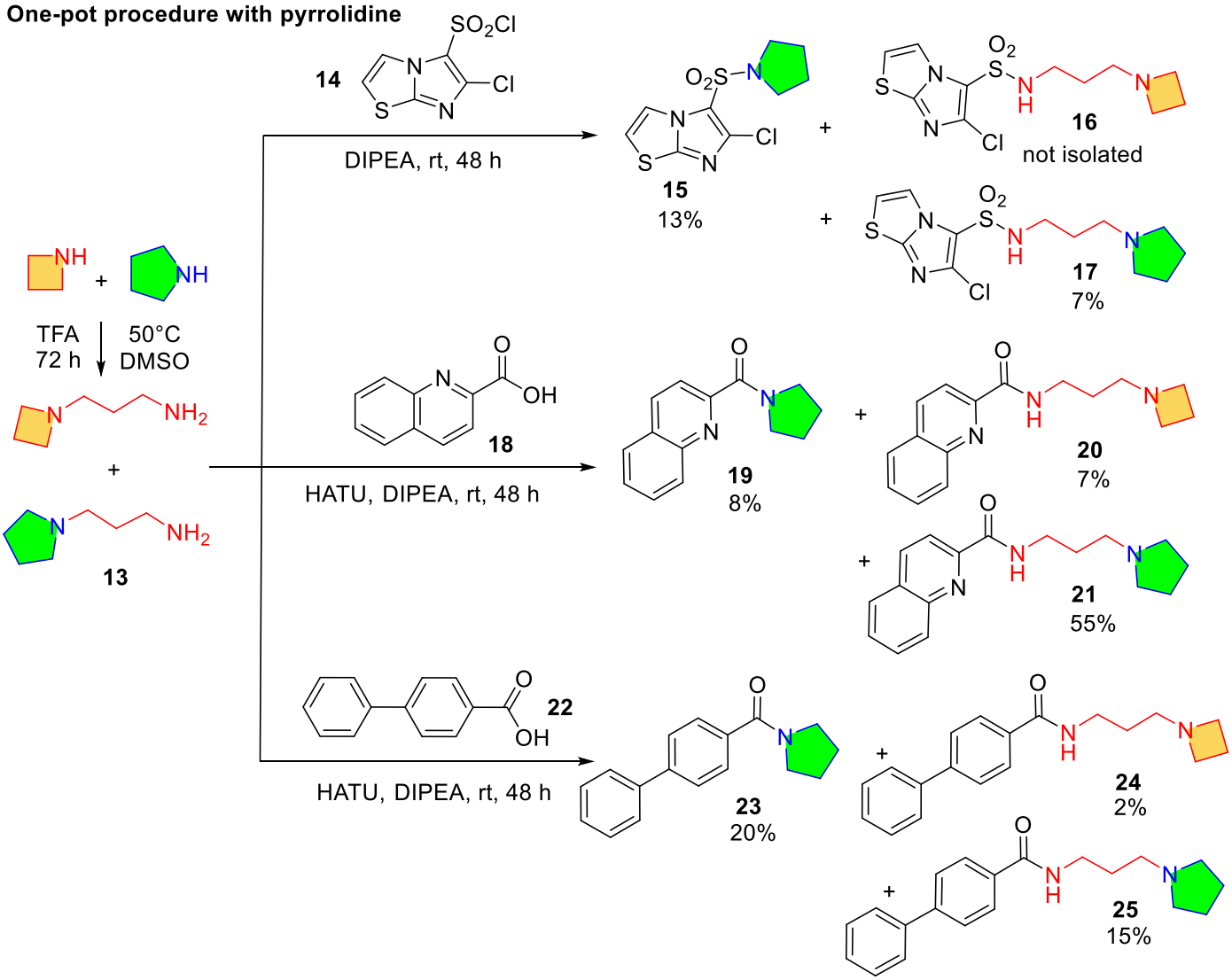
Reaction conditions: 20 µL azetidine in 0.6 mL DMSO-d_6, 0.5 eq TFA, indicated eq amine B, stirring for 72 h at 50°C;
*Composition of the product mixture calculated from ^{1}H NMR

Finally, we have set out to test the synthetic use of *in situ* azetidine ring opening for the preparation of amine building blocks relevant for medicinal chemistry.[36,37] After a first heating session to obtain compound **7**, the reagents for the second step (*e.g.*, alkylation, amide formation) were introduced directly into the DMSO solution of 3-(azetidin-1-yl)propan-1-amine (**7**) without work-up and isolation, affording the expected products in good yields after final chromatography (Scheme 5). As a proof of concept, the one-pot protocol was tested also for the azetidine-pyrrolidine dimerization, using, in this case, the unseparated mixture for further functionalization (Scheme 6). By chromatography).

One-pot procedure with azetidine



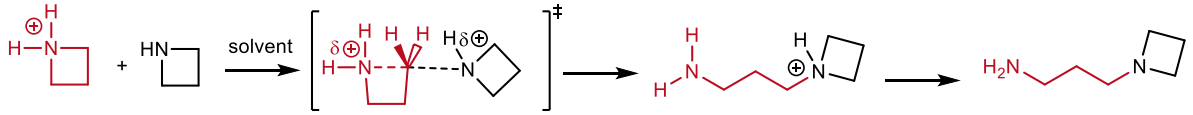
Scheme 5. One-pot aminopropylation followed by a substitution or amide-coupling.



Scheme 6. One-pot aminopropylation followed by sulfonamide or amide formation.

In order to explain the various reaction rates of the dimerization of azetidine (**A**), the reaction mechanism was explored by computational methods at M06-2X/6-31G(d,p) level of theory under different conditions. The dimerization of the base form of azetidine (**A**) resulted in a quite high activation barrier ($\Delta H^{\ddagger}$= 214.9 kJ mol^{-1}, Table 4, Entry 1), which is high enough to block the reaction at the temperature applied (below 100°C), although the reaction is strongly exothermic. When the attacking azetidine is protonated (**A+H$^+$**) while simultaneously acylating the base form of azetidine (**A**), the activation enthalpy dropped down to 29.4 kJ mol^{-1} computed *in vacuo* (Table 3, Entry 1). The greater the relative permittivity of the solvent, the higher the calculated reaction enthalpy of the reaction, which agrees with chemical intuitions. In the case of DMSO, applied in the experimental section, the activation gap exhibited 51.4 kJ mol^{-1}, which predicts a relatively fast reaction rate.

Table 3. Solvent effect on the dimerization of azetidine in the presence of a strong acid (TFA), computed at M06-2X/6-31G(d,p) level of theory using PCM solvent model. ε_r = relative permittivity.

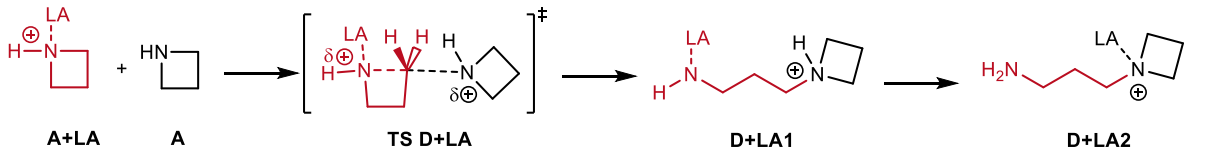


Entry	solvent	ε_r	A+H$^+$+ A	TS D+H$^+$		D+H$^+$		D	
			ΔH, ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
1	vacuo	1.0	0.0	29.4	40.1	-123.9	-114.4	-65.7	-57.0
2	toluene	2.4	0.0	39.7	48.5	-118.6	-111.9	-83.0	-77.7
3	THF	7.6	0.0	50.5	57.3	-111.9	-107.0	-92.6	-88.2
4	EtOH	24.3	0.0	50.8	64.3	-113.8	-102.8	-100.3	-89.1
5	MeOH	32.7	0.0	51.1	64.4	-113.7	-103.0	-100.8	-89.8
6	MeCN	35.6	0.0	51.2	64.6	-113.7	-102.8	-100.9	-89.8
7	DMSO	48.5	0.0	51.4	63.4	-113.7	-104.3	-101.3	-91.5
8	water	78.0	0.0	51.7	63.2	-113.6	-104.7	-101.8	-92.4

Besides the proton as the strongest Lewis acid (LA), the effect of some weaker LAs (Li^+, BF_3, $AlCl_3$) were also considered experimentally and theoretically (Table 4). The strongest LA character results in lower activation enthalpies, and $AlCl_3$ is at the forefront in the series (Table 4, Entry 4) after BF_3 (Table 4, Entry 3) and Li^+ (Table 4, Entry 2). These $\Delta H^‡$ values are in agreement with the experimental findings, as LiCl resulted in poor conversion (< 20% in 3 days), while $AlCl_3$ and BF_3 exhibited 80% and 70% conversion in 3 days, respectively. In the presence of oxonium ion (H_3O^+), the calculated activation enthalpy is practically equal with the value obtained with the protonated form (Table 4, Entry 6). Water provided almost the same value as Entry 1 (Table 4).

It is worth studying the same dimerization of different *N*-containing heterocycles, such as aziridine (Table 5, Entry 1), pyrrolidine (Table 5, Entry 3) and piperidine (Table 5, Entry 4), and comparing them to azetidine (Table 5, Entry 2). As expected, and in line with the computed $\Delta H^‡$ values presented in Table 5, aziridine exhibited relatively low activation enthalpy, while pyrrolidine and piperidine showed higher and higher activation gaps, with nearly negligible reaction enthalpies. According to the results of this study, only aziridine and azetidine can form dimers under mild reaction condition.

Table 4. Azetidine dimerization in the presence of various Lewis acids, computed at M06-2X/6-31G(d,p)//PCM(DMSO) level of theory.

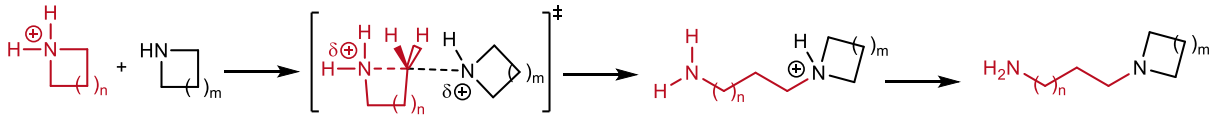


LA = nothing, Li^+, BF_3, $AlCl_3$, H^+

Entry	LA	A+LA + A	TS D+LA		D+LA1		D+LA2	
			ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
1	nothing	0.0	214.9	225.6	108.6	120.7	-120.8	-112.6
2	Li^+	0.0	143.2	154.2	-121.7	-110.1	-109.9	-97.5
3	BF_3	0.0	100.4	114.1	-131.5	-115.5	-116.4	-102.3
4	$AlCl_3$	0.0	75.4	86.9	-75.6	-61.7	-104.6	-90.7
5	H^+	0.0	51.4	63.4	-113.7	-104.3	-101.3	-91.5
6	H_3O^+	0.0	49.7	61.8	-98.9	-84.2	-78.1	-64.6
7	H_2O	0.0	202.0	220.1	98.5	115.7	-108.1	-103.2

When we attack the base form of pyrrolidine and piperidine with the protonated azetidine (Table 5, Entries 5 and 7), the activation enthalpies are close to the azetidine dimerization, predicting a smooth reaction. This is in contrast with the opposite situation in which the base form of azetidine is attacked by the protonated form of pyrrolidine and piperidine (Table 5, Entries 6 and 8), as the activation enthalpies represent much higher values.

Table 5. Dimerization of various *N*-heterocycles with different ring sizes, computed at M06-2X/6-31G(d,p)//PCM(DMSO) level of theory.



n, m = 0, 1, 2, 3

Entry	n	m	N+H$^+$ + M	TS NM+H$^+$		NM+H$^+$		NM	
				ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
1	0	0	0.0	41.3	48.9	-108.7	-99.8	-108.8	-100.0
2	1	1	0.0	51.4	63.4	-113.7	-104.3	-101.3	-91.5
3	2	2	0.0	85.3	97.0	-27.8	-20.9	-27.4	-22.6
4	3	3	0.0	113.5	123.3	-0.4	-1.3	53.1	49.9
5	1	2	0.0	48.2	61.5	-111.1	-102.5	-88.9	-81.6
6	2	1	0.0	85.4	93.3	-36.0	-31.6	-18.3	-12.8
7	1	3	0.0	56.8	65.8	-102.1	-92.3	-76.6	-70.5
8	3	1	0.0	105.4	118.6	-5.0	3.6	3.5	5.8

Conclusions

Acid-catalyzed ring opening of azetidine furnishes 3-(azetidin-1-yl)propan-1-amine (**7**) in good yields, moreover, in the presence of various secondary amines, it could serve as an operationally simple aminopropylation method. The obtained 3-(azetidin-1-yl)propan-1-amine (**7**) (or aminopropyl derivatives of cyclic amines) could be judiciously used for the one-pot synthesis of amine building blocks relevant for medicinal chemistry.

Experimental Section

General. All reagents and solvents were purchased from commercial sources and were utilized without further purification. Microwave (MW) irradiation experiments were carried out in a monomode CEM-Discover MW reactor, using the standard configuration as delivered, including proprietary software. The experiments were executed in 10 mL MW process vials, with control of the temperature by infrared detection. After completion of the reaction, the vial was cooled to 50 °C by air jet cooling. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature, in the solvent indicated, with a Varian Mercury Plus spectrometer (Agilent Technologies, Santa Clara, CA, USA) at a frequency of 400 (^{1}H) or 100 MHz (^{13}C) and are reported in parts per million (ppm). Chemical shifts are given on the δ-scale relative to the residual solvent signal as an internal reference. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q=quartet, qn=quintet, m = multiplet, dd = doublet of doublets, dm = doublet of multiplets, tm = triplet of multiplets, and br = broad. For structure elucidation, one-dimensional ^{1}H, ^{13}C, DEPT, two-dimensional ^{1}H-^{1}H-COSY, ^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC measurements were run. Reactions were monitored by a Shimadzu LC-MS 2020 system. Preparative HPLC was applied for purification in several cases using an Armen SPOT Prep II instrument with UV detector (200-600 nm scan) equipped with a Phenomenex Gemini C_{18}, 250×50.00 mm; 10 µm, 110A column. Gradient elution was employed using 0.08 g NH_4HCO_3 in 1 L water (A) and acetonitrile (B) or 2 mL TFA in 1 L water (A) and acetonitrile (B) as eluent systems, using the gradient method.

Theoretical calculations. Gaussian 16 program package (G16),[38] using default convergence criteria was used, respectively. Computations were carried out at M06-2X/6-31G(d,p) level of theory[39]. The method and basis sets were chosen for their reliability shown in earlier studies.[40] The vibrational frequencies were computed at the same levels of theory as used for geometry optimization to properly confirm that all structures reside at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions, such as energy (U), enthalpy (H), Gibbs free energy (G), and entropy (S) were computed for 398.15 K, using the quantum chemical, rather than the conventional thermodynamic reference state.

NMR monitoring experiments. In a typical experiment, 20 µL (0.30 mmol) azetidine was dissolved in 0.6 mL deuterated solvent. The respective Lewis or Bronsted acid catalyst was added as relevant, and the mixture was stirred at the indicated temperature. At specific time points (typically 0, 24, 48, 72 h), ^{1}H NMR spectra were recorded, whereas at the end of the experiment, one-dimensional ^{1}H, ^{13}C, DEPT, two-dimensional ^{1}H-^{1}H-COSY, ^{1}H-^{13}C-HSQC, ^{1}H-^{13}C-HMBC measurements were run for structure elucidation.

General procedure for the synthesis of 5-/7-amino-2-methylquinolines. 333 mg (1.5 mmol, 1.25 equiv.) 5- or 7-bromo-2-methylquinoline was dissolved in 5 mL toluene and 1.20 mmol (1 equiv.) of 3-(azetidin-1-yl)propan-1-amine (137 mg) was added to the solution. The solution was transferred into a closed microwave reaction tube equipped with a stir bar and 216 mg (2.25 mmol, 1.9 equiv.) NaO^tBu, 47 mg (0.08 mmol, 0.07 equiv.) rac-BINAP and 28 mg $Pddba_2$ (0.05 mmol, 0.04 equiv.) were also added to it. The tube was flushed with Argon and the reaction mixture was heated to 120 °C as fast as possible, then stirred at that temperature for 4 hours. After cooling to room temperature, the mixtures were diluted with 15 mL DCM and extracted with water (3 × 15 mL). The organic phase was washed with brine (15 mL) and dried over $MgSO_4$, then concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate gradient).

***N*-[3-(Azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (3).** Yellow oil, 96 mg (22%). ^{1}H NMR (δ, ppm (*J*, Hz), CD_3OD): δ_H 9.15 (d, *J* 9.0 Hz, 1H), 7.80 (t, *J* 8.4 Hz, 1H), 7.63 (d, *J* 8.9 Hz, 1H), 7.24 (d, *J* 8.4 Hz, 1H), 6.82 (d, *J* 7.8 Hz, 1H), 4.32-4.22 (m, 2H), 4.10 (q, *J* 10.0 Hz, 2 H), 3.43 (d, *J* 6.6 Hz, 2H), (3.38, dd, *J* 9.4, 6.1 Hz, 2H), 2.90 (s, 3H), 2.66-2.53 (m, 1H), 2.48-2.36 (m, 1H), 2.02 (qn, *J* 7.2 Hz, 2H). ^{13}C NMR (δ, ppm, CD_3OD): δc 157.7, 147.1, 142.0, 140.6, 137.7, 121.0, 118.7, 106.9, 106.7, 55.6, 53.9, 41.2, 24.3, 20.3, 17.1.

***N*-[3-(Azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (4).** Yellow oil, 90 mg (20%). ^{1}H NMR (δ, ppm (*J*, Hz), CD_3OD): δ_H 8.57 (d, *J* 7.8, 1H), 7.90 (d, *J* 8.8 Hz, 1H), 7.38 (d, *J* 8.0 Hz, 1H), 7.29 (dd, *J* 8.4, 2.4 Hz, 1H), 6.92 (s, 1H), 4.40-4.30 (m, 2H), 4.18 (q, *J* 9.6 Hz, 2H), 3.49-3.35 (m, 4H), 2.87 (s, 3H), 2.75-2.59 (m, 1H), 2.57-2.43 (m, 1H), 2.10-1.99 (m, 2H). ^{13}C NMR (δ, ppm, CD_3OD): δc 155.4, 155.3, 145.6, 143.3, 131.0, 122.5, 122.1, 117.8, 93.7, 55.7, 53.8, 40.8, 24.5, 20.2, 17.1.

Azetidine dimerization on synthetic scale (A). Azetidine (506 µL, 7.5 mmol, 1.0 eq) was dissolved in 15 mL DMSO-d_6 (to allow NMR monitoring of the process), followed by the addition of trifluoroacetic acid (287 µL, 3.75 mmol, 0.5 eq). The reaction mixture was stirred at 50 °C for 72 h (3-(azetidin-1-yl)propan-1-amine > 90%, Supplementary material, Figure S11). The obtained DMSO-d_6 solution was used directly for the synthetic experiments.

Azetidine dimerization on synthetic scale (B). Azetidine (2.02 mL, 30 mmol, 1.0 eq) was dissolved in 60 mL CH_3CN, followed by the addition of trifluoroacetic acid (1.15 mL, 15 mmol, 0.5 eq). The reaction mixture was stirred at 50°C for 72 h, then the solvent was removed under reduced pressure, resulting in a ~70% pure form of **7** (quant). Analytically pure sample could be obtained by treating the CH_3CN solution of **7** with trimethylamine (5 eq), removing the volatiles under reduced pressure and vacuum distillation.[36] (Supplementary material, Figure S12,S13).

Preparation of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (10). To 5 mL DMSO-d_6 solution of 3-(azetidin-1-yl)propan-1-amine (1.25 mmol) and trifluoroacetic acid (1.25 mmol), potassium carbonate (214 mg, 1.55 mmol, 1.25 eq) and 1-fluoro-2-nitrobenzene (163 µL, 1.55 mmol, 1.25 eq) were added and the mixture was stirred at ambient temperature for 48 h (LC-MS showing full conversion). The product was isolated by preparative HPLC. Gradient: 12-41% TFA-water/MeCN, UV: 225 nm.

***N*-[3-(Azetidin-1-yl)propyl]-2-nitroaniline TFA salt.** 189 mg orange oil (43%). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 12.48 (br s, 1H), 8.06 (d, *J* 6.0 Hz, 1H); 7.98 (br s, 1H); 7.40 (t, *J* 8.4 Hz, 1H); 6.80 (d, *J* 8.4 Hz, 1H); 6.62 (t, *J* 8.0 Hz, 1H); 4.43-4.22 (m, 2H); 3.96-3.76 (m, 2H); 3.41 (t, *J* 6.8 Hz, 2H); 3.32-3.15 (m, 2H); 2.75-2.58 (m, 1H); 2.44-2.30

(m, 1H); 1.99 (qn, *J* 6.4 Hz, 2H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 144.8; 136.5; 131.9; 126.7; 115.9; 113.5; 54.1; 52.8; 39.4; 23.8, 16.0.

Preparation of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (12). To 5 mL DMSO-d_6 solution of 3-(azetidin-1-yl)propan-1-amine (1.25 mmol) and trifluoroacetic acid (1.25 mmol), 1-(4-fluorobenzoyl)piperidine-4-carboxylic acid (389 mg, 1.55 mmol, 1.25 eq), HATU (589 mg, 1.55 mmol, 1.25 eq) and *N,N*-diisopropylethylamine (5.38 µl, 3.09 mmol, 2.5 eq) were added and the mixture was stirred at ambient temperature for 48 h (LC-MS showing full conversion). The product was isolated by preparative HPLC. Gradient: 24-54% TFA-water/MeCN, UV: 253 nm.
***N*-[3-(Azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt.** 232 mg (50%), yellow oil. ^{1}H NMR (δ, ppm (*J*, Hz), CD_3OD): δ_H 7.49-7.43 (m, 2H); 7.20 (tm, *J* 7.2 Hz, 2H); 4.32-4.18 (m, 2H); 4.05 (q, *J* 11.1 2H); 3.86-3.64 (m, 2H); 3.34-3.05 (m, 2H); 3.23 (t, *J* 6.6 Hz, 2H); 3.17 (t, *J* 7.6 Hz, 2H); 2.53 (m, 2H); 2.46-2.35 (m, 1H); 2.02-1.55 (m, 4H); 1.74 (qn, *J* 6.4 Hz, 2H). ^{13}C NMR (δ, ppm (*J*, Hz), CD_3OD): δc 177.7; 171.5; 164.8 (d, *J* 247 Hz); 133.2 (d, *J* 4 Hz); 130.4 (d, *J* 9 Hz); 116.6 (d, *J* 22 Hz); 55.7; 53.7; 48.6; 43.7; 36.8; 30.0; 25.8; 17.1.

Pyrrolidine aminopropylation in synthetic scale. Azetidine (506 µL, 7.5 mmol, 1.0 eq) and pyrrolidine (613 µL, 7.5 mmol, 1.0 eq) were dissolved in 15 mL DMSO-d_6 (to allow NMR monitoring of the process), followed by the addition of trifluoroacetic acid (287 µL, 3.75 mmol, 0.5 eq). The reaction mixture was stirred at 50°C for 72 h. The obtained DMSO-d_6 solution was used directly for the synthetic experiments.

Preparation of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole, *N*-[3-(azetidin-1-yl)propyl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide* and 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide. To 5 mL DMSO-d_6 solution of pyrrolidine, 3-(azetidin-1-yl)propan-1-amine, 3-(pyrrolidin-1-yl)propan-1-amine (18.5:21.1:60.4%) and trifluoroacetic acid (1.25 mmol), DIPEA (435 µL, 2.5 mmol, 2.0 eq)** and 5-chloro-3a*H*-thieno[2,3-*b*]pyrrole-4-sulfonyl chloride (321 mg, 1.25 mmol, 1.0 eq)** were added and the mixture was stirred at ambient temperature for 48 h. The crude reaction mixture was injected directly onto preparative HPLC for purification. Gradient: 20-50% TFA-water/MeCN, UV: 265 nm.
N-[3-(azetidin-1-yl)propyl]-6-chloroimidazo[2,1-b][1,3]thiazole-5-sulfonamide (16**) was detected by LC-MS in the reaction mixture but was not isolated*
***calculated for 100% (1.25 mmol) 3-(pyrrolidin-1-yl)propan-1-amine theoretical yield*

6-Chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (15). Yellow solid, 46 mg (13% for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 7.96 (d, *J* 4.2 Hz, 1H), 7.04 (d, *J* 4.0 Hz, 1H), 3.46-3.33 (m, 4H), 1.96-1.81 (m, 4H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 149.6, 137.2, 120.6, 118.7, 114.1, 47.9, 25.4.

6-Chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (17). 40 mg colourless oil (7% for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 7.89 (d, *J* 4.4 Hz, 1H), 7.07 (d, *J* 4.4 Hz, 1H), 3.78-3.64 (m, 2H), 3.26 (q, *J* 6.7 Hz, 2H), 3.13 (t, *J* 4.1 Hz, 2H), 2.94-2.82 (m, 2H), 2.15-1.97 (m, 6H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 149.8, 137.1, 120.4, 118.6, 114.4, 54.0, 52.6, 39.5, 25.8, 23.1.

Preparation of (pyrrolidin-1-yl)(quinolin-2-yl)methanone, *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide and *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide. To 5 mL DMSO-d_6 solution of pyrrolidine, 3-(azetidin-1-yl)propan-1-amine, 3-(pyrrolidin-1-yl)propan-1-amine (18.5:21.1:60.4%) and trifluoroacetic acid (1.25 mmol), DIPEA (522 µL, 3.0 mmol, 2.4 eq)*, HATU (713 mg, 1.88 mmol, 1.5 eq)* and quinoline-2-carboxylic acid (390 mg, 2.25 mmol,

1.8 eq)* were added and the mixture was stirred at ambient temperature for 48 h. The crude reaction mixture was injected directly onto preparative HPLC for purification. Gradient: 23-53% TFA-water/MeCN, UV: 296 nm.
**calculated for 100% (1.25 mmol) 3-(pyrrolidin-1-yl)propan-1-amine theoretical yield*

(Pyrrolidin-1-yl)(quinolin-2-yl)methanone (19). Colourless oil 48 mg (8 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 8.22 (d, *J* 8.4 Hz, 1H), 8.08 (d, *J* 7.6 Hz, 1H), 7.89 (d, *J* 8.8 Hz, 1H), 7.82 (d, *J* 8.0 Hz, 1H), 7.72 (tm, *J* 7.2 Hz, 1H), 7.57 (tm, *J* 8.0 Hz, 1H), 3.89-3.82 (m, 2H), 3.77-3.69 (m, 2H), 2.01-1.87 (m, 4H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 166.5, 154.1, 146.4, 136.7, 129.8, 129.6, 128.1, 127.5, 127.5, 120.7, 49.2, 46.8, 26.5, 24.0.

***N*-[3-(Azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (20).** Colourless oil 35 mg (7 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), CD_3OD): δ_H 8.45 (d, *J* 8.7 Hz, 1H), 8.18 (d, *J* 8.0 Hz, 1H), 8.15 (d, *J* 7.8 Hz, 1H), 7.98 (d, *J* 8.2 Hz, 1H), 7.82 (tm, *J* 7.6 Hz, 1H), 7.67 (tm, *J* 7.8 Hz, 1H), 4.17 (t, *J* 7.8 Hz, 4H), 3.57 (t, *J* 6.3 Hz, 2H), 3.29 (t, *J* 7.0 Hz, 2H), 2.50 (qn, *J* 7.2 Hz, 2H), 1.94 (qn, *J* 7.2 Hz, 2H). ^{13}C NMR (δ, ppm, CD_3OD): δc 167.5, 150.7, 148.0, 138.9, 131.5, 130.7, 130.6, 129.4, 129.0, 119.5, 55.7, 53.9, 37.3, 26.1, 17.1.

***N*-[3-(Pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (21).** Colourless oil 274 mg (55 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 8.74 (t, *J* 6.4 Hz, 1H), 8.19 (d, *J* 8.0 Hz, 1H), 8.07 (d, *J* 8.5 Hz, 1H), 8.04 (d, *J* 9.3 Hz, 1H), 7.75 (d, *J* 8.2 Hz, 1H), 7.67 (t, *J* 7.4 Hz, 1H), 7.52 (t, *J* 7.2 Hz, 1H), 3.85-2.70 (m, 4H), 3.58 (q, *J* 5.9 Hz, 2H), 3.21 (t, *J* 6.8 Hz, 2H), 2.10 (qn, *J* 6.0 Hz, 2H), 2.19-1.90 (m, 4H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 166.6, 148.1, 146.3, 137.6, 130.3, 129.7, 129.2, 128.2, 127.6, 118.8, 54.0, 52.3, 35.9, 26.1, 22.9.

Preparation of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone, *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide and *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide. To 5 mL DMSO-d_6 solution of pyrrolidine, 3-(azetidin-1-yl)propan-1-amine, 3-(pyrrolidin-1-yl)propan-1-amine (18.5:21.1:60.4%) and trifluoroacetic acid (1.25 mmol), DIPEA (522 µL, 3.0 mmol, 2.4 eq)*, HATU (713 mg, 1.88 mmol, 1.5 eq)* and [1,1'-biphenyl]-4-carboxylic acid (496 mg, 2.50 mmol, 2.0 eq)* were added and the mixture was stirred at ambient temperature for 48 h. The crude reaction mixture was injected directly onto preparative HPLC for purification. Gradient: 32-62% TFA-water/MeCN, UV: 260 nm.
**calculated for 100% (1.25 mmol) 3-(pyrrolidin-1-yl)propan-1-amine theoretical yield*

([1,1'-Biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (23). Grey solid 125 mg (20 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 7.62-7.60 (m, 6H), 7.45 (t, *J* 7.5 Hz, 2H), 7.37 (t, *J* 7.1 Hz, 1H), 3.67 (t, *J* 6.8 Hz, 2H), 3.50 (t, *J* 7.2 Hz, 2H), 1.98 (qn, *J* 6.7 Hz, 2H), 1.89 (qn, *J* 6.4 Hz, 2H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 169.5, 142.6, 140.3, 135.9, 128.8, 127.7, 127.7, 127.1, 126.9, 49.6, 46.2, 26.4, 24.4.

***N*-[3-(Azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (24).** White solid 9 mg (2 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), CD_3OD): δ_H 7.93 (d, *J* 8.4 Hz, 2H), 7.73 (d, *J* 8.5 Hz, 2H), 7.67 (d, *J* 7.2 Hz, 2H), 7.47 (t, *J* 7.0 Hz, 2H), 7.38 (t, *J* 7.3 Hz, 1H), 4.05 (t, *J* 8.1 Hz, 4H), 3.47 (t, *J* 6.7 Hz, 2H), 3.17 (t, *J* 7.4 Hz), 2.46 (qn, *J* 7.9 Hz, 2H), 1.87 (qn, *J* 6.7 Hz, 2H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 170.3, 145.9, 141.2, 133.9, 130.1, 129.2, 129.0, 128.1, 128.1, 55.8, 54.5, 37.8, 26.4, 17.3

***N*-[3-(Pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (25).** Brown solid 78 mg (15 % for 2 steps). ^{1}H NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ_H 7.96 (d, *J* 8.5 Hz, 2H), 7.93 (t, *J* 7.0 Hz, 1H), 7.64 (d, *J* 8.5 Hz, 2H), 7.59 (d, *J* 6.9 Hz, 2H), 7.44 (t, *J* 7.7 Hz, 2H), 2H 7.37 (t, J 7.4 Hz, 1H), 3.77-3.65 (m, 2H), 3.58 (q, *J* 6.0 Hz, 2H), 3.21 (q, *J* 6.7 Hz, 2H), 2.94-2.80 (m, 2H), 2.20-2.03 (m, 6H). ^{13}C NMR (δ, ppm, $CDCl_3$): δc 168.4, 144.5, 139.9, 131.8, 128.9, 128.0, 127.8, 127.2, 127.1, 53.7, 52.6, 36.5, 25.6, 23.1.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra, mass spectra and HPLC are provided in the Supplementary Material associated with this paper.

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