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Discovery of novel positive allosteric modulators of the α7 nicotinic acetylcholine receptor: Scaffold hopping approach

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ABSTRACT

The paper focuses on the scaffold hopping-based discovery and characterization of novel nicotinic alpha 7 receptor positive modulator (α7 nAChR PAM) ligands around the reference molecule (A-867744). First, substantial efforts were carried out to assess the importance of the various pharmacophoric elements on the *in vitro* potency (SAR evaluation) by chemical modifications. Subsequently, several new derivatives with versatile, heteroaromatic central cores were synthesized and characterized. A promising, pyrazole-containing new chemotype with good physicochemical and *in vitro* parameters was identified. Retrospective analysis based on homology modeling was also carried out. Besides its favorable *in vitro* characteristics, the most advanced derivative **69** also showed *in vivo* efficacy in a rodent model of cognition (scopolamine-induced amnesia in the mouse place recognition test) and acceptable pharmacokinetic properties. Based on the *in vivo* data, the resulting molecule with advanced drug-like characteristics has the possibility to improve cognitive performance in a biologically relevant dose range, further strengthening the view of the supportive role of α7 nACh receptors in the cognitive processes.

1. Introduction

Cognition, a highly complex function of the central nervous system (CNS) consists of various domains (*e.g.* learning, memory, attention, executive functions, etc.). Marketed drugs targeting cognitive functions (*e.g.* cholinesterase inhibitors) traditionally focus on enhancing the cholinergic neurotransmission. The neurotransmitter acetylcholine (ACh) exerts its biological functions through binding to muscarinic (mAChR) and/or nicotinic (nAChR) acetylcholine receptors. nAChRs, members of the pentameric ligand-gated ion channel superfamily are made up of five subunits [1,2] and divided into two groups, based on their amino acid sequences: one containing α, and another containing β subunits. Pentameric assemblies of various subunit compositions result in different nicotinic receptor subtypes with distinct pharmacological characteristics. The most predominant nAChR subtypes in the CNS are the $(\alpha4)_2(\beta2)_3$ and the homopentameric $(\alpha7)_5$ receptors [2]. Given that α7 nAChRs, a major nicotinic receptor subtype in the rat [3,4] and human [5] brain are abundantly expressed in the so-called "areas of cognition" (the prefrontal cortex [6,7], the hippocampus and other subcortical limbic structures [8,9]), activity changes of the α7 nAChRs have been implicated in a number of related conditions such as learning and memory disfunctions and other cognitive deficits as well. Procognitive role of α7 nAChR ligands are supported by *in vivo* studies in rodents [10,11] and non-human

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primates [12] as well as in humans [13,14]. As the specific distribution of α7 nAChRs in brain areas associated with cognition and the association of CHRNA7 gene with inhibitory sensory gating deficit in patients with schizophrenia suggests that activation of the nAChRs may play a role in the treatment of schizophrenia.

Activation of the nAChR ion channel is primarily controlled by ligand binding to the conventional agonist binding site. It is, however, also regulated by either negative or positive allosteric modulators (NAMs and PAMs). Allosteric model of nAChR activation involves at least a resting and an activated state as well as a desensitized state. Although the α7 nAChR is characterized by fast activation kinetics and high permeability to Ca^{2+} ions compared to other nAChR subtypes [15], it also exhibits rapid desensitization following exposure to orthosteric agonists [16–18]. Desensitization, therefore, limits the extent of agonist action, resulting in the insensitivity of the receptor to further stimulation. Suboptimal efficacy of the various α7 nAChR-selective agonists and partial agonists in clinical trials may well be attributed to this desensitization-induced receptor loss-of-function.

The phenomenon of rapid receptor desensitization and the subsequent insensitivity to stimulation can be overwhelmed by the application of PAMs by enhancing the endogenous agonist-induced receptor activation. Furthermore, selectivity issues often experienced with α7 nAChR agonists (especially towards 5-HT_3 receptors) are not usually reported for PAMs. Positive modulation of α7 nAChRs has been shown to have cognitive benefits in various preclinical models [19,20] and investigated extensively in clinical trials. The specific localization of α7 nAChRs in brain "cognitive areas", the positive modulation aiming at the inhibition of α7 nAChR channel desensitization and the advanced features of α7-selective nAChR ligands may lead to the development of clinically successful cognitive enhancers [14] (for representative structures, see Fig. 1, [21–23]).

The present paper aims at describing the synthetic activities at Gedeon Richter Plc. to discover novel positive modulators of the α7 nAChR. In the light of the limited knowledge on SAR from the available patents and scientific literature, generation of such compounds with sufficient potency and selectivity is a highly challenging task. Therefore, various complementary approaches (such as scaffold hopping, HTS and virtual screening) were utilized in a parallel manner to identify novel PAM compounds with significant affinity to the α7 nAChR. The focus of the present paper was put on the scaffold hopping approach applied on the selected **A-867744 (1)** reference structure. As a result, 8 chemotypes with various central cores were identified and characterized. Their general formulas or representative chemical structures can be seen in Fig. 2.

2. Results and discussions

2.1. Chemistry

2.1.1. Synthesis of compounds *1*–*36* with 1,5-diarylpyrrole central cores

The pyrrole-centered derivatives **1**, **3**, **10**–**33** were synthesized according to the synthesis depicted in Refs. [24,25]. In cases, where the synthesis was different (**2**, **4**, **5**, **6**, **7**, **8**, **9**, **34**, **35**, **36**) the applied methods can be seen in Scheme 1. The chemical structures are shown in Table 1. Compound **2** was synthesized in a Vilsmeier-Haack acylation. The synthesis of **4** was started from a hydroxyketone **4**–**1**, which was oxidized with pyridinium chlorochromate to dioxo compound **4**–**2** and then it was cyclized to a pyrrole derivative **4**–**3** using sulfanylamide in acetic acid. After a Friedel-Crafts acylation (**4**–**4**) and amide hydrolysis **4** was obtained. Starting from the corresponding 2-cyano-4-oxobutanoate derivatives (**5**–**1, 35**–**1**) and reacting them with sulfanilamide and 4-iodoaniline, respectively, the amino-pyrrole ring formations were achieved (**29**, **35**–**2**). *tert*-Butyl nitrite was used for the removal of the amino moiety (**26**, **35**). After the ester hydrolysis of **26** and the acid chloride formation from **5**–**2**, the amide of *N*,*O*-dimethylhydroxylamine (**5**–**3**) was synthesized. Further reacted it according to the Weinreb-Nahm ketone synthesis with EtMgBr compound **5** was yielded. The *N*-methylated derivatives (**6**, **7**) were synthesized starting from compound **1** using the MeI/NaH reagent system in THF. Starting from diketone **8**–**1** using 1-benzylpiperidin-4-amine the pyrrole derivative **8**–**2** was isolated. The application of the Vilsmeier-Haack conditions resulted in acylated derivative **8**–**3** and after the benzyl deprotection (**8**–**4**) and piperidine *N*-amidation compound **8** was obtained. Intermediate **9**–**1** and compound **3** were acylated (Friedel-Crafts conditions) to afford **9** and **34**–**1**, **36**–**1**, respectively. After amide hydrolysis in **34**–**1**, compound **34** while after catalytic reduction of **36**–**1** and subsequent amide hydrolysis in **36**–**2**, compound **36** was obtained.

2.1.2. Synthesis of derivatives *38*–*39* and *52*–*86* with pyrazole central cores

The pyrazole-centered compound **37** was synthesized according to the method cited in reference [26]. General synthesis of 1,5-diaryl-pyrazole family was exemplified in cases of **39** and **69** depicted in Scheme 2. The chemical structures are shown in Table 4. The synthesis started from benzene-1-sulfonamide derivatives (**38**–**1**, **39**–**1**). After protection of the sulfonamide moiety in **38**–**1** with bis(4-methoxybenzyl) group or in **39**–**1** with (dimethylamino)methylidene by the reaction with DMF-DMA, the acyl groups of **38**–**1** and **39**–**2** were elongated by Claisen condensation with diethyl oxalate upon deprotonation with LiHMDS. Cyclization of dioxoester **38**–**3** and **39**–**3** with 4-chlorophenylhydrazine resulted in the regioisomeric mixture of corresponding pyrazols. In case of **38**–**3** only one regioisomer was isolated, which after deprotection led to **38**. While in case of the reaction of **39**–**3** the two isomers were separated (**39**–**4**, **39**–**5**). **39**–**4** was hydrolyzed to carboxylic acid **39**–**6**, which was then transformed to acyl chloride **39**–**7** as a key intermediate suitable for carboxamide formation including Weinreb-Nahm amid **39**–**8**. Grignard reaction of **39**–**8** with ethylmagnesium bromide afforded ketone **39**–**9**. Basic deprotection of (dimethylamino)methylidene derivatives (**39**–**9**) yielded **39**. In case of the amide product **69** intermediate **39**–**7** was amidated using 3-azabicyclo[3.1.0]hexane and the resulted **69**–**1** was deprotected to gain compound **69**. For the 3,5-diaryl-pyrazol family (**80**–**86**) the applied synthesis was the same, however, it was started from intermediate **39**–**5**. The chemical structures of **80**–**86** are shown in Table 5.

2.1.3. Synthesis of derivatives with differently substituted pyrrole (*40*–*42*) and pyrazole (*43*–*46*) central cores

The synthesis of the 4,5-diarylpyrrole derivatives **40**–**42** is depicted in Scheme 3. The chemical structures are shown in Table 2. According to the Weinreb-Nahm ketone synthesis the bis(4-methoxybenzyl) protected sulfonamide derivative of benzoic acid **40**–**1** was amidated, followed by a Grignard reaction resulting in ketone **40**–**3**. After alkylation (**40**–**4**) and ketal removal the aldehyde derivative **40**–**5** was obtained. In a microwave assisted cyclization reaction pyrrole derivative **40**–**6** was yielded, which was then either directly (**40**–**7**) or after N-methylation (**42**–**1**) was acylated (**42**–**2**). After PMB deprotection with TFA compounds **40** and **42** were obtained. (In case of **41** the same methodology was applied.) Synthesis of compounds **43**–**46** was exemplified in case of **43**. Having hydrolyzed the ester derivative **43**–**1** to carboxylic acid **43**–**2** the Weinreb-Nahm ketone synthesis was applied resulting in the amide (**43**–**3**) and subsequently the ketone (**43**–**4**) intermediates. After the removal of (dimethylamino)methylidene

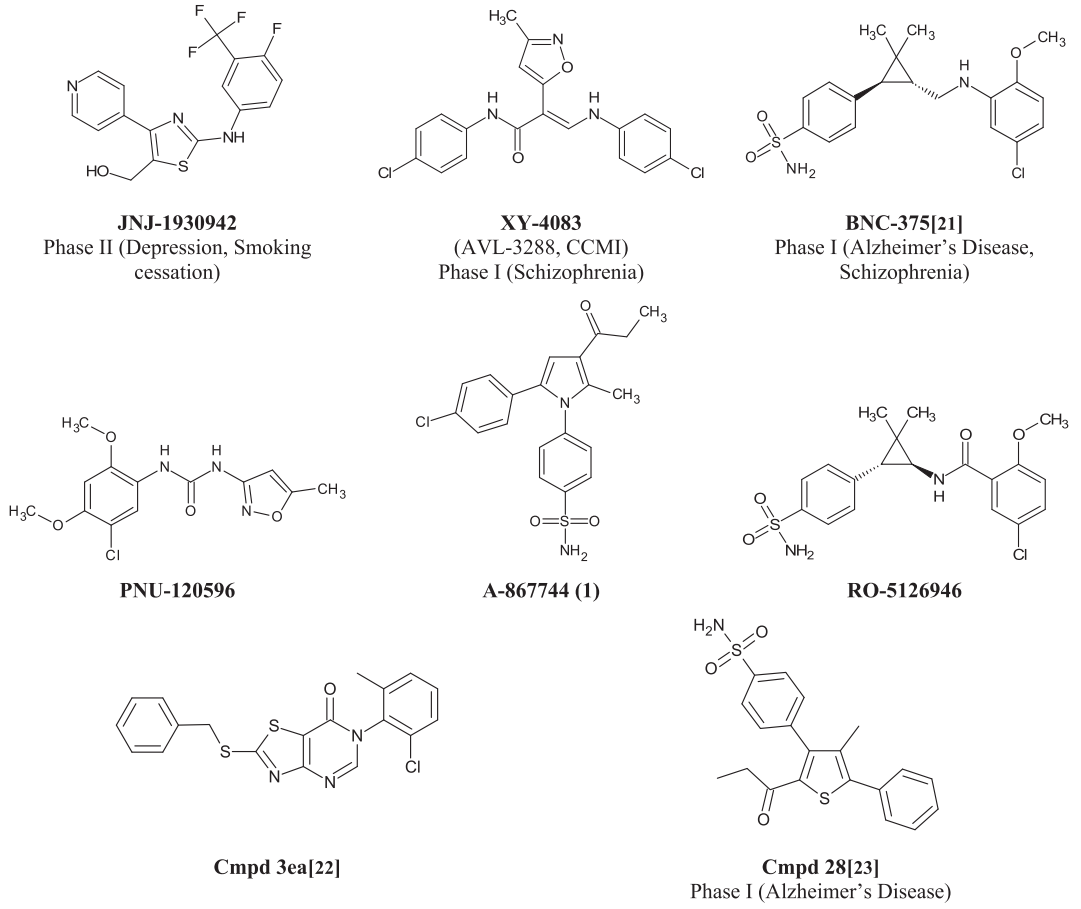


Fig. 1. PAM compounds with highly variable degree of inhibition of the agonist-evoked channel desensitization. If available, the clinical status and indication of the compounds are also indicated.

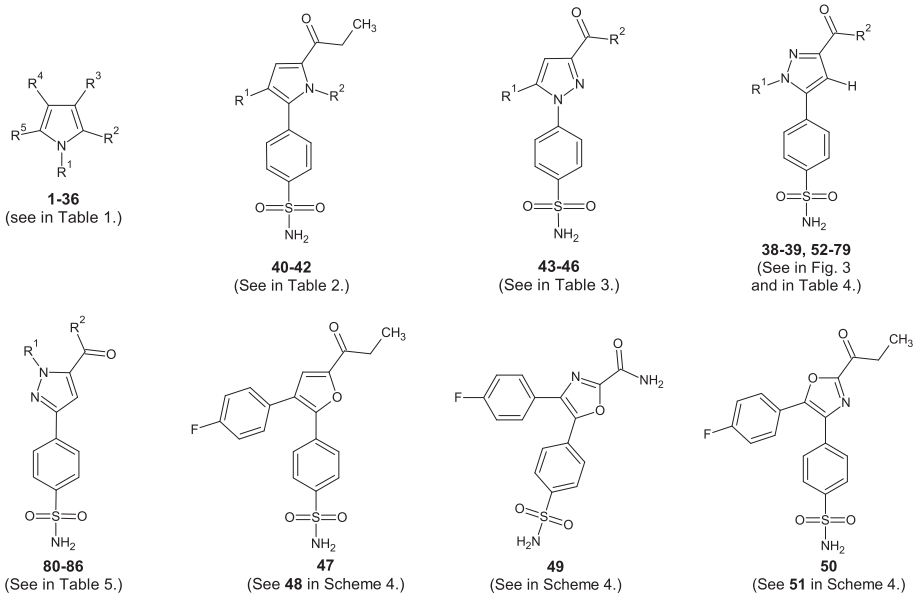
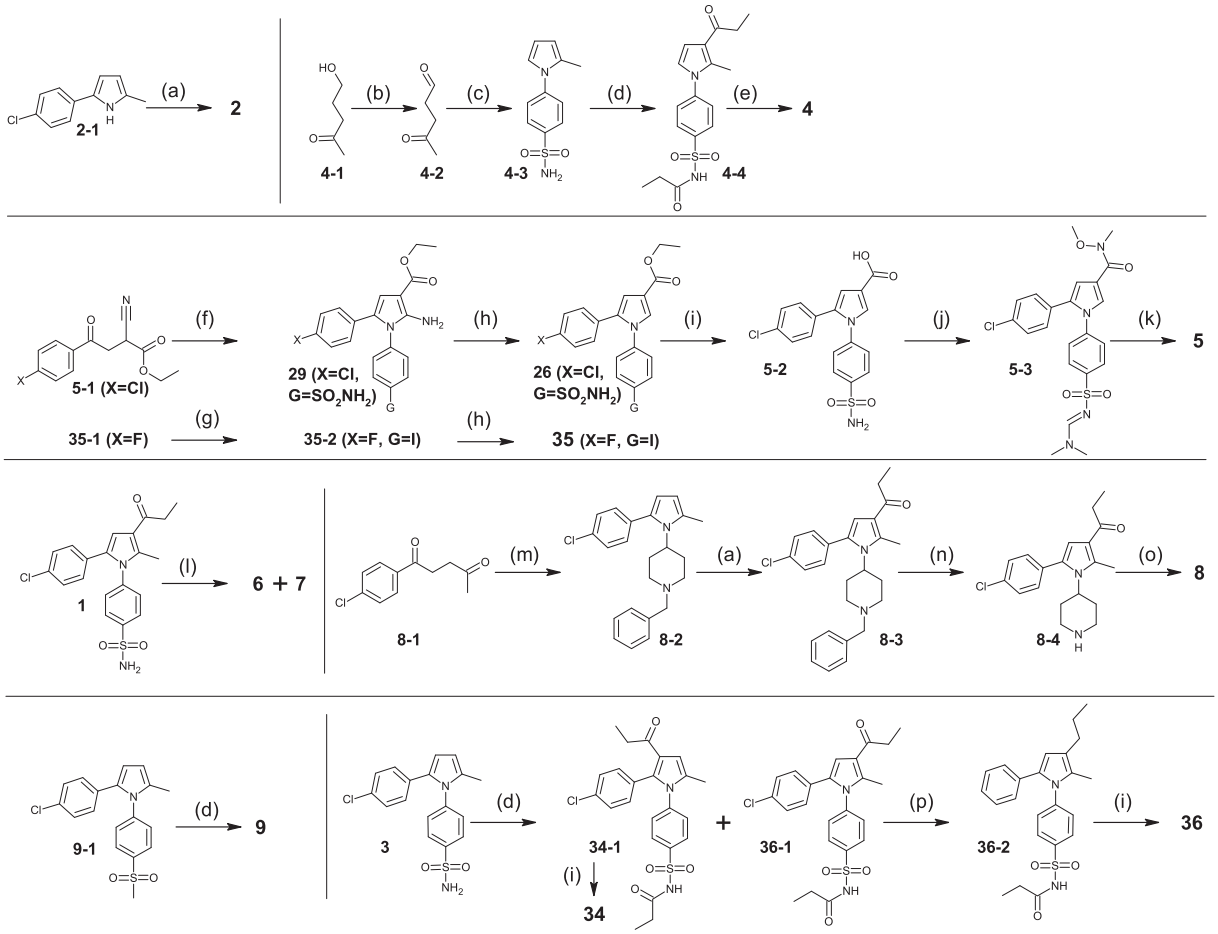


Fig. 2. General formulas and representative structures of the tested chemotypes.



Scheme 1. Synthesis of the derivatives **2**, **4**, **5**, **6**, **7**, **8**, **9**, **34**, **35**, **36**. Reagents and conditions: (a) $EtCON(Me)_2$, $POCl_3$, $ClCH_2CH_2Cl$, 0–80 °C; (b) PCC, CH_2Cl_2, rt; (c) sulfanylamide, AcOH, MeCN, rfx; (d) $(EtCO)_2O$, $AlCl_3$, $ClCH_2CH_2Cl$, 0 °C to rt; (e) NaOH, H_2O, rfx.; (f) sulfanylamide, cc HCl, rfx; (g) 4-iodoaniline, cc. HCl, rfx.; (h) ^tBuONO, DMF, 50 °C; (i) NaOH, H_2O, EtOH, rfx.; (j) 1. $(COCl)_2$, CH_2Cl_2, DMF, 2. MeHNOMe.HCl, CH_2Cl_2, Et_3N; (k) EtMgBr, THF, rfx.; (l) MeI, NaH, THF, rt.; (m) 1-benzylpiperidin-4-amine, toluene, AcOH, rfx; (n) $ClCOOCH_2CH_2Cl$, CH_2Cl_2, 0 °C to rt; (o) sulfamide, dioxane, rfx.; (p) H_2 (atm.), Pd/C, MeOH, THF, rt.

protecting group **43** was obtained. The chemical structures are shown in Table 3.

2.1.4. Synthesis of derivatives with furan (*47*, *48*) or oxazole (*49*–*51*) central cores

Syntheses of derivatives with furan (**47**, **48**) or oxazole (**49**–**51**) central cores are depicted in Scheme 4. For the furyl compounds, the starting material ester **47**–**1** was condensed with a 4-fluorophenylacetonitril into **47**–**2**, which was then *O*-alkylated with 1-bromobutan-2-one. The resulting **47**–**3** was cyclized into the aminofuryl derivative **47**–**4**. It was either directly deprotected forming compound **48** or the amino moiety was first removed by *tert*-butyl nitrite and after then the PMB deprotection resulted in compound **47**. The oxazole compound **49** was synthesized from **49**–**1** oxime reacted with ethyl oxalyl chloride to obtain **49**–**2** ester. It was reacted with chlorosulfuric acid and then with aqueous ammonia solution to derivative **49**. Similarly, compound **51** was synthesized from the oxime derivative **50**–**1** (which was formed from the ketone **40**–**3**) reacted with ethyl oxalyl chloride. Ester **51** was transformed to **50** according to the following reaction sequence: hydrolysis (**50**–**2**), Weinreb-Nahm ketone formation (**50**–**3**, **50**–**4**) and deprotection.

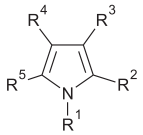
2.1.5. SAR evaluation of the derivatives of reference compound *1*

First, substantial efforts were carried out to assess the importance of the various pharmacophoric elements on the *in vitro* potency [27] (SAR evaluation) by chemically modifying compound **1**. Compounds were characterized for α7 nAChR PAM characteristics in α7 nAChR-expressing HEK293 cells by a functional $[Ca^{2+}]$ influx assay that is capable of detecting subtle $[Ca^{2+}]_i$ changes (it must also be noted that the assay is highly sensitive to the inhibition of desensitization). In addition to that kinetic solubility data measured by HPLC (in pH 7.4 phosphate-buffer with 1% DMSO) are summarized in Table 1.

Upon systematic removal of the substituents around the pyrrole central core, structures differing only in a single substituent from compound **1** were obtained. Somewhat surprisingly, removal of the R^1, R^3, R^5 substituents resulted in only inactive derivatives in the primary *in vitro* $[Ca^{2+}]_i$ assay (**2**–**4**), with the sole exception of the removal of the small R^2 methyl group (**5**). Beside this truncation, compound **1** was subjected to further systematic chemical modifications. Derivatives either with a single (**6**–**20**) or with multiple modifications (**21**–**36**) were synthesized and characterized. Unfortunately, the original 4-sulfamoylphenyl moiety (R^1) was not replaceable, since almost all modifications of this kind resulted in inactivity *in vitro* (**6**–**11**). Only certain modifications, such as in the R^3 (acetyl- and ester-derivatives, **12**–**13**) and R^5 groups (substitution pattern of phenyl group, **14**–**20**) yielded *in vitro* active compounds.

The analysis of these results further supported the steepness of SAR for α7 nAChR PAMs, already described in the scientific literature [28,29]. Therefore, establishing a continuous SAR seemed to be

Table 1
Systematically modified derivatives of A-867744 reference compound (**1**).



Comp.	R^1	R^2	R^3	R^4	R^5	Kin. sol. (μM)	$[Ca^{2+}]_i$ % response at 10 μM	$[Ca^{2+}]_i$ EC_{50} (μM)
1	4-sulfamoylphenyl	Me	EtCO	H	4-Cl-Ph	5.2	84	0.6
2	H	Me	EtCO	H	4-Cl-Ph	0.9	inact.	_
3	4-sulfamoylphenyl	Me	H	H	4-Cl-Ph	6.1	inact.	_
4	4-sulfamoylphenyl	Me	EtCO	H	H	100	inact.	_
5	4-sulfamoylphenyl	H	EtCO	H	4-Cl-Ph	19.5	100	0.4
6	4-(*N*-methylsulfamoyl)phenyl	Me	EtCO	H	4-Cl-Ph	8.7	inact.	_
7	4-(*N*,*N*-dimethylsulfamoyl)phenyl	Me	EtCO	H	4-Cl-Ph	1.2	inact.	_
8	N-sulfamoylpiperidine-1-yl	Me	EtCO	H	4-Cl-Ph	27.8	12	-
9	4-methylsulphonylphenyl	Me	EtCO	H	4-Cl-Ph	4.8	inact.	_
10	3-sulfamoylphenyl	Me	EtCO	H	4-Cl-Ph	0.2	inact.	_
11	indol-6-yl	Me	EtCO	H	4-Cl-Ph	5.1	inact.	_
12	4-sulfamoylphenyl	Me	MeCO	H	4-Cl-Ph	2.7	57	1.9
13	4-sulfamoylphenyl	Me	EtOCO	H	4-Cl-Ph	4.2	29	1.4
14	4-sulfamoylphenyl	Me	EtCO	H	Ph	14.1	74	1.7
15	4-sulfamoylphenyl	Me	EtCO	H	4-F-Ph	29.3	89	1.2
16	4-sulfamoylphenyl	Me	EtCO	H	4-MeO-Ph	12.8	86	1.3
17	4-sulfamoylphenyl	Me	EtCO	H	4-Me-Ph	1.0	93	1.2
18	4-sulfamoylphenyl	Me	EtCO	H	3-Cl-Ph	12.6	94	1.3
19	4-sulfamoylphenyl	Me	EtCO	H	2-Cl-Ph	38.2	97	3.1
20	4-sulfamoylphenyl	Me	EtCO	H	2,4-Di-Cl-Ph	7.7	89	2.3
21	4-sulfamoylphenyl	Me	EtOCO	H	4-F-Ph	12.6	49	0.7
22	4-sulfamoylphenyl	Me	EtOCO	H	4-MeO-Ph	16.1	46	1.0
23	4-sulfamoylphenyl	Me	EtOCO	H	3-Cl-Ph	9.2	51	2.1
24	4-sulfamoylphenyl	Me	EtOCO	H	2-Cl-Ph	13.7	55	3.5
25	4-sulfamoylphenyl	Me	EtOCO	H	4-Me-Ph	1.3	6%[a]	-
26	4-sulfamoylphenyl	H	EtOCO	H	4-Cl-Ph	10.8	99	0.3
27	4-sulfamoylphenyl	H	EtCO	H	4-F-Ph	63.0	100	1.1
28	4-sulfamoylphenyl	H	EtOCO	H	4-F-Ph	36.4	100	0.4
29	4-sulfamoylphenyl	NH_2	EtOCO	H	4-Cl-Ph	4.4	31	3.0
30	4-sulfamoylphenyl	NH_2	EtOCO	H	4-F-Ph	7.5	56	1.1
31	4-sulfamoylphenyl	Me	COOH	H	4-F-Ph	50	inact.	_
32	4-sulfamoylphenyl	Me	COOH	H	4-Me-Ph	10	inact.	_
33	4-sulfamoylphenyl	Me	COOH	H	3-Cl-Ph	100	inact.	_
34	4-sulfamoylphenyl	Me	H	EtCO	4-Cl-Ph	6.9	inact.	_
35	4-iodophenyl	H	EtOCO	H	4-F-Ph	0.3	inact.	_
36	4-sulfamoylphenyl	Me	nPr	H	Ph	3.8	inact.	_

[a] % measured @1 μM.

a highly difficult task, as subtle structural differences led to inactivity or significant activity loss.

As the next logical step, combination of the most useful structural elements led to several *in vitro* active compounds (**21**–**28**), alongside with two newly identified amine derivatives (in the position of R^2, **29**–**30**). However, use of carboxylic and propyl groups as R^3 (**31**–**33, 36**), propionyl as R^4 (**34**) or iodophenyl as R^2 (**35**) resulted again in loss of *in vitro* activity.

2.1.6. Identification of the new, pyrazole-based scaffold

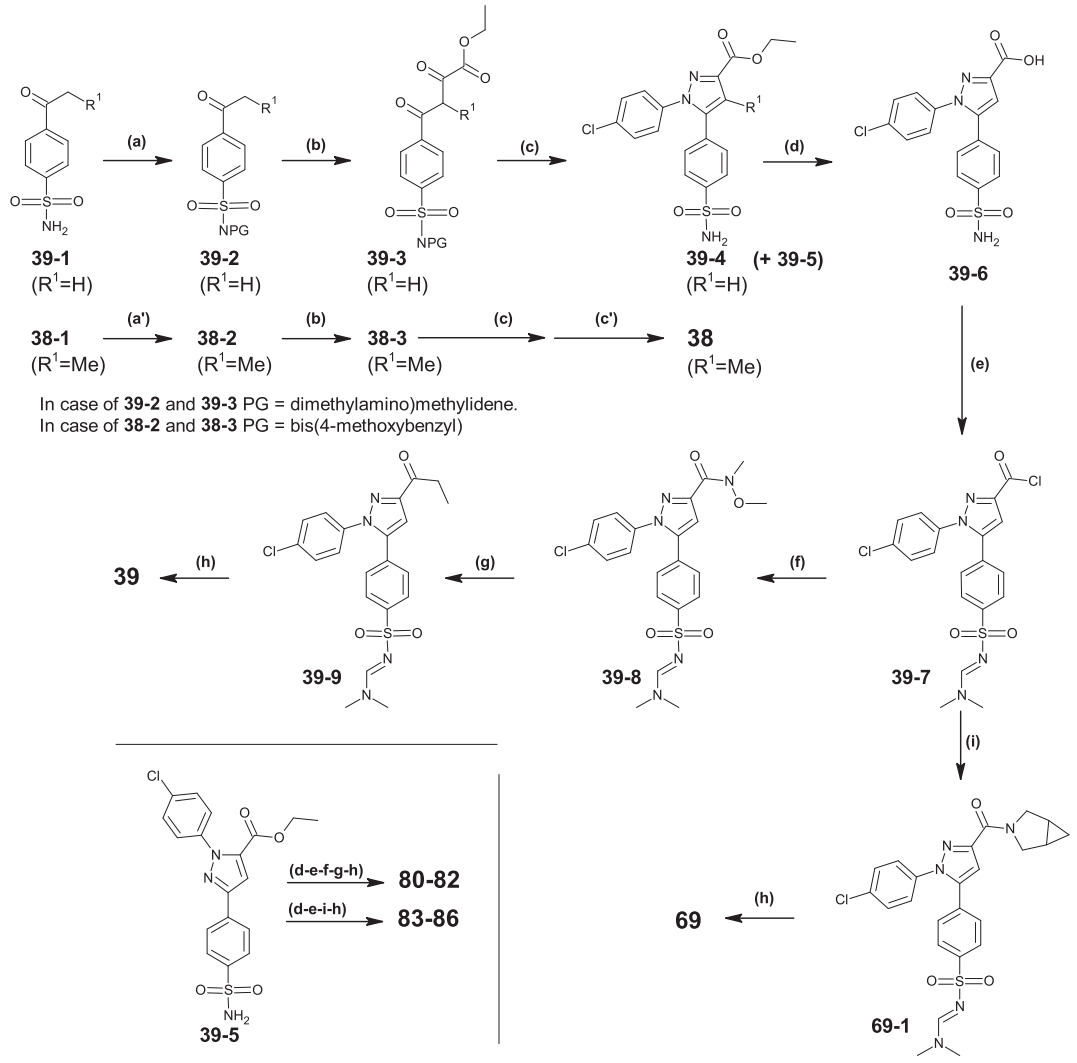
After thorough analysis of the obtained SAR of reference compound **1**, it was hypothesized that the correct substitution pattern around the central core is more important than the core structure itself. This hypothesis was tested by synthesizing new derivatives with versatile heteroaromatic rings as central cores. Since the only somewhat potent compound emerging from the virtual screen of the corporate compound collection was **37** possessing a pyrazole central core (a summary of the virtual screening can be seen in the Supplementary Data); the scaffold hopping approach was first tested using that pyrazole ring.

Merging compounds **13** and **37** resulted in compound **38**, which showed almost similar potency as the corresponding pyrrole compound **13** (Fig. 3.).

Considering the improved *in vitro* potency upon the elimination of the methyl group in the original pyrrole series (**5**), this modification was applied also in this novel sub-cluster. As a result, increased *in vitro* potency was detected with compound **39** compared to **38** (the PAM EC_{50} was improved from 2 to 0.5 μM in the primary $[Ca^{2+}]_i$ assay).

Based on this promising result, derivatives with other heteroaromatic rings were synthesized and characterized. As a result, several new chemotypes containing pyrrole, pyrazole, furan and oxazole rings were synthesized. Main characteristics of these derivatives are summarized in Table 2., Table 3.

Having analyzed the above *in vitro* data for the corresponding active derivatives with novel pyrrole and pyrazole central cores (**39** and **41** showed EC_{50} values of 0.5 and 1.0 μM, respectively, while **44** resulted in 11% enhancement at 10 μM), also, taking into



Scheme 2. Synthesis of compound **38**, **39** and **69**. Reagents and conditions: (a) DMF-DMA, DMF, EtOAc, rt; (a') 4-MeOBnCl, EtCOMe, NaI, K_2CO_3, rfx; (b) 1. LiHMDS, THF, −70 °C, 2. $(COOEt)_2$, −70 °C to rt; (c) 4-ClPhNHNH$_2$.HCl, EtOH, HCl, H_2O; (c') TFA, anisole, CH_2Cl_2, rt.; (d) KOH, H_2O, EtOH, rfx; (e) $(COCl)_2$, CH_2Cl_2, DMF, (f) MeHNOMe·HCl CH_2Cl_2, Et_3N; (g) EtMgBr, THF, rfx.; (h) KOH, MeOH, THF, rt; (i) 3-azabicyclo[3.1.0]hexane, CH_2Cl_2, Et_3N.

consideration the difficulties with the synthesis of the pyrrole ring system in the family of **41** as well as the narrow SAR in the chemotype of compound **44**, the conclusion was drawn that the pyrazole ring in compound **39** was the most favorable choice.

Furthermore, application of furan (**47**–**48**) and oxazole (**49**–**51**) rings as central cores were also attempted. The chemical structures and synthesis are shown in Scheme 4. Their synthesis, however, proved to be rather difficult and – somewhat surprisingly – none of the completed derivatives showed eligible *in vitro* activity. These results proved that despite our hypothesis, the central core may also exert some effect on the *in vitro* functional activity (one possible explanation is described later in section concerning *in silico* docking).

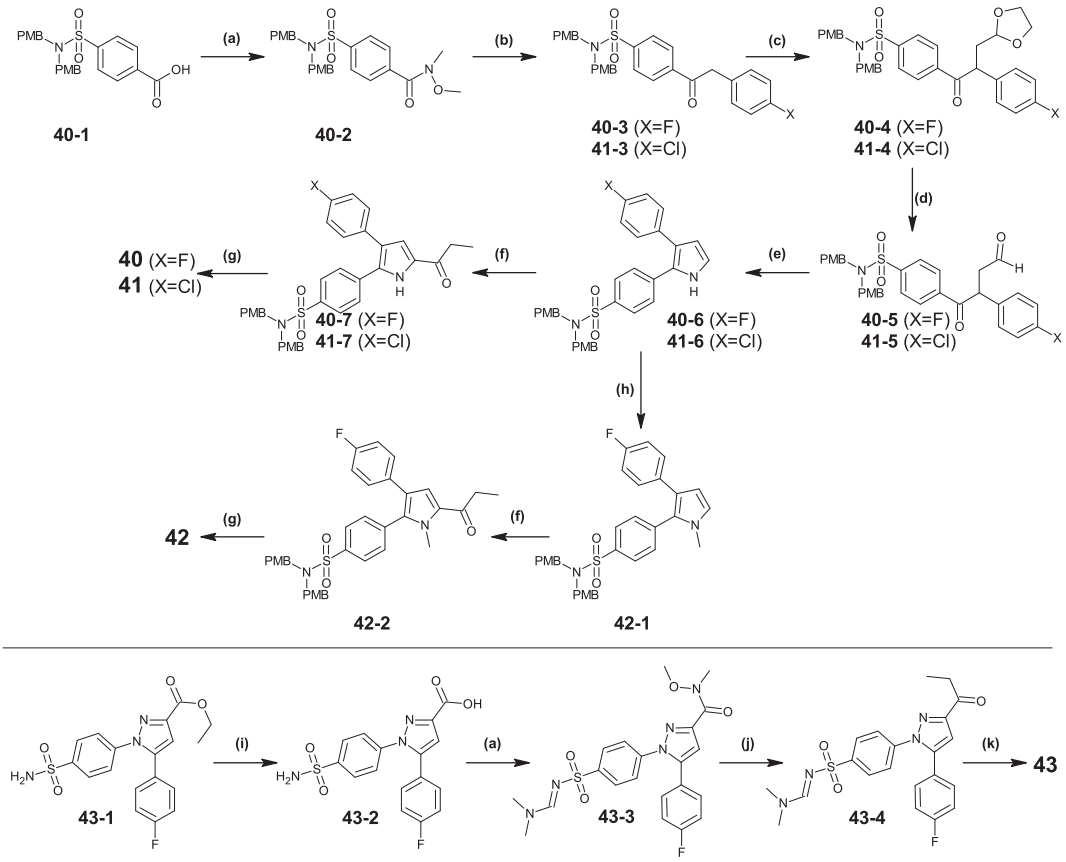
2.1.7. Optimization of the new chemotype

Based on the result above, all further optimization activities were carried out in the most favorable 1,5-diaryl-pyrazole compound family.

As we highlighted above, the experienced, steep SAR did not allow much space for additional optimization, therefore derivatives modified only in R^1 and R^2 positions were attempted to be synthesized (Table 4.). Results of the initial *in vitro* characterization of ketone and amide derivatives (R^1: alkyls or amines) are summarized in Table 4 below. Almost all synthesized ketones (**39** and **52**–**68**) proved to be potent *in vitro* in this series (however, with no improvement in potency). In contrast, almost half of the amides (**69**–**79**) showed inactivity in the primary *in vitro* assay. Regarding R^1 group the ethyl and 3-azabicyclo[3.1.0]hexane seemed to be the most favorable. As R^2 moiety the 4-chlorophenyl structural element seemed to be the most useful.

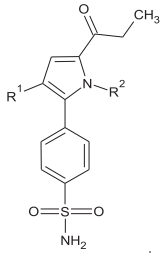
Based on the $[Ca^{2+}]_i$ data, the most potent ketone (**39**) and amide (**69**) compounds were chosen for detailed pharmacological characterization.

Results with the third, new pyrazole chemotype are summarized in Table 5. These derivatives derived from the 3,5-diaryl-pyrazol byproduct intermediate which was described in Scheme 4 (in that case **39**–**4**). Having further reacted these intermediates to the corresponding ketone and amide derivatives a new pyrazole compound family was identified. Unfortunately, apart from compound **80**, all synthesized analogues proved to be inactive.



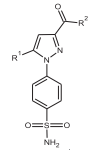
Scheme 3. Synthesis of compounds **40**–**42** and **43**. Reagents and conditions: (a) 1. $(COCl)_2$, CH_2Cl_2, DMF, 2. MeHNOMe.HCl, CH_2Cl_2, Et_3N; (b) 1. 4-F-BnCl or 4-Cl-BnBr, Mg, Et_2O, rt, 2. Weinreb amide, THF, rt; (c) 2-bromomethyl-1,3-dioxolane, NaH, THF, DMF, 0 °C to rfx; (d) HCl, H_2O, acetone, rt; (e) NH_4OAc, AcOH, 4 Å m. s., μW, 170 °C; (f) $EtCON(Me)_2$, $POCl_3$, $ClCH_2CH_2Cl$, 0–80 °C; (g) TFA, anisole, CH_2Cl_2, rt; (h) MeI, NaH, DMF, 0 °C to rt; (i) KOH, H_2O, EtOH, rfx; (a) 1. $(COCl)_2$, CH_2Cl_2, DMF, 2. MeHNOMe.HCl, CH_2Cl_2, Et_3N; (j) EtMgBr, THF, rfx; (k) KOH, MeOH, THF, rt.

Table 2
New, potent pyrrole derivatives.



Comp.	R^1	R^2	Kin. sol.(μM)	$[Ca^{2+}]_i$ % response at 10 μM	$[Ca^{2+}]_i$ EC_{50} (μM)
40	4-F-Ph	H	15.6	100	0.9
41	4-Cl-Ph	H	1.8	100	1.0
42	4-F-Ph	Me	1.4	77	2.2

Table 3
New, potent pyrazole derivatives.



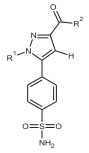
Comp.	R^1	R^2	Kin. sol. (μM)	$[Ca^{2+}]_i$ % response at 10 μM	$[Ca^{2+}]_i$ EC_{50} (μM)
43	4-F-Ph	Et	88.9	5	–
44	4-Cl-Ph	Et	37.8	11	–
45	4-F-Ph	EtO	56.4	90	7.4
46	4-Cl-Ph	EtO	53.3	95	2.0

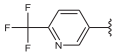
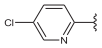
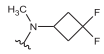
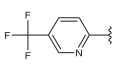
2.2. In silico evaluation

2.2.1. Retrospective analysis of the observed SAR

In order to attempt the retrospective analysis of the observed SAR, docking calculations were carried out based on a hypothesized binding mode. However, it should be noted that the process starting with the ligand binding event and leading to the functional behavior of the target protein is highly complex, so there is only indirect relationship between the binding position and the obtained functional readouts. So far, there has been no experimental 3D structures of the human α7 nAChR available in literature, however refined open- and closed-state homology models were reported with our reference compound **1** [30]. In our docking studies, the open-state homology model was used which contained compound **1** bound in the transmembrane region between the two α7 subunits (Fig. 4A and B.). This inter-subunit binding site, which was identified by Newcombe et al. in the course of a comprehensive docking study, differs from the earlier assumptions where an intra-subunit binding site was hypothesized [31]. According to our

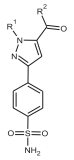
Table 4
1,5-diaryl-pyrazole derivatives.



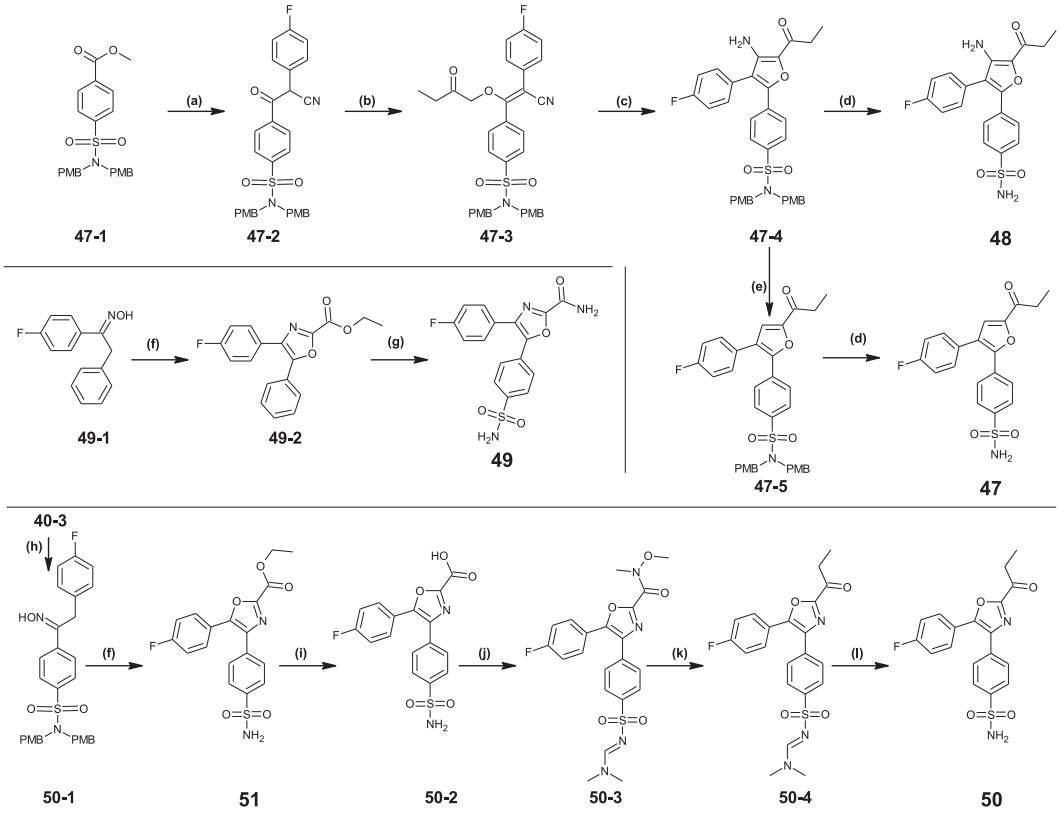
Compound	R^1	R^2	Kin. sol. (μM)	$[Ca^{2+}]_I$ % response at 10 μM	$[Ca^{2+}]_I$ EC_{50} (μM)
39	4-Cl-Ph	Et	41.9	84	0.5
52	4-Cl-Ph	Pr	25.8	100	1.1
53	4-Cl-Ph	Me	86.8	63	9.2
54	4-Cl-Ph	*t*Bu	6.6	29	_
55	4-Cl-Ph	iPr	_	10	_
56	4-Cl-Ph	cPr	25.6	28	_
57	4-Cl-Ph	cBu	17.2	51	2.5
58	4-Cl-Ph	cPe	4.6	18	_
59	4-Cl-Ph	cBuMe	4.3	89	2.5
60	4-Cl-Ph	cPeMe	2.6	23	_
61	4-CF_3-Ph	Et	7.5	100	0.9
62	4-F-Ph	Et	96.8	90	2.6
63	3-Cl-Ph	Et	6.9	73	5.8
64	2-Cl-Ph	Et	4.7	inact.	_
65	Ph	Et	47.2	33	_
66	4-MeO-Ph	Et	64.3	71	7.4
67		Et	99.4	75	5.9
68		Et	33.7	inact.	_
69	4-Cl-Ph		36.6	100	1.2
70	4-Cl-Ph		57.9	94	2.1
71	4-Cl-Ph		35.2	100	2.3
72	4-Cl-Ph		7.6	95	2.2
73	4-Cl-Ph		65.9	5	_
74	4-Cl-Ph		9.9	inact.	_
75	4-Cl-Ph		30.9	inact.	_
76	4-Cl-Ph		99.6	inact.	_
77	4-Cl-Ph		72.6	22	_
78	4-Cl-Ph		53.7	inact.	_
79			8.8	inact.	_

results, during the protein-ligand-complex refinement, a slightly modified binding pose was obtained (Fig. 4C.). In this binding mode the oxygen of the carbonyl seemed to be capable to form a hydrogen bond with the Ser-271/248 (sequence number in UniProt sequence P36544 and in the model of Newcombe et al. respectively [29]) and this interaction might explain the observed *in vitro* activity change in case of compounds **14** and **36**. After a visual inspection, it can be seen that the majority of the binding site had a lipophilic character, with the exception of that part, where the hydroxyl groups of Thr-300/277 and Tyr-296/273 were located. The

Table 5
3,5-diaryl-pyrazole derivatives..

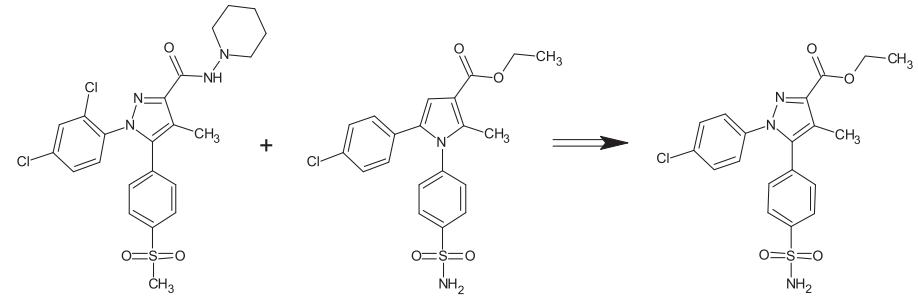


Compound	R^1	R^2	Kin. sol. (μM)	$[Ca^{2+}]_I$ % response at 10 μM	$[Ca^{2+}]_i$ EC_{50} (μM)
80	4-Cl-Ph	Et	49.6	100	1.0
81	3-Cl-Ph	Et	0.7	inact.	_
82	4-Cl-Ph	nPr	0.4	inact.	_
83	4-Cl-Ph		11.4	inact.	_
84	4-Cl-Ph		14.8	inact.	_
85	4-Cl-Ph		5.2	inact.	_
86	4-Cl-Ph		8.0	inact.	_



Scheme 4. Synthesis of compounds **47**–**51**. Reagents and conditions: (a) 4-F-PhCH$_2$CN, NaH, THF, rt to rfx; (b) 1-bromobutan-2-one, Et$_3$N, DMF, 50 °C; (c) NaOEt, EtOH, 100 °C; (d) TFA, anisole, CH$_2$Cl$_2$, rt; (e) *t*BuONO, DMF, 50 °C; (f) EtOOCCOCl, 120 °C; (g) 1. ClSO$_3$H, 0 °C to rt, 2. NH$_4$OH, H$_2$O, rt; (h) NH$_2$OH·HCl, NaOAc, EtOH, rfx; (i) KOH, H$_2$O, EtOH; (j) 1. (COCl)$_2$, CH$_2$Cl$_2$, DMF, 2. MeHNOMe.HCl, CH$_2$Cl$_2$, Et$_3$N; (k) EtMgBr, THF, rfx, (l) KOH, MeOH, THF, rt.

hydrophilicity of this region might be favorable for the polar sulfonamide moiety (R^1, in Table 1.). On the other hand, the environment around the methyl group (R^2, in Table 1.) was lipophilic, thus, hydrogen bond donor and acceptor groups were most probably not favored in this region and it might contribute to the observed inactivity of compounds **47**–**51**. However, on the opposite site of the central core acceptors might have an advantageous effect in the stabilization of the binding due to the proximity of the polar Ser-



37
$[Ca^{2+}]_i$ (% at 10 μM) = 16

13
$[Ca^{2+}]_i$ EC_{50} = 1.4 μM
(% at 10 μM = 95)

38
$[Ca^{2+}]_i$ EC_{50} = 2.0 μM
(% at 10 μM = 95)

Fig. 3. Hybridization of compounds **37** and **13** resulted in the first potent pyrazole derivative **38**.

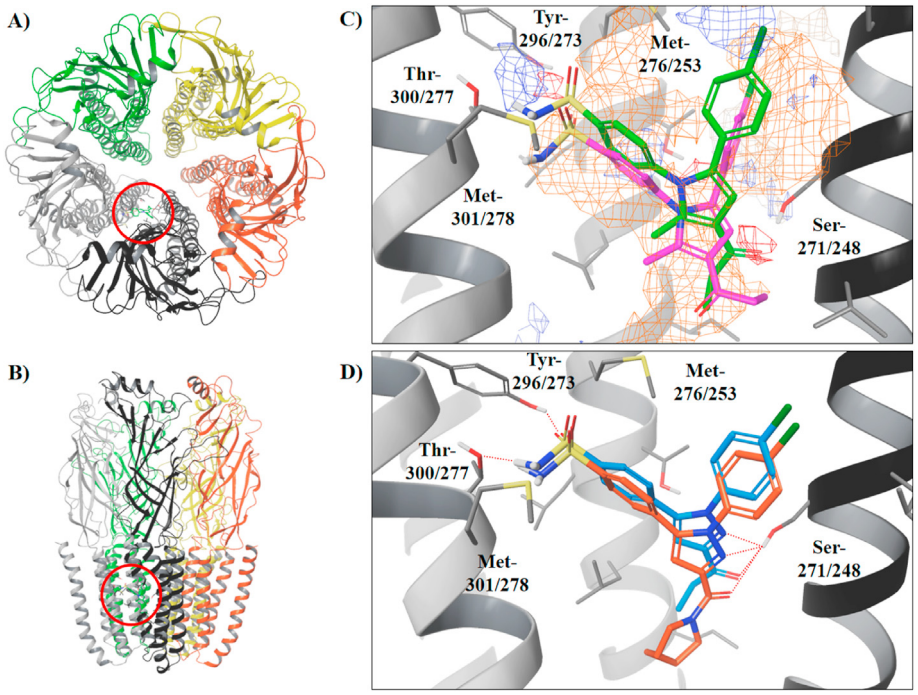


Fig. 4. Homology model of homopentameric α7 nAChR published by Newcombe et al. (**A.**, **B.**) which contains **A-867744**, **1** in the original (**C.**, magenta) and refined (**C.**, green) binding mode as well as compounds **39** (**D.**, blue) and **69** (**D.**, brown). The site map (**C.**) shows the areas favorable for lipophilic parts (orange grid) hydrogen bond acceptors (red grid) and donors (blue grid). The amino acid sequence numbers shown in the figure derive from the P36544 UniProt sequence and from the model of Newcombe et al. respectively.

271/248 side chain. In order to demonstrate it, the observed binding position of the two most potent compounds (**39, 69**) was presented (Fig. 4D.). This position was more or less in accordance with the observed experimental trends, however it should be noted that the resolution of contradictions in the literature requires further calculations [29,30].

2.2.2. *Drug-likeness evaluation of the new chemotype*

In order to evaluate drug-likeness of the compound series containing different central heteroaromatic cores, lipophilic ligand efficiency (LLE) diagram was analyzed (Fig. 5.) based on available potency data.

According to this, compounds having the highest lipophilic ligand efficiency belonged to either the original series (**1**–**36**, highlighted by red) or the most promising new series (**39, 52**–**79**, highlighted by green). In particular, compounds **69**, **39**, **28** and **26** possessed the highest LLE values. However, pyrrolo compounds **28** and **26** were judged suboptimal due to the metabolic liability of the ester group, as well as their inferior patentability potential. On the other hand, pyrazolo derivatives possessed the highest kinetic solubility values. Compounds **39** and **69** showed almost one order of magnitude increments in the kinetic solubility compared to the original Abbott reference compound **1** (5.2, 41.9 and 37.0 μM for **1**, **39** and **69**, respectively). This analysis supported the selection the best *in vitro* active 1,5-diaryl pyrazole ketone and amide derivatives (**39** and **69**, with $[Ca^{2+}]_i$ PAM EC_{50} values of 0.53 and 1.2 μM, respectively) for detailed *in vitro*/*in vivo* biological characterization.

2.3. *Biological characterization of compounds **39** and **69***

Effects of both **39** and **69** were characterized on the 10 mM choline-induced inward currents in the automated patch clamp system. Both compounds showed one order of magnitude larger enhancement of the choline-induced current amplitude than that

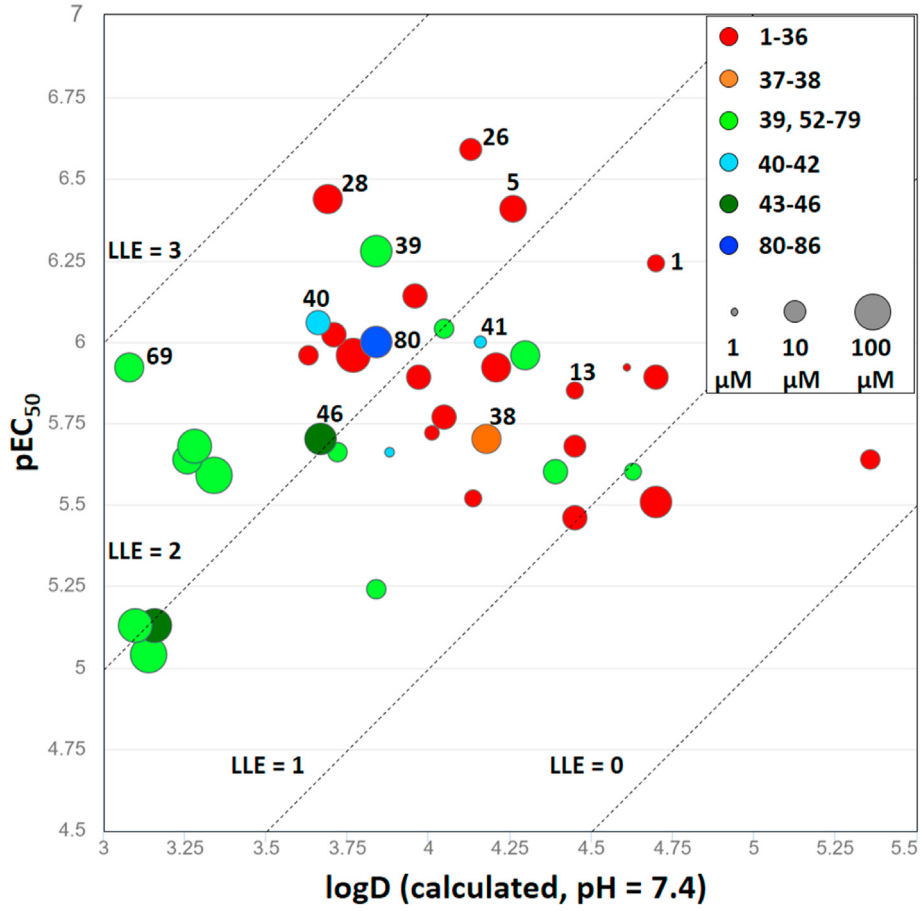


Fig. 5. Lipophilic ligand efficiency (LLE = pEC_{50} - logD) diagram of active compounds. The size of the markers is in line with the kinetic solubility values, while the colors represent different chemotypes. Numbers on the figure indicate the respective compounds.

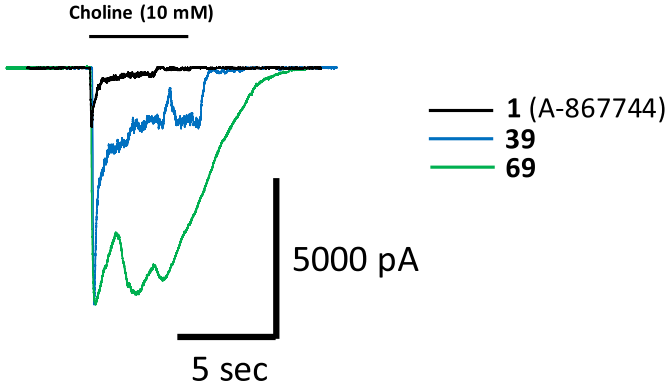


Fig. 6. 10 mM choline-induced current responses in the presence of **1** (A-867744), **39** and **69** on the representative current traces.

of **1**, demonstrated by the 16-, 168- and 162-fold enhancements by **1**, **39** and **69**, respectively (representative current traces for **39** and **69** are depicted in Fig. 6.). The molecules had moderate (human)/low (mouse, rat) (**39**) or low (human, mouse, rat) (**69**) intrinsic clearances in the liver microsomes of different species. In vinblastine-selected Caco-2 (VB-Caco-2) cultures of high level of P-gp expression [32], the efflux ratio (PDR) of **39** was 3.6 (tested at 10 μM), indicating a role of efflux in drug transport; no efflux was detected for **69** with a PDR value of 0.7 and $Papp_{A-B}$ 20×10^{-6} cm s^{-1}. Compounds **39** and **69** were further investigated for off-target liabilities in a commercial panel of 68 radioligand binding assays (Lead Profiling Screen, Eurofins). Both compounds proved to be specific at 10 μM with >50% displacement at only two off-targets (54 and 53% at the CB_1 receptor for **39** and **69**, respectively. **39**, furthermore resulted in 83% displacement of the phosphodiesterase-4 inhibitor rolipram, while **69** proved to be active at the androgen receptor with 73% displacement). Importantly, neither **39** nor **69** showed >20% displacement at 10 μM in binding assays relevant for ligand affinity to 5-HT_3 receptors ([^{3}H]GR-65630 binding in recombinant HEK cells), NMDA receptors ([^{3}H]CGP-39653, [^{3}H]MDL105,519 or [^{3}H]TCP binding in Wistar rat cerebral cortex preparations) or $GABA_A$ receptors ([^{3}H]flunitrazepam or [^{3}H]muscimol binding in Wistar Rat brain preparations minus cerebellum), with the sole exception of **39** showing 28% displacement of [^{3}H]flunitrazepam binding that suggests a moderate affinity to $GABA_A$ receptors (data provided by Eurofins). To further characterize the effects of **69** in functional assays, electrophysiological measurements were done in α4/β2 nACh- and $GABA_A$R-expressing recombinant cells. **69** elicited a concentration-dependent inhibition of the acethylcholine-evoked currents in α4β2 nAChR-expressing HEK cells, with an IC_{50} value of 1.8 μM (the minimum efficient concentration was 1 μM), while evoked no agonist current, when applied *per se* at 1 or 10 μM. In contrast, **69** showed no agonism or PAM activity in the same concentration range in α3β4 nACh-expressing cells in QPatch experiments (Dr. Hugh Chapman, personal communication). Furthermore, **69** showed concentration-dependent enhancement of GABA-evoked currents with a minimum efficient concentration of 1 μM on both

Table 6
Comparison of the *in vitro* and *in vivo* properties of **39** and **69** with **1** (A-867744). FI: fold increase of the 10 mM choline-induced inward current by 10 μM test substance. PR: place recognition test. RI: recognition index. NA: not available. n.e.: no effect.

		1	39	69
Kinetic solubility	**μM**	**5.2**	**41.9**	**36.6**
logP		4.7	3.8	3.1
$[Ca^{2+}]_i$	**EC_{50} (μM)**	0.6	0.5	1.2
Patch clamp	**FI/EC_{50} (μM)**	16/NA	168/6.1	162/4.5
Microsomal stability (Intrinsic clearance)	**CL_{int} (μL/min/mg/protein) (h,m,r)**	3, 26, 10	18, 16, 20	4, 5, 10
Penetration	**$Papp_{A-B} \times 10^{-6}$ cm s^{-1}/PDR**	9/2	20/0.7	18/3.6
VB-Caco-2		@1 μM	@10 μM	@10 μM
Off-targets	**Displacement > 50%**	NA	2 off-targets	2 off-targets
***In vivo* (PR)**	**RI (sign. effect)**	3 mg/kg or n.e.[a]	n.e.[b]	3 mg/kg

[a] Depending on the route of administration. **1** resulted in a significant effect on the recognition index with a minimal effective dose of 3 mg/kg following ip. administration, but had no effect after oral administration.
[b] No significant effect following ip. administration on the recognition index was found. However, there was a significant difference between times spent in the novel vs. familiar arms of the maze in one single dose (3 mg/kg).

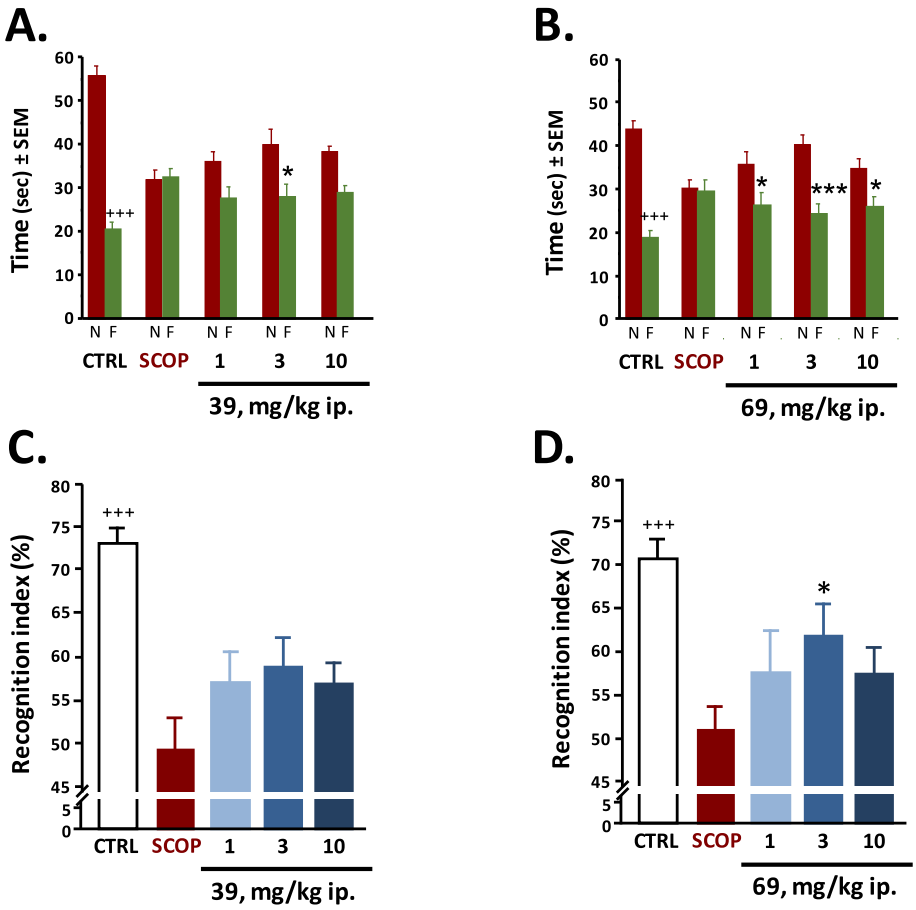


Fig. 7. Upper panel: Effect of ip. administration of **39** and **69** on the 1 mg/kg (ip.) scopolamine-induced amnesia in the mouse place recognition test (**A.**, **B.**: times spent in the novel and familiar arms of the maze; **C.**, **D.**: recognition index). N: novel; F: familiar. ***p < 0.001, *p < 0.05 (ANOVA, followed by post-hoc Dunnett-test). Lower panel: results of the pilot pharmacokinetic measurements from brain and blood samples taken from the experimental animals.

α1β3γ2 and α5β3γ2 $GABA_A$Rs (the compound increased the function of α1β3γ2 $GABA_A$R by 24%, 56% and 163% at 1, 3 and 10 μM, respectively, while the enhancement values for α5β3γ2 $GABA_A$R were 32%, 36% and 123% at 1, 3 and 10 μM, respectively (mean values, n = 5–10)). Results of the *in vitro* and *in vivo* characterization are summarized in Table 6.

Based on their promising *in vitro* properties, both **39** and **69** were further characterized *in vivo* in rodents. In mice, **39** and **69** were tested in the scopolamine-induced (ip., 1 mg/kg) amnesia model using the place recognition (Y-maze) paradigm, supported by pilot pharmacokinetic measurements from brain and blood samples taken from the experimental animals. In this model, mice are placed in a Y-maze where one arm is known by the animals from a former session and one is completely novel for them; time spent in familiar arm (F) and unfamiliar arm (N: novel arm) is measured as well as recognition index [RI=(N/N + F) × 100)] is calculated for the animals. Despite its better brain penetration, **39** did not change the recognition index in the place recognition test (Fig. 7C.), while significant time differences were measured across the novel and familiar arms of the maze at 3 mg/kg dose (Fig. 7A.).

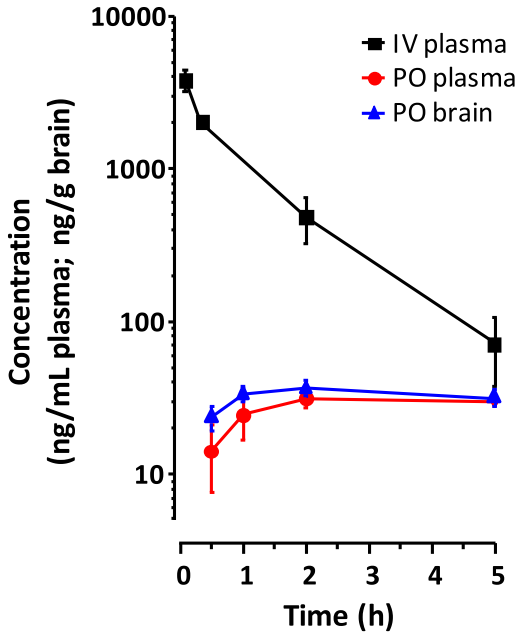


Fig. 8. Rat pharmacokinetic parameters of **69**.

In contrast, the amide **69** showed significant time changes at all doses (Fig. 7B.) as well as significant increase of the recognition index at 3 mg/kg with a bell-shaped dose-response relationship (Fig. 7D.) The more expressed *in vivo* efficacy of **69** (compared to that of **39**) may bolster our initial theory that the more pronounced inhibition of channel desensitization leads to better cognitive performance (see the different current traces for **39** and **69** in Fig. 6.).

Based on *in vitro* and *in vivo* performance, **69** was selected as lead molecule. To gain more information in rats, a detailed pharmacokinetic study was carried out with **69** in 3 mg/kg following ip. and p.o. administration to non-fasted, male Wistar rats. Compared to mice, the compound showed excellent brain penetration with relatively low bioavailability (3.83%). Like in mice, p.o. administration of **69** resulted in low, but relevant brain and plasma levels (Fig. 8.; Table 7.). Half-life of **69** following iv. administration was ~1 h.

3. Conclusions

Summarizing the above data, a promising new chemotype with good physicochemical and *in vitro* parameters was identified. The most advanced derivative (**69**) showed not only *in vitro*, but also *in vivo* efficacy in a rodent model of learning and memory with acceptable pharmacokinetic properties. Despite the steep SAR (which is not unusual in the field of allosteric modulators), the identified structural elements may allow further optimization of the presented lead compound. Based on the *in vivo* data with **69**, other highly advanced molecules from this chemotype also have the possibility of being cognitive enhancers in a biologically relevant dose range, further strengthening the supportive role of α7 nACh receptors in cognitive functions.

4. Experimental section

4.1. Chemistry and chemical methods

Commercially available reagents were used without further purification. Solvents and gases were dried according to standard procedures. Organic solvents were evaporated with reduced pressure using a rotary evaporator. Purity of the final compounds was verified using an Agilent 1200 HPLC system equipped with a diode array detector and with an Agilent 6410 triple quadrupole mass spectrometer (QQQ-MS). Eluent A was 0.1% TFA in water and eluent B was the mixture of acetonitrile and water at 95:5 with 0.1% TFA. The mobile phase flow rate was 1.2 mL/min and the applied linear gradient profile was: 0–4 min 0–100% B, 6 min 100%B, 6.01 min 0% B. Chromatograms were recorded at 220 ± 4 nm and the applied injection volume was 1.0 μL. MassHunter Workstation software (B.03.01) was used for data acquisition and processing. Chromatographic analyses were carried out at 40 °C on an Ascentis Express C18 50 × 3.0 mm, 2.7 μm (Sigma-Aldrich) column. The QQQ-MS operating parameters were the following: scanning in positive ionization (ESI+) mode, drying gas temperature of 350 °C, nitrogen flow rate of 12 L/min, nebulizer pressure of 45 psi, capillary voltage of 4 kV, fragmentor voltage 135 V. NMR measurements were performed in DMSO-d_6 at 25 °C on a 400 or 500 MHz Bruker Avance III HD spectrometer equipped with a ^{1}H–^{19}F/^{15}N–^{31}P Prodigy or a ^{1}H/^{13}C/^{15}N TCI Extended Temperature CryoProbe, respectively. Standard ^{1}H and ^{13}C NMR spectra were collected in all cases. In some cases, HSQC, HMBC and ROESY data were collected as well using the pulse programs available in the Topspin 3.5 p7 sequence library. Chemical shifts are referenced to internal TMS (0.00 ppm/^{1}H) or to residual solvent signal (39.5 ppm/^{13}C). For data interpretation and reporting the ACD/Spectrus Processor 2017.1.3 software (ACD/Labs, Canada) was used.

Electron impact high-resolution MS (HESI-HRMS) measurements were performed on a Thermo Velos Pro Orbitrap Elite (Thermo Fisher Scientific, Bremen, Germany) system. The ionization method was HESI and operated in positive ion mode. The capillary temperature was set at 390 °C. Resolving power of 60,000 (FWHM) at *m/z* 400. Data acquisition and analysis were accomplished with Xcalibur software version 4.0 (Thermo Fisher Scientific).

4.2. General methods for syntheses

General method 1A (Vilsmeier acylation reaction)

Under an inert atmosphere, *N,N*-dimethylpropionamide (0.071 mL, 1.3 eq) was treated with $POCl_3$ (0.061 mL, 1.3 eq) at 0–5 °C. The resulting reaction mixture was then allowed to reach room temperature and stirred for another hour, diluted with 1,2-dichloroethane (2 mL) cooled to 0 °C and the corresponding pyrrole derivative (0.5 mmol) dissolved in 1,2-dichloroethane or neat was added. After 1–5 h of heating under reflux, the mixture was cooled to 40 °C, an aqueous solution of NaOAc (0.21 g in 0.5 mL, 5 eq) was added and the heating was continued for another 30 min.

Table 7
Pharmacokinetic parameters of **69** after 3 mg/kg iv. and p.o. treatment in rats (mean, CV%, n = 4 males/dose group).

	Route of admin.	Dose (mg/kg)	AUC_{0-5h} (ng/mL*h plasma; ng/g brain)	Clearance (mL/min/kg)	V_d (L/kg)	T_{half} (h)	C_{max} (ng/mL)	T_{max} (h)
plasma	iv.	3	3492 (13.3)	14.1 (14.2)	1.17 (5.8)	0.97 (14.9)	_	_
plasma	p.o.	3	134	_	_	NC	31.6	2.0
brain	p.o.	3	158	_	_	NC	36.8	2.0

Water (15 mL) was added, the mixture was extracted with CH_2Cl_2, the combined organic phase was washed with sat. $NaHCO_3$ solution and water, dried, concentrated, and the residue was purified by column chromatography on silica.

General method 1B (Friedel-Crafts acylation)

Under an inert atmosphere (Ar) dry $AlCl_3$ (3 g, 22 mmol, 3 eq) was suspended in 1,2-dichloroethane or CH_2Cl_2 (45 mL). Into this suspension, propionic anhydride (1.46 mL, 11 mmol, 1.5 eq) was added dropwise under ice/water cooling and it was stirred for additional 15 min. Into the resulting solution, the corresponding pyrrole derivative (7.5 mmol) in 1,2-dichloroethane or dichloromethane (20 mL) was added and it was stirred for 3–6 h at room temperature. The reaction mixture was poured slowly into ice and the phases were separated. The aqueous phase was extracted with dichloromethane (5 × 100 mL) and the combined organic phase was dried over anhydrous sodium sulphate and filtered and evaporated. The crude product was purified by column chromatography on silica.

General method 2 (reductive deamination)

To *N,N*-dimethylformamide (1 mL) preheated to 50 °C was added *tert*-butyl nitrite (0.09 mL, 1.5 eq) followed by the addition of a solution of the corresponding heteroaromatic amino compound (0.5 mmol) in *N,N*-dimethylformamide (2 mL) and the mixture was heated at this temperature for further 20 min. After cooling the reaction mixture to 0 °C, the separated gummy material was filtered off, dissolved in CH_2Cl_2, (or the mixture was extracted with EtOAc), dried, concentrated. The residue was purified by column chromatography on silica.

General method 3 (ester hydrolysis)

To a solution or a suspension of the corresponding ester (1 mmol) in ethanol (10 mL), aqueous 5 M NaOH or KOH solution (5 eq, 1 mL) was added and the mixture was heated under reflux for 1–4 h. The mixture was concentrated under reduced pressure, water was added, acidified by the addition of 10% HCl solution, and the precipitated solid was filtered off, washed with water and dried, or the acidic mixture was extracted with ethyl acetate.

General method 4 (amidation)

To a suspension of the corresponding carboxylic acid (15 mmol) in CH_2Cl_2 (100 mL) was added DMF (4 drops if only catalyst, 2 equivalent if both catalyst and reagent) followed by the dropwise addition of oxalyl chloride (4.0 mL, 3 eq) at 0–5 °C and the mixture was stirred at room temperature for 1.5 h under an inert atmosphere.

The solvent and excess oxalyl chloride were evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (100 mL), *N,O*-dimethylhydroxylamine hydrochloride or the corresponding amine (1.2 eq) was added, followed by dropwise addition of triethyl amine (5.4 mL, 2.5 eq) at 0–5 °C and the mixture was stirred at room temperature overnight.

The reaction mixture was diluted with CH_2Cl_2 (150 mL), extracted with 10% HCl-solution, sat. $NaHCO_3$ solution and water, dried over Na_2SO_4, concentrated and the residue was purified by column chromatography on silica.

General method 5A (Grignard reaction)

In an inert atmosphere, to a stirred solution of the Weinreb amide (0.7 mmol) in THF (25 mL) was dropwise added ethyl magnesium bromide solution (1 M in THF, 3.5 mL 5 eq) while slightly cooling with tap water (T < 30 °C) and the mixture was heated under reflux for 3 h.

The reaction mixture was quenched by dropwise addition of sat. NH_4Cl solution and water while cooling with ice-water and extracted with EtOAc. The combined organic phase was washed with sat. NH_4Cl solution and water, dried and concentrated. The residue was purified by column chromatography.

General method 5B (Grignard reaction)

In an inert atmosphere, to a stirred mixture of Mg turnings (0.72 g, 30 mmol, 5 eq) and iodine (1 crystal) in diethyl ether (5 mL) was added dropwise a solution of the corresponding alkyl halide (32 mmol) in diethyl ether (30 mL). After consumption of the magnesium turnings, a solution of the Weinreb amide (6 mmol) in THF (100 mL) was added dropwise while slightly cooling with tap water (T < 30 °C) and the stirring was continued at room temperature or heated under reflux.

The reaction mixture was quenched by dropwise addition of sat. NH_4Cl solution and water while cooling with ice-water and extracted with EtOAc. The combined organic phase was washed with sat. NH_4Cl solution and water, dried and concentrated. The residue was purified by column chromatography.

General method 6 (bis-PMB-sulfonamide deprotection)

A mixture of the corresponding sulfonamide (0.41 mmol), trifluoroacetic acid (4.5 mL) and anisole (0.27 mL, 6 eq) in CH_2Cl_2 (6 mL) was stirred at RT overnight. The pH of the reaction mixture was adjusted to pH = 8 by the addition of saturated Na_2CO_3 solution, the mixture was extracted with CH_2Cl_2, the combined organic phase was dried, concentrated and the residue was purified by column chromatography on silica.

General method 7 (N-methylation)

To a solution of the corresponding pyrrole derivative (0.4 mmol) in DMF (3 mL), NaH (18 mg, 0.45 mmol, 60% in mineral oil) was added at 0 °C under an inert atmosphere and the mixture was stirred for 10 min at this temperature. Methyl iodide (0.03 mL, 0.48 mmol) was added and the mixture was allowed to reach RT and reacted for further 3 h. After cooling in an ice-water bath, water was added, the obtained precipitate was filtered off (or extracted with EtOAc) washed with water, dried and purified by column chromatography on silica.

General method 8 (N-(dimethylamino)methylidene sulfonamide deprotection)

A mixture of a solution of the corresponding *N*-(dimethylamino) methylidene derivative (0.15 mmol) in THF (2 mL) and a solution of KOH (40 mg, 0.6 mmol, 85%, 4 eq) in MeOH (1 mL) was stirred at RT overnight. The reaction mixture was acidified by adding 10% HCl solution while cooling. The volatile organic solvents were removed under reduced pressure and the residue was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, concentrated and the residue was purified by column chromatography on silica.

4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (1) [24,25]

Mp 253–256 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2ClS$ $[M+H]^+$: 403.08777; found: 403.08800; delta = 0.58 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.8 Hz, 2H), 7.51 (s, 2H), 7.44–7.50 (m, 2H), 7.30 (s, 1H), 7.28 (s, 1H), 7.05–7.10 (m, 2H), 6.97 (s, 1H), 2.85 (d, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 143.4, 139.1, 136.2, 131.2, 131.0, 130.0, 129.0, 128.5, 127.7, 126.3, 120.4, 110.3, 32.6, 11.9, 7.9.

1-[5-(4-chlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]propan-1-one (2)

Prepared according to *General method 1A* starting from 2-(4-chlorophenyl)-5-methyl-1*H*-pyrrole (**2**–**1**) [33] (0.25 g, 1.3 mmol). Yield: 49 mg (15%). See in the Supplementary material in Schemes S–1. Mp 216–217 °C; HESI-HRMS: calcd for $C_{14}H_{15}ONCl$ $[M+H]^+$: 248.08367; found: 248.08397; delta = 1.20 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (br s, 1H), 7.64–7.70 (m, 2H), 7.41–7.45 (m, 2H), 7.00 (d, J = 2.7 Hz, 1H), 2.75 (q, J = 7.3 Hz, 2H), 2.48–2.49 (s, 3H), 1.04 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.8, 135.4, 130.3, 129.6, 128.1, 127.4, 124.4, 120.5, 106.9, 32.1, 12.8, 7.9.

4-[2-(4-chlorophenyl)-5-methyl-1*H*-pyrrol-1-yl]benzenesulfonamide (3) [24]

Mp 215–218 °C; HESI-HRMS: calcd for $C_{17}H_{16}O_2N_2ClS$ $[M+H]^+$: 347.06155; found: 347.06159; delta = 0.11 ppm. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.83–7.88 (m, 2H), 7.47 (s, 2H), 7.37–7.42 (m, 2H), 7.22–7.27 (m, 2H), 6.98–7.03 (m, 2H), 6.38 (d, J = 3.6 Hz, 1H), 6.11 (dq, J = 0.9, 3.6 Hz, 1H), 2.09 (br, s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 142.4, 140.7, 131.5, 131.3, 131.1, 129.9, 128.3, 128.1, 127.7, 126.2, 109.5, 107.9, 12.4.

4-(2-Methyl-3-propanoyl-1*H*-pyrrol-1-yl)benzenesulfonamide (4)

See in Scheme 1.

*Step 1. 4-oxopentanal (**4**–**2**)*

Pyridinium chlorochromate (12.8 g, 60 mmol) was dissolved in dry dichloromethane (50 mL), 5-hydroxy-2-pentanone (**4**–**1**) (4 mL, 40 mmol) was added dropwise and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of silica (approx. 3 cm) and washed with diethyl ether twice. The combined organic phase was evaporated and the residue was used without any further purification.

*Step 2. 4-(2-methyl-1H-pyrrol-1-yl)benzenesulfonamide (**4**–**3**)*

To intermediate **4**–**2** acetic acid (40 mL), acetonitrile (60 mL) and sulfanylamide (3.5 g, 20 mmol) were added and the solution was refluxed for 2 h. After completion of the reaction, the solvent was evaporated, the obtained crude product was dissolved in EtOAc (250 mL), washed with sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica, eluent: dichloromethane - methanol (95:5). Yield: 4.48 g (95%).

*Step 3. N-[4-(2-methyl-3-propanoyl-1H-pyrrol-1-yl)benzenesulfonyl]propanamide (**4**-**4**)*

Prepared according to *General method 1B (Friedel-Crafts reaction)* starting from **4**–**3** (1.7 g, 7.5 mmol). Yield: 0.15 g (6%) of light pink crystals.

*Step 4. 4-(2-methyl-3-propanoyl-1H-pyrrol-1-yl)benzenesulfonamide (**4**)*

A mixture of **4**–**4** (76 mg, 0.22 mmol) and a solution of NaOH (150 mg, 3.3 mmol) in water (3 mL) was refluxed for 4 h. It was quenched by the addition of. cc. HCl (0.3 mL), extracted with CH_2Cl_2 (4 × 8 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica, eluent: CH_2Cl_2-methanol (99:1). Yield: 52 mg (81%). Mp 199 °C; HESI-HRMS: calcd for $C_{14}H_{17}O_3N_2S$ $[M+H]^+$: 293.09544; found: 29309591; delta = 1.6 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89–7.99 (m, 2H), 7.58–7.67 (m, 2H), 7.51 (s, 2H), 6.99 (d, J = 3.2 Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H), 2.79 (q, J = 7.3 Hz, 2H), 2.43 (s, 3H), 1.06 (s, 3H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.0, 143.3, 140.9, 133.9, 130.4, 126.9, 126.6, 126.4, 121.6, 110.4, 33.1, 12.4, 8.5.

4-[2-(4-chlorophenyl)-4-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (5)

See in Scheme 1.

*Step 1. ethyl 2-amino-5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylate (**29**)*

A mixture of ethyl 4-(4-chlorophenyl)-2-cyano-4-oxobutanoate (**5**–**1**) [34] (2.87 g, 10.8 mmol), sulfanylamide (13.0 g, 75.5 mmol) and cc. hydrochloric acid (37% aqueous, 5 drops) was heated under reflux for 2 days. (After 1 day of reflux, another 6 drops of cc. HCl was added.) After cooling to room temperature, the excess sulfanylamide crystalized out was filtered off, the filtrate was concentrated and purified by column chromatography on silica, eluent: EtOAc-cyclohexane, 1:2. Yield: 2.12 g (47%) of white crystals.

*Step 2. ethyl 5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylate (**26**)*

Prepared according to *General method 2 (reductive deamination)* starting from **29** (2.0 g, 4.8 mmol). Yield: 0.60 g (31%) of light pink crystals.

*Step 3. 5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylic acid (**5**–**2**)*

Prepared according to *General method 3 (ester hydrolysis)* starting from **26** (0.64 g, 1.6 mmol). Yield: 0.59 g (99%) of beige crystals.

*Step 4. 5-(4-chlorophenyl)-1-(4-{[(E)-[(dimethylamino)methylidene]amino]sulfonyl}phenyl)-N-methoxy-N-methyl-1H-pyrrole-3-carboxamide (**5**–**3**)*

The product was synthesized according to *General method 4 (amidation)* starting from **5**–**2** (0.58 g, 1.55 mmol). Yield: 0.34 g (46%) colourless amorphous solid.

*Step 5. 4-[2-(4-chlorophenyl)-4-propanoyl-1H-pyrrol-1-yl]benzenesulfonamide (**5**)*

Prepared according to *General method 5A (Grignard reaction)* starting from **5**–**3** (0.34 g, 0.71 mmol). Yield: 0.10 g (36%) white crystals. Mp 189–190 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_3N_2ClS$ $[M+H]^+$: 389.07212; found: 389.07282; delta = 1.81 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 1.8 Hz, 1H), 7.83–7.87 (m, 2H), 7.48 (br s, 2H), 7.41–7.46 (m, 2H), 7.35–7.40 (m, 2H), 7.13–7.18 (m, 2H), 6.85 (d, J = 1.8 Hz, 1H), 2.84 (q, J = 7.3 Hz, 2H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.0, 143.6, 141.6, 133.9, 132.7, 130.6, 130.4, 130.3, 129.0, 127.4, 126.5, 126.3, 111.1, 32.4, 9.1.

4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]-*N*-methylbenzenesulfonamide (6) and 4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]-*N*,*N*-dimethylbenzenesulfonamide (7)

See in Scheme 1.

Under an argon atmosphere, compound **1** (315 mg, 0.78 mmol) was dissolved in dry THF (40 mL) and the solution was cooled to 0–5 °C using ice-water cooling bath. Into this solution, NaH (60 mg, 2eq, 60% dispersion in mineral oil) and methyl iodide (0.29 mL, 6eq) were added. The solution was stirred at room temperature for 3 h. The reaction mixture was diluted with water and ethyl acetate (50 mL). After separation of the phases the aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organic phase was washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified and separated by column chromatography on silica using dichloromethane-ethyl acetate as elution system (solvent ratio was changed from 95:5 to 50:50). Yield for **6**: 39 mg (12%). Mp 220–222 °C; HESI-HRMS: calcd for $C_{21}H_{22}O_3N_2ClS$ $[M+H]^+$: 417.10342; found: 417.10392; delta = 1.20 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82–7.87 (m, 2H), 7.58 (q, J = 4.97 Hz, 1H), 7.49–7.53 (m, 2H), 7.26–7.31 (m, 2H), 7.02–7.07 (m, 2H), 6.99 (s, 1H), 2.86 (q, J = 7.3 Hz, 2H), 2.43 (d, J = 5.0 Hz, 3H), 2.35 (s, 3H), 1.08 (t, J = 7.3 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 139.7, 138.5, 136.2, 131.2, 130.9, 129.9, 128.9, 128.8, 127.7, 127.4, 120.4, 110.3, 32.6, 28.1, 11.9, 7.9.

Yield for **7**: 132 mg (40%). Mp 191–193 °C; HESI-HRMS: calcd for $C_{22}H_{24}O_3N_2ClS$ $[M+H]^+$: 431.11907; found: 431.11892; delta = −0.34 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80–7.85 (m,

2H), 7.52–7.57 (m, 2H), 7.25–7.32 (m, 2H), 7.00–7.04 (m, 2H), 7.01 (s, 1H), 2.86 (q, J = 7.3 Hz, 2H), 2.61 (s, 6H), 2.36 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 140.3, 136.2, 133.8, 131.2, 130.9, 129.8, 128.9, 128.8, 128.1, 127.7, 120.5, 110.3, 37.0, 32.6, 11.9, 7.9.

4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]piperidine-1-sulfonamide (8)

See in Scheme 1.

Step 1. 1-benzyl-4-[2-(4-chlorophenyl)-5-methyl-1H-pyrrol-1-yl*] piperidine (**8**–**2**)*

Under a nitrogen atmosphere, to a solution of **8**–**1** [35] (0.83 g, 3.96 mmol) in toluene (5 mL) was added 1-benzylpiperidin-4-amine (0.80 mL, 3.92 mmol) and glacial acetic acid (0.060 mL), and the mixture was heated under reflux conditions in a flask equipped with a Dean-Stark apparatus. The progress of the reaction was monitored by TLC. After 145 min of heating, 1-benzylpiperidin-4-amine (0.20 mL, 0.98 mmol) was added, after further 80 min two drops of acetic acid, 1-benzylpiperidin-4-amine (2 mL, 9.8 mmol) and toluene (2 mL) were added. Finally, after 7 h of reflux the reaction solution was cooled to room temperature and stirred overnight. Toluene (100 mL), saturated aqueous $NaHCO_3$ solution (30 mL), and water (10 mL) were added. The two layers were separated, the aqueous layer was extracted with toluene (40 mL). The combined organic layer was washed with water (6 × 70 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain a crude product, which was then purified by column chromatography on silica using 17% ethyl acetate in cyclohexane as an eluent to obtain the title compound. Yield: 1.11 g (77%). Mp 222–226 °C; HESI-HRMS: calcd for $C_{19}H_{25}O_3N_3ClS$ $[M+H]^+$: 410.12997; found: 410.12994; delta = −0.08 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49–7.53 (m, 2H), 7.37–7.41 (m, 2H), 6.78 (s, 2H), 6.54 (s, 1H), 4.00–4.09 (m, 1H), 3.46–3.61 (m, 2H), 2.72 (q, J = 7.3 Hz, 2H), 2.67 (s, 3H), 2.40–2.49 (m, 2H), 2.06–2.21 (m, 2H), 1.84–1.91 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.3, 134.6, 132.1, 131.5, 131.3, 131.0, 127.9, 110.2, 54.2, 45.5, 32.3, 29.3, 12.5, 8.0.

Step 2. 1-[1-(1-benzylpiperidin-4-yl*)-5-(4-chlorophenyl)-2-methyl-1H-pyrrol*-3-yl*]propan-1-one (**8**–**3**)*

Prepared according to *General method 1 (Friedel-Crafts reaction)* starting from **8**–**2** (1.0 g, 2.74 mmol). Yield: 0.61 g (52%).

Step 3. 1-[5-(4-chlorophenyl)-2-methyl-1-(piperidin-4-yl*)-1H-pyrrol*-3-yl*]propan-1-one (**8**–**4**)*

To a solution of **8**–**3** (99 mg, 0.235 mmol) in dichloromethane (6 mL) was added 1-chloroethyl chloroformate (0.033 mL, 0.31 mmol) in dichloromethane (2.5 mL) at 0–5 °C under argon atmosphere. The reaction mixture was stirred at the same temperature for 40 min, then allowed to warm to room temperature. After being stirred at the same temperature for 2.5 h the reaction mixture was evaporated. The residue was dissolved in methanol (9 mL) and heated to reflux for 1 h. The solution was allowed to cool to room temperature and concentrated. To the residue was added diethyl ether, after trituration and filtration the hydrogen chloride salt of the crude product was obtained. The salt was taken up in a mixture CH_2Cl_2 (90 mL) and 3% NaOH solution (30 mL), the layers were separated, aqueous layer was extracted with CH_2Cl_2 (10 mL), the combined organic layer was washed with water (5 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain a crude amine which was then purified by column chromatography using 10% methanol in dichloromethane to 14% methanol in dichloromethane as an eluent. Yield: 53 mg (68%).

*Step 4. 4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1H-pyrrol-*1-yl*]piperidine-1-sulfonamide (**8**)*

Under an argon atmosphere a mixture of **8**–**4** (98 mg, 0.30 mmol) and sulfamide (144 mg, 1.50 mmol) were heated in 1,4-dioxane (12 mL) under reflux for 4 h and 20 min. Upon completion of the reaction (as determined by TLC) the mixture was cooled and was diluted with ethyl acetate (45 mL) and water (15 mL). The mixture was extracted with saturated $NaHCO_3$ solution (25 mL), the layers were separated, the aqueous layer was extracted with EtOAc (20 mL), the combined organic layer was washed with water (5 × 40 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 0.6% methanol in CH_2Cl_2 to yield solid product, which was then triturated with diethyl ether, filtered and dried. Yield: 85 mg (69%).

1-[5-(4-chlorophenyl)-1-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-yl]propan-1-one (9)

See in Scheme 1. Prepared according to *General method 1B (Friedel-Crafts reaction)* starting from **9**–**1** 2-(4-chlorophenyl)-1-[4-(methanesulfonyl)phenyl]-5-methyl-1*H*-pyrrole(**9**–**1**) [24] (345 mg, 1 mmol). Yield: 0.21 g (52%). Mp 216–218 °C; HESI-HRMS: calcd for $C_{21}H_{21}O_3NClS$ $[M+H]^+$: 402.09252; found: 402.09278; delta = 0.66 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–8.04 (m, 2H), 7.54–7.58 (m, 2H), 7.27–7.32 (m, 2H), 7.03–7.08 (m, 2H), 6.99 (s, 1H), 3.29–3.30 (m, 3H), 2.86 (q, J = 7.3 Hz, 2H), 2.35 (s, 3H), 1.24 (br s, 2H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 140.7, 140.1, 136.2, 131.2, 131.0, 129.8, 128.9, 128.9, 127.8, 127.7, 120.5, 110.5, 42.7, 32.6, 12.0, 7.9.

3-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (10)

Synthesized in a manner analogous to the method described for compound **1** using 3-aminobenzenesulfonamide instead of 4-aminobenzenesulfonamide. Mp 236–240 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2ClS$ $[M+H]^+$: 403.08777; found: 403.08785; delta = 0.20 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (ddd, J = 1.1, 1.7, 7.8 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.65–7.66 (m, 1H), 7.51 (ddd, J = 1.2, 2.1, 8.1 Hz, 2H), 7.49 (s, 1H), 7.25–7.30 (m, 2H), 7.05–7.10 (m, 2H), 6.99 (s, 1H), 2.86 (q, J = 7.3 Hz, 2H), 2.32 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 196.4, 144.7, 136.8, 136.3, 131.3, 130.9, 129.8, 129.8, 128.8, 127.8, 125.2, 124.8, 120.3, 110.2, 32.5, 11.9, 7.9.

Ethyl 5-(4-chlorophenyl)-1-(1*H*-indol-6-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (11)

Synthesized in a manner analogous to the method described for compound **13** using 6-aminoindol instead of sulfanylamide. Mp 186–187 °C; HESI-HRMS: calcd for $C_{22}H_{20}O_2N_2Cl$ $[M+H]^+$: 379.12078; found: 379.12156; delta = 2.05 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (br s, 1H), 7.42–7.48 (m, 2H), 7.15–7.20 (m, 2H), 7.04–7.09 (m, 2H), 6.91 (dd, J = 2.0, 8.5 Hz, 1H), 6.73 (s, 1H), 6.45–6.48 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.28 (s, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.8, 138.0, 134.6, 131.8, 130.6, 130.4, 128.4, 128.2, 127.5, 127.0, 126.6, 120.5, 119.1, 111.5, 111.1, 108.9, 101.1, 58.4, 13.9, 11.7.

4-[3-Acetyl-5-(4-chlorophenyl)-2-methyl-1*H*-pyrrol-1-yl] benzenesulfonamide (12) [25]

Mp 259–260 °C HESI-HRMS: calcd for $C_{19}H_{18}O_3N_2ClS$ $[M+H]^+$: 389.07212; found: 389.07282; delta = 1.8 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82–7.95 (m, 2H), 7.51 (s, 2H), 7.45–7.50 (m, 2H), 7.23–7.33 (m, 2H), 7.03–7.12 (m, 2H), 6.97 (s, 1H), 2.43 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 194.2, 144.1, 139.7, 136.8, 131.8, 131.6, 130.5, 129.6, 129.1, 128.4, 126.9, 121.5, 111.5, 28.8, 12.5

Ethyl 5-(4-chlorophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (13) [24,25]

Mp 218–219 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_2ClS$ $[M+H]^+$: 419.08268; found: 419.08343; delta = 1.78 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.9 Hz, 2H), 7.46–7.53 (m, 4H), 7.28 (d, J = 7.7 Hz, 2H), 7.06 (d, J = 7.7 Hz, 2H), 6.75 (s, 1H), 5.76 (s, 1H), 4.24 (d, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.29 (t, J = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 143.4, 139.3, 137.3, 131.6, 131.0, 129.8, 129.0, 128.6, 127.8, 126.3, 112.1, 109.9, 58.6, 13.8, 11.6.

4-(2-Methyl-5-phenyl-3-propanoyl-1*H*-pyrrol-1-yl)benzenesulfonamide (14)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-phenylethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 246–248 °C; HESI-HRMS: calcd for $C_{20}H_{21}O_3N_2S$ $[M+H]^+$: 36912674; found: 369.12705; delta = 0.84 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85–7.90 (m, 2H), 7.51 (s, 2H), 7.43–7.50 (m, 2H), 7.15–7.26 (m, 2H), 7.05–7.11 (m, 2H), 6.92 (s, 1H), 2.85 (q, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 143.3, 139.4, 135.8, 132.6, 131.1, 128.5, 127.7, 127.4, 126.3, 126.2, 120.3, 109.8, 32.5, 11.9, 7.9.

4-[5-(4-fluorophenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (15)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(4-fluorophenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 239–240 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_2FS$ $[M+H]^+$: 387.11732; found: 387.11766; delta = 0.88 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84–7.91 (m, 2H), 7.50 (s, 2H), 7.43–7.49 (m, 2H), 7.04–7.15 (m, 4H), 6.90 (s, 1H), 2.85 (q, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 160.5, 143.4, 139.2, 135.7, 131.5, 129.6, 128.6, 127.6, 126.2, 120.2, 114.7, 109.8, 32.5, 11.9, 7.9.

4-[5-(4-methoxyphenyl)-2-methyl-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (16)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(4-methoxyphenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 218–220 °C; HESI-HRMS: calcd for $C_{21}H_{23}O_4N_2S$ $[M+H]^+$: 399.13730; found: 399.13729; delta = −0.04 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84–7.89 (m, 2H), 7.50 (s, 2H), 7.42–7.48 (m, 2H), 6.97–7.02 (m, 2H), 6.77–6.82 (m, 3H), 3.69 (s, 3H), 2.84 (d, J = 7.3 Hz, 2H), 2.31 (s, 3H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.4, 157.6, 143.2, 139.5, 135.1, 132.5, 128.9, 128.6, 126.1, 123.5, 120.1, 113.2, 108.9, 54.4, 32.5, 12.0, 7.9.

4-[2-Methyl-5-(4-methylphenyl)-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (17)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(4-methylphenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 251–253 °C; HESI-HRMS: calcd for $C_{21}H_{23}O_3N_2S$ $[M+H]^+$: 383.14239; found: 383.14312; delta = 1.91 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85–7.89 (m, 2H), 7.51 (s, 2H), 7.43–7.48 (m, 2H), 7.00–7.05 (m, 2H), 6.94–6.98 (m, 2H), 6.85 (s, 1H), 2.84 (q, J = 7.3 Hz, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.5, 144.3, 140.5, 136.7, 136.6, 133.7, 129.6, 129.4, 129.3, 128.4, 127.2, 121.3, 110.4, 33.6, 21.1, 13.0, 9.0.

4-[2-Methyl-5-(3-chlorophenyl)-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (18)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(3-chlorophenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 220–221 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2ClS$ $[M+H]^+$: 403.08777; found: 403.08786; delta = 0.22 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88–7.92 (m, 2H), 7.52 (s, 2H), 7.48–7.52 (m, 2H), 7.18–7.26 (m, 3H), 7.06 (s, 1H), 2.86 (q, J = 7.31 Hz, 2H), 2.33 (s, 3H), 1.08 (t, J = 7.32 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 197.1, 144.2, 139.7, 137.0, 133.7, 133.0, 131.5, 130.0, 129.1, 126.6, 126.9, 121.0, 111.4, 33.2, 12.5, 8.5.

4-[2-Methyl-5-(2-chlorophenyl)-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (19)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(2-chlorophenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 211–213 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2ClS$ $[M+H]^+$: 403.08777; found: 403.08809; delta = 0.80 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76–7.80 (m, 2H), 7.45 (s, 2H), 7.39–7.42 (m, 2H), 7.34–7.39 (m, 2H), 7.25–7.33 (m, 2H), 6.82 (s, 1H), 2.83 (q, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.9, 143.7, 139.3, 135.4, 133.6, 133.4, 130.9, 130.2, 129.7, 129.2, 128.7, 126.9, 126.3, 120.7, 111.5, 33.1, 12.6, 8.5.

4-[2-Methyl-5-(2,4-dichlorophenyl)-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (20)

Synthesized in a manner analogous to the method described for compound **1** using 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one instead of 2-bromo-1-(4-chlorophenyl)ethan-1-one. Mp 209–210 °C; HESI-HRMS: calcd for $C_{20}H_{19}O_3N_2Cl_2S$ $[M+H]^+$: 437.04880; found: 437.04912; delta = 0.73 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79–7.83 (m, 2H), 7.58 (t, J = 1.2 Hz, 1H), 7.46 (s, 2H), 7.39–7.43 (m, 2H), 7.38 (d, J = 1.2 Hz, 2H), 6.85 (s, 1H), 2.83 (q, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.9, 143.8, 139.1, 135.8, 134.6, 134.5, 133.8, 130.0, 128.8, 128.7, 128.5, 127.2, 126.4, 120.8, 111.9, 33.1, 12.6, 8.5.

Ethyl 5-(4-fluorophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (21)

An intermediate for the synthesis of compound **15**. Mp 224–225 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_2FS$ $[M+H]^+$: 403.11223; found: 403.11220; delta = −0.08 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J = 7.71 Hz, 2H), 7.50 (s, 2H), 7.45–7.49 (m, 2H), 7.03–7.12 (m, 4H), 6.69 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.3, 161.1, 144.0, 139.9, 137.4, 132.4, 130.2, 129.2, 128.1, 128.1, 126.8, 115.3, 112.5, 110.0, 59.1, 14.4, 12.2.

Ethyl 5-(4-methoxyphenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (22)

An intermediate for the synthesis of compound **16**. Mp 181–183 °C; HESI-HRMS: calcd for $C_{21}H_{23}O_5N_2S$ $[M+H]^+$: 415.13222; found: 415.13216; delta = −0.15 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82–7.90 (m, 2H), 7.50 (s, 2H), 7.43–7.48 (m, 2H), 6.96–7.02 (m, 2H), 6.75–6.80 (m, 2H), 6.59 (s, 1H), 4.23 (q, J = 7.2 Hz, 1H), 3.69 (s, 3H), 2.31 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.4, 158.2, 143.8, 140.2, 136.9, 133.4, 129.5, 129.2, 126.8, 124.0, 113.8, 112.3, 109.1, 59.1, 55.0, 14.4, 12.2.

Ethyl 5-(3-chlorophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate [23]

An intermediate for the synthesis of compound **18**. Mp 197–199 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_2ClS$ $[M+H]^+$: 419.08268; found: 419.08316; delta = 1.14 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87–7.92 (m, 2H), 7.53 (s, 2H), 7.48–7.52 (m, 2H), 7.22–7.26 (m, 1H), 7.19–7.22 (m, 1H), 7.17–7.18 (m, 1H), 6.93 (td, J = 1.6, 7.3 Hz, 1H), 6.81 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.2, 144.2, 139.8, 138.1, 133.5, 133.0, 131.8, 130.0, 129.2, 127.5, 126.9, 126.8, 126.4, 112.8, 110.9, 59.2, 14.4, 12.2.

Ethyl 5-(2-chlorophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (24)

An intermediate for the synthesis of compound **19**. Mp 235–237 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_2ClS$ $[M+H]^+$: 419.08268; found: 419.08305; delta = 0.89 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, J = 7.7 Hz, 2H), 7.46 (s, 2H),

7.39–7.43 (m, 2H), 7.37 (dd, J = 1.3, 7.9 Hz, 1H), 7.21–7.34 (m, 3H), 6.60 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.3, 143.7, 139.4, 136.5, 133.5, 133.3, 130.7, 130.2, 130.0, 129.3, 128.8, 126.9, 126.3, 112.3, 111.2, 59.2, 14.4, 12.2.

Ethyl 2-methyl-5-(4-methylphenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (25)

An intermediate for the synthesis of compound **17**. Mp 217–218 °C; HESI-HRMS: calcd for $C_{21}H_{23}O_4N_2S$ $[M+H]^+$: 399.13730; found: 399.13719; delta = −0.30 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85–7.89 (m, 2H), 7.51 (s, 2H), 7.44–7.48 (m, 2H), 7.00–7.03 (m, 2H), 6.93–6.96 (m, 2H), 6.64 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.3, 143.9, 140.2, 137.2, 136.3, 133.5, 129.1, 128.9, 128.7, 127.9, 126.7, 112.5, 109.5, 59.1, 20.6, 14.4, 12.2.

Ethyl 5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (26)

An intermediate for the synthesis of compound **5**. Mp 200–201 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_4N_2ClS$ $[M+H]^+$: 405.06703; found: 405.06729; delta = 0.65 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82–7.86 (m, 2H), 7.81 (d, J = 1.8 Hz, 1H), 7.48 (br s, 2H), 7.42–7.46 (m, 2H), 7.35–7.38 (m, 2H), 7.13–7.17 (m, 2H), 6.83 (d, J = 1.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 143.2, 141.0, 133.1, 132.2, 130.0, 130.0, 129.4, 128.6, 126.9, 126.1, 116.9, 111.7, 59.6, 14.4.

4-[2-(4-fluorophenyl)-4-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (27)

Synthesized in a manner analogous to the method described for the synthesis of compound **5** using ethyl 4-(4-fluorophenyl)-2-cyano-4-oxobutanoate [34] instead of ethyl 4-(4-chlorophenyl)-2-cyano-4-oxobutanoate. Mp 185–187 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_3N_2FS$ $[M+H]^+$: 373.10167; found: 373.10190; delta = 0.6 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, J = 1.8 Hz, 1H), 7.80–7.88 (m, 2H), 7.48 (s, 2H), 7.38–7.45 (m, 2H), 7.09–7.23 (m, 4H), 6.80 (d, J = 1.8 Hz, 1H), 2.84 (q, J = 7.3 Hz, 2H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.5, 161.5, 143.0, 141.2, 133.7, 130.5, 129.4, 127.7, 126.8, 126.0, 125.7, 115.5, 110.2, 31.9, 8.7.

Ethyl 5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (28)

An intermediate for the synthesis of compound **27**. Mp 200–201 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_4N_2FS$ $[M+H]^+$: 389.09658; found: 389.09675; delta = 0.44 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80–7.84 (m, 2H), 7.79 (d, J = 1.9 Hz, 1H), 7.48 (s, 2H), 7.38–7.45 (m, 2H), 7.09–7.22 (m, 4H), 6.77 (q, J = 1.9 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.28–1.28 (m, 1H), 1.28 (t, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 161.4, 143.0, 141.1, 133.4, 130.5, 128.9, 127.6, 126.8, 126.1, 116.7, 115.5, 111.2, 59.5, 14.4.

Ethyl 2-amino-5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (29)

An intermediate for the synthesis of compound **5**. Mp 240–243 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_4N_3ClS$ $[M+H]^+$: 420.07793; found: 420.07808; delta = 0.34 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86–7.90 (m, 2H), 7.50 (br s, 2H), 7.42–7.46 (m, 2H), 7.18–7.23 (m, 2H), 6.96–7.00 (m, 2H), 6.51 (s, 1H), 5.94 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.9, 148.7, 143.7, 138.6, 130.7, 130.4, 128.7, 128.3, 128.2, 127.1, 125.2, 108.5, 92.8, 58.5, 14.6.

Ethyl 2-amino-5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylate (30)

An intermediate for the synthesis of compound **27**. Mp 216–218 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_4N_3FS$ $[M+H]^+$: 404.10748; found: 404.10739; delta = −0.23 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85–7.89 (m, 2H), 7.50 (s, 2H), 7.40–7.44 (m, 2H), 7.02 (s, 2H), 7.00 (d, J = 1.4 Hz, 2H), 6.43 (s, 1H), 5.89 (s, 2H), 4.20 (d, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.0, 160.6, 148.4, 143.6, 138.7, 129.0, 128.7, 128.4, 127.0, 125.5, 115.2, 107.7, 92.6, 58.5, 14.6.

5-(4-fluorophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylic acid (31)

An intermediate for the synthesis of compound **15**.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68–7.76 (m, 2H), 6.99–7.02 (m, 4H), 6.50 (s, 1H), 2.33 (s, 3H). Mp > 350 °C; HESI-HRMS: calcd for $C_{18}H_{16}O_4N_2FS$ $[M+H]^+$: 375.08093; found: 375.08128; delta = 0.9 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68–7.76 (m, 2H), 6.99–7.02 (m, 4H), 6.50 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.5, 160.4, 145.2, 140.7, 132.8, 129.8, 129.6, 129.1, 128.6, 126.4, 123.2, 115.0, 112.4, 12.0.

2-Methyl-5-(4-methylphenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylic acid (32)

An intermediate for the synthesis of compound **17**. Mp > 350 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_4N_2S$ $[M+H]^+$: 371.10600; found: 371.10616; delta = 0.42 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75–7.80 (m, 2H), 7.22–7.29 (m, 2H), 6.95–6.98 (m, 2H), 6.85–6.89 (m, 2H), 6.58 (br s, 2H), 6.48 (s, 1H), 2.34 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7, 134.7, 132.5, 130.6, 130.4, 128.7, 128.5, 127.1, 126.3, 123.1, 112.0, 20.5, 12.0.

5-(3-chlororophenyl)-2-methyl-1-(4-sulfamoylphenyl)-1*H*-pyrrole-3-carboxylic acid (33)

An intermediate for the synthesis of compound **18**. Mp 237–240 °C; HESI-HRMS: calcd for $C_{18}H_{16}O_4N_2ClS$ $[M+H]^+$: 391.05138; found: 391.05171; delta = 0.83 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 7.87–7.92 (m, 2H), 7.51–7.54 (m, 2H), 7.47–7.52 (m, 2H), 7.18–7.25 (m, 2H), 7.15 (t, J = 1.8 Hz, 1H), 6.93 (td, J = 1.8, 6.8 Hz, 1H), 6.78 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 144.1, 140.0, 137.9, 133.7, 133.0, 131.5, 130.0, 129.2, 127.5, 126.8, 126.6, 126.3, 113.6, 111.4, 12.1.

4-[2-(4-chlorophenyl)-5-methyl-3-propanoyl-1*H*-pyrrol-1-yl]benzenesulfonamide (34)

See in Scheme 1.

Step 1. N-{4-[2-(4-chlorophenyl)-5-methyl-3-propanoyl-1H-pyrrol-1-yl*]benzenesulfonyl}-propanamide (**34**–**1**)*

Prepared according to *General method 1B (Friedel-Crafts reaction)* starting from compound **3** (3.21 g). Compound **34**–**1** was isolated by column chromatography from the isomeric mixture of mono and diacylated compounds. (See regioisomer at compound **36**.) Yield: 0.42 g (10%).

Step 2. 4-[2-(4-chlorophenyl)-5-methyl-3-propanoyl-1H-pyrrol-1-yl*]benzenesulfonamide (**34**)*

A mixture of a suspension of **34**–**1** (415 mg, 0.9 mmol) in ethanol (20 mL) and a solution of KOH (1.3 g) in water (5 mL) was heated under reflux overnight. Water was added and the mixture was acidified by the addition of 10% HCl during cooling with ice. The precipitate obtained was collected by filtration, washed until neutral, dried and recrystallized from methanol. Yield: 120 mg (33%) white crystals. Mp 250–251 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2ClS$ $[M+H]^+$: 403.08777; found: 403.08763; delta = −0.35 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77–7.79 (m, 2H), 7.46 (s, 2H), 7.37–7.41 (m, 2H), 7.28–7.31 (m, 2H), 7.18–7.21 (m, 2H), 6.60 (q, J = 1.0 Hz, 1H), 2.55 (q, J = 7.3 Hz, 2H), 2.03 (d, J = 0.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.7, 143.7, 139.7, 134.9, 132.9, 132.7, 130.8, 130.2, 129.2, 127.7, 126.4, 122.1, 108.6, 33.2, 12.6, 8.3.

Ethyl 5-(4-fluorophenyl)-1-(4-iodophenyl)-1*H*-pyrrole-3-carboxylate (35)

See in Scheme 1.

*Step 1. ethyl 2-amino-5-(4-fluorophenyl)-1-(4-iodophenyl)-1H-pyrrole-3-carboxylate (**35**–**2**)*

Synthesized in a manner analogous to the method described for the synthesis of compound **29** using ethyl 4-(4-fluorophenyl)-2-cyano-4-oxobutanoate (**35**–**1**) [34] instead of ethyl 4-(4-chlorophenyl)-2-cyano-4-oxobutanoate and 4-iodoaniline instead of sulfanylamide. Mp 41–43 °C; HESI-HRMS: calcd for $C_{19}H_{16}O_2NFI$ $[M+H]^+$: 436.02043; found: 436.02021; delta = −0.51 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74–7.79 (m, 2H), 7.69 (d, J = 1.9 Hz, 1H), 7.12–7.18 (m, 4H), 7.02–7.06 (m, 2H), 6.74 (d, J = 1.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.5, 161.4, 138.4, 138.1, 133.3, 130.4, 128.8, 127.9, 127.6, 116.4, 115.4, 110.8, 93.8, 59.4, 14.4.

*Step 2. ethyl 5-(4-fluorophenyl)-1-(4-iodophenyl)-1H-pyrrole-3-carboxylate (**35**)*

Prepared according to *General method 2 (reductive deamination)* starting from **35**–**2** (138 mg, 0.31 mmol). Yield: 34 mg (25%) of white solid.

4-(2-Methyl-5-phenyl-3-propyl-1*H*-pyrrol-1-yl)benzenesulfonamide (36)

See in Scheme 1.

Mp 158–162 °C; HESI-HRMS: calcd for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$: 355.14748; found: 355.14752; delta = 0.13 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79–7.85 (m, 2H), 7.46 (s, 2H), 7.30–7.39 (m, 2H), 7.14–7.19 (m, 2H), 7.05–7.11 (m, 1H), 6.96–7.01 (m, 2H), 6.27 (s, 1H), 2.37–2.43 (m, 2H), 1.99 (s, 3H), 1.57 (sxt, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.7, 141.9, 132.8, 132.1, 128.8, 128.2, 127.3, 127.2, 126.6, 125.7, 120.9, 110.6, 27.9, 23.8, 14.0, 10.7.

Step 1. N-{4-[5-(4-chlorophenyl)-2-methyl-3-propanoyl-1H-pyrrol-1-yl*]benzenesulfonyl}-propanamide (**36**–**1**)*

Prepared according to *General method 1B (Friedel-Crafts reaction)* starting from **3** (3.21 g). The desired product was isolated by column chromatography from the isomeric mixture of mono and diacylated compounds. (See regioisomer at compound **34**.) Yield: 0.95 g (23%) of yellow solid.

Step 2. N-[4-(2-methyl-5-phenyl-3-propyl-1H-pyrrol-1-yl*)benzenesulfonyl]propanamide (**36**–**2**)*

A solution of **36**–**1** (0.94 g, 2 mmol) in a mixture of tetrahydrofuran (20 mL) and methanol (40 mL) was vigorously stirred under hydrogen gas at atmospheric pressure in the presence of Pd/C (100 mg, 10%Pd) at room temperature overnight. After removal of the catalyst by filtration, the filtrate was concentrated and purified by column chromatography on silica using a 5 to 95 mixture of EtOAc and CH_2Cl_2 as the eluent. Yield: 0.42 g (50%) of white crystals.

Step 3. 4-(2-methyl-5-phenyl-3-propyl-1H-pyrrol-1-yl*)benzenesulfonamide (**36**)*

A mixture of a suspension of **36**–**2** (410 mg, 1 mmol) in ethanol (20 mL) and a solution of KOH (1.3 g) in water (5 mL) was heated under reflux overnight. Water was added and the mixture was acidified by the addition of 10% HCl during cooling with ice. The precipitate obtained was collected by filtration, washed until neutral, dried and purified by column chromatography on silica using a 25 to 75 mixture of EtOAc and cyclohexane as the eluent. Yield: 130 mg (36%) white crystals.

1-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (37)

Synthesized in a manner analogous to the method described in the literature [26] for 1-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide using 2,4-dichlorophenylhydrazine instead of 2-chlorophenylhydrazine. Mp 275–276 °C; HESI-HRMS: calcd for $C_{23}H_{25}O_3N_4Cl_2S$ $[M+H]^+$: 507.10189; found: 507.10199; delta = 0.20 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92–7.99 (m, 4H), 7.87 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 2.3 Hz, 1H), 7.64 (dd, J = 2.3, 8.5 Hz, 1H), 7.46–7.56 (m, 2H), 3.39 (br s, 4H), 3.26 (s, 3H), 2.32 (s, 3H), 1.78–1.89 (m, 4H), 1.37–1.60 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.8, 158.4, 142.7, 141.8, 141.2, 135.7, 135.2, 132.7, 132.0, 130.5, 129.8, 128.6, 127.3, 118.6, 115.2, 82.7, 56.4, 43.1, 23.1, 21.1, 9.0.

Ethyl 1-(4-chlorophenyl)-4-methyl-5-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (38)

See in Scheme 2.

*Step 1. N,N-bis[(4-methoxyphenyl)methyl]-4-propanoylbenzenesulfonamide (**38**–**2**)*

In an inert atmosphere, a mixture of 4-propanoylbenzene-1-sulfonamide **38**–**1** (1.16 g, 5.4 mmol), 4-methoxybenzyl chloride (1.5 mL), K_2CO_3 (1.51 g) and NaI (1.63 g) in methyl ethyl ketone (90 mL) was heated under reflux for 2 days while 3 times 4-methoxybenzyl chloride (1.5 mL), K_2CO_3 (1.51 g) and methyl ethyl ketone were repeatedly added. After cooling, water was added and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated and purified with column chromatography on silica, eluent: EtOAc- cyclohexane (1:4). Yield: 1.82 g (75%).

*Step 2. ethyl 4-(4-{bis[(4-methoxyphenyl)methyl]sulfamoyl}phenyl)-3-methyl-2,4-dioxobutanoate (**38**–**3**)*

In an inert atmosphere, to a mixture of diethyl ether (10 mL) and 1 M LiHMDS solution in THF (4.9 mL) was dropwise added a solution of **38**–**2** (2.18 g, 4.8 mmol) in a mixture of diethyl ether (3 mL) and THF (3 mL) at −70 °C and the mixture was stirred at −70 °C for 1 h. Diethyl oxalate (0.74 mL, 1.1 eq) was dropwise added and stirring was continued for further 2 h at −70 °C, then overnight at RT. The precipitated solid was filtered off, washed with ether, dried in vacuo, suspended in ethanol (4 mL), acidified with 6 M HCl (1 mL), water was added and the mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated. Yield: 610 mg (23%).

*Step 3. ethyl 5-(4-{bis[(4-methoxyphenyl)methyl]sulfamoyl}phenyl)-1-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate (**38**–**4**)*

A mixture of **38**–**3** (609 mg, 1.1 mmol), 4-chlorophenylhydrazine hydrochloride (207 mg, 1.1 eq), ethanol (4 mL) and aqueous HCl solution (6 M, 0.2 mL) was heated under reflux for 24 h. The reaction mixture was concentrated, purified by column chromatography on silica, eluent: EtOAc-cyclohexane (1:4) Yield: 101 mg (14%).

*Step 4. ethyl 1-(4-chlorophenyl)-4-methyl-5-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**38**)*

Prepared according to *General method 6 (bis-PMB-sulfonamide deprotection)* starting from **38**–**4** (101 mg, 0.15 mmol). Yield: 28 mg (44%). Mp 244–249 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_4N_3ClS$ $[M+H]^+$: 420.07793; found: 420.07861; delta = 1.61 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.83–7.86 (m, 2H), 7.47–7.52 (m, 2H), 7.42–7.48 (m, 4H), 7.27–7.32 (m, 2H), 4.34 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.1,

144.2, 141.8, 140.7, 137.8, 132.9, 131.9, 130.6, 129.2, 127.2, 126.0, 119.6, 60.3, 14.2, 9.4.

4-[1-(4-chlorophenyl)-3-propanoyl-1*H*-pyrazol-5-yl]benzene-1-sulfonamide (39)

See in Scheme 2.

*Step 1. N'-(4-acetylbenzene-1-sulfonyl)-N,N-dimethylmethanimidamide (**39**–**2**)*

To a suspension of 4-acetylbenzenesulfonamide (**39**–**1**) (2.68 g 13.4 mmol) in a mixture of EtOAc (25 mL) and DMF (5 mL), DMF-DMA (2 mL, 1.1 eq) was dropwise added. After stirring for 4 h at RT, the reaction mixture was concentrated in vacuo, triturated with diethyl ether (20 mL), the solid was collected, washed with ether and dried. Yield: 3.22 g of beige solid. MS: $[M + H^+] = 255.1$.

*Step 2. ethyl 4-(4-{[(dimethylamino)methylidene]sulfamoyl}phenyl)-2,4-dioxobutanoate (**39**–**3**)*

To a mixture of THF (20 mL) and 1 M LiHMDS solution in THF (10 mL) was dropwise added a suspension of **39**–**2** (2.54 g, 10 mmol) in THF (30 mL) under −70 °C in an inert atmosphere and the mixture was stirred at −70 °C for 1 h. Diethyl oxalate (1.5 mL, 1.1 eq) was dropwise added and stirring was continued for further 2 h at −70 °C, then overnight at RT (TLC eluent: MeOH–CH_2Cl_2, 5:95). The precipitated solid was filtered off, washed with ether, dried in vacuo, suspended in water (200 mL), acidified with cc. HCl (1 mL) and stirred for 15 min. The solid was collected by filtration, washed till neutral with water and dried. Yield: 2.40 g of beige solid. MS: $[M + H^+] = 355.3$.

*Step 3. ethyl 1-(4-chlorophenyl)-5-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**39**–**5**)*

A mixture of dioxoester (**39**–**3**) (1.20 g, 3.39 mmol), 4-chlorophenylhydrazine hydrochloride (667 mg, 1.1 eq), ethanol (15 mL) and aqueous HCl solution (20%, 0.6 mL) was heated under reflux for 12 h (TLC eluent: MeOH–CH_2Cl_2, 5:95). The solid precipitated upon cooling overnight was filtered off, washed with cold ethanol and dried affording 126 mg of ethyl 1-(4-chlorophenyl)-3-(4-sulfamoylphenyl)-1*H*-pyrazole-5-carboxylate (**39**–**4**). The filtrate was concentrated, purified with column chromatography on silica, eluent: EtOAc- cyclohexane (1:3, then 2:3) resulting in 31 mg of **39**–**4** and 550 mg of *ethyl 1-(4-chlorophenyl)-5-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate* (**39**–**5**). Yield: 550 mg. MS: $[M + H^+] = 406.0$.

*Step 4. 1-(4-chlorophenyl)-5-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylic acid (**39**–**6**)*

To a solution of **39**–**5** (540 mg, 1.3 mmol) in ethanol (20 mL) was added a solution of KOH (390 mmol, 6 eq) in water (1 mL) and the mixture was heated under reflux 30 min. The mixture was cooled with ice, water (40 mL) was added and the pH was adjusted to 2 by adding 1 M HCl solution (6 mL). The mixture was extracted with CH_2Cl_2, and EtOAc, the collected organic layer was dried over Na_2SO_4 and concentrated under vacuum. Yield: 390 mg of light yellow solid. MS: $[M + H^+] = 378.0$.

*Step 5. 1-(4-chlorophenyl)-5-(4-{[(dimethylamino)methylidene]sulfamoyl}phenyl)-N-methoxy-N-methyl-1H-pyrazole-3-carboxamide (**39**–**8**)*

Under an inert atmosphere, compound **39**–**6** (385 mg, 1.0 mmol) was suspended in CH_2Cl_2 (10 mL), DMF (0.15 mL, 1.9 eq) was added followed by a dropwise addition of a solution of oxalyl chloride (0.26 mL, 3 eq) in CH_2Cl_2 (1.5 mL) while cooling with ice. The mixture was stirred at RT for 4 h, the solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (10 mL). Next, *N,O*-dimethylhydroxylamine hydrochloride (110 mg, 1.1 eq) was added, followed by a dropwise addition of triethylamine (0.36 mL, 2.5 eq) during cooling in an ice-water bath and the mixture was stirred overnight at RT. The reaction mixture was diluted with CH_2Cl_2 (20 mL), extracted with 5% HCl, saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated. The residue was purified with column chromatography on silica, eluent: MeOH– CH_2Cl_2 (1:99). Yield: 270 mg of light yellow amorphous solid. MS: $[M + H^+] = 476.1$.

*Step 6. N'-{4-[1-(4-chlorophenyl)-3-propanoyl-1H-pyrazol-5-yl]benzene-1-sulfonyl}-N,N-dimethylmethanimidamide (**39**–**9**)*

Under an inert atmosphere, Mg turnings (68 mg, 2.8 mmol) and a small I_2 crystal was covered with anhydrous THF (1 mL). A solution of ethyl bromide (0.21 mL, 2.8 mmol) in THF (1 mL) was dropwise added during vigorous stirring. After all Mg had reacted, a suspension of the Weinreb amide **39**–**8** (261 mg) in THF (5 mL) was added and the mixture was heated under reflux for 3 h. After cooling with ice, a saturated NH_4Cl solution (10 mL) was dropwise added and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated and purified with column chromatography on silica, eluent: EtOAc-CH_2Cl_2 (5:95). Yield: 159 mg of white crystals. MS: $[M + H^+] = 445.1$.

*Step 7. 4-[1-(4-chlorophenyl)-3-propanoyl-1H-pyrazol-5-yl]benzenesulfonamide (**39**)*

Compound **39**–**9** (153 mg, 0.34 mmol) was dissolved in THF (5 mL), a solution of KOH (94 mg, ~4.5 eq, 90%) in MeOH (2.5 mL) was added and the mixture was stirred overnight at RT. (TLC eluent: EtOAc). After cooling with ice, water (10 mL) was added, acidified with 10% HCl and the organic solvents were evaporated. The aqueous residue was extracted with CH_2Cl_2, the organic phase was washed with water, dried over Na_2SO_4, concentrated and purified with column chromatography on silica, eluent: EtOAc-CH_2Cl_2 (1:9). Yield: 82 mg of white crystals. HPLC purity: 99.7%.

Mp 202–204 °C; HESI-HRMS: M + H = 390.06658 (delta = −2.0 ppm; $C_{18}H_{17}O_3N_3ClS$). HR-ESI-MS-MS (CID = 45%; rel. int. %): 373(100); 334(35); 309(1); 292(1).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.79–7.82 (2H, m, H-16, 15), 7.55–7.59 (2H, m, H-10, 9), 7.46–7.50 (2H, m, H-14, 13), 7.44 (2H, br s, H-22), 7.39–7.43 (2H, m, H-8, 7), 7.21 (1H, s, H-4), 3.05 (2H, q, *J* = 7.3 Hz, H-24), 1.12 (3H, t, *J* = 7.3 Hz, H-26); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 195.8 (C-23), 150.8 (C-5), 144.2 (C-17), 143.5 (C-2), 137.8 (C-6), 133.3 (C-11), 131.9 (C-12), 129.5 (C-10, 9), 129.2 (C-14, 13), 127.4 (C-8, 7), 126.0 (C-16, 15), 108.4 (C-4), 31.5 (C-24), 7.9 (C-26).

4-[3-(4-fluorophenyl)-5-propanoyl-1*H*-pyrrol-2-yl]benzenesulfonamide (40)

See in Scheme 3.

*Step 1. N-methoxy-N-methyl-4-[N,N-bis(4-methoxybenzyl)sulfamoyl]benzamide (**40**–**2**)*

Prepared according to *General method 4 (amidation)* starting from 4-[*N,N*-bis(4-methoxybenzyl)sulfamoyl]benzoic acid (**40**–**1**) [36,37] (6.75 g, 15.3 mmol). Yield: 7.14 g (95%) of colourless oil.

*Step 2. N,N-bis(4-methoxybenzyl)-4-[(4-fluorophenyl)acetyl]benzenesulfonamide (**40**–**3**)*

General method 5B (Grignard reaction) starting from **40**–**2** (2.9 g, 6 mmol). Yield: 2.29 g (72%) of white solid.

*Step 3. N,N-bis(4-methoxybenzyl)-4-[3-(1,3-dioxolan-2-yl)-2-(4-fluorophenyl)propanoyl]-benzenesulfonamide (**40**–**4**)*

Under an inert atmosphere, a solution of **40**–**3** (2.285 g, 4.28 mmol) in a mixture of DMF (12 mL) and THF (12 mL) cooled with ice-water was treated with NaH (206 mg, 1.2 eq, 60% in mineral oil) in portions. 2-Bromomethyl-1,3-dioxolane (0.5 mL, 1.1 eq) was added and the mixture was heated under reflux for 10 h (TLC eluent: EtOAc-cyclohexane, 3:7).

Water was added, and the mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica (eluent: EtOAc-cyclohexane, 1:9 to 1:1). (The slower eluted component is the product.) Yield: 807 mg (30%) of yellowish oil.

*Step 4. N,N-bis(4-methoxybenzyl)-4-[2-(4-fluorophenyl)-4-oxobutanoyl]benzenesulfonamide (**40**–**5**)*

A solution of **40**–**4** (800 mg, 1.29 mmol) in acetone (50 mL) was treated with 3 M HCl solution (10 mL) and the mixture was stirred at RT overnight. After repeated addition of HCl solution (2 × 2 mL) the reaction mixture was stirred at RT for another 2 days. After neutralization with 3 M NaOH solution during cooling with ice, the volatile organic solvent was removed under reduced pressure, the aqueous residue was extracted with ether, dried and concentrated. Yield: 0.79 g (quant.) of yellowish solid (used without further purification).

*Step 5. N,N-bis(4-methoxybenzyl)-4-[3-(4-fluorophenyl)-1H-pyrrol-2-yl]benzenesulfonamide (**40**–**6**)*

A solution of **40**–**5** (785 mg, 1.33 mmol) in THF (10 mL) was divided into 5 equal portions and placed into 5 pieces of 10 mL microwave reaction vessels, respectively. Acetic acid (2-2 mL), NH_4OAc (1-1 g) and 4 Å molecular sieves (20-20 pieces) were added to each portion of the reaction mixture. The vessels were closed and consecutively irradiated in CEM Voyager microwave reactor at 170 °C for 15 min. The reaction mixture portions were united, diluted with EtOAc (200 mL), washed with sat. $NaHCO_3$ solution and brine, dried, concentrated, and the residue was purified by column chromatography on silica (eluent: CH_2Cl_2). Yield: 403 mg (54%) of white solid.

*Step 6 N,N-bis(4-methoxybenzyl)-{4-[3-(4-fluorophenyl)-5-propanoyl-1H-pyrrol-2-yl]}benzenesulfonamide (**40**–**7**)*

Prepared according to *General method 1A (Friedel-Crafts reaction)* starting from **40**–**6** (280 mg, 0.5 mmol). Yield: 260 mg (85%) of pinkish solid.

*Step 7. 4-[3-(4-fluorophenyl)-5-propanoyl-1H-pyrrol-2-yl]benzenesulfonamide (**40**)*

Prepared according to *General method 6 (bis-PMB-sulfonamide deprotection)* starting from **40**–**7** (250 mg, 0.41 mmol). Yield: 55 mg (36%) of pinkish solid. Mp 279 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_3N_2FS$ $[M+H]^+$: 373.10167; found: 373.10203; delta = 0.97 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.21 (br s, 1H), 7.71–7.80 (m, 2H), 7.48–7.57 (m, 2H), 7.40 (s, 2H), 7.23–7.28 (m, 2H), 7.21 (s, 1H), 7.13–7.19 (m, 2H), 2.86 (q, J = 7.4 Hz, 2H), 1.12 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 190.7, 161.0, 142.9, 134.5, 132.8, 131.9, 131.6, 130.2, 128.9, 125.6, 123.2, 117.7, 115.4, 30.7, 9.0.

4-[3-(4-chlorophenyl)-5-propanoyl-1*H*-pyrrol-2-yl]benzenesulfonamide (41)

Synthesized in a manner analogous to the method described for the synthesis of compound **40** using 4-chlorobenzyl bromide instead of 4-fluorobenzyl chloride. Mp 288–289 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_3N_2ClS$ $[M+H]^+$: 389.07212; found: 389.07273; delta = 1.58 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (br s, 1H), 7.66–7.84 (m, 2H), 7.49–7.61 (m, 2H), 7.33–7.46 (m, 4H), 7.09–7.30 (m, 3H), 2.86 (q, J = 7.4 Hz, 2H), 1.12 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.7, 143.1, 134.4, 134.1, 133.0, 132.0, 131.1, 130.0, 129.0, 128.6, 125.7, 122.8, 117.6, 30.7, 8.9.

4-[3-(4-fluorophenyl)-1-methyl-5-propanoyl-1*H*-pyrrol-2-yl]benzenesulfonamide (42)

See in Scheme 3.

*Step 1. N,N-bis(4-methoxybenzyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrrol-2-yl]benzene-sulfonamide (**42**–**1**)*

Prepared according to *General method 7 (N-methylation)* starting from **40**–**6** (225 mg, 0.4 mmol). Yield: 292 mg of colourless amorphous solid.

*Step 2. N,N-bis(4-methoxybenzyl)-{4-[3-(4-fluorophenyl)-1-methyl-5-propanoyl-1H-pyrrol-2-yl]}benzenesulfonamide (**42**–**2**)*

Prepared according to *General method 1A (Friedel-Crafts reaction)* starting from **42**–**1** (200 mg, 0.35 mmol). Yield: 125 mg of off-white solid.

*Step 3. 4-[3-(4-fluorophenyl)- 1-methyl-5-propanoyl-1H-pyrrol-2-yl]benzenesulfonamide (**42**)*

The title compound was synthesized according to *General method 6 (bis-PMB-sulfonamide deprotection)* starting from **42**–**2** (122 mg, 0.2 mmol). Yield: 58 mg of light yellow solid. Mp 250–251 °C HESI-HRMS: calcd for $C_{20}H_{20}O_3N_2FS$ $[M+H]^+$: 387.11732; found: 387.11718; delta = −0.35 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 7.71 Hz, 2H), 7.52 (d, J = 8. 6 Hz, 2H), 7.48 (br s, 2H), 7.44 (s, 1H), 7.07 (s, 4H), 3.68 (s, 3H), 2.92 (q, J = 7.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.2, 160.1, 143.5, 133.4, 130.8, 130.4, 129.9, 128.9, 125.4, 117.8, 114.6, 33.9, 31.3, 8.5.

4-[5-(4-fluorophenyl)-3-propanoyl-1*H*-pyrazol-1-yl]benzenesulfonamide (43)

See in Scheme 3.

*Step 1. 5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylic acid (**43**–**2**)*

Prepared according to *General method 3 (ester hydrolysis)* starting from ethyl 5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (**43**–**1**) [38] (418 mg, 1.1 mmol). Yield: 368 mg (95%) yellowish crystals.

*Step 2. 1-(4-{[(Z)-[(dimethylamino)methylidene]amino]sulfonyl}phenyl)-5-(4-fluorophenyl)-N-methoxy-N-methyl-1H-pyrazole-3-carboxamide (**43**–**3**)*

Prepared according to *General method 4 (amidation)* starting from **43**–**2** (702 mg, 1.9 mmol). Yield: 518 mg (58%) white solid.

*Step 3 (Z)-N'-{4-[5-(4-fluorophenyl)-3-propanoyl-1H-pyrazol-1-yl]benzenesulfonyl}-N,N-dimethylmethanimidamide (**43**–**4**)*

Prepared according to *General method 5A (Grignard reaction)* starting from **43**–**3** (513 mg, 1.1 mmol). Yield: 170 mg (35%).

*Step 4. 4-[5-(4-fluorophenyl)-3-propanoyl-1H-pyrazol-1-yl]benzene-1-sulfonamide (**43**)*

Prepared according to *General method 8 (N-(dimethylamino) methylidene sulfonamide deprotection)* starting from **43**–**4** (165 mg, 0.39 mmol). Yield: 104 mg (73%). Mp 199–200 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3FS$ $[M+H]^+$: 374.09692; found: 374.09671; delta = −0.55 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86–7.91 (m, 2H), 7.52–7.57 (m, 2H), 7.50 (s, 2H), 7.32–7.39 (m, 2H), 7.24–7.30 (m, 2H), 7.12 (s, 1H), 3.05 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 161.8, 150.4, 143.4, 143.2, 140.7, 130.6, 126.2, 125.2, 115.3, 107.5, 30.9, 7.4.

4-[5-(4-chlorophenyl)-3-propanoyl-1*H*-pyrazol-1-yl]benzenesulfonamide (44)

Synthesized in a manner analogous to the method described for the synthesis of compound **43** starting from ethyl 5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate instead of ethyl 5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (**43**–**1**). Mp 188–189 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3ClS$ $[M+H]^+$: 390.06737; found: 390.06717; delta = −0.50 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87–7.91 (m, 2H), 7.53–7.58 (m, 2H), 7.46–7.52 (m, 4H), 7.30–7.36 (m, 2H), 7.16 (s, 1H), 3.05 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.2, 150.4, 143.2, 143.2, 140.6, 133.4, 130.0, 128.3, 127.1, 126.3, 125.3, 107.7, 30.9, 7.4.

Ethyl 5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (45) [38]

Mp 216–217 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_4N_3FS$ $[M+H]^+$: 390.09183; found: 390.09218; delta = 0.89 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83–7.91 (m, 2H), 7.47–7.56 (m, 4H), 7.31–7.41 (m, 2H), 7.22–7.32 (m, 2H), 7.17 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 161.1, 162.4, 144.1, 143.8, 143.7, 141.2, 131.2, 126.8, 125.9, 125.2, 115.9, 110.4, 60.7, 14.2.

Ethyl 5-(4-chlorophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (46) [39]

Mp 209–210 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_4N_3ClS$ $[M+H]^+$: 406.06228; found: 406.06286; delta = 1.42 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81–7.94 (m, 2H), 7.51–7.56 (m, 4H), 7.46–7.51 (m, 2H), 7.29–7.35 (m, 2H), 7.20 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 144.2, 143.9, 143.5, 141.2, 134.0, 130.6, 128.9, 127.5, 126.8, 125.9, 110.5, 60.7, 14.2.

4-[3-(4-fluorophenyl)-5-propanoylfuran-2-yl]benzenesulfonamide (47)

See in Scheme 4.

*Step 1. 4-[2-cyano-2-(4-fluorophenyl)acetyl]-N,N-bis[(4-methoxyphenyl)methyl]benzene-1-sulfonamide (**47**–**2**)*

A suspension of (4-fluorophenyl)acetonitrile (1.8 mL, 14.95 mmol) in THF (80 mL) was treated with NaH (1.43 g, 2.4 eq, 60% in mineral oil) at RT. After 5 min of stirring, a solution of methyl 4-[*N*,*N*-bis(4-methoxybenzyl)sulfamoyl]benzoate [36] (**47**–**1**) (6.81 g, 1 eq) in THF (120 mL) was added and the mixture was heated under reflux for 3 h. The reaction was quenched by dropwise addition of water at 0 °C followed by acidification with 1 M HCl solution. The volatile organic solvent was removed under reduced pressure and the aqueous residue was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica (eluent: EtOAc-CH_2Cl_2, 0 to 5:95). Yield: 5.51 g (66%) of yellow oil.

Step 2. 4-[(1E)-2-cyano-2-(4-fluorophenyl)-1-(2-oxobutoxy)eth-1-en-1-yl]-N,N-bis[(4-methoxyphenyl)methyl]benzenesulfonamide (47–3)

To a solution of **47**–**2** (5.50 g, 9.85 mmol) in DMF (17 mL), was added 1-bromo-2-butanone (0.96 mL, 9.4 mmol) followed by triethyl amine (1.4 mL, 10 mmol). The mixture was placed into an oil bath preheated to 50 °C and stirred for 10 min at this temperature. After cooling to RT, water was added, the precipitated gummy material was decantated, dissolved in CH_2Cl_2, dried, concentrated and purified by column chromatography on silica (eluent: CH_2Cl_2). Yield: 3.86 g (62%) of light yellow oil.

*Step 3. 4-[4-amino-3-(4-fluorophenyl)-5-propanoylfuran-2-yl]-N,N-bis[(4-methoxyphenyl)-methyl]benzenesulfonamide (**47**–**4**)*

To a solution of **47**–**3** (3.86 g) in ethanol (26 mL), was added freshly prepared 0.67 M NaOEt solution (13 mL) and the mixture was heated under reflux in an oil bath preheated to 100 °C and for 10 min. After cooling in an ice bath, the crystals separated were filtered off, washed with cold ethanol and dried. Yield: 2.49 g (65%) of yellow crystals.

*Step 4. 4-[3-(4-fluorophenyl)-5-propanoylfuran-2-yl]-N,N-bis[(4-methoxyphenyl)methyl]-benzenesulfonamide (**47**–**5**)*

Prepared according to *General method 2 (reductive deamination)* starting from **47**–**4** (314 mg, 0.5 mmol). Yield: 38 mg (12%) of yellow oil.

*Step 5. 4-[3-(4-fluorophenyl)-5-propanoylfuran-2-yl]benzenesulfonamide (**47**)*

Prepared according to *General method 6 (bis-PMB-sulfonamide deprotection)* starting from **47**–**5**) (190 mg, 0.31 mmol). Yield: 72 mg (63%) of yellow solid. Mp 221–225 °C; HESI-HRMS: calcd for $C_{19}H_{17}O_4NFS$ $[M+H]^+$: 374.08568; found: 374.08542; delta = −0.72 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82–7.87 (m, 2H), 7.74 (s, 1H), 7.66–7.72 (m, 2H), 7.45 (s, 4H), 7.27–7.35 (m, 2H), 2.95 (d, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.7, 161.4, 143.6, 131.5, 130.1, 127.6, 126.5, 125.7, 120.5, 115.5, 30.5, 7.5.

4-[4-Amino-3-(4-fluorophenyl)-5-propanoylfuran-2-yl]benzenesulfonamide (48)

See in Scheme 4.

Prepared according to *General method 6 (bis-PMB-sulfonamide deprotection)* starting from *4-[(1E)-2-cyano-2-(4-fluorophenyl)-1-(2-oxobutoxy)eth-1-en-1-yl]-N,N-bis[(4-methoxyphenyl)methyl]benzenesulfonamide* (47–4) (95 mg, 0.15 mmol). Yield: 40 mg (69%) yellow solid. Mp 251–254 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_4N_2FS$ $[M+H]^+$: 389.09658; found: 389.09640; delta = −0.48 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76–7.80 (m, J = 8.7 Hz, 2H), 7.52–7.61 (m, J = 8.7 Hz, 2H), 7.32–7.45 (m, 6H), 5.94 (s, 2H), 2.80 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.2, 161.5, 148.1, 143.7, 143.5, 133.3, 131.6, 131.4, 126.1, 125.5, 125.4, 115.8, 115.4, 29.6, 7.7.

4-(4-fluorophenyl)-5-(4-sulfamoylphenyl)-1,3-oxazole-2-carboxamide (49)

See in Scheme 4.

*Step 1. ethyl 4-(4-fluorophenyl)-5-phenyl-1,3-oxazole-2-carboxylate (**49**–**2**)*

A mixture of 1-(4-fluorophenyl)-*N*-hydroxy-2-phenylethanimine (**49**–**1**) [40] (5.53 g, 24.1 mmol) and ethyl chlorooxoacetate (8.1 mL, 3 eq.) was stirred at RT for 15 min then at 120 °C for 2 h. After cooling to 0 °C, the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, brine, dried and concentrated. The residue was purified by column chromatography on silica (eluent: EtOAc-cyclohexane, 5:95). Yield: 3.55 g (47%) of white solid.

*Step 2. 4-(4-fluorophenyl)-5-(4-sulfamoylphenyl)-1,3-oxazole-2-carboxamide (**49**)*

To chlorosulfonic acid (60 mL) cooled to 0 °C was added solid compound **49**–**2** (2.58 g, 8.29 mmol) portionwise with stirring. The mixture was stirred at the same temperature for another 30 min then at RT for 3 h. The reaction mixture was dropwise added to crushed ice (Caution! Violent reaction!) The precipitated product was filtered off with suction, washed with water, dissolved in dioxane (200 mL) and the solution obtained was dropwise added to NH_4OH solution (25%) cooled to 0 °C. After 64 h of stirring at RT, the mixture was concentrated under reduced pressure, the residue was suspended in water, acidified to pH = 3 by addition of 10% HCl solution. The precipitate was filtered off, washed with water, dried and purified by column chromatography on silica (eluent: EtOAc-CH_2Cl_2, 1:9 to 1:1). Yield: 965 mg (32%) of white solid. Mp 225–227 °C; HESI-HRMS: calcd for $C_{16}H_{13}O_4N_3FS$ $[M+H]^+$: 362.06053; found: 362.06035; delta = −0.51 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40–8.40 (m, 1H), 8.43 (s, 1H), 8.04 (s, 1H), 7.88–7.92 (m, 1H), 7.77–7.81 (m, 2H), 7.60–7.70 (m, 2H), 7.48 (br s, 2H), 7.25–7.39 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 155.4, 153.4, 144.9, 144.0, 138.4, 135.6, 129.8, 129.6, 126.5, 125.8, 115.4.

4-[5-(4-fluorophenyl)-2-propanoyl-1,3-oxazol-4-yl]benzenesulfonamide (50)

*Step 1. 4-[2-(4-fluorophenyl)-1-(hydroxyimino)ethyl]-N,N-bis[(4-methoxyphenyl)methyl]-benzenesulfonamide (**50**–**1**)*

See in Scheme 4.

A solution of **40**–**3** (3.73 g, 7 mmol), hydroxylamine hydrochloride (7.3 g, 1.5 eq) and NaOAc (8.6 g, 1.5 eq) in ethanol (50 mL) was heated under reflux for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with ice water, allowed to stand in a refrigerator, the precipitated solid was filtered off, washed with water and dried. Yield: 3.605 g (94%) white solid.

*Step 2. Ethyl 5-(4-fluorophenyl)-4-(4-sulfamoylphenyl)-1,3-oxazole-2-carboxylate (**51**)*

A mixture of **50**–**1** (3.60 g, 6.6 mmol) and ethyl chlorooxoacetate (2.2 mL, 19.7 mmol) was stirred at RT for 15 min, then at 120 °C for 2 h. After cooling in an ice bath, the waxy residue was dissolved in CH_2Cl_2, washed with brine, dried and concentrated. The residue was purified by column chromatography on silica (eluent: EtOAc-CH_2Cl_2, 1:9). Yield: 515 mg (20%) of beige solid.

*Step 3. 5-(4-fluorophenyl)-4-(4-sulfamoylphenyl)-1,3-oxazole-2-carboxylic acid (**50**–**2**)*

Prepared according to *General method 3 (ester hydrolysis)* starting from ethyl 5-(4-fluorophenyl)-4-(4-sulfamoylphenyl)-1,3-oxazole (**51**) (460 mg, 1.18 mmol). Yield: 360 mg (84%) of off-white solid.

Step 4. 4-(4-{[(Z)-[(dimethylamino)methylidene]amino]sulfonyl}phenyl)-5-(4-fluorophenyl)-N-methoxy-N-methyl-1,3-oxazole-2-carboxamide (50–3)

Prepared according to *General method 4 (amidation)* starting from **50**–**2** (360 mg, 0.92 mmol). Yield: 270 mg (64%) of colourless oil.

*Step 5. N-[(dimethylamino)methylidene]-4-[5-(4-fluorophenyl)-2-propanoyl-1,3-oxazol-4-yl]benzenesulfonamide (**50**–**4**)*

Prepared according to *General method 5A (Grignard reaction)* starting from **50**–**3** (270 mg, 0.59 mmol). Yield: 70 mg (28%) of white solid.

*Step 6. 4-[5-(4-fluorophenyl)-2-propanoyl-1,3-oxazol-4-yl]benzenesulfonamide (**50**)*

Prepared according to *General method 8 (N-(dimethylamino) methylidene sulfonamide deprotection)* starting from **50**–**4** (66 mg, 0.15 mmol). Yield: 26 mg (46%) of white solid. Mp 204–209 °C; HESI-HRMS: calcd for $C_{18}H_{16}O_4N_2FS$ $[M+H]^+$: 375.08093; found: 375.08046; delta = −1.26 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86–7.93 (m, 2H), 7.76–7.83 (m, 2H), 7.65–7.73 (m, 2H), 7.43–7.53 (m, 2H), 7.35–7.43 (m, 2H), 3.37–3.41 (m, 4H), 3.14 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.4, 163.1, 147.8, 146.5, 144.1, 134.1, 130.0, 128.0, 126.3, 123.5, 116.6, 32.0, 7.5.

Ethyl 5-(4-fluorophenyl)-4-(4-sulfamoylphenyl)-1,3-oxazole-2-carboxylate (51)

Intermediate of the synthesis of compound **50**. Mp 196–197 °C; HESI-HRMS: calcd for $C_{18}H_{16}O_5N_2FS$ $[M+H]^+$: 391.07585; found: 391.07574; delta = −0.26 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84–7.94 (m, 2H), 7.75–7.82 (m, 2H), 7.64–7.72 (m, 2H), 7.46 (s, 2H), 7.30–7.44 (m, 2H), 4.43 (q, J = 7.09 Hz, 2H), 1.36 (t, J = 7.09 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 154.4, 150.2, 147.5, 143.5, 134.5, 133.3, 129.5, 127.3, 125.7, 122.8, 116.0, 61.8, 13.4.

Compounds **52**–**68** were synthesized in a manner analogous to the method described for the synthesis of compound **39**. See it in Scheme 2.

4-[3-Butanoyl-1-(4-chlorophenyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (52)

Mp 190–191 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_3N_3ClS$ $[M+H]^+$: 404.08302; found: 404.08305; delta = 0.08 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76–7.84 (m, 2H), 7.53–7.61 (m, 2H), 7.45–7.52 (m, 2H), 7.37–7.45 (m, 4H), 7.21 (s, 1H), 3.01 (t, J = 7.2 Hz, 2H), 1.69 (sxt, J = 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.7, 150.5, 143.6, 143.0, 137.2, 132.8, 131.3, 128.9, 128.6, 126.9, 125.4, 107.8, 39.5, 16.5, 13.1.

4-[3-Acetyl-1-(4-chlorophenyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (53)

Mp 183–184 °C; HESI-HRMS: calcd for $C_{17}H_{15}O_3N_3ClS$ $[M+H]^+$: 376.05172; found: 376.05207; delta = 0.92 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68–7.89 (m, 2H), 7.52–7.64 (m, 2H), 7.38–7.51 (m, 6H), 7.21 (s, 1H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.4, 150.7, 143.6, 143.1, 137.1, 132.8, 131.3, 128.9, 128.6, 126.9, 125.4, 107.7, 25.8.

4-[1-(4-chlorophenyl)-3-(2,2-dimethylpropanoyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (54)

Mp 178 °C; HESI-HRMS: calcd for $C_{20}H_{21}O_3N_3ClS$ $[M+H]^+$: 418.09867; found: 418.09880; delta = 0.33 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10–10.12 (m, 1H), 7.75–7.87 (m, 2H), 7.53–7.64 (m, 2H), 7.36–7.52 (m, 6H), 7.17 (s, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 199.1, 149.1, 143.5, 141.9, 137.2, 132.6, 131.4, 128.9, 128.7, 126.6, 125.3, 110.0, 43.0, 26.5.

4-[1-(4-chlorophenyl)-3-(2-methylpropanoyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (55)

ESI-LRMS: $[M+H]^+$: 404. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75–7.87 (m, 2H), 7.52–7.63 (m, 2H), 7.35–7.52 (m, 6H), 7.22 (s, 1H), 3.62–3.74 (m, 1H), 1.17 (d, 6H).

4-[1-(4-chlorophenyl)-3-(cyclopropanecarbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (56)

Mp 215 °C; HESI-HRMS: calcd for $C_{19}H_{17}O_3N_3ClS$ $[M+H]^+$: 402.06737; found: 402.06754; delta = 0.43 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77–7.84 (m, 2H), 7.54–7.61 (m, 2H), 7.47–7.51 (m, 2H), 7.43–7.47 (m, 4H), 7.21 (s, 1H), 3.02–3.08 (m, 1H), 1.07 (d, J = 6.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.2, 150.8, 143.6, 143.1, 137.2, 132.8, 131.3, 128.9, 128.7, 126.9, 125.4, 107.5, 16.4, 10.6.

4-[1-(4-chlorophenyl)-3-(cyclobutanecarbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (57)

Mp 221–222 °C; HESI-HRMS: calcd for $C_{20}H_{19}O_3N_3ClS$ $[M+H]^+$: 416.08302; found: 416.08298; delta = −0.08 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 7.37–7.50 (m, 5H), 7.21 (s, 1H), 4.17 (quin, J = 8.3 Hz, 1H), 2.18–2.34 (m, 4H), 1.98–2.10 (m, 1H), 1.70–1.87 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.1, 149.2, 143.6, 142.9, 137.1, 132.7, 131.3, 128.8, 128.7, 126.8, 125.3, 108.2, 40.9, 23.8, 17.1.

4-[1-(4-chlorophenyl)-3-(cyclopentanecarbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (58)

Mp 197–200 °C; HESI-HRMS: calcd for $C_{21}H_{21}O_3N_3ClS$ $[M+H]^+$: 430.09867; found: 430.09893; delta = 0.60 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75–7.84 (m, 2H), 7.53–7.62 (m, 2H), 7.46–7.51 (m, 2H), 7.38–7.46 (m, 4H), 7.22 (s, 1H), 3.88 (quin, J = 8.0 Hz, 1H), 1.86–2.01 (m, 2H), 1.73–1.85 (m, 2H), 1.52–1.71 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.6, 150.8, 144.2, 143.5, 137.8, 133.3, 132.0, 129.5, 129.3, 127.4, 126.0, 108.8, 46.4, 29.4, 25.8.

4-[1-(4-chlorophenyl)-3-(cyclobutylacetyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (59)

Mp 171–173 °C; HESI-HRMS: calcd for $C_{21}H_{21}O_3N_3ClS$ $[M+H]^+$: 430.09867; found: 430.09929; delta = 1.44 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.86 (m, 2H), 7.53–7.61 (m, 2H), 7.38–7.51 (m, 6H), 7.19 (s, 1H), 3.14 (d, J = 7.3 Hz, 2H), 2.79 (spt, J = 7.7 Hz, 1H), 1.98–2.20 (m, 2H), 1.58–1.96 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.6, 151.1, 144.2, 143.6, 137.8, 133.4, 131.9, 129.5, 129.3, 127.5, 126.0, 108.3, 45.2, 31.4, 27.9, 18.4.

4-[1-(4-chlorophenyl)-3-(2-cyclopentylacetyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (60)

Mp 113–115 °C; HESI-HRMS: calcd for $C_{22}H_{23}O_3N_3ClS$ $[M+H]^+$: 444.11432; found: 444.11447; delta = 0.34 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.90 Hz, 1H), 7.57 (d, J = 7.91 Hz, 1H), 7.40–7.49 (m, 3H), 7.21 (s, 1H), 3.04 (d, J = 7.21 Hz, 1H), 2.35 (td, J = 7.89, 15.28 Hz, 1H), 1.73–1.85 (m, 1H), 1.40–1.66 (m, 2H), 1.09–1.35 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.6, 150.6, 143.6, 143.0, 137.2, 132.8, 131.3, 128.9, 128.7, 126.9, 125.4, 107.8, 43.6, 34.9, 31.5, 23.9.

4-{3-Propanoyl-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl}benzenesulfonamide (61)

Mp 209–211 °C; HESI-HRMS: calcd for $C_{19}H_{17}O_3N_3F_3S$ $[M+H]^+$: 424.09372; found: 424.09336; delta = −0.86 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86–7.91 (m, 2H), 7.79–7.84 (m, 2H), 7.58–7.65 (m, 2H), 7.48–7.53 (m, 2H), 7.45 (s, 2H), 7.25 (s, 1H), 3.07 (q, J = 7.3 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.2, 150.6, 143.7, 143.1, 141.4, 131.3, 128.7, 128.2, 126.1, 125.6, 125.4, 123.2, 108.3, 30.9, 7.3.

4-[1-(4-fluorophenyl)-3-propanoyl-1*H*-pyrazol-5-yl]benzenesulfonamide (62)

Mp 191–193 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3FS$ $[M+H]^+$: 374.09692; found: 374.09714; delta = 0.6 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74–7.84 (m, 2H), 7.44–7.48 (m, 4H), 7.43 (br s, 2H), 7.30–7.39 (m, 2H), 7.21 (s, 1H), 3.04 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.9, 161.7, 150.6, 144.1, 143.6, 132.0, 129.2, 128.1, 125.9, 116.4, 108.0, 31.5, 8.0.

4-[1-(3-chlorophenyl)-3-propanoyl-1*H*-pyrazol-5-yl]benzenesulfonamide (63)

Mp 182 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3ClS$ $[M+H]^+$: 390.06737; found: 390.06788; delta = 1.32 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.9 Hz, 1H), 7.42–7.61 (m, 3H), 7.27 (ddd, J = 1.0, 2.0, 7.9 Hz, 1H), 7.22 (s, 1H), 3.06 (q, J = 7.3 Hz, 1H), 1.12 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 150.3, 143.6, 143.0, 139.5, 133.0, 131.3, 130.4, 128.7, 128.3, 125.3, 125.0, 123.9, 107.8, 30.9, 7.3.

4-[1-(2-chlorophenyl)-3-propanoyl-1*H*-pyrazol-5-yl]benzenesulfonamide (64)

Mp 214 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3ClS$ $[M+H]^+$: 390.06737; found: 390.06772; delta = 0.91 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72–7.80 (m, 3H), 7.55–7.67 (m, 3H), 7.37–7.47 (m, 4H), 7.28 (s, 1H), 3.02 (q, J = 7.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 150.5, 144.4, 143.6, 136.0, 131.3, 131.1, 130.0, 129.8, 129.7, 128.0, 127.7, 125.3, 106.3, 30.9, 7.4.

4-(1-Phenyl-3-propanoyl-1*H*-pyrazol-5-yl)benzenesulfonamide (65)

Mp 185–186 °C; HESI-HRMS: calcd for $C_{18}H_{18}O_3N_3S$ $[M+H]^+$: 356.10634; found: 356.10627; delta = 0.20 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.80 (m, 2H), 7.36–7.53 (m, 9H), 7.21 (s, 1H), 3.05 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 150.0, 143.4, 142.8, 138.4, 131.6, 128.8, 128.5, 128.3, 125.3, 125.2, 107.5, 30.9, 7.4.

4-[1-(4-methoxyphenyl)-3-propanoyl-1*H*-pyrazol-5-yl]benzenesulfonamide (66)

Mp 198–199 °C; HESI-HRMS: calcd for $C_{19}H_{20}O_4N_3S$ $[M+H]^+$: 386.11690; found: 386.11636; delta = −1.41 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.81 (m, 2H), 7.36–7.51 (m, 4H), 7.28–7.34 (m, 2H), 7.18 (s, 1H), 7.00–7.06 (m, 2H), 3.80 (s, 3H), 3.03 (q, J = 7.30 Hz, 2H), 1.12 (t, J = 7.34 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 158.7, 149.7, 143.3, 142.8, 131.7, 131.4, 128.5, 126.6, 125.2, 113.9, 107.1, 54.9, 30.8, 7.4.

4-{3-Propanoyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-pyrazol-5-yl}benzenesulfonamide (67)

Mp 163 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_4F_2S$ $[M+H]^+$: 407.09839; found: 407.09815; delta = −0.61 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 2.2 Hz, 1H), 8.11–8.15 (m, 1H), 8.04–8.10 (m, 1H), 7.81–7.86 (m, 2H), 7.53–7.60 (m, J = 8.6 Hz, 2H), 7.47 (br s, 2H), 7.30 (s, 1H), 3.09 (q, J = 7.3 Hz, 2H), 1.77–1.78 (m, 1H), 1.14 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.1, 151.2, 145.8, 143.9, 143.6, 144.9, 137.4, 134.2, 130.8, 129.0, 125.5, 121.0, 120.7, 108.6, 31.0, 7.3.

4-[1-(5-chloropyridin-2-yl)-3-propanoyl-1*H*-pyrazol-5-yl]benzenesulfonamide (68)

HESI-HRMS: calcd for $C_{17}H_{16}O_3N_4ClS$ $[M+H]^+$: 391.06262; found: 391.06325; delta = 1.63 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (dd, J = 0.5, 2.6 Hz, 1H), 8.25 (dd, J = 2.6, 8.6 Hz, 1H), 7.90 (dd, J = 0.5, 8.6 Hz, 1H), 7.74–7.82 (m, 2H), 7.46–7.54 (m, 2H), 7.44 (s, 2H), 7.22 (s, 1H), 3.08 (q, J = 7.3 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.8, 151.1, 149.9, 146.8, 143.9, 143.8, 139.5, 132.6, 131.0, 129.0, 125.7, 120.7, 109.1, 31.5, 7.9.

4-(3-{3-azabicyclo[3.1.0]hexane-3-carbonyl}-1-(4-chlorophenyl)-1*H*-pyrazol-5-yl)-benzene-1-sulfonamide (69)

See in Scheme 2.

*Step 1 N'-[4-(3-{3-azabicyclo[3.1.0]hexane-3-carbonyl}-1-(4-chlorophenyl)-1H-pyrazol-5-yl)-benzenesulfonyl]-N,N-dimethylmethanimidamide (**69**–**1**)*

Under an inert atmosphere, the carboxylic acid **39**–**6** (0.915 mmol) was suspended in CH_2Cl_2 (12 mL), DMF (0.135 mL, 1.9 eq) was added followed by a dropwise addition of a solution of oxalyl chloride (0.23 mL, 3 eq) in CH_2Cl_2 (1 mL) while cooling with ice. The mixture was stirred at RT for 1.5 h, the solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (12 mL). Next, 3-azabicyclo[3.1.0]hexane hydrochloride (219 mg, 2 eq) was added, followed by a dropwise addition of triethylamine (0.51 mL, 4 eq) during cooling in an ice-water bath and the mixture was stirred overnight at RT. The reaction mixture was diluted with CH_2Cl_2 (20 mL), extracted with 5% HCl, saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated. The residue was purified with column chromatography on silica, eluent: EtOAc-cycloxexane (1:1). Yield: 50 mg of light yellow amorphous solid. MS: $[M + H^+] = 498.1$.

*Step 2. 4-(3-{3-azabicyclo[3.1.0]hexane-3-carbonyl}-1-(4-chlorophenyl)-1H-pyrazol-5-yl)-benzenesulfonamide (**69**)*

Compound **69**–**1** (50 mg, 0.1 mmol) was dissolved in THF (2 mL), a solution of KOH (30 mg, ~5 eq, 90%) in MeOH (2 mL) was added and the mixture was stirred overnight at RT. After cooling with ice, water (7 mL) was added, acidified with 10% HCl (1 mL) and the organic solvents were evaporated. The aqueous residue was extracted with CH_2Cl_2, organic phase washed with water, dried on Na_2SO_4, concentrated and purified with column chromatography on silica, eluent: EtOAc-hexane. Yield: 25 mg. HPLC purity: 99.1%.

Mp 210–216 °C; HRMS: M + H = 443.09270 (delta = −2.7 ppm; $C_{21}H_{20}O_3N_4ClS$). HR-ESI-MS-MS (CID = 35%; rel. int. %): 426(3); 425(6); 389(3); 378(100); 360(45); 325(1).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.78–7.82 (2H, m, H-9, 10), 7.53–7.57 (2H, m, H-15, 16), 7.45–7.49 (2H, m, H-8, 7), 7.44 (2H, br s, H-24), 7.37–7.41 (2H, m, H-14, 13), 7.08 (1H, s, H-5), 4.25 (1H, d, J = 11.5 Hz, H-27*), 3.89 (1H, d, J = 12.0 Hz, H-26*), 3.84 (1H, dd, J = 11.5 Hz, J = 4.3 Hz, H-27*), 3.48 (1H, dd, J = 12.1 Hz, J = 4.4 Hz, H-26*), 1.66 (1H, tt, J = 7.5 Hz, J = 3.9 Hz, H-29$^{\#}$), 1.58 (1H, tt, J = 7.5 Hz, J = 3.9 Hz, H-28$^{\#}$), 0.71 (1H, td, J = 7.6 Hz, J = 5.0 Hz, H-30), 0.09 (1H, q, J = 4.2 Hz, H-30); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 161.2 (C-18), 148.4 (C-4), 144.0 (C-11), 142.1 (C-3), 137.9 (C-12), 133.0 (C-17), 132.1 (C-6), 129.4 (C-15, 16), 129.2 (C-8, 7), 127.2 (C-14, 13), 126.0 (C-9, 10), 110.6 (C-5), 50.3 (C-27*), 48.6 (C-26*), 16.2 (C-29$^{\#}$), 13.5 (C-28$^{\#}$), 9.1 (C-30).

*, $^{\#}$: interchangeable assignments.

Compounds **70**–**79** were synthesized in a manner analogous to the method described for the synthesis of compound **69**. See in Scheme 2.

4-[1-(4-chlorophenyl)-3-(pyrrolidine-1-carbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (70)

Mp 247 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_4ClS$ $[M+H]^+$: 431.09392; found: 431.09357; delta = −0.80 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.86 (m, 2H), 7.51–7.60 (m, 2H), 7.45–7.51 (m, 2H), 7.43 (br s, 2H), 7.35–7.41 (m, 2H), 7.11 (s, 1H), 3.89 (t, J = 6.7 Hz, 2H), 3.52 (t, J = 6.7 Hz, 2H), 1.74–1.96 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.6, 148.1, 143.4, 141.4, 137.3, 132.3, 131.6, 128.8, 128.6, 126.6, 125.4, 110.0, 47.7, 45.9, 25.4, 22.8.

4-[1-(4-chlorophenyl)-3-(3,3-difluoroazetidine-1-carbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (71)

Mp 275–278 °C; HESI-HRMS: calcd for $C_{19}H_{16}O_3N_4ClF_2S$ $[M+H]^+$: 453.05942; found: 453.05941; delta = −0.03 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 7.9 Hz, 2H), 7.52–7.58 (m, 2H), 7.46–7.50 (m, 2H), 7.44 (br s, 2H), 7.39–7.44 (m, 2H), 7.20 (s, 1H), 4.98 (t, J = 12.4 Hz, 2H), 4.52 (t, J = 12.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.8, 143.6, 142.1, 137.1, 132.6, 131.3, 128.8, 128.7, 126.5, 125.4, 116.2, 109.4, 63.6, 59.3.

4-[1-(4-chlorophenyl)-3-(3,3-difluoropyrrolidine-1-carbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (72)

Mp 138 °C; HESI-HRMS: calcd for $C_{20}H_{18}O_3N_4ClF_2S$ $[M+H]^+$: 467.07507; found: 467.07514; delta = 0.14 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 7.3 Hz, 2H), 7.39–7.58 (m, 8H), 7.18 (d, J = 2.1 Hz, 1H), 4.39 (t, J = 12.9 Hz, 1H), 4.20 (t, J = 7.4 Hz, 1H), 3.95 (t, J = 13.3 Hz, 1H), 3.77 (t, J = 7.5 Hz, 1H), 2.40–2.62 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1/160.8,* 148.0/147.8*, 144.6, 142.9/142.8*, 138.3, 133.6, 132.5, 129.9, 129.7, 128.6, 127.7/127.7,* 111.3/111.2, 54.9/53.1*, 46.8/44.4*, 34.3/31.8*.

*due to amide rotamers.

4-[1-(4-chlorophenyl)-3-(piperidine-1-carbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (73)

Mp 215–216 °C; HESI-HRMS: calcd for $C_{21}H_{22}O_3N_4ClS$ $[M+H]^+$: 445.10957; found: 445.10950; delta = −0.16 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78–7.82 (m, 2H), 7.35–7.56 (m, 8H), 7.01 (s, 1H), 3.75–3.89 (m, 2H), 3.45–3.66 (m, 3H), 1.58–1.68 (m, 2H), 1.50–1.58 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 148.4, 144.5, 142.6, 138.3, 133.4, 132.7, 129.9, 129.6, 127.7, 126.5, 110.7, 47.9, 43.2, 26.9, 25.9, 24.6.

4-[1-(4-chlorophenyl)-3-(morpholine-4-carbonyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (74)

Mp 223 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_4ClS$ $[M+H]^+$: 447.08883; found: 447.08876; delta = −0.16 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.9 Hz, 2H), 7.37–7.57 (m, 8H), 7.07 (s, 1H), 3.98 (br s, 2H), 3.57–3.73 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 147.8, 144.5, 142.7, 138.3, 133.5, 132.5, 129.9, 129.7, 127.8, 126.5, 111.2, 67.0, 66.6, 47.7, 42.8.

1-(4-chlorophenyl)-*N*-(3,3-difluorocyclobutyl)-*N*-methyl-5-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxamide (75)

Mp 114–116 °C; HESI-HRMS: calcd for $C_{21}H_{20}O_3N_4ClF_2S$ $[M+H]^+$: 481.09072; found: 481.09059; delta = −0.27 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78–7.83 (m, 2H), 7.52–7.60 (m, 2H), 7.46–7.51 (m, 2H), 7.44 (br s, 2H), 7.35–7.41 (m, 2H), 7.06 (s, 1H), 4.90–5.16 (m, 0.5H)/4.62–4.87 (m, 0.5H)*, 3.26 (br s, 1.5H)/3.02 (br s, 1.5H)*, 2.82–3.09 (m, 4H). ^{13}C NMR (partial) (101 MHz, DMSO-d_6) δ 162.8, 147.0, 143.5, 141.6, 137.2, 132.4, 131.5, 128.8, 128.6, 126.6, 125.4, 109.8. *due to amide rotamers.

1-(4-chlorophenyl)-*N*-cyclopropyl-*N*-methyl-5-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxamide (76)

Mp 200–201 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_4ClS$ $[M+H]^+$: 431.09392; found: 431.09367; delta = −0.56 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74–7.85 (m, 2H), 7.51–7.57 (m, 2H), 7.45–7.50 (m, 2H), 7.43 (s, 2H), 7.32–7.40 (m, 2H), 3.11 (br s, 1H), 3.01 (br s, 3H), 0.65–0.80 (m, 2H), 0.59 (br s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.0, 147.9, 143.4, 141.3, 137.4, 132.2, 131.7, 128.8, 128.5, 126.6, 125.4, 109.2, 109.1, 33.5, 31.9, 8.5.

1-(4-chlorophenyl)-*N*-cyclopropyl-5-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxamide (77)

Mp 221–224 °C; HESI-HRMS: calcd for $C_{19}H_{18}O_3N_4ClS$ $[M+H]^+$: 417.07827; found: 417.07853; delta = 0.63 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 4.5 Hz, 1H), 7.70–7.86 (m, 2H), 7.50–7.60 (m, 2H), 7.44–7.49 (m, 2H), 7.43 (s, 2H), 7.37–7.42 (m, 2H), 7.11 (s, 1H), 2.77–2.95 (m, 1H), 0.50–0.83 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 147.0, 143.4, 142.4, 137.2, 132.5, 131.6, 128.7, 128.5, 126.9, 125.4, 108.0, 22.0, 5.1.

1-(4-chlorophenyl)-*N*-(piperidin-1-yl)-5-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxamide (78)

Mp 294–296 °C; HESI-HRMS: calcd for $C_{21}H_{23}O_3N_5ClS$ $[M+H]^+$: 460.12046; found: 460.11957; delta = −1.9 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.75–7.84 (m, 2H), 7.52–7.60 (m, 2H), 7.44–7.48 (m, 2H), 7.38–7.44 (m, 4H), 7.12 (s, 1H), 2.80 (t, J = 5.3 Hz, 4H), 1.59 (quin, J = 5.5 Hz, 4H), 1.32–1.41 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.6, 146.5, 143.4, 142.3, 137.2, 132.5, 131.5, 128.7, 128.5, 127.0, 125.4, 108.3, 54.7, 24.7, 22.4.

4-{3-(pyrrolidine-1-carbonyl)-1-[5-(trifluoromethyl)pyridin-

2-yl]-1*H*-pyrazol-5-yl}benzenesulfonamide (79)

Mp 255–257 °C; HESI-HRMS: calcd for $C_{20}H_{19}O_3N_5F_3S$ $[M+H]^+$: 466.11552; found: 466.11650; delta = 2.10 ppm.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68–8.72 (m, 1H), 8.49 (dd, J = 2.1, 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.78–7.82 (m, 2H), 7.53–7.57 (m, 2H), 7.44 (s, 2H), 7.13 (s, 1H), 3.93 (t, J = 6.8 Hz, 2H), 3.54 (t, J = 6.8 Hz, 2H), 1.90–1.99 (m, 2H), 1.81–1.90 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.8, 154.2, 149.5, 145.1, 143.7, 142.9, 137.2, 133.1, 129.0, 125.5, 124.3, 123.1, 118.3, 112.1, 48.2, 46.5, 26.0, 23.3.

Compounds **80**–**86** were synthesized in an analogous manner to the synthesis of **39** using intermediate **39**–**4** instead of **39**–**5**. See in Scheme 2.

4-[1-(4-chloro-3-propanoylphenyl)-1*H*-pyrazol-3-yl]benzenesulfonamide (80)

Mp 277–282 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3ClS$ $[M+H]^+$: 390.06737; found: 390.06757; delta = 0.51 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05–8.15 (m, J = 8.3 Hz, 2H), 7.99 (s, 1H), 7.87–7.95 (m, J = 8.3 Hz, 2H), 7.50–7.60 (m, 4H), 7.41 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 191.2, 149.4, 143.6, 141.0, 139.1, 134.7, 132.8, 128.5, 127.5, 126.2, 125.6, 110.6, 33.3, 7.6.

4-[1-(3-chloro-5-propanoylphenyl)-1*H*-pyrazol-3-yl]benzenesulfonamide (81)

Mp 223–224 °C; HESI-HRMS: calcd for $C_{18}H_{17}O_3N_3ClS$ $[M+H]^+$: 390.06737; found: 390.06768; delta = 0.81 ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06–8.17 (m, 2H), 8.00 (s, 1H), 7.88–7.95 (m, 2H), 7.65 (t, J = 1.7 Hz, 1H), 7.45–7.60 (m, 3H), 7.41 (s, 2H), 3.07 (q, J = 7.2 Hz, 2H), 2.20–2.21 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.6, 149.0, 143.2, 140.9, 140.6, 134.2, 132.1, 129.6, 127.8, 125.7, 125.2, 125.1, 124.1, 110.2, 32.8, 7.1.

4-[1-(3-butanoyl-4-chlorophenyl)-1*H*-pyrazol-3-yl]benzenesulfonamide (82)

Mp 245 °C; HESI-HRMS: calcd for $C_{19}H_{19}O_3N_3ClS$ $[M+H]^+$: 404.08302; found: 404.08292; delta = −0.23 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07–8.15 (m, 2H), 8.02 (s, 1H), 7.88–7.95 (m, 2H), 7.54–7.61 (m, 2H), 7.47–7.55 (m, 2H), 7.42 (s, 2H), 3.01 (t, J = 7.2 Hz, 2H), 1.62 (sxt, J = 7.3 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 190.8, 149.5, 143.7, 141.2, 139.2, 134.8, 132.9, 128.6, 127.6, 126.3, 125.7, 110.9, 41.9, 16.9, 13.5.

4-{1-[4-chloro-3-(morpholine-4-carbonyl)phenyl]-1*H*-pyrazol-3-yl}benzenesulfonamide (83)

Mp 178–180 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_4N_4ClS$ $[M+H]^+$: 447.08883; found: 447.08923; delta = 0.90 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07–8.14 (m, 2H), 7.88–7.95 (m, 2H), 7.60–7.67 (m, 2H), 7.55–7.60 (m, 2H), 7.42 (br s, 2H), 7.36 (s, 1H), 3.59 (br s, 4H), 3.40 (br s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.7, 149.9, 143.7, 137.9, 137.5, 134.9, 132.4, 129.4, 126.3, 125.9, 124.7, 106.6, 65.9, 65.7, 47.0, 42.0.

4-{1-[4-chloro-3-(3,3-difluoroazetidine-1-carbonyl)phenyl]-1*H*-pyrazol-3-yl}benzenesulfonamide (84)

Mp 277–286 °C; HESI-HRMS: calcd for $C_{19}H_{16}O_3N_4ClF_2S$ $[M+H]^+$: 453.05942; found: 453.05963; delta = 0.46 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03–8.15 (m, 2H), 7.84–7.96 (m, 2H), 7.61–7.70 (m, 3H), 7.52–7.61 (m, 2H), 7.42 (s, 2H), 4.89–5.12 (m, 2H), 4.35–4.61 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.7, 149.6, 143.8, 138.5, 135.2, 134.8, 132.6, 128.7, 126.6, 126.3, 125.8, 108.2, 63.2, 59.9).

2-Chloro-*N*,*N*-dimethyl-5-[3-(4-sulfamoylphenyl)-1*H*-pyrazol-1-yl]benzamide(85)

Mp 246–247 °C; HESI-HRMS: calcd for $C_{18}H_{18}O_3N_4ClS$ $[M+H]^+$: 405.07827; found: 405.07846; delta = 0.48 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09–8.12 (m, 2H), 7.89–7.92 (m, 2H), 7.54–7.62 (m, 4H), 7.41 (s, 2H), 7.35 (s, 1H), 2.97 (s, 3H), 2.95 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.0, 149.8, 143.7, 138.2, 138.1, 135.0, 132.2, 129.4, 126.3, 125.8, 124.4, 106.3, 38.1, 34.5.

2-Chloro-*N*-cyclopropyl-N-methyl-5-[3-(4-sulfamoylphenyl)-1*H*-pyrazol-1-yl]benzamide (86)

Mp 209–210 °C; HESI-HRMS: calcd for $C_{20}H_{20}O_3N_4ClS$ $[M+H]^+$: 431.09392; found: 431.09429; delta = 0.88 ppm. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06–8.16 (m, 2H), 7.85–7.95 (m, 2H), 7.57–7.66 (m, 2H), 7.50–7.56 (m, 2H), 7.45 (br s, 1H), 7.41 (s, 2H), 2.95 (br s, 3H), 2.54–2.62 (m, 1H), 0.43–0.69 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 149.6, 143.7, 138.4, 135.1, 132.2, 129.3, 126.3, 125.8, 124.5, 107.0, 34.0, 31.8, 8.3.

4.3. Biological assay methods

4.3.1. Generation of HEK293 cells expressing human α7 nAChR

Recombinant HEK-293 cell lines stably expressing both the target hCHRNA7 protein and the hRIC3 chaperone (for proper functionality) were generated at Gedeon Richter Plc. To achieve robust expression cDNAs were optimized for human codon usage and the "Flip-In" technique was employed for proper genomic integration. The following cDNAs and vector constructs were used: for hRIC3 expression the synthesized cDNA (Construct ID: 12AAHCLC, LifeTechnologies) in a pcDNA3.1-V5-HAS (resistance gene: Neomycin) vector; for hCHRNA7 expression the synthesized cDNA (Construct ID: 12AAHDHC, LifeTechnologies) in a pcDNA5/FRT (resistance gene: Hygromycin B) vector. First the hRIC-3 then the hCHRNA7 gene were integrated into the HEK-293 Flip-In cells. Following the consecutive selection steps 8 clones having robust (ΔF/F > 4, PNU-282987 at 1 μM) hCHRNA7-related $[Ca^{2+}]_i$ responses were obtained.

4.3.2. Fluorometric $[Ca^{2+}]_i$-assay on cells expressing human α7 nAChR

Orthosteric agonists of the α7 nAChR (*e.g.* PNU-282987) *per se* evoke no Ca^{2+}-influx in most *in vitro* cellular systems, unless they are co-applied with PAMs that concurrently hinder the channel desensitization. However, in the presence of agonists, PAMs with such characteristics result in robust and concentration-dependent Ca^{2+}-influx (it must be noted that the assay is insensitive to PAMs lacking effect on channel desensitization).

Flp-In HEK293 cells stably expressing the human α7 nAChR and the RIC-3 chaperon were cultured in DMEM (Gibco) supplemented by 10% FBS (Gibco), 2 mM glutamine (Sigma), 50 μg/mL hygromycin B, 400 μg/mL G418 and 1% penicillin-streptomycin antimycotic solution (Sigma). Cells were split 1:3–4 twice a week by trypsinisation. For the $[Ca^{2+}]_i$ measurements, cells were seeded onto 96-well microplates at a density of 60.000 cells/well and maintained overnight in a tissue culture incubator at 37 °C under an atmosphere of 95% air and 5% CO_2. Before the $[Ca^{2+}]_i$ measurement, 50 μl of the growth medium was aspirated with a cell washer (BioTek Elx405UCVWS, Biotek, Winooski, VT, USA), then 50 μl/well Calcium 5 kit (diluted 2-fold in assay buffer containing 140 mM NaCl, 5 mM KCl, 10 mM HEPES, 2 mM $MgCl_2$, 2 mM $CaCl_2$, 10 mM glucose and 2 mM probenecid; pH = 7.4) was added manually using an 8-channel pipette. After an incubation period of 20 min at 37 °C, 50 μl/well assay buffer containing vehicle (Dimethyl sulfoxide [DMSO], 4% added) or test compounds (4 × of the final concentration) were added. Cells were then incubated for an additional 10 min at 37 °C.

Baseline and agonist-evoked $[Ca^{2+}]_i$-changes were measured with a FlexStation II^{96} (Molecular Devices, San Jose, CA).Fluorescence measurements were carried out at 37 °C. The dye was excited at 485 nm, emission was sampled at 525 nm at 1.4-s intervals. Baseline was recorded for 20 s followed by agonist stimulation. 50 μl 4 × concentrated agonist (PNU-282987, 1 μM) solution was added to all wells using the pipettor of FlexStation II and fluorescence was monitored for an additional 20 s. Final DMSO

concentration was 1% for all treatments. To achieve this, a series of DMSO stock solutions were prepared from all test compounds. These stocks were stored under 0 °C and were further diluted in assay buffer to obtain the desired final concentration immediately before the measurement. Positive control: PNU-120596, 2.5 μM.

Results were expressed as ΔF/F values using SoftMax Pro software (Molecular Devices), where F was the resting fluorescence preceding agonist application and ΔF was the increase in fluorescence at a given time (ΔF = maximum fluorescence intensity values after stimulation minus average fluorescence intensity values before stimulation). In all experiments, all treatments were measured in multiple wells in parallel, and the mean ΔF/F values were used for analysis. ΔF/F data were converted to corrected % response values by normalizing responses to the control PNU-120596 response. In each individual experiment, the EC_{50} and E_{max} values were determined from 4-parameter sigmoidal concentration-response curves fitted to the corrected response data using SoftMax Pro, with the lower asymptote fixed to zero. EC_{50} and E_{max} values from individual experiments were averaged and presented as mean ± SD.

4.3.3. Patch clamp studies

Channel physiology of α7 nAChRs was studied by automated (QPatch) whole-cell patch clamp. Whole-cell patch clamp recordings were made from Flp-In HEK293 cells stably expressing hRIC3/hCHRNA7 2 days after plating at a holding potential of −80 mV. Inward currents were evoked by 3-*s*-long application of the agonist (choline, 10 mM) at 2-4-min intervals in the absence and in the presence of test compounds and recorded at 10 kHz sampling frequency. After agonist application, wash-out was applied 4 times. The control solution contained the same concentration of the vehicle (0.1% DMSO) as the solutions with the test compounds. Solutions containing the test compounds were applied to the cells for 6−10 min. The fold increase (FI) value was calculated from the ratio of the peak current amplitudes evoked by choline in the presence or in the absence of the test compounds. EC_{50} values were calculated based on FI values at several test compound concentrations.

For electrophysiological measurements using α4/β2 nACh receptors, HEK293 cells stably expressing human nAChR α4/β2 receptors (Eurofins; CYL3106SS) were used for automated patch clamp recordings using the QPatch-HTX system (Sophion, Denmark) at room temperature. Whole-cell patch clamp recordings were made from cells at a holding potential of −80 mV in single-cell mode. The control solution contained the same concentration of the vehicle (DMSO) as the solutions of the test compound. When testing modulation, inward currents were evoked by 3-*s*-long applications of the agonist (acethylcholine, 1 μM) in the absence (control responses) followed by the presence of the test compound. Peak amplitudes of current evoked by acetylcholine was measured from the baseline current. The modulation values were calculated from the comparison of peak currents in the absence and in the presence of the test compound. The concentration dependent relative response data of the test compound was analyzed using Origin 6.0. The concentration causing half-maximal inhibition (IC50) was used to characterize the potency of the test compound. When testing agonism, control response was evoked by application acetylcholine (1 μM) then the test compound was applied once at 1 or 10 μM for 3 s.

For electrophysiological measurements using $GABA_A$ receptors, HEK293 cells stably expressing human α1β3γ2 and α5β3γ2 $GABA_A$Rs (Eurofins, CYL3053 and CYL3073) were investigated by whole-cell patch clamp using the QPatch-HTX automated patch clamp system in single-cell mode. Whole-cell patch clamp recordings were made from cells 2−4 days after plating at a holding potential of −80 mV at room temperature. Inward currents were evoked by 3-*s*-long application of the agonist GABA (1 μM) at 2-4-min intervals in the absence, then and in the presence of test compound. Solutions containing the test compound were applied to the cells for 7−10 min. The control solution contained the same concentration of the vehicle (0.1% DMSO) as the solutions of the test compound. Peak amplitudes of current evoked by GABA was measured from the baseline current. The modulation values were calculated from the comparison of peak currents in the absence and in the presence of the test compound.

4.3.4. Metabolic stability assay

In vitro metabolic stability was assessed using human (Xenotech, LLC, USA), Wistar rat and NMRI mouse (*In vitro* Metabolism Research, Gedeon Richter Plc, Hungary) liver microsomes. Test compounds were incubated at 1 or 2.5 μM initial test concentration at longest up to 40 min with the liver microsomes (0.5 mg/mL). *In vitro* intrinsic clearance (CL_{int}, μL/min/mg protein) was calculated using the basic concept of clearance prediction [41] according to the following equations: $CL_{int} = V_{max}/K_M$, or if $S \ll K_M$, $CL_{int} = V/S$; V_{max} = maximal rate of enzyme reaction; K_M = affinity constant of substrate concentration; V = actual rate of enzyme reaction under first order conditions, S = substrate concentration in the incubations.

4.3.5. Permeability assay

Bi-directional permeability ($Papp_{A-B}$ and $Papp_{B-A}$) and efflux ratio (PDR = $Papp_{B-A}/Papp_{A-B}$) of test compounds were measured using vinblastine-treated Caco-2 (VB-Caco-2) cells described in Hellinger et al., 2010 [31]. Briefly, the permeability of test compounds (at 1 or 10 μM) were measured in the apical-to-basolateral (A-B) and basolateral-to-apical (B-A) directions in HBSS-HEPES (Hank's Buffered Salt Solution containing 25 mM HEPES) using iso-pH conditions (pH 7.4_A−7.4_B) at 37 °C with moderate shaking (120 rpm). The incubations with test compounds were performed at longest up to 180 min, using appropriate duration of time determined based on preliminary studies for each compound tested. Samples were analyzed using HPLC or UHPLC-MS/MS.

4.3.6. Place recognition (Y maze) test

Animal maintenance and experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. All procedures using animals were approved by the local ethics committee (Institutional Animal Welfare Committee of Gedeon Richter Plc. and conformed to the rules and principles of the European Animal Protection Directives (Directive 2010/63/EU).

The task was carried out in a transparent plexiglass Y-maze (each arm has a length of 40 cm, an inner width of 11 cm and a height of 30 cm). Numerous visual cues were placed around the arms and were kept constant during the experiment. The test consisted of two trials (T1 and T2) separated by an intertrial interval of 30 min. Male NMRI mice (Toxicoop, Hungary) were placed in the starting arm of the maze at the beginning of each trial. In T1, one of the symmetric arms of the maze was closed (it will be novel in T2) and the animals could explore the maze for 5 min (acquisition phase). In T2, mice had free access to all three arms for 2 min (retrieval phase). Test compounds were administered 30 min before T1; scopolamine (1 mg/kg, ip.) was administered after the acquisition trial at a volume of 0.1 mL/10 g. The time spent with exploration in the novel and familiar arms during T2 was measured. Differences between the exploration times spent in the familiar vs. novel arms of the maze for each group were evaluated by MANOVA, followed by Duncan post hoc test.

4.3.7. Pharmacokinetics

Pharmacokinetic study was carried out after 3 mg/kg iv. (n = 4) or p.o. (n = 3/sampling time) administration to non-fasted, male Hsd Wistar rats (Toxicoop, Hungary). The dosing volume was 2.5 (iv.) or 5 mL/kg (p.o.). The compound (**69**) was formulated as 30% PFG-KIT#1 in deionized water solution for IV or 5% Tween 80 in deionized water suspension for PO administration. Dosing of the animals was carried out via injection into the tail vein (iv.) or via gavage (p.o.). Blood samples were taken from the retroorbital plexus at 5 min, 20 min, 2 h and 5 h (iv.) or 0.5 h, 1 h, 2 h and 5 h (p.o.) post-dose into Li-heparin tubes and centrifuged at 2000 g for 20 min at 4 °C to gain plasma. In the p.o. dose group whole brains were also removed after exsanguination from vena femoralis. Brain homogenate samples were prepared by homogenizing the whole brain with deionized water (brain: water = 1: 2.5, w/w). Plasma and brain homogenate samples were analyzed after protein precipitation with acetonitrile using HPLC MS/MS method. Pharmacokinetic parameters were calculated from the plasma and brain concentration-time profiles with Kinetica 5.1. software using the model independent approach.

Following each experiment in the Y maze apparatus, brain and blood samples were taken from the sacrificed experimental animals (NMRI mice) for the purpose of supporting PK studies. The dosing volume was 10 mL/kg. The compounds were formulated as 5% Tween 80 in phosphate buffer solution; sampling time was 1 h.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] A. Karlin, M.H. Akabas, Toward a structural basis for the function of nicotinic acetylcholine receptors and their cousins, Neuron 15 (1995) 1231–1244, https://doi.org/10.1016/0896-6273(95)90004-7.
[2] D. Paterson, A. Nordberg, Neuronal nicotinic receptors in the human brain, Prog. Neurobiol. 61 (2000) 75–111, https://doi.org/10.1016/s0301-0082(99)00045-3.
[3] P.B. Clarke, R.D. Schwartz, S.M. Paul, C.B. Pert, A. Pert, Nicotinic binding in rat brain: autoradiographic comparison of [^{3}H]acetylcholine, [^{3}H]nicotine and [^{125}I]-alpha-bungarotoxin, J. Neurosci. 5 (1985) 1307–1315, https://doi.org/10.1523/JNEUROSCI.05-05-01307.1985.
[4] E. Tribollet, D. Bertrand, A. Marguerat, M. Raggenbass, Comparative distribution of nicotinic receptor subtypes during development, adulthood and aging: an autoradiographic study in the rat brain, Neuroscience 124 (2004) 405–420, https://doi.org/10.1016/j.neuroscience.2003.09.028.
[5] C. Gotti, M. Zoli, F. Clementi, Brain nicotinic acetylcholine receptors: native subtypes and their relevance, Trends Pharmacol. Sci. 27 (1997) 482–491, https://doi.org/10.1016/j.tips.2006.07.004.
[6] Z. Gil, B.W. Connors, Y. Amitai, Differential regulation of neocortical synapses by neuromodulators and activity, Neuron 19 (1997) 679–686, https://doi.org/10.1016/S0896-6273(00)80380-3.
[7] C. Vidal, J.P. Changeux, Nicotinic and muscarinic modulations of excitatory synaptic transmission in the rat prefrontal cortex in vitro, Neuroscience 56 (1993) 23–32, https://doi.org/10.1016/0306-4522(93)90558-W.
[8] J.P. Changeux, D. Bertrand, P.J. Corringer, S. Dehaene, S. Edelstein, C. Léna, N. Le Novère, L. Marubio, M. Picciotto, M. Zoli, Brain nicotinic receptors: structure and regulation, role in learning and reinforcement, Brain Res. Rev. 26 (1998) 198–216, https://doi.org/10.1016/s0165-0173(97)00040-4.
[9] C. Gotti, D. Fornasari, F. Clementi, Human neuronal nicotinic receptors, Prog. Neurobiol. 53 (2006) 199–237, https://doi.org/10.1016/s0301-0082(97)00034-8.
[10] B. Lendvai, F. Kassai, Á. Szájli, Zs Némethy, α7 Nicotinic acetylcholine receptors and their role in cognition, Brain Res. Bull. 93 (2013) 86–96, https://doi.org/10.1016/j.brainresbull.2012.11.003.
[11] A. Nikiforuk, T. Kos, A. Potasiewicz, P. Popik, Positive allosteric modulation of alpha 7 nicotinic acetylcholine receptors enhance recognition memory and cognitive flexibility in rats, Eur. Neuropsychopharmacol 25 (2015) 1300–1313, https://doi.org/10.1016/j.euroneuro.2015.04.018.
[12] M.R. Weed, J. Polino, L. Signor, M. Bookbinder, D. Keavy, Y. Benitex, D.G. Morgan, D. King, J.E. Macor, R. Zaczek, R. Olson, L.J. Bristow, Nicotinic alpha 7 receptor agonists EVP-6124 and BMS-933043, attenuate scopolamine-induced deficits in visuo-spatial paired associates learning, PloS One 12 (2017), e0187609. https://dx.doi.org/10.1371/journal.pone.0187609.
[13] A.S. Lewis, G.I. van Schalkwyk, M.H. Bloch, Alpha-7 nicotinic agonists for cognitive deficits in neuropsychiatric disorders: a translational meta-analysis of rodent and human studies, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 75 (2017) 45–53, https://doi.org/10.1016/j.pnpbp.2017.01.001.
[14] K. Antonio-Tolentino, C.R. Hopkins, Selective α7 nicotinic receptor agonists and positive allosteric modulators for the treatment of schizophrenia – a review, Expet Opin. Invest. Drugs 29 (2020) 603–610, https://doi.org/10.1080/13543784.2020.1764938.
[15] O. Delbono, M. Gopalakrishnan, M. Renganathan, L.M. Monteggia, M.L. Messi, J.P. Sullivan, Activation of the recombinant human α7 nicotinic acetylcholine receptor significantly raises intracellular free calcium, J. Pharmacol. Exp. Therapeut. 280 (1997) 428–438.
[16] N.G. Castro, E.X. Albuquerque, Brief-lifetime, fast-inactivating ion channels account for the α-bungarotoxin-sensitive nicotinic response in hippocampal neurons, Neurosci. Lett. 164 (1993) 137–140, https://doi.org/10.1016/0304-3940(93)90876-M.
[17] S. Couturier, D. Bertrand, J.M. Matter, M.C. Hernandez, S. Bertrand, N. Millar, S. Valera, T. Barkas, M. Ballivet, A neuronal nicotinic acetylcholine receptor subunit (alpha 7) is developmentally regulated and forms a homo-oligomeric channel blocked by alpha-BTX, Neuron 5 (1990) 847–856, https://doi.org/10.1016/0896-6273(90)90344-F.
[18] M. Alkondon, S. Reinhardt, C. Lobron, B. Hermsen, A. Maelicke, E.X. Albuquerque, Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons. II. The rundown and inward rectification of agonist-elicited whole-cell currents and identification of receptor subunits by in situ hybridization, J. Pharmacol. Exp. Therapeut. 271 (1994) 494–506.
[19] M.S. Thomsen, H.H. Hansen, D.B. Timmerman, J.D. Mikkelsen, Cognitive improvement by activation of alpha7 nicotinic acetylcholine receptors: from animal models to human pathophysiology, Curr. Pharmaceut. Des. 16 (2010) 323–343, https://doi.org/10.2174/138161210790170094.
[20] S. Sahdeo, T. Wallace, R. Hirakawa, F. Knoflach, D. Bertrand, H. Maag, D. Misner, G.C. Tombaugh, L. Santarelli, K. Brameld, M.E. Milla, D.C. Button, Characterization of RO5126946, a novel a7 nicotinic acetylcholine receptor–positive allosteric modulator, J. Pharmacol. Exp. Therapeut. 350 (2014) 455–468, https://doi.org/10.1124/jpet.113.210963.
[21] A.J. Harvey, T.D. Avery, L. Schaeffer, C. Joseph, B.C. Huff, R. Singh, C. Morice, B. Giethlen, A.A. Grishin, C.J. Coles, P. Kolesik, S. Wagner, E. Andriambeloson, B. Huyard, E. Poiraud, D. Paul, Ss M. O'Connor, Discovery of BNC375, a potent, selective, and orally available type I positive allosteric modulator of α7nAChRs, ACS Med. Chem. Lett. 10 (2019) 754–760, https://doi.org/10.1021/acsmedchemlett.9b00001.
[22] Y. Li, L. Sun, T. Yang, W. Jiao, J. Tang, X. Huang, Z. Huang, Y. Meng, L. Luo, X. Wang, X. Bian, F. Zhang, K. Wang, Q. Sun, Design and synthesis of novel positive allosteric modulators of α7 nicotinic acetylcholine receptors with the ability to rescue auditory gating deficit in mice, J. Med. Chem. 62 (2019) 159–173, https://doi.org/10.1021/acs.jmedchem.7b01492.
[23] N. Sinha, N.P. Karche, M.K. Verma, S.S. Walunj, P.B. Nigade, G. Jana, S.P. Kurhade, A.K. Hajare, A.R. Tilekar, G.R. Jadhav, B.R. Thube, J.S. Shaikh, S. Balgude, L.B. Singh, V. Mahimane, S.K. Adurkar, G. Hatnapure, F. Raje, Y. Bhosale, D. Bhanage, S. Sachchidanand, R. Dixit, R. Gupta, A.M. Bokare, M. Dandekar, A. Bharne, M. Chatterjee, S. Desai, S. Koul, D. Modi, M. Mehta, V. Patil, M. Singh, J. Gundu, R.N. Goel, C. Shah, S. Sharma, D. Bakhle, R.K. Kamboj, V.P. Palle, Discovery of novel, potent, brain-permeable, and orally efficacious positive allosteric modulator of α7 nicotinic acetylcholine receptor [4-(5-(4-Chlorophenyl)-4-methyl-2-propionylthiophen-3-yl)benzenesulfonamide]: structure–Activity relationship and preclinical characterization, J. Med. Chem. 63 (2020) 944–960, https://doi.org/10.1021/acs.jmedchem.9b01569.
[24] Lab Abbott, R. El Kouhen, R. Faghih, G. Gfesser, M. Gopalakrishnan, S. Gopalakrishnan, E.J. Gubbins, J. Li, C.L. Lynch, J. Malysz, Pyrrole Derivatives and Their Methods of Use, 2008, WO2008002974.
[25] R. Faghih, S.M. Gopalakrishnan, J.H. Gronlien, J. Malysz, C.A. Briggs, C. Wetterstrand, H. Ween, M.P. Curtis, K.A. Sarris, G.A. Gfesser, R. El-Kouhen, H.M. Robb, R.J. Radek, K.C. Marsh, W.H. Bunnelle, M. Gopalakrishnan, Discovery of 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide (A-867744) as a novel positive allosteric modulator of the alpha7 nicotinic acetylcholine receptor, J. Med. Chem. 52 (2009) 3377–3384,

https://doi.org/10.1021/jm9003818.
[26] S.R. Donohue, C. Halldin, V.W. Pike, Synthesis and structure-activity relationships (SARs) of 1,5-diarylpyrazole cannabinoid type-1 (CB1) receptor ligands for potential use in molecular imaging, Bioorg. Med. Chem. 14 (2006) 3712–3720, https://doi.org/10.1016/j.bmc.2006.01.047.
[27] J. Malysz, J.H. Grønlien, D.J. Anderson, M. Håkerud, K. Thorin-Hagene, H. Ween, C. Wetterstrand, C.A. Briggs, R. Faghih, W.H. Bunnelle, M. Gopalakrishnan, In vitro pharmacological characterization of a novel allosteric modulator of alpha 7 neuronal acetylcholine receptor, 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide (A-867744), exhibiting unique pharmacological profile, J. Pharmacol. Exp. Therapeut. 330 (2009) 257–267, https://doi.org/10.1124/jpet.109.151886.
[28] P.J. Conn, S.D. Kuduk, D. Doller, Drug design strategies for GPCR allosteric modulators, Annu. Rep. Med. Chem. 47 (2012) 441–457, https://doi.org/10.1016/b978-0-12-396492-2.00028-x.
[29] S. Lu, X. He, D. Ni, J. Zhang allosteric modulator discovery: from serendipity to structure-based design, J. Med. Chem. 62 (2019) 6405–6421, https://doi.org/10.1021/acs.jmedchem.8b01749.
[30] J. Newcombe, A. Chatzidaki, T.D. Sheppard, M. Topf, N.S. Millar, Diversity of nicotinic acetylcholine receptor positive allosteric modulators revealed by mutagenesis and a revised structural model, Mol. Pharmacol. 93 (2018) 128–140, https://doi.org/10.1124/mol.117.110551.
[31] T. Collins, G.T. Young, N.S. Millar, Competitive binding at a nicotinic receptor transmembrane site of two α7-selective positive allosteric modulators with differing effects on agonist-evoked desensitization, Neuropharmacology 61 (2011) 1306–1313. https://dx.doi.org/10.1016/j.neuropharm.2011.07.035.
[32] E. Hellinger, M.L. Bakk, P. Pócza, K. Tihanyi, M. Vastag, Drug penetration model of vinblastine-treated Caco-2 cultures, Eur. J. Pharmaceut. Sci. 41 (2010) 96–106, https://doi.org/10.1016/j.ejps.2010.05.015.
[33] G.E. Veitch, K.L. Bridgwood, K. Rands-Trevor, S.V. Ley, Magnesium nitride as a convenient source of ammonia: preparation of pyrroles, Synlett 17 (2008) 2597–2600, https://doi.org/10.1055/s-0028-1083504.
[34] G.A. Pinna, M.M. Curzu, M. Sechi, G. Chelucci, E. Maciocco, Synthesis and dopamine D2-like receptor binding affinity of substituted 5-phenyl-pyrrole-3-carboxamides, Il Farmaco 54 (1999) 542–550, https://doi.org/10.1016/S0014-827X(99)00061-0.
[35] M. Biava, G.C. Porretta, G. Poce, A. De Logu, M. Saddi, R. Meleddu, F. Manetti, E. De Rossi, M. Botta, 1,5-Diphenylpyrrole derivatives as antimycobacterial agents. Probing the influence on antimycobacterial activity of lipophilic substituents at the phenyl rings, J. Med. Chem. 51 (2008) 3644–3648, https://doi.org/10.1021/jm701560p.
[36] Senomix Inc, M. Arellano, J.R. Fotsing, D.S. Karanewsky, C. Tachdjian, Identification of Human T2R Receptors that Respond to Bitter Compounds that Elicit the Bitter Taste in Compositions, and the Use Thereof in Assays to Identify Compounds that Inhibit (Block) Bitter Taste in Compositions and Use Thereof, 2016, p. US9247759.
[37] Senomix Inc, J. Fotsing, M. Arellano, D.S. Karanewsky, C. Tachdjian, Identification of Human T2R Receptors that Respond to Bitter Compounds that Elicit the Bitter Taste in Compositions, and the Use Thereof in Assays to Identify Compounds that Inhibit (Block) Bitter Taste in Compositions and Use Thereof, 2010. US2010254916.
[38] Pfizer Products Inc, W.K.M. Chong, A.M. Haidle, L. Li, S. Nukui, M.A. Ornelas, E.Y. Rui, M. Teng, W.F. Vernier, J.Z. Zhou, J. Zhu, Heterocycles Useful as Inhibitors of Carbonic Anhydrase, 2008. WO200817932.
[39] G.D. Searle, Co, Substituted Pyrazolyl Benzensulfonamides, 1995. US5466823A.
[40] T. Li, H. Yan, X. Li, C. Wang, B. Wan, Ruthenium-catalyzed [3+2] cycloaddition of 2H-azirines with alkynes: access to polysubstituted pyrroles, J. Org. Chem. 81 (2016) 12031–12037, https://doi.org/10.1021/acs.joc.6b02322.
[41] A. Rane, G.R. Wilkinson, D.G. Shand, Prediction of hepatic extraction ratio from in vitro measurement of intrinsic clearance, J. Pharmacol. Exp. Therapeut. 200 (1977) 420–424.