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FULL PAPER

Tetrahydroindoles as Multipurpose Screening Compounds and Novel Sirtuin Inhibitors

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Abstract: Indoles are privileged structures in medicinal and bioorganic chemistry that are particularly suited to serve as platform for diversity. Among many other therapeutic areas, the indole scaffold has been utilized to design aromatic compounds useful to interfere with enzymes engaged in regulation of substrate acylation status such as sirtuins. However, the planarity of the indole ring is not necessarily optimal for all target enzymes, especially when a decoration with aromatic side-chains is required. Replacement of flat scaffolds by shapely molecular cores dominated by sp^3 hybridization is a common strategy to escape the disadvantages associated with poor solubility and high promiscuitivity, while covering less well-explored areas of chemical space. Thus, we synthesized fragment-like tetrahydroindoles suitable for fragment-based drug discovery as well as a well-characterized small library intended as multipurpose screening compounds. For proof of principle, these compounds were screened against sirtuins 1-3, enzymes known to be addressable by indoles. We found that 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamides are potent and selective SIRT2 inhibitors. Compound **16t** displayed an IC_{50} of 0.98 µM and could serve as exquisite starting point for a hit-to-lead profiling.

Introduction

Comparing the contents of present diversity-oriented screening collections with the properties of orally available drugs and natural products [1], the latter two classes of compounds have more stereo centers and sp^3 hybridized carbon atoms, even when size in terms of number of heavy atoms is accounted for. Thus, biologically relevant compound space might not be ideally populated from a synthetic point of view so far [2]. Oral bioavailability seems linked with the selection of shapely scaffolds, whereas “fat and flat” compounds might bind very well to proteins but are suboptimal starting points for hit-to-lead profiling [3]. In addition, many privileged structures, such as the benzodiazepines, are characterized by only 6 π electrons in the central ring system and a three-dimensional, shapely form brought about by a partly hydrogenated annelated ring. This architecture allows for the attachment of further aromatic rings as substituents out of plane of the diversity platform.

Connections between histone modifications (e.g. acylation/ deacylation) and genetic regulation are complex and promising options for therapeutic intervention, at the same time, and remain a central topic in biomedical research. Enzymes that cleave off acetyl groups from lysine residues on histones and thereby alter the transcription of the histone-associated DNA are key to understanding epigenetic modifications on a molecular level. In humans four classes of HDACs have been recognized, where the classes I, II and IV termed classical HDACs catalyse the hydrolysis of acetyl-lysine zinc-dependently. In clinical practice, some pan-inhibitors of these zinc-dependent HDACs (esp. hydroxamic acid derivatives like panobinostat) are already applied for therapy of oncological diseases like multiple myeloma. Class III enzymes, also termed sirtuins (due to their homology with yeast gene-silencing protein Sir2p) cleave acetyl-groups off from lysines NAD^+-dependently. Humans possess seven subtypes of sirtuins (SIRT1-7), which differ in cellular localisation and substrate selectivity. As mentioned, sirtuins catalyse deacetylation by the use of the cofactor NAD^+. The products of this catalysis mechanism are *O*-Acetyl ADP ribose and nicotinamide. Therefore, in contrast to classical HDACs, these enzymes are not hydrolases but belong to the enzyme class of transferases.

Splitomicin (**1a**) was described as screening hit for sirtuin inhibition, but did not turn out to be an ideal starting point for the hit-to-lead profiling towards epigenetic modifiers. In analogy to known SIRT2 inhibitors with β-phenyl-splitomicin scaffold (e.g.

1b) we initially synthesized compounds with carbamate (e.g. **1c**) and thiocarbamate (**1d**) substructure (Figure 1) [4]. Although carbamates like **1c** are easily accessible by multi-component reaction (MCR) applying 2-naphthol, benzaldehyde, urea, and catalytic amounts of an acidic component [5], the preparation of analogous thiocarbamates by the replacement of urea by thiourea is unexpectedly far more demanding. Following the MCR synthesis procedure with thiourea afforded the isourea derivative **1e**, exclusively. We made many attempts towards realizing an MCR for the synthesis of compound **1d** and finally we accomplished the synthesis with potassium thiocyanate in methanolic hydrochloric acid. This reaction represents, to the best of our knowledge, the first MCR for thiocarbamate derivatives like **1d**. But due to the fat and flat structure and presumably poor cell penetration [6], we did not pursue this scaffold any further and searched the literature for a new starting point with more favorable physicochemical properties.

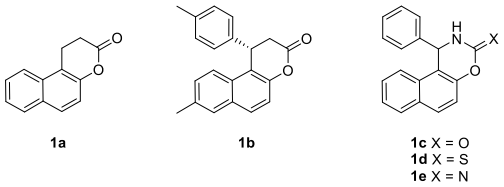


Figure 1. Experimental sirtuin inhibitor splitomicin (**1a**) and analogues **1b**-**e** derived from its structure

Through deacetylation of histones and other cellular proteins, sirtuins plays an important role in a wide field of biological processes like apoptosis, cell cycle and life span regulation. The past few years highlighted the crucial role of SIRT2 especially in cancer progression and tumor resistance. These findings lead to the discovery and development of potent and subtype specific inhibitors. Among the published sirtuin inhibitors, numerous compounds with an indole scaffold [7] were synthesized to date (Figure 2).

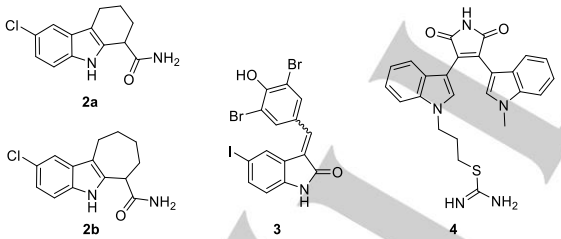


Figure 2. Known sirtuin inhibitors with indole substructure

The indole derivative selisistat (**2a**) exhibits the most potent SIRT1 inhibition (IC_{50} = 98 nM) [8] by far, both in vitro and in vivo [9-11]. Structure-activity relationship studies revealed that expansion of the partially hydrogenated six-membered ring system of **2a** to the homologous derivative **2b** is feasible [8]. In fact, selisistat (**2a**) already passed clinical trial phase II for the treatment of Huntington disease [12,13].

Indole substructures are also implied in potent sirtuin inhibitors found in a rational screening approach of known adenosine mimetics [14]. This screening afforded oxindoles [15] (e.g. **3**) and bisindolylmaleimides (e.g. **4**), both scaffolds revealing low to submicromolar inhibitory and SIRT2-selective activity. From these findings we derived the hypothesis, that less flat indole derivatives could be the searched for surrogate for compound class **1**. A database search for the former in ChEMBL 24 revealed less than 1000 compounds. Consequently, we started a scaffold hopping approach from lipophilic splitomicin analogs that where difficult to optimize to a new tetrahydroindole scaffold.

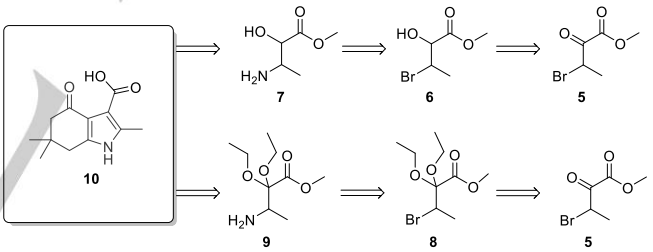
Results and Discussion

Chemistry

Synthesis of tetrahydroindole scaffold 10

Starting with in-house ligand screening, we investigated potential SIRT2 inhibitors with 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide scaffold. This partially hydrogenated indole substructure with linked carboxylic acid amides in position 3 is underrepresented in literature, although being an attractive chemical entity in the context of sp^3-rich fragments [1] and hydrophilic substituents. Several amides with 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole substructure were thus synthesized, characterised and tested for sirtuin inhibitory activity in bioassays.

First, we tried to synthesize the tetrahydroindole scaffold by the reaction of dimedone with aliphatic amino-oxo-acid derivatives like **9** (Scheme 1).



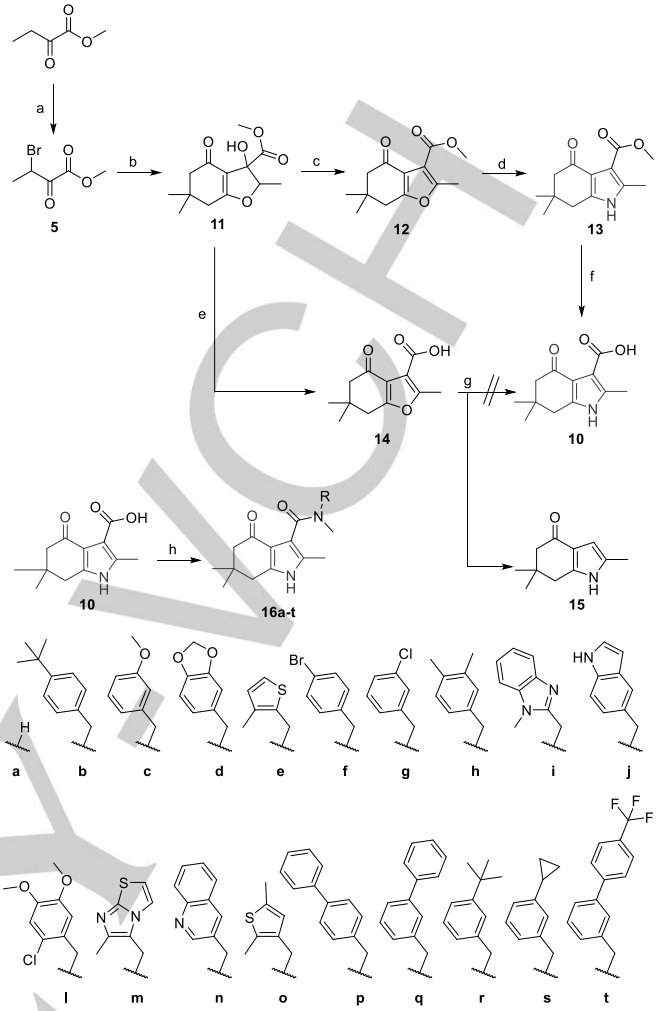
Scheme 1. Retrosynthetic analysis of tetrahydro-4-oxindol 3-carboxylic acid **10** as the key starting point for diversity-oriented amide couplings

For this purpose, we primarily brominated the commercially available methyl 2-oxo-butanoate with copper(II) bromide in chloroform/ethyl acetate. Utilizing a mixture of chloroform/ethyl acetate was thought to be more advantageous in terms of yield and purity[4]. In contrast to bromine, copper(II) bromide was preferable concerning selectivity and the almost quantitative formation of monosubstituted derivatives. The reaction progress could be well recognized by reduction of the inorganic copper salt provoking a color change from black to a white-green slurry. Product **5** was obtained in high yield by fractional distillation. After successful halogenation, we protected the ketone carbonyl group in **5**, preventing intermolecular reaction with amines, to form pyrazole derivatives [7], which represents a well-known side reaction. Therefore, reaction of the synthesized ester **5** was conducted with neat triethyl orthoformate and sulfuric acid in a microwave reactor to afford intermediate **8**.

In the next step, the bromine atom had to be replaced by an amino group in a substitution reaction. Due to steric effects, it was not possible to substitute the bromine atom with nitrogen, neither with azide (Staudinger reaction [9]), phthalimide (Gabriel synthesis [10]) nor methenamine (Delépine reaction [11]). With respect to the published palladium catalyzed indole synthesis [12] of β-amino alcohols reacting with 1,3-diketones, we planned the alternative route as reduction and subsequent primary amine synthesis of the ester **5** to compound **7**. Again, we did not succeed in forming the desired reduction product **6** as neither sodium borohydride [13] nor palladium/hydrogen gas for catalytic reduction were effective in reducing the ketone substructure of **5**. Therefore, we envisioned the formation of the intermediate **11** and subsequently furan derivative **12** via a Feist–Benary reaction [14]. Furan **12** was transformed to annelated pyrrole derivative **13** by heteroatom exchange reaction and subsequently, to key building block **10** (Scheme 2).

The Feist–Benary reaction was conducted with the brominated oxo ester **5** reacting with dimedone and ammonium acetate [15] as a mild chemical base in aqueous methanol. In the first step, the CH-acidic compound dimedone was deprotonated, yielding a dynamic keto-enol equilibrium of the carbanion and the enolate-ion. The two nucleophilic centers reacted with the partial positive charged halide and carbonyl carbon atom likewise in order to form the bicyclic ring system **11**. In the next step, this intermediate was dehydrated under acidic conditions to yield **12** characterized by an aromatic furan structure. Water elimination using toluene in a Dean–Stark apparatus [15] was not applicable due to the small amount of the intermediate **11**. Attempts to eliminate water in toluene without a distilling trap failed, only the carboxylic acid derivative **14** could be isolated. In order to overcome this problem, we replaced toluene with methanol making use of the alcohol's ability to retain water by exothermic solvation [16]. This slightly modified reaction procedure afforded ester **12** in good yields of 84%. This furan derivative **12** afforded final compound **10** by replacing the heterocyclic oxygen atom with nitrogen. For this exchange, we used ammonium acetate [17] as a neutral ammonia releasing reagent. When synthesis was conducted under acidic conditions, it promoted decarboxylation to compound **15**. Similarly, in presence of base, ammonolysis reaction was potentially favored converting the ester group to an unreactive [18] primary amide. Starting O-N-substitution reaction from compound **14**, which contains a carboxylic acid, with ammonium acetate in DMF, we obtained decarboxylated indole compound **15**, exclusively. Thereupon we used the methyl ester **13** as starting product to synthesize **10**. Compared to reaction with **14**, substitution reaction with ester derivative **13** was apparently hindered. After 17 h at 100 °C [17], there was only a small degree of conversion detectable. Because of its vinylogous carbamate substructure, required building block **10** showed no reaction with Ehrlich's reagent (as a typical staining reagent for indoles [19]) which made it demanding to detect the final product on a TLC plate.

Beyond this issue, synthesis afforded compound **10** in only modest yield of about 20%, which is in accordance with the published theoretical yield of 21% in similar transformations [17].



Scheme 2. Synthesis of **16a-t** from building block **10** generated via O-N-exchange reaction of the Feist–Benary products **12** and **14**. a) $CuBr_2$, EtAc/$CHCl_3$, 19 h reflux; b) dimedone, NH_4Ac, MeOH/H_2O, 3 h at 90°C; c) TsOH, MeOH, µw: 1 h at 100 °C; d) NH_4Ac, DMF, µw: 15 min at 120 °C; e) TsOH, toluene, µw: 1.5 h at 110 °C; f) NaOH, 20 min reflux, HCl; g) NH_4Ac, DMF, µw: 1 h at 100 °C; h) e. g. HATU, DIPEA, DMF, methyl amine derivative, 1.5 h–3 d at 20–60 °C or as stated in experimental section.

Accelerated conditions in terms of both temperature or reaction time led to increased conversion to the isolated by-product **15**.

To prepare an adequate amount of the key compound **10**, we attempted to improve the yield of the prior described O-N-substitution reaction. We received best results performing the reaction with anhydrous solvents in a microwave reactor for 20 min and 110 °C under counter cooling conditions. These adjustments ensured continuous irradiation with microwaves avoiding overheating of the reaction mixture. Afterwards the obtained methyl ester **13** was subsequently hydrolyzed by adding alkaline solution to afford carboxylic acid **10**. Finally, we were able to obtain **10** via the furan derivative **12**.

Having appropriate amounts of **10** in hand, we were able to synthesize a small library of amide compounds **16a**-**q**. Whereas most of the necessary amines were commercially available at reasonable costs, the secondary methylamine derivatives **17r**-**t** had to be synthesized by reductive amination, utilizing suitable aromatic aldehyde derivatives and methylamine in methanolic

solution (Figure 3). Intermediate imines were reduced by addition of aqueous sodium borohydride solution [20].

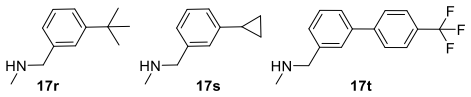


Figure 3. Methylamines **17r**-**t** as reagents for amide couplings with **10** were synthesized by reductive amination

Synthesis of multipurpose screening compounds 16a-t

For amide coupling, a multitude of reagents optimized for peptide synthesis are available. The method of choice in our case proved to be the highly efficient [21] peptide-coupling reagent 1-bis(dimethylamino)methylene-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU), affording amides **16a**-**t** in good yields. Synthesis was performed with HATU and **10** in the presence of an amine component and a non-nucleophilic base like ethyldiisopropylamine in DMF. Stirring the reaction mixture at room temperature or in an oil bath at 60 °C was effective as well. Furthermore, microwave assisted synthesis could reduce reaction time from hours and days to a few minutes. The obtained product mixtures were subsequently purified by column chromatography. NMR analysis of the purified amides (like **16b**) in DMSO-d_6 showed double signalsIn order to investigate this finding, we conducted an alternative synthesis via Mitsunobu reaction with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP). While the Mitsunobu reaction is widely known to be applicable in ester and ether synthesis, the conditions are appropriate for amide coupling, too. The successful alternative synthesis route afforded **16b** in good yields and identical NMR-signals with the integration intensity observed before. Furthermore, upon analysis with HPLC/MS, only one pure compound with predicted mass-to-charge ratio was detectable. Additionally we obtained the secondary amide derivative **16a** from the amine *N*-methyl-1-(4-methyl-4*H*-thieno[3,2-*b*]pyrrol-2-yl)methenamine and **10**. During purification, the product decomposed by cleaving the N-C-bond of the amine substructure. Repetitive synthesis reaffirmed this observed degradation. The sterically less crowded amide **16a** showed no duplicated signals in NMR spectra. From this observation, the assumption arose that in solution two types of molecular conformations (rotational isomers) exist. To confirm our hypothesis, we utilized a temperature replica exchange molecular dynamics simulation (T-REMD) to sample the conformational space of the amide **16b** as a representative for verification. The ligand molecule was solvated in DMSO to achieve conditions similar to NMR experiments. To find global energy minimum structures and to ensure convergence of the Boltzman-weighted ensemble, the simulation was analyzed by coordinate principle component analysis with Boltzman inversion (cPCA, Figure 4).

We found that the bond rotation at position 3 is blocked by both substituents of the tertiary amide which interact with the carbonyl group in position 4. A significant energy barrier (>RT) indicates two individual conformers that explain the presence of two sets of NMR data, convincingly (Figure 4A). Running the same calculations with the analogous secondary amide derivative **18b** (demethylated *in silico*), the energy barrier is drastically decreased and bond rotation at position 3 is not restricted anymore (Figure 4B). Thus, the duplication of NMR signals seen in **16b**-**t** does not indicate insufficient purity, which would be detrimental for biological evaluation.

Bioassay

The inhibitory effect of compounds **16a**-**t** on SIRT1-3 was detected via a previously reported fluorescence based assay [22]. The synthetic substrate Z-Lys(Acetyl)-AMC (ZMAL) releases 7-aminomethylcumarin (AMC) upon deacetylation through the sirtuins, leading to a fluorescent readout. All compounds were tested at 100 µM and 10 µM respectively. For compounds that showed more than 50% inhibition at 10 µM an IC_{50} value was determined. Inhibition measurements were performed in biological duplicates for all compounds. At 100 µM concentration, for all compounds except **16d**, at least a weak inhibitory activity was found. Compounds **16a**-**c**, **o** and **s** displayed inhibition only at the highest concentration tested, ranging from 7.4 to 74% inhibition of SIRT2. At 10 µM concentration, compounds **16e**-**n**, **p**, and **r** showed moderate inhibition ranging from 10 to 31%. When comparing the amine residues, no difference is distinguishable between the activity of heterocyclic and aromatic substituents. However, for **16q** and **t**, IC_{50} values in the single digit micromolar range could be obtained (Table 1).

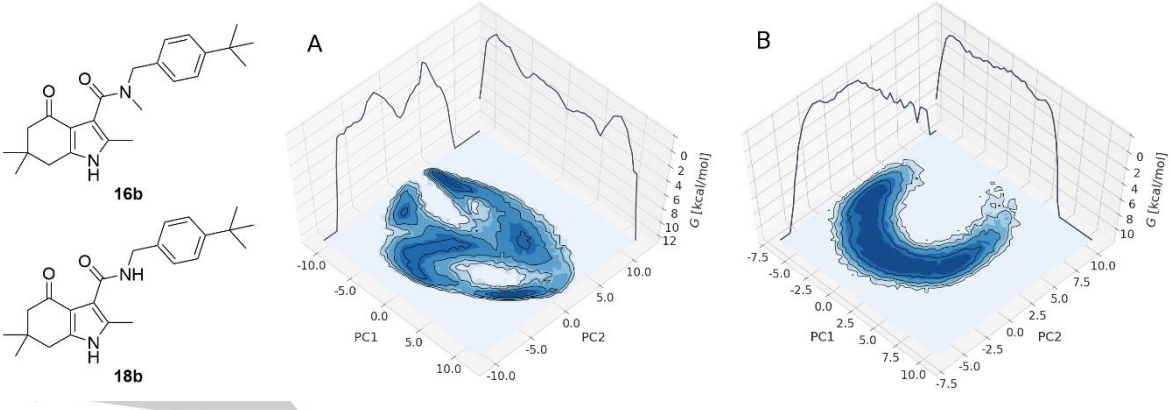


Figure 4. Conformational free energy landscape from the first two coordinate PCA eigenvectors of **16b** (A) and its secondary amide derivative **18b** (B).

Table 1 Inhibition of SIRT1-3 by synthesized tetrahydroindole derivatives **16a-t**

Entry	SIRT1 inhibition[a]	SIRT2 inhibition[a]	SIRT3 inhibition[a]
16a	no inhibition	7 @ 100 µM	9 @ 100 µM
16b	31 @ 100 µM	74 @ 100 µM	53 @ 100 µM
16c	21 @ 100 µM	41 @ 100 µM	27 @ 100 µM
16d	11 @ 100 µM	no inhibition	34 @ 100 µM
16e	16 @ 10 µM	13 @ 10 µM	37 @ 100 µM
16f	25 @ 100 µM	14 @ 10 µM	5 @ 10 µM
16g	26 @ 100 µM	17 @ 10 µM	4 @ 10 µM
16h	28 @ 100 µM	23 @ 10 µM	11 @ 10 µM
16i	no inhibition	22 @ 10 µM	35 @ 100 µM
16j	17 @ 10 µM	24 @ 10 µM	36 @ 10 µM
16k	no inhibition µM	22 @ 10 µM	no inhibition
16l	24 @ 100 µM	11 @ 10 µM	11 @ 10 µM
16m	83 @ 100 µM	14 @ 10 µM	12 @ 100 µM
16n	no inhibtion	10 @ 10 µM	18 @ 100 µM
16o	42 @ 100 µM	59 @ 100 µM	42 @ 100 µM
16p	36 @ 100 µM	31 @ 10 µM	10 @ 10 µM
16q	46 @ 100 µM	5.83 ± 0.91 µM	22 @ 10 µM
16r	30 @ 100 µM	25 @ 100 µM	6 @ 10 µM
16s	19 @ 100 µM	29 @ 100 µM	46 @ 100 µM
16t	10 @ 10 µM	0.98 ± 0.10 µM	32 @ 10 µM

[a] Inhibition in % related to controls given @ indicated concentration or IC_{50} values with statistical limits.

Computational Chemistry

For a better understanding of the experimentally determined IC_{50}-values and their structural foundation, we used a combined docking and molecular dynamics approach for predicting possible binding modes. All compounds were docked to the substrate pocket of SIRT2 with a thienopyrimidinone based inhibitor **19** [23] as template and visually inspected. The docking poses of **16q** were passed to molecular dynamics simulations for post-processing and refinement. The ligand movements were monitored by its RMSD value to ensure a stable final binding pose (see supporting informations).

Binding to the protein mainly consists of lipophilic interactions and two π-π-stackings with Phe96 and Phe190, whereas hydrogen bonds are mediated by water molecules (Figure 5).

As previously described in literature, bulky aromatic substituents are necessary to fill the so called 'selectivity pocket' in SIRT2 [23]. It is highly probable that the biphenyl derivatives have a similar binding pose compared to the cocrystalized thienopyrimidinone based inhibitors. This assumption is supported by the structural similarity of **16t** with **19** (Figure 6)**Figure 6.** Structural similarity of **16t** with a known thienopyrimidinone based inhibitor **19**. and our experimental results. Especially the compounds **16q** and **16t** have a significantly higher selectivity for SIRT2 over SIRT1 and SIRT3.

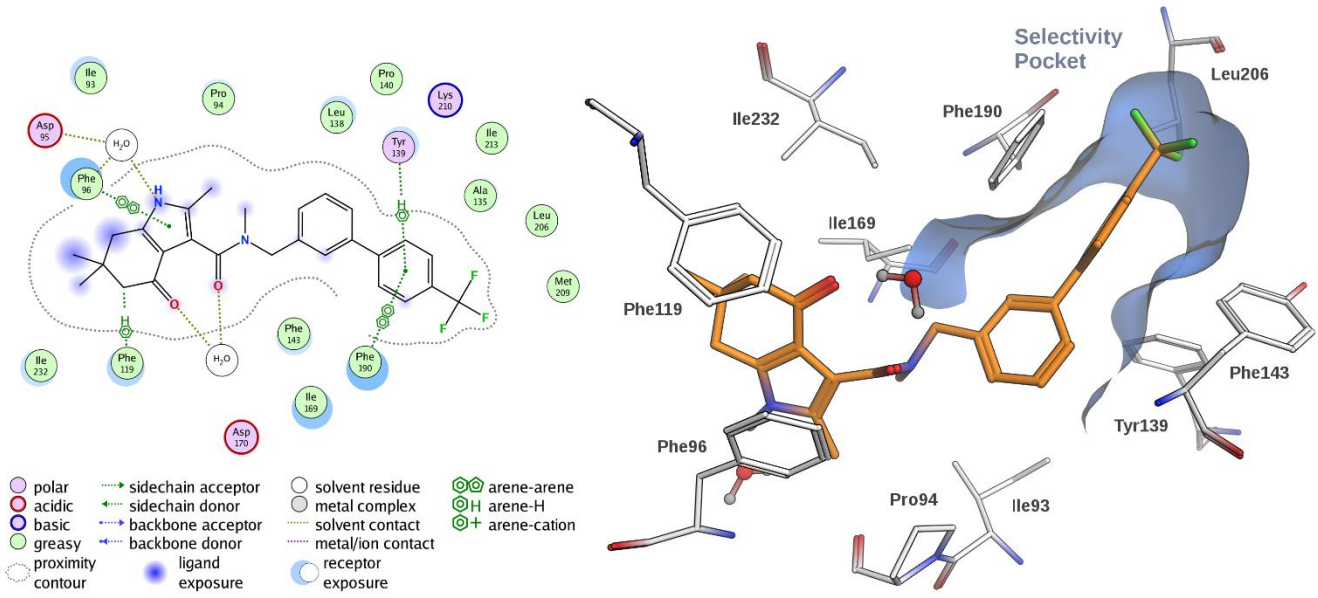


Figure 5. Predicted binding pose of inhibitor **16t** in substrate binding pocket refined by molecular dynamics simulation (PDB: 5MAT).

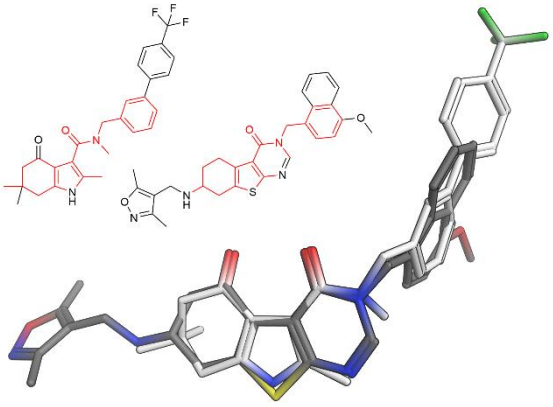


Figure 6. Structural similarity of **16t** with a known thienopyrimidinone based inhibitor **19**. Both compounds have a similar ligand efficiency (LE) with values of 0.206 and 0.209, respectively.

Conclusions

An in-house screening was the starting point for the synthesis of SIRT2 inhibitors with rarely promulgated 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide scaffold. We accomplished the synthesis of parent scaffold **10** in satisfying yields of 49% by reaction of the Feist–Benary-precursor **12** with ammonium acetate under microwave irradiation. Coupling conditions for the carboxylic acid scaffold **10** and a series of secondary methyl amines could be found applying the reagent HATU. The achieved yields of the final products vary from 14.7% to 96%. The resulting test compounds were subjected to homogeneous deacetylase inhibition assays towards SIRT1, 2, and 3.

Almost all synthesized inhibitors show moderate to low inhibition in vivo. Beyond these findings, the amide **16q** was active in the low micromolar range. Structure-activity optimization led to synthesis of compound **16t**. Post-synthesis docking analysis adumbrate the binding region of the most potent inhibitors, the hydrophobic nicotinamide SIRT2 subpocket. Thus, biphenyl substituents seem to be crucial for efficient inhibition by providing a π-π-stacking with Phe190 of the enzyme. Direct binding to the protein mainly consists of lipophilic interaction, whereas hydrogen bonds are mediated by water molecules, indirectly.

NMR analysis of the tertiary amides **16b-t** indicate the existence of two inseparable isomers in DMSO solution. We carried out replica exchange molecular dynamic simulations for one of the synthesized inhibitors (**16b**) and its demethylated secondary amide counterpart (**18b**) to confirm our hypothesis for the existence of rotational isomers. For the present scaffold, two low energy conformations could be found.

Compounds **16r-t** were synthesized as a consequence of the good inhibition and selectivity of biphenyl derivative **16q**. Replacement of the distal aromatic ring either with an aliphatic *tert*-butyl (**16r**) or cyclopropyl (**16s**) group with partial sp^2-hybridization-character [24] led to decreased inhibition. Best inhibition was demonstrated for the compound containing a *p*-trifluoromethyl substituted biphenyl system. This derivative **16t** inhibited SIRT2 highly selective in submicromolar concentrations (IC_{50} = 0.98 µM).

Experimental Section

Computational methods

Docking All calculations were performed using the Molecular Operating Environment (MOE) software suite (version 2018.01). The cocrystalized ligand (PDB: 5MAT) was used for template guided docking based on maximum common substructure (MCS). Protein residues around 4.5 Å of these ligand atoms where defined as binding site. For each molecule, 30 poses were placed on the template structure and refined with an Induced Fit and MM/GBVI scoring. A total of 10 final poses per ligand were generated and visually inspected. Any other parameters were left as default. The closest pose of **16q** to the reference was used as initial structure for molecular dynamics simulation.

Molecular Dynamics The complex from molecular docking was analyzed using a two-stage molecular dynamics protocol. The system was minimized for 50 ps followed by 250 ps NVT and 250 ps NPT at 300 K for equilibration using NAMD 2.12 with GPU acceleration [25]. Another 30 ns NPT were simulated as production run. The timestep was set to 4 fs with hydrogen mass repartition applied by ParmED [26]. Counterions and AMBER 16 force field parameters were assigned by tLeap (Ambertools 17). RESP charges were determined according to GAFF [27] from QM calculations with Gaussian 09. Electrostatic and van der Waals interactions were treated with PME. Explicit water was described by the TIP3P model with periodic boundary conditions. Pressure and temperature were controlled by a Langevin piston barostat and Langevin thermostat, respectively. The frequency of collected snapshots was set to 1 ps and the simulation trajectory was analyzed using VMD 1.9.3 [28].

tREMD For the temperature replica exchange method, the same parameters as described above were applied. Inhibitor **16b** was solvated in DMSO [29] and 32 independent replicas were used at temperatures between 300 K and 600 K with exchange rates around 20%. The number of exchange attempts was set to 50000 with 1000 simulation steps each, resulting in the same number of baseline structures at 300 K within 200 ns (6.4 µs total). The same procedure was applied to the secondary amide derivative of **16b**.

Material and Methods.

All chemicals and solvents were purchased from commercial suppliers and used without further purification. Melting points were determined with a Büchi “Schmelzpunkt M-565” apparatus and are uncorrected. Microwave-assisted synthesis was performed using a microwave synthesis reactor Monowave 300 (“closed vessel” mode, G10-vials: 6 mL total capacity vessel, G30-vials: 20 mL temperature control via IR sensor) from Anton Paar, while stirring at 600 rpm. Unless otherwise indicated, the syntheses were carried out without permanent compressed air countercooling. NMR spectroscopic measurements were recorded with a Bruker Biospin Avance III Ultrashield 400 instrument (^{1}H: 400.2 MHz, ^{13}C: 100.6 MHz). Samples were dissolved in deuterated solvents, and chemical shifts (δ) in ^{1}H and ^{13}C NMR spectra are given in parts per million (ppm) with tetramethylsilane (TMS) signals as reference. Abbreviations are defined as follows: s = singlet, d = doublet, t = triplet, q = quartet.

Assignment of ^{13}C signals to isomers 1 and 2 of **16a**-**t**, respectively, was based on heteronuclear 2 D correlation experiments (HSQC, HMBC). Mid-infrared spectra were recorded on an ALPHA FT-IR instrument from Bruker Optics with diamond ATR accessory. High resolution mass spectra (HRMS) were obtained after high performance liquid chromatography (HPLC) with a mass spectrometer (LC-IT-TOF) from Shimadzu based on a deviance tolerance limit ≤ 5ppm. High performance liquid chromatography (HPLC) was performed using Shimadzu devices CBM-20A, LC-20A P, SIL-20A, and FRC-10A with a SPD 20A UV-Vis detector and LiChrospher100 RP-18 endcapped (250×25mm) HPLC columns. Preparative column chromatography was done on silica gel from Macherey-Nagel (particle size 50–100 µm,140–270 mesh ASTM). TLC was performed using pre-coated aluminum foil sheets silica gel 60 F_{254} provided by Macherey-Nagel. Preparative TLC was performed on silica gel 60 F_{254} platelets 20×20 cm and 1 mm thickness after chamber saturation was ensured.

Synthesis of the amides, Method A: In a dried G10 vial (max. loading volume 10 mL) compound **10** (1.0 equiv.), HATU (2.0 equiv.) and the amine component (1.0 equiv.) were solved in dried DMF (2–3 mL). To the stirred solution DIPEA (5.0 equiv.) was added. Reaction mixture was covered with inert nitrogen gas, sealed and stirred under further specified conditions. The solvent was removed under reduced pressure. Separation by column chromatography (*n*-hexane/ethyl acetate/ethanol, 10:7:2) afforded the isolated amides.

Synthesis of the N-methyl-amines, Method B: In a two-necked flask the aromatic aldehyde (1.0 equiv.) and methanolic methylamine solution (1.1 equiv.) were solved in methanol (20 mL). Reaction mixture was stirred under protective atmosphere at 50 °C. Right after complete consumption of starting product was detected, mixture was allowed to cool down at room temperature. $NaBH_4$ (3.0 equiv.) was subsequently added as aqueous solution and reaction mixture was stirred for 30 min. Hereafter solvent was removed under reduced pressure. Residue was dissolved in diethyl ether and solution was extracted with 1 M HCl solution (2 × 50 mL). Combined aqueous phases were alkalized with KOH at pH>10. Basic solution was extracted with dichloromethane (3 × 40 mL), combined phases were acidified with HCl and solvent was evaporated under reduced pressure. Crystallization (2-propanol/diethyl ether) of the residue afforded the amine.

1-Phenyl-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazine-3-thione (**1d**)

A mixture of 2-naphthol (0.43 g, 3.0 mmol, 1.0 equiv.), benzaldehyde (0.35 mL, 0.36 g, 3.0 mmol, 1.0 equiv.),and potassium thiocyanate (0.29 g, 3.0 mmol, 1,0 equiv.) were suspended in methanol (4 mL). Under continuous stirring HCl (36%, 0.4 mL, 5.0 mmol, 17 equiv.) were added. Reaction mixture was stirred for 22 h at 60 °C in an oil bath. After this solvent was evaporated under reduced pressure. Residue was dissolved in 50 mL DCM and extracted with water (3 × 30 mL). Organic phase was concentrated under reduced pressure and subsequently purified by column chromatography (ethyl acetate/*n*-hexane). Crystallisation in 2-propanol afforded desired product. Yield = 0.43 g (49%) colorless crystals, mp: 218 °C (degradation). IR: $\tilde{\nu}$ (cm^{-1}) = 3142 (m); 3021 (w); 1164 (s). ^1H-NMR (DMSO-d_6): δ = 6.24 (d, 1H, ^3J = 3.6 Hz), 7.27–7.38 (m, 5H), 7.46–7.52 (m, 3H), 7.82 (d, 1H, ^3J = 8.8 Hz), 7.98 (d, 1H, ^3J = 9.2 Hz), 8.04 (d, 1H, ^3J = 9.2 Hz), 11.13 (d, 1H, ^3J = 2.8 Hz); ^{13}C-NMR (DMSO-d_6) δ = 53.9, 113.3, 116.8, 123.1, 125.6, 127.3, 127.6, 128.3, 128.6, 128.7, 129.0, 130.6, 130.9, 141.4, 146.1, 180.3; HRMS (ESI, *m*/*z*) $[M+H]^+$: calcd for $C_{18}H_{14}NOS^+$: 292.0791, found: 292.0788.

1-Phenyl-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-imine (**1e**)

A mixture of 2-naphthol (1.45 g, 10.0 mmol, 1.0 equiv.), thiourea (0.77 g, 10.1 mmol, 1.0 equiv.), trichlortriazin (0.19 g, 1.0 mmol, 0.1 equiv.), and benzaldehyde (1.05 mL, 1.11 g, 10.4 mmol, 1.0 equiv.) was moistened with 3 droplets of water. Reaction mixture was stirred for 15 min at 135 °C. After this 30 mL water were added and slurry was refluxed for 20 min. Mixture was extracted with 3 × 50 mL ethyl acetate. Organic phase was extracted successively with Na_2CO_3-solution (10%) and HCl (1 M). Precipitation was filtered and crystallized in methanol/water (3:1). Yield = 0.79 g (29%) colorless solid, mp: 135 °C. IR: $\tilde{\nu}$ (cm^{-1}) = 3443 (m); 3020 (w); 1703 (s). ^1H-NMR (DMSO-d_6): δ = 6.07 (s, 1H), 6.17 (s, 1H), 7.14–7.18 (m, 1H), 7.23–7.29 (m, 5H), 7.38 – 7.46 (m, 2H), 7.78 (d, 1H, ^3J = 8.4 Hz), 7.89–7.92 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ = 54.8, 115.8, 116.3, 123.0, 124.5, 126.8, 126.9, 127.1, 128.5, 129.1, 129.5, 130.5, 145.6, 146.8, 148.8; HRMS (ESI, *m*/*z*) $[M+H]^+$: calcd for $C_{18}H_{15}N_2O^+$: 275.1179, found: 276.1183.

Methyl-3-bromo-2-oxobutanoate (**5**). To a slurry of $CuBr_2$ (50.01 g, 223.8 mmol, 3.0 equiv.) in 130 mL ethyl acetate a solution of methyl 2-oxobutanoate (13.00 g, 112.0 mmol, 1.0 equiv.) in freshly distilled chloroform (70 mL) were added. Reaction mixture was refluxed for 19 h. Subsequently solid residues were filtered off and filtrate was used for further purification. Solvent evaporation and distillation of the oily residue afforded desired product. Yield = 21.14 g (97%) pale yellow oil, bp: 85–95 °C (30 mbar). IR: $\tilde{\nu}$ (cm^{-1}) = 3263 (m); 1747 (s); 1614 (s). ^1H-NMR ($CDCl_3$): δ = 1.12 (s, 6H), 1.43 (d, 3H, ^3J = 6.8 Hz), 2.23 (s, 2H), 2.37 (s, 2H), 3.70 (s, 1H), 3.83 (s, 3H), 4.91 (q, 1H, ^3J = 6.8 Hz); ^{13}C-NMR ($CDCl_3$) δ = 13.6, 28.8, 34.5, 38.1, 51.0, 53.9, 80.0, 89.0, 116.1, 173.9, 179.1, 193.6; HRMS (ESI, *m*/*z*) $[M+H]^+$: calcd for $C_{13}H_{19}O_5^+$: 255.1227, found: 255.1222.

Methyl-3-bromo-2,2-diethoxybutanoate (**8**). A mixture of **5** (3.90 g, 20.0 mmol, 1.0 equiv.), triethyl orthoformate (9.00 g, 60.7 mmol, 3.0 equiv.) and concentrated sulfuric acid (0.6 mL, 1.10 g, 11.2 mmol, 0.5 equiv.) were weighted in a G10-vial. The vial was sealed and placed in a microwave field (110 °C) for 30 min. After that, the reaction mixture was poured in 50 mL saturated solution of $NaHCO_3$ in water. Aqueous emulsion was extracted with 3 × 50 mL dichloromethane. Subsequent evaporation and distillation in vacuum afforded the desired product. Yield = 2.13 g (38%) colorless oil, bp: 95–100 °C (at 5 mbar). IR: $\tilde{\nu}$ (cm^{-1}) = 2979 (w); 1739 (s); 1260 (s). ^1H-NMR ($CDCl_3$): δ = 1.23 (t, 3H, ^3J = 7.2 Hz), 1.26 (t, 3H, ^3J = 7.2 Hz), 1.34 (t, 3H, ^3J = 7.2 Hz), 1.77 (d, 3H, ^3J = 6.8 Hz), 3.52–3.71 (m, 4H), 4.28–4.35 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ = 14.5, 15.4, 21.1, 48.1, 58.3, 60.1, 62.0, 101.8, 167.2.

2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid (**10**).

In a G10-vial were suspended compound **12** (0.98 g, 4.1 mmol, 1.0 equiv.) and ammonium acetate (0.64 g, 8.2 mmol, 2.0 equiv.) in 2 mL dry DMF. Vial was sealed and placed in a microwave field (110 °C, with counter cooling) for 20 min. Afterwards mixture was diluted with 50 mL water and was subsequently extracted with 2 × 25 mL *n*-hexane. Aqueous phase was alkalized by adding NaOH (4 g) and was afterwards refluxed for 20 min. Precipitation was filtered off and filtrate was acidified with HCl to pH < 3.

Mixture was stored for 30 min at 5 °C and accrued precipitation subsequently filtered and washed with water. Yield = 0.45 g (49%) amorphous solid, mp: 250–255 °C (degradation). IR: ṽ (cm^{-1}) = 3078 (w); 2954 (m); 1669 (s). ^{1}H-NMR (DMSO-d_6): δ = 1.09 (s, 6H), 2.46 (s, 3H), 2.47 (s, 2H), 2.69 (s, 2H), 12.21 (s, 1H), 14.17 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 12.3, 27.7, 35.3, 35.4, 50.0, 108.7, 114.5, 140.2, 145.6, 163.6, 197.23; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{12}H_{16}NO_3^+$: 222.1125, found: 222.1116.

Methyl-3-hydroxy-2,6,6-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-carboxylate (**11**).

A mixture of ammonium acetate (6.11 g, 43,6 mmol, 1.0 equiv.) dimedone and 3.36 g (43.6 mmol, 1.0 equiv.) were dissolved in 30 mL MeOH/H_2O (7:3). Reaction mixture was stirred in an oil bath at 80 °C for 1 h. Then a solution of compound **5** (8.50 g, 43.6 mmol, 1.0 equiv.) in 20 mL MeOH/H_2O (7:3) was added slowly to the reaction mixture and continue to stir for 3 h at 80 °C. Solvent was removed under reduced pressure and residue was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1). Product was subsequently crystallized in diethyl ether/ petrol ether. Yield = 7.50 g (74%) colorless crystals, mp: 101 °C. IR: ṽ (cm^{-1}) = 2957 (w); 1730 (s); 1275 (s). ^{1}H-NMR ($CDCl_3$): δ = 1.29 (d, 3H, ^3J = 6.8 Hz), 3.93 (s, 3H), 5.17 (q, 1H, ^3J = 6.8 Hz); ^{13}C-NMR ($CDCl_3$) δ = 18.6, 42.5, 53.6, 161.2, 185.9.

Methyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**12**).

A mixture of compound **11** (0.13 g, 0.5 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (0.05 g, 0.25 mmol, 0.5 equiv.) were dissolved in 5 mL methanol. Vial was sealed and placed in a microwave field (100 °C) for 1 h. Solvent was subsequently removed under reduced pressure. Residue was dissolved in 30 mL ethyl acetate and extracted with 2 × 10 mL aqueous K_2CO_3-solution and hereinafter with 2 × 20 mL water. Ethyl acetate was evaporated and residue was purified by column chromatography (*n*-hexane/ethyl acetate, 10:5). Yield = 0.10 g (84%) pale yellow, waxy oil, bp: 318 °C (degradation). IR: ṽ (cm^{-1}) = 2955 (m); 1683 (s); 1080 (s). ^{1}H-NMR ($CDCl_3$): δ = 1.13 (s, 6H), 2.40 (s, 2H), 2.52 (s, 3H), 2.71 (s, 2H), 3.88 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ = 13.7, 28.6, 35.0, 37.5, 52.0, 53.3, 111.4, 118.5, 159.5, 164.1, 164.9, 191.9.

Methyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (**13**)

A mixture of compound **12** (0.50 g, 2.1 mmol, 1.0 equiv.) and ammonium acetate (0.33 g, 4.2 mmol, 2.0 equiv.) were suspended in a G10 vial in dry DMF (2 mL). The vial was sealed and placed in microwave field (120 °C, with counter cooling) for 15 min. Afterwards mixture was diluted with 50 mL water and was subsequently extracted with dichloromethane (3 × 30 mL). Solvent was evaporated under reduced pressure and residue was purified via preparative Thin Layer Chromatography (TLC). Yield = 0.11 g (22%) pale brown, waxy solid, mp: 207–211 °C. IR: ṽ (cm^{-1}) = 3255 (m); 2953 (m); 1686 (s). ^{1}H-NMR ($CDCl_3$): δ = 1.09 (s, 6H), 2.37 (s, 2H), 2.43 (s, 3H), 2.64 (s, 2H), 3.81 (s, 3H), 9.24 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ = 13.3, 28.6, 35.6, 37.0, 51.5, 53.6, 109.8, 117.7, 137.3, 143.0, 166.0, 192.6, HRMS (APCI, *m*/*z*) [*M*-H]$^-$: calcd for $C_{13}H_{16}NO_3^-$: 234.1136, found: 234.1135.

2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid (**14**).

A mixture of compound **11** (0.13 g, 0.5 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (0.05 g, 0.25 mmol, 0.5 equiv.) were dissolved in 5 mL methanol. Vial was sealed and placed in a microwave field (100 °C) for 1 h. Solvent was subsequently removed under reduced pressure. Residue was dissolved in ethyl acetate (30 mL) and extracted with 2 × 10 mL aqueous K_2CO_3-solution and hereinafter with 2 × 20 mL water. Ethyl acetate was evaporated and residue was purified by column chromatography (*n*-hexane/ethyl acetate, 10:5). Yield = 0.10 g (84%) pale yellow, waxy oil, bp: 318 °C (degradation). IR: ṽ (cm^{-1}) = 2955 (m); 1683 (s); 1080 (s). ^{1}H-NMR ($CDCl_3$): δ = 1.13 (s, 6H), 2.40 (s, 2H), 2.52 (s, 3H), 2.71 (s, 2H), 3.88 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ = 13.7, 28.6, 35.0, 37.5, 52.0, 53.3, 111.4, 118.5, 159.5, 164.1, 164.9, 191.9.

2,6,6-Trimethyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (**15**). A mixture of compound **14** (0.50 g, 2.2 mmol, 1.0 equiv.) and ammonium acetate (0.29 g, 3.8 mmol, 1.7 equiv.) were suspended in dry DMF (3 mL). Reaction mixture was flushed with nitrogen, sealed and placed in a microwave field (100 °C) for 1 h. Solvent was subsequently evaporated under reduced pressure and residue was purified by column chromatography. Product was crystallized in acetone. Yield = 0.09 g (15%) colorless crystals, mp: 194 °C. IR: ṽ (cm^{-1}) = 3236 (s); 2956 (m); 1625 (s). ^{1}H-NMR ($CDCl_3$): δ = 1.10 (s, 6H), 2.23 (s, 3H), 2.33 (s, 2H), 2.63 (s, 2H), 6.16 (q, 1H, ^4J = 1.6 Hz), 8.62 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ = 13.1, 28.8, 36.0, 37.0, 52.2, 102.8, 119.6, 129.2, 142.4, 194.1; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{11}H_{16}NO^+$: 178.1226, found: 178.1234.

***N*,2,6,6-Tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16a**). By method A, amine: *N*-methyl-1-(4-methyl-4*H*-thieno[3,2-*b*]pyrrol-2-yl)methenamine, 3 h at 50 °C, yield = 0.07 g (74%) blue colored crystals, mp: 163 °C. IR: ṽ (cm^{-1}) = 3229 (m); 2957 (m); 1625 (s). ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.35 (s, 2H), 2.47 (s, 3H), 2.64 (s, 2H), 2.72 (d, 3H, ^3J = 4.4 Hz), 10.18 (q, 1H, ^3J = 4.1 Hz), 11.71 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 13.0, 25.1, 27.7, 34.7, 35.9, 52.1, 111.8, 114.1, 136.3, 143.9, 164.5, 194.7; HRMS (ESI, *m*/*z*) [*M*-H]$^-$: calcd for $C_{13}H_{17}N_2O_2^-$: 233.1296, found: 233.1301.

***N*-[4-(*tert*-Butyl)benzyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16b**). By method A, 3 h at 50 °C, yield = 0.15 g (96%) colorless solid, mp: 125–129 °C. IR: ṽ (cm^{-1}) = 3085 (w); 2951 (w); 1657 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 1.28 (s, 9H), 2.10 (s, 3H), 2.21 (s, 2H), 2.62 (s, 2H), 2.67 (s, 3H), 4.54 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.65 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 7.33 (d, 2H, ^3J = 8.4 Hz), 7.36 (d, 2H, ^3J = 8.8 Hz), 11.34 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 28.2, 31.2, 35.1, 34.1, 35.2, 35.8, 49.0, 51.9, 112.8, 115.9, 125.0, 127.0, 127.7, 137.7, 141.0, 149.0, 167.1, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 1.24 (s, 9H), 2.07 (s, 3H), 2.21 (s, 2H), 2.59 (s, 2H), 2.79 (s, 3H), 4.09 (AX, 1H, $^2J_{AX}$ = 15.6 Hz), 4.50 (AX, 1H, $^2J_{AX}$ = 15.6 Hz), 6.99 (d, 2H, ^3J = 8.0 Hz), 7.30 (d, 2H, ^3J = 8.4 Hz), 11.30 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 31.1, 32.1, 34.1, 35.2, 35.8, 51.9, 53.0, 112.7, 115.8, 125.2, 126.7, 127.5, 134.6, 141.0, 149.5, 167.1, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{24}H_{33}N_2O_2^+$: 381.2537, found: 381.3522.

***N*-(3-Methoxybenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16c**). By method A, 1.5 h at 50 °C and 14 h at 30 °C, yield = 0.13 g (91%) pale yellow solid, mp: 142–144 °C. IR: ṽ (cm^{-1}) = 3085 (w); 1657 (s); 1266 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.11 (s, 3H), 2.21 (s, 2H); 2.62 (s, 2H), 2.67 (s, 3H), 3.78 (s, 3H), 4.53 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.71 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 6.80 (m, 1H), 6.97 (d, 1H, ^3J = 7.6 Hz), 7.01 (s, 1H), 7.25 (t, 1H, ^3J = 8.0 Hz), 11.36 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.9, 35.1, 35.2, 35.8, 49.3, 51.9, 55.0, 112.5, 112.6, 112.8, 115.8, 119.6, 127.5, 129.3, 139.5, 141.0, 159.5, 167.2, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6):

δ = 1.04 (s, 6H), 2.07 (s, 3H), 2.21 (s, 2H), 2.60 (s, 2H), 2.81 (s, 3H), 3.70 (s, 3H), 4.15 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 4.48 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 6.62 (s, 1H), 6.66 (d, 1H, ^3J = 7.6 Hz), 6.80 (m, 1H), 7.20 (t, 1H, ^3J = 8.0 Hz), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 28.2, 32.1, 35.2, 35.8, 53.4, 51.9, 55.0, 112.3, 112.8, 112.8, 115.8, 119.2, 127.6, 129.5, 139.4, 141.1, 159.4, 167.1, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{21}H_{27}N_2O_3^+$: 355.2016, found: 355.2006.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16d**). By method A, 3 h at 50 °C, yield = 0.13 g (87%) colorless solid, mp: 173–175 °C. IR: ῡ (cm^{-1}) = 3218 (m); 1647 (s); 1490 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.09 (s, 3H), 2.20 (s, 2H), 2.61 (s, 2H), 2.65 (s, 3H), 4.41 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.68 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 5.99 (s, 2H), 6.81 (d, 1H, ^3J = 8.0 Hz), 6.86 (s, 1H), 7.04 (s, 1H), 11.34 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.3, 28.2, 34.9, 35.2, 35.8, 49.0, 51.4, 100.9, 108.0, 112.8, 115.9, 120.7, 127.4, 131.7, 141.1, 146.1, 147.4, 167.1, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.08 (s, 3H), 2.20 (s, 2H), 2.60 (s, 2H), 2.78 (s, 3H), 4.09 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.40 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 5.97 (s, 2H), 6.55 (d, 1H, ^3J = 8.0 Hz), 6.62 (s, 1H), 6.86 (s, 1H), 11.33 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.3, 28.2, 31.8, 35.2, 35.8, 53.1, 51.9, 100.9, 107.5, 108.1, 112.7, 115.8, 120.4, 127.6, 131.4, 141.1, 146.3, 147.4, 166.9, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{21}H_{27}N_2O_3^+$: 355.2016, found: 355.2006.

***N*,2,6,6-Tetramethyl-*N*-[(3-methylthiophen-2-yl)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16e**). By method A, 17 h at 45 °C, yield = 0.07 g (53%) colorless, waxy solid, mp: 188 °C. IR: ῡ (cm^{-1}) = 3093 (m); 1652 (s); 1533 (m). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.08 (s, 3H), 2.18 (s, 2H), 2.22 (s, 3H), 2.60 (s, 2H), 2.66 (s, 3H), 4.36 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 5.03 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 6.84 (d, 1H, ^3J = 4.8 Hz), 7.31 (d, 1H, ^3J = 4.8Hz), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 13.4, 27.9, 28.2, 31.9, 35.2, 35.8, 42.2, 51.9, 112.6, 115.8, 123.7, 127.8, 129.7, 133.5, 134.3, 141.1, 166.6, 191.1; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 1.99 (s, 3H), 2.07 (s, 3H), 2.18 (s, 2H), 2.62 (s, 2H), 2.84 (s, 3H), 4.21 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 4.65 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 6.78 (d, 1H, ^3J = 4.8 Hz), 7.29 (d, 1H, ^3J = 4.8 Hz), 11.37 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.1, 12.9, 27.9, 28.2, 34.6, 35.2, 35.8, 46.3, 51.9, 112.4, 115.7, 123.7, 127.6, 130.0, 133.8, 134.8, 140.9, 166.6, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{19}H_{25}N_2O_2S^+$: 345.1631, found: 345.1626.

***N*-(4-Bromobenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16f**). By method A, 3 h at 50 °C, yield = 0.12 g (79%) colorless solid, mp: 188 °C. IR: ῡ (cm^{-1}) = 3102 (w); 1654 (s); 1462 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.10 (s, 3H), 2.21 (s, 2H), 2.62 (s, 2H), 2.68 (s, 3H), 4.46 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.76 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.41 (d, 2H, ^3J = 8.4 Hz), 7.54 (d, 2H, ^3J = 8.4Hz), 11.36 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 35.2, 35.3, 35.7, 48.9 , 51.9, 112.6, 115.9, 119.9, 127.7, 129.8, 131.3, 137.4, 141.1, 167.2, 191.4; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.05 (s, 3H), 2.21 (s, 2H), 2.59 (s, 2H), 2.82 (s, 3H), 4.17 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 4.48 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 7.03 (d, 2H, ^3J = 8.4 Hz), 7.48 (d, 2H, ^3J = 8.0 Hz), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 32.2, 35.2, 35.8, 51.8, 52.8, 112.5, 115.7, 120.2, 127.7, 129.2, 131.2, 137.2, 141.1, 167.2, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{20}H_{24}N_2O_2Br^+$: 403.1016, found: 403.1012.

***N*-(3-Chlorobenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16g**). By method A, 18 h at 40 °C, yield = 0.03 g (15%) colorless, waxy solid, mp: 165–166 °C. IR: ῡ (cm^{-1}) = 3085 (w); 1658 (s); 1466 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.11 (s, 3H), 2.22 (s, 2H), 2.62 (s, 2H), 2.71 (s, 3H), 4.48 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.83 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 7.28–7.42 (m, 3H), 7.52 (s, 1H), 11.38 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 32.3, 35.3, 35.8, 49.0, 51.9, 112.5, 116.0, 126.0, 126.7, 127.1, 127.7, 130.1, 133.1, 140.5, 141.1, 167.3, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.06 (s, 3H), 2.21 (s, 2H), 2.59 (s, 2H), 2.84 (s, 3H), 4.22 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.50 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 7.05 (d, 1H, ^3J = 7.2 Hz), 7.10 (s, 1H), 7.28–7.42 (m, 2H), 11.33 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 35.2, 35.3, 35.8, 51.9, 52.8, 112.5, 115.7, 125.7, 126.8, 127.1, 127.7, 130.3, 133.2, 140.4, 141.2, 167.2, 191.4; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{20}H_{24}N_2O_2^+$: 359.1521, found: 359.1511.

***N*-(3,4-Dimethylbenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16h**). By method A, 22 h at 40 °C, yield = 0.08 g (72%) colorless, waxy solid, mp: 157–159 °C. IR: ῡ (cm^{-1}) = 3101 (w); 1652 (s); 1464 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.10 (s, 3H), 2.15 (s, 3H), 2.20 (s, 3H), 2.20 (s, 2H), 2.61 (s, 2H), 2.64 (s, 3H), 4.56 (s, 2H), 7.08–7.12 (m, 2H), 7.19 (s, 1H), 11.34 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 19.0, 19.4, 27.9, 28.2, 35.0, 35.2, 35.8, 49.0, 51.9, 112.9, 115.9, 124.9, 127.3, 128.7, 129.4, 134.5, 135.0, 136.0, 141.0, 167.1, 191.2; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.10 (s, 3H), 2.15 (s, 3H), 2.20 (s, 3H), 2.20 (s, 2H), 2.61 (s, 2H), 2.64 (s, 3H), 4.07 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.44 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 6.79 (d, 1H, ^3J = 7.6 Hz), 6.81 (s, 1H), 7.03 (d, 1H, ^3J = 7.6 Hz), 7.08–7.12 (m, 1H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 18.9, 19.3, 27.8, 28.2, 32.0, 35.2, 35.8, 52.0, 53.1, 112.8, 115.8, 124.5, 127.6, 128.2, 129.5, 134.9, 136.2, 141.0, 167.0, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{22}H_{29}N_2O_2^+$: 353.2224, found: 353.2214.

***N*,2,6,6-Tetramethyl-*N*-[(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16i**). By method A, 21 h at 40 °C, yield = 0.09 g (73%) colorless, waxy solid, mp: 250–254 °C. IR: ῡ (cm^{-1}) = 3231 (w); 1623 (s); 1061 (m). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.00 (s, 3H), 1.01 (s, 3H), 2.12 (s, 3H), 2.15 (s, 2H), 2.60 (s, 2H), 2.69 (s, 3H), 3.87 (s, 3H), 4.76 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 5.20 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 7.19 (t, 1H, ^3J = 7.6 Hz), 7.26 (t, 1H, ^3J = 7.6 Hz), 7.56 (d, 1H, ^3J = 8.0 Hz), 7.60 (d, 1H, ^3J = 8.0 Hz), 11.38 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 29.9, 34.8, 35.2, 35.7, 42.3, 51.8, 110.1, 112.2, 115.9, 118.8, 121.4, 122.1, 128.1, 136.2, 141.2, 142.0, 150.7, 166.8, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 3H), 1.05 (s, 3H), 2.01 (s, 3H), 2.23 (s, 2H), 2.60 (s, 2H), 2.93 (s, 3H), 4.48 (AB, 1H, $^2J_{AB}$ = 16.4 Hz), 4.81 (AB, 1H), 7.17–7.28 (m, 2H), 7.46 (d, 1H, ^3J = 7.6 Hz), 7.55–7.61 (m, 1H), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 29.2, 32.6, 35.2, 35.7, 46.6, 52.0, 109.9, 112.2, 115.8, 118.8, 121.4, 122.0, 128.7, 135.9, 141.2, 141.9, 150.8, 167.2, 191.4; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{22}H_{27}N_4O_2^+$: 379.2129, found: 379.2126.

***N*-[(1*H*-Indol-5-yl)methyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16j**).By method A, 6 d at 35 °C, yield = 0.09 g (76%) colorless, waxy solid, mp: 179–181 °C. IR: ῡ (cm^{-1}) = 3219 (w); 1636 (s); 1062 (m). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.08 (s, 3H), 2.21 (s, 2H), 2.61 (s, 2H), 2.65 (s, 3H), 4.52 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 5.24 (AB, 1H,

$^2J_{AB}$ = 14.8 Hz), 6.62 (s, 1H), 6.99–7.08 (m, 2H), 7.26–7.32 (m, 2H), 11.11 (s, 1H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 34.9, 35.2, 35.8, 47.6, 51.9, 99.7, 110.4, 113.1, 116.0, 117.9, 120.8, 124.8, 126.5, 128.2, 128.5, 135.8, 141.0, 166.8, 191.2; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.12 (s, 3H), 2.23 (s, 2H), 2.59 (s, 2H), 2.81 (s, 3H), 4.34 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.86 (AB,1H, $^2J_{AB}$ = 15.6 Hz), 6.22 (s, 1H), 6.72 (d, 1H, ^3J = 6.8 Hz), 6.99–7.08 (m, 1H), 7.26–7.32 (m, 2H), 11.11 (s, 1H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 32.1, 35.2, 35.8, 51.7, 52.0, 98.7, 110.5, 112.9, 115.9, 117.3, 120.8, 125.2, 126.0, 127.2, 128.5, 135.8, 140.9, 167.0, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{22}H_{26}N_3O_2^+$: 364.2020, found: 364.2006.

***N*,2,6,6-Tetramethyl-*N*-[(2-methylisoindolin-5-yl)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16k**). By method A, 16 h at 40 °C, product was additionally purified via prepHPLC (ACN/H_2O, 50:50). yield = 0.03 g (22%) colorless solid, mp: 158–159 °C. IR: ṽ (cm^{-1}) = 2952 (w); 1652 (s); 1600 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.09 (s, 3H), 2.20 (s, 2H), 2.47 (s, 3H), 2.61 (s, 2H), 2.65 (s, 3H), 3.73 (s, 2H), 3.78 (s, 2H), 4.56 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 4.65 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 7.17 (d, 1H, ^3J = 7.6 Hz), 7.22 (d, 1H, ^3J = 8.0 Hz), 7.28 (s, 1H), 11.36 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 35.0, 35.2, 35.8, 41.9, 49.3, 51.9, 60.1, 60.3, 112.8, 115.9, 121.3, 121.8, 125.9, 127.4, 136.2, 139.3, 140.9, 141.0, 167.1, 191.2; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.06 (s, 3H), 2.20 (s, 2H), 2.44 (s, 3H), 2.59 (s, 2H), 2.80 (s, 3H), 3.73 (s, 2H), 3.79 (s, 2H), 4.13 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.49 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 6.88 (d, 1H, ^3J = 7.6 Hz), 6.91 (s, 1H), 7.12 (d, 1H, ^3J = 7.6 Hz), 11.33 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 32.0, 35.2, 35.7, 41.9, 51.9, 53.3, 60.0, 60.1, 112.7, 115.8, 120.7, 122.0, 125.4, 127.6, 136.1, 139.7, 141.0, 141.1, 167.0, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{23}H_{30}N_3O_2^+$: 380.2333, found: 380.2329.

***N*-(2-Chloro-4,5-dimethoxybenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16l**). By method A, 17 h at 40 °C, yield = 0.11 g (85%) colorless, waxy solid, mp: 224 °C. IR: ṽ (cm^{-1}) = 2847 (w); 1652 (s); 1509 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.12 (s, 3H), 2.22 (s, 2H), 2.62 (s, 2H), 2.73 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 4.41 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.88 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 7.02 (s, 1H), 7.21 (s, 1H), 11.39 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.8, 28.2, 35.2, 35.5, 35.8, 47.0, 51.9, 55.9, 111.6, 112.5, 112.6, 115.9, 123.0, 126.5, 127.9, 141.2, 148.2, 148.3, 167.3, 191.4; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.07 (s, 3H), 2.22 (s, 2H), 2.60 (s, 2H), 2.82 (s, 3H), 3.74 (s, 6H), 4.22 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.54 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 6.70 (s, 1H), 6.95 (s, 1H), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.6, 28.3, 32.0, 35.2, 35.8, 50.6, 51.9, 55.7, 55.9, 111.9, 112.5, 112.7, 116.0, 122.8, 126.2, 127.8, 141.2, 147.9, 148.6, 167.2, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{22}H_{28}N_2O_4Cl^+$: 419.1732, found: 419.1722.

***N*,2,6,6-Tetramethyl-*N*-[(6-methylimidazo[2,1-*b*]thiazol-5-yl)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16m**). By method A, 16 h at 40 °C, yield = 0.09 g (77%) pale orange, waxy solid, mp: 229–230 °C. IR: ṽ (cm^{-1}) = 2957 (w); 1659 (s); 1600 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.00 (s, 3H), 1.02 (s, 3H), 2.04 (s, 3H), 2.15 (s, 2H), 2.28 (s, 3H), 2.59 (s, 2H), 2.61 (s, 3H), 4.76 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.88 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.18 (d, 1H, ^3J = 4.4 Hz), 7.86 (d, 1H, ^3J = 4.4 Hz), 11.34 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 13.1, 27.8, 28.2, 34.1, 35.2, 35.7, 38.3, 51.8, 111.5, 112.3, 115.9, 118.0, 119.6, 127.6, 141.0, 142.2, 147.3, 167.2, 191.1; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.00 (s, 3H), 1.02 (s, 3H), 2.11 (s, 3H), 2.15 (s, 2H), 2.28 (s, 3H), 2.64 (s, 2H), 2.75 (s, 3H), 4.45 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.71 (AB, 1H), 7.20 (d, 1H, ^3J = 4.4 Hz), 7.37 (d, 1H, ^3J = 4.4 Hz), 11.46 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = interpretation wasn't feasible due to low signal intensity; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{20}H_{25}N_4O_2S^+$: 385.1693, found: 385.1683.

***N*,2,6,6-Tetramethyl-4-oxo-*N*-(quinolin-3-ylmethyl)-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16n**). By method A, 21 h at 40 °C, product was additionally purified via prepHPLC 1. (ACN/H_2O, 75:25) and 2. (ACN/H_2O, 50:50), yield = 0.03 g (15%) colorless solid, mp: 119–121 °C. IR: ṽ (cm^{-1}) = 2956 (w); 1651 (s); 1602 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.13 (s, 3H), 2.24 (s, 2H), 2.63 (s, 2H), 2.78 (s, 3H), 4.61 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 5.12 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.60–7.64 (m, 1H), 7.72–7.76 (m, 1H), 7.90–8.05 (m, 2H), 8.48 (s, 1H), 8.95 (s, 1H), 11.39 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 35.2, 35.4, 35.8, 47.5, 51.9, 112.5, 116.0, 126.7, 127.6, 127.8, 128.6, 128.7, 129.0, 130.8, 133.8, 141.2, 146.8, 150.9, 167.4, 191.5; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.21 (s, 6H), 2.03 (s, 3H), 2.24 (s, 2H), 2.60 (s, 2H), 2.93 (s, 3H), 4.47 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 4.69 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 7.60–7.64 (m, 1H), 7.72–7.76 (m, 1H), 7.90–8.05 (m, 2H), 8.44 (s, 1H), 8.56 (s, 1H), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.2, 27.9, 28.2, 32.5, 35.3, 35.8, 51.3, 51.9, 112.5, 116.0, 126.8, 127.7, 127.8, 128.6, 128.7, 129.0, 130.9, 133.6, 141.2, 146.9, 150.9, 167.4, 191.5; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{23}H_{26}N_3O_2^+$: 376.2020, found: 376.2023.

***N*-[(2,5-Dimethylthiophen-3-yl)methyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16o**). By method A, 3 d at 20 °C, product was additionally purified via prepHPLC (ACN/H_2O, 60:40), yield = 0.10 g (62%) colorless solid, mp: 91–93 °C. IR: ṽ (cm^{-1}) = 2957 (w); 1659 (s); 1600 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.07 (s, 3H), 2.19 (s, 2H), 2.33 (s, 3H), 2.34 (s, 3H), 2.60 (s, 2H), 2.61 (s, 3H), 4.37 (AB, 1H, $^2J_{AB}$ = 14.4 Hz), 4.51 (AB, 1H, $^2J_{AB}$ = 14.4 Hz), 6.74 (s, 1H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9,12.0, 14.9, 27.9, 28.2, 34.6, 35.2, 35.8, 42.6, 51.9, 112.9, 115.9, 126.1, 127.3, 132.3, 133.5, 134.4, 140.9, 166.6, 191.1; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 2.05 (s, 3H), 2.10 (s, 3H), 2.21 (s, 2H), 2.29 (s, 3H), 2.60 (s, 2H), 2.78 (s, 3H), 3.97 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.31 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 6.35 (s, 1H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9,12.5, 14.7, 27.8, 28.2, 31.8, 35.2, 35.8, 46.6, 52.0, 112.8, 115.9, 127.2, 127.9, 132.1, 133.2, 135.0, 141.0, 166.6, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{20}H_{27}N_2O_2S^+$: 359.1788, found: 359.1785.

***N*-[(1,1′-Biphenyl)-4-ylmethyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16p**). By method A, 3 d at 20 °C, product was additionally purified via prepHPLC (ACN/H_2O, 75:25), yield = 0.16 g (65%) colorless solid, mp: 133–135 °C. IR: ṽ (cm^{-1}) = 3026 (w); 1652 (s); 1593 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.13 (s, 3H), 2.22 (s, 2H), 2.63 (s, 2H), 2.72 (s, 3H), 4.61 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 4.77 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.33–7.38 (m, 1H), 7.43–7.53 (m, 2H), 7.59 (d, 2H, ^3J = 8.0 Hz), 7.62–7.69 (m, 4H), 11.35 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.8, 28.2, 35.2, 35.2, 35.8, 49.1, 51.9, 112.8, 115.9, 126.6, 127.3, 127.8, 128.0, 128.9, 137.1, 138.7, 140.0, 141.0, 167.2, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.10 (s, 3H), 2.22 (s, 2H), 2.60 (s, 2H), 2.85 (s, 3H),).4.21 (AB, 1H, $^2J_{AB}$ = 16.0 Hz), 4.54 (AB, 1H), 7.17 (d, 2H, ^3J = 8.0 Hz), 7.33–7.38 (m, 1H), 7.43–7.53 (m, 2H), 7.62–7.69 (m, 4H), 11.35 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.9, 28.2, 32.2, 35.2, 35.8, 51.9, 53.1. 112.7, 115.8, 126.6, 126.8, 127.4, 127.6,

127.8, 128.9, 136.9, 139.0, 139.7, 141.1, 167.2, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{26}H_{29}N_2O_2^+$: 401.2224, found: 401.2208.

***N*-[(1,1′-Biphenyl)-3-ylmethyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16q**). By method A, 3 d at 20 °C, product was additionally purified via prepHPLC (ACN/H_2O, 75:25), yield = 0.14 g (55%) colorless solid, mp: 120–121 °C. IR: ṽ (cm^{-1}) = 3035 (w); 1653 (s); 1595 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.12 (s, 3H), 2.22 (s, 2H, C(4)H2), 2.63 (s, 2H), 2.73 (s, 3H), 4.64 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.81 (AB,1H, $^2J_{AB}$ = 15.2 Hz), 7.33–7.39 (m, 1H), 7.44–7.48 (m, 4H), 7.61–7.62 (m, 1H), 7.69–7.73 (m, 3H), 11.37 (s,1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.9, 28.2, 35.2, 35.2, 35.8, 49.5, 51.9, 112.8, 115.9, 125.2, 125.7, 126.5, 126.8, 127.4, 127.6, 128.8, 129.0, 138.5, 140.1, 140.3, 141.0, 167.2, 191.3; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.04 (s, 6H), 2.06 (s, 3H), 2.22 (s, 2H), 2.60 (s, 2H), 2.87 (s, 3H), 4.28 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.57 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 7.09 (d, 1H, ^{3}J = 7.6 Hz), 7.33–7.39 (m, 3H), 7.44–7.48 (m, 3H), 7.51–7.62 (m, 2H), 11.33 (s,1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 32.2, 35.2, 35.8, 51.9, 53.4, 112.7, 115.8, 125.4, 125.5, 126.2, 126.7, 127.5, 127.6, 128.9, 129.1, 138.4, 139.9,
140.4, 141.1, 167.2, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{26}H_{29}N_2O_2^+$: 401.2224, found: 401.2213.

***N*-[3-(*tert*-Butyl)benzyl]-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16r**). A mixture of 0.16 g (0.7 mmol, 1.0 equiv.) compound **10**, 0.53 g (1.4 mmol, 2.0 equiv.) HATU and 0.15 g (0.7 mmol, 1.0 equiv.) **17r** were weighted in a dried G10 vial and dissolved in 6 mL dry DMF. To the stirred solution 590 µL (0.45 g, 3.5 mmol, 5.0 equiv.) DIPEA were added. The reaction mixture was covered with inert nitrogen gas, sealed and placed in a microwave field (140 °C, with counter cooling) for 5 min. Afterwards solvent was evaporated (under reduced pressure) and residue was purified by column chromatography. Product was additionally purified via prepHPLC 1. (MeOH/H_2O, 80:20) and 2. (ACN/H_2O, 90:10). Yield = 0.08 g (27%) colorless solid, mp: 79 °C. IR: ṽ (cm^{-1}) = 2955 (m); 1654 (s); 1463 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 1.29 (s, 9H), 2.11 (s, 3H), 2.21 (s, 2H), 2.62 (s, 2H), 2.67 (s, 3H), 4.54 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.71 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 7.19–7.28 (m, 3H), 7.39 (s, 1H), 11.35 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.9, 28.2, 31.1, 34.3, 35.1, 35.2, 35.8, 49.6, 51.9, 112.8, 115.9,123.7, 124.1, 124.6, 127.5, 128.0, 137.4, 141.0, 150.7, 167.1, 191.2; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.03 (s, 6H), 1.23 (s, 9H), 2.04 (s, 3H), 2.21 (s, 2H), 2.60 (s, 2H), 2.82 (s, 3H), 4.15 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.50 (AB, 1H, $^2J_{AB}$ = 16.4 Hz), 6.90 (d. 1H, ^3J = 7.2 Hz), 7.03 (s, 1H), 7.19–7.28 (m, 2H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 11.0, 27.9, 28.2, 31.1, 32.2, 34.3, 35.2, 35.8, 51.9, 53.7, 112.8, 115.8,123.6, 123.9, 124.2, 127.6, 128.1, 137.3, 141.0, 150.9, 167.1, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{24}H_{33}N_2O_2^+$: 381.2537, found: 381.2553.

***N*-(3-Cyclopropylbenzyl)-*N*,2,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16s**). By method A, 20 h at 60 °C, product was additionally purified via prepHPLC (ACN/H_2O, 75:25), yield = 0.13 g (49%) colorless solid, mp: 74 °C. IR: ṽ (cm^{-1}) = 3008 (w); 1652 (s); 1461 (s). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 0.59–1.00 (m, 4H), 1.04 (s, 6H), 1.81–1.95 (m, 1H), 2.11 (s, 3H), 2.21 (s, 2H), 2.62 (s, 2H), 2.66 (s, 3H), 4.55 (AB, 1H, $^2J_{AB}$ = 14.8 Hz), 4.64 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 6.91–7.23 (m, 4H), 11.35 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 9.4, 10.9, 15.0, 27.9, 28.2, 35.1, 35.2, 35.8, 49.3, 51.9, 112.8, 115.9, 123.8, 124.2, 124.4, 127.4, 128.2, 137.7, 141.0, 143.8, 167.1, 191.2; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 0.59–1.00 (m, 4H), 1.04 (s, 6H), 1.81–1.95 (m, 1H), 2.07 (s, 3H), 2.21 (s, 2H), 2.60 (s, 2H), 2.80(s, 3H), 4.12 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.60 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 6.74 (s, 1H), 6.84 (d, 1H, ^3J = 7.6 Hz), 6.91–7.23 (m, 2H), 11.31 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 9.3, 10.9, 14.9, 27.9, 28.2, 32.1, 35.2, 35.8, 51.9, 53.4, 112.7, 115.8, 123.9, 124.0, 124.2, 127.5, 128.3, 137.6, 141.0, 143.9, 167.0, 191.2; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{23}H_{29}N_2O_2^+$: 365.2224, found: 365.2235.

***N*,2,6,6-Tetramethyl-4-oxo-*N*-{[4'-(trifluoromethyl)-(1,1'-biphenyl)-3-yl]methyl}-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide** (**16t**). By method A, 20 h at 60 °C, product was additionally purified via prepHPLC (MeOH/H_2O, 90:10), yield = 0.08 g (26%) colorless solid, mp: 121–122 °C. IR: ṽ (cm^{-1}) = 3048 (w); 1652 (s); 1463 (m). isomer 1: ^{1}H-NMR (DMSO-d_6): δ = 1.05 (s, 6H), 2.12 (s, 3H), 2.24 (s, 2H), 2.63 (s, 2H), 2.74(s, 3H), 4.56 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 4.92 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.41–7.85(m, 8H), 11.38 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.8, 28.2, 35.2, 35.3, 35.8, 49.4, 51.9, 112.7, 116.0,124.4 (q, $^1J_{C,F}$ = 271 Hz), 125.5, 125.7 (q, $^3J_{C,F}$ = 4 Hz), 126.0, 127.5, 127.6, 129.9 (q, $^2J_{C,F}$ = 28 Hz), 129.9, 129.2, 138.7, 138.8, 141.1, 144.2, 167.2, 191.4; isomer 2: ^{1}H-NMR (DMSO-d_6): δ = 1.05 (s, 6H), 2.05 (s, 3H), 2.22 (s, 2H), 2.60 (s, 2H), 2.88(s, 3H), 4.32 (AB, 1H, $^2J_{AB}$ = 15.6 Hz), 4.56 (AB, 1H, $^2J_{AB}$ = 15.2 Hz), 7.17 (d, 1H, ^3J = 7.6 Hz), 7.41–7.85(m, 5H), 7.98 (d, 2H, ^3J = 8.0 Hz), 11.32 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ = 10.9, 27.8, 28.2, 32.3, 35.2, 35.8, 51.9, 53.4, 112.7, 115.9,124.4 (q, $^1J_{C,F}$ = 271 Hz), 125.5, 125.7 (q, $^3J_{C,F}$ = 4 Hz), 125.9, 127.1, 127.6, 129.9 (q, $^2J_{C,F}$ = 28 Hz), 129.9, 129.3, 138.7, 138.8, 141.1, 143.9, 167.2, 191.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{27}H_{28}N_2O_2F_3^+$: 469.2097, found: 469.2093.

1-[3-(*tert*-Butyl)phenyl]-*N*-methylmethanaminium chloride (**17r**). By method B, yield = 0.99 g (84%) colorless crystals, mp: 133–136 °C. IR: ṽ (cm^{-1}) = 2952 (m); 2759 (s); 1440 (m). ^{1}H-NMR (DMSO-d_6): δ = 1.29 (s, 9H), 2.50 (s, 3H), 4.07 (s, 2H), 7.31–7.36 (m, 2H), 7.42 (t, 1H, ^3J = 8.4 Hz), 7.66 (s, 1H), 9.51 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ = 31.1, 31.9, 34.5, 54.4, 125.5, 127.0, 128.2, 131.8, 151.1; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{12}H_{20}N^+$: 178.1590, found: 178.1594.

1-(3-Cyclopropylphenyl)-*N*-methylmethanaminium chloride (**17s**). By method B, yield = 1.05 g (82%) colorless crystals, mp: 118–122 °C. IR: ṽ (cm^{-1}) = 2922 (m); 2754 (s); 1473 (m). ^{1}H-NMR (DMSO-d_6): δ = 0.95–0.98 (m, 2H), 1.19 (t, 2H, ^3J = 7.6 Hz), 1.87–1.94 (m, 1H), 2.47 (s, 3H), 4.02 (s, 2H), 7.12–7.14 (m, 1H), 7.25–7.31 (m, 3H), 9.53 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ = 9.5, 15.0, 31.8, 51.1, 126.1, 126.5, 126.7, 128.4, 132.0, 144.3; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{11}H_{16}N^+$: 162.1277, found: 162.1284.

***N*-Methyl-1-[4′-(trifluoromethyl)-(1,1′-biphenyl)-3-yl]methanaminium chloride** (**17t**). By method B, yield = 1.37 g (54%) colorless crystals, mp: 208–209 °C. IR: ṽ (cm^{-1}) = 3009 (w); 2762 (s); 1322 (m). ^{1}H-NMR (DMSO-d_6): δ = 2,55 (s, 2H), 4,19 (s, 2H), 7,57 (t, 1H, ^3J = 7.6 Hz), 7.60 (d, 1H, ^3J = 7.6 Hz), 7.79 (d, 1H, ^3J = 7.2 Hz), 7.85 (d, 2H, ^3J = 8.4 Hz), 7.96 (d, 2H, ^3J = 8.4 Hz), 8.04 (s, 1H), 9.55 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ = 31.9, 51.0, 124.3 (q, $^1J_{C,F}$ = 270 Hz), 125.8 (q, $^3J_{C,F}$ = 4 Hz), 127.4, 127.5, 128.1 (q, $^2J_{C,F}$ = 32 Hz), 128.9, 129.4, 130.0, 133.0, 138.8, 143.6; HRMS (ESI, *m*/*z*) [*M*+H]$^+$: calcd for $C_{15}H_{15}NF_3^+$: 266.1151, found: 266.1145.

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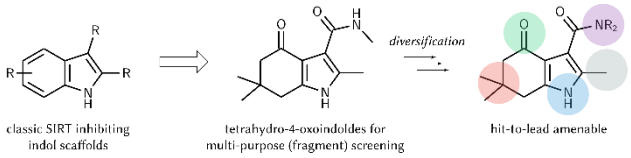

Non-flat platform for diversity: The indole scaffold can be attributed as very important structural subunit in medicinal chemistry. Starting from this privileged structure we synthesized a fragment-like, shapely tetrahydroindole carboxylic acid amide that was designed to serve as multipurpose fragment screening compound. By decoration with various aromatic side-chains a promising screening hit for SIRT2 inhibition could be obtained.