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Polymer-Supported Stereoselective Synthesis of Benzimidazolinopiperazinones

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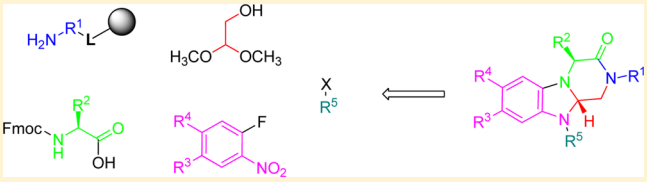
Supporting Information

ABSTRACT: We describe the efficient synthesis of 4,7,8,10-tetrasubstituted-(((4*S*,10a*S*)-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-2(1*H*)-yl)alkyl)amides on solid phase via tandem *N*-acyliminium ion cyclization–nucleophilic addition reactions. The synthesis proceeded with complete stereocontrol of a newly formed stereogenic center, provided crude material of high purity, and used commercially available building blocks under mild reaction conditions.



INTRODUCTION

Roughley,[1] Walters,[2] and co-workers reported intriguing papers devoted to the impact of hybridization of carbon atoms on the biological and physicochemical properties of compounds. They emphasized that the incorporation of a greater proportion of chiral compounds with higher degrees of unsaturation could improve clinical outcomes, a conclusion that was drawn from Lovering's study.[3] Lovering introduced a fractional sp^3-character (Fsp3) as a ratio of the number of sp^3-hybridized carbon atoms and total carbon count. It is reported that marketed drugs tend to have a higher Fsp3 than discovery compounds do.[1,2] On the other hand, Roughley,[1] and co-workers documented that between one-quarter and one-half of carbon atoms are sp^3-hybridized, although it seems that most of the recently prepared compounds by medicinal chemists are "flat". To contribute to syntheses of chiral compounds with higher degrees of unsaturation, we developed efficient synthesis of 4,7,8,10-tetrasubstituted-(((4*S*,10a*S*)-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-2(1*H*)-yl)alkyl)-amides.

The synthesis of 1,2,10,10a-tetrahydrobenzo[4,5]imidazo-[1,2-*a*]pyrazin-3(4*H*)-ones **I** (termed "benzimidazolinopiperazinones" hereafter, Figure 1) has not been described, although the preparation of 1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrazin-3(4*H*)-ones **II** (Figure 1) has already been reported. Two main routes lead to those compounds; the first starts from benzimidazole scaffold,[4−9] whereas the second utilizes piperazin-2-one as the starting material.[10] The latter synthetic approach involved a four-component Ugi–Smiles reaction, which was followed by an acid-catalyzed cyclization, an intramolecular reductive cyclization, and an oxidation.[10]

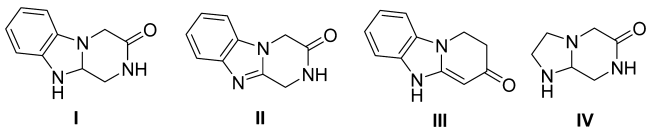


Figure 1. Heterocyclic cores.

Other related derivatives, such as deazaanalogues of compound **II**, 1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-3(5*H*)-ones **III** (Figure 1), are reportedly anxiolytic,[11−13] antiviral,[14] and antimicrobial[15] agents. 3,4,4a,5-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridin-1(2*H*)-ones linked by benzimidazoles have also been documented.[16] The aromatic part of 1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-3(4*H*)-ones **II**, benzimidazoles, were synthesized several times, in solution[17−21] and on solid phase.[22−25] Benzimidazole derivatives can serve as angiotensin II receptor antagonists,[26] as inhibitors of trypsin-like serine protease (factor Xa),[27] and as antibacterial agents.[28] The synthesis of benzimidazolines and their closely related compounds, 2-oxo/thioderivatives and spiro-benzimidazolines, has also been described.[16,29−34]

On the other hand, 1,2,10,10a-tetrahydrobenzo[4,5]imidazo-[1,2-*a*]pyrazin-3(4*H*)-ones **I** can be considered not only as benzimidazolines fused with piperazin-2-one cycle but also as hexahydroimidazo[1,2-*a*]pyrazin-6(5*H*)-ones **IV** (Figure 1) fused with benzene ring. The synthesis of hexahydroimidazo-[1,2-*a*]pyrazin-6(5*H*)-ones **IV** and their closely related compounds has been reported many times, in solution[35−38] and on solid phase.[39] Analogous compounds have also been used for the preparation of aza-ligands[40] or azacyclododecane derivatives.[41] Derivatives of imidazolopyrazine **IV** have intriguing biological properties; they can be used for the

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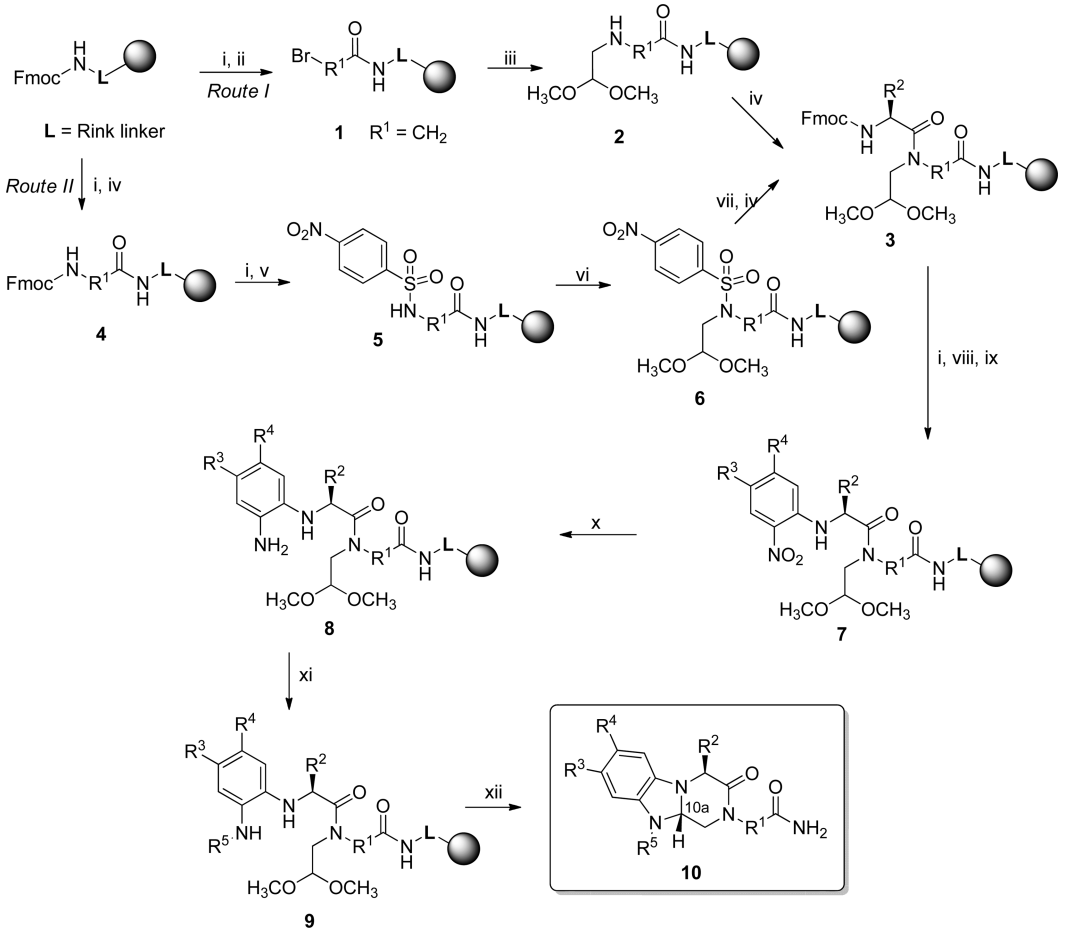
Scheme 1. Stereoselective Synthesis of Benzimidazolinopiperazinones 10 on Solid Phase[a]



[a]Reagents and conditions: (i) 50% piperidine in DMF, rt, 15 min; (ii) bromoacetic acid (2 equiv), DIC (1 equiv), DCM, 5 min, then DIEA (1 equiv), rt, 16 h; (iii) aminoacetaldehyde dimethyl acetal, DIEA, DMF, rt, 2 h; (iv) Fmoc-amino acid (1 equiv), HOBt (1 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16 h; (v) 4-nitrobenzenesulfonyl chloride, lutidine, DCM, rt, 4 h; (vi) glycolaldehyde dimethyl acetal, PPh_3, DIAD, anhydrous THF, 0−50 °C, 16 h, repetition; (vii) 2-mercaptoethanol, DBU, DMF, rt, 5 min; (viii) *o*-fluoronitrobenzene, DIEA, DMSO, 50 °C, 16 h or 4,5-disubstituted *o*-fluoronitrobenzenes, DIEA, DMSO, rt, 16 h; (ix) for R^4 = piperidin-1-yl: piperidine, DMSO, 50 °C, 16 h; (x) $SnCl_2 \cdot 2H_2O$, DIEA, DMF, rt, 16 h; (xi) Ac_2O, rt, 16 h or carboxylic acid (2 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16 h or 4-nitrobenzenesulfonyl chloride, lutidine, DCM, rt, 16 h; (xii) 50% TFA in DCM, rt, 90 min.

treatment of anorexia,[38] cancer,[39] and fibrotic disorders,[42] and can also serve as integrin-mediated cell adhesion inhibitors.[36]

The stereoselective synthesis of different bicyclic nitrogenous heterocycles utilizing iminium salts has been described several times. Iminium salts have been used, for example, for the preparation of quinolizidines,[43] pyrrolo[2,1-*a*]isoquinolines,[44] octahydropyrazino[1,2-*a*]pyrimidin-6-ones,[45] bicyclic derivatives containing lactone,[46] and 6,6-fused bicyclic scaffold-containing compounds derived from tripeptides,[47] among others. The chemistry of iminium ions and its application to the synthesis of diverse heterocycles has been published in excellent reviews.[48−51]

Although benzimidazolines fused with other heterocycles have been subject of synthesis research, no attention has been paid to benzimidazolines fused with piperazin-2-one. Herein we report their solid-phase synthesis from acyclic intermediates via *N*-acyliminium ion cyclization−nucleophilic addition. The acid-mediated unmasking of the aldehyde was followed by spontaneous formation of the cyclic *N*-acyliminiums. The mechanism of the acid hydrolysis of acetals in anhydrous conditions has been reported.[52] The nitrogen derived from the amino acid was substituted with *o*-fluoronitrobenzenes, and the nitro group was subsequently reduced to the amino group to serve as an internal nucleophile for the creation of the fused ring upon acid-mediated cleavage from solid support.

Herein reported compounds do not suffer from the above-mentioned shortcomings, such as "flatness" etc. We developed the synthesis of benzimidazolinopiperazinones characterized by the presence of two chiral carbons and three sp^3-hybridized carbon atoms on the skeleton, compounds that have potential biological and therapeutic value. The biological activities will be reported in due time.

RESULTS AND DISCUSSION

Our research aimed to design a general route to benzimidazolinopiperazinones with the following criteria in mind: (i) nonplanar scaffold (sp^3 hybridization), (ii) stereoselectivity, (iii) transformations providing high purity of crude target compounds, (iv) diverse scaffolds, and (v) commercially available building blocks.

The synthesis was carried out on Rink amide resin using four different starting carboxylic acids: bromoacetic acid, Fmoc-*β*-Ala-OH, Fmoc-*γ*-Abu-OH, and Fmoc-4-aminomethylbenzoic

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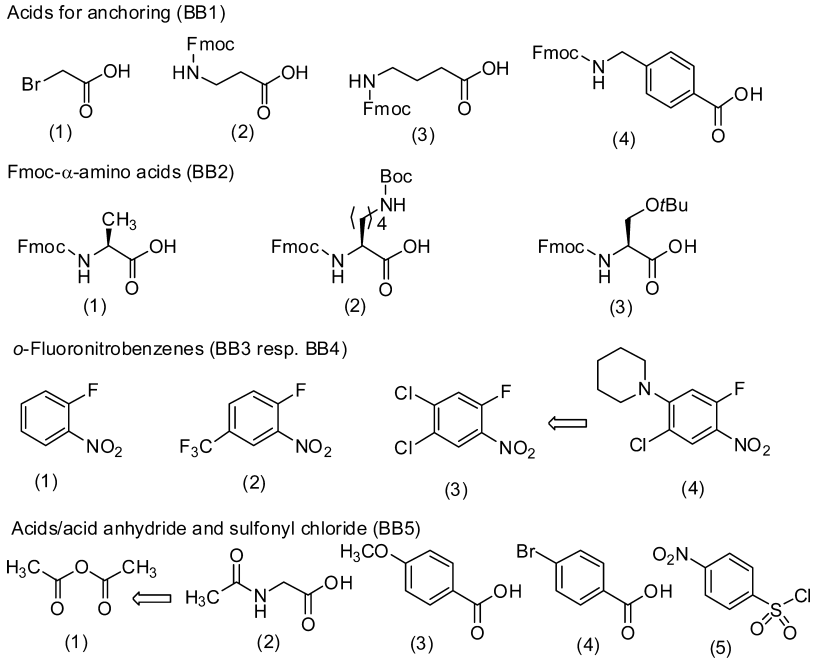

Figure 2. Building blocks used for the synthesis of benzimidazolinopiperazinones **10**.

acid. Bromoacetic acid was immobilized via symmetric anhydride in the presence of an *N*,*N*′-disopropylethylamine (DIEA) (Scheme 1, *Route I*). The bromine was subsequently substituted with aminoacetaldehyde dimethyl acetal to afford polymer-supported 2-((2,2-dimethoxyethyl)amino)acetyl bromide **2**. The secondary amines were further acylated with different Fmoc-amino acids to yield polymer-supported amides **3**.

Alternatively, these intermediates can also be obtained using *Route II*. The advantage of the *Route II* over *Route I* is the possibility of extending the scope of the target compounds to a more diverse scaffold. The acylation of Rink resin with various Fmoc-amino acids was carried out via activation with diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) to afford intermediates **4** (Scheme 1, *Route II*). After removal of the Fmoc-protecting group in 50% piperidine in dimethylformamide (DMF) for 15 min, the resin-bound primary amines were activated with 4-nitrobenzenesulfonyl chloride (4-Nos-Cl) in dichloromethane (DCM) in the presence of lutidine to yield appropriate sulfonamides **5**. The subsequent Mitsunobu alkylation with glycolaldehyde dimethyl acetal afforded *N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamides **6**. The Mitsunobu alkylation proceeded without any impurities, but the conversion did not exceed 90%. As a result we examined different solvents, namely, anhydrous tetrahydrofuran (THF), anhydrous DMF, and anhydrous DCM, as well as different phosphines (triphenylphosphine or tributylphosphine), and repeated the reaction two times (3 × 16 h). However, none of these reaction conditions afforded complete conversion. Finally, 0.1 M solution of the alcohol, 0.1 M PPh_3, and 0.1 M diisopropyl azodicarboxylate (DIAD) in double volume of anhydrous THF (e.g., we used 20 mL of solution for 1 g of resin) at 50 °C for 16 h and repetition of the Mitsunobu reaction one time provided satisfactory *N*-alkylation. Interestingly, the Mitsunobu reaction with glycolaldehyde diethyl acetal failed to yield *N*-alkylated product.

The resin-bound sulfonamides **6** were treated with 2-mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF for 5 min to remove the 4-Nos-protecting group. Acylation with different Fmoc-amino acids afforded *N*-acylated intermediates **3** (Scheme 1). Three different Fmoc-amino acids, namely, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, and Fmoc-Ser(*t*Bu)-OH, were used for acylation, and all of them afforded expected products. The Fmoc-protecting group was then cleaved, and the resin-bound primary amines were treated with three different unsubstituted/4,5-disubstituted *o*-fluoronitrobenzenes to yield intermediates **7**. While the substitution of an amino group with activated *o*-fluoronitrobenzenes, such as 1-fluoro-2-nitro-4-(trifluoromethyl)benzene and 1,2-dichloro-4-fluoro-5-nitrobenzene, proceeded at room temperature, the reaction with unsubstituted *o*-fluoronitrobenzene required elevated temperature (∼50 °C). To further increase the diversity of the final benzimidazolinopiperazinones, the chlorine in *para* position with regard to the nitro group was substituted with piperidine. All building blocks used in this synthesis are shown in Figure 2.

Subsequent reduction of the nitro group was carried out with tin(II) chloride dihydrate in the presence of a base (DIEA) to afford intermediates **8**. Acylation with either Ac_2O or carboxylic acid activated via symmetric anhydride (Fmoc-Gly-OH, 4-methoxybenzoic acid, 4-bromobenzoic acid) was used for the final derivatization of the amino group. Reaction with 4-Nos-Cl afforded appropriate sulfonamides. It was critical for the aniline nitrogen to be functionalized; otherwise 3,4-dihydro-1*H*-quinoxalin-2-one **11** (Scheme 2) was formed as a result of cyclative cleavage.[53] We detected 3,4-dihydro-1*H*-quinoxalin-2-ones **11** by LC−MS during routine analysis of intermediates **8**.

The target benzimidazolinopiperazinones **10** were obtained by cleavage of resin-bound intermediates **9** from the resin in 50% trifluoroacetic acid (TFA) in DCM for 90 min. The substitution patterns of prepared benzimidazolinopiperazinones **10** are described in Table 1. The purity of final crude compounds was exceptionally high, in the range of 71−99%, and the total yields were respectable considering a 9- to 13-step synthesis.

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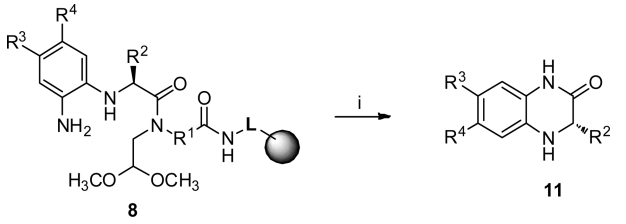
Scheme 2. Formation of 3,4-Dihydro-1*H*-quinoxalin-2-ones 11[a]



[a]Reagents and conditions: (i) 50% TFA in DCM, rt, 30 min.

Importantly, the benzimidazolinopiperazinones **10** are stable and are not air-oxidized in comparison with the *N*(10)-unsubstituted derivatives, benzimidazolinopiperazinones **14** (Scheme 3). To intentionally prepare benzimidazolopiperazinones **15**, intermediates **8** were treated with Fmoc-Cl in the presence of DIEA in DCM for 30 min and yielded intermediate **12**. The Fmoc-group served as temporary derivatization of the primary aniline nitrogen to prevent formation of 3,4-dihydro-1*H*-quinoxalin-2-ones **11**. Following unmasking of the aldehyde by 2% TFA in DCM for 16 h, cleavage of the Fmoc-group with 50% piperidine in DMF afforded polymer-supported benzimidazolinopiperazinones **14**. Finally, the target benzimidazolopiperazinone **15** was obtained after cleavage of the intermediate **14** from the resin with 50% TFA in DCM for 30 min followed by air oxidation.

The synthesis of benzimidazolinopiperazinones **10** proceeded with full stereocontrol; the formation of one diastereoisomer was confirmed by ^{1}H and ^{13}C NMR analyses. The presence of a proton attached to the carbon 10a indicated the formation of a fused ring system. The crucial proton resonated as doublet of doublets at a chemical shift in the range of 5.6−6.3 ppm (depending on the distribution of electrons). The *J* constants were 7−9 Hz and 3−4 Hz, which unequivocally indicated the configuration of a newly formed stereogenic center. Our results are in concord with stereoselective synthesis of related bicyclic derivatives tetrahydro-1*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*,8*H*)-diones; the absolute configuration was confirmed by X-ray crystallography.[54] In conlusion, we have confirmed that (*S*)-configuration on an amino acid of the acyclic precursor induced the (*S*)-configuration on a newly formed stereogenic center (carbon 10a).

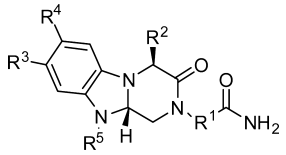
It is worth noting that the occurrence of two rotamers depending on the substitution patterns (bulkiness as well as electronic properties) was observed in NMR spectra. In general, a bulky R^1 substituent increased the amount of the second rotamer. A similar effect was caused by the electronic properties of an R^4 substituent when the chlorine was replaced by piperidine. The presence of two rotamers was apparent mainly at singlet corresponding to the methyl derived from the acetyl (see the Experimental Section). Herein we reported the NMR spectra of the major rotamers. ^{1}H NMR spectra of target compounds acylated with 4-substituted benzoic acids showed very broad unresolved peaks for both methylene protons at ambient temperature; therefore, the spectra of derivative **10(1,1,2,4)** was measured at elevated temperature (50 °C).

To conclude, we described an efficient solid-phase synthesis of benzimidazolinopiperazinones via *N*-acyliminium ion cyclization−nucleophilic addition under mild reaction conditions using commercially available building blocks. Target compounds with four diversity positions were prepared with full stereocontrol of the newly formed stereogenic center.

EXPERIMENTAL SECTION

Cleavage of Fmoc-Protecting Group and Acylation with Bromoacetic Acid (Resin 1). Rink resin (100−200 mesh, 0.68 mmol/g, 1 g) was swollen in DCM, washed 3× with DMF, and treated with 50% piperidine in DMF for 15 min. After washing 3× with DMF and 3× with DCM, a solution of bromoacetic acid (5 mmol, 700 mg) in 10 mL of DCM was made in a syringe, and DIC (2.5 mmol, 386 μL) was added. After 5 min, DIU was filtered and DIEA (2.5 mmol, 436 μL) was added to the solution. That solution was added to the

Table 1. Synthesized Derivatives of Benzimidazolinopiperazinones 10



10

cmpd	R^1	R^2	R^3	R^4	R^5	purity[a] [%]	MS [M + H]$^+$	yield[b] [%]
10(1,1,1,1)	$-CH_2-$	$-CH_3$	−H	−H	CH_3-CO−	89	303	39
10(1,1,2,1)	$-CH_2-$	$-CH_3$	$-CF_3$	−H	CH_3-CO−	87	371	36
10(1,1,2,2)	$-CH_2-$	$-CH_3$	$-CF_3$	−H	CH_3-CONH-CH_2-CO−	95	428	66
10(1,1,2,3)	$-CH_2-$	$-CH_3$	$-CF_3$	−H	−*p*-CH_3OPh-CO−	76	463	57
10(1,1,2,4)	$-CH_2-$	$-CH_3$	$-CF_3$	−H	−*p*-BrPh-CO−	85	511	63
10(1,1,2,5)	$-CH_2-$	$-CH_3$	$-CF_3$	−H	−*p*-NO_2Ph-SO_2−	71	514	63
10(1,1,4,1)	$-CH_2-$	$-CH_3$	−Cl	piperidin-1-yl	CH_3-CO−	74	420	34
10(1,2,3,1)	$-CH_2-$	$-(CH_2)_4NH_2$	−Cl	−Cl	CH_3-CO−	99	428	19
10(2,2,1,1)	$-(CH_2)_2-$	$-(CH_2)_4NH_2$	−H	−H	CH_3-CO−	94	374	13
10(3,1,3,1)	$-(CH_2)_3-$	$-CH_3$	−Cl	−Cl	CH_3-CO−	90	399	23
10(3,3,3,1)	$-(CH_2)_3-$	$-CH_2OH$	−Cl	−Cl	CH_3-CO−	92	415	36
10(4,1,3,1)	−*p*-CH_2Ph−	$-CH_3$	−Cl	−Cl	CH_3-CO−	82	447	13
10(4,3,3,1)	−*p*-CH_2Ph−	$-CH_2OH$	−Cl	−Cl	CH_3-CO−	94	463	21
10(4,3,4,1)	−*p*-CH_2Ph−	$-CH_2OH$	−Cl	piperidin-1-yl	CH_3-CO−	93	512	30

[a]Purity of the crude product before purification. [b]Total yield after purification of target compounds prepared in a 9- to 13-step synthesis.

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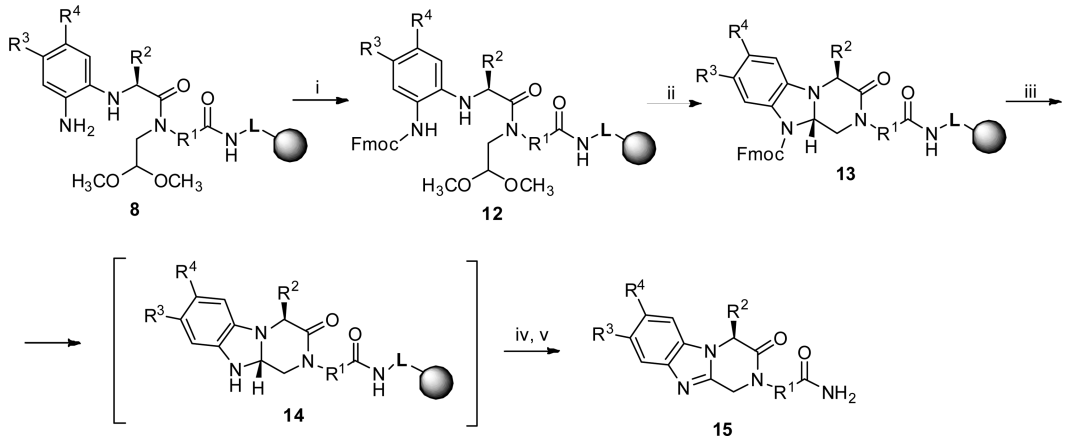
Scheme 3. Preparation of Benzimidazolopiperazinones 15[a]



[a]Reagents and conditions: (i) FmocCl, DIEA, DCM, rt, 30 min; (ii) 2% TFA in DCM, rt, 16 h; (iii) 50% piperidine in DMF, rt, 15 min; (iv) 50% TFA in DCM, rt, 30 min; (v) 50% TFA in DCM, rt, 16 h.

syringe with the Rink resin and shaken at rt for 16 h and then washed 5× with DCM.

Reaction with Aminoacetaldehyde Dimethyl Acetal (Resin 2). Resin **1** (1 g) was swollen in DCM and washed 3× with DMF. A solution of aminoacetaldehyde dimethyl acetal (10 mmol, 1.09 mL) and DIEA (10 mmol, 1.74 mL) in 10 mL of DMF was added to the resin slurry and shaken at rt for 2 h. The resin was washed 3× with DMF and 3× with DCM.

Acylation with Fmoc-Amino Acids (Resins 3). Resin **2** (1 g) was swollen in DCM, and a 0.3 M solution of Fmoc-amino acids (3 mmol), HOBt (3 mmol, 460 mg), and DIC (3 mmol, 464 μL) in 10 mL of DCM/DMF (1:1) was added. The resins were shaken at rt for 16 h and washed 3× with DMF and 3× with DCM.

Acylation with Fmoc-Amino Acids (Resins 4). Rink resin (100−200 mesh, 0.68 mmol/g, 1 g) was swollen in DCM, washed 3× with DMF, and treated with 50% piperidine in DMF for 15 min. After washing 3× with DMF and 3× with DCM, a 0.3 M solution of Fmoc-amino acids (3 mmol), HOBt (3 mmol, 460 mg), and DIC (3 mmol, 464 μL) in 10 mL of DCM/DMF (1:1) was added. The resins were shaken at rt for 16 h and washed 3× with DMF and 3× with DCM.

Cleavage of Fmoc-Protecting Group and Reaction with 4-Nos-Cl (Resins 5). Resins **4** (1 g) were washed 3× with DCM and 3× with DMF and treated with 50% piperidine in DMF for 15 min. After washing 3× with DMF and 3× with DCM, a solution of 4-Nos-Cl (3 mmol, 663 mg) and lutidine (3.3 mmol, 382 μL) in 10 mL of DCM was added to the resin, and the resin slurry was shaken at rt for 4 h. The resin was washed 3× with DCM.

Mitsunobu Alkylation with Glycolaldehyde Dimethyl Acetal (Resins 6). Resins **5** (1 g) in 20 mL plastic reaction vessel were washed 3× with anhydrous THF, and a solution of a 0.1 M glycolaldehyde dimethyl acetal (2 mmol, 202 μL), PPh_3 (2 mmol, 525 mg), and 10 mL of anhydrous THF was added to the reaction vessel. A 10 mL plastic reaction vessel was charged with 0.1 M DIAD (2 mmol, 404 μL) in 10 mL of anhydrous THF. This syringe was connected to the plastic reaction vessel containing the resin **5**. Connected syringes were left in a freezer for 30 min, and the DIAD solution was drawn into the syringe with a resin. The resin slurry was shaken at rt for 10 min and then transferred to a vial and shaken at 50 °C for 16 h. The resin was washed 3× with anhydrous THF and 3× with DCM. The reaction was repeated for quantitative alkylation.

Cleavage of Nos-Protecting Group and Acylation with Fmoc-Amino Acids (Resins 3). Resins **6** (1 g) were swollen in DCM and washed 3× with DMF. A solution of 0.6 M 2-mercaptoethanol (6 mmol, 420 μL) and 0.2 M DBU (2 mmol, 300 μL) in 10 mL of DMF was added, and resin slurries were shaken for 5 min. The resins were washed 3× with DMF and 3× with DCM. The resins were subsequently treated with a 0.3 M solution of Fmoc-amino acids (3 mmol), HOBt (3 mmol, 460 mg), and DIC (3 mmol, 464 μL) in 10 mL of DCM/DMF (1:1) at rt for 16 h, and were washed 3× with DMF and 3× with DCM.

Cleavage of Fmoc-Protecting Group and Reaction with Unsubstituted or 4,5-Disubstituted *o*-Fluoronitrobenzenes (Resins 7). Resins **3** (0.25 g) were swollen in DCM, washed 3× with DMF, and treated with 50% piperidine in DMF for 15 min. After washing 3× with DMF and 5× with DMSO, a solution of a 1 M unsusbtituted or 4,5-disubstituted *o*-fluoronitrobenzenes (2.5 mmol, 330 μL) and 1 M DIEA (2.5 mmol, 435 μL) in 2.5 mL of dimethyl sulfoxide (DMSO) was added to the resin, and the resin slurry was shaken at 50 °C (for unsubstituted *o*-fluoronitrobenzene) or rt (for 4,5-disubstituted *o*-fluoronitrobenzenes) for 16 h. The resins were washed 3× with DMSO and 3× with DCM.

Substitution of Chlorine with Piperidine (Resins 7). Resins **3** (0.25 g) (after substitution with 1,2-dichloro-4-fluoro-5-nitrobenzene) were swollen in DCM and washed 3× with DMSO, a 0.5 M solution of piperidine (1.5 mmol, 150 μL) in 3 mL of DMSO was added, and the resin slurries were shaken at 50 °C for 16 h. The resins were washed 3× with DMSO and 3× with DCM.

Reduction of the Nitro Group with Tin(II) Chloride Dihydrate (Resins 8). Resins **7** (0.25 g) were swollen in DCM, washed 3× with DMF (saturated with N_2), and a solution of tin(II) chloride dihydrate (2.5 mmol, 564 mg) and DIEA (2.5 mmol, 433 μL) in 2.5 mL of DMF (saturated with N_2) was added to the resin. The resin slurries were shaken at rt for 16 h. The resins were thoroughly washed 3× with DMF and 3× with DCM.

Acylation with Acetic Anhydride (Resins 9). Resins **8** (0.25 g) were swollen in DCM, acetic anhydride was added to the resins, and the resins were shaken at rt for 16 h. The resins were washed 3× with DCM.

Acylation with Carboxylic Acids (Resins 9). Resins **8** (0.25 g) were swollen in DCM, and a solution of carboxylic acid (1 mmol) and DIC (0.5 mmol, 77 μL) in 2.5 mL of DCM/DMF (1:1) was added. The resins were shaken at rt for 16 h. The resins were washed 3× with DMF and 3× with DCM.

Sulfonylation with 4-Nos-Cl (Resin 9). Resin **8** (0.25 g) was washed 3× with DCM. A 0.5 M solution of 4-Nos-Cl (1.25 mmol, 276 mg) and 0.5 M lutidine (1.25 mmol, 145 μL) in 2.5 mL of DCM was added to the resin, and the reaction slurry was shaken at rt for 16 h. The resin was washed 5× with DCM.

Reaction with FmocCl (Resin 12). Resin **8** (0.25 g) was swollen in DCM, and a 0.5 M solution of FmocCl (1.25 mmol, 325 mg) and 0.5 M DIEA (1.25 mmol, 218 μL) in 2.5 mL of DCM was added. The resin was shaken at rt for 30 min. The resin was washed 3× with DCM.

Cyclization on Resin (Resin 13). Resin **12** (0.25 g) was swollen in DCM, and a solution of 2% TFA in 2.5 mL of DCM was added.

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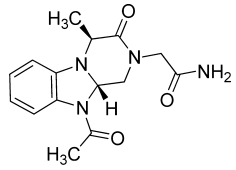
The resin was shaken at rt for 16 h. The resin was washed 3× with DCM.

Cleavage of Fmoc-Protecting Group (Resin 14). Resin **13** (0.25 g) was swollen in DCM, washed 3× with DMF, and treated with 50% piperidine in DMF for 15 min. The resin was washed 3× with DMF and 3× with DCM.

Cleavage, Cyclization (10), Cleavage (15), and Isolation. Resins **9** and **14** (0.25 g) were treated with 50% TFA in DCM at rt for 90 min. TFA solution was collected, resin was washed 3× with 50% TFA in DCM, and combined extracts were evaporated by a stream of nitrogen. The oily residue was dissolved in 1 mL of DMSO and diluted with 9 mL of 10 mM aqueous ammonium acetate. Depending on the type of compound, a solution or opalescent solution, occasionally with precipitation, was formed.

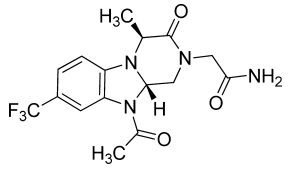
A fritted 10 mL syringe was charged with 2 g octadecyl-functionalized silica gel, and the plug was covered with another porous disk. Sorbent was wetted with 5 mL of MeCN and washed with 5 mL of 10 mM aqueous ammonium acetate. The solution of the target compound was passed through the column and was washed with 5 mL of 10 mM aqueous ammonium acetate, and the target compound was eluted with 5−10 mL of MeCN. The MeCN was evaporated, and the products were purified by semipreparative reverse HPLC. All products were isolated by freeze-drying as amorphous solids and characterized by LC−MS, HRMS, and ^{1}H and ^{13}C NMR.

Analytical Data of Individual Compounds. *2-((4S,10aS)-10-Acetyl-4-methyl-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo-*



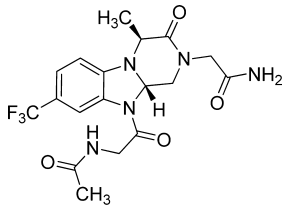
[1,2-a]pyrazin-2(1H)-yl)acetamide ***10(1,1,1,1)***. Yield 9.1 mg of amorphous solid (39%): ESI-MS m/z = 303, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.69 (d, J = 7.3 Hz, 1 H), 7.44 (br. s., 1 H), 7.10 (br. s., 1 H), 6.92 (t, J = 7.5 Hz, 1 H), 6.70−6.62 (m, 2 H), 6.03 (dd, J = 4.7, 7.0 Hz, 1 H), 4.24−4.17 (m, 1 H), 3.98 (d, J = 16.7 Hz, 1 H), 3.91 (d, J = 16.7 Hz, 1 H), 3.63−3.59 (m, 2 H), 2.22 (s, 3 H), 1.45 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.7, 168.7, 166.9, 141.4, 130.7, 124.7, 118.3, 115.3, 106.8, 71.5, 52.9, 49.7, 49.4, 23.0, 18.2; HRMS (TOF) m/z calcd for $C_{15}H_{19}N_4O_3$ $[M + H]^+$ 303.1457, found 303.1452.

2-((4S,10aS)-10-Acetyl-4-methyl-3-oxo-8-(trifluoromethyl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)-



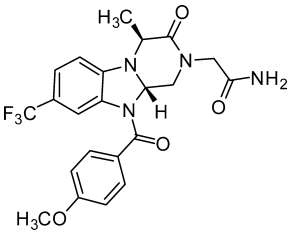
acetamide ***10(1,1,2,1)***. Yield 16.3 mg of amorphous solid (36%): ESI-MS m/z = 371, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.91 (s, 1 H), 7.46 (br. s., 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.13 (br. s., 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 6.21 (dd, J = 8.4, 3.7 Hz, 1 H), 4.38 (q, J = 7.0 Hz, 1 H), 4.03 (d, J = 16.7 Hz, 1 H), 3.88 (d, J = 16.7 Hz, 1 H), 3.62−3.73 (m, 2 H), 2.24 (s, 3 H), 1.45 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.7, 168.1, 167.7, 144.1, 131.2, 124.9 (q, J = 270 Hz), 122.7, 117.8 (q, J = 32.5 Hz), 111.2, 105.4, 71.6, 52.4, 50.1, 49.9, 23.0, 17.8; HRMS (TOF) m/z calcd for $C_{16}H_{18}F_3N_4O_3$ $[M + H]^+$ 371.1331, found 371.1326.

2-((4S,10aS)-10-(2-Acetamidoacetyl)-4-methyl-3-oxo-8-(trifluoromethyl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)acetamide ***10(1,1,2,2)***. Yield 20.9 mg of amorphous solid (66%): ESI-MS m/z = 428, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.34 (t, J = 5.7 Hz, 1 H), 7.90 (br. s., 1 H), 7.47 (br. s., 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.15 (br. s., 1 H), 6.82 (d, J = 8.5 Hz, 1



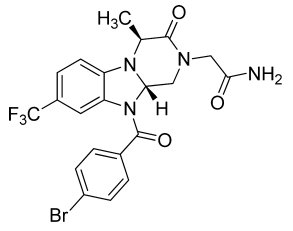
H), 6.44−6.26 (m, 1 H), 4.40 (q, J = 6.9 Hz, 1 H), 4.14 (dd, J = 4.3, 16.6 Hz, 1 H), 4.06−3.99 (m, 2 H), 3.89 (d, J = 16.7 Hz, 1 H), 3.79−3.62 (m, 2 H), 1.90 (s, 3 H), 1.46 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.9, 169.6, 168.0, 166.9, 143.8, 131.0, 124.8 (q, J = 270 Hz), 123.9, 123.0 (m), 117.8 (q J = 32.5 Hz), 111.3 (m), 105.6, 70.5, 52.4, 49.9, 41.6, 22.2, 17.9; HRMS (TOF) m/z calcd for $C_{18}H_{21}F_3N_5O_4$ $[M + H]^+$ 428.1546, found 428.1540.

2-((4S,10aS)-10-(4-Methoxybenzoyl)-4-methyl-3-oxo-8-(trifluoromethyl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-



2(1H)-yl)acetamide ***10(1,1,2,3)***. Yield 19.8 mg of amorphous solid (57%): ESI-MS m/z = 463, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.59 (d, J = 8.5 Hz, 2 H), 7.40 (br. s., 1 H), 7.24 (d, J = 8.2 Hz, 1 H), 7.09 (br. s., 1 H), 7.07 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.2 Hz, 1 H), 6.19 (dd, J = 3.8, 8.8 Hz, 1 H), 4.43 (q, J = 7.0 Hz, 1 H), 3.93 (d, J = 16.7 Hz, 1 H), 3.83 (s, 3 H), 3.78 (d, J = 16.7 Hz, 1 H), 3.71 (dd, J = 8.8, 12.0 Hz, 1 H), 1.45 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.3, 168.0, 167.0, 161.4, 144.0, 130.9, 129.2, 126.9, 122.5, 124.7 (q, J = 270 Hz), 117.5 (q, J = 32.5 Hz), 114.2, 110.3, 105.7, 71.8, 55.5, 52.3, 50.1, 49.8, 16.9; HRMS (TOF) m/z calcd for $C_{22}H_{22}F_3N_4O_4$ $[M + H]^+$ 463.1588, found 463.1570.

2-((4S,10aS)-10-(4-Bromobenzoyl)-4-methyl-3-oxo-8-(trifluoromethyl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-



2(1H)-yl)acetamide ***10(1,1,2,4)***. Yield 24.4 mg of amorphous solid (63%): ESI-MS m/z = 511, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.75 (d, J = 8.5 Hz, 2 H), 7.59 (d, J = 8.5 Hz, 2 H), 7.29 (br. s., 1 H), 7.26 (d, J = 8.5 Hz, 1 H), 6.94 (br. s., 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 6.17−6.11 (m, 1 H), 4.41 (q, J = 6.9 Hz, 1 H), 3.92 (d, J = 16.7 Hz, 1 H), 3.80 (d, J = 16.7 Hz, 1 H), 3.74 (td, J = 1.5, 10.1 Hz, 1 H), 3.47 (br. s., 1 H), 1.46 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.0, 167.7, 166.0, 143.9, 133.9, 131.8, 130.4, 128.9, 124.3, 124.0 (q, J = 270 Hz), 123.5, 117.5 (q, J = 32.5 Hz), 110.4 (m), 105.6, 71.6, 52.2, 49.9, 49.6, 16.8; HRMS (TOF) m/z calcd for $C_{21}H_{19}BrF_3N_4O_3$ $[M + H]^+$ 511.0563, found 511.0587.

2-((4S,10aS)-4-Methyl-10-((4-nitrophenyl)sulfonyl)-3-oxo-8-(trifluoromethyl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]-pyrazin-2(1H)-yl)acetamide ***10(1,1,2,5)***. Yield 24.5 mg of amorphous solid (63%): ESI-MS m/z = 514, $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.35 (d, J = 9.1 Hz, 2 H), 8.02 (d, J = 9.1 Hz, 2 H), 7.48 (d, J = 1.8 Hz, 1 H), 7.45 (br. s., 1 H), 7.37 (dd, J = 1.2, 8.2 Hz, 1 H), 7.14 (s, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 6.17 (dd, J = 4.1, 9.4 Hz, 1 H), 4.24 (q, J = 7.0 Hz, 1 H), 4.01 (d, J = 16.4 Hz, 1 H), 3.82 (d, J =

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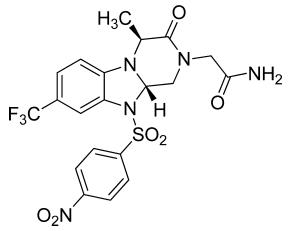
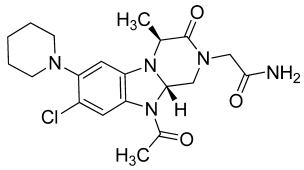


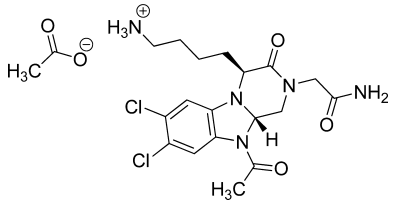
16.7 Hz, 1 H), 3.76 (dd, J = 9.4, 12.0 Hz, 1 H), 3.48 (dd, J = 4.1, 11.7 Hz, 1 H), 1.16 (d, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.5, 167.8, 150.8, 144.9, 140.5, 129.0, 128.5, 125.5 (m), 124.7, 124.5 (q, J = 270 Hz), 118.5 (q, J = 32.5 Hz), 113.3 (m), 107.1, 72.2, 52.1, 50.7, 50.1, 17.6; HRMS (TOF) m/z calcd for $C_{20}H_{19}F_3N_5O_6S$ [M + H]$^+$ 514.1003, found 514.0983.

2-((4S,10aS)-10-Acetyl-8-chloro-4-methyl-3-oxo-7-(piperidin-1-yl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-



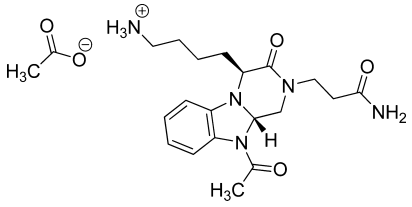
yl)acetamide ***10(1,1,4,1)***. Yield 11.3 mg of amorphous solid (34%): APCI-MS m/z = 420, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.65 (s, 1 H), 7.45 (br. s., 1 H), 7.11 (br. s., 1 H), 6.50 (s, 1 H), 6.05 (dd, J = 7.3, 4.4 Hz, 1 H), 4.31 (q, J = 6.8 Hz, 1 H), 4.00 (d, J = 16.7 Hz, 1 H), 3.87 (d, J = 16.7 Hz, 1 H), 3.59−3.64 (m, 2 H), 2.79−2.92 (m, 4 H), 2.20 (s, 3 H), 1.62 (dt, J = 11.1, 5.5 Hz, 4 H), 1.46−1.54 (m, 2 H), 1.44 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.7, 168.6, 166.7, 147.3, 141.0, 126.2, 116.5, 115.4, 99.8, 71.5, 52.6, 52.5, 49.8, 49.5, 25.9, 23.8, 22.7, 18.3; HRMS (TOF) m/z calcd for $C_{20}H_{26}ClN_5NaO_3$ [M + Na]$^+$ 442.1616, found 442.1618.

4-((4S,10aS)-10-Acetyl-2-(2-amino-2-oxoethyl)-7,8-dichloro-3-oxo-1,2,3,4,10,10a-hexahydrobenzo[4,5]imidazo[1,2-a]pyrazin-4-



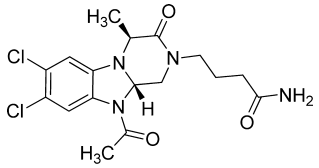
yl)butan-1-aminium acetate ***10(1,2,3,1)***. Yield 6.6 mg of amorphous solid (19%): APCI-MS m/z = 428, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.77 (s, 1 H), 7.45 (br. s., 1 H), 7.11 (br. s., 1 H), 6.93 (s, 1 H), 6.11 (dd, J = 8.1, 4.0 Hz, 1 H), 4.28 (dd, J = 7.9, 4.1 Hz, 1 H), 4.02 (d, J = 16.7 Hz, 1 H), 3.81 (d, J = 16.7 Hz, 1 H), 3.60−3.70 (m, 2 H), 2.60 (t, J = 5.9 Hz, 2 H), 2.24 (s, 3 H), 1.83−1.93 (m, 2 H), 1.40−1.50 (m, 4 H), 1.28−1.37 (m, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 173.5, 169.5, 167.7, 167.4, 141.9, 130.8, 126.2, 118.3, 115.8, 107.3, 71.8, 56.8, 49.8, 49.7, 40.1, 31.7, 30.6, 23.1, 22.9, 22.3; HRMS (TOF) m/z calcd for $C_{18}H_{24}Cl_2N_5O_3$ [M + H]$^+$ 428.1251, found 428.1243.

4-((4S,10aS)-10-Acetyl-2-(3-amino-3-oxopropyl)-3-oxo-1,2,3,4,10,10a-hexahydrobenzo[4,5]imidazo[1,2-a]pyrazin-4-yl)-



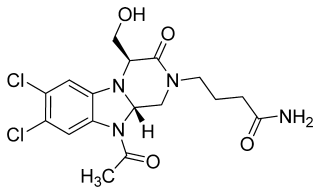
butan-1-aminium Acetate ***10(2,2,1,1)***. Yield 7.0 mg of amorphous solid (13%): APCI-MS m/z = 374, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.70 (d, J = 7.9 Hz, 1 H), 7.38 (br. s., 1 H), 6.89 (t, J = 7.6 Hz, 1 H), 6.86 (br. s., 1 H), 6.67 (d, J = 8.2 Hz, 1 H), 6.60−6.65 (m, 1 H), 5.89 (dd, J = 8.5, 3.8 Hz, 1 H), 4.07 (dd, J = 7.5, 4.0 Hz, 2 H), 3.66 (dd, J = 11.9, 3.7 Hz, 2 H), 3.53 (dd, J = 12.0, 8.8 Hz, 2 H), 3.47 (t, J = 6.9 Hz, 2 H), 2.58−2.65 (m, 2 H), 2.36 (br. s., 1 H), 2.27−2.32 (m, 1 H), 2.25 (s, 2 H), 1.88 (td, J = 9.0, 4.7 Hz, 1 H), 1.78 (s, 3 H), 1.46 (d, J = 5.0 Hz, 2 H), 1.34−1.40 (m, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 173.2, 172.5, 167.3, 166.9, 141.5, 130.4, 124.7, 118.1, 115.4, 106.5, 71.4, 56.9, 48.6, 44.2, 40.1, 33.1, 32.0, 30.5, 23.1, 22.9, 22.5; HRMS (TOF) m/z calcd for $C_{19}H_{28}N_5O_3$ [M + H]$^+$ 374.2187, found 374.2212.

4-((4S,10aS)-10-Acetyl-7,8-dichloro-4-methyl-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)butanamide



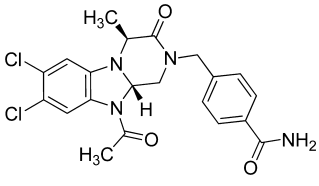
10(3,1,3,1). Yield 12.0 mg of amorphous solid (23%): APCI-MS m/z = 399, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.76 (s, 1 H), 7.24 (br. s., 1 H), 6.92 (s, 1 H), 6.73 (br. s., 1 H), 6.10 (dd, J = 7.5, 3.1 Hz, 1 H), 4.29 (q, J = 7.0 Hz, 1 H), 3.61−3.67 (m, 1 H), 3.54−3.61 (m, 1 H), 3.38−3.41 (m, 1 H), 3.22−3.29 (m, 1 H), 2.27 (s, 3 H), 1.96−2.04 (m, 2 H), 1.59−1.74 (m, 2 H), 1.42 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 173.8, 167.6, 167.5, 141.3, 130.9, 126.2, 118.4, 115.8, 107.2, 71.6, 52.5, 48.3, 46.5, 32.3, 22.9, 22.6, 17.9; HRMS (TOF) m/z calcd for $C_{17}H_{21}Cl_2N_4O_3$ [M + H]$^+$ 399.0985, found 399.0956.

4-((4S,10aS)-10-Acetyl-7,8-dichloro-4-(hydroxymethyl)-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)-



butanamide ***10(3,3,3,1)***. Yield 20.0 mg of amorphous solid (36%): APCI-MS m/z = 415, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.76 (s, 1 H), 7.23 (br. s., 1 H), 6.89 (s, 1 H), 6.73 (br. s., 1 H), 6.07 (dd, J = 8.7, 4.0 Hz, 1 H), 5.06 (br. s., 1 H), 4.24 (dd, J = 4.5, 3.4 Hz, 1 H), 3.88 (dd, J = 10.4, 4.5 Hz, 1 H), 3.75 (dd, J = 10.3, 2.1 Hz, 1 H), 3.54−3.64 (m, 1 H), 3.46 (dt, J = 13.5, 7.0 Hz, 1 H), 3.29−3.39 (m, 1 H), 3.21 (dt, J = 13.4, 6.8 Hz, 1 H), 2.26 (s, 3 H), 1.98−2.06 (m, 2 H), 1.58−1.73 (m, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 173.8, 167.4, 165.1, 141.6, 130.5, 126.2, 117.9, 115.9, 107.1, 72.5, 62.9, 59.0, 48.1, 46.6, 32.3, 22.8, 22.6; HRMS (TOF) m/z calcd for $C_{17}H_{21}Cl_2N_4O_4$ [M + H]$^+$ 415.0934, found 415.0930.

4-(((4S,10aS)-10-Acetyl-7,8-dichloro-4-methyl-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)methyl)-



benzamide ***10(4,1,3,1)***. Yield 8.0 mg of amorphous solid (13%): APCI-MS m/z = 447, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.93 (br. s., 1 H), 7.80 (d, J = 8.2 Hz, 2 H), 7.73 (s, 1 H), 7.34 (br. s., 1 H), 7.29 (d, J = 7.6 Hz, 2 H), 6.96 (s, 1 H), 6.17 (dd, J = 7.3, 3.2 Hz, 1 H), 4.73 (d, J = 15.3 Hz, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 3.68

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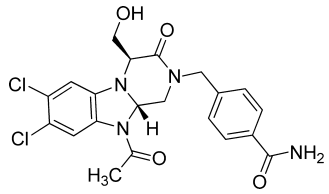
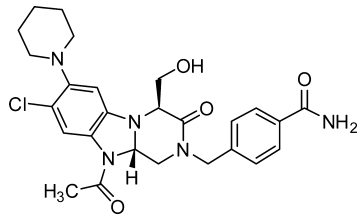
(dd, J = 12.2, 2.8 Hz, 1 H), 3.52−3.58 (m, 1 H), 2.17 (s, 3 H), 1.47 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 168.1, 167.5, 167.5, 141.2, 140.0, 133.3, 130.9, 127.7, 127.3, 126.2, 118.7, 115.8, 107.5, 71.6, 52.7, 49.8, 48.7, 22.9, 17.6; HRMS (TOF) m/z calcd for $C_{21}H_{21}Cl_2N_4O_3$ [M + H]$^+$ 447.0985, found 447.0978.

4-(((4S,10aS)-10-Acetyl-7,8-dichloro-4-(hydroxymethyl)-3-oxo-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-2(1H)-yl)-



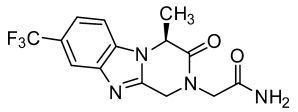
methyl)benzamide ***10(4,3,3,1)***. Yield 13.7 mg of amorphous solid (21%): APCI-MS m/z = 463, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.93 (br. s., 1 H), 7.81 (d, J = 8.5 Hz, 2 H), 7.72 (s, 1 H), 7.28−7.39 (m, 3 H), 6.92 (s, 1 H), 6.14 (dd, J = 8.8, 3.2 Hz, 1 H), 5.13−5.20 (m, 1 H), 4.76 (d, J = 15.3 Hz, 1 H), 4.49 (d, J = 15.3 Hz, 1 H), 4.41 (t, J = 3.7 Hz, 1 H), 3.98 (dd, J = 10.0, 4.4 Hz, 1 H), 3.76−3.83 (m, 1 H), 3.63 (dd, J = 12.0, 2.9 Hz, 1 H), 3.49−3.56 (m, 1 H), 2.16 (s, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 167.5, 167.3, 165.7, 141.5, 139.9, 133.2, 130.5, 127.7, 127.3, 126.2, 118.0, 115.9, 107.2, 72.6, 63.0, 59.0, 50.0, 48.5, 22.8; HRMS (TOF) m/z calcd for $C_{21}H_{21}Cl_2N_4O_4$ [M + H]$^+$ 463.0934, found 463.0923.

4-(((4S,10aS)-10-Acetyl-8-chloro-4-(hydroxymethyl)-3-oxo-7-(piperidin-1-yl)-3,4,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]-



pyrazin-2(1H)-yl)methyl)benzamide ***10(4,3,4,1)***. Yield 21.4 mg of amorphous solid (30%): APCI-MS m/z = 512, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.89−7.97 (m, 1 H), 7.81 (d, J = 7.9 Hz, 2 H), 7.61 (s, 1 H), 7.25−7.36 (m, 3 H), 6.52−6.59 (m, 1 H), 6.06 (dd, J = 9.0, 3.7 Hz, 1 H), 5.13−5.18 (m, 1 H), 4.71 (d, J = 15.6 Hz, 1 H), 4.52 (d, J = 15.3 Hz, 1 H), 4.35−4.43 (m, 1 H), 3.97−4.09 (m, 1 H), 3.77 (d, J = 4.1 Hz, 1 H), 3.59 (dd, J = 12.2, 3.7 Hz, 1 H), 3.41−3.49 (m, 1 H), 2.78−2.91 (m, 4 H), 2.12 (s, 3 H), 1.58−1.66 (m, 4 H), 1.48−1.52 (m, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 167.6, 166.9, 166.3, 147.3, 141.0, 139.9, 133.3, 127.7, 127.3, 125.6, 116.7, 115.0, 99.8, 72.3, 63.4, 58.9, 52.5, 49.9, 48.1, 25.9, 23.8, 22.6; HRMS (TOF) m/z calcd for $C_{26}H_{31}ClN_5O_4$ [M + H]$^+$ 512.2059, found 512.2053.

(S)-2-(4-Methyl-3-oxo-8-(trifluoromethyl)-3,4-dihydrobenzo[4,5]-imidazo[1,2-a]pyrazin-2(1H)-yl)acetamide ***15(1,1,2)***. Yield 4.6 mg of



amorphous solid (14%): ESI-MS m/z = 327, [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.00 (s, 1 H), 7.92 (d, J = 8.5 Hz, 1 H), 7.60 (dd, J = 8.5, 1.2 Hz, 1 H), 7.57 (br. s., 1 H), 7.18 (br. s., 1 H), 5.34 (q, J = 6.9 Hz, 1 H), 5.03 (d, J = 16.4 Hz, 1 H), 4.80 (d, J = 16.7 Hz, 1 H), 4.14 (d, J = 16.7 Hz, 1 H), 4.04 (d, J = 16.7 Hz, 1 H), 1.63 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 169.3, 166.6, 147.9, 142.8, 135.1, 124.1, 123.3 (m), 118.8 (m), 116.1 (m), 111.8, 52.6, 49.0, 46.0, 18.9 HRMS (TOF) m/z calcd for $C_{14}H_{14}F_3N_4O_2$ [M + H]$^+$ 327.1062, found 327.1063.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra associated with this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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