Electronic Supplementary Material (ESI) for Green Chemistry.

Supplementary Information

Beyond Organic Solvents: Synthesis of a 5-HT_4 Receptor Agonist in Water

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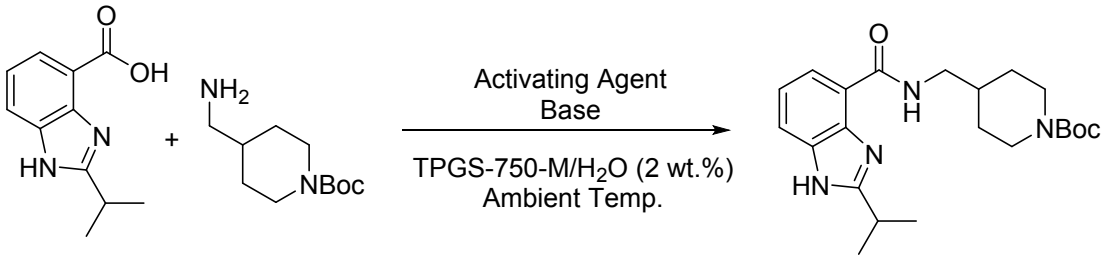
2. General Information

Reagents were purchased from Millipore-Sigma, Acros Organics, Chem-impex int'l INC, Asta Tech, Chemrio, Combi-Blocks, and PHT. 2,3-diaminobenzoic acid starting material purchased from Combi-Blocks required purification via charcoal filtration before use. All other reagents were used without further purification. TPGS-750-M was purchased from PHT and Millipore-Sigma as a wax and the desired 2 wt. % aqueous solution was prepared using de-ionized water. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Avance III spectrometer (Bruker BioSpin Corporation [Billerica, MA, USA]) equipped with a 5.0 mm BBO probe. Proton spectra were acquired with excitation sculpting to suppress the water signal. HSQC and HMBC data were acquired using a non-uniform sampling (NUS) protocol. Data was processed by MNova V 14.0 (Mestrelab Research [Santiago de Compostela, Spain]). DMSO-d_6, $CDCl_3$, and D_2O were used as solvent; Residual peaks for $(CH_3)_2SO$ in $(CD_3)_2SO$ (^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm) and $CDCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.20 ppm) have been assigned. The chemical shifts are reported in ppm, the coupling constant J values are given in Hz. The peak patterns are indicated as follows: brs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. IR spectra were recorded on a Nicolet iS10 FTIR spectrometer.

3. Activating Agent Screen for Amide Coupling of Acid 11 and Amine 4



11 **4** **5**

General Procedure:

2-isopropyl-1H-benzo[d]imidazole-4-carboxylic acid **11** (250 mg, 1.2 mmol) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate **4** (257 mg, 1.2 mmol) were placed in a 4 mL vial. 2 wt. % TPGS-750-M in water (2.5 mL) and the indicated base were added followed by the indicated activating agent. The reaction mixture was stirred at the indicated temperature for 24 hours. A sample of the reaction mixture was then analyzed for conversion by HPLC.

Entry	Activating Agent (amount)	Base (amount)	Temperature	Conversion (HPLC area %)
1	DMTMM (3.0 equiv)	4-methylmorpholine (3.0 equiv)	Ambient	97
2	DIC (1.0 equiv)	None	Ambient	23
3	TNTU (1.5 equiv)	N,N-diisopropylethylamine (2.0 equiv)	40 °C	16
4	EDCI (1.5 equiv), HOBt (1.2	4-Methylmorpholine	Ambient	34

	equiv)	(3.0 equiv)		
5[a]	Thionyl chloride (7 equiv)	K_2CO_3 (8 equiv)	50 °C	59
6	Cyanuric chloride (1.0 equiv)	4-Methylmorpholine (1.0 equiv)	Ambient	19
7	Isobutyl chloroformate (1.3 equiv)	4-Methylmorpholine (1.4 equiv)	Ambient	30
8	EEDQ	None	Ambient	22
9	TCFH (1.5 equiv)	1-Methylimidazole (3.0 equiv)	Ambient	>98

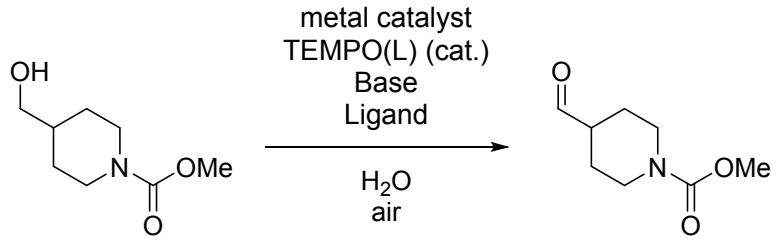
[a] The acid chloride of **11** was pre-formed in neat thionyl chloride before addition to an aqueous solution of **4** and K_2CO_3.

Activating Agent Abbreviations:

- DIC: *N,N′*-Diisopropylcarbodiimide
- DMTMM: 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
- EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
- EEDQ: *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
- HOBt: 1-Hydroxybenzotriazole
- TCFH: Chloro-*N*,*N*,*N′*,*N′*-tetramethylformamidinium hexafluorophosphate
- TNTU: *O*-(5-Norbornene-2,3-dicarboximido)-*N*,*N*,*N′*,*N′*-tetramethyluronium tetrafluoroborate

4. Oxidation Condition Screen for Conversion of Alcohol 13 to Aldehyde 14

4.1. Aerobic Oxidation Conditions



13 **14**

General Procedure:

Methyl 4-(hydroxymethyl)piperidine-1-carboxylate **13** (100 mg, 0.58 mmol) was added to a 4 mL vial with magnetic stir bar. Water (1.00 mL) was added and all solids dissolved. The indicated metal catalyst, TEMPO or TEMPOL, ligand, base, and any other additives were added to the reaction mixture. The mixture was stirred open to air at the indicated temperature for approximately 24 hours. The mixture was then extracted three times with dichloromethane (3 x 1

mL). The combined organic layer was washed successively with aqueous sodium bicarbonate and brine. The organic layer was then dried over sodium sulfate, concentrated to dryness via rotary evaporator, and analyzed for reaction conversion by ^{1}H NMR in D_2O.

Entry	Metal Catalyst (amount)	Catalyst (amount)	Base (amount)	Ligand (amount)	Reaction Temp.	Conversion to Aldehyde **14**[a]
1[1]	$Fe(NO_3)_3.9H_2O$ (5 mol %)	TEMPOL (10 mol %), NaCl (10 mol %)	None	None	Ambient	None Detected
2[2]	CuBr (5 mol %)	TEMPO (5 mol %)	1-Methylimidazole (10 mol %)	2,2'-Bipyridine (5 mol %)	50 °C	None Detected
3[2]	$CuBr_2$ (5 mol %)	TEMPO (5 mol %)	1-Methylimidazole (10 mol %)	2,2'-Bipyridine (5 mol %)	50 °C	None Detected
4[3]	$FeCl_3$ (5 mol %)	TEMPO (5 mol %), $NaNO_2$ (8 mol %)	None	None	50 °C	None Detected
5[4]	$Cu(NCCH_3)_4.CF_3SO_3$ (5 mol %)	TEMPO (5 mol %)	1-Methylimidazole (10 mol %)	2,2'-Bipyridine (5 mol %)	Ambient	None Detected
6	CuI (5 mol %)	TEMPO (10 mol %)	1-Methylimidazole (20 mol %)	2,2'-Bipyridine (10 mol %)	50 °C	Trace

[a] Determined from peak ratios in ^{1}H NMR of crude product mixture.

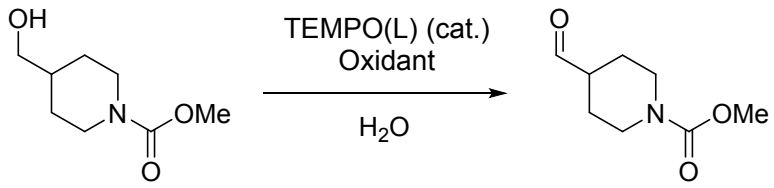
Abbreviations:

- TEMPO: 2,2,6,6-Tetramethylpiperidine 1-oxyl
- TEMPOL: 4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl

References:

1. X. Jiang, J. Liu, S. Ma *Org. Process Res. Dev.* 2019, **23**, 825
2. J.M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* 2011, **133**, 16901
3. W. Yin, C. Chu, Q. Lu, J. Tao, X. Liang, R. Liu, *Adv. Synth. Catal.* 2010, **352**, 113
4. J. M. Hoover, J. E. Steves, S. S. Stahl *Nat. Protoc*. 2012, **7**, 1161

4.2. Stoichiometric Oxidation Conditions



13 **14**

General Procedure:

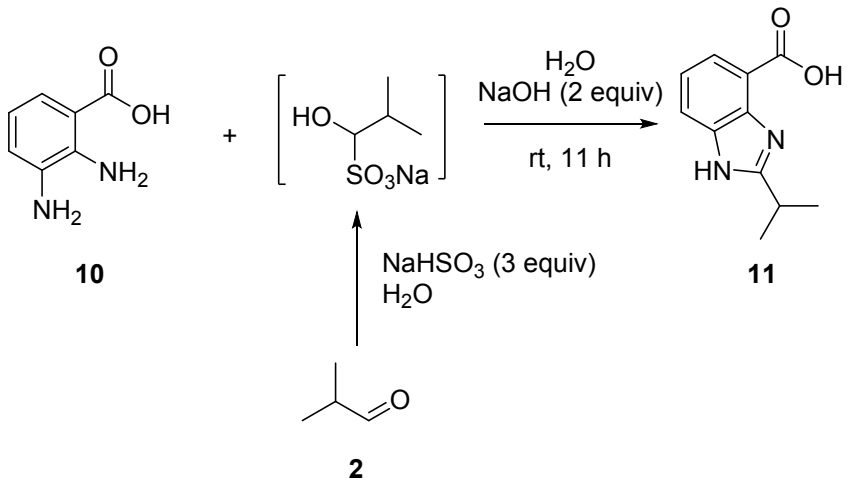
Methyl 4-(hydroxymethyl)piperidine-1-carboxylate **13** (100 mg, 0.57733 mmol) was added to a 4 mL vial with magnetic stir bar. Water (1.00 mL) was added and all solids dissolved. TEMPO or TEMPOL, stoichiometric oxidant, and any other additives were added to the reaction mixture. The mixture was stirred at ambient temperature for approximately 24 hours. The mixture was then extracted three times with dichloromethane (3 x 1 mL). The combined organic layer was washed successively with aqueous sodium bicarbonate and brine. The organic layer was then dried over sodium sulfate, concentrated to dryness via rotary evaporator, and analyzed for reaction conversion by ^{1}H NMR in D_2O.

Entry	Catalyst (Amount)	Surfactant (Amount)	Co-Solvent (Amount)	Oxidant	Conversion (%)[a]	Overoxidation to Acid (%)[a]
1	TEMPO (5 mol %), $NaHCO_3$ (7 mol %), NaBr (5 mol %)	None	None	NaOCl (1.5 equiv)	30	30
2	TEMPO (5 mol %)	None	None	(Diacetoxyiodo)benzene (1.1 equiv)	11	None Detected
3	TEMPO (5 mol %)	TPGS-750-M (2 wt%)	None	(Diacetoxyiodo)benzene (1.1 equiv)	40	None Detected
4	TEMPOL (5 mol %)	TPGS-750-M (2 wt%)	None	(Diacetoxyiodo)benzene (1.1 equiv)	50	None Detected
5	TEMPO (5 mol %)	TPGS-750-M (2 wt%)	THF (15% v/v)	(Diacetoxyiodo)benzene (1.1 equiv)	70	None Detected
6	TEMPOL (5 mol %)	TPGS-750-M (2 wt%)	THF (15% v/v)	(Diacetoxyiodo)benzene (1.1 equiv)	70	None Detected

[a] Determined from peak ratios in ^{1}H NMR of crude product mixture.

5. **Procedures for the Synthesis of TAK-954**

*5.1. 2-Isopropyl-1H-benzo[d]imidazole-4-carboxylic acid (**11**)*



Preparation of Aldehyde-Bisulfite Adduct Solution:

2-Methylpropanal **2** (47.4 g, 657 mmol, 1.25 equiv) was dissolved in H_2O (875 mL). $NaHSO_3$ (164 g, 1.58 mol, 3.00 equiv) was added and the resulting solution was stirred at ambient temperature for 1 hr. A sample of the solution was then removed, diluted with D_2O, and analyzed by ^1H NMR, which showed that no aldehyde was present.

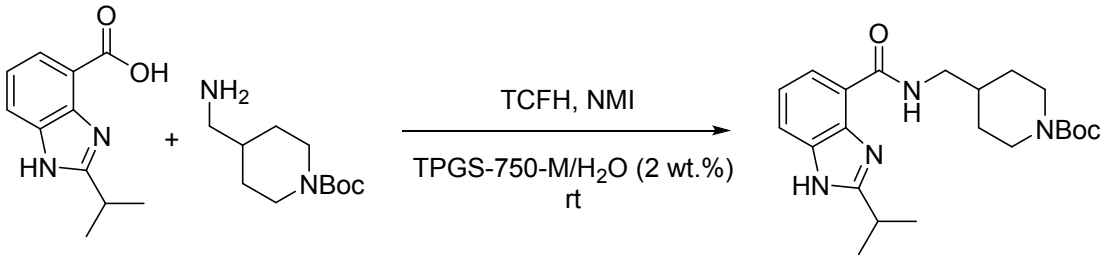
Cyclization:

2,3-Diaminobenzoic acid **10** (100 g, 526 mmol, 80 mass % potency, 1.00 equiv) was charged to a separate reaction vessel. Water (500 ml) and NaOH (4M in water, 263 mL, 2.00 equiv) were charged to the vessel. Agitation was initiated at ambient temperature and all solids dissolved. The previously prepared solution of isobutyraldehyde-bisulfite adduct was added to the reaction vessel over 2 hours via peristaltic pump while maintaining an internal temperature between 15 °C and 25 °C. The reaction solution was stirred at 15-25 °C for 11 hours. A sample of the reaction mixture was then removed and analyzed by HPLC, which indicated complete consumption of 2,3-diaminobenzoic acid starting material.

Crystallization:

HCl (1.50 eq, 4M in water) was added over 2 hours via peristaltic pump to adjust the pH of the product mixture to approximately 5. A thick slurry formed during HCl addition and was left to stir at room temperature for 12 hours to equilibrate. The slurry was then filtered. Water at pH 5 (2 x 100 mL) was used to rinse the reaction vessel and was then transferred to the filter to wash the filter cake. The filter cake was washed a second time with MeCN (100 mL x 2). The filter cake was deliquored and dried in a vacuum oven at 45 °C for 12 hours. Benzimidazole **11** was obtained as an off-white, crystalline solid (100 g, 79% assay corrected yield, 85% potency).

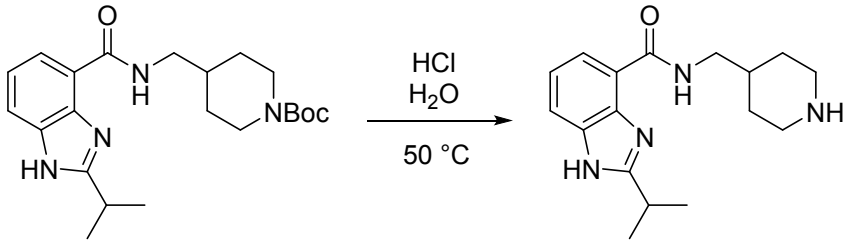
*5.2. Tert-butyl 4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido) methyl) piperidine-1-carboxylate (**5**)*



11 **4** **5**

2-Isopropyl-1H-benzimidazole-4-carboxylic acid **11** (90 g, 397 mmol, 90% purity, 1.00 equiv) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate **4** (111 g, 516 mmol, 1.30 equiv) were charged to a reaction vessel. Water (760 mL), tetrahydrofuran (135 mL), and N-methylimidazole (114 g, 1.39 mol, 3.50 equiv) were charged to the reaction vessel sequentially. Agitation was initiated and all solids dissolved. Chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (166.8 g, 594 mmol, 1.50 equiv) was added in three equal portions (55.6 g, 198 mmol, 0.50 equiv each), waiting 15 minutes between each addition. The resulting slurry was stirred at ambient temperature for 11 hours. A sample of the reaction mixture was then removed and analyzed by HPLC, which indicated complete consumption of carboxylic acid starting material **11**. The slurry was filtered, washed with water (200 mL), and dried in a vacuum oven at 45°C for 12 hours. Amide **5** was obtained as an off-white, crystalline solid (169 g, 91% assay corrected yield, 95% potency).

*5.3. 2-isopropyl-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide (**6**)*

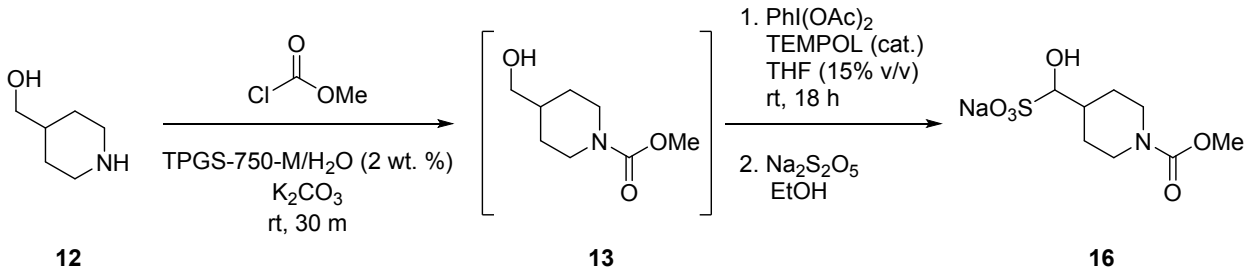


5 **6**

Tert-butyl 4-[[(2-isopropyl-1h-benzimidazole-4-carbonyl)amino]methyl]piperidine-1-carboxylate **5** (150 g, 356 mmol, 95 mass % potency, 1.00 equiv), water (1400 mL), acetonitrile (74 mL) and hydrochloric acid (4M in water, 266.85 mL, 3.00 equiv) were charged to a reaction vessel. Agitation was initiated and the resulting solution was heated to 50°C. The reaction mixture was stirred at 50°C for 1 hour. A sample of the reaction mixture was then removed and analyzed by HPLC, which indicated complete consumption of Boc-protected starting material **5.** The reaction mixture was cooled to ambient temperature, and the pH of the mixture was adjusted to approximately 11 through the addition of sodium hydroxide (4M in water, 532.9 mmol, 4.5 equiv) via peristaltic pump over 1 hour at ambient temperature. The resulting slurry was equilibrated at room temperature for 12 hours. The slurry was then filtered, and the filter cake was washed twice with water (2 x 150 mL). The isolated solids were dried in a vacuum oven at 45 °C for 12 hours. Piperidine **6** was obtained as an off-white, crystalline solid (98 g, 88% assay corrected yield, 96%

potency).

*5.4. sodium hydroxy(1-(methoxycarbonyl)piperidin-4-yl)methanesulfonate (**16**)*



12 **13** **16**

Methyl Carbamate Formation

4-Piperidylmethanol **12** (1.00 g, 8.68 mmol, 1.00 equiv), potassium carbonate (1.80 g, 13.0 mmol, 1.50 equiv), and TPGS-750-M (2 wt. % in water, 3 mL) were charged to a 250 mL round bottom flask. Methyl chloroformate (0.81 mL, 10.4 mmol, 1.2 equiv) was added slowly via addition funnel while maintaining an internal temperature below 30 °C and controlling the rate of off-gassing. The reaction mixture was then stirred at room temperature for 1 hour. A sample of the mixture was removed and analyzed by GC, which indicated complete consumption of starting material **12**.

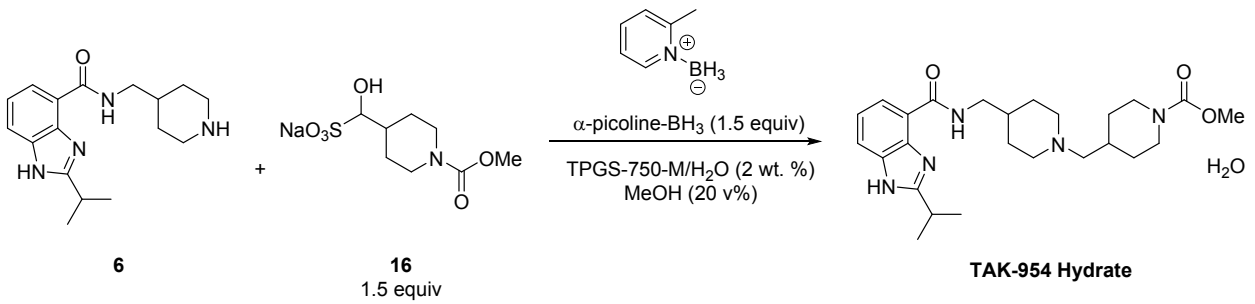
Oxidation

Tetrahydrofuran (1 ml, 10 mmol) was added to the reaction mixture. 4-Hydroxy-tempo (0.075 g, 0.434 mmol, 0.05 equiv) and iodobenzene diacetate (6.15 g, 19.1 mmol, 2.2 equiv) were added sequentially to the reaction mixture. The reaction mixture was then heated to 60 °C and stirred for 24 hours. The reaction mixture was then cooled to room temperature and was polish filtered. The collected salts were discarded.

Aldehyde-Bisulfite Adduct Formation and Isolation

The filtrate was heated to 60 °C. Sodium metabisulfite (1.16 g, 6.08 mmol, 0.7 equiv) was added at 60 °C, and the mixture was held at 60 °C for 2 hours. Ethanol (16 mL) was added to the mixture at 60 °C over 3 hours via syringe pump. After ethanol addition was complete, the mixture was cooled to ambient temperature and held at ambient temperature for 18 hours, during which time a slurry formed. The solids were collected by filtration, washed with ethanol (2 mL), and dried in a vacuum oven at 45 °C for 18 hours. Aldehyde-bisulfite adduct **16** was obtained as a white, crystalline solid (1.44 g, 37.7% overall assay corrected yield, 75% potency).

*5.5. methyl 4-((4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido) methyl)piperidin-1-yl)methyl)piperidine-1-carboxylate hydrate (**TAK-954 Hydrate**)*



2-Isopropyl-n-(4-piperidylmethyl)-1h-benzimidazole-4-carboxamide **6** (90 g, 288 mmol, 96 mass % potency, 1.00 equiv), [hydroxy-(1-methoxycarbonyl-4-piperidyl)methyl]sulfonyloxysodium **16** (136 g, 431.43 mmol, 87 mass% purity, 1.50 equiv) and α-picoline borane (46.2 g, 431 mmol, 1.50 equiv) were charged to a reaction vessel. TPGS-750-M (2 wt. % in water, 720 mL) and methanol (180 mL) were added to the vessel. Agitation was initiated and the mixture was heated at 60°C for 12 hours. A sample of the reaction mixture was removed and analyzed by HPLC, which indicated that starting material **6** had been completely consumed. The reaction mixture was cooled to ambient temperature. Sodium hydroxide (1M in water, 520 mL), water (900 mL), and **TAK-954 Hydrate** seed crystals (0.90 g, 1 wt. %) were combined in a separate vessel and stirred at ambient temperature. The reaction mixture was then added to this seeded aqueous hydroxide mixture over 3 hours at ambient temperature via peristaltic pump. The resulting slurry was filtered to collect the solids. The filter cake was washed with water (180 mL) and was dried in a vacuum oven at 45 °C for 12 hours. **TAK-954 Hydrate** was obtained as a white, crystalline solid (130 g, 91% assay corrected yield, 95% potency).

*5.6. Recrystallization of methyl 4-((4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido) methyl)piperidin-1-yl)methyl)piperidine-1-carboxylate hydrate (**TAK-954 Hydrate**)*

TAK-954 Hydrate (130 g, 261 mmol, 95 mass % potency, 1.00 equiv) and acetonitrile (1300 mL) were charged to a reaction vessel. The resulting suspension was heated to 82 °C and held at 82 °C until all solids dissolved. The mixture was then cooled to 20 °C over 3 hours, and the resulting slurry was equilibrated at 20 °C for 14 hours. The solids were collected by filtration. The filter cake was washed twice with acetonitrile (2 x 130 mL) and was dried in a vacuum oven at 45 °C for 12 hours. **TAK-954 Anhydrate** was obtained as a white, crystalline solid (115 g, 97% assay corrected yield, 100% potency).

6. Process Mass Intensity (PMI) Calculations

$$PMI = \frac{Total\ Mass\ of\ Material\ Inputs\ (kg)}{Mass\ of\ Product\ (kg)}$$

*6.1. Preparation of Benzimidazole **11***

	Material	Amount (g)
Limiting Reagent Input	Diaminobenzoic Acid **10**	100.0
Product Output	Benzimidazole **11**	100.0
Reagents	Isobutyraldehyde **2**	47.4
	$NaHSO_3$	164.0
Solvents	Acetonitrile	157.2
Aqueous	Water (bisulfite adduct formation)	875.0
	Water (cyclization reaction)	500.0
	4M Aqueous NaOH	302.5
	4M Aqueous HCl	108.5
	Water (filter cake wash)	200.0
Totals	All Materials	2454.6
	Reagents	211.4
	Solvents	157.2
	Aqueous	1986.0

Step PMI	24.5
Step PMI Solvents	1.6
Step PMI Water	19.9

*6.2. Preparation of Amide **5***

	Material	Amount (g)
Limiting Reagent Input	Benzimidazole **11**	90.0
Product Output	Amide **5**	169.0
Reagents	Piperidine **4**	111.0
	NMI	114.0
	TCFH	166.8
Solvents	THF	120.0
Aqueous	Water (reaction)	760.0
	Water (filter cake wash)	200.0
Totals	All Materials	1561.8
	Reagents	391.8
	Solvents	120.0
	Aqueous	960.0

Step PMI	9.2
Step PMI Solvents	0.7
Step PMI Water	5.7

*6.3. Preparation of Aldehyde-Bisulfite Adduct **16***

	Material	Amount (g)
Limiting Reagent Input	4-piperidylmethanol **12**	1.00

Product Output	Aldehyde-Bisulfite Adduct **14**	1.08
Reagents	K_2CO_3	1.80
	TPGS-750-M	0.06
	Methyl Chloroformate	0.98
	Iodobenzene Diacetate	6.15
	TEMPOL	0.07
	Sodium Metabisulfite	1.16
Solvents	THF	0.89
	EtOH (antisolvent)	12.63
	EtOH (filter cake wash)	1.60
Aqueous	Water (reaction)	2.90
Totals	All Materials	29.24
	Reagents	10.22
	Solvents	15.12
	Aqueous	2.90

Step PMI	27.1
Step PMI Solvents	14.0
Step PMI Water	2.7

*6.4. Preparation of Amine **6***

	Material	**Amount (g)**
Limiting Reagent Input	Amide **5**	150.0
Product Output	Amine **6**	98.0
Reagents	N/A	0
Solvents	Acetonitrile	58.2
Aqueous	Water (reaction)	1400
	4M Aqueous HCl	293.6
	4M Aqueous NaOH	153.2
	Water (filter cake wash)	300.0
Totals	All Materials	2355.0
	Reagents	0
	Solvents	58.2
	Aqueous	2146.8

Step PMI	24.0
Step PMI Solvents	0.6
Step PMI Water	21.9

*6.5. Preparation of **TAK-954 Hydrate***

	Material	**Amount (g)**
Limiting Reagent Input	Amine **6**	90.0
Product Output	TAK-954.H_2O	130.0
Reagents	Bisulfite Adduct **14**	136.0

	α-Picoline Borane	46.2
	TPGS-750-M	14.4
	TAK-954 Seed	0.90
Solvents	Methanol	180.0
Aqueous	Water (reaction)	705.6
	1M Aqueous NaOH	563.2
	Water (crystallization)	900.0
	Water (filter cake wash)	180.0
Totals	All Materials	2816.3
	Reagents	197.5
	Solvents	180
	Aqueous	2349

Step PMI	21.7
Step PMI Solvents	1.4
Step PMI Water	18.1

*6.6. Preparation of **TAK-954***

	Material	**Amount (g)**
Limiting Reagent Input	TAK-954.H_2O	130.0
Product Output	TAK-954	115.0
Reagents	N/A	0
Solvents	Acetonitrile (crystallization)	1021.8
	Acetonitrile (filter cake wash)	204.4
Aqueous	N/A	0
Totals	All Materials	1356.2
	Reagents	0
	Solvents	1226.2
	Aqueous	0

Step PMI	11.8
Step PMI Solvents	10.7
Step PMI Water	0

6.7. Calculation of Cumulative PMI

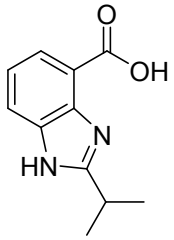
Step	**Step Product**	**MW**	**Yield (%)**	**Usage Factor (kg)***	**Step PMI**	**Cumulative PMI Contribution**	**Step PMI Solvents**	**Cumulative PMI Contribution Solvents**	**Step PMI Water**	**Cumulative PMI Contribution Water**
1	**11**	204.23	79	0.634	24.5	15.5	1.6	1.0	19.9	12.6
2	**5**	400.52	91	1.132	9.2	10.4	0.7	0.8	5.7	6.5
3	**6**	300.41	88	0.747	24.0	17.9	0.6	0.4	21.9	16.4
4	**TAK-954 Hydrate**	473.62	91	1.072	21.7	23.3	1.4	1.5	18.1	19.4
5	**TAK-954**	455.60	97	1.000	11.8	11.8	10.7	10.7	0	0

* Usage Factor = Amount of Compound in kg Required to Produce 1 kg of TAK-954

Cumulative PMI	78.9
Cumulative PMI Solvents	14.4
Cumulative PMI Water	54.9

7. Compound Characterization Data

*7.1. [**11**] 2-isopropyl-1H-benzo[d]imidazole-4-carboxylic acid*



11

Appearance off-white solid

Melting Point 127°C-133°C

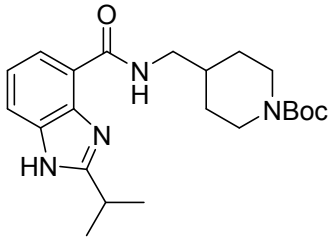
IR ν_{max}/cm^{-1} 3427 (OH), 2978 (NH), 1709 (CO)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.81 (dd, J = 7.6, 1.0 Hz, 1H), 7.32 (t, J = 7.8, 1H), 3.42 (hept, J = 6.9 Hz, 1H), 1.37 (d, J = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 161.7, 140.3, 133.5, 124.4, 121.8, 121.6, 115.3, 27.5, 21.2.

HRMS $C_{11}H_{12}N_2O_2$ TOF MS ES+ calcd: 205.0899; found: 205.0990

*7.2. [**5**] tert-butyl 4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido) methyl)piperidine-1-carboxylate:*



5

Appearance off-white solid

IR ν_{max}/cm^{-1} 3413 (NH), 3185 (NH), 1694 (CO), 1636 (CO)

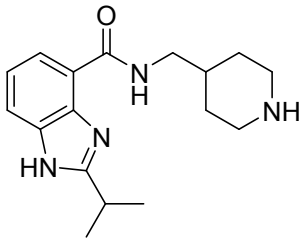
Melting Point 175°C-180°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 4.12 (brs, 2H), 3.47 (brs, 2H), 3.38 (hept, *J* = 7.0 Hz, 1H), 2.72 (t, *J* = 10.2 Hz, 2H), 1.83 (m, 3H), 1.51 (d, *J* = 7.0 Hz, 6H), 1.45 (s, 9H); 1.27 (qd, *J* = 12.5, 4.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.2, 155.0, 140.5, 134.9, 123.1, 122.9, 120.8, 116.4, 79.6, 45.2, 43.9, 36.7, 30.1, 28.7, 28.6, 21.3.

HRMS $C_{22}H_{32}N_4O_3$ TOF MS ES+ calcd: 401.2474; found: 401.2527

*7.3. [**6**] 2-isopropyl-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide*



6

Appearance off-white solid

IR ν_{max}/cm^{-1} 3431 (NH), 3254 (NH), 3097 (NH), 1647 (CO)

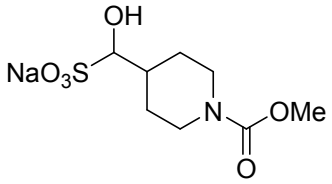
Melting Point 200°C-205°C

^{1}H NMR (400 MHz, $CDCl_3$) A mixture of two rotamers, with a ratio of 3.4:1. Major Rotamer: δ 10.28 (brs, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 3.52 (m, 2H), 3.26 (hept, *J* = 6.9 Hz, 1H), 3.16 (dt, *J* = 12.6, 3.2 Hz, 2H), 2.66 (m, 1H), 1.87 (m, 3H), 1.46 (d, *J* = 6.9 Hz, 6H), 1.35 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) A mixture of two rotamers, with a ratio of 3.4:1. Major Rotamer: δ 166.3, 160.3, 141.1, 134.1, 123.2, 122.6, 122.3, 114.0, 46.4, 45.5, 36.9, 31.3, 29.0, 21.4.

HRMS $C_{17}H_{24}N_4O$ TOF MS ES+ calcd: 301.1950; found: 301.2037

*7.4. [**16**] sodium hydroxy(1-(methoxycarbonyl)piperidin-4-yl)methanesulfonate*



16

Appearance white solid

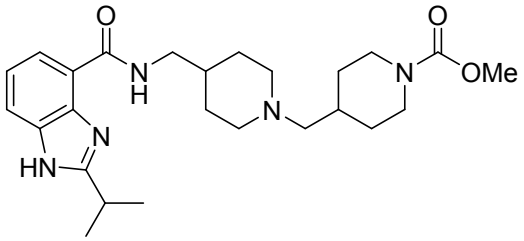
IR ν_{max}/cm^{-1} 3508 (OH), 1686 (CO)

^{1}H NMR (400 MHz, D_2O) A mixture of two rotamers, with a ratio of 1:1. Rotamer 1: δ 4.27 (d, *J* = 5.5 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 2H), 3.70 (s, 3H), 2.89 (d, *J* = 12.0 Hz, 2H), 2.11 (m, 1H), 1.99 (d, *J* = 13.3 Hz, 2H), 1.38 (m, 2H). Rotamer 2: δ 4.27 (d, *J* = 5.5 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 2H), 3.70 (s, 3H), 2.89 (d, *J* = 12.0 Hz, 2H), 2.11 (m, 1H), 1.87 (d, *J* = 13.3 Hz, 2H), 1.47 (m, 2H).

^{13}C NMR (100 MHz, D_2O) A mixture of two rotamers, with a ratio of 1:1. Rotamer 1: δ 86.8, 52.9, 43.7, 37.6, 28.6. Rotamer 2: δ 86.8, 52.9, 43.6, 37.6, 26.0

HRMS $C_8H_{14}NNaO_6S$ TOF MS ES+ calcd: 276.0440; found: 276.0473

*7.5. [**TAK-954**] methyl 4-((4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido)methyl)piperidin-1-yl)methyl)piperidine-1-carboxylate*



TAK-954

Appearance white solid

IR ν_{max}/cm^{-1} 3300 (NH), 3125 (NH), 1697 (CO), 1641 (CO)

Melting Point 145°C-150°C

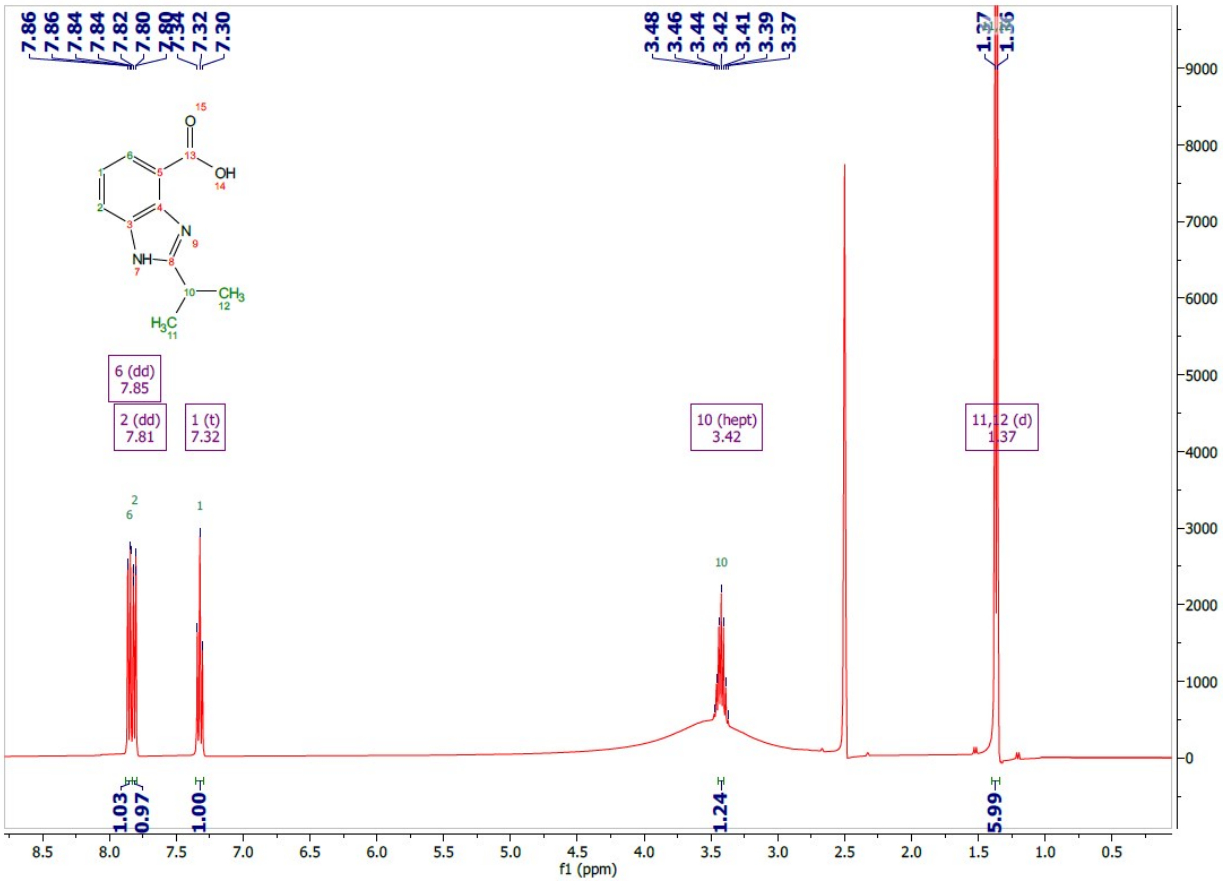
^{1}H NMR (400 MHz, $CDCl_3$) A mixture of two rotamers, with a ratio of 5:1. Major Rotamer: δ 10.26 (brs, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 4.12 (brs, 2H), 3.68 (s, 3H), 3.50 (m, 2H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.99 (brs, 2H), 2.75 (t, *J* = 12.8 Hz, 2H), 2.25 (m, 2H), 2.02 (m, 2H), 1.82 (m, 8H), 1.46 (d, *J* = 7.0 Hz, 6H), 1.12 (m, 2H).

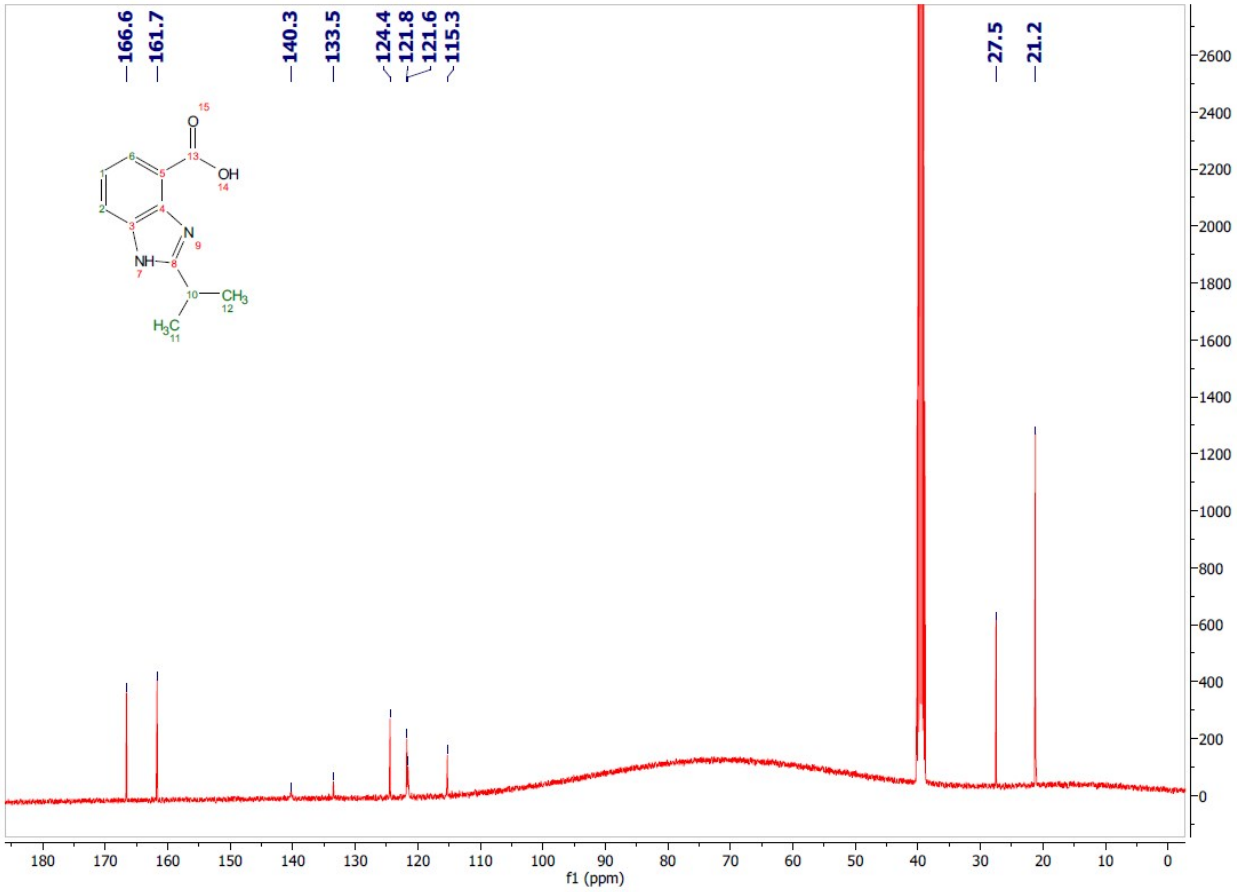
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.5*, 160.4, 161.9*, 156.1, 141.1, 139.5*, 134.0, 126.7*, 125.5*, 123.2, 122.5, 122.3, 118.8*, 114.8*, 114.1, 64.7, 54.1, 52.7, 45.0, 43.9, 35.8, 33.2, 31.0, 29.0, 28.4, 22.2, 21.5. (* signals from minor rotamer)

HRMS $C_{25}H_{37}N_5O_3$ TOF MS ES+ calcd: 456.2896; found: 456.2962

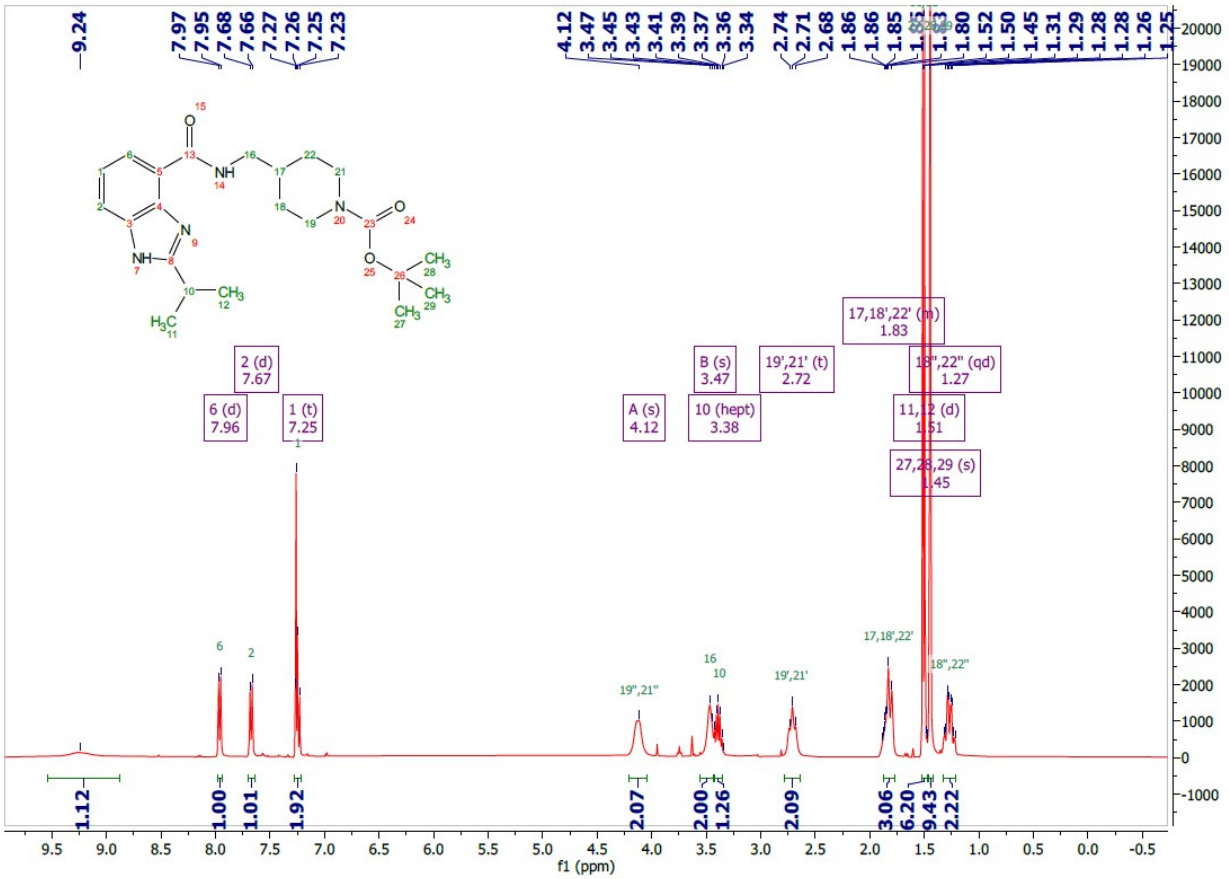
8. **NMR Spectra**

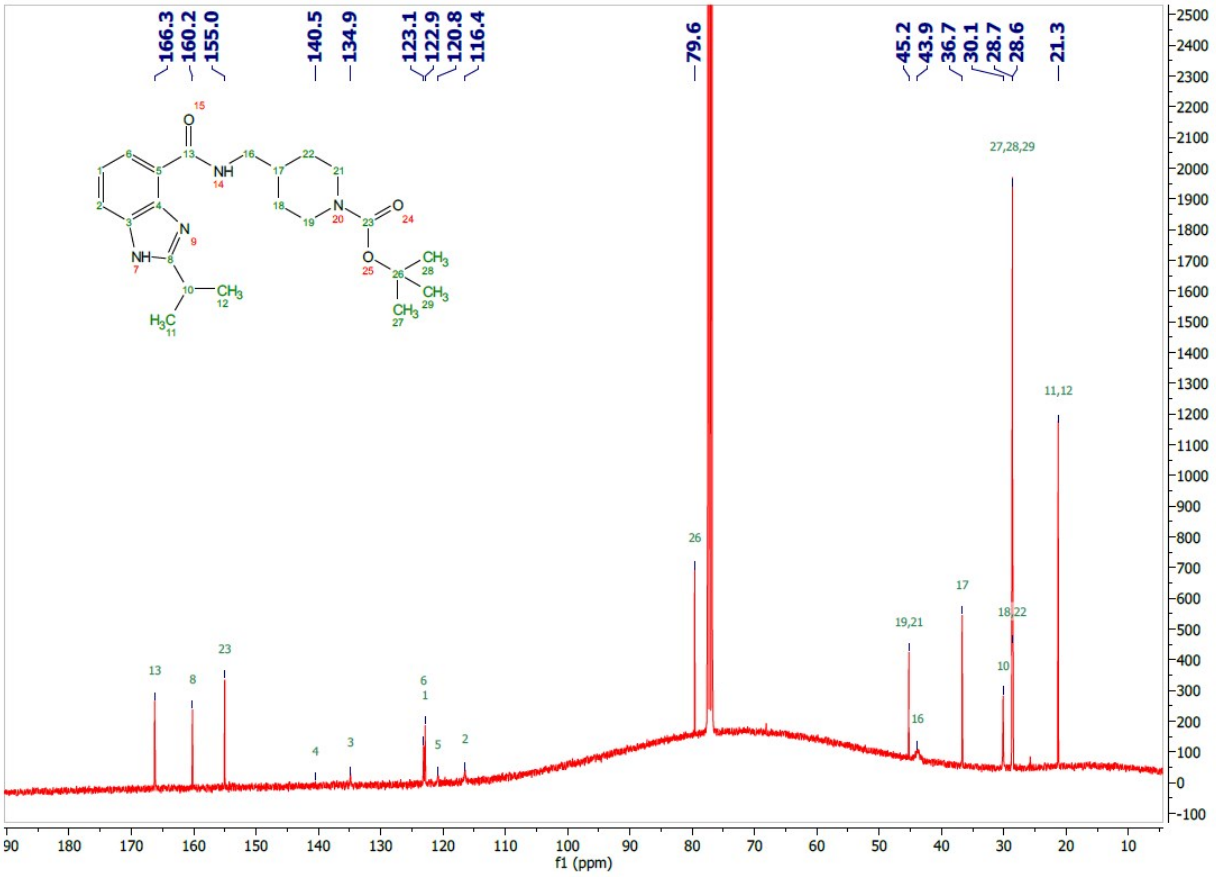
8.1. 2-isopropyl-1H-benzo[d]imidazole-4-carboxylic acid



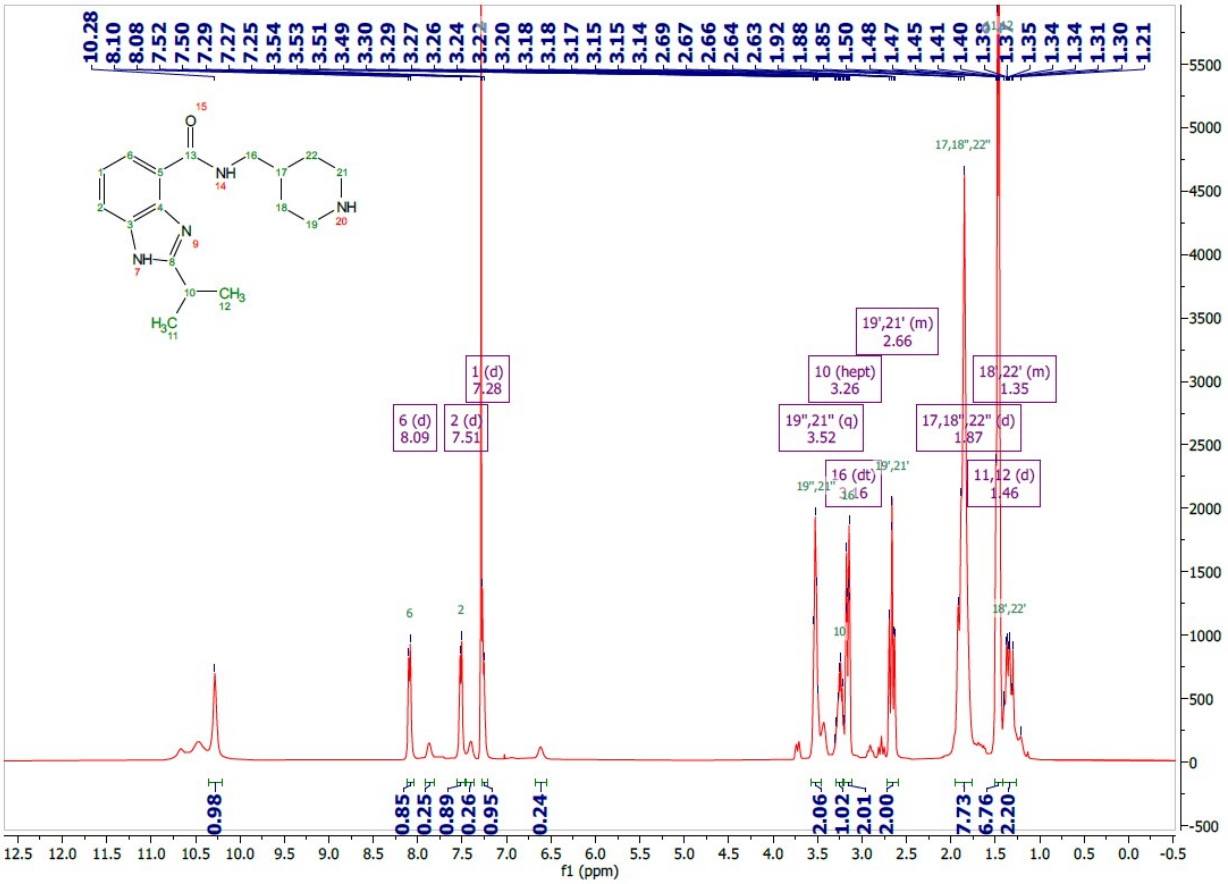

166.6
161.7
140.3
133.5
124.4
121.8
121.6
115.3
27.5
21.2
O
15
13
OH
14
6
5
1
2
4
3
N
9
NH
7
8
10
CH3
12
H3C
11
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

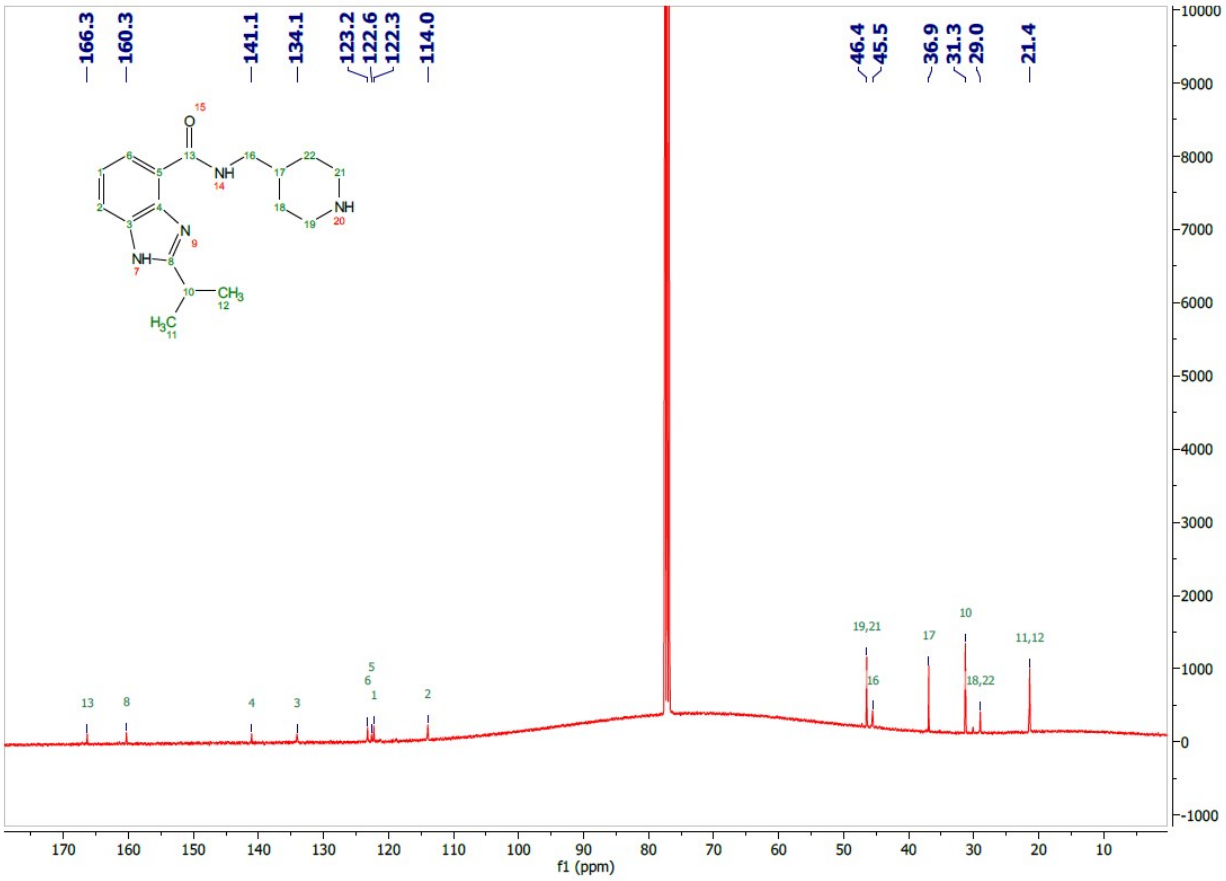
8.2. tert-butyl 4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido) methyl) piperidine-1-carboxylate



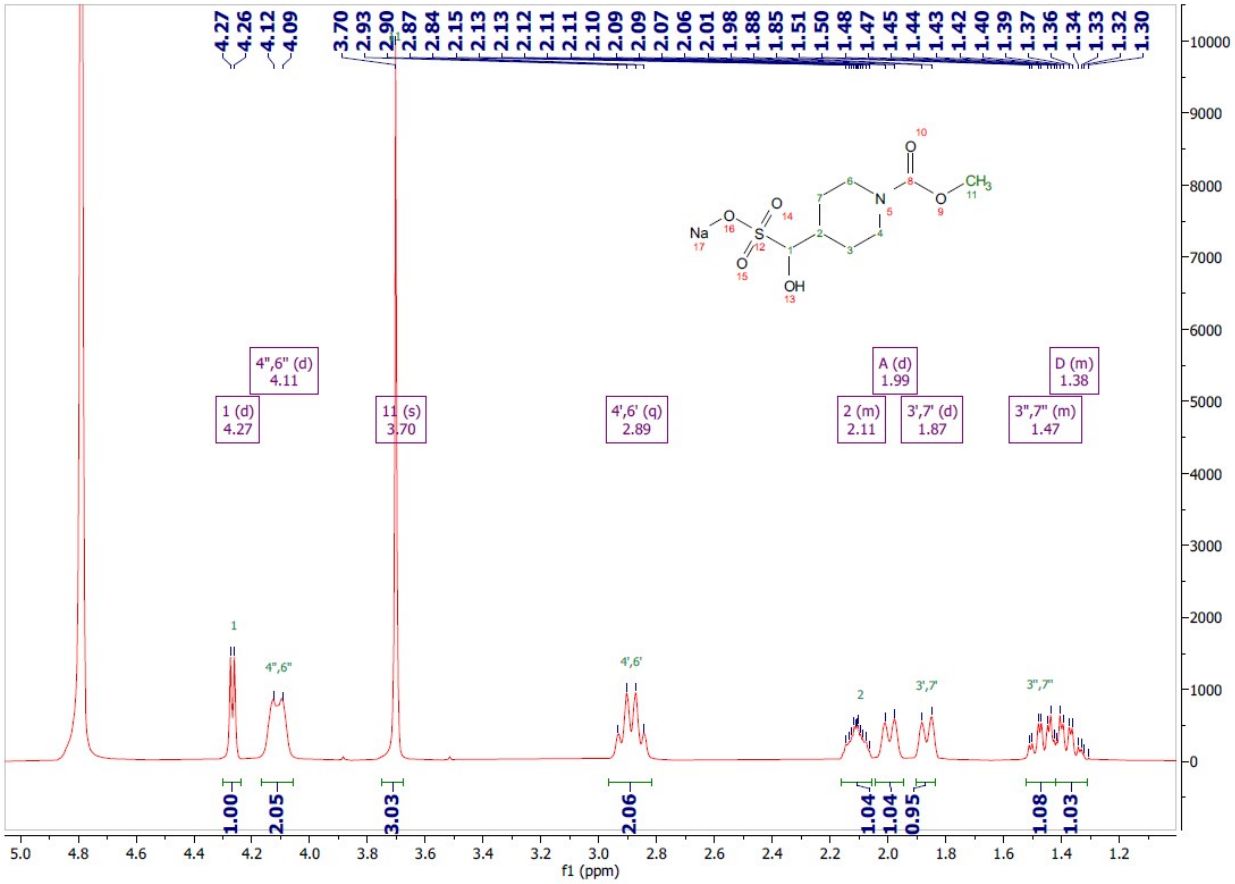

166.3
160.2
155.0
140.5
134.9
123.1
122.9
120.8
116.4
79.6
45.2
43.9
36.7
30.1
28.7
28.6
21.3
27,28,29
11,12
26
17
19,21
18,22
13
8
23
6
1
4
3
5
2
16
10
f1 (ppm)

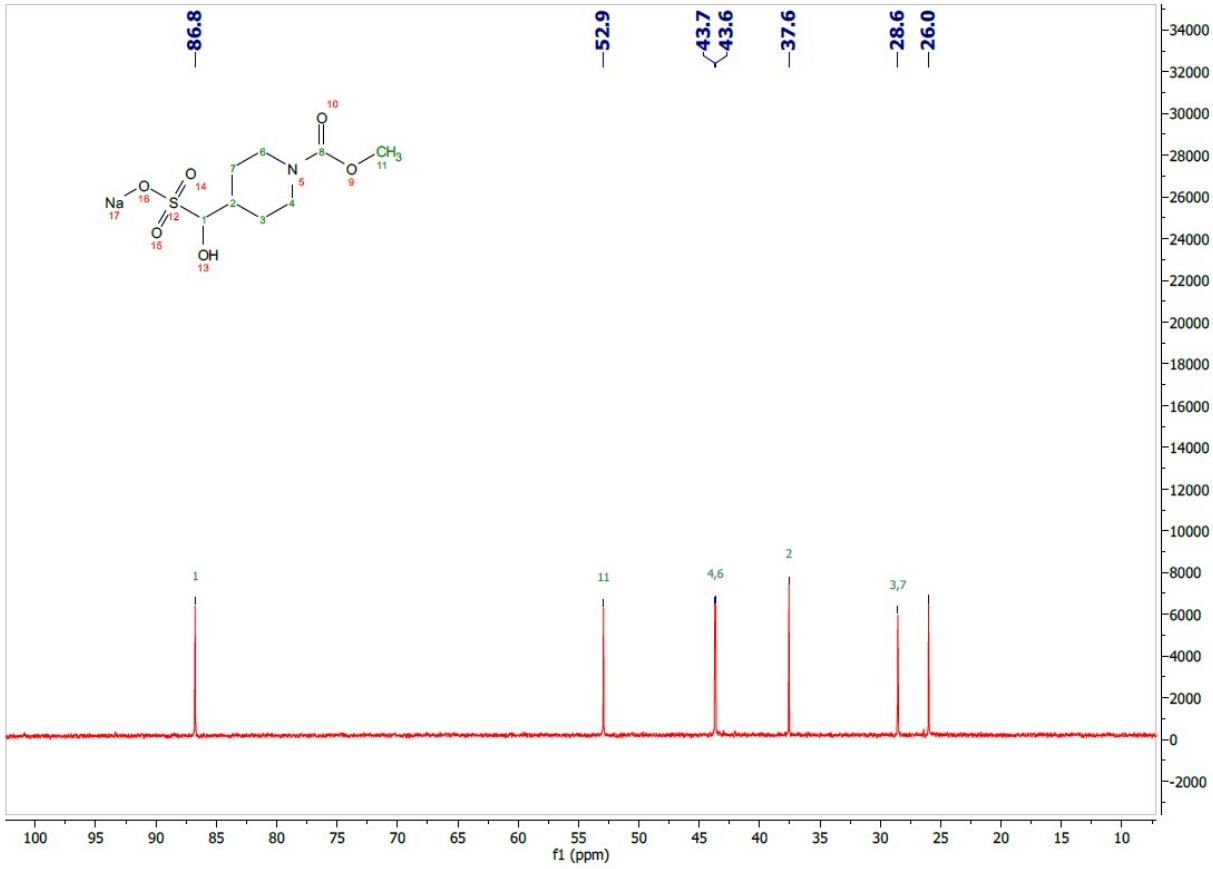
8.3. 2-isopropyl-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide



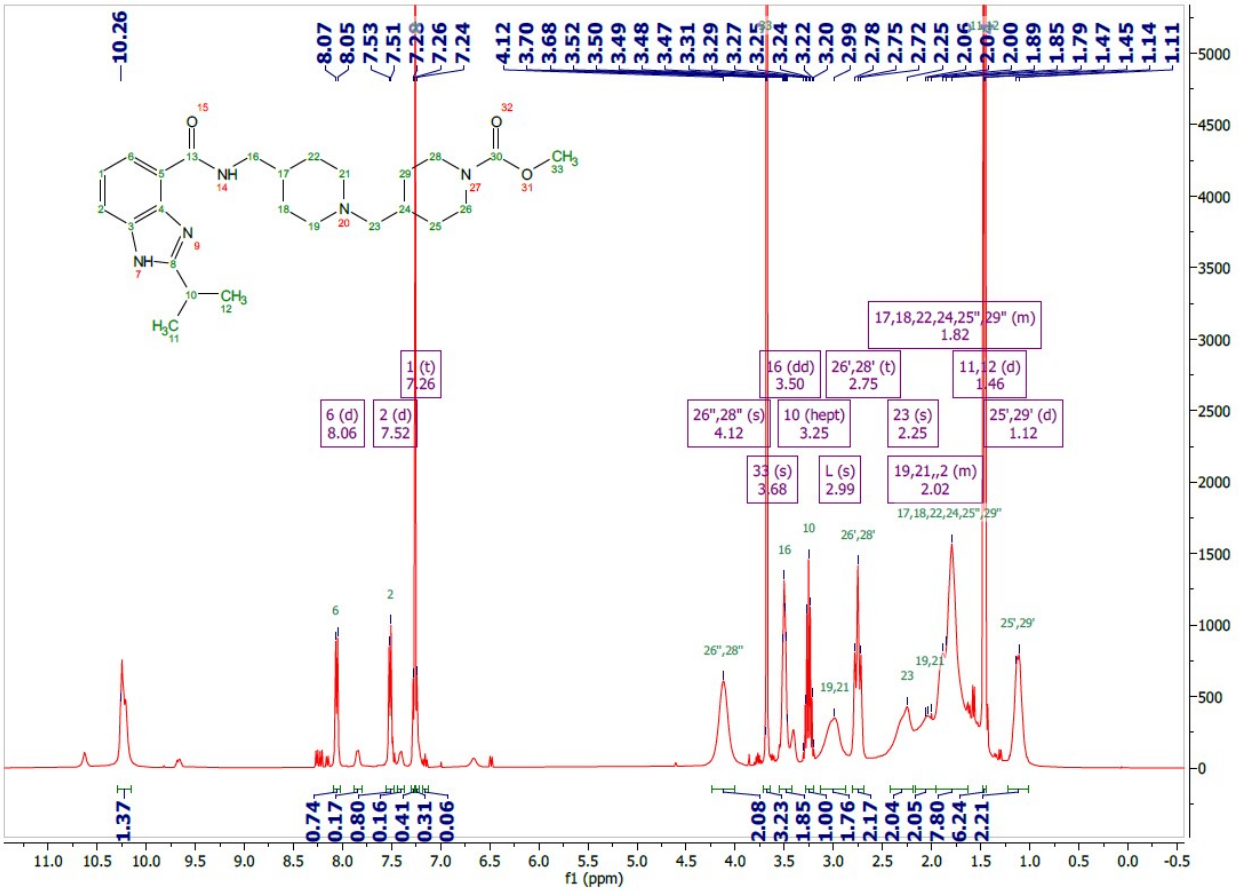

166.3
160.3
141.1
134.1
123.2
122.6
122.3
114.0
46.4
45.5
36.9
31.3
29.0
21.4
19,21
17
10
11,12
16
18,22
13
8
4
3
5
6
1
2
f1 (ppm)

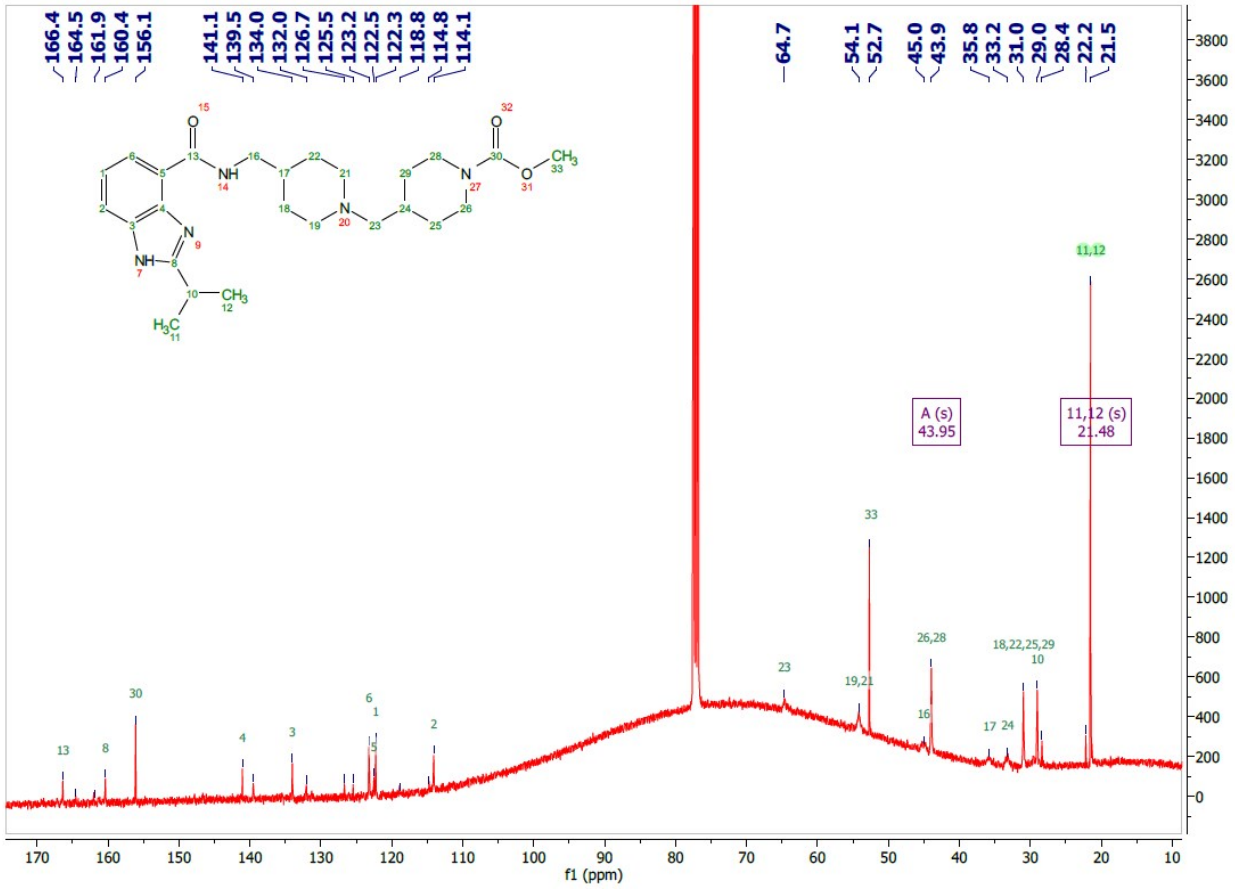
8.4. sodium hydroxy(1-(methoxycarbonyl)piperidin-4-yl)methanesulfonate

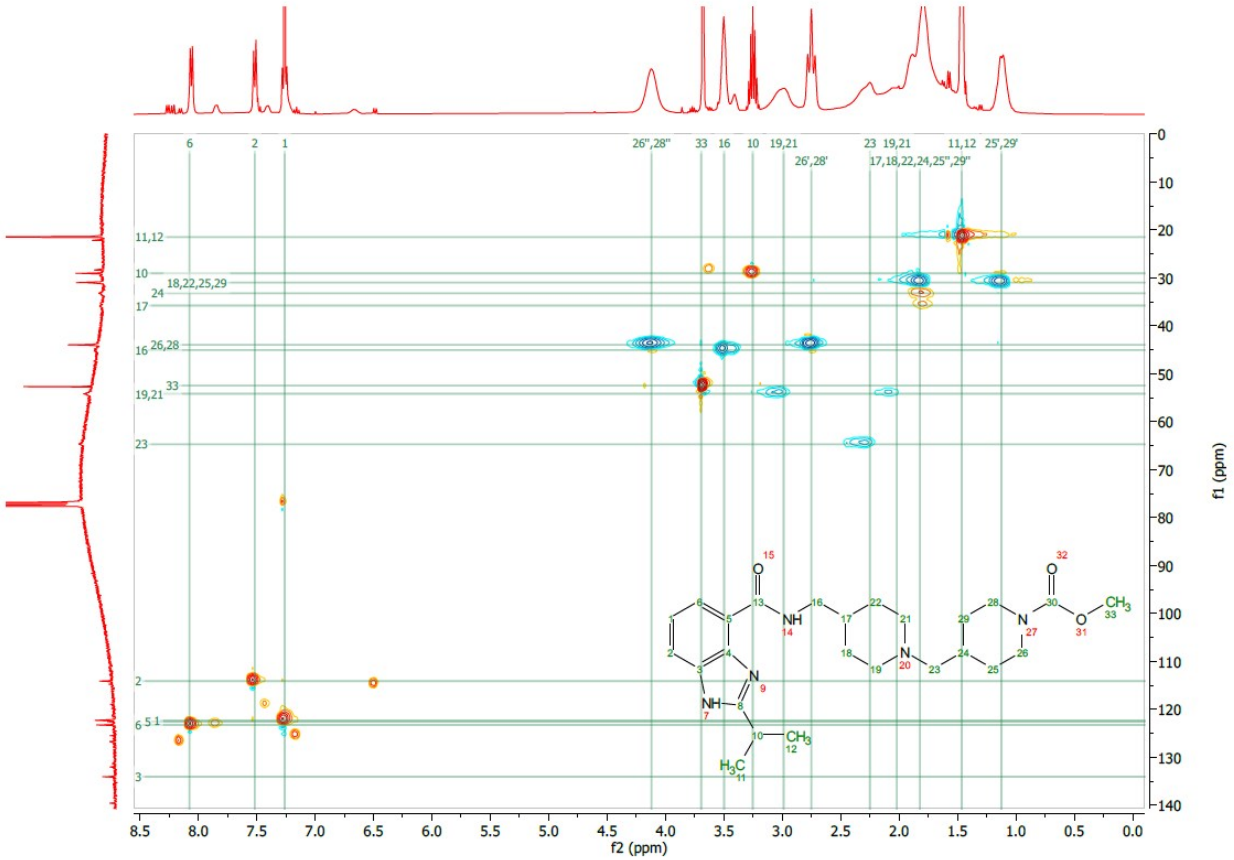


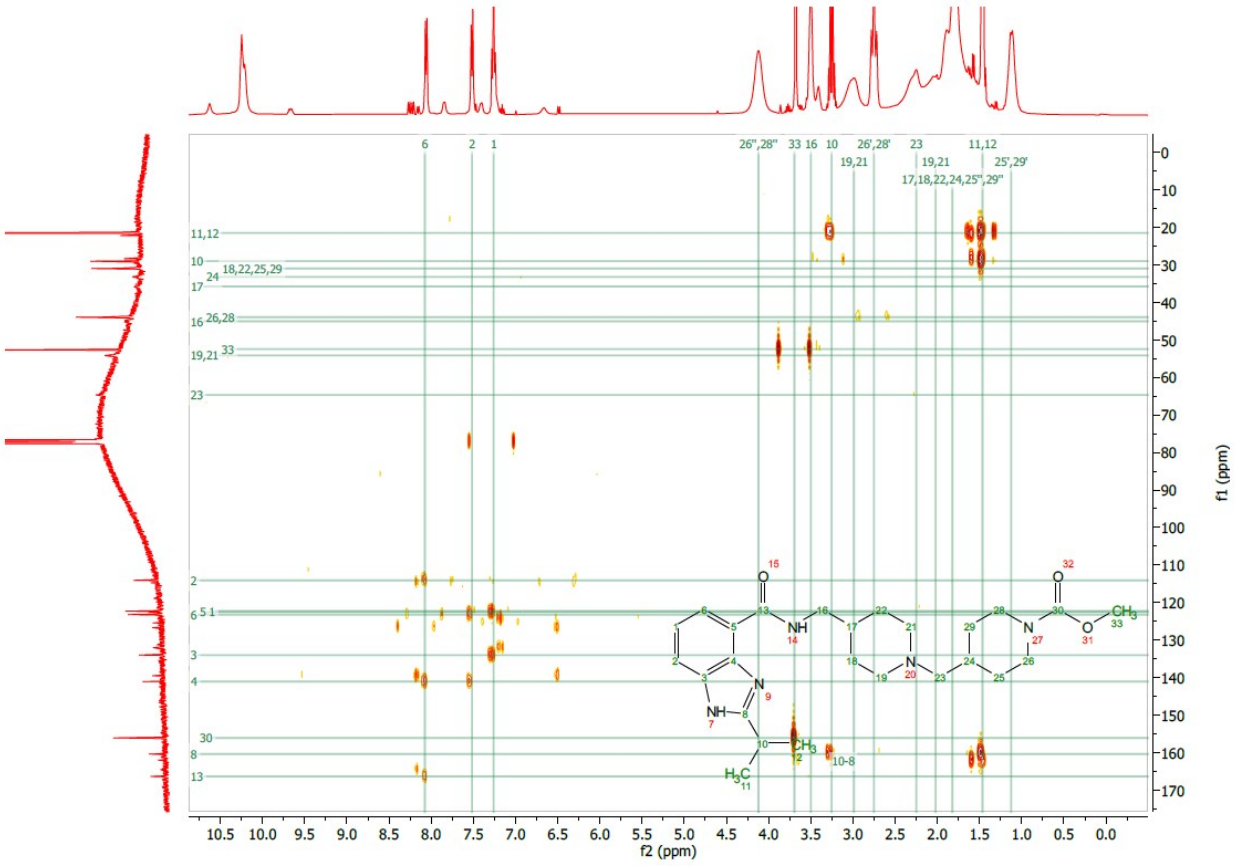

86.8
52.9
43.7
43.6
37.6
28.6
26.0
1
11
4,6
2
3,7
f1 (ppm)

8.5. methyl 4-((4-((2-isopropyl-1H-benzo[d]imidazole-4-carboxamido)methyl)piperidin-1-yl)methyl)piperidine-1-carboxylate




166.4
164.5
161.9
160.4
156.1
141.1
139.5
134.0
132.0
126.7
125.5
123.2
122.5
122.3
118.8
114.8
114.1
64.7
54.1
52.7
45.0
43.9
35.8
33.2
31.0
29.0
28.4
22.2
21.5
A (s)
43.95
11,12 (s)
21.48
11,12
33
26,28
18,22,25,29
10
23
19,21
16
17 24
30
6
1
2
13
8
4
3
5
f1 (ppm)


f2 (ppm)
f1 (ppm)
6
2
1
26'',28''
33
16
10
19,21
26',28'
23
19,21
17,18,22,24,25'',29''
11,12
25',29'
11,12
10
18,22,25,29
24
17
16
26,28
19,21
33
23
2
6
5
1
3
NH
N
NH
CH3
H3C
CH3
O
O
O
N
N


f2 (ppm)
f1 (ppm)