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# Efficient and scalable synthesis of thiazole fused benzazepine as a D2 partial agonist

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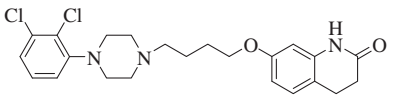
ABSTRACT

The development of an efficient and scalable synthetic route to prepare the selective D2 partial agonist (**1**) is described here. Regioselective nitration of tetrahydrobenzazepine **2**, followed by reductive amination, hydrogenation, and oxidative cyclization afforded **1** in good yield, without the need of column chromatography.

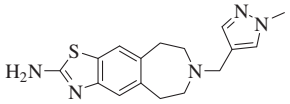


One consistent feature across the most marketed antipsychotics is their functional D2 antagonism, though other various pharmacological activities also contribute to the overall efficacy/tolerability profile.[1] In the last decade, Aripiprazole (Abilify®), a D2 partial agonist with activities at multiple 5-HT receptors, was approved by the FDA for the treatment of psychiatric disorders, including schizophrenia, bipolar disorder, and major depressive disorder.[2] It has reportedly demonstrated antipsychotic efficacy and an improved side effect profile over existing therapies.[3] This prompted the active discovery and development of various D2 partial agonists as clinical candidates from pharmaceutical companies.[4] Our own efforts in this research area identified compound **1** (Fig. 1) as a partial agonist of the D2 receptor (D2 binding $K_i$ 15 nM, D2 functional antagonism $IC_{50}$ 870 nM, 31% partial agonist effect). In order to support further investigations of this compound, a scalable, efficient, and high yielding synthesis was desired. This Letter details our efforts in developing the improved route.

The tetrahydro-1*H*-benzo[d]azepine motif displayed in **1** is arguably one of the more privileged structures in medicinal chemistry.[5] Our medicinal chemistry route (Scheme 1) to **1** started from commercially available tetrahydrobenzazepine **2**,[6] which was first acylated, and then nitrated to afford **3**. Subsequent protective group manipulation and hydrogenation of the nitro group provided intermediate **4**. Aniline **4** was treated with potassium thiocyanate and copper sulfate pentahydrate in refluxing methanol[7] to give a 2.5:1 mixture of isomeric benzoaminothiazole **5a** and **5b**, which was separated by Supercritical Fluid Chromatography (SFC). The linear isomer **5a** was then treated with TFA to remove the Boc group, and the resulting secondary amine reacted with 1-methyl-1*H*-pyrazole-4-carbaldehyde to provide compound **1** in 39% yield.



**Aripiprazole**



**1**

**Figure 1.** Chemical structure of D2 partial agonists: Aripiprazole and **1**.

The late diversification step in this synthetic route had served us well during our structure activity relationship (SAR) exploration campaign. However, we were not satisfied with the overall efficiency and scalability of this route. Several steps were spent on protective group manipulation, and extensive purification effort was required to separate the linear isomer **5a** from its angular isomer **5b**. Minor impurities were also always observed in the last reductive amination step, presumably stemming from the weak reactivity of free $NH_2$ in the aminothiazole group. Once compound **1** was identified as a potential candidate drug, we embarked on the exploration of a more efficient synthesis to provide sufficient supply of **1** to support its further profiling.

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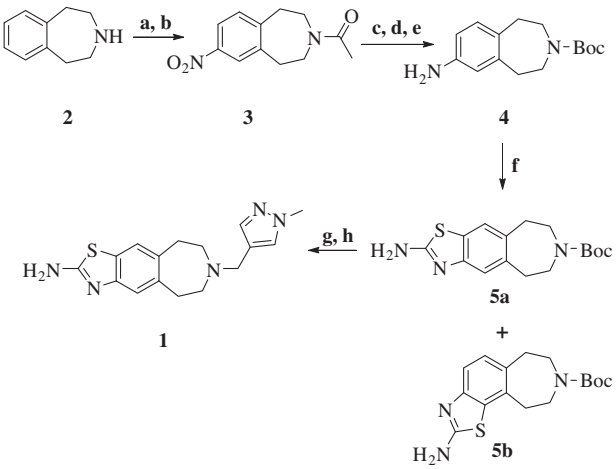



**Scheme 1.** Reagents and conditions: (a) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, 50%; (b) conc. $HNO_3$, 86%; (c) 37% aq HCl, Δ, 89%; (d) $Boc_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 92%; (e) Pd/C, $H_2$, MeOH, 93%; (f) 4 equiv KSCN, 2 equiv $CuSO_4{\cdot}5H_2O$, MeOH, reflux; **5a**: 53%, **5b**, 20%; (g) TFA, $CH_2Cl_2$, 90%; (h) 1-methyl-1*H*-pyrazole-4-carbaldehyde, $NaBH_3CN$, AcONa, MeOH, 39%.

## Nitration of compound 2

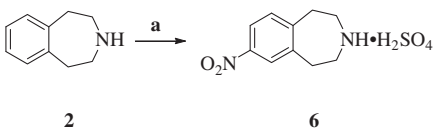
To avoid protective group manipulation, we first explored the direct nitration of tetrahydrobenzazepine **2** (Scheme 2).[8] Slow addition of a slight excess of nitric acid to a solution of **2** in sulfuric acid and TFA at 0 °C resulted in a clean and regioselective formation of the desired nitro compound **6**. The crude reaction mixture was then diluted with EtOAc to isolate **6** as its hydrogensulfate salt in 90% yield.[9] In the absence of TFA or replacing it with AcOH, low conversion and poor yield were observed.

## Cyclization via pyrazole carboxamide 7

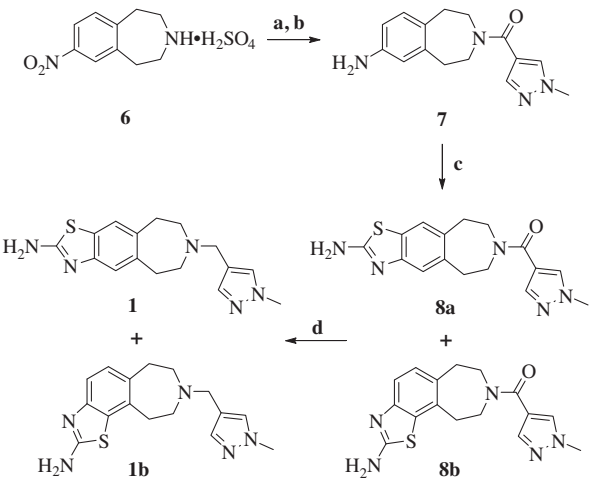
As shown in Scheme 3, amide coupling of **6** and subsequent nitro reduction cleanly gave aniline **7** in 97% yield. Aniline **7** was then treated with potassium thiocyanate and copper sulfate pentahydrate in refluxing methanol to give a 3:1 mixture of **8a** and **8b** in 94% yield. The ensuing amide reduction of **8a** and **8b** using borane resulted in a low yield, probably due to the limited solubility of these compounds in organic solvents.

## Cyclization via pyrazole methyl amine 10

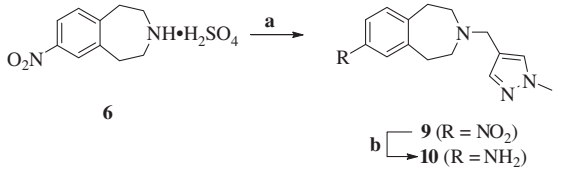
Next we turned our attention to the preparation and cyclization reaction of pyrazole methyl amine **9**. As shown in Scheme 4, reductive amination of nitrobenzazepine **6** with 1-methyl-1*H*-pyrazole-4-carbaldehyde proceeded cleanly with $NaBH_3CN$ as the reductant. The slight excess of aldehyde used in the reaction was reductively coupled with sarcosine after the completion of the reaction. Simple recrystallization under basic aqueous conditions removed sarcosine and its derivatives, therefore allowing the isolation of the desired product **9** as a yellow solid in 97% yield.[10] We found that $NaBH(OAc)_3$ was not an effective reductant for this reaction. Catalytic hydrogenation of **9** in EtOH in a Parr shaker (50 psi, 40–45 °C)




**Scheme 2.** Reagents and conditions: (a) 1.1 equiv $HNO_3$, 4 equiv $H_2SO_4$, 8 equiv TFA, 0 °C, 90%.




**Scheme 3.** Reagents and conditions: (a) 1-methyl-1*H*-pyrazole-4-carboxylic acid, TBTU, DIPEA, DMF, 98%; (b) Pd/C, $H_2$, EtOH, 100%; (c) 4 equiv KSCN, 2 equiv $CuSO_4{\cdot}5H_2O$, MeOH, reflux; 94%; (d) $BH_3$-DMS, THF, reflux, 40%.




**Scheme 4.** Reagents and conditions: (a) 1-methyl-1*H*-pyrazole-4-carbaldehyde, $NaBH_3CN$, AcONa, MeOH, 97%; (b) $H_2$, 10% Pd/C, EtOH, 76%; or H-Cube Midi, 10% Pd/C, 60 bar, 50 °C, AcOH, 0.14 M in MeOH, 10 mL/min, 100%.

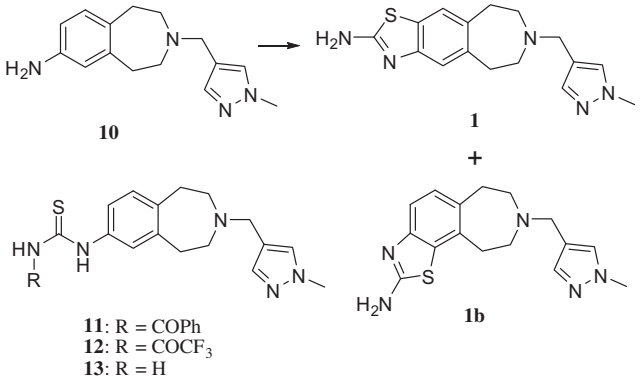
gave aniline **10** in 76% yield.[11] Alternatively, flow hydrogenation also proved to be effective. A solution of **9** (0.14 M in 10% AcOH in MeOH) was hydrogenated on H-Cube Midi (60 bar, 50 °C, 100% $H_2$ production; flow rate 10 mL/min) using 10% Pd/C cartridge. The resulting solution was concentrated and the residue was partitioned between 1N NaOH and DCM to afford compound **10** in quantitative yield and high purity.

With compound **10** in hand, we explored various conditions with which to form the aminothiazole ring, as detailed in Table 1. Treatment of **10** under the conditions from discovery work using $KSCN/CuSO_4$ in refluxing MeOH with or without the presence of acetic acid gave low conversions (entries 1, 2). Direct conversion from aniline to thiourea **13** using $NH_4SCN$ with TFA resulted in the formation of the corresponding trifluroacetamide **12** in 86% yield (entry 4).

As shown in entry 5, aniline **10** was treated with benzoyl isothiocyanate in MeOH to afford the benzoyl protected thiourea **11**, which was then brominated with N-bromosuccinimide. This resulted in a ~40% yield of a mixture of the regioisomeric thiazoles (15% isolated yield of the desired isomer). One major impurity appeared to be the double addition product of aniline to 2 equiv of benzoyl isothiocyanate. The subsequent deprotection of the benzoyl group using aqueous HBr gave compound **1** in near quantitative yield.

Alternatively in entry 6, the benzoyl protected thiourea intermediate **11** was then treated with NaOMe in MeOH to give the free thiourea intermediate **13** after aqueous workup. After trying several different solvents (TFA, TFA/DCM, etc.,), we found that the optimal conditions for the cyclization involved the treatment of the thiourea with NBS in a mixture solvent system of TFA and MsOH (4:1) at room temperature overnight.[12] Hence, a mixture of compound **1** and **1b** was isolated in greater than 70% yield.

**Table 1**
Thiazole formation from aniline **10**




| Entries | Conditions | Result |
|---|---|---|
| 1 | KSCN, $CuSO_4$, MeOH | 30% of **1** and **1b** |
| 2 | KSCN, $CuSO_4$, MeOH, AcOH | Low conversion |
| 3 | $NH_4SCN$, TFA, NBS | No desired product |
| 4 | $NH_4SCN$, TFA | Formation of trifluroacetamide **12** |
| 5 | (a) PhCONCS; (b) NBS, TFA; (c) HBr, $H_2O$ | **1** (16%) |
| 6 | (a) PhCONCS, MeOH; (b) NaOMe, MeOH; (c) NBS, TFA/MsOH | **1** (50%) |

However, numerous attempts to separate **1** from **1b** through recrystallization of the isolated mixture were not successful. Ultimately, we were able to recrystallize and isolate compound **1** directly from the crude reaction mixture. After removal of the volatiles from the reaction, the residue was diluted with $CH_3CN$ and then treated with an excess of aqueous 5N NaOH. Addition of seed crystals of **1** resulted in selective precipitation and clean isolation of **1** in 50% yield.[13]

In conclusion, we have demonstrated an efficient and scalable synthesis of the D2 partial agonist **1** from tetrahydrobenzazepine **2**, in four steps and 30% overall yield. Regioselective nitration, followed by reductive amination, hydrogenation, and oxidative cyclization and in situ recrystallization afforded more than 60 g of **1** in good yield, without the need of chromatography in the entire synthetic sequence.

## Acknowledgments

The authors are grateful to all members of the excellent drug discovery and development community that once thrived at AstraZeneca-Wilmington. We would like to thank Jennifer Van Anda, James Hall, Xiaomei Ye, Timothy Blake, Don Pivonka, and Russ Spreen for analytical chemistry support; many thanks to the biologists and DMPK staff who supported this effort. We also thank James Muir, ThomasSimpson, Chad Elmore, Dean Brown, and Martin Hentemann for helpful discussions.

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9. 7-Nitro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine monosulfate 6. To a stirred solution of 840 mL of TFA in a 12 L 3-neck RB flask, equipped with a thermometer, mechanical stirring, and dropping funnel with $N_2$ inlet, in an ice bath was added 2,3,4,5-tetrahydro-1*H*-benzo[d]azepine 2 (200 g, 1.36 mol) dropwise over ~0.5 h, followed by the addition of 98% sulfuric acid (296 mL, 5.44 mol) over 15 min. The mixture was then cooled to <5 °C, before the addition of 70% nitric acid (96 mL, 1.49 mol) over ~2 h while maintaining the internal temp lower than 10 °C. The mixture was then stirred in the ice bath for 2 h. 2 L of EtOAc was then added over 0.5 h, followed by the addition of 4 L EtOAc in a single portion and the mixture was stirred overnight in the ice bath. The white precipitate was collected by filtration, washed with EtOAc (2 × 1 L) and dried in vacuo at 50 °C to afford the title compound (356 g, 90%). $^1$H NMR (500 MHz, $d^6$-DMSO) $\delta$ ppm 3.23 (m, 8H), 7.52 (d, $J$ = 8.2 Hz, 1H), 8.06 (dd, $J$ = 8.2, 2.4 Hz, 1H), 8.13 (d, $J$ = 2.4 Hz, 1H), 8.91 (br. s., 2H).
10. 3-((1-methyl-1*H*-pyrazol-4-yl)methyl)-7-nitro-2,3,4,5-tetrahydro-1H-benzo-[d]azepine, 9. To a 22 L 3-neck RB flask in an ambient temperature water bath was charged with 7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine monosulfate 6 (400 g, 1.38 mol) and sodium acetate (237 g, 2.89 mol) as solids, followed by 5 L MeOH. 1-methyl-1*H*-pyrazole-4-carbaldehyde (176 g, 1.60 mol) was then added in a single portion. The mixture was stirred for ~1 h, before the addition of sodium cyanoborohydride (143 g, 2.27 mol) in three portions over 15 min. After 2 h, additional sodium cyanoborohydride (13 g) was added, and it was stirred for another 4 h. Sarcosine (19 g, 0.21 mol) was then added and it was stirred at rt overnight. The solution was cooled to ~10 °C, before the addition of 8 L water over 0.5 h while cooling in an ice bath. Then 2.5 L of 2N NaOH solution was added over 2.5 h (pH > 12). Additional 1.5 L water was added in a single portion. It was cooled in an ice bath and stirred overnight. The precipitate was collected by filtration, washed with water (2 × 1 L), and dried in vacuum at 50–60 °C to afford the title compound (381.7 g, 97%). $^1$H NMR

(500 MHz, $d^6$-DMSO) $\delta$ ppm 2.49–2.53 (m, 4H), 2.96–2.99 (m, 4H), 3.28 (s, 2H), 3.78 (s, 3H), 7.28 (s, 1H), 7.38 (d, $J$ = 8.0 Hz, 1H), 7.54 (s, 1H), 7.95–7.80 (m, 2H).

11. 3-((1-methyl-1*H*-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-amine, 10. To a suspension of 10% Pd/C (5 g) in 300 mL of abs. EtOH under $N_2$, was added a solution of 3-((1-methyl-1*H*-pyrazol-4-yl)methyl)-7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (9, 100 g, 0.35 mol) in 1200 mL of EtOH. It was hydrogenated on a Parr shaker at 50 psi at rt for ~1 mol h, then heated to 40–45 °C for 3 h. It was then cooled to rt, purged with $N_2$ for 15 min before filtering off the catalyst. The filtrate was concentrated to give an oil which was dissolved in 600 mL of 1N HCl, and extracted once with $CH_2Cl_2$ (300 mL). The aqueous layer was then basified to pH 9 with 500 mL of 2N NaOH and extracted with $CH_2Cl_2$ (500 mL, then 3 × 250 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give an orange–yellow solid. It was triturated with 300 mL of diethyl ether while stirring for 0.5 h to give the title compound (68.3 g, 76%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 2.56–2.59 (m, 4H), 2.79–2.81 (m, 4H), 3.51 (br. s., 2H), 3.55 (s, 2H), 3.86 (s, 3H), 6.41–6.44 (m, 2H), 6.85 (d, $J$ = 7.5 Hz, 1H), 7.26 (s, 1H), 7.37 (s, 1H).
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13. 7-(1-methyl-1*H*-pyrazol-4-ylmethyl)-6,7,8,9-tetrahydro-5*H*-1-thia-3,7-diaza-cyclohepta[f]inden-2-ylamine, 1. To a stirred solution of 3-((1-methyl-1*H*-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-amine, 10 (100.0 g, 0.39 mol) in 800 mL of MeOH in a 2-neck RB flask was added benzoyl isothiocyanate (70 g, 0.43 mol) over 0.5 h, while maintaining the temperature between 25 and 30 °C using ice/water bath. It was stirred at this temp for 1 h, before the addition of 25 wt % NaOMe in MeOH solution (104 mL, 1.82 mol) over 15 min. After 1 h, the solution was concentrated and the resulting oil was partitioned between 1000 mL of $CH_2Cl_2$ and 800 mL of $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 300 mL). The combined organic layers were washed with brine (400 mL), dried with $Na_2SO_4$ filtered and concentrated to give a light yellow solid which was triturated with diethyl ether to afford the thiourea intermediate 13 (86.7 g, 71%). The solid was added portion wise over 10 min to 380 mL of TFA and 95 mL of methanesulfonic acid in an ice-cooled 3-neck RB flask bath equipped with a mechanical stirrer, thermometer, and $N_2$ inlet. After 1 hr, it was added a solution of N-bromosuccinimide (51.5 g, 0.29 mol) in 140 mL of TFA over 30 min, maintaining the temperature between 10 and 15 °C. The mixture was stirred at rt overnight and then concentrated on a rotovap under high vacuum to remove most TFA. The resulting oil was dissolved in 800 mL of MeCN and transferred to a 3 L single-neck flask with a mechanical stirrer, thermometer, and $N_2$ inlet. The solution was treated with 5N NaOH (900 mL) over ~0.5 h, while maintaining the temperature between 25 and 30 °C with an ice/$H_2O$ bath. It was next placed in a 40 °C water bath before adding seed crystals. The water bath was removed, and then stirred for 1.5 h. The precipitate was collected by filtration, washed with 135 mL of 1: 2 $CH_3CN/H_2O$ and with 450 mL of $H_2O$, and then dried in vacuum at 50–60 °C for 2 h to afford the title compound (61.5 g, 50%). $^1$H NMR (500 MHz, $d^6$-DMSO) $\delta$ ppm 2.43–2.49 (m, 4H) 2.78–2.85 (m, 4H) 3.46 (s, 2H) 3.77 (s, 3H), 7.07 (s, 1H) 7.26 (s, 2H) 7.27 (s, 1H) 7.33 (s, 1H) 7.53 (s, 1H); HRMS ($C_{16}H_{19}N_5S$) $[M+H]^+$: 314.1434 (Calcd), 314.1433 (obs.).