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First synthesis of thiazepino[3,4-a]isoquinolines, a facile new synthetic route to diazepino[3,4-a]isoquinolines and assessment of their dopamine and σ receptor affinities

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Abstract

Heterocycles that bear the novel 5,6,14,14a-tetrahydro-8H-benzo[6,7][1,4] thiazepino[3,4-a]isoquinoline and the 5,6,14,14a-tetrahydro-8H-13l2-benzo [6,7][1,4]diazepino[3,4-a]isoquinoline frameworks were synthesized in a facile manner. These tetrahydroprotoberberine (THPB)-inspired scaffolds demonstrate selective affinity for the σ_1 R in contrast to the naturally occurring THPB congeners that show D_1 R and σ_2 R selectivity.

As members of the isoquinoline class of alkaloids, tetrahydroprotoberberine (THPB) alkaloids have been the focus of several synthetic and pharmacological studies. THPBs have been isolated from a number of plant sources including members of the Menispermaceae, Annonaceae, Papaveraceae, and Euphorbiaceae families.^[1–7] In terms of structural variations in naturally occurring THPBs, Mother Nature has sought to decorate the core THPB template with oxygen-bearing functionalities on the aromatic rings of the tetracyclic scaffold. In this regard the presence of oxygenated functionalities at C2 and C3 of ring A is a particularly common motif in naturally occurring THPBs.

With regard to biological activities, THPBs have enjoyed a rich history as ligands for dopamine receptors.^[8] THPBs such as (*S*)-stepholidine, (*S*)-isocorypalmine, (*S*)-govadine, and (*S*)-tetrahydropalmatine (Figure 1) have featured in several studies investigating their bioactivities as dopamine receptor ligands.^[9–14]

There are five subtypes of dopamine receptor (D_1 R– D_5 R) and these are grouped into two families: D_1 -like and D_2 -like based on differences in signal transduction mechanisms and structure. The D_1 -like family includes the structurally related D_1 R and D_5 R subtypes, while the D_2 -like family is represented by D_2 R– D_4 R.^[15] Structure-activity relationship (SAR) studies to date indicate that THPBs exert a preference for binding to D_1 -like receptors although several compounds also display good affinity for D_2 -like receptors.^[9,11,13,16] Their

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SUPPORTING INFORMATION

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profound dopamine receptor activities and interesting polypharmacology have led to the examination of THPBs in animal studies relevant to dopamine-related disorders including schizophrenia, Parkinsons disease, and drug abuse.^[12,14,17–25]

Our lab recently discovered a number of THPBs with strong D₁R affinity (ranging in K_i values from 6 to 40 nM) and strong σ_2 receptor (σ_2 R) affinity (ranging in K_i values from 1 to 107 nM).^[10] The σ_2 R is highly expressed in a number of cancers and has been targeted for both cancer diagnosis and cancer therapy.^[26–30] Within the central nervous system (CNS) realm, the related σ_1 receptor (σ_1 R) is known to play a role in depression, addiction and schizophrenia (among other neuropsychiatric disorders).^[31–34] THPBs thus remain a promising scaffold for the identification of novel CNS receptor ligands, pharmacological probes and therapeutic drug leads.

We are interested in the structural diversification of THPBs towards the identification of novel, CNS receptor ligands and, a therapeutic drug leads. In that regard, we were curious to examine the extent to which expansion of the ring C moiety of THPBs via formation of heterocyclic motifs would impact affinity of the scaffold for dopamine and σ receptors. In this manuscript, we describe efforts in this vein, wherein the ring C motif of the THPB framework is expanded via the inclusion of sulfur and nitrogen atoms in the synthesis of THPB-inspired thiazepino and diazepino derivatives respectively. We also report for the first time, the pharmacological evaluation of these novel natural product-inspired heterocyclic scaffolds at dopamine and σ receptors.

The synthesis of compounds containing the analogous 5,6,14,14a-tetrahydro-8H-benzo [6,7] [1,4]oxazepino[3,4-a] isoquinoline framework (ie, containing an oxygen hetero-atom in ring C instead of sulfur) has been described in the literature. Here, construction of the tetracyclic framework **1a** was effected via an intramolecular Pictet-Spengler reaction of an in situ generated cyclic acyliminium ion derived from **2** to generate racemic derivatives (Figure 2).^[35]

We sought to engage a different retrosynthetic approach to the sulfur-containing thiazepino[3,4-a]isoquinoline framework as depicted in Figure 2. Accordingly, the thiazepino framework **1b** was anticipated to be synthesized from the tetrahydroisoquinoline alcohol intermediate **5**. We envisaged that **5** would be readily transformed into the expected product **1b** via intramolecular *N*-alkylation of the corresponding alkyl chloride (generated in situ). Compound **5** in turn would be derived from imine **6** via reduction with lithium aluminum hydride. Furthermore, we presumed that variations to this route would allow for enantioselective synthesis of **1b** via chiral reduction of the precursor imine **6**. Imine **6** would be derived from readily available amide (**7**) and thiol ester substrate **8**.

We initially targeted synthesis of the racemic thiazepino derivative **12** as a prototype for our synthetic studies. Thus, as depicted in Scheme 1, readily available compound **7**^[36] was reacted with methyl thiosalicylate affording **9**. Bischler-Napieralski cyclization of **9** generated an intermediate imine **10** which was treated with lithium aluminum hydride, thus effecting simultaneous reduction of the imine and ester functionalities to yield tetrahydroisoquinoline **11**. Finally, compound **11** was cyclized to the desired tetracyclic ($\pm$)-

thiazepino[3,4-*a*]isoquinoline **12** by treatment with SOCl₂ (via an in situ generated alkyl chloride intermediate).

Dihydroisoquinoline **10** was used as a key intermediate to synthesize the chiral derivatives. Thus, reduction of **10** with (*R,R*) Noyori's catalyst,^[37] followed by immediate reduction of the ester **13** with lithium aluminum hydride gave the corresponding (*R*) thiazepino enantiomer (**14**). Likewise, the (*S*) enantiomeric product **17** was obtained via the intermediacy of compound **16** which was formed upon treatment of **10** with (*S,S*) Noyori's catalyst. In a manner similar to that depicted for synthesis of the (±)-thiazepino[3,4-*a*]isoquinoline framework (**12**), cyclization of the chiral amino alcohols (**14** and **17**) was achieved by treatment with SOCl₂ to yield the corresponding (*R*-**15**) and (*S*-**18**) isomers respectively.

Following on the successful synthesis of the thiazepino derivatives in Scheme 1, we engaged a similar approach for synthesis of the diazepino[3,4-*a*]isoquinoline scaffold. Thus, the amide **19** was prepared by reaction of **7** with methyl anthranilate (Scheme 2). However, attempts at Bischler-Napieralski cyclization of **19** failed and we were unable to identify any of the desired product **20**.

Fortunately, we were also investigating another route to the diazepino scaffold in parallel, which as it turns out was successful, as shown in Scheme 3. Here, readily available compound **21** was subjected to Bischler-Napieralski cyclization and reduction of the intermediate imine with sodium borohydride to give tetrahydroisoquinoline ester **22**. Coupling of amine **22** with anthranilic acid afforded an intermediate amide which was treated with sodium hydroxide to effect hydrolysis of the ester group. The resulting intermediate anilino acid underwent intramolecular amide coupling with HBTU to effect formation of the tetracyclic compound **23**. Finally, compound **23** was reduced with lithium aluminum hydride to deliver the desired diazepino [3,4-*a*]isoquinoline product **24**.

The synthesis of compounds with a diazepino[3,4-*a*] isoquinoline framework has only been described once in the literature.^[38] The previously described route was serendipitously discovered and required the prior synthesis of nitrated oxoprotoberberine substrates, necessitating multiple synthetic steps. Our route is much shorter, simpler, potentially more versatile for analogue diversification and avoids any complications in synthesis arising from the required nitration reaction of the previous route. Furthermore, we anticipate that the route may be manipulated to allow for synthesis of enantiopure analogues (eg, via the *R* and *S* isomers of **22**).

Compounds **12**, **15**, **18**, and **24** were assayed for affinity at dopamine receptors (D₁R-D₅R) and at σ receptor subtypes (σ_1 R and σ_2 R). These results are summarized in Table 1. The compounds lacked affinity at all dopamine receptors. The racemic thiazepino[3,4-*a*]isoquinoline analogue **12** was devoid of affinity at σ_1 R and σ_2 R. However, the separated *R* and *S* enantiomers (**15** and **18** respectively) both displayed micromolar affinities for the σ_1 R (1.00 and 0.44 μ M respectively). The *R* thiazepino enantiomer **15** lacked affinity for the σ_2 R, however the *S* enantiomer showed affinity (1.91 μ M). Though preliminary, these results for the chiral thiazepino analogues indicate a binding preference at both σ_1 R and

σ_2 R for the *S* enantiomeric configuration in comparison the *R* enantiomer. In addition, the available data suggest that there is selective binding to the σ_1 R subtype over the σ_2 R in the thiazepino scaffold, since both compounds **15** and **18** had stronger affinity for σ_1 R than for σ_2 R. This σ_1 R vs σ_2 R selectivity deviates from the SAR with our previously discovered THPB σ R ligands where the opposite selectivity was observed. In addition, the compounds show a selectivity for binding to σ receptors over dopamine receptors, which is unusual in the parent natural product THPB scaffold. Therefore, these data suggest that the novel THPB-inspired heterocycles may interact with the σ_1 R, σ_2 R and dopamine receptors in qualitatively different ways than compounds from the THPB class.

The racemic diazepino analogue **24** displayed stronger affinity than its sulfur containing counterpart **15** at both σ_1 R and σ_2 R. It will be interesting to examine the extent to which the enantiomers of **24** bind to both receptors in future studies, especially in light of the increased affinity observed in the thiazepino group of compounds.

In conclusion, we have accomplished the first synthesis of compounds with a thiazepino[3,4-a]isoquinoline framework and developed a new synthetic route to the rarely described diazepino[3,4-a]isoquinoline scaffold. The syntheses were accomplished in a straightforward manner using readily available starting materials and standard synthetic transformations. The synthesis of the compounds allowed for preliminary structure-affinity relationship data to be obtained. In that regard, the compounds were found to be selective for binding to σ receptors over dopamine receptors. The σ R selectivity as well as the favorable Lipinski-like predicted physicochemical properties,^[39] affords these compounds as promising new chemotypes for optimization as novel σ R selective agents. The simple, efficient synthetic routes herein will be applicable to the synthesis of structurally diverse compounds bearing these scaffolds. Such studies are already underway in our laboratory and will allow for thorough investigation of structure-activity correlations and ligand optimization work in future.

Supplementary Material

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(S)-stepholidine

(S)-isocorypalmine

(S)-govadine

(S)-tetrahydropalmatine

FIGURE 1.
Structures of dopamine receptor targeting THPBs-(*S*)-stepholidine, (*S*)-isocorypalmine, (*S*)-govadine, and (*S*)-tetrahydropalmatine

FIGURE 2.

Previous strategy and our retrosynthetic approach to synthesis of compounds containing the thiazepino[3,4-a] isoquinoline framework

SCHEME 1.

Reagents and conditions: A, NaH, THF, 0°C: reflux. B, Tf₂O, 2-ClPyr, CH₂Cl₂, –78°C to rt, 1 hour. C, LiAlH₄, THF, rt, 1 hour, 40.5% over three steps for compound **11**; 52% for compound **14**; 49% for compound **17**. D, SOCl₂, DCM, NaHCO₃, rt, 48 hours, 50%–54%. E, (Ru[(*R,R*)-Tsdpen](*p*-cymene), DMF, HCOOH/TEA 5:2, rt, 24 hours, 71%, 92% ee. F, (Ru[(*S,S*)-Tsdpen](*p*-cymene), DMF, HCOOH/TEA 5:2, rt, 24 hours, 64%, 92% ee

SCHEME 2.

A, Methyl anthranilate, NaI, acetone, 24 hours, reflux, 72%. B, TiF_2O , 2-ClPyr, CH_2Cl_2 , -78°C to rt, 1 hour

SCHEME 3.

A, (i) TiF_2O , 2-ClPyr, CH_2Cl_2 , -78°C to rt, 1 hour; (ii) NaBH_4 , CH_3OH , 0°C to rt, 1 hour; 60.5% over 2 steps. B, (i) anthranilic acid, HBTU, THF, DIPEA, rt, 24 hours; (ii) NaOH (aq.), THF, 2 hours, rt; (iii) HBTU, THF, rt, 24 hours, 41% over 3 steps. C, LiAlH_4 , THF, reflux, 4 hours, 69%

TABLE 1

Affinity of analogues at dopamine and σ receptors

K_i (μ M) ^a	Cmpd # ^b	X	Config.	D ₁ R ^b	D ₂ R ^c	D ₃ R ^c	D ₄ R ^c	D ₅ R ^b	σ_1 R ^d	σ_2 R ^e	c log P ^f
	12	S	Racemic	na ^g	Na	na	na	na	na	na	3.61
	15	S	(R)	na	Na	na	na	na	1.00	na	3.61
	18	S	(S)	na	Na	na	na	na	0.44	1.91	3.61
	24	NH	Racemic	na	Na	na	na	na	1.10	1.68	2.67

Note: Ligands displayed <10% inhibition in a primary assay at a ligand concentration of 10 μ M.

^aExperiments conducted in duplicate.

^b[3H]-SCH23390 used as radioligand.

^c[3H]N-methylspiperone used as radioligand.

^d[3]-(+)-Pentazocine used as radioligand.

^e[3H]-DTG used as radioligand.

^fCalculated with ChemDraw Professional version 16.0.

^gna: not active.