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Discovery of new SCH 39166 analogs as potent and selective dopamine D_1 receptor antagonists

Li Qiang [a,*], T. K. Sasikumar [a], Duane A. Burnett [a], Jing Su [a], Haiqun Tang [a], Yuanzan Ye [a], Robert D. Mazzola Jr. [a], Zhaoning Zhu [a], Brian A. McKittrick [a], William J. Greenlee [a], Ahmad Fawzi [b], Michelle Smith [b], Hongtao Zhang [b], Jean E. Lachowicz [b]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[b] Department of Metabolic Disorders, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

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ABSTRACT

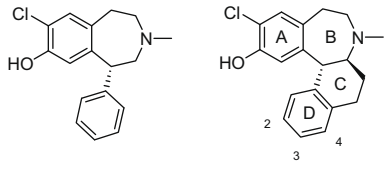
A series of novel dopamine D_1 antagonists derived from functionalization of the D-ring of SCH 39166 were prepared. A number of these compounds displayed subnanomolar D_1 activity and more than 1000-fold selectivity over D_2. We found C-3 derivatization afforded compounds with superior overall profile in comparison to the C-2 and C-4 derivatization. A number of highly potent D_1 antagonists were discovered which have excellent selectivity over other dopamine receptors and improved PK profile compared to SCH 39166.

Dopamine (DA) is a small-molecule neurotransmitter involved in the regulation of several biological functions, including locomotor activity, emotion, cognition, and neuroendocrine secretion.[1] The actions of DA are mediated by five different receptor subtypes classified into two families: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4).[2] DA is the primary neurotransmitter in the reward pathway and it has been reported that D_1-like receptors play a role in food intake in animal models.[3a,3b] Therefore, at the onset of these studies, we believed a safe and efficacious D_1 antagonist may have therapeutic potential for the treatment of obesity in humans.[4]

The discovery of benzazepine **1** (SCH 23390), one of the first highly potent and selective D_1/D_5 antagonists, represented a major breakthrough in dopaminergic receptor research.[5a,5b] This compound, however, could not be further developed as a drug due to the poor oral absorption and short duration of action.[6] The conformationally restricted analogue **2** (SCH 39166) was subsequently discovered to have similar affinity and selectivity as a D_1/D_5 antagonist and improved overall pharmacologic profile.[6,7] Compound **2**, also known as ecopipam, was developed as a potential treatment for obesity and studied in phase III clinical trials.[4,8] (Fig. 1)

SCH 39166 still retained some undesirable pharmacologic properties as a drug development candidate, such as low oral bioavailability.[9a,9b] Our goal was to discover a novel, highly potent and selective dopamine D_1/D_5 antagonist with an improved PK profile. A-ring modifications of SCH 39166 have been reported by W. Wu et al.[10] This present Letter describes the fuctionalization of the D-ring of SCH 39166 with the emphasis on the exploration of the C-3 and C-4 positions and complements the preceding Letter by T. K. Sasikumar et al.[11]

Our initial efforts on SAR exploration of the bicyclic analog SCH 23390 investigated the modification of the pendent phenyl ring. We started with optically pure compound **1**.[5a] The phenolic group was first protected by reacting with 4-nitrobenzoyl chloride. Subsequent bromination[12] of this protected intermediate **3** led to a mixture of para-bromination product **4**, ortho-bromination product **5**, and dibromination product **6**, which could be carefully



1 (SCH 23390) **2 (SCH 39166)**

Figure 1. Benzazepine D_1 antagonists.

* Corresponding author. Tel.: +1 908 7404232; fax: +1 908 7407164.
E-mail address: li.qiang@merck.com (L. Qiang).

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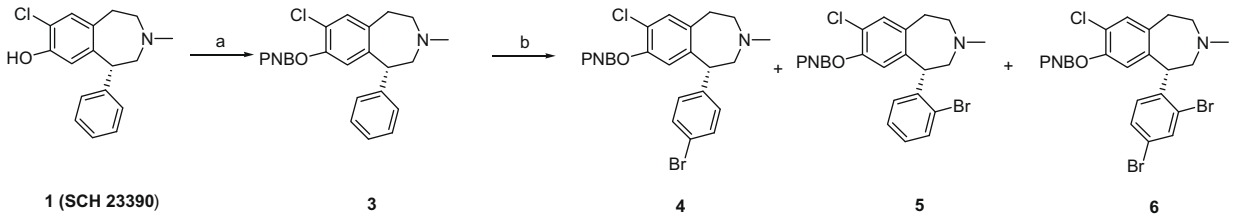
separated by silica gel chromatography (Scheme 1). Compound **4** was used as a key intermediate to introduce different functionalities to this phenyl ring as part of our SAR exploration.[13]

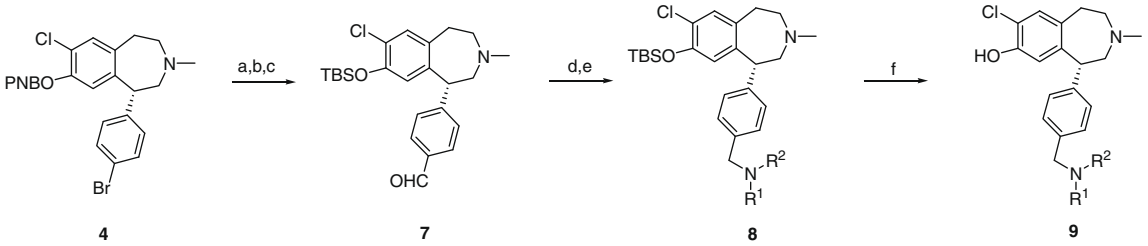
An example of further SAR development using intermediate **4** is shown in Scheme 2. The phenolic protecting group was first exchanged to TBS via hydrolysis and silylation. Formylation was accomplished by lithiation and trapping with DMF. Final functionalizations were realized by reductive amination and/or capping strategies. This effort led to a discovery of a series of highly potent and selective D_1/D_5 antagonists. A number of representative examples are shown in Table 1. SAR result demonstrated that both D_1 affinity and selectivity over D_2 were maintained or improved with derivatization of the para-position with a high steric tolerance for substitution.[14]

With this SAR information on SCH 23390 analogs in mind, we moved on to explore the D-ring functionalization of the conformational restricted tetracyclic series focusing on the C-3 position, as shown in Scheme 3. Additionally, C-2 and C-4 derivatization would also be of high interest because they are in close proximity with the C-3 position. For the regioselective functionalization of the D-ring, we still faced the same challenge as we did for SCH 23390.

We used the optically pure SCH 39166 as our starting material,[15] protecting the phenolic group on the A-ring with a 4-nitrobenzoyl group to afford the common intermediate **10**. This protected intermediate was used in all reactions for D-ring derivatizations. A non-selective bromination was carried out and subsequent SAR development is reported in the preceding Letter.[11] Chlorosulfonylation of intermediate **10** selectively functionalized C-2 of the D-ring, but sulfonamides thus derived had low D_1 activities.[16] We next decided to try the nitration on the D-ring. A mild nitration condition was used (Scheme 3) and we isolated all three C-2, C-3, and C-4 regio isomers **11**, **12**, and **13** by HPLC in the ratio of 1:1.4:4.[17] The structures of the nitration products **11**, **12**, and **13** were assigned based on proton NOE data.

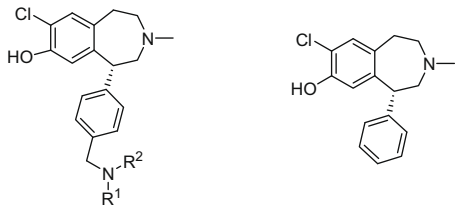


Scheme 1. Reagents and conditions: (a) 4-nitrobenzoyl chloride, TEA, CH_2Cl_2, rt, 98%; (b) $Hg(OCOCF_3)_2$, Br_2, rt, 54% **4**, 37% **5** and 5% **6**.



Scheme 2. Reagents and conditions: (a) NaOH, rt; (b)TBSCl, 88% for two steps; (c) *n*-BuLi, DMF, 95%; (d) $Ti(OiPr)_4$, R_1NH_2, $NaBH_4$; (e) RCOOH, EDCI, or RCOCl, DIEA, DMF or RSO_2Cl, pyridine or ROCOCl, DIEA, CH_2Cl_2 or RNCO, CH_2Cl_2 or RNCOCl, DIEA, DMF; (f) TBAF, rt, 95%.

Table 1
Dopamine binding properties for compounds **9a**–**g** and **1**



Compound	R^1, R^2	K_i[a] (nM)			
		D_1	D_5	D_2	D_4
1	–	1.4	2.8	1000	
9a	$-C_4H_7$, –H	0.9	3.9	2000	>10,000
9b	$-C_4H_7$, $-COCH_3$	0.2	13	159	>10,000
9c	$-C_4H_7$, $-SO_2CH_3$	0.5	5.9	2000	>10,000
9d	$-CH_3$, $-SO_2CH_3$	0.5		6000	
9e	$-CH_3$, $-SO_2C_6H_5$	0.6	1.2	331	4331
9f	$-C_6H_5$, –H	2		2000	
9g	$-CH_2C_6H_5$, 2,4–$F_2C_6H_3$	0.7		552	

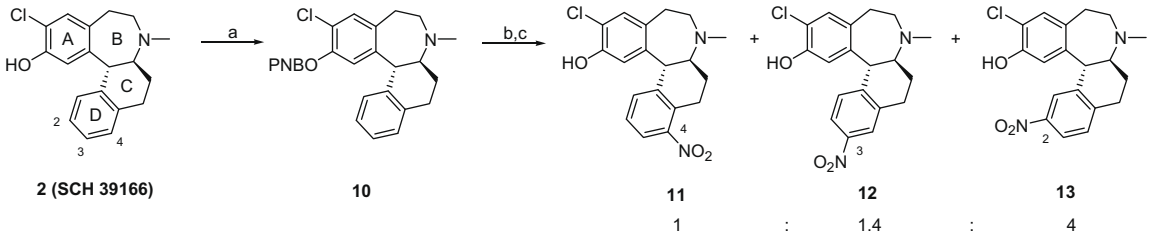
[a] The standard error was 10%, and variability was less than twofold from assay to assay.

To quickly explore the SAR from these intermediates, we utilized a high-throughput synthesis strategy, since compounds **11**, **12**, and **13** are ideal for solid-phase library synthesis. The example of compound **12** being coupled with Wang resin and subsequent library synthesis is described in Scheme 4. After Mitsunobu attachment to the resin, the nitro group was selectively reduced using $SnCl_2$ to afford aniline **15**. Our derivatization of the C-3 aniline included sulfonylation, acylation, urea formation and carbamate formation. The reductive alkylation did not give a satisfactory result, instead, we used the amide intermediate **18** followed by borane reduction to make these compounds as described in Scheme 5. The final products could be cleaved from the resin using 30% TFA in dichloromethane. This high-throughput synthetic strategy turned out to be a very efficient way to allow us to quickly access a thorough SAR. Twelve focused libraries with a total number of three hundred compounds were accomplished in a short period of time. All compounds were evaluated by LCMS and those with a purity of >70% were then submitted for biological evaluation.

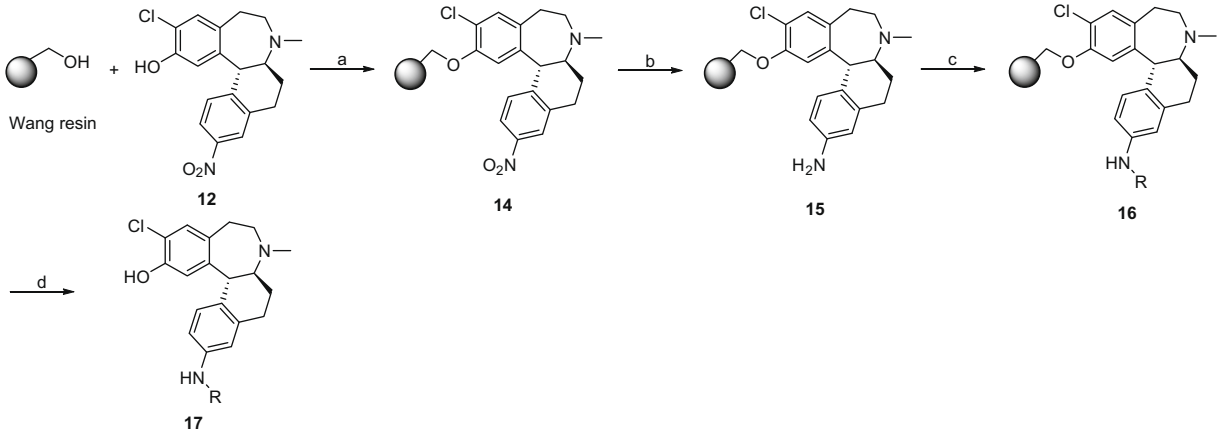
In a similar manner, we investigated the SAR of all three regioisomers. Derivatization on C-2 position generally gave moderate to low D_1 affinity.[18] Both C-3 and C-4 derivatization afforded compounds with high D_1 affinity. A large number of compounds from these two series showed single digit nanomolar or lower D_1 affinity. In addition, C-3 derivatization generated compounds with excellent selectivity over D_2, often greater than 1000-fold. C-4 modification, however, only afforded compounds with moderate selectivity over D_2. Selected binding results from the libraries of these two isomers are listed in Table 2.

The profile of one of the representative compounds **17c** from C-3 series is shown in Figure 2. This compound not only had subnanomolar D_1 affinity, but also demonstrated almost 10-fold improvement of selectivity over D_2, D_4, and D_5 compared to SCH 39166. Both 5HT2a and α2a receptor selectivity also improved over SCH 39166. More interestingly, we saw a significant improvement of PK and oral bioavailability, a major goal for our program. To this end, rapid rat AUC[19] improved more than 10-fold to 2486 ng/ml h and oral bioavailability increased to 29%.

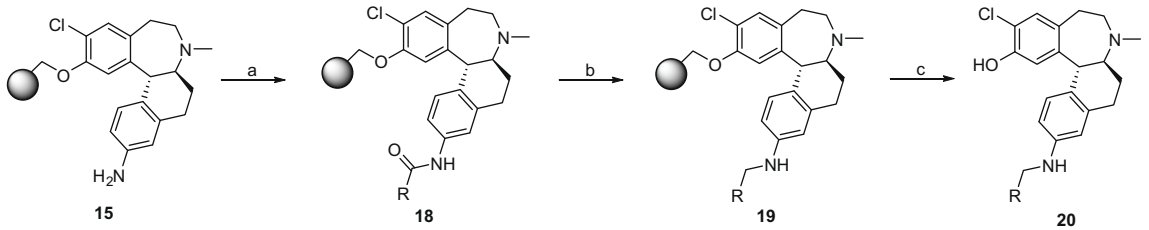
In summary, we discovered a practical method to functionalize the D-ring of SCH 39166 which provided access to functionalization of C-2, C-3, and C-4 positions. We have utilized a parallel



Scheme 3. Reagents and conditions: (a) 4-nitrobenzoyl chloride, TEA, CH_2Cl_2, rt, 98%; (b) BF_4NO_2, MeCN, rt, 12 h; (c) LiOH, THF–H_2O, rt, 56% for combined isomers after two steps. After HPLC separation, the ratio of isomers **11**, **12**, and **13** is 1:1.4:4.

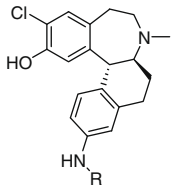


Scheme 4. Reagents and conditions: (a) PPh_3, 1,1'-(azodicarbonyl)dipiperidine, THF/CH_2Cl_2, rt, 12 h; (b) $SnCl_2{\cdot}2H_2O$, DIEA, DMF, rt, 24 h; (c) RCOOH, DIC, HOBT, DMAP, NMP or RCOCl, DIEA, DMF or RSO_2Cl, pyridine or ROCOCl, DIEA, CH_2Cl_2 or RNCO, CH_2Cl_2 or RNCOCl, DIEA, DMF; (d) 30% TFA/ CH_2Cl_2, rt, 15 min.

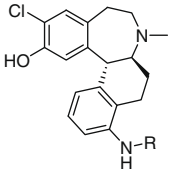


Scheme 5. Reagents and conditions: (a) RCOOH, DIC, HOBT, DMAP, NMP or RCOCl, DIEA, DMF; (b) $BH_3{\cdot}THF$; (c) 30% TFA/CH_2Cl_2, rt, 15 min.

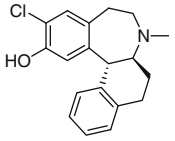
Table 2
Dopamine binding properties for compounds **17a–f**, **21a–f** and **2**



17a-f



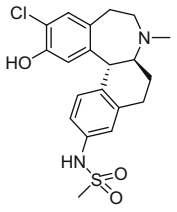
21a-f



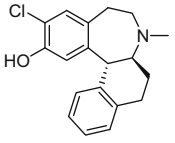
2 (SCH 39166)

R	Compd	K_i[a] (nM)				Compd	K_i[a] (nM)			
		D_1	D_5	D_2	D_4		D_1	D_5	D_2	D_4
—	**2**	1.2	2.0	980	5515					
–H	**17a**	7	8.3	5400	>10,000	**21a**	2.8	7.0	2100	>10,000
$-COC_3H_5$	**17b**	2.3		>10,000		**21b**	5.7		2137	
$-SO_2CH_3$	**17c**	0.5	5.8	3000	>10,000	**21c**	4.7		1000	
$-SO_2CH_2CH_3$	**17d**	0.7	5.6	3300	>10,000	**21d**	5.8		618	
$-CONHCH_2CH_3$	**17e**	1.5	7.1	6000	>10,000	**21e**	2.4		900	
$-CONH\text{-}2,6\text{-}Cl_2C_6H_3$	**17f**	0.7		1093		**21f**	7.1		566	
$-CO_2CH_2CH_3$	**17g**	1.4	3.3	3900	>10,000	**21g**	2.3		500	

[a] The standard error was 10%, and variability was less than twofold from assay to assay.



17c
D_1 Ki = 0.5 nM
D_2/D_1 = 6000
D_4/D_1 > 20000
D_5/D_1 = 11.6
5HT2a/D_1 =1300
α2a/D_1=3600
Rat AUC = 2486 ng/mL.hr
rat bioavailability 29%



2 (SCH 39166)
D_1 Ki = 1.2 nM
D_2/D_1 = 816.7
D_4/D_1 = 4595
D_5/D_1 = 1.7
5HT2a/D_1 =70
α2a/D_1=630
Rat AUC = 156 ng/mL.hr
rat bioavailability 0.6%

Figure 2. Discovery of compound **17c** with improved profile compared to SCH 39166.

synthetic strategy to quickly develop SAR of all three different regions of D-ring. Functionalization of the C-3 position produced a series of sulfonamido D_1 antagonists with high affinity, high selectivity, and in some cases improved PK. Compound **17c** was discovered to have excellent affinity, selectivity, and PK as compared to SCH 39166. Further efforts in this series were discontinued as results from long term clinical trials of ecopipam revealed untoward mechanism-based side effects.[4]

Acknowledgments

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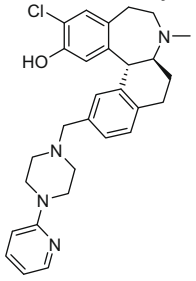
16. *A typical experimental method is given below:* Compound **10** (0.17 g, 0.37 mmol) was dissolved in dichloromethane (5 ml) and cooled to 0 °C under atmosphere of nitrogen. Chlorosulfonic acid (2 ml, excess) was added dropwise to this solution. The reaction was then raised to room temperature and stirred for 3 h. The reaction was quenched with ice water and light brown solid was precipitated out from the solution. The liquid was descanted and the resulting solid was dried by forming the azeotropic solution with toluene. The crude solid material was redissolved in acetonitrile and added amines (excess amount) dropwise. The reaction mixture was left to stir at room temperature over night. Saturated ammonium chloride solution was used to quench the reaction followed by extraction with dichloromethane. The final product was isolated by preparative TLC with the yield ranging from 20–50%.
17. *A typical experimental method is given below:* To a solution of compound **10** (2.0 g, 4.3 mmol) in 30 ml acetonitrile was added BF_4NO_2 (1.6 g, 12.9 mmol) and the reaction mixture was left to stir for 3 h. The reaction was then

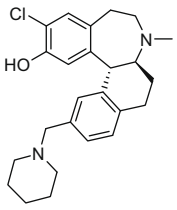
quenched with water and neutralized with saturated sodium bicarbonate solution. This mixture was extracted with dichloromethane and the solvent was evaporated under vacuum. The residue was redissovled in tetrahydrofuran/water solution (3:1), treated with 1 N LiOH aqueous solution and stir at room temperature for 3 h. The reaction mixture was then quenched with acetic acid, extracted with dichloromethane and dried with sodium sulfate. The solvent was evaporated and the resulting crude material was passed through a short silicon gel column to remove baseline material. The mixture was then purified by HPLC (silica gel column, eluting solvent 95% ethyl acetate/hexane, 0.25% triethylamine) to give three regioisomers.

18. Formylation of 39166 followed by reductive amination were used to generate a small library of C-2 aminomethyl substituted SCH 39166 analogs. For several of these analogs, D_2/D_1 selectivity was reversed due to decreased D_1 affinity and increased D_2 affinity. Two examples are shown as below:



D_1 Ki = 152 nM
D_2 Ki = 1.3 nM
D_1/D_2 = 117

i



D_1 Ki = 225 nM
D_2 Ki = 26 nM
D_1/D_2 = 8.7

ii

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