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trans-2,6-, 3,6- AND 4,6-DIAZA-5,6,6a,7,8,12b-HEXAHYDRO-BENZO[*C*]PHENANTHRENE-10,11-DIOLS AS DOPAMINE AGONISTS

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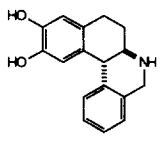
Abstract: The title compounds were synthesized by replacing the thiophene moiety of A-86929(**2a**) with variously substituted pyridines. Dopamine D-1 and D-2 binding and adenylate cyclase assays indicate that 4,6-diaza compounds **15** are potent and selective full D1 agonists when R^1 is H or a small substituent and R^2 = H, with D1 binding affinity and adenylate cyclase functional potency equivalent to that of A-86929(**2a**).

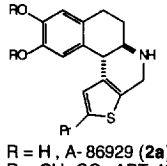
Dopamine is an important neurotransmitter in the central nervous system (CNS). Dopamine imbalance is believed to play a key role in a number of CNS-related disorders such as schizophrenia, Parkinson's disease (PD), drug abuse, eating disorders, and depression. Dopamine also has several important roles in the peripheral nervous system, such as in the control of blood to the kidneys and in autonomic ganglion transmission. Dopamine receptors have traditionally been divided into two general receptor classes, designated D-1-like and D-2-like, based on biochemical and pharmacological differences between the two receptor types.[1] Recent molecular biology studies have indicated an even greater heterogeneity of dopamine receptors: the D-2, D-3, and D-4 constitute the D-2-like class, while the D-1 and D-5 receptors comprise the D-1-like class.[2]

PD is a progressive disease that arises as a result of the degeneration of dopaminergic neurons in the zona compacta of the substantia nigra.[3] Currently, levodopa remains the most effective treatment for PD.[4] However, significant loss of efficacy and severe side effects[5] associated with the chronic treatment of levodopa warrant the development of alternative therapies. Dopamine D2 agonists have been used for the treatment of PD, often in combination with levodopa.[6]

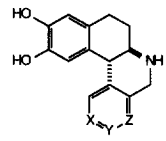
Recently, the development of dopamine D1 agonists as an alternative for the treatment of PD emerged with the hope of improving the side effect profile. Dihydrexidine(**1**),[7] a selective D1 full agonist, showed a promising preclinical pharmacological profile. A-86929(**2a**) is also a selective full D1 agonist that is effective in rodent and primate models of PD after both acute and chronic administration.[8] ABT-431 (**2b**)[8], the diacetyl prodrug of A-86929(**2a**), has shown efficacy in human clinical trials.[9] We have extended our SAR studies by replacing the thiophene moiety of A-86929(**2a**) with variously substituted pyridines and would like to report our latest results.



Dihydrexidine **1**)



R = H, A-86929 (**2a**)
R = CH_3CO, ABT-431 (**2b**)



X, Y, Z = N, CR^1, CR^2 (**3**)

Synthesis

Treatment of *t*-butyl 2-(or 4-)pyridinecarboxamide derivatives **4**[10] (or **5**[11]) with 2 equiv of *n*-BuLi at –78 °C generated the 3-lithiopyridine dianions which were condensed with nitroolefin **6**[8] followed by the

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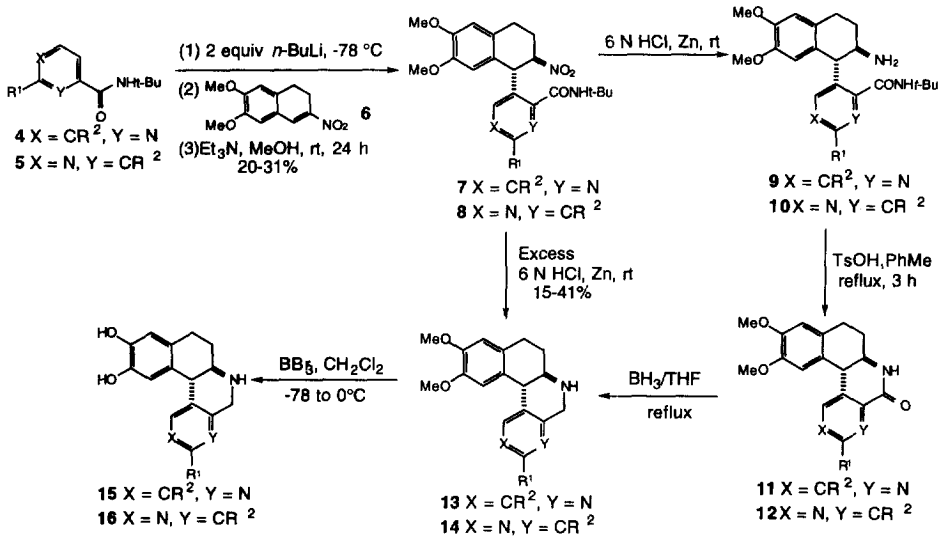
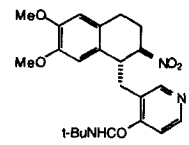
triethylamine-mediated equilibration of the resulting *cis/trans* adduct mixture to afford compounds **7** and **8** in low yield. Reduction of the nitro group of compounds **7** and **8** with Zn/HCl provided the corresponding primary amines **9** and **10**. When compounds **7** and **8** were reacted with large excess of zinc dust and 6 N HCl, in addition to the formation of the primary amines **9** and **10**, the tetracyclic compounds **13** and **14** were obtained directly in poor to moderate yield, accompanied by the formation of the diamines with both nitro and amide groups being reduced. Further treatment of **9** and **10** with excess of Zn/6 N HCl did not provide any cyclized compounds **13** and **14**, indicating that **9** and **10** are not intermediates involved in the formation of compounds **13** and **14**. When **7** (R^1 = F, R^2 = H) was reacted with a large excess of zinc dust and 6 N HCl, however, the tetracyclic compound **13** (R^1 = F, R^2 = H) was not observed. Compound **13** (R^1 = F, R^2 = H) was synthesized in an alternative three-step sequence. Reduction of nitro group to an amine **9** (R^1 = F, R^2 = H) followed by treatment with acid in refluxing toluene provided the lactam **11** (R^1=F, R^2=H) in 60% yield. Reduction of the lactam **11** (R^1 = F, R^2 = H) with borane afforded **13** (R^1 = F, R^2 = H) and the desfluoro compound (**13**, R^1 = R^2 = H) in 23% and 18% yield, respectively (Scheme 1). The cleavage of the methyl ethers of **13** and **14** with boron tribromide finally provided catecholamines **15** and **16**.

Scheme 1



In contrast, when **5** (R^1 = H, R^2 = Me) was treated with 2 equiv of *n*-BuLi and then reacted with the nitroolefin **6**,[8] the desired Michael adduct **8** (R^1 = H, R^2 = Me) was not observed. Instead, compound **17** was isolated as the major product via lithiation of the methyl hydrogen[12] of **5** (R^1 = H, R^2 = Me) and subsequent addition of the resulting anion to nitroolefin **6**.[8] An alternative synthetic route was developed to synthesize the target compound **16c** (Scheme 2). Halogen-metal exchange of 3-bromo-5-methyl-4-pyridinemethanol MOM ether **18**[13] with *n*-BuLi followed by addition of the 3-lithiopyridine intermediate to nitroolefin **6**[8] and subsequent base-promoted equilibration gave rise to compound **20** in good yield. The reduction of the nitro group with Zn/6 N HCl, cleavage of MOM ether, and protection of the primary amine afforded **22** in good yield. The construction of the piperidine ring was accomplished via a three-step sequence: Conversion of the primary alcohol **22** to the corresponding chloride, deprotection of the amine, and ring closure provided compound **23**. Finally, cleavage of methyl ether with boron tribromide afforded target molecule **16c**.



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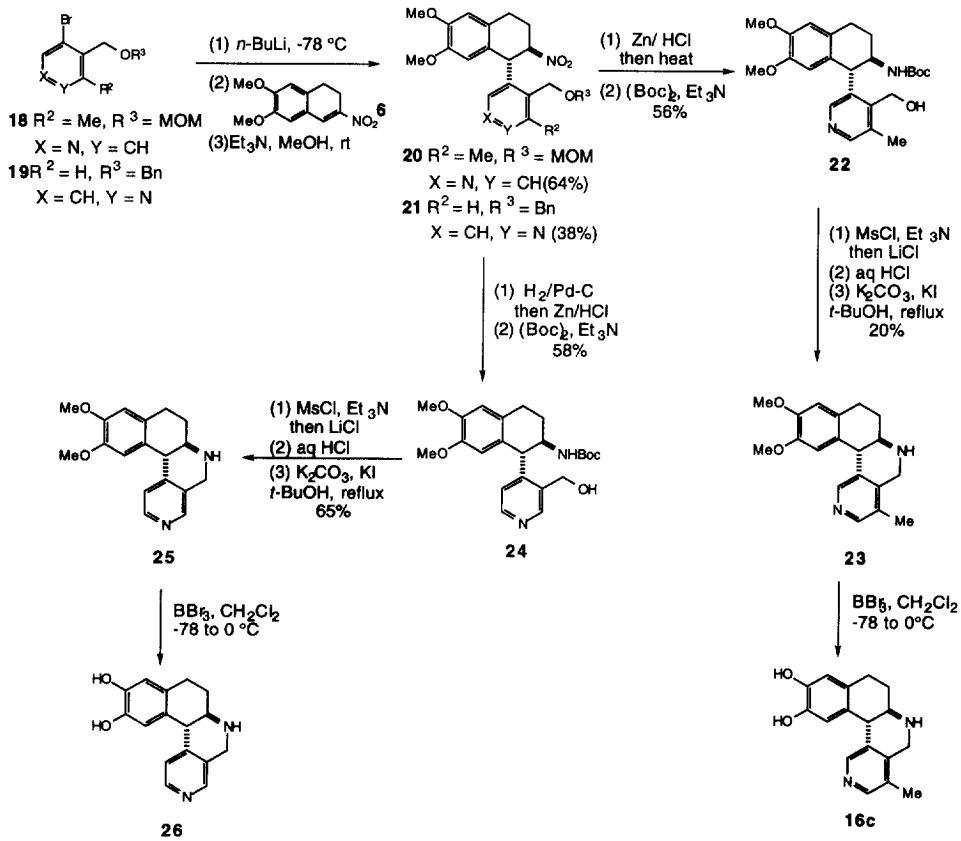
Compound **26**, a regioisomer of compound **16**, was synthesized from 4-bromo-3-pyridinemethanol benzyl ether **19**[14] by employing a similar synthetic route (Scheme 2). The overall yield of compound **26** is 14% from starting material **19**.

Scheme 2



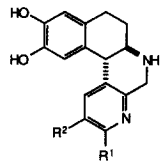
Results and Discussion

The binding affinities to both human D1 and human D2 receptors were measured, and the results for the 4,6-diaza derivatives are shown in Table 1. Dihydrexidine (**1**) and A-86929(**2a**) are included as reference compounds. In the 4,6-diaza series, the unsubstituted pyridine compound **15a** (R^1 = R^2 = H) exhibited high affinity for the D1 receptor (K_i = 65 nM). **15a** has high potency in adenylate cyclase functional assay (EC_{50} = 6.7 nM) and greater intrinsic activity relative to dopamine (IA = 125%). These results indicate that **15a** is a potent, full agonist at the D1 receptor, with an in vitro profile comparable to that produced by A-86929(**2a**). Compound **15a** has significantly weaker affinity for the D2 receptor (K_i = 2,500 nM), thus a more selective D1 agonist (D2/D1 = 38) than A-86929 (**2a**) (D2/D1 = 14).

Previous structure–activity relationship (SAR) studies on D1 ligands suggested that the D1 but not the D2 receptor possesses a lipophilic binding pocket that can bind a bulky substituent such as adamantyl group.[15] SAR studies on A-86929 analogs (**27**) and its regioisomers(**28**) revealed that introduction of a small R group (methyl, ethyl or *n*-propyl) increases affinity for D1-like receptor relative to the parent compounds (**27** and **28**, R = H). Increase in D2 receptor affinity by **27** and **28** relative to the parent was not as significant.[16] Nichols and coworkers

reported that dihydrexidine analog **29** (R = Me) did not produce such a boost in affinity relative to the parent.[17] In contrast, introduction of a methyl group at C3 position of the 4,6-diaza series (**15b**) resulted in a 2-fold decrease in D1 affinity and 2-fold increase in D2 affinity, and therefore a 4-fold drop of D1 selectivity relative to the parent compound **15a**. Interestingly, C3 fluorine substituted compound **15c** showed similar D1 binding affinity and selectivity to **15b**, indicating that the contribution of electronic effect to dopamine affinity is relatively insignificant in the 4,6-diaza series. When a larger substituent is introduced at the C3 position (**15d,e**), D1 affinity remains unaffected, whereas D2 affinity increases by about 4-fold, leading to a lower D2/D1 ratio compared to the parent compound **15a**. It is interesting to note that when the size of the substituent R^1 increases, D2 affinity increases accordingly (*n*-Pr > OMe > Me > F > H), whereas the effect on D1 affinity varies. In an adenylate cyclase based functional assay, compounds **15d,e** exhibited high potency as the parent compound **15a**, while **15b,c** were less potent (2- to 3-fold) than **15a**, in parallel with their decreased D1 binding affinity.

Table 1. Competitive binding and D1 functional activities of 4,6-diaza-5,6,6a,7,8,12b-hexahydrobenzo[*c*]phenanthrene-10,11-diols[a]



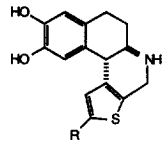
15

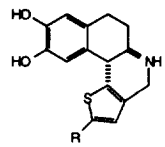
			D1			D2	
compd	**R^1**	**R^2**	**K_i (nM)**	**EC_{50} (nM)**	**IA (%)[b]**	**K_i (nM)**	**D2/D1**
1			33 ± 2(6)	14 ± 5(6)	121 ± 7(6)	1520 ± 527(5)	45
2a			49 ± 5(32)	9 ± 2(29)	125 ± 3(29)	710 ± 80(52)	14
15a	H	H	65 ± 7(6)	6.7 ± 2(3)	125 ± 3(3)	2500 ± 620(5)	38
15b	Me	H	140 ± 14(10)	23 ± 4(3)	121 ± 6(3)	1400 ± 390(9)	10
15c	F	H	180 ± 16(5)	18 ± 3(3)	141 ± 13(3)	2200 ± 500(3)	12
15d	OMe	H	49 ± 11(6)	8.8 ± 2(3)	114 ± 13(3)	520 ± 72(5)	11
15e	n-Pr	H	45 ± 5(5)	8.6 ± 2(3)	116 ± 12(3)	450 ± 84(6)	10
15f	H	Me	240 ± 43(6)	110 ± 41(4)	156 ± 4(4)	12000(1)	50
15g	H	n-Bu	890 ± 230(7)	180 ± 58(3)	118 ± 7(3)	1900 ± 220(6)	2
15h	Me	Me	280 ± 37(6)	120 ± 44(3)	134 ± 11(3)	9100 ± 1500(3)	33
15i	$-(CH_2)_4-$		560 ± 68(6)	63 ± 5(3)	136 ± 9(3)	3600(1)	6

[a]Values represent the mean ±SEM, with the number of experiments in parentheses. Binding and adenylate assays were carried out in HEK and LTK cells transfected with the human D1[18] and D2[19] receptors, respectively. Binding ligands were as follows: D1, [^{125}I]SCH23982; D2, [^{3}H]-spiperone. Binding K_i and cyclase EC_{50} values were determined as previously described.[20]
[b]IA = Intrinsic activity relative to dopamine.

A significant loss (4-fold) of D1 affinity was observed when the parent compound **15a** was substituted with a methyl group at the C2 position(**15f**). In contrast to compound **15b**, **15f** also showed a 5-fold decrease of D2 binding affinity, thus a higher D1 selectivity (D2/D1 = 50) than **15a**. Previous studies on dihydrexidine analogs **30** also indicated that the optimal D2/D1 selectivity was achieved when R = Me.[17] Increasing the size of the substituent at C2 position (e.g., R^2 = *n*-Bu) resulted in a further decrease in D1 binding affinity and increase in D2 affinity (**15g** vs **15f**). C2 and C3 disubstituted compounds also showed a decreased D1 binding affinity relative to the parent compound **15a**. Dimethyl substituted compound **15h** is four times less potent than **15a** in both D1 and D2 binding. Further increasing the size of the substituents at C2 and C3 positions resulted in a decrease in D1 binding affinity but an increase in D2 affinity (**15h** vs **15i**). In adenylate cyclase based functional assay, C2 monosubstituted (**15f,g**) and C2,C3 disubstituted (**15h,i**) 4,6-diaza derivatives showed lower potency relative to the parent compound **15a** and their C3 monosubstituted analogs (**15b–e**). Although the same trend is

also observed in D1 binding assay as described above, the decrease of functional activity (10- to 27-fold) is more dramatic than that of D1 binding affinity (4- to 14-fold). 4,6-Diaza derivatives have greater intrinsic activity relative to dopamine.


27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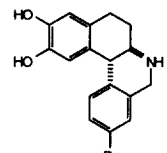
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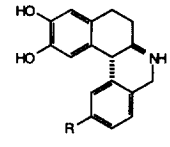
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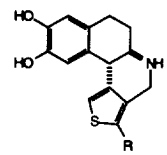
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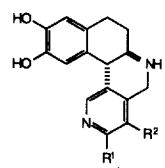
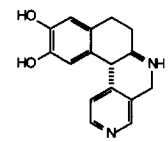
Previous studies revealed that the different regioisomers of thiophene derivatives **27**, **28**, and **31** exhibited comparable affinity for the D1 receptor, although **28** showed higher (ca. 3-fold) affinity on D2 binding than the other two regioisomers.[16] In the current study, D1 affinity decreases dramatically (17-fold) when the pyridine nitrogen is moved from C4 to C2 position (**15a** vs **16a**), whereas the effect on D2 binding is less pronounced, with a 2-fold increase in D2 binding affinity (Table 2). An even more dramatic decrease in functional activity (48-fold) was observed. This result may provide insight for the design of selective D1 ligands. The reasons for the significant decrease of D1 affinity of **16a** remain unclear, although may be due to the unfavorable electrostatic interaction of the lone pair electrons of the pyridine nitrogen with the D1 receptor. When a strong electron-withdrawing substituent was introduced to reduce the availability of the lone pair electrons, an increase (3-fold) in D1 binding affinity was observed (**16b**). The methyl substituted analog **16c** showed the same D1 binding affinity and a 3-fold increase in D2 binding affinity relative to its parent compound **16a**. In fact, compound **16c** is the only compound in this study which binds more potently to the D2 receptor than the D1 receptor in dopamine binding assay. The 2,6-Diaza derivatives **16a–c** also exhibited weak potency in stimulating adenylate cyclase (EC_{50} = 0.23–0.80 μM). It is noteworthy that compound **16b** is 2.5- to 3.5-fold less potent in D1 functional assay than **16a** and **16c**, although **16b** showed higher (3-fold) D1 binding affinity.

Compound **26**, the only compound in the 3,6-diaza series tested in this study, exhibited weaker dopamine binding affinity (2-fold) and functional activity (6-fold) relative to its regioisomer **15a**.

Table 2. Competitive binding and D1 functional activities of 2,6- and 3,6-diaza-5,6,6a,7,8,12b-hexahydrobenzo-[*c*]phenanthrene-10,11-diols[a]


16 R^1=H


26

compd	R^2	D1 K_i (nM)	D1 EC_{50} (nM)	D1 IA (%)[b]	D2 K_i (nM)	D2/D1
2a		49 ± 5(32)	9 ± 2(29)	125 ± 3(29)	710 ± 80(52)	14
16a	H	1100 ± 310(8)	320 ± 150(3)	81 ± 8(3)	1300 ± 480(8)	1
16b	F	390 ± 110(3)	800 ± 230(3)	126 ± 11(3)	890 ± 170(7)	2
16c	Me	1100 ± 160(3)	230 ± 59(4)	75 ± 12(4)	400 ± 100(3)	0.36
26		140 ± 20(6)	38 ± 17(4)	131 ± 7(4)	4400 ± 1400(6)	31

[a]Values represent the mean ±SEM, with the number of experiments in parentheses. Binding and adenylate assays were carried out in HEK and LTK cells transfected with the human D1[18] and D2[19] receptors, respectively. Binding ligands were as follows: D1, [^{125}I]SCH23982; D2, [^{3}H]-spiperone. Binding K_i and cyclase EC_{50} values were determined as previously described.[20]
[b]IA = Intrinsic activity relative to dopamine.

In conclusion, different pyridine regioisomers of A-86929(**2a**) have been synthesized, and their binding affinity to D1 and D2 receptors and functional activity in adenylate cyclase assay have been determined. In the 2,6-diaza series, when R^2 is H and R^1 is H or a small substituent, compounds **15a–e** are full D1 agonists (>100% intrinsic activity relative to dopamine), exhibiting high D1 binding affinity and selectivity (D2/D1 ≥ 10). Substitution at the C2 position (**15**, R ≠ H) resulted in a decreased D1 binding affinity and functional activity, whereas effect on D2 binding varies (**15f–i**). 4,6-Diaza derivatives **16** are poor dopamine ligands, showing low affinity and poor selectivity for dopamine receptors.

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References and Notes

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10. Prepared from the corresponding pyridinecarboxylic acids unless otherwise indicated. The pyridinecarboxylic acids are either commercially available ($R^1 = R^2 = H$; R^1 = Me, R^2 = H; R^1 = H, R^2 = *n*-Bu) or synthesized according to Shuman *et al.*, *J. Org. Chem.* **1990**, *55*, 738 (R^1 = *n*-Pr, R^2 = H; $R^1 = R^2$ = Me; $R^1 = R^2 = -(CH_2)_4-$) and Cooper *et al.*, *Synthesis* **1971**, 31 (R^1 = F, R^2 = H). **4** (R^1 = OMe, R^2 = H) was prepared from 6-bromo-2-methoxypyridine (*J. Org. Chem.* **1990**, *55*, 69.) via halogen–metal exchange and subsequent reaction with *t*-butyl isocyanate. **4** (R^1 = H, R^2 = Me) was prepared from the corresponding ethyl ester (*Inorg. Syn.* **1994**, 4112) by employing the procedure of Weinreb *et al.*, *Tetrahedron Lett.* **1977**, *18*, 4171.
11. Compound **5** ($R^1 = R^2$ = H) was prepared from isonicotinic acid. Compound **5** (R^1 = H, R^2 = F) was synthesized from 3-fluoropyridine via lithiation with LDA (*Tetrahedron Lett.* **1980**, *21*, 4137) and subsequent reaction with *tert*-butyl isocyanate.
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