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SYNTHESIS AND EVALUATION OF NOVEL-N-[2-(BIS-ARYL-METHOXY)ETHYL-N'-ARALKYL-α,ω-ALKANEDIAMINES AS POTENT AND SELECTIVE DOPAMINE REUPTAKE INHIBITORS: *SECO* ANALOGS OF GBR12935 AND GBR12909

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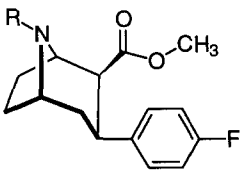
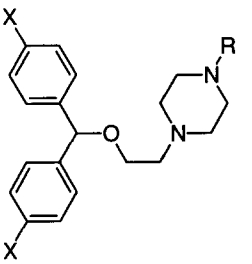
Abstract: A series of analogs of the N-[2-bis arylmethoxy]-N'-phenylpropyl-piperazines GBR12909 and 12935 was synthesized and evaluated as inhibitors of synaptic monoamine transporters. The data indicated that all of the new compounds demonstrated a selectivity for the dopamine transporter compared to the other monoamine transporters with IC_{50} values approaching 10 nM. The results suggest that the internal piperazine moiety is not required for activity and may be replaced with a more flexible diamine unit. © 1997 Elsevier Science Ltd.

The dopaminergic (DA) neurotransmitter systems are intimately involved with a number of central nervous system (CNS) disorders including those involved with movement (e.g., Parkinson's Disease[1] and reinforcing effects [e.g., cocaine dependency.[2]]) Interest in these two disorders in particular has stimulated research efforts to develop specific agents that can be used either diagnostically, to evaluate the extent of the disease, or therapeutically, to antagonize the effect of cocaine. The common target for compounds that would fullfill these objectives is the dopamine transporter (DAT), a 12-transmembrane spanning presynaptic protein that removes the dopamine from the synaptic cleft following its release.[3] Two classes of competitive drugs that have been examined are the stable tropane analogs of cocaine, represented by WIN35,428[4], **1a** and the piperazine derivatives, characterized by GBR-12935[5] **2a** (Figure 1). Both exert their effect at nM concentrations.

Figure 1





1a R = CH_3 WIN 35,428 (CFT)

1b R = CH_2 CH=CHI (E) Iodoaltropane

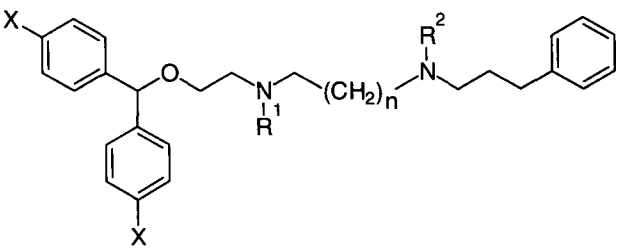
2a R = $CH_2CH_2CH_2C_6H_5$ X = H GBR 12,935

2b R = CH_2CH=CHI (E)

2c R = CH_2CH=CHI (Z)

Our research efforts to develop new agents with higher DAT affinity and selectivity have been directed at both classes of compounds. We have previously described the initial development and preclinical evaluation of iodoaltropane **1b** (IACFT),[6,7] a WIN 35,428 analog with improved pharmacological properties that, in its radiolabeled form, is currently in clinical trials. Our initial effort to replace the *N*-aralkyl group of the GBR series with an *N*-iodoallyl moiety **2b,c** produced a significant loss in receptor affinity.[8] Therefore, we directed our attention to modifications of the piperazine group based upon reports that alterations in this region may be better tolerated. Our synthetic strategy was designed such that we would be able to selectively modify each nitrogen of the polymethylene diamine group with an appropriate R^1/R^2 group (Figure 2). The success of this approach, plus the recent work by both Matecka[9] and Dutta[10] on structurally similar compounds, prompted us to present the results of our preliminary study.

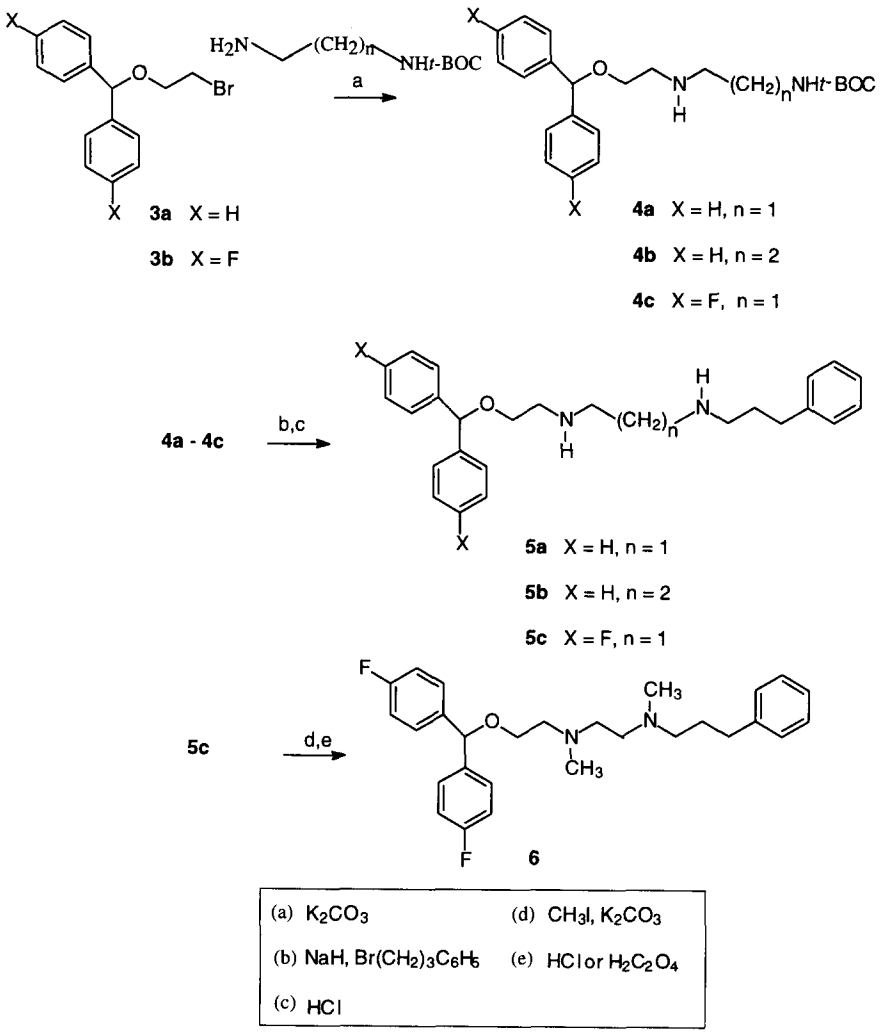
Figure 2



Seco GBR Analogs

The synthetic scheme for the preparation of representative N-[2-(bisarylmethoxy)ethyl-N'-aralkyl-α,ω-alkane diamines is depicted in Scheme 1. The requisite starting materials **3a,b** (85%, 86%), and the mono *t*BOC diamines were prepared according to literature procedures.[5,11]

SCHEME 1



The key factor in our scheme was the utilization of the N-[2-bisarylmethoxy)ethyl-N-*t*BOC-polymethylenediamine. The monoalkylation proceeded in good yield (78–83%) to give intermediates **4a-c** in which the amines possess very different physicochemical properties. We, therefore, could selectively functionalize each amino moiety to provide examples of our target series. The terminal *t*BOC-protected amine

could be selectively alkylated with 3-phenylpropyl bromide and sodium hydride in DMF to give the intermediates in 50–59% yields. The *t*BOC group would be removed with acid (HCl-dioxane) to give the bis secondary amines **5a-c** (32-37% yields). The *N,N'*-dimethyl product **6** was obtained by deprotection of the intermediate followed by dialkylation with methyl iodide in DMF using potassium carbonate as the base (yield ~ 25%). The products were characterized by IR, NMR, and elemental analysis and were consistent with the proposed structures. The products were converted to salts, either oxalate or hydrochloride, submitted to NOVASCREEN and evaluated for their ability to inhibit the neurotransmitter (dopamine-DA, norepinephrine-NE, and serotonin-5-HT) reuptake systems. The results for our initial products are shown in Table 1. The results indicate that most of the new compounds demonstrate the ability to inhibit dopamine uptake at concentrations comparable to or lower than that reported for cocaine. The IC_{50} values approach those cited for the potent inhibitors GBR12909 and GBR12935. The *N,N'*-dimethyl derivative **6** which possessed the highest affinity, also demonstrated high selectivity for the dopamine transporter (10 nM) as compared to norepinephrine (>10,000 nM) or serotonin (1500 nM) transporters. These results which were determined for **6** were slightly better than those reported by Matecka[9] for the nonfluorinated analog of **6**.

TABLE 1

IC_{50} Values of test agents at biogenic amine transporters and their selectivity for dopamine (DA) transporters

	IC_{50}[a]			Selectivity	
Compound	DA[b]	5-HT[c]	NE[d]	DA/5-HT	DA/NE
	^{3}H-Dopamine	^{3}H-Serotonin	^{3}H-Norepinephrine		
5a	1230	>10,000	>10,000	>8	>8
5b	150	>10,000	>10,000	>65	>65
5c	49	500	>10,000	10	>200
6	10	1,500	>10,000	150	>1,000
2b	505	>10,000	>10,000	>20	>20
2c	780	>10,000	2,190	>13	3
GBR12909[e]	4.3	70	----	16	----
GBR12935[f]	37	290		78	----
Cocaine[g]	89	1.045	3,300	2	

[a] IC_{50} values represent the average of triplicate assays for N = 2 runs.
[b] Bupropion hydrochloride as standard competitive ligand, IC_{50} = 1230 nM.
[c] Desipramine hydrochloride as standard competitive ligand IC_{50} = 2.5 nM.
[d] Imipramine hydrochloride as standard competitive ligand, IC_{50} - 2.6 nM.
[e] Reference 12.
[f] Reference 13.
[g] Reference 14.

The preliminary data suggest that the intact piperazine group present in GBR12909 and GBR12935 is not required for binding and may be replaced by a more conformationally flexible polymethylenediamine (n = 1,2) moiety. Both ethylene and propylene spacers for the bis secondary amines possessed submicromolar IC_{50} values which approach that of the piperazine GBR12935. Compound **6** and the *N,N'*-dimethyl analog of **5c** demonstrated greater affinity and selectivity compared to the bis secondary amine. The presence of the 4,4'-difluoro groups in these derivatives also seems to impart a significant enhancement of DAT binding as indicated by **5c** vs. **5a**. A further comparison of the GBR products to their *E*- and *Z*-iodoallyl analogs suggested that the presence of the terminal aromatic group plays a significant role in the transporter binding and it cannot be replaced by another group with a similar molecular weight (e.g., an iodo substituent) without a major decrease in affinity.

In summary, this initial series of analogs of the piperazine containing DAT inhibitors, in which the piperazine group has been replaced with a polymethyenediamine moiety, demonstrates substantial affinity and selectivity for the dopamine transporter. The synthetic strategy provides for the efficient synthesis of symmetrically or assymmetrically substituted nitrogens within this linking moiety. Based upon the findings of this preliminary study we are extending our efforts to explore the in vivo properties of GBR analog **6** and to prepare and evaluate more derivatives of this series. The results of these studies will be reported in greater detail in subsequent publications.

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