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Identification of a Novel Partial Inhibitor of Dopamine Transporter Among 4-Substituted 2-Phenylquinazolines

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Abstract—In an attempt to identify novel ligands for the dopamine transporter, a series of 4-substituted-2-phenylquinazolines were synthesized and evaluated. Among the compounds studied, 4-[(diphenylmethyl)amino]-2-phenylquinazoline (**4g**) was identified as a novel partial inhibitor of [^{125}I]RTI-55 binding to the dopamine transporter and a partial inhibitor of [^{3}H]dopamine uptake.

Cocaine (**1**) is a powerful stimulant of the central nervous system with severe addiction liability. The reinforcing and stimulant properties of cocaine are thought to be mediated through its binding and inhibition of monoamine transport systems, in particular the dopamine (DA) transporter (DAT).[1] Other neurotransmitters such as norepinephrine[2] and serotonin[3] likely contribute to the addictive effects of cocaine in humans. The binding of cocaine at the DAT blocks the translocation of dopamine from the synaptic cleft into the presynaptic neurons leading to potentiation of the actions of dopamine at the postsynaptic receptors. Although numerous cocaine analogues and a variety of other structural classes of compounds with exceptional binding potency for DAT have been reported, many of these compounds have been found to display a cocaine-like behavioral profile in animal models of drug abuse.[4] Major classes of DAT ligands that have been identified thus far include 3-aryltropanes,[5] 8-oxa-3-aryltropanes,[6] benztropines,[7] piperazines and pipieridines related to the GBR-series of compounds,[8] mazindol[9] and methylphenidate analogues.[10] Accumulating evidence indicates that these disparate DAT inhibitors do not all interact with the DAT in the same manner.[11,12] Moreover, several lines of evidence indicate the presence of distinct binding sites at DAT for dopamine and other DAT-binding ligands raising the possibility of development of a small molecule cocaine antagonist which would specifically inhibit cocaine binding at DAT while permitting the normal transport of dopamine.[12,13] Despite this theoretical possibility, however, the discovery and development of such a ligand remains to be achieved.[14] Recent evidence suggests that certain classes of dopamine uptake inhibitors that are structurally distinct from cocaine exhibit a non-cocaine like pharmacological profile.[15,16] Hence, in the search for novel therapeutics for cocaine abuse there is a renewed interest in compounds that are structurally divergent from those that have been tested todate, as novel pharmacophoric elements may engender novel modes of interaction at the DAT and provide ligands with the desired pharmacological profile.

In an effort to identify novel ligands structurally distinct from hitherto investigated classes, we focused our attention on a small group of readily accessible quinazoline derivatives. Recently, Meltzer and coworkers reported their finding that simple aromatic compounds such as **2** and **3** display surprisingly potent binding to the DAT with affinities (**2**, $IC_{50} = 0.548$ μM; **3**, $IC_{50} = 0.145$ μM) in the same range as that of cocaine ($IC_{50} = 0.09$ μM).[17] Molecular overlays indicated that a template such as the 2-phenylquinazoline could mimic the aromatic systems present in **2** and **3**. On this basis we used the 2-phenylquinazoline nucleus to append substituent groups at the easily derivatized 4-position to generate and examine a small group of compounds

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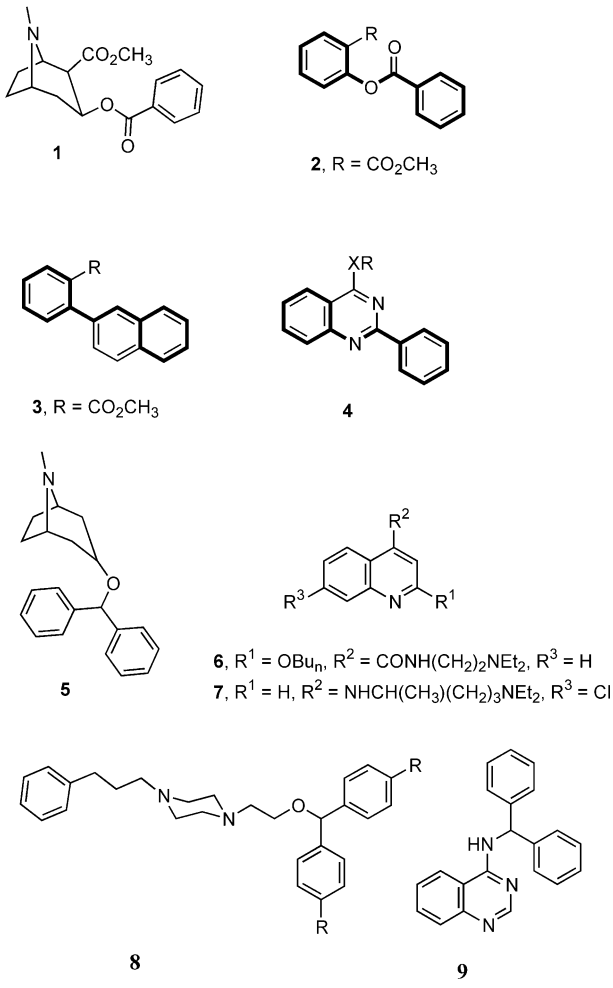
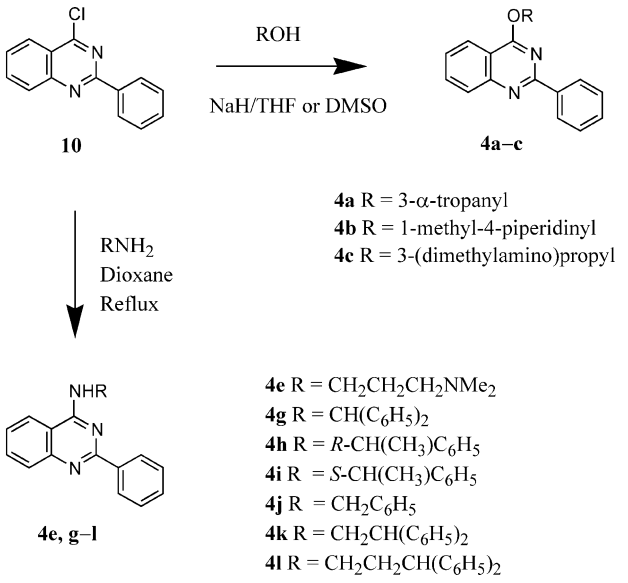


represented by the generic structure **4** as DAT ligands. We chose to derivatize the 4-position of the 2-phenylquinazoline nucleus with substituents carrying a pendant dialkylamino or diphenylmethyl group as these structural motifs occur as pharmacophoric functions in benztropine (**5**) dibucaine (**6**), chloroquine (**7**) and piperazine-GBR series of DAT ligands (**8**). Although the quinolines **6** and **7** reportedly bind to DAT with relatively low affinities (K_i for **6** = 10.8 μM; K_i for **7** = 24 μM), among a group of compounds that were examined for DAT binding and DA uptake inhibition under identical assay conditions, these two compounds displayed significant differential in the binding and DA uptake inhibition (K_i uptake/K_i binding = 9.04 and 10.21 for **6** and **7**, respectively).[18]

As shown in Scheme 1, all of the 4-alkoxy- and 4-alkylamino-2-phenylquinazolines including **4j**[19] were prepared by nucleophilic displacement reaction of 4-chloro-2-phenylquinazoline (**10**) with the appropriate sodium alkoxide generated from the aminoalcohol and sodium hydride in THF or DMSO or with an excess of appropriate amine in refluxing dioxane. The thioether derivatives **4d**[20] and **4f** were obtained through the alkylation of 4-mercapto-2-phenylquinazoline with the appropriate alkyl halide in the presence of a base.[21–23]

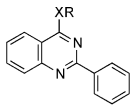


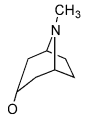
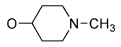
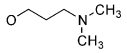
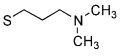
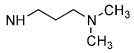
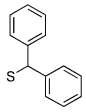
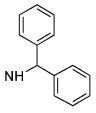
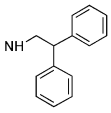
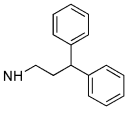
Scheme 1. Synthesis of 4-alkoxy- and 4-alkylaminoquinazolines.

The affinities of the compounds for the dopamine transporter (DAT) and serotonin transporter (SERT) in rat caudate membranes were determined by displacement assays using [^{125}I]RTI-55 as the radioligand. As described elsewhere, when assaying DAT either 100 nM paroxetine or 100 nM citalopram was used to block SERT binding and when assaying SERT, 100 nM GBR12935 was used to block DAT binding.[24] The binding affinity data are presented in Table 1. The alkoxy and alkylthio compounds **4a–d** possessing a pendant basic nitrogen displayed DAT binding affinities in the 5–10 μM range with the tropanyloxy derivative **4a** showing the highest affinity within this group. Among the diphenylmethyl compounds, while the diphenylmethylthio compound **4f** was devoid of any significant binding affinity to DAT, the binding profile of the diphenylmethylamino compound **4g** turned out to be of particular interest. In the binding studies with DAT, **4g** inhibited [^{125}I]RTI-55 binding in a biphasic manner with the inhibition curve reaching a plateau at about 20% of control. Characterization of the binding of **4g** to DAT using binding surface analysis[25] showed that a two site model fit the data better than one site model. According to the two site model of DAT binding in rat caudate the compound discriminates the two sites binding with a K_i value of 530 nM at one site and with negligible affinity at the other site.[26] In the dopamine uptake experiment using [^{3}H]dopamine, the compound again displayed partial inhibition of dopamine uptake with an apparent plateau at about 50% of control. The estimated IC_{50} value for the inhibition of [^{3}H] dopamine uptake was 6.38 μM.[26] Although some studies have reported high and low affinity binding sites associated with DAT, we have consistently observed a single [^{125}I]RTI-55 binding site as well as one component of [^{3}H]dopamine uptake in rat caudate membranes.[24,27] The binding and uptake inhibition profile of **4g** therefore appears to be unique among DAT ligands.

In an effort to investigate the importance of the diphenylmethylamino moiety for DAT binding, we synthesized

Table 1. Binding affinities at the dopamine and serotonin transporters



Compd	XR	DAT binding K_i, μM[a]	SERT binding K_i, μM[a]
4a		5.1 (±0.4)	5.1 (±0.3)
4b		9.1 (±0.3)	>10
4c		9.9 (±0.3)	>10
4d[b]		6.1 (±0.2)	9.6 (±0.4)
4e		>10	>10
4f		>10	>10
4g		0.53 (±0.1)[c]	>10
4h		6.1 (±0.3)	>10
4i		1.8 (±0.07)	>10
4j[d]		7.9 (±0.4)	>10
4k		5.4 (±0.1)	>10
4l		>10	>10
1	Cocaine	0.46 (±0.03)	0.13 (±0.01)

[a]Values are means of three experiments, standard deviation is given in parentheses.
[b]Ref 20.
[c]See Table 4 in ref 26.
[d]Ref 19.

and evaluated a few other analogues in which the diphenylmethyl goup was replaced with a 1-phenylethyl or benzyl group (**4h**–**j**) and in which the diphenylmethyl group was incorporated as a pendant group on an aminoalkyl chain (**4k** and **4l**). Unlike **4g** all of these compounds displayed DAT binding profile similar to that of cocaine. The partial and full inhibition profiles displayed by **4g**, **4i** and cocaine are shown in Figure 1. Compound **4j** lacking one of the phenyl groups of the diphenylmethyl moiety displays only weak affinity for DAT ($K_i = 7.9$ μM). Interestingly, while introduction of a methyl group in the *R* configuration on the prochiral methylene carbon of **4j** did not produce any significant change in the binding affinity (**4h**, $K_i = 6.1$ μM), the introduction of the methyl group in the *S* configuration (**4i**, $K_i = 1.8$ μM) led to a 4-fold enhancement in binding affinity. These results indicate sterically defined lipophilic interactions with two aryl groups or an aryl and an alkyl group are involved in the binding of these ligands at the ligand binding site in the DAT. Moreover, the phenyl group at the 2-position of the quinazoline ring also seems to be essential for binding at the DAT since compound **9**, an analogue of **4g** lacking this feature did not display appreciable binding affinity ($K_i > 10$ μM). With the exception of **4a** and **4d**, all of the quinazolines were devoid of any significant binding affinity to the serotonin transporter.

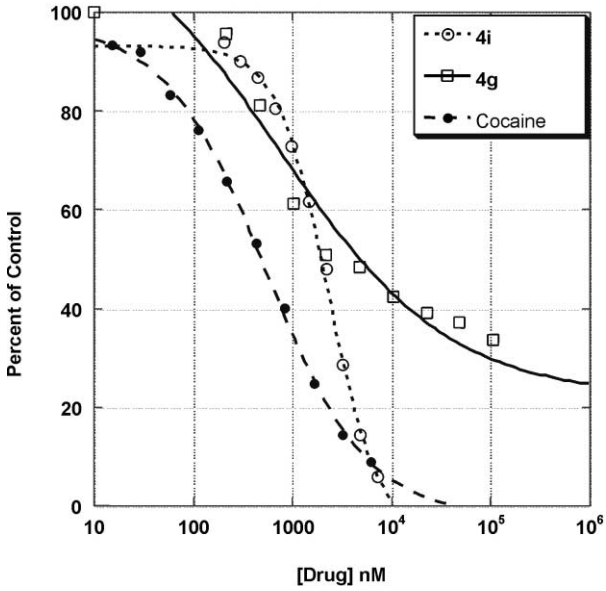


Figure 1. Inhibition of [^{125}I]RTI-55 binding to DAT by **4g**, **4i** and cocaine.

In summary, we have examined a series of 4-substituted-2-phenylquinazolines as ligands for dopamine transporter and have identified **4g** as a novel ligand that functions as a partial inhibitor of dopamine transporter binding and dopamine uptake. Further molecular manipulations should lead to the identification of newer DAT ligands with novel binding and activity profiles. Moreover studies with **4g** and related compounds might lead to the discovery of ligands with unique pharmacological and behavioral profiles that are desired in a pharmacotherapeutic agent for the treatment of cocaine addiction.

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21. All compounds were characterized by elemental analysis and ^{1}H NMR and Mass spectral data.
22. Representative procedure for 4-alkoxyquinazolines. Exemplified for **4a**. Sodium hydride (60% dispersion in mineral oil; 1.2 g, 30 mmol) was added to a stirred solution of tropine (3.53 g, 25 mmol) in DMSO (25 mL) under an atmosphere of argon. After 30 min, 4-chloro-2-phenylquinazoline (**10**) (6.02 g, 25 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was treated with half-saturated aqueous $NaHCO_3$ solution (100 mL). The solid obtained was collected by filtration, dissolved in $CHCl_3$ and the solution was washed with H_2O and dried (Na_2SO_4). The crude product obtained on removal of the solvent was purified by chromatography over a column of silica using $CHCl_3$–MeOH (99:1 to 97:3 gradient) as the eluent to obtain **4a** (5.45 g, 63%) as a colorless crystalline solid: mp 136–137 °C; TLC, R_f 0.24 ($CHCl_3$–MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21–2.07 (m, 6H, CH_2's), 2.33 (m, 2H, CH_2), 2.36 (s, 3H, N–CH_3), 3.22 (m, 2H, H-1,5), 5.81 (bt, J = 5.2 Hz, 1H, H-3), 7.51–7.46 (m, 3H, Ph), 7.52 (dt, 1H, H-6′), 7.81 (dt, 1H, H-7′), 7.99 (ddd, 1H, H-5′), 8.12 (ddd, 1H, H-8′); 8.54 (m, 2H, Ph); FABMS m/z 346 $(MH)^+$. Anal. ($C_{22}H_{23}N_3O$) C, H, N.
23. Representative procedure for 4-alkylaminoquinazolines. Exemplified for **4g**. A suspension of **10** (1.2 g, 5 mmol) and aminodiphenylmethane (1.83 g, 10 mmol) in dioxane (20 mL) was heated at reflux for 24 h. The mixture was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (60 mL) and the solution was washed successively with 5% aqueous NaOH (2×30 mL) and H_2O (40 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by chromatography over a column of silica using $CHCl_3$ as the eluent to obtain **4g** (1.23 g, 63%) as a white crystalline solid: mp 172–74 °C; TLC, R_f 0.38 ($CHCl_3$–MeOH 99:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.0 Hz, 1H, $CHPh_2$), 7.25–7.30 (m, 2H, Ph_2); 7.35–7.40 (m, 4H, Ph_2), 7.45–7.54 (m, 8H, H-5, H-6, H-7, Ph_2 and Ph) 7.93 (m, 2H, Ph), 8.46 (m, 2H, Ph), 8.59 (bdt, 1H, H-8), 8.96 (d, J = 8.0 Hz, 1H, NH); FABMS m/z 388 $(MH)^+$. Anal. ($C_{27}H_{21}N_3$) C, H, N.
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