Solution Phase Parallel Synthesis of Substituted 3-Phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazolines: Selective Serotonin 5-HT$_6$ Receptor Antagonists

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Here we present the solution phase parallel synthesis of a combinatorial library consisting of 776 new substituted 3-phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazolines and a study of the relation of their structure with a 5-HT$_6$ receptor antagonistic activity in a functional cell (HEK 293) analysis and radioligand competitive binding. We have found highly active and selective 5-HT$_6$R antagonists. The most active 5-HT$_6$R antagonists have IC$_{50}$ <100 nM in a functional assay, and K_i <10 nM in a binding assay, which is 100 times higher than the activity with respect to other serotonin receptors.

Introduction

Serotonin 5-HT$_6$ receptor (5-HT$_6$R) is a very unusual member of the family of serotonin receptors. It is distributed almost exclusively within the central nervous system (CNS).[1,2] 5-HT$_6$Rs in mammals are located primarily in the areas of the brain responsible for learning and memory.[3] It is also known[4] that 5-HT$_6$Rs act as modulators of several neurotransmitter systems including the cholinergic, noradrenergic, glutamatergic, and dopaminergic systems. Given the fundamental role of such systems in normal cognitive processes and their dysfunction in neurodegeneration, the exclusive role of 5-HT$_6$R becomes apparent in the formation of normal or pathologic memory. In this regard, application of 5-HT$_6$R antagonists is considered to be a promising treatment for some CNS diseases.[5,6]

Another attractive feature of 5-HT$_6$R antagonists is their ability to suppress appetite, which may lead to the creation of a fundamentally new means to treat obesity.[7]

Since the discovery of 5-HT$_6$R,[1,2] many ligands have been synthesized, the vast majority of which are heterocyclic compounds possessing sulfonyl substituents.[5,8] A number of 5-HT$_6$R antagonists have reached clinical trials.[9,10] Indeed, interest for developing 5-HT$_6$R antagonists as CNS drugs so far has not weakened.[6]

As a result of screening a focused library of 2880 compounds containing the sulfonyl group, we found a new group of 5-HT$_6$R antagonists, represented by a 3-phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazolin (PSTQ) core.

In this paper, we describe a solution phase parallel synthesis of combinatorial libraries (CL), which includes 776 new PSTQ compounds (Figure 1), and a study of the 5-HT$_6$R antagonist structure−activity relationship (SAR).

Results and Discussion

A CL of substituted 5-amino-PSTQ was prepared by solution phase parallel synthesis (Scheme 1) based on 5-chloro-PSTQ **1**{*1−14*} and amines **2**{*1−60*} (Chart 1). The reaction was carried out in *N*,*N*-dimethylformamide (DMF) in the presence of tetraethylammonium (TEA) at 100−120 °C. A total of 773 5-Amino-PSTQs **3** {*1−14,1−60*} were isolated with 70−90% yield by precipitation with water and subsequent recrystallization from methanol.

Key building blocks **1**{*1−14*} for the synthesis of PSTQ CL were obtained with high yield in a three-stage synthesis (Scheme 2) based on anthranilic acid esters **4**{*1,2*}.

Azides **5**{*1,2*} were formed by diazotization of **4**{*1,2*} and treatment of the formed diazonium salts with sodium azide. Reaction of azides **5**{*1,2*} with arylsulfonylacetonitriles **6**{*1−11*}, by analogy with phenylacetonitrile,[13] in ethanol in the presence of sodium ethoxide resulted in 5-hydroxy-PSTQ **7**{*1−14*} (Scheme 2). As acetonitriles **6**{*1−11*}, along with unsubstituted phenylsulfonylacetonitrile **6**{*1*}, we used 4-methyl- **6**{*2*}, 4-ethyl- **6**{*3*}, 4-*tert*-butyl- **6**{*4*}, 4-fluoro- **6**{*5*}, 4-chloro- **6**{*6*}, 4-bromo- **6**{*7*}, 2,5-dimethyl- **6**{*8*}, 3,4-dimethyl- **6**{*9*}, 2,4,6-trimethyl- **6**{*10*}, and 2,5-dimethox-

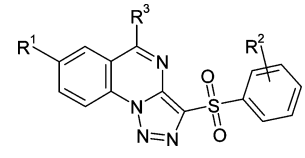

Figure 1. PSTQ compounds.

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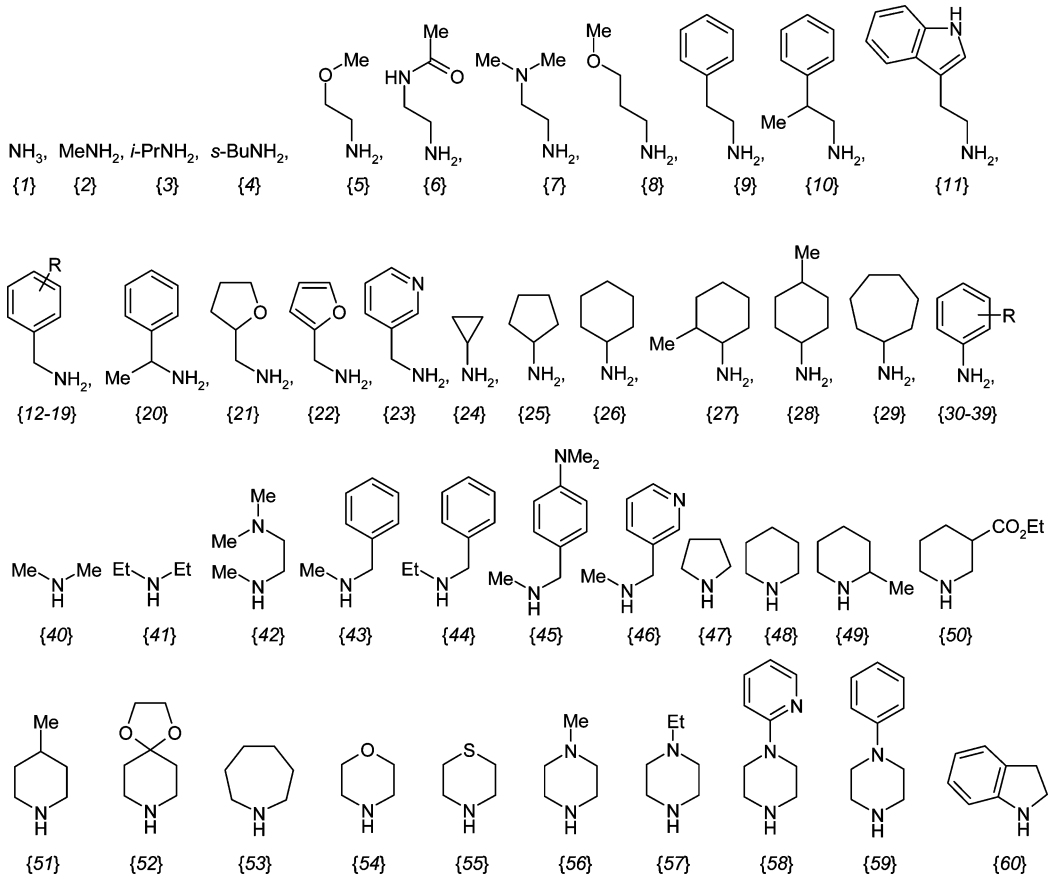
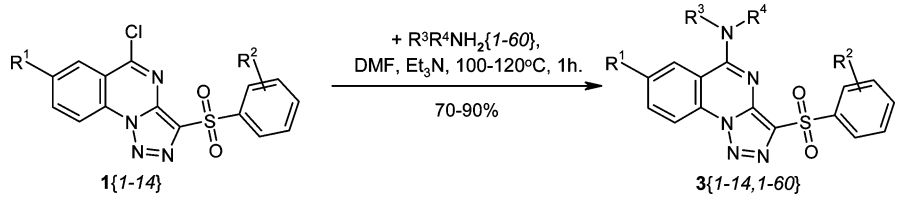
Chart 1. List of Amines 2{*1*−*60*} for Combinatorial Library of 773 Substituted 5-Amino-PSTQ 3

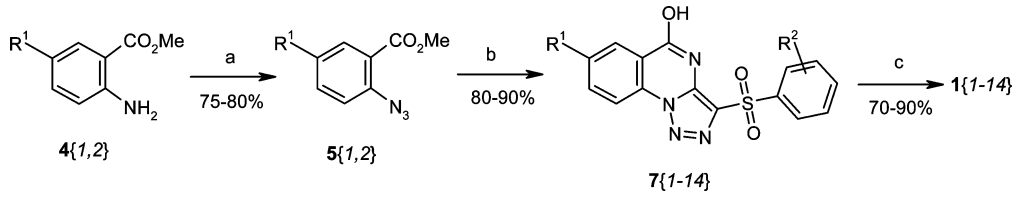


2{*12-19*}: R = H {*12*}, 2-Cl {*13*}, 2-MeO {*14*}, 3-MeO {*15*}, 4-Me {*16*}, 4-MeO {*17*}, 4-F {*18*}, 4-Cl {*19*}; **2**{*30-39*}: R = H {*30*}, 2-Et {*31*}, 3-Me {*32*}, 3-MeO {*33*}, 3-CF_3 {*34*}, 4-MeO {*35*}, 4-Cl {*36*}, 2,3-di-Me {*37*}, 2,4-di-MeO {*38*}, 2,5-di-MeO {*39*}.

Scheme 1. CL Synthesis of Substituted 5-Amino-PSTQ



Scheme 2. 5-Chloro-PSTQ **1**{*1*−*14*} Synthesis



ybenzene-sulfonylacetonitrile **6**{*11*}. 5-Hydroxy-PSTQ **7**{*1*−*14*} were converted into key building blocks **1**{*1*−*14*} by the action of phosphorus oxychloride in the presence of triethylamine.

For the reaction with 5-chloro-PSTQ **1**{*1*−*14*} we used ammonia **2**{*1*}, primary amines: alkylamines **2**{*2*−*23*}, cycloalkylamines **2**{*24*−*29*}, anilines **2**{*30*−*39*} and secondary amines: dialkylamines **2**{*40*−*46*}, pyrrolidine **2**{*47*}, piperidines **2**{*48*−*52*}, azepan **2**{*53*}, morpholine **2**{*54*}, thiomorpholin **2**{*55*}, piperazines **2**{*56*−*59*}, and 2,3-dihydro-1*H*-indole **2**{*60*}.

For a more complete SAR of PSTQ, we synthesized unsubstituted PSTQ **8**, 5-ethylthio-PSTQ **9**, and 5-(2-methoxyethyloxy)-PSTQ **10** (Scheme 3). PSTQ **8** was formed by hydrogenation of 5-chloro-PSTQ **1**{*1*} on Pd /C in methanol−benzene mixture. 5-Ethylthio-PSTQ **9** was obtained by reaction of 5-chloro-PSTQ **1**{*1*} with EtSK in dimethylsulfoxide (DMSO), and 5-(2-methoxyethyloxy)-PSTQ **10** - with 2-methoxyethanol in the presence of TEA (Scheme 3).

The purities and structural identities of the synthesized PSTQs were confirmed by liquid chromatography-mass spectroscopy (LC-MS) analysis and NMR spectroscopy.

Scheme 3. Synthesis of PSTQ **8**, **9**, **10**

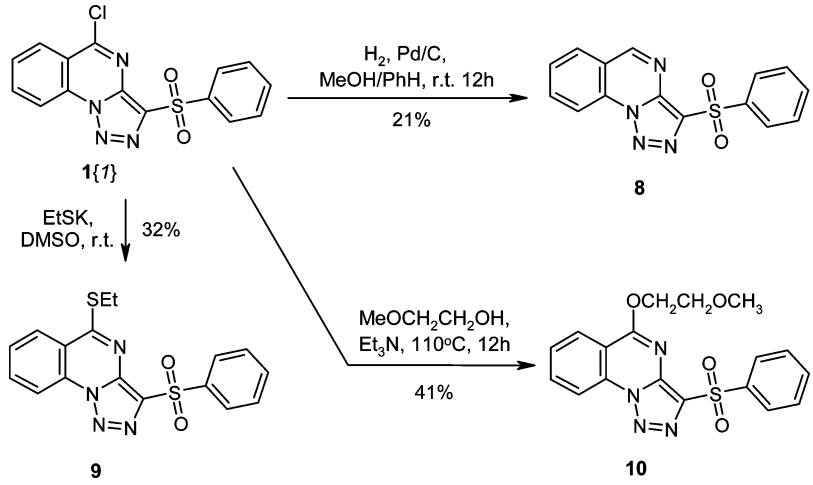


Table 1. Antagonistic 5-HT_6R Activity of PSTQ **1**, **7**−**10**

compd	R^1	R^2	R^3	IC_{50}, nM, (%)[a]
7{*1*}	H	H	OH	(18)
7{2}	H	4-*t*-Bu	OH	(25)
7{*3*}	H	4-MeO	OH	(0)
1{*1*}	H	H	Cl	(42)
1{2}	H	Cl	Cl	(27)
8	H	H	H	5736.0
9	H	H	EtS	1049.0
10	H	H	$MeOCH_2CH_2O$	1374.0

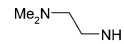
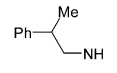
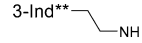
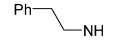
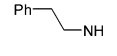
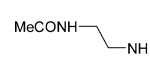
[a] Percentage of inhibition of adenylyl cyclase activity at concentrations of 10 μM PSTQ.

According to the LC-MS, purity of the synthesized PSTQs exceeded 98%, while the masses of their molecular ions were consistent with their molecular weights.

In the NMR spectra of 5-hydroxy-PSTQ **7**{*1*−*3*} there is a broad signal at 12.09−12.85 ppm characteristic of the enolic forms of these compounds. Hydroxy state of 5-hydroxy-PSTQ **7** is also confirmed by IR spectrum of **7**{*1*}, where there are no valence vibration signals in the 1690−1650 cm^{-1} characteristic for the carbonyl group of an amide fragment. Note that the described[11] 3-phenyl analogue had the structure of 3-phenyl-[1,2,3]triazolo[1,5-*a*]quinazolin-5(^{4}H)-one with valence vibration signals in the 1680 cm^{-1}.

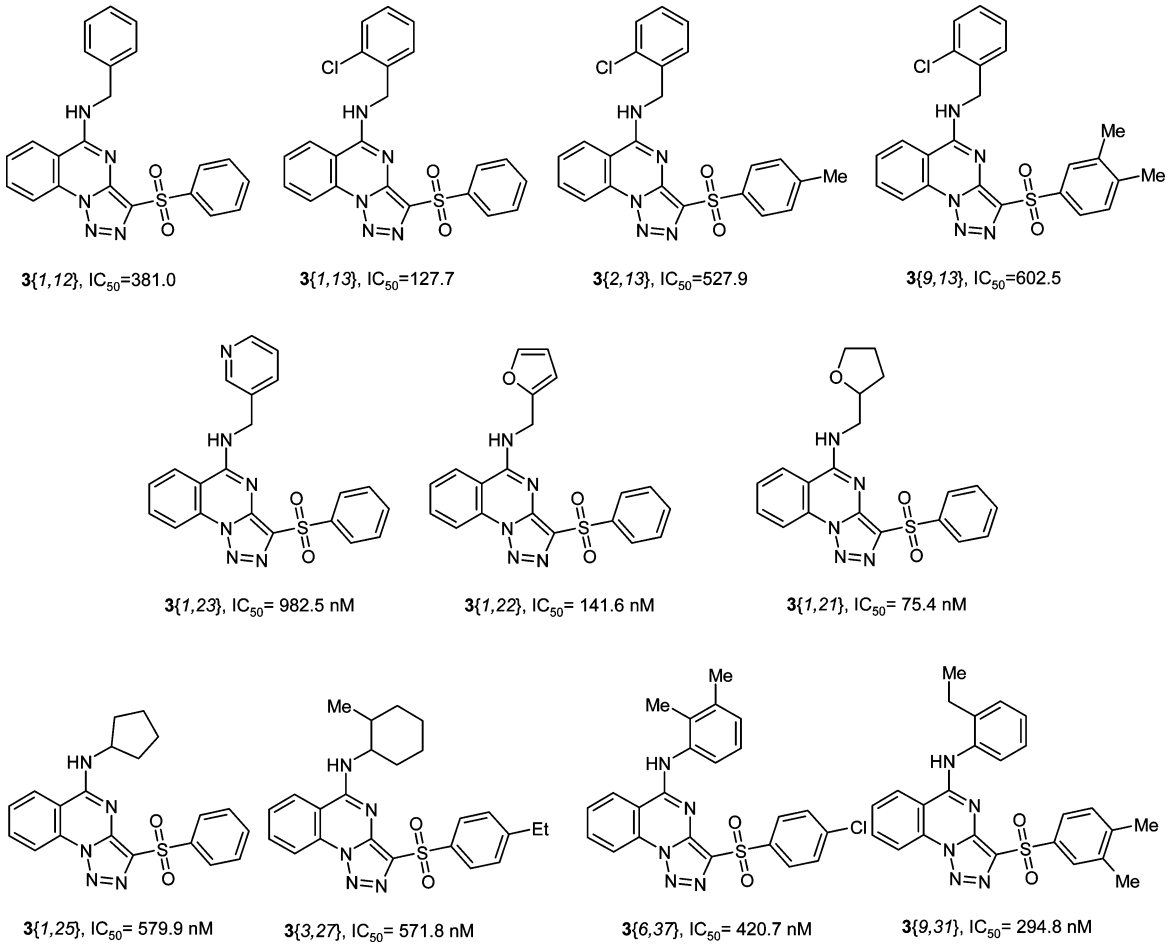
In the NMR spectra of the synthesized PSTQs, chemical shifts of protons are consistent with their structure. In the experimental section there are some examples of PSTQ NMR

Table 2. Antagonistic 5-HT_6R Activity of 5-Alkylamino-PSTQ **3**

compd	R^1	R^2	R^3	IC_{50}, nM, (%)*
3{*1,2*}	H	H	MeNH	(22)[a]
3{*1,4*}	H	H	*s*-BuNH	(55)[b]
3{*1,7*}	H	H		(49)[a]
3{*2,10*}	H	4-Me		606.0
3{*3,11*}	H	4-Et		(25)[a]
3{*6,9*}	H	4-Cl		(46)[a]
3{*8,4*}	H	2,5-di-Me	*sec*-BuNH	(54)[b]
3{*9,9*}	H	3,4-di-Me		2,010.0
3{*10,3*}	H	2,4,6-tri-Me	*i*-PrNH	2,181.0
3{*10,4*}	H	2,4,6-tri-Me	*s*-BuNH	964.3
3{*13,1*}	Cl	4-Et	NH_2	(-3)[a]
3{*13,6*}	Cl	4-Et		(-2)[a]

* Percentage of inhibition of adenilylciclaze activity at concentrations as indicated in the footnotes *a* and *b*. [a] 5 μM. [b] 10 μM PSTQ.** Indol-3-yl.

Chart 2. Dependence of 5-HT$_6$R Antagonist Activity on the Structure of PSTQ 3{*1,12−13; 1,21−23; 1,25; 2,13; 3,27; 6,37; 9,13; 9,31*}



spectra, which are characterized by the signals of aromatic protons of quinazoline moiety and arylsulfonyl substituents. The former (if unsubstituted) are represented by two doublets: C(6)*H* at 8.39−8.77 ppm and C(9)*H* at 8.35−8.51 ppm, and two triplets: C(7)*H* at 7.95−8.08 ppm and C(8)*H* at 7.55−7.86 ppm. The amino group in 5-amino-PSTQ **3** gave rise to several broad range signals because of the shift in a strong field. In 7-chloro-PSTQ **3**{*12−14*, *1−60*} NMR signals of the proton at C(6) appear as a singlet and at C(8) as a doublet. Chemical shifts of the protons at C(6), C(8), and C(9) remained virtually unchanged throughout the series. NMR signals of protons of arylsulfonyl substituents vary depending on the location and nature of substituents in the aryl group. The signals of protons in the unsubstituted phenylsulfonyl substituents PSTQ **3**{*1,1−60*}, **3**{*12,1−60*} presented as a doublet at 8.25 ppm (2H), a triplet at 7.65 ppm (1H) and multiplet at 7.55 ppm (2H), while in the 4-substituted PSTQ **3**{*2−7,1−60*}, **3**{*13,1−60*} proton signals appear as two doublets at 8.0−7.8 ppm and 7.8−7.5 ppm.

Signals of substituents at C-5 are different for each substance; their shape and chemical shifts depend upon the structure of the substituents. In the NMR spectrum of PSTQ **8** unsubstituted at position 5, the corresponding singlet at 9.31 ppm appears, and 5-ethylthio-PSTQ **9** has signals characteristic to the ethyl group: quadruplet at 3.55 and triplet at 1.58 ppm.

In the spectrum of 5-(2-methylcyclohexylamino)-PSTQ **3**{*1,27*} the signals of the secondary amino group and the methyl group appear in a form of two doublets (8.70, 8.22 and 0.89, 0.86 ppm, respectively), because of the *cis-trans* isomerism, characteristic of the 2-methylcyclohexyl fragment.

Screening of PSTQ for 5-HT$_6$R antagonistic activity was performed in vitro by testing the ability to inhibit functional cellular responses to serotonin at compound concentrations of 1 μM, 5 μM, and 10 μM. Stimulation of the HEK 293 cells, stably expressing recombinant human 5-HT$_6$R, activates adenylyl cyclase, which leads to increased synthesis of intracellular cAMP, which was estimated with the help of LANCE technology.[12] PRX-07034 and SB-742,457 were used as standards of comparison.

For 37 of the PSTQ that inhibited the synthesis of cAMP by more than 50% at a concentration of 5 μM, we determined the IC$_{50}$, namely, the concentration of a substance that leads to the 50% inhibition of adenylyl cyclase activity (Figure 1, Tables 1−6).

Among PSTQ **1**, **7**−**10** (Figure 1, Table 1), 5-ethylthio-PSTQ **9** is the most active with IC$_{50}$ = 1049.0 nM, and the least active are the 5-hydroxy-PSTQ **7**{*1−3*}, which weakly inhibit 5-HT$_6$R (from 0% to 25%) at a concentration of 10 μM. PSTQ **8**, which is unsubstituted at position 5, also has weak activity (IC$_{50}$ = 5736.0 nM).

The activities of 5-alkylamino-PSTQ **3**{*1,2; 1,4; 1,7; 2,10; 3,11; 6,9; 8,4; 9,9; 10,3−4; 13,1; 13,6*} (Figure 1, Table 2)

vary widely, and it is not possible to establish a clear link between their structures and activities. These activities strongly depend on the presence and position of substituents in the molecule PSTQ. We note only that in this series of compounds the most active were 5-(2-phenylpropylamino)-PSTQ **3**{*2,10*} with IC_{50} = 606.0 nM and 5-*s*-butylamino-PSTQ **3**{*10,4*} with IC_{50} = 964 nM.

Better 5-HT_6R antagonists were found among 5-benzylamine-PSTQ, their hetero analogues **3**{*1,12−13; 1,20−23; 2,12−13; 2,20−21; 3,12; 6,20; 9,13; 9,18; 9,20−21; 10,21; 12,21; 13,22*} and 5-(2-phenylpropylamino)-PSTQ **3**{*2,10*} (Tables 2, 3). In the series of 5-benzylamine-PSTQ **3**{*1,12−13; 1,20; 2,12−13; 2,20; 3,12; 6,20; 9,13; 9,18; 9,20*} the most active are 5-(2-chloro-benzylamino-PSTQ **3**{*1,13; 2,13; 9,13*}. Note, that the introduction of methyl substituents in the 3-phenylsulfonyl fragment leads to a decrease in activity (Chart 2).

The transition from 5-benzylamino-PSTQ to their heteroanalogues is accompanied by a significant change in their activity (Chart 2). Thus, 5-(pyridin-3-ylmethylamino)-PSTQ **3**{*1,23*} is 2.6 times less active than 5-benzylamino-PSTQ **3**{*1,12*}, and the latter is 2.7 times less active than 5-(furan-2-ylmethylamino-PSTQ **3**{*1,22*}, and 5 times less active than 5-(tetrahydrofuran-2-ylmethylamino-PSTQ **3**{*1,21*}. It should be noted that the introduction of any additional substituents in the molecule of 5-(tetrahydrofuran-2-ylmethylamino)-PSTQ **3**{*2,21; 9−10,21; 12,21*} leads to a drastic reduction in activity. For example, 5-(tetrahydrofuran-2-ylmethylamino)-7-chloro-PSTQ **3**{*12,21*} has IC_{50} = 1802.0 nM, and 5-(tetrahydrofuran-2-ylmethylamino)-3-(4-methylphenylsulfonyl)-derivative 3{*2,21*} has IC_{50} = 1483.0 nM (Figure 1, Table 3).

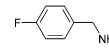
Among the investigated 5-cycloalkylamino- and 5-arylamino-PSTQ (Figure 1, Table 4) the most active were antagonists **3**{*1,25; 3,27; 6,37; 9,31*} with IC_{50} from 294.8 nM to 579.9 nM (Chart 2). At the same time, among the 5-azaheterocyclyl-PSTQ only one moderately active PSTQ 3{*9,58*} was found with IC_{50} = 1198.0 nM (Figure 1, Table 5).

In the series of 5-dialkylamino-PSTQ **3**{*1,40−44; 1,46; 1,50; 1,54; 3,60; 7,43; 7,52; 9,44; 9,53; 9,58; 12,41; 12,44; 12,58; 13,56; 14,43; 14,50*} (Table 5) 5-(*N*-alkyl-*N*-benzylamino)-PSTQ **3**{*1,43−44; 9,44*} are active, with **3**{*1,44*} IC_{50} = 163.9 nM being the most potent one.

We studied 5-HT_6R activity of several PSTQ **3** in a competitive radioligand binding assay. The results are presented in Table 6, which shows that PSTQ **3** effectively displace radioligand from its complex with 5-HT_6R. The most active ligand is 5-(2-methylcyclohexylamino)-PSTQ **3**{*1,27*} with K_i = 2.86 nM, and the least active is 5-*iso*-propylamino-PSTQ 3{*1,3*} with K_i = 49.5 nM. Note that the activity PSTQ **3** in a competitive radioligand binding and functional cell analyses varies greatly (Figure 1, Table 6), apparently because of the kinetics of interaction of PSTQ **3** with 5-HT_6R.

In a competitive radioligand binding, we investigated the activity of one of our most active compounds, PSTQ **3**{*1,21*}, on a panel of serotonin receptors (Figure 2). At a concentration of 1 μM, PSTQ **3**{*1,21*} displaces less than 12% of radioligand from complexes with 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_7 receptors, and 46% from the radioligand's complex with 5-HT_{2A}R. These data suggest that the efficiency of interaction of PSTQ **3**{*1,21*} with 5-HT_6R is more than 100 times higher than the interaction with other serotonin receptors.

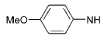
Table 3. Antagonistic 5-HT_6R Activity of 5-Benzylamine-PSTQ and Their Hetero Analogues **3**

compd	R^1	R^2	R^3	IC_{50}, nM (%)*
3{*1,12*}	H	H		381.0
3{*1,13*}	H	H		127.7
3{*1,20*}	H	H		not active
3{*1,21*}	H	H		75.4
3{*1,22*}	H	H		141.6
3{*1,23*}	H	H		982.5
3{*2,12*}	H	4-Me		320.4
3{*2,13*}	H	4-Me		527.9
3{*2,20*}	H	4-Me		740.4
3{*2,21*}	H	4-Me		1483.0
3{*3,12*}	4-Et	H		not active
3{*6,20*}	H	4-Cl		628.0
3{*9,13*}	H	3,4-di-Me		602.5
3{*9,18*}	H	3,4-di-Me		(42)
3{*9,20*}	H	3,4-di-Me		355.8
3{*9,21*}	H	3,4-di-Me		779.0
3{*10,21*}	H	2,4,6-tri-Me		1455.0
3{*12,21*}	Cl	H		1802.0
3{*13,22*}	Cl	4-Et		(4)

* Percentage of inhibition of adenilylciclaze activity at concentrations of 5 μM PSTQ.

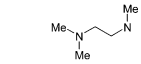
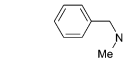
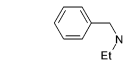
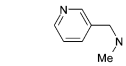
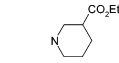
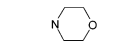
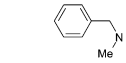
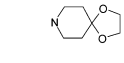
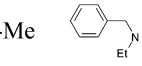
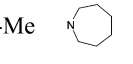
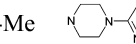
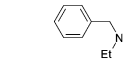
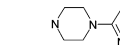
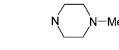
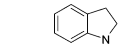
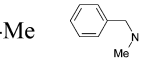
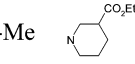
In summary, we have invented a new scaffold for 5-HT_6R antagonists, which is a (3-phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazolin-5-yl)-amine, and synthesized a combinatorial library, which includes 776 new ligands. A study of 5-HT_6R activity in a functional cell (HEK 293) analysis and radioligand competitive binding assay was performed. The most active 5-HT_6R ligands in a binding assay were secondary amines with K_i from 2.9 nM to 50.0 nM, among which the most active were *N*-(2-methylcyclohexyl)-3-(phenylsulfonyl)-

Table 4. Antagonistic 5-HT$_6$R Activity of 5-Cycloalkylamino-PSTQ **3** and 5-Arylamino-PSTQ **3**

compd	R^1	R^2	R^3	IC_{50}, nM, (%)*
3{*1,25*}	H	H		579.9
3{*1,27*}	H	H		(42)[a]
3{*1,28*}	H	H		(102)[b]
3{*1,30*}	H	H		(0)[a]
3{*3,27*}	H	4-Et		571.8
3{*5,39*}	H	4-F		(1)[a]
3{*6,31*}	H	Cl		627.6
3{*6,36*}	H	4-Cl		(41)[a]
3{*6,37*}	H	Cl		420.7
3{*6,38*}	H	4-Cl		(2)
3{*7,31*}	H	4-Br		1434.0
3{*7,37*}	H	4-Br		703.7
3{*8,31*}	H	2,5-di-Me		769.8
3{*9,31*}	H	3,4-di-Me		294.8
3{*10,32*}	H	2,4,6-tri-Me		1001.0
3{*10,33*}	H	2,4,6-tri-Me		670.1
3{*11,34*}	H	2,5-di-MeO		(31)[a]
3{*12,30*}	Cl	H		(28)[a]
3{*12,35*}	Cl	H		(3)[a]
3{*13,24*}	Cl	4-Et		(1)[a]
3{*14,30*}	Cl	3,4-di-Me		(-1)[a]

* Percentage of inhibition of adenilylciclaze activity at concentrations as indicated in the footnotes *a* and *b*. [a] 5 μM. [b] 10 μM PSTQ.

Table 5. Antagonistic 5-HT$_6$R Activity of 5-Dialkylamino- and Azaheterocyclyl-PSTQ **3**

compd	R^1	R^2	R^3	IC_{50}, nM, (%)*
3{*1,40*}	H	H	Me_2N	not active
3{*1,41*}	H	H	Et_2N	not active
3{*1,42*}	H	H		(33)
3{*1,43*}	H	H		563.7
3{*1,44*}	H	H		163.9
3{*1,46*}	H	H		(40)
3{*1,50*}	H	H		(8)
3{*1,54*}	H	H		(17)
3{*7,43*}	H	Br		(45)
3{*7,52*}	H	Br		(0)
3{*9,44*}	H	3,4-di-Me		970.7
3{*9,53*}	H	3,4-di-Me		1314.0
3{*9,58*}	H	3,4-di-Me		1198.0
3{*12,41*}	Cl	H	Et_2N	(18)
3{*12,44*}	Cl	H		(35)
3{*12,58*}	Cl	H		(-5)
3{*13,56*}	Cl	4-Et		(-2)
3{*13,60*}	Cl	4-Et		(36)
3{*14,43*}	Cl	3,4-di-Me		(8)
3{*14,50*}	Cl	3,4-di-Me		(1)

* Percentage of inhibition of adenilylciclaze activity at concentrations of 5 μM PSTQ.

[1,2,3]triazolo[1,5-*a*]quinazolin-5-amine 3{*1,27*} with K_i = 2.9 nM and *N*-(furan-2-ylmethyl)-3-(phenylsulfonyl)-[1,2,3]triazolo[1,5-*a*]quinazolin-5-amine **3**{*1,22*} with K_i = 3.5 nM. Additionally, it was shown that PSTQ **3**{*1,21*} possesses selective binding to 5-HT$_6$R over a panel of other serotonin receptors.

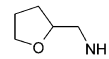
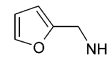
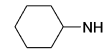
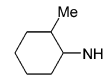
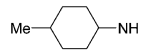
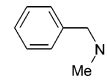
Experimental Section

LC-MS analyses were performed with a Shimadzu HPLC equipped with a Waters XBridge C18 3.5 μm (4.6 × 150 mm) column, mass detector PE SCIEX API 150 EX and spectrophotometric detector Shimadzu (λ_{max} 220 and 254 nm). According to LC-MS data, purity of the compounds obtained exceeded 98.0%. ^{1}H NMR spectra were recorded on a Varian (400 MHz, 27 °C) using DMSO-d_6 and $CDCl_3$ as solvents. IR spectra of PSTQ **7** were recorded on a Specord 75 IR in nujol.

5-HT$_6$R binding activities of synthesized PSTQ were determined in a radioligand binding assay using a panel of 8 serotonin receptors.[13]

General Procedure for Synthesis of 3-Arylsulfonyl-5-hydroxy-[1,2,3]triazolo[1,5-*a*]quinazolines 7{*1*−*14*}. A solution of $NaNO_2$ (3.33 mmol) in water (10 mL) was added gradually with stirring to a solution of anthranilic acid methyl

Table 6. 5-HT_6R Activity of PSTQ **3** in a Competitive Radioligand Binding Assay

compd	R^1	R^2	R^3	Binding assay	
				IC_{50}, nM	K_i, nM
3{*1,2*}	H	H	MeNH	>>300.0	
3{*1,3*}	H	H	*i*-PrNH	107.0	49.5
3{*1,4*}	H	H	*sec*-BuNH	15.2	7.04
3{*1,21*}	H	H		28.4	13.2
3{*1,22*}	H	H		7.62	3.54
3{*1,25*}	H	H		27.8	12.9
3{*1,26*}	H	H		10.8	5.01
3{*1,27*}	H	H		6.17	2.86
3{*1,28*}	H	H		59.5	27.6
3{*1,40*}	H	H	Me_2N	>30	
3{*1,42*}*	H	H		>30	
3{*1,43*}	H	H		16.5	7.65
3{*1,49*}	H	H		42.1	19.5
3{*8,4*}	H	2,5-di-Me	*sec*-BuNH	35.9	16.7

* As hydrochloride.

ester **4**{*1,2*} (2.34 mmol) in 18% HCl (25 mL) at 5 °C. The mixture was allowed to stir for 15 min at room temperature, then it was added dropwise to a stirred solution of NaN_3 (3.33 mmol) in water (10 mL) at −5 °C. The resulting mixture was stirred at 0 °C for 5 min and then stirred for 90 min at room temperature. The precipitate was filtered and washed with water, with hexane, and dried to give 2-azidobenzoic acid methyl esters. Yield 81%.

Sodium (21.7 mmol) was added portion wise to absolute ethanol (15 mL) at room temperature. After complete dissolution of sodium, 2-arylsulfonylacetonitrile **6**{*1*−*11*} (9.5 mmol) was added and the solution was stirred for 20 min. A solution of 2-azidobenzoic acid methyl ester (6.1 mmol) in ethanol (50 mL) was added gradually, and the resulting mixture was refluxed for 20 h. After cooling to room temperature, ethanol was removed in vacuo, the residue was dissolved in water, and extracted with $CHCl_3$. The water layer was acidified with 18% HCl (to pH 2), the formed precipitate was collected, washed with water, hexane, and dried to give the desired product with a yield from 80% to 90%.

General Procedure for the Synthesis of 3-Arylsulfonyl-5-chloro-[1,2,3]triazolo[1,5-*a*]quinazolines 1{*1*−*14*}. To a mixture of triazoloquinozaline **7**{*1*−*14*} (1.75 mmol) and TEA (12 mL) was added $POCl_3$ (8 mL) with ice-cooling. The resulting mixture was refluxed for 12 h, cooled, poured into crushed ice, and extracted with $CHCl_3$. The organic layer was washed with 5% aqueous $NaHCO_3$, then water, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give 5-chloro-PSTQ **1**{*1*−*14*} in yields from 70% to 90%.

3-Phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazoline 8. To a suspension of 5-chloro-PSTQ **1**{*1*} (0.87 mmol) in a mixture of MeOH (60 mL) and PhH (20 mL), Pd/C (10%, 100 mg) was added. The mixture was stirred for 24 h in an atmosphere of H_2, filtered through Celite and concentrated in vacuum. Product **8** was isolated by HPLC (yield 21%). ESI-MS *m*/*z* 311; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.31

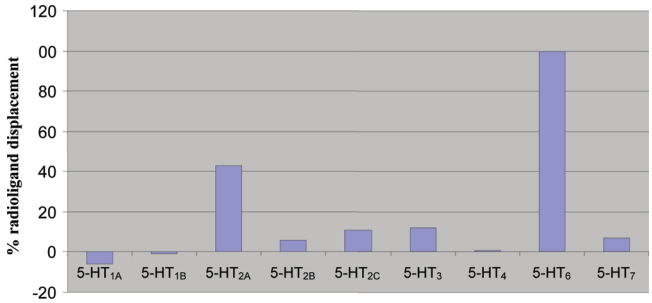


Figure 2. Selectivity profile of PSTQ **3**{*1,21*} against serotonin receptors as measured in a competitive radioligand binding assay at a concentration of 1 μM.

(s, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.28 (m, 2H), 8.18 (d, J = 8.0 Hz, 1H), 8.13 (m, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.61 (m, 1H), 7.54 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.50, 141.42, 138.91, 137.42, 136.50, 133.90, 132.61, 129.92, 129.50, 129.15, 127.32, 119.27, 115.07.

5-Ethylthio-3-phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazoline 9. To a mixture of EtSK (2.09 mmol) in DMSO (10 mL) 5-chloro-PSTQ **1**{*1*} (1.74 mmol) was added portionwise and stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuum. Product **9** was isolated by column chromatography, eluent PhH/AcOEt = 50:1 (yield 32%). ESI-MS m/z 371;^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.64 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 8.23 (m, 3H), 8.00 (m, 1H), 7.73 (m, 1H), 7.60 (m, 1H), 7.53 (m, 2H), 3.55 (q, J = 7.2 Hz, 2H), 1.58 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.84, 141.52, 137.97, 136.08, 135.16, 133.81, 131.36, 129.48, 129.08, 127.30, 125.68, 117.88, 115.80, 24.73, 13.81.

5-(2-Methoxyethoxy)-3-phenylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazoline 10. A mixture of 5-chloro-PSTQ **1**{*1*} (0.29 mmol) and TEA (0.44 mmol) in 2-methoxyethanol (2 mL) was stirred at 110 °C for 12 h. After reaction completion, the reaction mixture was poured into water (100 mL). The precipitate was filtered, washed with water, dried in air, and recrystallized from EtOH. Yield 46 mg (41%). ESI-MS m/z 385; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.52 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.11 (m, 3H), 7.84 (t, J = 7.6 Hz, 1H), 7.72 (m, 1H), 7.65 (m, 2H), 4.78 (t, J = 3.8 Hz, 2H), 3.86 (t, J = 3.8, Hz, 2H), 3.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.12, 141.05, 138.53, 135.91, 134.23, 133.87, 129.45, 128.82, 127.25, 125.70, 115.23, 112.11, 69.40, 67.59, 58.25.

General Procedure for Solution Phase Parallel Synthesis of Substituted 5-Amino-3-arylsulfonyl-[1,2,3]triazolo[1,5-*a*]quinazolines 3{*1*−*14*,*1*−*60*}. To a mixture of 5-chloro-PSTQ **1**{*1*−*14*} (1 mmol) and TEA (1 mL) in DMF (2 mL) amine **2**{*1*−*60*} (1.1 mmol) was added. The resulting mixture was heated for 1 h at 100−120 °C then cooled to room temperature and water (10 mL) was added. The resulting precipitate was separated and crystallized from MeOH (yields from 70% to 90%).

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Monsma, F. J., Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. *Mol. Pharmacol.* **1993**, *43*, 320–327.
(2) Ruat, M.; Traiffort, E.; Arrang, J. -M.; Tardivel-Lacombe, J.; Diaz, J.; Leurs, R.; Schwartz, J.-C. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 268–276.
(3) Gérard, C.; Martres, M.-P.; Lefèvre, K.; Miquel, M.-C.; Vergé, D.; Lanfumey, L.; Doucet, E.; Hamon, M.; El Mestikawy, S. *Brain Res.* **1997**, *746*, 207–219.
(4) Dawson, L. A.; Nguyen, H. Q.; Li, P. *Neuropsychopharmacology* **2001**, *25*, 662–668.
(5) Holenz, J.; Pauwels, P. J.; Díaz, J. L.; Mercè, R.; Codony, X.; Buschmann, H. *Drug Discovery Today* **2006**, *11*, 283–299.
(6) Heal, D. J.; Smith, S. L.; Fisas, A.; Codony, X.; Buschmann, H. *Pharmacol. Ther.* **2008**, *117*, 207–231.
(7) Geldenhuys, W. J.; Van der Schyf, C. J. *Curr. Top. Med. Chem.* **2008**, *8*, 1035–1048.
(8) Kim, H.-J.; Doddareddy, M.;R.; Choo, H.; Cho, Y. S.; No, K. T.; Park, W.-K.; Pae, A. N. *J. Chem. Inf. Model.* **2008**, *48*, 197–206.
(9) Upton, N.; Chuang, T. T.; Hunter, A. J.; Virley, D. J. *Neurotherapeutics* **2008**, *5*, 458–469.
(10) http://integrity.prous.com.
(11) Tennant, G. *J. Chem. Soc. C* **1966**, 2290–2295.
(12) Kasila, P.; Harney, H. http://las.perkinelmer.com/Content/RelatedMaterials/Posters/PST_LANCEcAMPGasGaiCoupledReceptors.pdf
(13) Okun, I.; Tkachenko, S. E.; Khvat, A.; Mitkin, O.; Kazey, V.; Ivachtchenko, A. V. *Curr. Alzheimer Res.* **2010**, *7*, 97–112.

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