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Synthesis and biological study of 3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines as potent and selective serotonin 5-HT$_6$ receptor antagonists

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ABSTRACT

A number of 3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines were prepared and their 5-HT$_6$ receptor binding affinity and ability to inhibit the functional cellular responses to serotonin were evaluated. 3-[(3-Chlorophenyl)sulfonyl]-*N*-(tetrahydrofuran-2-ylmethyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine **2**{*5,26*} appeared to be the most active in a functional assay (IC$_{50}$ = 29.0 nM) and 3-(phenylsulfonyl)-*N*-(2-thienylmethyl) thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine **2**{*1,28*} demonstrated the greatest affinity in a 5-HT$_6$ receptor radioligand binding assay (K_i = 1.7 nM). A screening of 5-HT$_{2A}$ and 5-HT$_{2B}$ receptor affinity revealed that 3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines are highly selective 5-HT$_6$ receptor ligands.

1. Introduction

5-HT$_6$ receptor, one of seven (5-HT$_1$–5-HT$_7$) families of serotonin receptors, belongs to G-protein coupled receptors and is positively linked to adenylyl cyclase via G$_S$-protein.[1] In spite of the fact that it was discovered more than 10 years ago, it's physiological functions are still under debate.[2] Almost exclusive localization of 5-HT$_6$R within the CNS in regions that play key roles in modulating cognitive processes and neurotransmitter release[3,4] together with high 5-HT$_6$R affinity for several antipsychotics[5] suggest this receptor as an attractive target for drug development.[6,7] This interest inspired the discovery of a number of highly active and selective ligands and even clinical candidates among 5-HT$_6$ antagonists for treating CNS disorders,[8] such as Alzheimer's disease[9–12] and schizophrenia.[13]

Another well-known attractive feature of 5-HT$_6$R antagonists is their ability to suppress appetite, which may be used for the development of safe and more effective anti-obesity drugs.[7,14,15]

On the basis of a sufficient number of ligands, several authors have described pharmacophore modeling studies for 5-HT$_6$R antagonists.[16] Such models assist in the elaboration of new pharmacologically active compounds.

Consistent with this,[17] during the combined virtual screening, which includes the construction of HipHop pharmacophore model and recursive partitioning technique, it was found that 3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines (PSTTP's),

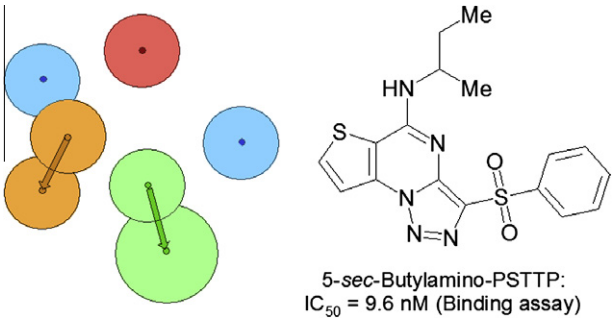

Figure 1. The best HipHop pharmacophore model (cyan: hydrophobic groups; green: hydrogen bond acceptor feature with a vector in the direction of the putative hydrogen donor; orange: aromatic ring; and red: positive ionizable group)[17] and the most 5-HT$_6$R active PSTTP.

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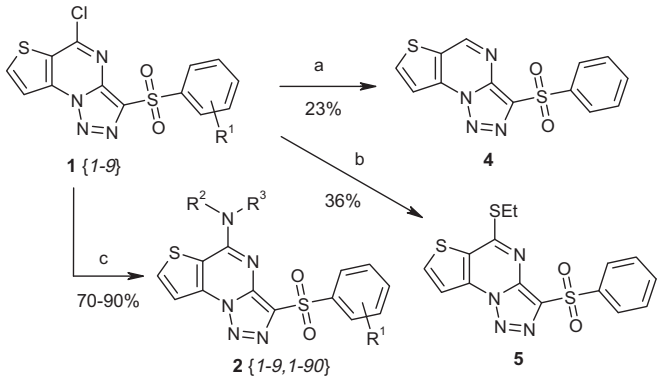


1{*1-9*}, **2**{*1-9,1-90*}: R^1 = H, 4-Me, 4-Et, 4-*i*-Pr, 3-Cl, 4-Cl, 4-Br, 2,5-di-Me, 3,4-di-Me; NR^2R^3 = amino groups (see Chart 1).

Scheme 1. Parallel liquid-phase synthesis of combinatorial libraries of PSTTP's. Reagents and conditions: (a) H_2, Pd/C, rt, MeOH/benzene, 12 h; (b) KSEt, DMF, rt, 1 h; (c) R^2R^3NH **3**{*1–90*}, DMF, Et_3N, 100–120 °C, 1 h.

containing substituted amino groups in position 5, are promising 5-HT_6R ligands (Fig. 1). The present work is focused on a detailed investigation of PSTTP as a template for highly effective and selective 5-HT_6R ligands.

2. Chemistry

In this paper we report a new combinatorial library (CL) of 466 substituted PSTTP's and biological study of PSTTP's as potent and selective 5-HT_6R antagonists.

Parallel liquid-phase synthesis of a CL of PSTTP's **2** was based on 5-chloro-PSTTP's **1**{*1–9*} (Scheme 1). The reaction of 5-chloro-PSTTP's **1**{*1–9*} with amines **3**{*1–90*} (Chart 1), was carried out in DMF in the presence of Et_3N. The reaction products 2{*1–9,1–90*} were isolated with a yield of 70–90% by adding water to precipitate solids and subsequent recrystallization from methanol.

PSTTP **4** and 5-ethylthio-PSTTP **5** were obtained by hydrogenation of 5-chloro-PSTTP **1**{*1*} and by treatment of 5-chloro-PSTTP **1**{*1*} with KSEt in DMF, respectively.

The resulting CL (Fig. 2) included three 5-amino- and 44 5-alkylamino-PSTTP's (**2A**), 95 5-benzylamino- (**2B**), 29 5-heteroarylmethylamino- (**2C**), 23 5-cycloalkylamino- (**2D**), 185 5-arylamino- (**2E**) and 87 5-azaheterocyclyl-PSTTP's (**2F**). Some representatives of this series of compounds are presented in Tables 1–8.

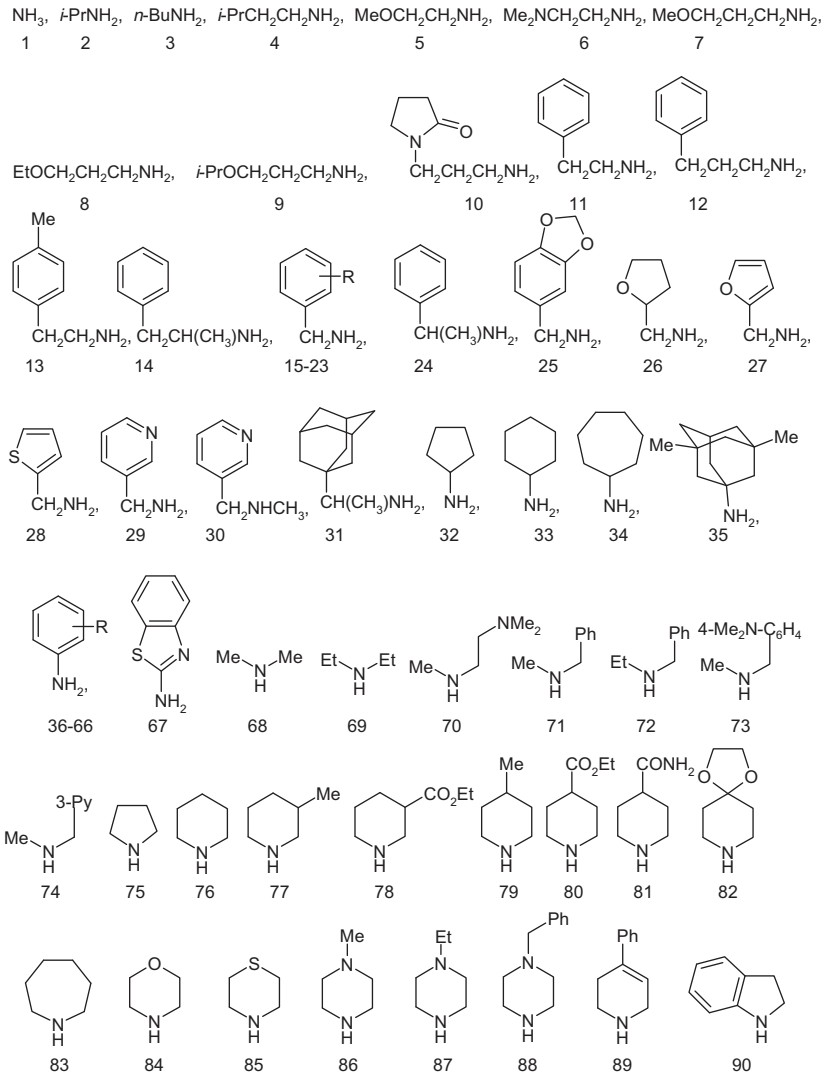


Chart 1. Building blocks **3**{*1–90*}. **3**{*15–23*}: R = H {*15*}, 2-Cl {*16*}, 2-MeO {*17*}, 3-Cl {*18*}, 3-MeO {*19*}, 4-MeO {*20*}, 4-F {*21*}, 4-Cl {*22*}, 3,4-di-MeO {*23*}. **3**{*36–66*}: R = H {*36*}, 2-MeO {*37*}, 2-EtO {*38*}, 3-Me {*39*}, 3-Et {*40*}, 3-MeO {*41*}, 3-MeS {*42*}, 3-F {*43*}, 3-CF_3 {*44*}, 4-Me {*45*}, 4-MeO {*46*}, 4-Et {*47*}, 4-EtO {*48*}, 4-*i*-Pr {*49*}, 4-F {*50*}, 4-Cl {*51*}, 4-AcNH {*52*}, 2,3-di-Me {*53*}, 2,4-di-Me {*54*}, 2,4-di-MeO {*55*}, 2,5-di-Me {*56*}, 2,5-di-MeO {*57*}, 3,4-di-Me {*58*}, 3,4-di-MeO {*59*}, 3-Cl-4-F {*60*}, 3-Me-6-MeO {*61*}, 3,5-di-Me {*62*}, 3,5-di-MeO {*63*}, 3-Cl-4-Me {*64*}, 3-Cl-4-MeO {*65*}, 3-Cl-5-Me {*66*}.

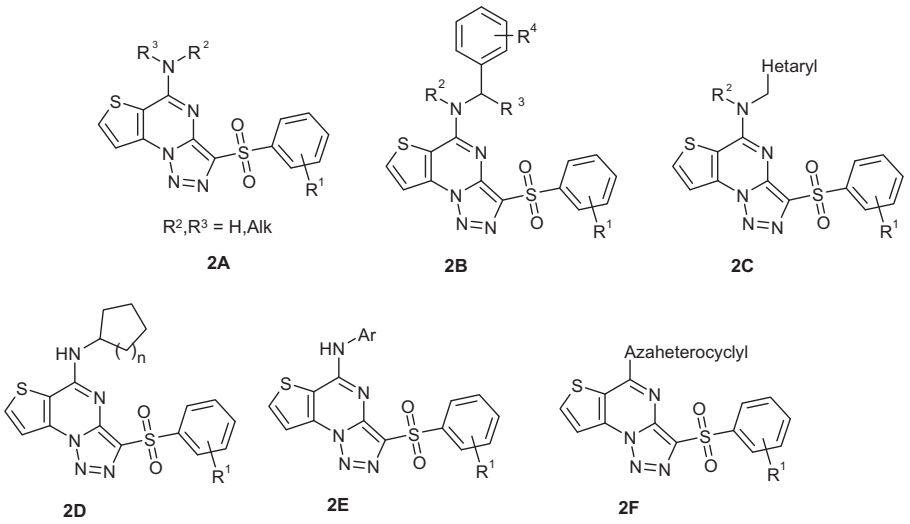


Figure 2. Basic templates included in the combinatorial library of PSTTP's.

Table 1
Biological data of 5-amino-PSTTP's **2A** as 5-HT_6R antagonists in functional assay

Compds **2A**	R^1	R^2	R^3	IC_{50} (μM)
2{*1,2*}	H	*i*-Pr	H	0.37
2{*1,3*}	H	Bu	H	0.069
2{*1,5*}	H	2-MeO-Et	H	0.19
2{*1,7*}	H	3-MeO-Pr	H	0.26
2{*1,11*}*	H	$PhCH_2CH_2$	H	1.16
2{*1,14*}*	H	$PhCH_2CH(CH_3)$	H	1.08
2{*1,70*}	H	$Me_2NCH_2CH_2$	Me	0.87
2{*2,4*}	4-Me	3-Me-Bu	H	0.58
2{*2,5*}	4-Me	2-MeO-Et	H	1.49
2{*2,11*}	4-Me	$PhCH_2CH_2$	H	0.96
2{*3,2*}	4-Et	*i*-Pr	H	1.60
2{*3,4*}	4-Et	3-Me-Bu	H	>5.00
2{*3,7*}	4-Et	3-MeO-Pr	H	>5.00
2{*3,11*}	4-Et	$PhCH_2CH_2$	H	1.05
2{*3,69*}	4-Et	Et	Et	1.90
2{*4,3*}	4-*i*-Pr	Bu	H	>5.00
2{*4,4*}	4-*i*-Pr	3-Me-Bu	H	>5.00
2{*4,5*}	4-*i*-Pr	2-MeO-Et	H	>5.00
2{*5,1*}	3-Cl	H	H	0.69
2{*5,2*}	3-Cl	*i*-Pr	H	0.47
2{*5,3*}	3-Cl	Bu	H	0.060
2{*5,4*}	3-Cl	3-Me-Bu	H	0.068
2{*5,5*}	3-Cl	2-MeO-Et	H	0.11
2{*5,6*}[a]	3-Cl	$Me_2NCH_2CH_2$	Me	0.78
2{*5,7*}	3-Cl	3-MeO-Pr	H	0.15
2{*5,11*}	3-Cl	$PhCH_2CH_2$	H	0.82
2{*5,69*}	3-Cl	Et	Et	1.22
2{*5,70*}	3-Cl	$Me_2NCH_2CH_2$	Me	0.58
2{*6,2*}	4-Cl	*i*-Pr	H	1.20
2{*6,5*}	4-Cl	2-MeO-Et	H	2.17
2{*6,7*}	4-Cl	3-MeO-Pr	H	>5.00
2{*7,1*}	4-Br	H	H	0.61
2{*7,7*}	4-Br	3-MeO-Pr	H	>5.00
2{*8,1*}	2,5-di-Me	H	H	1.22
2{*8,2*}	2,5-di-Me	*i*-Pr	H	0.35
2{*8,4*}	2,5-di-Me	3-Me-Bu	H	0.86
2{*8,5*}	2,5-di-Me	2-MeO-Et	H	0.86
2{*8,7*}	2,5-di-Me	3-MeO-Pr	H	1.29
2{*8,11*}	2,5-diMe	$PhCH_2CH_2$	H	0.67
2{*8,12*}	2,5-di-Me	$PhCH_2CH_2CH_2$	H	1.22
2{*9,2*}	3,4-di-Me	*i*-Pr	H	0.75
2{*9,4*}	3,4-di-Me	3-Me-Bu	H	0.046
2{*9,5*}	3,4-di-Me	2-MeO-Et	H	1.57
2{*9,7*}	3,4-di-Me	3-MeO-Pr	H	2.38
2{*9,14*}	3,4-di-Me	$PhCH_2CH(CH_3)$	H	0.68

[a] As hydrochloride.

Table 2
Biological data of 5-benzylamino-PSTTP's **2B** as 5-HT_6R antagonists in functional assay

Compds **2B**	R^1	R^2	R^3	R^4	IC_{50} (μM)
2{*1,15*}	H	H	H	H	0.059
2{*1,16*}	H	H	H	2-Cl	0.032
2{*1,17*}	H	H	H	2-MeO	0.29
2{*1,19*}	H	H	H	3-MeO	1.37
2{*1,21*}	H	H	H	4-F	0.69
2{*1,22*}	H	H	H	4-Cl	1.17
2{*1,24*}	H	H	Me	H	0.037
2{*1,25*}	H	H	H	3,4-CH_2O_2	0.29
2{*1,71*}	H	Me	H	H	0.17
2{*2,15*}	4-Me	H	H	H	0.26
2{*2,17*}	4-Me	H	H	2-MeO	0.58
2{*2,18*}	4-Me	H	H	3-Cl	0.12
2{*2,19*}	4-Me	H	H	3-MeO	2.21
2{*2,21*}	4-Me	H	H	4-F	0.74
2{*2,24*}	4-Me	H	Me	H	0.18
2{*2,25*}	4-Me	H	H	3,4-CH_2O_2	1.25
2{*2,72*}	4-Me	Et	H	H	0.30
2{*4,16*}	4-*i*-Pr	H	H	2-Cl	1.83
2{*5,17*}	3-Cl	H	H	2-MeO	0.78
2{*5,21*}	3-Cl	H	H	4-F	0.48
2{*5,24*}	3-Cl	H	Me	H	0.15
2{*5,71*}	3-Cl	Me	H	H	0.92
2{*5,72*}	3-Cl	Et	H	H	0.54
2{*6,15*}	4-Cl	H	H	H	0.27
2{*6,17*}	4-Cl	H	H	2-MeO	1.15
2{*6,24*}	4-Cl	H	Me	H	0.28
2{*6,71*}	4-Cl	Me	H	H	1.19
2{*6,72*}	4-Cl	Et	H	H	0.57
2{*7,17*}	4-Br	H	H	2-MeO	0.93
2{*7,24*}	4-Br	H	Me	H	0.54
2{*7,71*}	4-Br	Me	H	H	1.95
2{*7,72*}	4-Br	Et	H	H	0.58
2{*8,24*}	2,5-di-Me	H	Me	H	0.17
2{*8,71*}	2,5-di-Me	Me	H	H	1.48
2{*8,72*}	2,5-di-Me	Et	H	H	1.10
2{*9,16*}	3,4-di-Me	H	H	2-Cl	0.60
2{*9,17*}	3,4-di-Me	H	H	2-MeO	0.47
2{*9,21*}	3,4-di-Me	H	H	4-F	0.52
2{*9,71*}	3,4-di-Me	Me	H	H	1.33

Key building blocks, 5-chloro-PSTTP's **1**{*1–9*}, were obtained on the basis of 3-amino-thiophene-2-carboxylic acid methyl ester **6**. Azide **7** was prepared by the standard method from **6**; based-catalyzed condensation of **7** with arylsulfonylacetonitriles **8**{*1–9*}

Table 3
Biological data of 5-heteroarylmethylamino-PSTTP's **2C** as 5-HT$_6$R antagonists in functional assay

Compds **2C**	R^1	R^2	Heteroaryl[a]	IC_{50} (μM)
2{*1,26*}	H	H	2-THFu	0.063
2{*1,27*}	H	H	2-Fu	0.040
2{*1,28*}	H	H	2-Th	0.11
2{*1,29*}	H	H	3-Py	0.26
2{*1,30*}	H	Me	3-Py	0.50
2{*2,26*}	4-Me	H	2-THFu	0.25
2{*2,27*}	4-Me	H	2-Fu	0.50
2{*2,28*}	4-Me	H	2-Th	0.22
2{*5,26*}	3-Cl	H	2-THFu	0.029
2{*5,27*}	3-Cl	H	2-Fu	0.19
2{*5,28*}	3-Cl	H	2-Th	0.15
2{*5,29*}	3-Cl	H	3-Py	1.25
2{*6,26*}	4-Cl	H	2-THFu	0.48
2{*6,27*}	4-Cl	H	2-Fu	0.41
2{*6,28*}	4-Cl	H	2-Th	0.65
2{*7,26*}	4-Br	H	2-THFu	1.62
2{*8,26*}	2,5-di-Me	H	2-THFu	0.89
2{*8,28*}	2,5-di-Me	H	2-Th	0.71
2{*9,27*}	3,4-di-Me	H	2-Fu	0.77
2{*9,28*}	3,4-di-Me	H	2-Th	0.090

[a] 3-Py—pyridine-3-yl, 2-THFu—tetrahydrofuran-2-yl, 2-Th—thiophen-2-yl.

Table 4
Biological data of 5-cycloalkylamino-PSTTP's **2D** as 5-HT$_6$R antagonists in functional assay

Compds **2D**	*n*	R^1	IC_{50} (μM)
2{*1,32*}	1	H	0.14
2{*1,33*}	2	H	0.20
2{*1,34*}	3	H	0.17
2{*2,32*}	1	4-Me	2.03
2{*2,33*}	2	4-Me	0.73
2{*2,34*}	3	4-Me	0.79
2{*5,32*}	1	3-Cl	0.17
2{*5,33*}	2	3-Cl	0.069
2{*5,34*}	3	3-Cl	0.14
2{*6,33*}	2	4-Cl	0.96
2{*8,32*}	1	2,5-di-Me	0.59
2{*9,33*}	2	3,4-di-Me	0.82
2{*9,34*}	3	3,4-di-Me	0.35

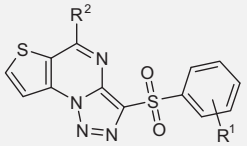
Table 5
Biological data of 5-anilino-PSTTP's **2E** as 5-HT$_6$R antagonists in functional assay

Compds **2E**	R^1	Ar	IC_{50} (μM)
2{*1,36*}	H	Ph	~5.00
2{*1,44*}	H	3-CF_3-C_6H_4	0.82
2{*1,50*}	H	4-F-C_6H_4	0.60*
2{*1,67*}	H	Benzothiazol-2-yl	>5.00
2{*2,39*}	4-Me	3-Me-C_6H_4	5.22
2{*2,40*}	4-Me	3-Et-C_6H_4	1.38
2{*2,43*}	4-Me	3-F-C_6H_4	3.81
2{*2,53*}	4-Me	2,3-di-Me-C_6H_3	0.59
2{*3,39*}	4-Et	3-Me-C_6H_4	1.75
2{*4,39*}	4-*i*-Pr	3-Me-C_6H_4	0.59
2{*4,41*}	4-*i*-Pr	3-MeO-C_6H_4	0.90
2{*4,53*}	4-*i*-Pr	2,3-di-Me-C_6H_3	1.00
2{*4,58*}	4-*i*-Pr	3,4-di-Me-C_6H_3	1.11
2{*5,36*}	3-Cl	Ph	0.92
2{*5,44*}	3-Cl	3-CF_3-C_6H_4	1.07
2{*5,45*}	3-Cl	4-Me-C_6H_4	1.21
2{*5,50*}	3-Cl	4-F-C_6H_4	2.50
2{*5,56*}	3-Cl	2,5-di-Me-C_6H_3	0.74
2{*6,37*}	4-Cl	2-MeO-C_6H_4	1.15
2{*6,53*}	4-Cl	2,3-di-Me-C_6H_3	0.80
2{*7,56*}	4-Br	2,5-di-Me-C_6H_3	2.01
2{*7,58*}	4-Br	3,4-di-Me-C_6H_3	1.35
2{*9,41*}	3,4-di-Me	3-MeO-C_6H_4	0.86
2{*9,51*}	3,4-di-Me	4-Cl-C_6H_4	1.43
2{*9,66*}	3,4-di-Me	3-Cl-5-Me-C_6H_3	2.26

Table 6
Biological data of 5-azaheterocyclyl-PSTTP's **2F** as 5-HT$_6$R antagonists in functional assay

Compds **2F**	R^1	Azaheterocyclyl	IC_{50} (μM)
2{*1,77*}	H	3-Methylpiperidin-1-yl	2.03
2{*1,82*}	H	4-Aminocarbonylpiperidin-1-yl	1.99
2{*5,77*}	3-Cl	3-Methylpiperidin-1-yl	2.00
2{*5,79*}	3-Cl	4-Methylpiperidin-1-yl	1.12
2{*5,83*}	3-Cl	Azepan-1-yl	1.54
2{*5,84*}	3-Cl	Morpholin-4-yl	1.04
2{*8,76*}	2,5-di-Me	Piperidin-1-yl	1.52
2{*8,79*}	2,5-di-Me	4-Methylpiperidin-1-yl	1.99
2{*8,84*}	2,5-di-Me	Morpholin-4-yl	1.93
2{*8,86*}	2,5-di-Me	1-Methylpiperazin-4-yl	1.34

Table 7
Biological data of PSTTP's **2** as 5-HT$_6$R ligands in radioligand binding assay



R^1	R^2	5-HT$_6$R IC_{50} (nM)	5-HT$_6$R K_i (nM)
H	*i*-PrNH	65.0	30.2
H	$Me_2NCH_2CH_2NH$	>300.0	
H	Me_2N	>30.0	
H	$Me_2NCH_2CH_2NMe$	>300.0	
4-Br	3-Me-BuNH	34.3	15.9
2,5-di-Me	NH_2	99.1	46
2,5-di-Me	*i*-PrNH	28.3	13.2
H	Adamantan-1-yl-CH(Me)NH	221.0	103.0
H	BnNMe	5.0	2.3
3-Cl	BnNMe	7.5	3.5
4-Br	Benzo[1,3]dioxol-5-yl-CH_2NH	62.1	28.8
H	Tetrahydrofuran-2-yl-CH_2NH	17.5	8.1
H	Furan-2-yl-CH_2NH	6.1	2.8
H	Thiophen-2-yl-CH_2NH	3.6	1.7
H	Pyridin-3-yl-CH_2NH	>30.0	
H	Pyridin-3-yl-CH_2NMe	>30.0	
3-Cl	Pyridin-3-yl-CH_2NMe	31.7	14.7
H	Cyclopentyl-NH	11.9	5.5
H	Cyclohexyl-NH	6.9	3.2
H	3,5-Dimethyladamantan-1-yl-NH	56.7	26.3
H	Pyrrolidin-1-yl	188.0	87.5

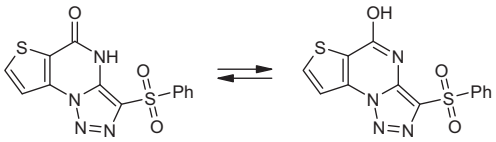
afforded 3-arylsulfonyl-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-ones **9**{*1–9*}. Applied arylsulfonylacetonitriles **8**{*1–9*}, along with an unsubstituted one **8**{*1*}, were 4-methyl- **8**{*2*}, 4-ethyl- **8**{*3*}, 4-*i*-propyl- **8**{*4*}, 3-chloro- **8**{*5*}, 4-chloro- **8**{*6*}, 4-bromo- **8**{*7*}, 2,5-dimethyl- **8**{*8*}, and 3,4-dimethylphenylsulfonyl-acetonitrile **8**{*9*}. Thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-ones **9**{*1–9*} were transformed to desired 5-chloro-PSTTP's **1**{*1–9*} by the action of $POCl_3$ in the presence of Et_3N (Scheme 2).

Unfortunately, the ^{1}H NMR spectra of 3-arylsulfonyl-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-ones **9**{*1–9*} (e.g., **9**{*1*}) indicate two sets of signals, suggesting the existence of two tautomeric forms. The last are in line with the data of IR spectroscopy

Table 8
% of radioligands displacement from the complexes with serotonin receptors using 1 μM PSTTP's **2** in radioligand binding assay

Serotonin receptor	PSTTP's	
	2B{*1,71*}	**2B**{*5,71*}
	% Displacement	
5-HT_{1A}	2	9
5-HT_{1B}	1	3
5-HT_{2A}	15	50
5-HT_{2B}	12	46
5-HT_{2C}	2	15
5-HT_3	−7	−3
5-HT_4	33	41
5-HT_6	103	106
5-HT_7	−2	6

indicating the presence of valent vibration band of the amide carbonyl group at 1670 cm^{-1}. Note that a similar signal at 1670 cm^{-1} is reported[18] in the IR spectrum of 3-bromo-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-one.



For the reaction with 5-chloro-PSTTP's **1**{*1–9*} (Scheme 1) the following amines were used (Chart 1): ammonia **3**{*1*}, primary amines: alkylamines **3**{*2–30*}, cycloalkylamines **3**{*31–35*}, anilines **3**{*36–66*}, 2-aminobenzotiazole **3**{*67*} and secondary amines: dialkylamines **3**{*68–74*}, pyrrolidine **3**{*75*}, piperidines **3**{*76–82*}, azepane **3**{*83*}, morpholine **3**{*84*}, thiomorpholine **3**{*85*}, piperazines **3**{*86–88*}, 4-phenyl-1,2,3,6-tetrahydropyridine **3**{*89*}, and 2,3-dihydro-1*H*-indole **3**{*90*}.

3. Biological assays

Screening of 5-HT_6R antagonistic activity of PSTTP's **2** was performed in concentrations of 5 μM and 10 μM by testing in vitro the ability to inhibit the functional cellular responses to serotonin. Stimulation of cells (HEK293) stably expressing recombinant human 5-HT_6R by serotonin activates adenylyl cyclase, which catalyzes the synthesis of cAMP, the level of which is estimated with the help of LANCE[19] technology. PRX-07034 and SB-742457 were used as standards of comparison. For 148 compounds that inhibited the synthesis of cAMP at 5 μM by more than 50%, we determined IC_{50} (Tables 2–8).

Inhibition of the hERG Potassium Ion Channel in a patch clamp assay and screening of 5-HTR activity of PSTTP's in a competitive radioligand binding assay were performed by MDS Pharma Services.[20]

4. Results and discussion

Among of PSTTP's **1**{*1*}, **4**, and **5** the most active 5-HT_6R antagonists are 5-ethylthio-PSTTP **5** with IC_{50} = 0.51 μM and 5-chloro-PSTTP **1**{*1*} with IC_{50} = 0.57 μM and the least active antagonist is 5-unsubstituted PSTTP **4** with IC_{50} = 3.0 μM.

The activity of 5-amino-PSTTP's **2A** (Table 1) strongly depends on the nature of the substituents and ranges from IC_{50} = 0.046 μM to IC_{50} >5.0 μM. For example, in a series of 5-amino-3-(3-chlorobenzenesulfonyl)-PSTTP's **2A**{*5,1–7*; *5,11*; *5,69–70*} the activity changes 20-fold: the most active antagonists are 5-butylamino-PSTTP **2A**{*5,3*} with IC_{50} = 0.060 μM and 5-(3-methylbutylamino)-PSTTP **2A**{*5,4*} with IC_{50} = 0.068 μM, while the least active antagonist is 5-diethylamino-PSTTP **2A**{*5,69*} with IC_{50} = 1.22 μM. Activity of other 5-amino-3-(3-chlorobenzenesulfonyl)-PSTTP's decreases in the series, presented below, from IC_{50} = 0.11 μM to IC_{50} = 0.82 μM.

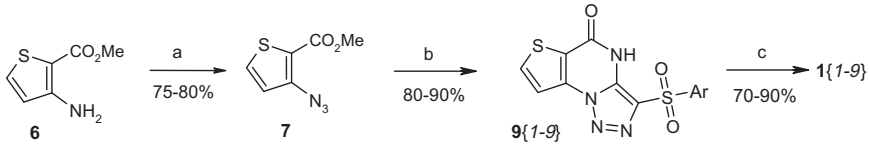
2A{*5,5*} > **2A**{*5,7*} > **2A**{*5,2*} > **2A**{*5,70*} > **2A**{*5,1*} > **2A**{*5,6*} > **2A**{*5,11*} = 0.11 μM > 0.15 μM > 0.47 μM > 0.58 μM > 0.69 μM > 0.78 - μM > 0.82 μM, respectively.

The nature and position of the substituents in the benzenesulfonyl fragment (Table 1) also strongly influence on activity. For example, in a series of 5-(2-methoxyethylamino)-PSTTP's **2A**{*1–2,5*;*4–6,5*;*8–9,5*} transition from 3-benzenesulfonyl derivative **2A**{*1,5*} with IC_{50} = 0.19 μM to 3-(3-chlorobenzenesulfonyl) derivative **2A**{*5,5*} with IC_{50} = 0.11 μM slightly increases activity. However, substitution of position 4 of this moiety by chlorine (**2A**{*6,5*}), IC_{50} = 2.2 μM), methyl (**2A**{*2,5*}, IC_{50} = 1.49 μM) or *iso*-propyl group (**2A**{*4,5*}, IC_{50} >5.0 μM) or incorporation of two substituents (**2A**{*8–9,5*}) considerably reduces the activity. The most active antagonists in this series of PSTTP's **2A** were 3-benzenesulfonyl derivative **2A**{*1,5*} and 3-(3-chlorobenzenesulfonyl) derivative **2A**{*5,5*}. As an exception appears 3-(3,4-dimethylbenzenesulfonyl) derivative **2A**{*9,4*} with IC_{50} = 0.046 μM.

In the series of 5-benzylamino-PSTTP's **2B** (Table 2) the most promising compounds are 3-benzenesulfonyl- **2B**{*1,15–16*; *1,24*} and 3-(3,4-dimethylbenzenesulfonyl)- **2B**{*9,16*} with IC_{50} = 0.032–0.059 μM. The most active 5-HT_6R antagonist is 2-chlorobenzylamino-PSTTP **2B**{*1,16*} with IC_{50} = 0.032 μM. The least active 5-HT_6R antagonist is 5-(2-methoxybenzylamino)-3-(*p*-tolylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **2B**{*2,19*} with IC_{50} = 2.21 μM.

The activity of 5-heteroarylmethylamino-PSTTP's **2C** (Table 3) is similar to that of 5-benzylamino-PSTTP's **2B** (Table 2). Among 5-(tetrahydrofuran-2-ylmethylamino)-PSTTP's **2C** {*1–2,26*; *5–8,26*} the most active 5-HT_6R antagonist is 3-(3-chlorobenzenesulfonyl) derivative **2C**{*5,26*} with IC_{50} = 0.029 μM, while the least active antagonist is 3-(4-bromobenzenesulfonyl) derivative **2C**{*7,26*} with IC_{50} = 1.62 μM. In the series of 5-(furan-2-ylmethylamino)-PSTTP's **2C**{*1–2,27*; *5–6,27*; *8–9,27*}, PSTTP **2C**{*1,27*} with IC_{50} = 0.04 μM is the most active, and in a row of 5-(thiophen-2-ylmethylamino)-PSTTP's **2C**{*1–2,28*; *5–6,28*; *8–9,28*}, PSTTP **2C**{*9,28*} with IC_{50} = 0.090 μM is the most active.

Among 5-cycloalkylamino-PSTTP's **2D** (Table 4) again the most promising antagonists are 3-(3-chlorobenzenesulfonyl) compounds **2D**{*5,32–34*}. For example, 5-cyclohexylamino-3-(3-chlorobenzenesulfonyl) derivative **2D**{*5,33*} with IC_{50} = 0.069 μM is 10.6 times more active than 3-(4-methylbenzenesulfonyl) analogue **2D**{*2,33*} with IC_{50} = 0.73 μM and 14 times more active than 3-(4-chlorobenzenesulfonyl) analogue **2D**{*6,33*} with IC_{50} = 0.96 μM.



Scheme 2. Synthesis of 5-chloro-PSTTP's **1**{*1–9*}. Reagents and conditions: (a) $NaNO_2$, H_2O, 18% aq HCl, 0.5 h at 25 °C; (b) $ArSO_2CH_2CN$ **8**{*1–9*}, EtONa, 20 h reflux; (c) $POCl_3$, Et_3N, 12 h reflux.

5-anilino-PSTTP's **2E** (Table 5) don't have any significant 5-HT$_6$R antagonistic activity (the highest IC_{50} is about 0.6 μM).

Finally, in a series of 5-azaheterocyclyl-PSTTP's **2F** (Table 6) activity does not get better than IC_{50} = 1.04 μM, which corresponds to 5-(morpholin-4-yl)-3-(3-chlorobenzenesulfonyl)-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **2F**{*5,84*}.

The findings described above allowed us to select the most active antagonists with IC_{50} <100.0 nM: 5-alkylamino- **2A**{*1,3*; *5,3–4*}, 5-benzylamino- **2B**{*1,15–16*; *1,24*; *9,16*}, 5-heterocyclylmethylamino **2C**{*1,26–27*; *5,26*; *9,28*}, and 5-cycloalkylamino-3-benzenesulfonyl-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **2D**{*5,33*} (Fig. 3).

We also have studied the activity of some PSTTP's in a radioligand binding assay. As it follows from Table 7, the most active 5-HT$_6$R ligands (Fig. 4) are 5-heterocyclylmethylamino- **2C**{*1,26–28*}, 5-(*N*-benzyl-*N*-methylamino)- **2B**{*1,71*; *5,71*}, and 5-cycloalkylamino-PSTTP's **2D**{*1,32–33*} with K_i <10 nM. The most active ligands identified in radioligand binding assays are in good agreement with the most active antagonists identified in terms of functional assay.

Using radioligand binding assay, we studied the selectivity of two potent PSTTP's, namely **2B**{*1,71*; *5,71*} on a panel of serotonin receptors (Fig. 4). The data for displacement of radioligands from their complexes with serotonin receptors are presented in Table 8. Except for some interactions of PSTTP **2B**{*5,71*} with a 5-HT$_{2A}$R (50%) and 5-HT$_{2B}$R (46%), these ligands display a high selectivity towards 5-HT$_6$R.

In a patch clamp assay, two of the studied 5-HT$_6$R antagonists demonstrated very weak inhibition of hERG Potassium Ion Channel, (~20% inhibition at 15.0 μM and 30 μM, respectively, for **2B**{*1,71*} and **2B**{*5,71*}. (Fig. 5)

5. Conclusions

In summary, a number of new potent and selective 5-HT$_6$ receptor antagonists were developed. Of particular note are the compounds with benzyl, heteroarylmethyl or tetrahydrofurylmethyl moiety at the N-5 atom and unsubstituted or with *m*-chlorine atom in the phenylsulfonyl portion such as **2B**{*1,15–16*}, **2B**{*1,24*}, **2B**{*9,16*}, **2C**{*1,26–28*}, **2C**{*1,32–33*}, and **2C**{*5,26*}. The most

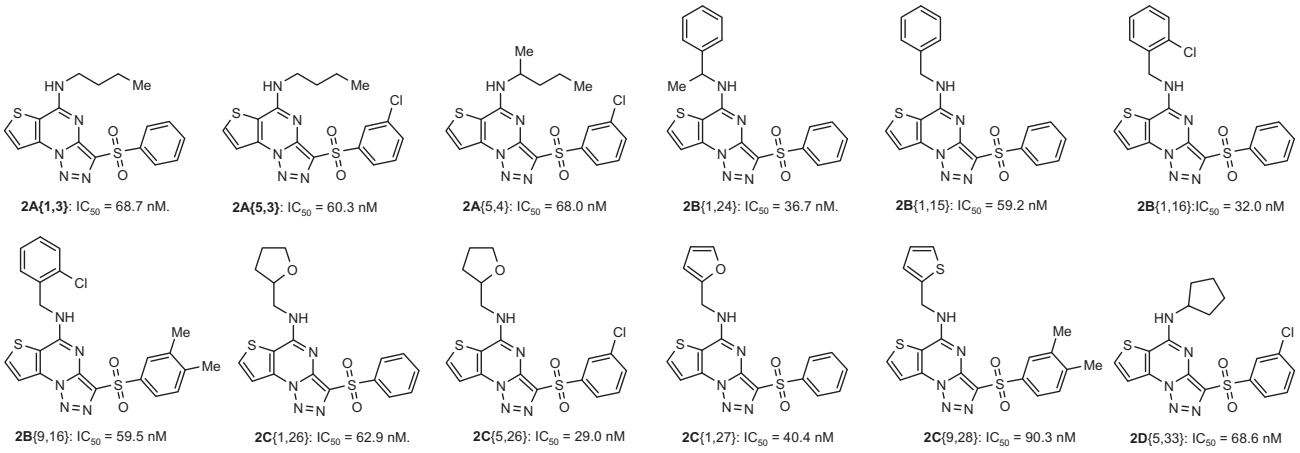


Figure 3. The most active 5-HT$_6$R antagonists of PSTTP's combinatorial library in functional assay.

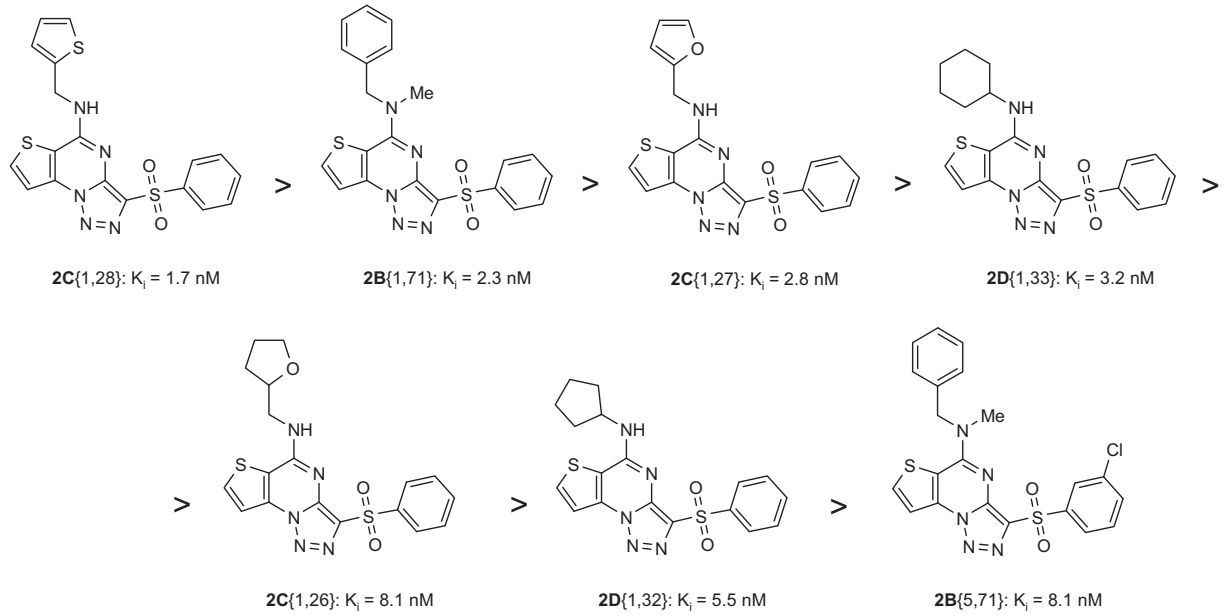


Figure 4. The most active 5-HT$_6$R ligands of PSTTP's combinatorial library in radioligand binding assay.

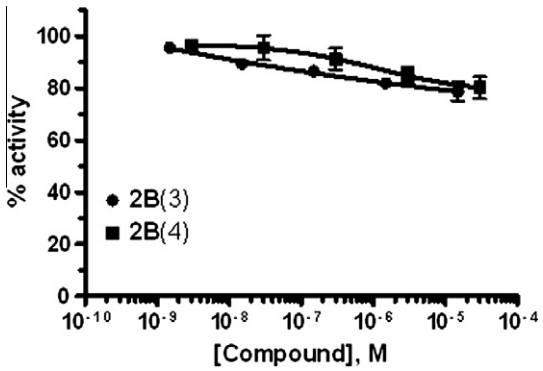


Figure 5. Inhibition of hERG Potassium Ion Channel PSTTP's 2 in a patch clamp assay.

promising antagonists are compounds **2C**{*5,26*} and **2C**{*1,28*}. Further investigation of the therapeutic potential of 3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines is in progress.

6. Experimental

6.1. General experimental

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 (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 PSTTP **9**{*1*} were recorded on a Specord 75 IR in nujol.

5-HT$_6$R binding activities of synthesized PSTTP's were determined in a radioligand binding assay using a panel of eight serotonin receptors.[21]

6.1.1. General procedure for synthesis of (3-phenylsulfonyl)-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-one 9{*1–9*}

To a stirred solution of EtONa (0.5 g, 21.7 mmol of Na in 15 mL of EtOH), 2-phenylsulfonylacetonitrile **8**{*1–9*} (9.5 mmol) was added. After 20 min a solution of methyl 3-azido-2-thiophenecarboxylate **7** (1.13 g, 6.1 mmol) in 50 mL of EtOH was added for 40 min, then the mixture was heated under reflux for 20 h. The reaction mixture was concentrated in vacuo, treated with H_2O and extracted with $CHCl_3$. Product **9**{*1–9*} precipitated from the aqueous layer after acidification (pH 2) with concd HCl, was collected by filtration and washed with H_2O. Yields of products **9**{*1–9*} as creamy crystalline powders were 80–90%.

6.1.1.1. (3-Phenylsulfonyl)-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-one 9{*1*}.

IR (nujol) 1670 cm^{-1}. ESI-MS *m*/*z* 333. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.43, 8.39 (2d, *J* = 5.2 Hz, 1H), 8.16, 8.05 (2d, *J* = 7.6 Hz, 2H), 7.92, 7.51 (2d, *J* = 5.2 Hz, 1H), 7.73 (m, 1H), 7.66 (m, 2H).

6.1.2. General procedure for the synthesis of 5-chloro-(3-phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 1{*1–9*}

A solution of 3-phenylsulfonyl-4*H*-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-one **9**{*1–9*} (1.75 mmol) in 12 mL of Et_3N was cooled in an ice-bath (0–5 °C), 8 mL of $POCl_3$ were added and the mixture was heated under reflux for 12 h. After cooling, the reaction mixture was poured into crushed ice and quickly extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 6% $NaHCO_3$, H_2O, dried and evaporated. Yields of products **1**{*1–9*} as slightly colored solids were 70–90%.

6.1.2.1. 5-Chloro-(3-phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 1{*1*}.

ESI-MS *m*/*z* 351. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.76 (d, *J* = 5.2 Hz, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 8.06 (m, 2H), 7.72 (m, 1H), 7.65 (m, 2H).

6.1.3. (3-Phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 4

To a solution of 5-chloro-3-phenylsulfonyl-thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **1**{*1*} (304.5 mg, 0.87 mmol) in a mixture of 60 mL of MeOH and 20 mL of benzene, Pd/C (10%, 100 mg) was added and stirred for 24 h in an atmosphere of H_2. The mixture was filtered through Celite and concentrated under vacuum. Product **4** was isolated by HPLC to yield 63.2 mg (23%) as white powder. Mp: 217–218 °C. ESI-MS *m*/*z* 317. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.65 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 8.23 (dd, J_1 = 5.6 Hz, J_2 = 0.4 Hz, 1H), 8.09 (m, 2H), 7.70 (m, 1H), 7.63 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.88, 141.58, 141.16, 139.16, 138.48, 135.55, 134.02, 129.63, 127.23, 125.06, 115.70.

6.1.4. 5-Ethylthio-(3-phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 5

To a solution of KSEt (209 mg, 2.09 mmol) in 10 mL DMSO the chloro-derivative **1**{*1*} (609 mg, 1.74 mmol) was added portionwise and the mixture was stirred at room temperature for 1 h. The resulting mixture was poured into water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. Product **5** was isolated by column chromatography, eluent benzene/AcOEt = 50:1. The yield of PSTTP **5** as white solid was 236 mg (36%). Mp: 190–192 °C. ESI-MS *m*/*z* 377. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (m, 2H), 8.05 (q, *J* = 5.2 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8 Hz, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 1.60 (t, *J* = 7.2 Hz, 3H).

6.1.5. General procedure for the synthesis of (3-phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amines 2

To a solution of the chloro- derivative **1**{*1–9*} (1 mmol) in 2 mL of anhydrous DMF and 1 mL of Et_3N, amine **3**{*1–90*} (1.1 mmol) was added and the mixture was heated at 120 °C for 1 h. After cooling, 10 mL of H_2O was added. Separated solid was filtered off and purified by recrystallization from methanol. Yields of PSTQ's **2** as white to creamy crystalline powders were 70–90%.

6.1.5.1. *N*-Isopropyl-(3-phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,2*}.

Mp: 205–207 °C. ESI-MS *m*/*z* 373. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.61 (d, *J* = 7.2 Hz, 1H), 8.38 (d, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 6.4 Hz, 2H), 7.95 (d, *J* = 5.2 Hz, 1H), 7.67 (m, 1H), 7.59 (m, 2H), 7.57 (sep, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.56, 141.69, 141.11, 138.02, 136.43, 133.55, 130.17, 129.32, 127.08, 116.16, 114.12, 43.13, 21.73.

6.1.5.2. *N*,*N*-Dimethyl-*N*′-[(3-Phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-yl]ethane-1,2-diamine dihydrochloride 2{*1,6*}.

Mp: 206–208 °C. ESI-MS *m*/*z* 416. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.90 (s,1H), 9.17 (t, *J* = 5.2 Hz, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 8.05 (m, 2H), 8.03 (d, *J* = 5.6 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 8 Hz, 2H), 3.95 (m, 2H), 3.44 (m, 2H), 2.89 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.82, 141.78, 141.01, 138.02, 137.06, 133.62, 130.44, 129.55, 126.94, 116.00, 114.67, 55.55, 42.61, 36.21.

6.1.5.3. *N*-(2-Phenylethyl)-(3-phenylsulfonyl)thieno[2,3-*e*][1,2,-3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,11*}. Mp: 254–256 °C (dec). ESI-MS *m*/*z* 435. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.98 (t, J = 4.8 Hz, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 7.2 Hz, 2H), 7.98 (d, J = 5.6 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 8 Hz, 2H), 7.33 (m, 4H), 7.22 (t, J = 6.8 Hz, 1H), 3.77 (m, 2H), 3.03 (t, J = 7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.41, 141.96, 141.28, 139.30, 138.02, 136.43, 133.50, 130.31, 129.29, 128.78, 128.47, 126.90, 126.30, 116.26, 114.21, 42.84, 34.23.

6.1.5.4. *N*(1-Phenylethyl)-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,24*}. Mp: 230–232 °C. ESI-MS *m*/*z* 435. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.22 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 7.96 (d, J = 5.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 5.60 (m, 1H), 1.62 (d, J = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.59, 143.93, 141.94, 141.03, 138.21, 136.74, 133.34, 130.28, 129.29, 128.46, 127.00, 126.73, 126.42, 116.19, 114.00, 50.29, 21.89.

6.1.5.5. 3-Phenylsulfonyl-*N*-(tetrahydrofuran-2-ylmethyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,26*}. Mp: 221–223 °C. ESI-MS *m*/*z* 415. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.98 (t, J = 5.6 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.97 (d, J = 5.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 8 Hz, 2H), 4.15 (m, 1H), 3.83 (m, 1H), 3.67 (m, 1H), 3.61 (m, 2H), 1.96 (m, 1H), 1.88 (m, 2H), 1.68 (m, 1H).

6.1.5.6. *N*-Cyclopentyl-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,32*}. Mp: 235–237 °C. ESI-MS *m*/*z* 399. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.69 (d, J = 6.8 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 5.2 Hz, 1H), 7.67 (m, 1H), 7.59 (m, 2H), 4.53 (m, 1H), 2.06 (m, 2H), 1.77 (m, 2H), 1.65 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.89, 141.60, 140.94, 137.83, 136.30, 133.42, 130.15, 129.15, 126.98, 115.97, 114.00, 52.93, 31.63, 23.93.

6.1.5.7. *N*-Cyclohexyl-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,33*}. Mp: 228–230 °C. ESI-MS *m*/*z* 413. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.61 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 5.6 Hz, 1H), 7.68 (m, 1H), 7.58 (m, 2H), 4.13 (m, 1H), 1.98 (m, 2H), 1.87 (m, 2H), 1.72 (m, 1H), 1.43 (m, 4H), 1.22 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.49, 141.63, 141.05, 138.07, 136.50, 133.62, 130.14, 129.17, 127.10, 116.15, 114.08, 50.63, 31.66, 25.34, 25.13.

6.1.5.8. *N*-Phenyl-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo [1,5-*a*]pyrimidin-5-amine 2{*1,36*}. Mp: 259–261 °C (dec). ESI-MS *m*/*z* 408. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.43 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.06 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.96 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H), 7.50 (t, J = 8.0 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.41, 141.58, 140.34, 138.64, 138.36, 137.30, 133.50, 130.88, 129.25, 128.58, 126.82, 124.65, 122.36, 116.11, 114.64.

6.1.5.9. 3-(3-Chloro-4-methylphenylsulfonyl)-*N*-phenylthieno [2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,64*}. Mp: 262–264 °C. ESI-MS *m*/*z* 443. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.46 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.06 (m, 3H), 7.80 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.65 (m, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.21, 141.80, 140.33, 138.81, 137.77, 137.55, 133.63, 133.13, 131.22, 131.19, 131.03, 129.44, 126.88, 121.91, 120.42, 116.25, 114.78, 19.11.

6.1.5.10. *N*-1,3-Benzothiazol-2-yl-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,67*}. Mp: 272–274 °C. ESI-MS *m*/*z* 465. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.49 (d, J = 5.2 Hz, 1 H), 8.19 (m, 2H), 8.08 (d, J = 5.2 Hz, 1H), 8.02 (m, 1H), 7.64 (m, 4H), 7.52 (m, 2H), 7.38 (m, 1H).

6.1.5.11. 3-Phenylsulfonyl-*N*,*N*-dimethylthieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidin-5-amine 2{*1,68*}. Mp: 234–236 °C. ESI-MS *m*/*z* 359. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.49 (d, J = 5.6 Hz, 1H), 8.08 (m, 2H), 7.99 (d, J = 5.2 Hz, 1H), 7.63 (m, 3H), 3.49 (s, 6H).

6.1.5.12. *N*-Benzyl-*N*-methyl-3-(phenylsulfonyl)thieno[2,3-*e*] [1, 2,3]triazolo[1,5-*a*]pyrimidin-5-amine 3 2{*1,71*}. Mp: 235–237 °C. ESI-MS *m*/*z* 435. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.51 (d, J = 5.6 Hz, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.60 (m, 1H), 7.40 (m, 7H), 5.18 (s, 2H), 3.58 (s, 3H).

6.1.5.13. 3-(Phenylsulfonyl)-5-pyrrolidin-1-ylthieno[2,3-*e*] [1,2, 3]triazolo[1,5-*a*]pyrimidine 2{*1,75*}. Mp: 233–235 °C. ESI-MS *m*/*z* 386. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.48 (d, J = 5.6 Hz, 1H), 8.09 (m, 2H), 7.99 (d, J = 5.6 Hz, 1H), 7.63 (m, 3H), 4.12–3.64 (br m, 4H), 2.19–1.92 (br m, 4H).

6.1.5.14. 3-(Phenylsulfonyl)-5-piperidin-1-ylthieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine 2{*1,76*}. Mp: 221–223 °C. ESI-MS *m*/*z* 400. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.49 (d, J = 5.2 Hz, 1H), 8.04 (m, 3H), 7.67 (m, 1H), 7.61 (m, 2H), 4.03(m, 4H), 1.71 (m, 6H).

6.1.5.15. 5-(3-Methylpiperidin-1-yl)-3-(phenylsulfonyl)thieno [2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*1,77*}. Mp: 192–194 °C. ESI-MS *m*/*z* 414. ^{1}H NMR (DMSO-d_6, 40 MHz) δ 8.48 (d, J = 5.6 Hz, 1H), 8.05 (m, 2H), 8.02 (d, J = 5.6 Hz, 1H), 7.67 (m, 1H), 7.60 (m, 2H), 4.62 (m, 1H), 4.55 (m, 1H), 3.36 (m, 1H), 3.09 (dd, J_1 = 13.2 Hz, J_2 = 10.4 Hz, 1H), 1.84 (m, 2H), 1.74 (m, 1H), 1.54 (m, 1H), 1.32 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.25, 141.74, 140.17, 139.35, 136.57, 133.59, 129.97, 129.35, 127.00, 116.11, 112.39, 66.41, 54.11, 47.67, 32.30, 31.21, 24.88.

6.1.5.16. 5-Azepan-1-yl-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine 2{*1,83*}. Mp: 211–214 °C. ESI-MS *m*/*z* 414. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.50 (d, J = 5.6 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 8.01 (d, J = 5.6 Hz, 1H), 7.67 (t, J = 6.8 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 4.01 (t, J = 5.6 Hz, 4H), 1.89 (m, 4H), 1.54 (m, 4H).

6.1.5.17. 5-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)thieno [2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*1,86*}. Mp: 247–249 °C. ESI-MS *m*/*z* 415. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.52 (d, J = 5.6 Hz, 1H), 8.05 (m, 3H), 7.68 (m, 1H), 7.61 (m, 2H), 4.04 (m, 4H), 2.54 (m, 4H), 2.27 (s, 3H).

6.1.5.18. 5-(2,3-Dihydro-1*H*-indol-1-yl)-3-(phenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*1,90*}. Mp: 263–265 °C. ESI-MS *m*/*z* 434. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.98 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.09 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.34 (m, 2H), 7.14 (t, J = 6.8 Hz, 1H), 4.76 (t, J = 8.0 Hz, 2H), 3.36 (m, 2H).

6.1.5.19. 3-(4-Ethylphenylsulfonyl)-5-thiomorpholin-4-ylthieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*3,85*}. Mp: 206–208 °C. ESI-MS *m*/*z* 446. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 4.33 (m, 4H), 2.82 (m, 4H), 2.65 (q, *J* = 8.0 Hz, 2H), 1.15 (t, *J* = 8.0 Hz, 3H).

6.1.5.20. 3-(4-Ethylphenylsulfonyl)-5-(4-phenyl-3,6-dihydropyridin-1(2*H*)-yl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]*pyrimidine* 2{*3,89*}. Mp: 223–225 °C. ESI-MS *m*/*z* 502. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.54 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.39 (m, 1H), 4.72 (m, 2H), 4.25 (t, *J* = 5.6 Hz, 2H), 2.77 (m, 2H), 2.64 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H).

6.1.5.21. 3-(4-Isopropylphenylsulfonyl)-5-thiomorpholin-4-ylthieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*4,85*}. Mp: 206–208 °C (dec). ESI-MS *m*/*z* 460. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 5.6 Hz, 1H) 7.96 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.33 (m, 4H), 2.95 (sep, *J* = 6.4 Hz, 1H), 2.82 (m, 4H), 1.17 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.49, 153.25, 139.65, 139.39, 139.01, 136.78, 130.59, 127.26, 127.25, 116.03, 112.58, 49.98, 33.39, 26.16, 23.33.

6.1.5.22. 3-(3-Chlorophenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*5,1*}. Mp: 253–255 °C. ESI-MS *m*/*z* 366. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.45 (s, 2H), 8.42 (d, *J* = 5.6 Hz, 1H), 7.99 (m, 3H), 7.74 (m, 1H), 7.64 (t, *J* = 7.6 Hz, 1H).

6.1.5.23. *N*′-[3-(3-Chlorophenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-yl]-*N*,*N*-dimethylethane-1,2-diamine dihydrochloride 2{*5,6*}. Mp: 204–206 °C. ESI-MS *m*/*z* 437. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.09 (s, 1H), 8.60 (d, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 5.6 Hz, 1H), 8.02 (m, 2H), 7.69 (m, 1H), 7.63 (m, 2H), 4.29 (t, *J* = 6.0 Hz, 2H), 3.66 (s, 3H), 3.50 (q, *J* = 6.0 Hz, 2H), 2.91 (d, *J* = 4.8 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.93, 143.56, 141.27, 138.06, 137.17, 133.97, 133.63, 131.77, 129.66, 126.37, 125.72, 115.98, 114.76, 55.42, 42.56, 36.23.

6.1.5.24. 3-(3-Chlorophenylsulfonyl)-*N*-(4-fluorobenzyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*5,21*}. Mp: 246–248 °C. ESI-MS *m*/*z* 474. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.43 (t, *J* = 6.0 Hz, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 7.99 (m, 2H), 7.92 (m, 1H), 7.72 (m, 1H), 7.53 (m, 3H), 7.16 (m, 2H), 4.77 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.57, 160.16, 153.37, 143.54, 141.29, 138.12, 136.64, 134.50, 134.47, 133.79, 133.39, 131.37, 130.06, 129.98, 129.36, 126.24, 125.39, 116.18, 115.15, 114.93, 114.11, 43.54.

6.1.5.25. 3-(3-Chlorophenylsulfonyl)-*N*-(pyridin-3-ylmetnyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*5,29*}. ESI-MS *m*/*z* 457. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.76 (m, 1H), 9.04 (s, 1H), 8.82 (d, *J* = 4.8 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.97 (m, 4H), 7.63 (t, *J* = 6.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 4.92 (d, *J* = 4.8 Hz, 2H).

6.1.5.26. *N*-Benzyl-3-(3-chlorophenylsulfonyl)-*N*-methylthieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*5,71*}. Mp: 203–205 °C. ESI-MS *m*/*z* 470. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.51 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 5.6 Hz, 1H), 8.00 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.40 (m, 2H), 7.36 (m, 3H), 5.17 (s, 2H), 3.56 (s, 3H).

6.1.5.27. 3-(4-Chlorophenylsulfonyl)-5-(1,4-dioxa-8-azaspiro[4,5]-dec-8-yl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*6,82*}. Mp: 233–235 °C. ESI-MS *m*/*z* 493. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.51 (d, *J* = 5.6 Hz, 1H), 8.04 (m, 3H), 7.69 (m, 2H), 4.07 (m, 4H), 3.97 (s, 4H), 1.82 (m, 4H).

6.1.5.28. 3-(4-Chlorophenyl)sulfonyl)-5-morpholin-4-ylthieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine 2{*6,84*}. Mp: 202–204 °C. ESI-MS *m*/*z* 437. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.54 (d, *J* = 5.6 Hz, 1H), 8.05 (m, 3H), 7.69 (m, 2H), 4.03 (t, *J* = 4.8 Hz, 4H), 3.81 (t, *J* = 5.2 Hz, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.00, 140.23, 139.86, 139.36, 138.53, 136.92, 129.80, 129.48, 128.99, 115.93, 112.54, 65.65, 46.81.

6.1.5.29. 3-(4-Bromophenylsulfonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-amine 2{*7,1*}. Mp: 275–277 °C. ESI-MS *m*/*z* 410. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8,42 (M, 3H), 7,98 (d, *J* = 5.2 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.48, 141.67, 141.33, 138.28, 136.93, 132.38, 128.84, 128.57, 127.29, 116.09, 113.69.

6.1.5.30. 3-(2,5-Dimethylphenylsulfonyl)thieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidin-5-amine 2{*8,1*}. Mp: 251–253 °C. ESI-MS *m*/*z* 359. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.41 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 2H), 7.98 (d, *J* = 5.2 Hz, 1H), 7.92 (m, 1H), 7.35 (m, 1H), 7.22 (m, 1H), 2.37 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.24, 141.48, 139.56, 138.25, 136.74, 135.79, 134.31, 133.91, 132.39, 129.36, 128.63, 116.11, 113.64, 20.37, 19.16.

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