Bioorganic & Medicinal Chemistry 18 (2010) 6156–6169

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Further optimization of novel pyrrole 3-carboxamides for targeting serotonin 5-HT$_{2A}$, 5-HT$_{2C}$, and the serotonin transporter as a potential antidepressant

Suk Youn Kang [a], Eun-Jung Park [a], Woo-Kyu Park [b], Hyun Jung Kim [a], Gildon Choi [b], Myung Eun Jung [a], Hee Jeong Seo [a], Min Ju Kim [a], Ae Nim Pae [c], Jeongmin Kim [a], Jinhwa Lee [a,*]

[a] Research Center, Green Cross Corporation, 303 Bojeong-Dong, Giheung-Gu, Yongin 446-770, Republic of Korea
[b] Pharmacology Research Center, Korea Research Institute of Chemical Technology (KRICT), 100 Jang-Dong, Yuseong-Gu, Daejeon 305-343, Republic of Korea
[c] Biochemical Research Center, Korea Institute of Science and Technology, 39-1 Hawolgok-Dong, Seongbuk-Gu, Seoul 136-791, Republic of Korea

ARTICLE INFO

Article history:
Received 15 April 2010
Revised 11 June 2010
Accepted 11 June 2010
Available online 25 June 2010

Keywords:
Depression
Antidepressant
Serotonin
Piperazine
Pyrrole

ABSTRACT

In the continuing search for novel compounds targeting serotonin 5-HT$_{2A}$, 5-HT$_{2C}$, and serotonin transporter, new arylpiperazine-containing pyrrole 3-carboxamide derivatives were synthesized and evaluated. Based on the lead reported previously, structural modifications regarding *N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide **5**, were accomplished for improvements in not only binding affinity against serotonin receptors and transporter, but also in hERG channel inhibition. Along the line, both the forced swimming tests and spontaneous locomotor activity tests were performed to distinguish between antidepressant activity and false positive results. As potential antidepressant agents, both 2,4-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide and 5-*tert*-butyl-2-methyl-1*H*-pyrrole-3-carboxamide derivatives exhibited favorable in vitro and in vivo activities, warranting further investigation around these scaffolds.

1. Introduction

Depression, especially major depression, is an extremely serious disease affecting about 121 million people and is one of the leading causes of disability worldwide. And unipolar depression is predicted to be the second main cause of disability in 2020 by the World Health Organization.[1,2] Over the past decades, the synaptic actions of monoamine neurotransmitters such as norepinephrine (NE) and serotonin (SER, 5-HT) were considered as important indications to psychiatric disease,[3,4] including anxiety and depression. And individually, various psychotropic drugs were developed associated with these neurotransmitters. After great success of a series of selective serotonin reuptake inhibitors (SSRI), it was rationalized the relationship between extracellular levels of serotonin and a number of psychiatric indications, especially depressive disorder, by inhibiting serotonin transporters and consequently elevating synaptic serotonin levels. SSRIs such as fluoxetine, sertraline, paroxetine, and citalopram have been the most widely prescribed antidepressants since 1980s.[5]

Despite numerous usage of SSRIs, they also have some side effects including anxiety, sedation, headache, tremor, and sexual dysfunction. In addition, SSRIs are troublesome in that it is generally effective only less than two-third patients.[6] Recently, there has been achievement of important development for antidepressant, which interacts with dual or multiple targets.[7] Because numerous side effects are associated with non-selective binding at post-synaptic 5-HT receptors, addition of 5-HT receptor antagonist component to 5-HT reuptake inhibitor has been proposed.[8–10] With this approach, it was expected to increase the level of synaptic 5-HT and eventually achieve rapid onset time. Along the line, various compounds have been proposed and developed as potential antidepressant with dual activity (Fig. 1).[11–14]

From the literature, common structure of antidepressants known to have dual activities appeared to exhibit combination of two distinct structural motifs. Thus, aryl piperazine elements and heterocyclic motifs were connected to each other using a linker frequently to serve as SERT and 5-HT receptor inhibitors. As a similar strategy, we recently disclosed a new class of antidepressant compounds involving pyrrole 3-carboxamide compounds.[15] Particularly, compound **5** showed good in vitro activity against 5-HT$_{2A/2C}$ receptors and serotonin reuptake inhibition, and also demonstrated excellent oral bioavailability and brain penetrative properties (Fig. 2). As a continuation of our investigation, we wish to describe further exploration of the structure–activity relationships (SAR) in this novel series. Evaluation of their in vitro and in vivo profiles was conducted in terms of efficacy versus side effects.

* Corresponding author. Tel.: +82 31 260 9892; fax: +82 31 260 9020.
E-mail addresses: jinhwalee@greencross.com, jinhwa_2_lee@hotmail.com (J. Lee).

0968-0896/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2010.06.037

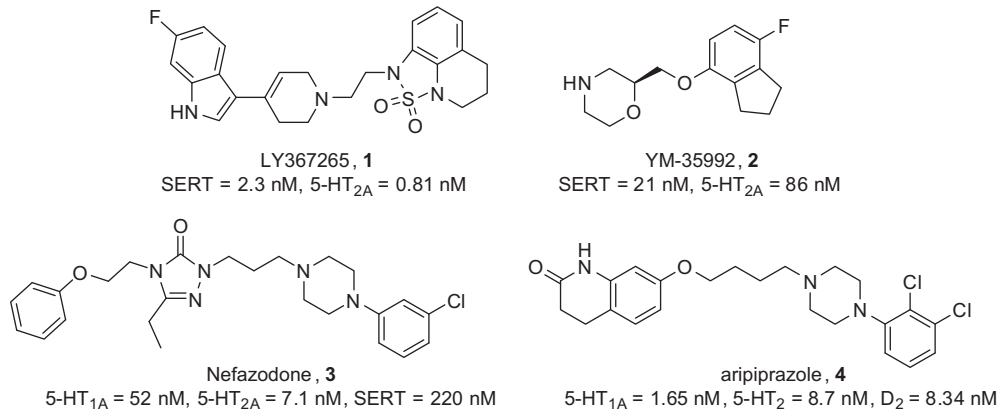


Figure 1. Chemical structures of representative antidepressant compounds.

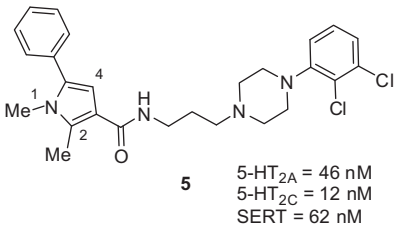


Figure 2. Representative compound for targeting serotonin 5-$HT_{2A/2C}$, and the SERT as a antidepressant.

2. Chemistry

Based on the previous results, structural modification of lead compound **5** was initiated as shown in Figure 3.[15] The structure–activity relationship study began with evaluation of the effect by substitution of various arylpiperazinyl groups. Thus, novel compounds can be readily prepared by typical amide coupling at the final stage with modified acid and amine. Pyrrole 3-carboxylic acid **A** and arylpiperazinyl alkyl amine **B** can be used as acid and amine partners, respectively.

Bromoketone **9** was selected for the preparation of pyrrole derivatives, particularly consisting of 5-substituted and 3-carboxylic acid (Scheme 1).[16] Substitution at nitrogen of pyrrole was focused on within proton to *n*-propyl based on the previous result. Hydrolysis of pyrrole ester **12** using sodium hydroxide in refluxed ethanol afforded the corresponding acids **13**.

As shown in Scheme 2, preparation of aminoalkyl arylpiperazine **17** started from the corresponding bromoalkyl-phthalimide **14** and arylpiperazine **15**.[17] Treatment of bromoalkyl-phthalimide **14** with arylpiperazine hydrochloride **15** in the presence of potassium carbonate in DMF at room temperature afforded N-protected amine **16**. Compound **16** was then treated with hydrazine in ethanol at 80 °C to give amine **17**. For the sake of convenience of handling on scale, liquid amine **17** was transformed to hydrochloride salt form **17a** with 4 N HCl in dioxane.

As shown in Scheme 3, typical amide coupling was conducted under conditions involving EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide), HOBT (1-hydroxybenzotriazole) and NMM (4-methylmorpholine) in methylene chloride or DMF to produce amide **18**. As reaction was completed, purification was performed using preparative reverse-phase HPLC with 0.2% TFA mixture of acetonitrile and water solution. The neutral form of product **18** was converted to HCl salt form **18a** to increase the overall solubility for biological evaluation.

3. Biology

For further evaluation of our lead compound **5**, spontaneous locomotor activity test was performed. Although the sensitivity of FST (forced swimming test) to a broad range of antidepressant drugs is one of the most important features supporting primary

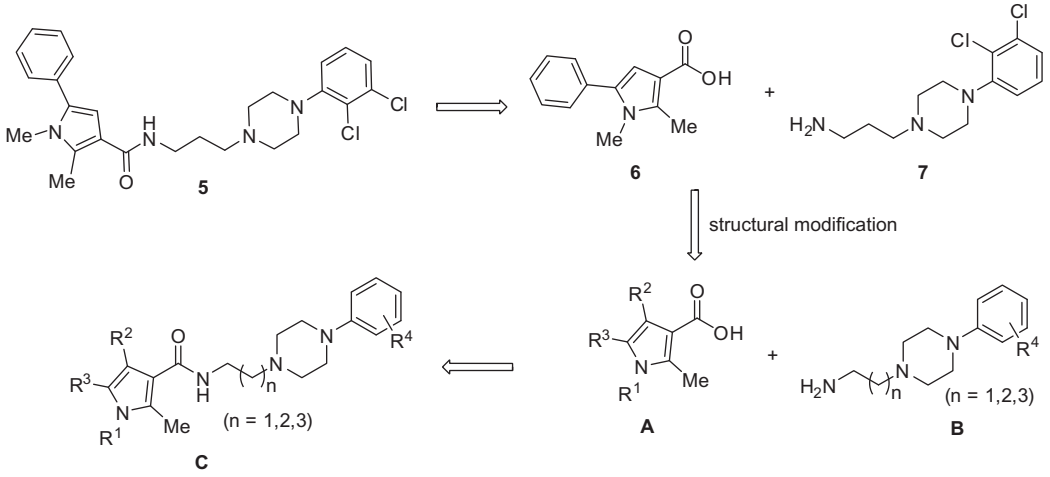
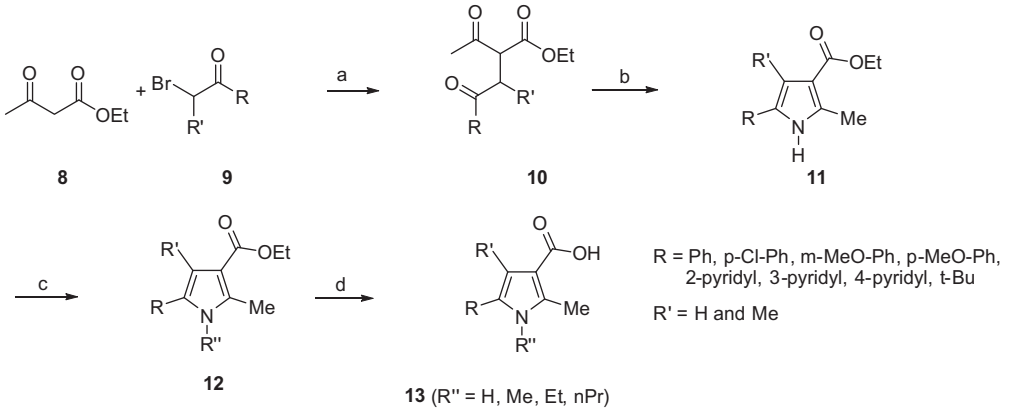
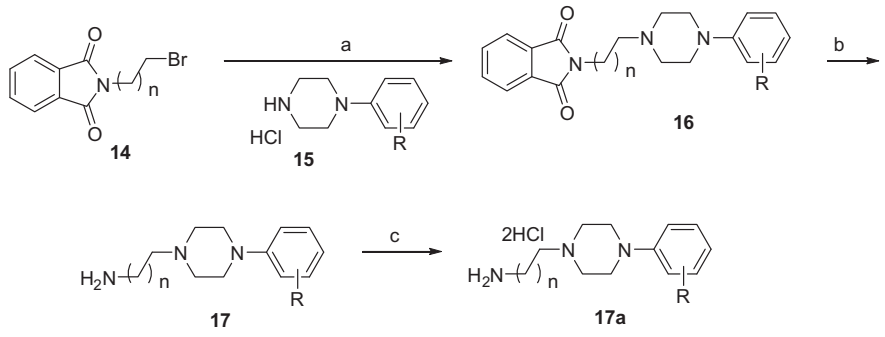


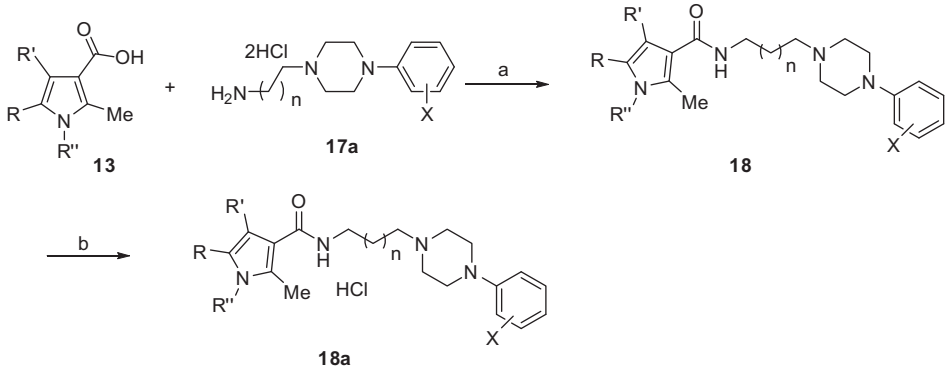
Figure 3. Preparation of target compounds using amide bond formation.



Scheme 1. Reagents and conditions: (a) NaH, THF; (b) NH_4OAc, AcOH, 80 °C; (c) NaH, Alkyl iodide, DMF; (d) NaOH, EtOH, reflux.



Scheme 2. Reagents and conditions: (a) K_2CO_3, DMF, rt; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, rt; (c) 4 N HCl in dioxane.



Scheme 3. Reagents and conditions: (a) EDCI, HOBT, NMM, CH_2Cl_2 or DMF; (b) HCl, MeOH, 0 °C.

usage as a viable animal model, the activity in the FST is also known to be detected by either anticholinergic or antihistamine drugs depending on test conditions.[21] The major false positives in the FST are psychomotor stimulants, which affect immobility in the FST. They are not anticipated to have clinical efficacy. From these reasons, our lead compound **5** was subjected to screening against spontaneous locomotor activity along with the FST. The results were summarized in Figure 4. Fluoxetine, a clinically established reference, shows lower spontaneous locomotor activity regardless of dosing amounts. And compound **5** tends to display increasing locomotor activities with dose dependency. It means that our compound shows antidepressant-like activity by reducing immobility in the FST, but its efficacy was falsely produced from hyperactivity of the compounds. That is the reason why we focused our efforts to remove spontaneous locomotor activity, while maintaining immobility in FST experiments.

Biological evaluations were performed upon compounds prepared by the above synthetic pathway. The binding affinity of current compounds against 5-$HT_{2A/2C}$ receptor and serotonin transporter, stably expressed in CHO-K1 cells, were evaluated by displacement binding using [^{3}H]Ketanserin, [^{3}H]Mesulergine and, [^{3}H]Imipramine, respectively, as radioligands.[18]

Based on our previous report,[15] derivatization of arylpiperazine was expanded to various pyrroles **13** including 1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid and 2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxylic acid. The results are summarized in Table 1. In the case of *N*-methyl pyrrole, overall derivatization showed less favorable binding affinity than that of 2,3-dichlorophenyl group. Particularly, 4-fluorophenyl and 8-quinolinyl group showed more potent binding affinity at 5-HT_{2A} and SERT, respectively (**24**, **25**, and **38**). But it turned out to result in inferior activity with consideration of other receptors. On the other hand, derivati-

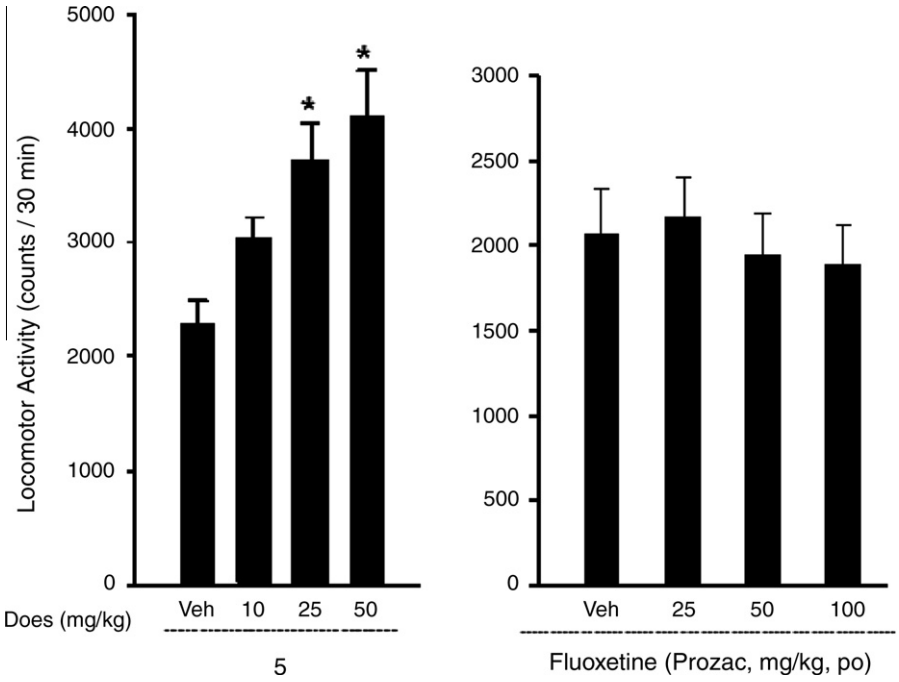
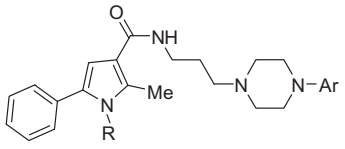


Figure 4. Locomotor activities of the mice treated with compounds or vehicle were counted for 30 min by Activity Analyzer. Compound (10, 25, and 50 mg/Kg) or vehicle was administered orally (po) 60 min before the test. Data were expressed as mean ± SEM of 6–7 mice. $^{*}P$ <0.05, when compared to vehicle control group.

Table 1
Competition binding assays at 5-HT_{2A} and 5-HT_{2C} receptor and the serotonin transporter to arylpipierazinyl pyrrole 3-carboxamide derivatives (IC_{50} values)



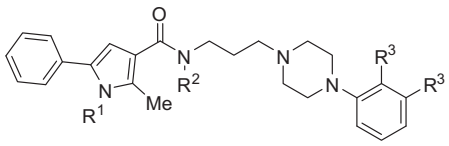
unit: nM

Ar	R							
	Me				*n*Pr			
	No.	5-HT_{2A}	5-HT_{2C}	SERT	No.	5-HT_{2A}	5-HT_{2C}	SERT
3-Chlorophenyl	**19**	92	160	11	**28**	191	273	93
2,3-Dimethylphenyl	**20**	57	133	12	**29**	129	225	76
2,3-Dichlorophenyl	**5**	46	12	62	**30**	324	628	420
2,4-Dichlorophenyl	**21**	213	349	23				
3,4-Dichlorophenyl					**31**	54	324	284
2-Bromophenyl	**22**	221	633	225				
3-Bromophenyl					**32**	221	633	225
2-Methoxyphenyl					**33**	953	1408	1084
3-Methoxyphenyl					**34**	153	452	322
2,3-Dimethoxyphenyl	**23**	666	782	1259	**35**	874	977	1981
4-Fluorophenyl	**24**	22	493	183				
2,5-Difluorophenyl					**36**	135	1006	854
3-Trifluoromethylphenyl					**37**	410	619	381
8-Quinolinyl	**25**	352	233	22	**38**	210	420	82
2-Methyl-8-quinolinyl	**26**	832	653	300				
4-Pyridinyl	**27**	4559	5257	>10,000				

zation in *N*-propyl pyrrole case shows similar binding affinity with 2,3-dichlorophenyl group. It can be possibly explained that lead 2,3-dichlorophenyl compounds showed less favorable potency than 2,3-dimethyl compounds. Nevertheless, overall binding affinity displays IC_{50} <1 μM, implying that these compounds might hold promises as a potential antidepressant. Thus, either 2,3-dimethylphenyl or 2,3-dichlorophenyl group was adopted constantly as the piperazinyl substituent and further SAR studies were performed.

In order to improve binding affinity against 5-$HT_{2A/2C}$ receptors and the serotonin transporter as well as to improve metabolic stability, methylation at amide nitrogen was performed (Table 2). In addition to that, methylation at C-4 position was also performed and the results were displayed at Table 3. In the case of 2,3-dimethylphenylpiperazinyl series, compound **39** showed highly improved binding affinity to 5-$HT_{2A/2C}$ receptors, but decreased at SERT as a trade. When compound **5** was modified into compound **40** by way of N-methylation at amide group, there appears to slightly increase in binding affinity against serotonin receptors. And when *N*-methyl at pyrrole was changed to *N*-propyl pyrrole derivative **41**, binding affinity against 5-$HT_{2A/2C}$ increased dramat-

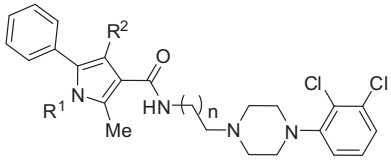
Table 2
Binding affinities for 5-HT_{2A} and 5-HT_{2C} receptor and serotonin transporter of arylpipierazinyl pyrrole 3-carboxamide derivatives



unit: nM

No.	R^1	R^2	R^3	5-HT_{2A}	5-HT_{2C}	SERT
5	Me	H	Cl, Cl	46	12	62
20	Me	H	Me, Me	57	13	12
29	*n*Pr	H	Me, Me	129	225	76
30	*n*Pr	H	Cl, Cl	324	628	420
39	*n*Pr	Me	Me, Me	17	12	163
40	Me	Me	Cl, Cl	39	35	98
41	*n*Pr	Me	Cl, Cl	33	21	102

Table 3
Binding affinities against 5-HT_{2A} and 5-HT_{2C} receptors and inhibition against serotonin transporter of arylpipierazinyl pyrrole 3-carboxamide derivatives



unit: nM

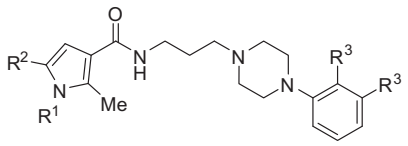
No.	R^1	R^2	*n*	5-HT_{2A}	5-HT_{2C}	SERT
42	H	H	1	40	37	87
43	Me	H	1	175	156	57
44	*n*Pr	H	1	408	310	32
45	H	H	2	300	599	137
46	H	Me	1	37	13	162
47	Me	Me	1	33	16	78
48	*n*Pr	Me	1	25	75	78
49	H	Me	2	39	16	36

ically, thereby displaying similar level of affinity as against serotonin transporter.

As another practice, instead of N-methylation at amide group, methylation at C-4 position of pyrrole displayed somewhat different results (Table 3). Thus, it was observed that when 2,3-dichlorophenylpiperazinyl part and pyrrole 3-carboxilic acid part was connected with ethylene linker, and binding affinities were at level of IC_{50} <80 nM for C-4 methylated analogues, except compound **46** (IC_{50} = 162 nM) at SERT. Favorable binding affinities against 5-HT, 5-HT, and SERT were also observed for compound **49** as shown in Table 3.

Limited exploration of the effects of substitution on the phenyl of pyrrole C-5 position was also undertaken (Table 4). At N-alkylated pyrrole series, 4-chlorophenyl modification tends to reduce binding affinity against 5-HT_{2A} and inhibition against SERT but increase binding affinity against 5-HT_{2C} receptor (**51** vs **54** and **56** vs **59**). On the other hand, in the case of N–H pyrrole compounds, the exactly opposite trends are displayed (**50** vs **52**). With this in mind, replacement of phenyl group with more hydrophilic pyridinyl group was also conducted. 2-Pyridinyl substituted compound **61** is more potent than phenyl compound **50**, especially against 5-HT_{2A} and SERT. However, when N-alkylation at pyrrole N-1 position was changed to methyl or propyl, binding affinity about 5-HT_{2C} and SERT decreased while maintaining 5-HT_{2A} activity (**61** vs **62** vs **63**). 3-Pyridinyl and 4-pyridinyl compounds displayed similar level of activities. Most of pyridinyl compounds exhibited

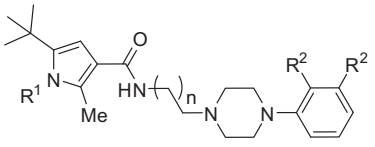
Table 4
Binding affinities against 5-HT_{2A} and 5-HT_{2C} receptors and inhibition against serotonin transporter of arylpipierazinyl pyrrole 3-carboxamide derivatives



unit: nM

No.	R^1	R^2	R^3	5-HT_{2A}	5-HT_{2C}	SERT
50	H	Phenyl	Me, Me	300	615	77
51	Et	Phenyl	Me, Me	75	139	36
56	Et	Phenyl	Cl, Cl	376	66	182
52	H	4-Chlorophenyl	Me, Me	92	189	19
53	Me	4-Chlorophenyl	Me, Me	213	129	129
54	Et	4-Chlorophenyl	Me, Me	151	39	93
55	*n*Pr	4-Chlorophenyl	Me, Me	192	26	131
57	H	4-Chlorophenyl	Cl, Cl	105	106	56
58	Me	4-Chlorophenyl	Cl, Cl	232	39	733
59	Et	4-Chlorophenyl	Cl, Cl	153	22	629
60	*n*Pr	4-Chlorophenyl	Cl, Cl	333	41	1159
61	H	2-Pyridinyl	Cl, Cl	21	221	28
62	Me	2-Pyridinyl	Cl, Cl	43	267	110
63	*n*Pr	2-Pyridinyl	Cl, Cl	58	639	397
64	Me	3-Pyridinyl	Cl, Cl	209	92	7
65	*n*Pr	3-Pyridinyl	Cl, Cl	46	344	133
66	Me	4-Pyridinyl	Cl, Cl	39	175	85
67	*n*Pr	4-Pyridinyl	Cl, Cl	34	420	78

Table 5
Binding affinities for 5-HT_{2A} and 5-HT_{2C} receptor and serotonin transporter of arylpipierazinyl pyrrole 3-carboxamide derivatives



unit: nM

No.	R^1	R^2	*n*	5-HT_{2A}	5-HT_{2C}	SERT
68	Me	Me, Me	1	36	2227	908
69	Me	Me, Me	2	386	1145	252
70	Me	Cl, Cl	1	50	109	45
71	H	Cl, Cl	2	107	1392	860
72	Me	Cl, Cl	2	163	1021	375

more favorable activity against 5-HT_{2A} than against 5-HT_{2C} and SERT.

Introduction of *t*-butyl group at phenyl position of pyrrole was also studied, and the results were summarized in Table 6. Although its *C*log *P* value is similar to that of phenyl compound (*C*log *P* = 6.60 at **5**) and *t*-butyl compound (*C*log *P* = 6.33 at **72**), Compound **72** which is *t*-butyl version of lead compound **5**, showed poor binding affinity against 5-HT_{2C} (IC_{50} = 1021 nM) and moderate activity against 5-HT_{2A} (IC_{50} = 163 nM) and SERT (IC_{50} = 375 nM). 2,3-Dimethylphenyl compound **69** appeared to show similar level of binding affinity. To date the best result of t-butyl scaffold was obtained when 2,3-dichlorophenylpiperazinyl group was connected with C2 linker (compound **70**) (see Table 5).

For further evaluation of this series of compounds, several selected compounds were subjected to hERG channel inhibition assay.[19] Patch-clamp technique method was used for in vitro assay for hERG blocking. And the results are summarized in Table 6. Lead compound **5** turned out be a significant inhibitor of hERG channel

Table 6
The hERG channel blocking data assayed for selected compounds

No.	hERG	No.	hERG	No.	hERG
5	0.14	**45**	0.10	**64**	6.80
30	0.54	**61**	0.90	**68**	11.8
39	0.70	**62**	1.70	**70**	6.90
40	0.50	**63**	1.00	Prozac	3.10[a]

[a] See Ref. 23.

(IC_{50} = 0.14 μM). Similar result was also obtained for N–H pyrrole compound **45** (IC_{50} = 0.10 μM). hERG inhibition decreased by about fourfold when *N*-methyl was replaced with *N*-*n*-propyl (IC_{50} = 0.54 μM, **5** vs **30**).

N-methylation at amide group resulted in reduced hERG inhibition in approximately 3.5-fold (**5** vs **40**), suggesting that hERG inhibition profiles can be altered when compound is structurally modified by removing a hydrogen bond donor in amide functional group.

Pyridinyl groups were not able to improve hERG channel blocking except compound **64** (IC_{50} = 6.8 μM). However, 5-*t*-butylpyrrole compounds **68**, **70** indeed showed significant improvement toward hERG channel inhibition compared to other scaffolds. For the reference, IC_{50} value for fluoxetine was reported to be 3.1 μM.[23] Therefore, the compounds near this value for hERG channel inhibition appear to be promising for current stage of research.

The representative compounds were tested in vivo models in mice to further confirm its ability to inhibit the monoamine transport and produce antidepressant-like effects. As the first experiment, the potential antidepressant-like effect of current compounds was evaluated in the forced swimming test (FST), which is sensitive to known antidepressant drugs.[20] The compound was administered orally 30 min before the test in mice at 50 or 100 mg/kg. And the results were displayed in Figure 5. Compared with reference compound Prozac, ten compounds show similar or even better antidepressant-like efficacy. Modification of arylpiperazinyl group did not lead to good efficacy. N-Methylated amide compounds **39** and **40** appeared to enhance efficacy, even with dimethylphenyl analogue **39**. C-4 Methyl compounds displayed nice structure–activity correlation (**46**, **47**, **48**, and **49**) in that antidepressant-like effects increase for ethylene carbon linker when *N*-alkyls are elongated from proton to propyl (H **46** vs Me **47** vs *n*Pr **48**). Thus, while compound **46** do not show good in vivo efficacy on FST, significant enhancement was demonstrated for its propylene version **49**.

Compound **58**, 4-chlorophenyl group at pyrrole, appears to reduce efficacy than lead compound **5**. And this result was well-correlated with in vitro data (compound **5**: 5-HT_{2A} IC_{50} = 46 nM, 5-HT_{2C} IC_{50} = 12 nM, SERT IC_{50} = 62 nM and compound **58**: 5-HT_{2A} IC_{50} = 232 nM, 5-HT_{2C} IC_{50} = 39, SERT IC_{50} = 733 nM). 2-Pyridinyl compound **62** shows better antidepressant-like activity than that of the corresponding 3-pyridinyl or 4-pyridinyl compound. 5-*t*-Butyl pyrrole analogues **70**, **71**, and **72** produce more favorable activity compared to fluoxetine (Prozac). The best result was obtained when 5-*t*-butylpyrrole moiety was connected to 2,3-dichlorophenylpyridinyl via C3-carbon linker **72** (immobility = 12.5 ± 4.8%).

The second in vivo test involves spontaneous locomotor activity test. Compounds **64**, **68**, and **70** which show moderate safety in hERG blocking experiment were selected. And the results were summarized in Table 7.

Although various pyrrole derivatives were changed, most compounds showed hyperactivity. At this point, we also observed that when arylpiperazine was altered from dichlorophenyl into dimethylphenyl, a degree of locomotor activity was also decreased. Thus,

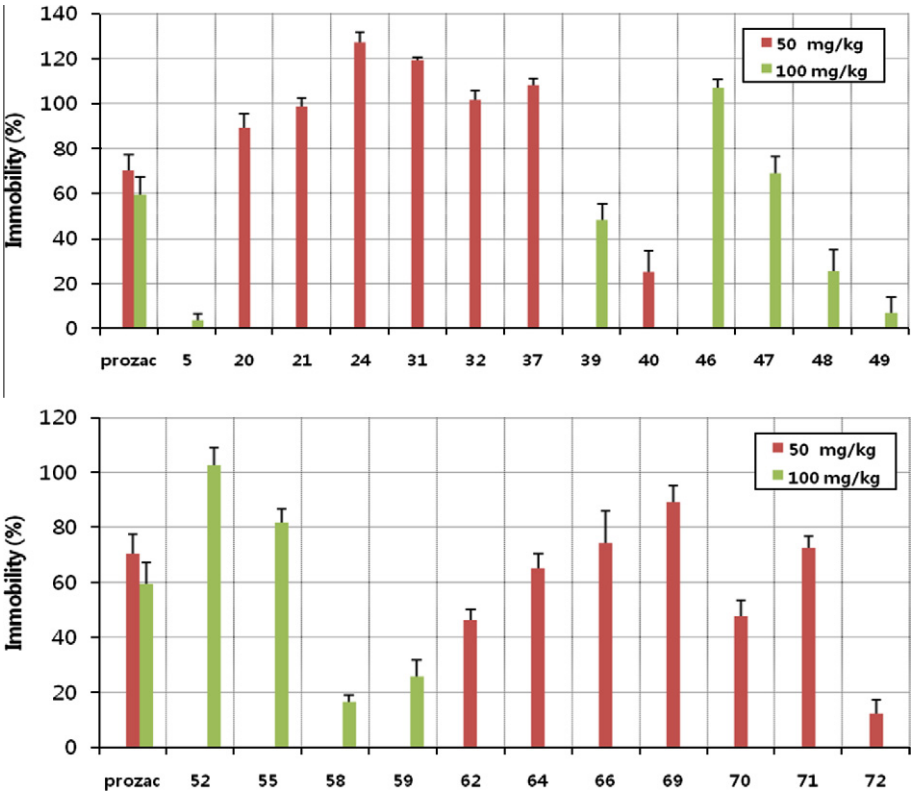


Figure 5. Effects of drugs on immobility in forced swimming test on mice. Drugs (100 and 50 mg/kg) were injected orally (po) 60 min before the testing, and total duration of immobility was recorded during the last 5 min of the 6-min testing period. Values are means ± S.E.M and vehicle = 100%.

Table 7
Locomotor activities of the mice treated with compounds (25 mg/kg) or vehicle were counted for 30 min by Activity Analyzer

No.	Locomotor activity	Hyperactivity sign
64[a]	—	Hyperactive[a]
68	7302 ± 2414	Mid-hyperactive
70	14860 ± 1531	Hyperactive
72	15804 ± 5162	Hyperactive
Effexor[b]	7158 ± 484	Mid-hyperactive
Prozac[b]	5931 ± 1979	Normal
Vehicle	−5000	Normal

Data were expressed as mean ± S.E.M of 6–7 mice.
[a] See Ref. 22.
[b] In-house data.

in order to reduce hyperactivity with maintaining antidepressant activity, 3-chloro-2-methylphenyl piperazine was introduced as a novel arylpepierazine moiety, and with consideration of hERG blocking issue, *t*-butylpyrrole analogues were selected. Derivatives of compound **68** or **70** were evaluated and the in vitro and in vivo results are shown in Table 8.

Comparing with 2,3-dichlorophenyl compound **43**, 2-methyl-3-chlorophenyl compound **73** showed similar profiles to 5-HT_{2A} and SERT and mild decrease to 5-HT_{2C} (compound **43**: 5-HT_{2A} IC_{50} = 175 nM, 5-HT_{2C} IC_{50} = 156 nM, SERT IC_{50} = 57 nM and compound **73**: 5-HT_{2A} IC_{50} = 152 nM, 5-HT_{2C} = 233 nM, SERT = 64 nM). In a series of *t*-butylpyrrole, when 2-methyl-3-chlorophenyl compound **74** was compared with 2,3-dimethyl analogue **68**, compound **74** was observed to show slight decrease against 5-HT_{2A} and outstanding activity improvement against 5-HT_{2C} and SERT (compound **68**: 5-HT_{2A} IC_{50} = 36 nM, 5-HT_{2C} IC_{50} = 2227 nM, SERT IC_{50} = 908 nM and compound **74**: 5-HT_{2A} IC_{50} = 54 nM, 5-HT_{2C} = 210 nM, SERT = 315 nM). On the contrary to 2,3-dimethylphenyl, when compound **74** is compared with 2,3-dichlorophenyl compound **70**, they showed similar binding affinity against 5-HT_{2A}, and 2 and sevenfold reduction against 5-HT_{2C} and SERT, respectively (compound **70**: 5-HT_{2A} IC_{50} = 50 nM, 5-HT_{2C} IC_{50} = 109 nM, SERT IC_{50} = 45 nM and compound **74**: 5-HT_{2A} IC_{50} = 54 nM, 5-HT_{2C} = 210 nM, SERT = 315 nM). Additionally, compound **74** showed 3.6 μM about hERG channel inhibition assay. With compounds **73** and **74**, forced swimming test (FST) and spontaneous locomotor activity test (SLA) were also performed. Compound **73** showed moderate hyperactivity and showed less antidepressant-like activity. However, in the case of *t*-butyl version, compound **74** displayed good antidepressant activity with normal behavior.

Although compound **5** in our prior work[15] demonstrated good in vitro and in vivo antidepressant-like activity, **5** also suffered from negative aspects including strong hERG inhibition and false positive effects. Current research successfully identified compound **74** bearing *t*-butyl group at pyrrole C-5, overcoming the inherent problems of compound **5**.

4. Conclusion

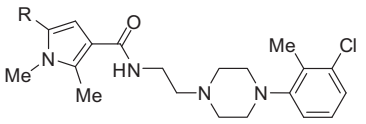
In summary, we investigated new arylpiperazine-containing pyrrole 3-carboxamide series of compounds as our continuing effort to identify novel compounds targeting 5-$HT_{2A/2C}$ and SERT for the treatment of depressive disorders. Based on the lead compound **5**, a number of structural modifications are presented including modification of arylpiperazinyl group, N-alkylation of amide group, C-4 methylation at pyrrole, and replacement of phenyl group of pyrrole with *p*-chlorophenyl, pyridinyl, or *t*-butyl. All the prepared compounds were evaluated by competition binding assays against 5-$HT_{2A/2C}$ and SERT. Structure–activity relationships (SARs) were established. hERG blocking assay was conducted for further evaluation of this series. A few of selected compounds were tested in vivo FST animal models. More than ten compounds in this series produced similar or better antidepressant-like activity compared with fluoxetine, well-established reference antidepressant. Spontaneous locomotor activity test was conducted to distinguish the false positive effects in the FST. In order to overcome hyperactivity issue, 3-chloro-2-methylphenyl group was introduced into the series. Through a series of lead optimization efforts, compound **74** was identified to possess good binding affinity (5-HT_{2A} IC_{50} = 54 nM, 5-HT_{2C} IC_{50} = 210 nM, SERT IC_{50} = 315 nM) in addition to relatively safe hERG inhibition (IC_{50} = 3.6 μM). By in vivo efficacy study, compound **74** also showed reasonable antidepressant activity without exhibiting hyperactivity. Thus, novel pyrrole 3-carboxamides targeting serotonin 5-HT_{2A}, 5-HT_{2C}, and the serotonin transporter may have potential as a pharmacotherapy for the treatment of depressive disorders.

5. Experimental

5.1. General methods

All reactions are conducted under an inert atmosphere at room temperature, unless otherwise noted. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise indicated. Microwave reaction was conducted with a Biotage Initiator microwave reactor. NMR spectra were obtained on a Varian 400-MR (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ = 0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, and br = broad), coupling constant, and integration. ^{13}C NMR spectra were referenced to the residual $CDCl_3$ (δ = 77.0) or DMSO-d_6 (δ = 39.7). Mass spectra were obtained with an Agilent 6110 quadruple LC-MSD (ESI+). Preparative HPLC purifications were performed on a Gilson purification system. For preparative HPLC, ca. 100 mg of a product was injected in 1 ml of methanol onto a SunFire Prep C18 OBD 5 μm 30 × 100 mm Column

Table 8
Binding affinities against 5-HT_{2A} and 5-HT_{2C} receptors and inhibition against serotonin transporter of compound **73** and **74** and effects on immobility in forced swimming test on mice and locomotor activities



R	No.	5-HT_{2A} (nM)	5-HT_{2C}(nM)	SERT (nM)	FST (%)	SLA (cm)
Phenyl	**73**	152	233	64	86.15 ± 10.89	7096 ± 1926
t-Butyl	**74**	54	210	315	49.12 ± 14.50	6217 ± 2903

For FST, drugs (25 mg/kg) were injected orally (po) 60 min before the testing, and total duration of immobility was recorded during the last 5-min of the 6-min testing period. For locomotor activities, locomotion of mice treated with compounds or vehicle were counted for 30 min by Activity Analyzer. Data were expressed as mean ± S.E.M.

with a 30 min gradient from 5% to 90% acetonitrile in water and a 45 ml/min flow rate. Biotage SP1 and Isolera purification systems were used for normal phase column chromatography with ethyl acetate and hexane. Flash chromatography was performed using E. Merck 230–400 mesh silica gel according to the procedure of Still et al. Reactions were monitored by either thin-layer chromatography (TLC) on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and *p*-anisaldehyde solution as visualizing agents or HPLC analysis on an Agilent 1200 series system.

5.2. Chemistry

5.2.1. 1,2-Dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (6)

5.2.1.1. Step 1: Ethyl 2-acetyl-4-oxo-4-phenylbutanoate. To a solution of ethyl acetoacetate (10 g, 76.8 mmol) in tetrahydrofuran (50 ml) at 0 °C was added sodium hydride (4 g, 60% in mineral oil, 100 mmol) portionwise. The reaction mixture was stirred for 30 min, and 2-bromoacetophenone (16.8 g, 84.5 mmol) in tetrahydrofuran (20 ml) was added dropwisely. After warming the mixture to room temperature, it was stirred for 4 h. The resulting solution was quenched with water and normal work-up was conducted with diethyl ether. The organic layer was dried with $MgSO_4$, and purified by silica gel column chromatography (EtOAc/Hex = 1:5) to produce the desired compound (19 g, 98%) as light yellow color oil. MH+ 249.

5.2.1.2. Step 2: Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate. Ethyl 2-acetyl-4-oxo-4-phenylbutanoate (19 g, 76.8 mmol) was treated with NH_4OAc (29.4 g, 384 mmol) in acetic acid (100 ml) at room temperature. After stirring 10 min, the reaction mixture was heated to 80 °C for overnight. After cooling to room temperature, acetic acid was evaporated under reduced pressure and subsequently water (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. Purification by normal phase preparative LC provided the desired compound (13.3 g, 76%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.45 (dd, J = 8.4, 1.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.20 (dd, J = 7.2, 1.1 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 4.29 q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.36 (t, J = 6.8 Hz, 3H). MH+ 230.

5.2.1.3. Step 3: Ethyl 1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylate. To ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (3 g, 13 mmol) in THF (50 ml) was added iodomethane (4 ml, 65 mmol) and sodium hydride (630 mg, 60% in mineral oil, 15.6 mmol) at 0 °C. After warming the reaction mixture to room temperature, it was stirred for 1 day. Water (20 ml) was added and extracted the resulting mixture with diethyl ether. With normal phase preparative LC, purification was conducted to gave the title compound (3 g, 94%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 6.58 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.50 (s, 3H), 2.60 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). MH+ 244.

5.2.1.4. Step 4: 1,2-Dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (6). To the solution of ethyl 1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (3 g, 13 mmol) in EtOH (50 ml) was added NaOH (1.6 g, 39 mmol) at room temperature. The reaction mixture was refluxed for 1 day with LC–MS monitoring. After the reaction was completed, EtOH was evaporated under reduced pressure. Water (50 ml) was added and extracted the aqueous layer with diethyl ether twice. 1 N HCl solution was added to the aqueous layer until the solution became acidic (pH <3). And extraction was accomplished with EtOAc. The organic layer was dried with $MgSO_4$ and the filtered organic volatiles were evaporated in vacuo to provide the title compound (2.6 g, 95%) as yellow solid. Without further purification, the acid was used for the next amide coupling.

5.2.2. 2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethanamine dihydrochloride (7)

5.2.2.1. Step 1: 2-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione. 1-(2,3-Dichlorophenyl)piperazine hydrochloride (3.16 g, 11.8 mmol) and potassium carbonate (4.08 g, 29.5 mmol) were added to the solution of 2-(3-bromopropyl)isoindoline-1,3-dione (3.16 g, 11.8 mmol) in DMF (20 ml). The reaction mixture was stirred for overnight at room temperature. After reaction was completed, water (40 ml) was added and then normal work-up was conducted. The residue was purified with normal phase preparative column chromatography to afford the title compound (4 g, 81% yield) as white solid. MH+ 418.

5.2.2.2. Step 2: 3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propan-1-amine dihydrochloride. To a stirred solution of 2-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (4 g, 9.57 mmol) in ethanol (50 ml) was added hydrazine (3 ml) at room temperature. The reaction mixture was heated to 80 °C and stirred for 1 day at that temperature. The resulting solution was cooled down to room temperature, and the volatiles were evaporated under reduced pressure. The residue was work-up with EtOAc and saturated sodium bicarbonate solution. After evaporation of organic layer under reduced pressure, it was poured into 1 N HCl solution. The aqueous solution was washed with ethyl ether, and then basified with aqueous ammonia. CH_2Cl_2 was used for work-up organic layer, dried with $MgSO_4$. After solvent was removed under reduced pressure, 4 N HCl in dioxane (5 ml) was added at 0 °C and stirred 10 min to produce HCl salt form. Light yellow solid title compound (3.1 g, 89%) was obtained by evaporation and drying in vacuo volatile compounds. MH+ 274 (–2HCl).

5.2.3. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (5)

To the mixture of 1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (100 mg, 0.46 mmol) and 3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propan-1-amine dihydrochloride (166 mg, 0.46 mmol) in CH_2Cl_2 (5 ml) were added EDCI (178 mg, 0.92 mmol), HOBT (130 mg, 0.9 mmol) and NMM (0.3 ml, 1.8 mmol). After stirring for 1 day at room temperature, MeOH was added to the resulting solution, and filter off. After evaporation under reduced pressure, the residue was purified by reverse-phase preparative HPLC to provide the title compound (149 mg, 71%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.24–7.13 (m, 6H), 6.87–6.73 (m, 4H), 6.27 (s, 1H), 3.54 (dd, J = 11.2, 5.2 Hz, 2H), 3.48 (s, 3H), 3.25–3.19 (m, 5H), 2.64 (s, 3H), 2.60–2.44 (m, 6H), 1.80 (m, 2H). MH+ 451.

5.2.4. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (5a)

HCl solution (4 N in dioxane, 0.5 ml) was added to the solution of *N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (100 mg) in methanol (5 ml). After stirring for 10 min, the volatiles were evaporated under reduced pressure and dried in vacuo to produce HCl salt form as light yellow solid.

5.2.5. *N*-(3-(4-(3-Chlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (19)

Compound **19** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.24–7.13 (m, 6H), 6.87–6.73 (m, 4H), 6.27 (s, 1H), 3.54 (dd, J = 11.2, 5.2 Hz, 2H), 3.48 (s, 3H), 3.25–3.19 (m, 5H), 2.64 (s, 3H), 2.60–2.44 (m, 6H), 1.80 (m, 2H). MH+ 451.

5.2.6. *N*-(3-(4-(2,3-Dimethylphenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (20)

Compound **20** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 7.39–7.31 (m, 5H), 6.94 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.40 (s, 1H), 3.54 (dd, J = 11.2, 5.6 Hz, 2H), 3.49 (s, 3H), 2.92 (t, J = 4.0 Hz, 4H), 2.65 (s, 3H), 2.60 (t, J = 5.2 Hz, 2H), 2.26 (s, 3H), 2.19 (s, 3H), 1.83–1.79 (m, 2H). MH+ 445.

5.2.7. *N*-(3-(4-(2,4-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (21)

Compound **21** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (br s, 1H), 7.91 (br s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.43–7.28 (m, 6H), 7.19 (d, J = 8.4 Hz, 1H), 6.58 (s, 1H), 4.38–4.28 (m, 4H), 3.54–3.52 (m, 2H), 3.44 (s, 3H), 3.38–3.35 (m, 2H), 3.25–3.13 (m, 4H), 2.51 (s, 3H), 1.94–1.91 (m, 2H). MH+ 485 (–HCl).

5.2.8. *N*-(3-(4-(2-Bromophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (22)

Compound **22** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61–7.59 (m, 1H), 7.43–7.32 (m, 6H), 7.23–7.21 (m, 1H), 7.05–7.02 (m, 1H), 3.63 (s, 3H), 3.54–3.45 (m, 4H), 3.33–3.15 (m, 8H), 2.59 (s, 3H), 2.07 (m, 2H). MH+ 495.

5.2.9. *N*-(3-(4-(2,3-Dimethoxyphenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (23)

Compound **23** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 1H), 7.31–7.25 (m, 5H), 6.90 (t, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.4, 1.2 Hz, 1H), 6.41 (dd, J = 8.4, 1.2 Hz, 1H), 6.35 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.53 (quartet, J = 6.0 Hz, 2H), 3.45 (s, 3H), 3.17 (br s, 4H), 2.70–2.62 (m, 7H), 2.58 (t, J = 6.0 Hz, 2H), 1.80 (quartet, J = 6.0 Hz, 2H). MH+ 477.

5.2.10. *N*-(3-(4-(4-Fluorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (24)

Compound **24** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (br s, 1H), 7.36–7.25 (m, 5H), 7.00 (t, J = 8.8 Hz, 2H), 6.91–6.88 (m, 2H), 6.49 (s, 1H), 3.43 (s, 3H), 3.20 (q, J = 6.0 Hz, 2H), 3.08–3.01 (m, 4H), 2.49 (s, 3H), 2.54–2.46 (m, 4H), 2.39–2.32 (m, 2H), 1.68–1.62 (m, 2H). MH+ 435.

5.2.11. 1,2-Dimethyl-5-phenyl-*N*-(3-(4-(quinolin-8-yl)piperazin-1-yl)propyl)-1*H*-pyrrole-3-carboxamide (25)

Compound **25** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 1.6, 4.0 Hz, 1H), 8.10 (dd, J = 1.6, 8.0 Hz, 1H), 7.45–7.31 (m, 8H), 7.13 (dd, J = 3.6, 5.2 Hz, 1H), 6.46 (br s, 1H), 6.30 (s, 1H), 3.58 (q, J = 6.0 Hz, 2H), 3.50 (s, 3H), 3.46 (br s, 3H), 2.87 (br s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.64 (s, 3H), 1.58–1.52 (m, 2H). MH+ 467.

5.2.12. 1,2-Dimethyl-*N*-(3-(4-(2-methylquinolin-8-yl)piperazin-1-yl)propyl)-5-phenyl-1*H*-pyrrole-3-carboxamide (26)

Compound **26** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 1.6, 8.0 Hz, 1H), 7.44–7.32 (m, 8H), 7.15 (dd, J = 3.6, 5.2 Hz, 1H), 6.46 (br s, 1H), 6.31 (s, 1H), 3.57 (q, J = 6.0 Hz, 2H), 3.52 (s, 3H), 3.46 (br s, 3H), 2.87 (br s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.64 (s, 3H), 2.53 (s, 3H), 1.58–1.52 (m, 2H). MH+ 481.

5.2.13. 1,2-Dimethyl-5-phenyl-*N*-(3-(4-(pyridin-4-yl)piperazin-1-yl)propyl)-1*H*-pyrrole-3-carboxamide dihydrochloride (27)

Compound **27** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.6 Hz, 2H), 7.92–7.87 (m, 1H), 7.43–7.35 (m, 4H), 7.32–7.28 (m, 1H), 7.25 (d, J = 7.6 Hz, 2H), 6.58 (s, 1H), 3.44 (s, 3H), 4.21–3.88 (m, 4H), 3.34–3.22 (m, 6H), 3.08–3.04 (m, 2H), 2.50 (s, 3H), 1.94–1.92 (m, 2H). MH+ 418 (–2HCl).

5.2.14. *N*-(3-(4-(3-Chlorophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (28)

Compound **28** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 2H), 7.24–7.20 (m, 1H), 7.18–7.13 (m, 5H), 6.87–6.71 (m, 4H), 6.23 (s, 1H), 3.80(t, J = 7.6 Hz, 2H), 3.53 (dd, J = 11.6, 5.6 Hz, 2H), 3.22–3.18 (m, 4H), 2.64 (s, 3H), 2.64–2.56 (m, 5H), 1.80 (t, J = 4.0 Hz, 2H), 1.61–1.51 (m, 2H), 0.73 (t, J = 7.2 Hz, 3H). MH+ 479.

5.2.15. *N*-(3-(4-(2,3-Dimethylphenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (29)

Compound **29** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 6H), 6.96–6.87 (m, 3H), 6.63 (d, J = 7.6 Hz, 1H), 6.36 (s, 1H), 3.84–3.80 (m, 3H), 3.53 (t, J = 6.0 Hz, 2H), 2.91–2.88 (m, 6H), 2.65 (s, 3H), 2.61–2.57 (m, 5H), 2.25 (s, 3H), 2.19 (s, 3H), 1.79–1.77 (m, 2H), 1.55–1.54 (m, 2H), 0.74 (t, J = 7.6 Hz, 3H). MH+ 473.

5.2.16. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (30)

Compound **30** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 6H), 7.14 (dd, J = 8.4, 1.6 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 6.65 (dd, J = 8.4, 1.6 Hz, 1H), 6.34 (s, 1H), 3.82 (t, J = 8.0 Hz, 2H), 3.56–4.51 (m, 2H), 3.20 (m, 4H), 2.66 (s, 3H), 2.59 (t, J = 6.4 Hz, 3H), 1.83–1.74 (m, 3H), 1.60–1.51 (m, 5H), 0.81–0.73 (m, 4H). MH+ 513.

5.2.17. *N*-(3-(4-(3,4-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (31)

Compound **31** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 7.90 (br, 1H), 7.43–7.30 (m, 6H), 7.21 (d, J = 2.8 Hz, 1H), 6.97 (dd, J = 8.8, 2.8 Hz, 1H), 6.53 (s, 1H), 3.87–3.79 (m, 4H), 3.53–3.47 (m, 2H), 3.22–3.13 (m, 4H), 3.10–3.02 (m, 4H), 2.52 (s, 3H), 1.93–1.90 (m, 2H), 1.46–1.37 (m, 2H), 0.63 (t, J = 7.2 Hz, 3H). MH+ 513 (–HCl).

5.2.18. *N*-(3-(4-(2-Bromophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (32)

Compound **32** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.0, 1.2 Hz, 1H), 7.34 (m, 5H), 7.12 (td, J = 8.0, 1.2 Hz, 1H), 6.89 (td, J = 7.6, 1.2 Hz, 1H), 6.74 (dd, J = 8.0, 1.6 Hz, 1H), 3.82 (t, J = 7.6 Hz, 2H), 3.55–3.51 (m, 2H), 3.05 (m, 4H), 2.65 (s, 3H), 2.60 (t, J = 6.0 Hz, 3H), 1.82–1.76 (m, 2H), 1.63–1.50(m, 5H), 0.74 (t, J = 7.6 Hz, 3H). MH+ 523.

5.2.19. *N*-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (33)

Compound **33** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (br s, 1H), 7.39–7.28 (m, 5H), 6.92–6.86 (m, 2H), 6.83–6.78 (m, 2H), 6.46 (s, 1H), 3.80 (d, J = 8.0 Hz, 2H), 3.72 (s, 3H), 3.18 (q, J = 6.8 Hz, 2H), 2.95–2.87 (m, 4H), 2.50 (s, 3H), 2.52–2.42 (m, 4H), 2.36–2.32 (m, 2H), 1.64–1.60 (m, 2H), 1.43–1.37 (m, 2H), 0.62 (t, J = 7.2 Hz, 3H). MH+ 475.

5.2.20. *N*-(3-(4-(3-Methoxyphenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (34)

Compound **34** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (br s, 1H), 7.36–7.29 (m, 5H), 7.08 (t, J = 8.0 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.46 (s, 1H),

6.42 (s, 1H), 6.35 (d, J = 6.0 Hz, 1H), 3.80 (d, J = 7.6 Hz, 2H), 3.68 (s, 3H), 3.21–3.19 (m, 2H), 3.14–3.02 (m, 4H), 2.51 (s, 3H), 2.52–2.35 (m, 6H), 1.72–1.65 (m, 2H), 1.46–1.36 (m, 2H), 0.63 (t, J = 7.2 Hz, 3H). MH+ 475.

5.2.21. *N*-(3-(4-(2,3-Dimethoxyphenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (35)

Compound **35** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 6H), 6.90 (t, J = 8.0 Hz, 1H), 6.61 (dd, J = 8.4, 1.2 Hz, 1H), 6.38 (dd, J = 8.4, 1.2 Hz, 1H), 6.31 (s, 1H), 3.87–3.78 (m, 8H), 3.53 (quartet, J = 5.6 Hz, 2H), 3.17 (br s, 4H), 2.69–2.55 (m, 9H), 1.78 (quartet, J = 6.0 Hz, 2H), 1.62–1.49 (m, 2H), 0.74 (t, J = 7.2 Hz, 3H). MH+ 505.

5.2.22. *N*-(3-(4-(2,4-Difluorophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (36)

Compound **36** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 7.91 (br, 1H), 7.43–7.40 (m, 2H), 7.34–7.30 (m, 3H), 7.25–7.19 (m, 1H), 7.14–7.09 (m, 1H), 6.53 (s, 1H), 3.81 (t, J = 7.6 Hz, 2H), 3.53–3.46 (m, 2H), 3.37–3.32 (m, 2H), 3.23–3.10 (m, 8H), 2.52 (s, 3H), 1.96–1.90 (m, 2H), 1.46–1.37 (m, 2H), 0.63 (t, J = 7.6 Hz, 3H). MH+ 481 (–HCl).

5.2.23. 2-Methyl-5-phenyl-1-propyl-*N*-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)-1*H*-pyrrole-3-carboxamide hydrochloride (37)

Compound **37** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48–7.39 (m, 3H), 7.35–7.33 (m, 3H), 7.28–7.27 (m, 2H), 7.19–7.18 (m, 1H), 3.96–3.88 (m, 4H), 3.73–3.64 (m, 3H), 3.50–3.47 (m, 2H), 3.26–3.17 (m, 4H), 2.57 (s, 3H), 2.11–2.08 (m, 2H), 1.53–1.44 (m, 2H), 0.69 (t, J = 7.6 Hz, 3H). MH+ 513 (–HCl).

5.2.24. 2-Methyl-5-phenyl-1-propyl-*N*-(3-(4-(quinolin-8-yl)piperazin-1-yl)propyl)-1*H*-pyrrole-3-carboxamide (38)

Compound **38** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, J = 1.6, 4.0 Hz, 1H), 8.12 (dd, J = 1.6, 8.0 Hz, 1H), 7.46–7.30 (m, 8H), 7.14 (dd, J = 4.0, 5.2 Hz, 1H), 6.50 (br s, 1H), 6.31 (s, 1H), 3.86 (t, J = 7.2 Hz, 2H), 3.55 (q, J = 5.6 Hz, 2H), 3.08 (br s, 4H), 2.69 (br s, 4H), 2.61 (t, J = 6.0 Hz, 2H), 1.83–1.77 (m, 2H), 1.71–1.61 (m, 3H), 0.79 (t, J = 7.6 Hz, 3H). MH+ 467.

5.2.25. *N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (39)

Compound **39** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.35–7.31 (m, 3H), 7.28–7.26 (m, 2H), 7.19–7.16 (m, 1H), 6.45 (br s, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.82 (d, J = 11.6 Hz, 2H), 3.72 (t, J = 5.6 Hz, 2H), 3.55 (d, J = 13.2 Hz, 2H), 3.50–3.11 (m, 8H), 1.53–1.44 (m, 2H), 0.70 (t, J = 7.6 Hz, 3H). MH+ 499.

5.2.26. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-*N*,1,2-trimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide (40)

Compound **40** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.26 (m, 6H), 7.19–7.04 (m, 2H), 3.68–3.64 (m, 2H), 3.52 (s, 3H), 3.33 (s, 3H), 3.30–3.22 (m, 8H), 2.38 (s, 3H). MH+ 499.

5.2.27. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-*N*,2-dimethyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (41)

Compound **41** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.46–7.37 (m, 5H), 7.06 (t, J = 7.5 Hz, 1H), 7.01 (m, 2H), 4.26 (t, J = 6.9 Hz, 2H), 4.13 (s, 3H), 3.70–3.64 (m, 2H), 3.58 (s, 3H), 3.48–3.23 (m, 8H), 2.09–2.06 (m, 4H), 1.10 (t, J = 6.8 Hz, 3H). MH+ 527 (–HCl).

5.2.28. *N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide (42)

Compound **42** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.35–7.27 (m, 4H), 7.20–7.16 (m, 2H), 3.83 (d, J = 12.0 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.56 (t, J = 13.6 Hz, 2H), 3.45 (t, J = 5.6 Hz, 2H), 3.36 (t, J = 9.6 Hz, 2H), 3.20 (t, J = 9.6 Hz, 2H), 2.56 (s, 3H). MH+ 457.

5.2.29. *N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-1-ethyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (43)

Compound **43** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.43–7.26 (m, 7H), 7.17 (dd, J = 6.4, 2.8 Hz, 1H), 3.96 (q, J = 6.8 Hz, 2H), 3.82 (d, J = 12.4 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 3.55 (d, J = 13.2 Hz, 2H), 3.43 (t, J = 5.6 Hz, 3.38–3.15 (m, 4H), 2.61 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H). MH+ 485 (–HCl).

5.2.30. *N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-2-methyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (44)

Compound **44** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.35–7.31 (m, 3H), 7.28–7.26 (m, 2H), 7.19–7.16 (m, 1H), 6.45 (br s, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.82 (d, J = 11.6 Hz, 2H), 3.72 (t, J = 5.6 Hz, 2H), 3.55 (d, J = 13.2 Hz, 2H), 3.50–3.11 (m, 8H), 1.53–1.44 (m, 2H), 0.70 (t, J = 7.6 Hz, 3H). MH+ 499.

5.2.31. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide (45)

Compound **45** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.53 (m, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.21–7.13 (m, 2H), 6.98 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 3.57–3.53 (m, 2H), 3.13 (br s, 4H), 2.71 (br s, 5H), 2.63 (s, 3H), 1.84–1.79 (m, 2H). MH+ 471.

5.2.32. *N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-2,4-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (46)

Compound **46** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.40–7.31 (m, 4H), 7.30–7.28 (m, 2H), 7.26–7.18 (m, 1H), 7.16–7.15 (m, 1H), 3.84–3.80 (m, 4H), 3.56 (d, J = 12.8 Hz, 2H), 3.49–3.43 (m, 2H), 3.38 (d, J = 11.2 Hz, 2H), 3.21 (t, J = 11.2 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H). MH+ 471 (–HCl).

5.2.33. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2,4-trimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (47)

Compound **47** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.46–7.42 (m, 2H), 7.38–7.31 (m, 1H), 7.30–7.23 (m, 4H), 7.20–7.15 (m, 1H), 3.70 (d, J = 11.6 Hz, 2H), 3.58–3.53 (m, 4H), 3.37–3.10 (m, 6H), 3.35 (s, 3H), 2.42 (s, 3H), 2.19–2.12 (m, 2H), 2.06 (s, 3H). MH+ 499 (–HCl).

5.2.34. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2,4-dimethyl-5-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (48)

Compound **48** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.45–7.42 (m, 2H), 7.39–7.37 (m, 1H), 7.35–7.18 (m, 4H), 7.17–7.18 (m, 1H), 3.76–3.68 (m, 4H), 3.57–3.53 (m, 4H), 3.36–3.18 (m, 4H), 2.44 (s, 3H), 2.18–2.11 (m, 2H), 2.02 (s, 3H), 1.47–1.40 (m, 2H), 0.66 (t, J = 7.2 Hz, 3H). ^{13}C

NMR (100 MHz, MeOH-d_4) δ 170.2, 149.3, 133.7, 132.0, 131.9, 130.6, 128.2, 128.0, 127.6, 127.2, 125.6, 119.2, 114.9, 112.8, 54.0, 52.0, 48.2, 45.3, 37.1, 23.8, 23.5, 10.4, 9.8, 9.6. MH+ 527 (–HCl).

5.2.35. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2,4-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxamide hydrochloride (49)

Compound **49** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.41–7.35 (m, 4H), 7.31–7.28 (m, 2H), 7.26–7.20 (m, 1H), 7.18–7.16 (m, 1H), 3.70 (d, J = 11.6 Hz, 2H), 3.58–3.53 (m, 4H), 3.36–3.19 (m, 6H), 2.43 (s, 3H), 2.28 (s, 3H), 2.20–2.12 (m, 2H). MH+ 485 (–HCl).

5.2.36. *N*-(3-(4-(2,3-Dimethylphenyl)piperazin-1-yl)propyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide (50)

Compound **50** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.58 (m, 1H), 7.44–7.42 (m, 2H), 7.32–7.26 (m, 2H), 7.23–7.19 (m, 1H), 6.96–6.81 (m, 3H), 6.67 (d, J = 2.4 Hz, 1H), 3.55 (dd, J = 11.6, 5.6 Hz, 2H), 2.98 (t, J = 4.8 Hz, 4H), 2.64 (s, 3H), 2.62–2.57 (m, 2H), 2.26 (s, 3H), 2.21 (S, 3H), 1.84–1.78 (m, 2H), 1.63–1.60 (m, 2H). MH+ 431.

5.2.37. *N*-(3-(4-(2,3-Dimethylphenyl)piperazin-1-yl)propyl)-1-ethyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide (51)

Compound **51** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03–7.35 (m, 7H), 6.96–6.87 (m, 2H), 6.64 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 3.91 (q, J = 7.2 Hz, 2H), 3.54 (dd, J = 11.6, 5.6 Hz, 2H), 2.92–2.89 (m, 3H), 2.67 (s, 3H), 2.60 (t, J = 6.0 Hz, 3H), 2.56 (s, 3H), 2.19 (s, 3H), 1.81–1.77 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H). MH+ 459.

5.2.38. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-2-methyl-1*H*-pyrrole-3-carboxamide hydrochloride (52)

Compound **52** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.52 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 8.4 Hz, 2H), 3.63 (d, J = 11.2 Hz, 2H), 3.49 (t, J = 6.4 Hz, 2H), 3.30–3.11 (m, 8H), 2.54 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H), 2.12–2.06 (m, 2H). MH+ 465 (–HCl).

5.2.39. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride (53)

Compound **53** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.38 (dd, J = 8.0, 20.8 Hz, 4H), 7.07 (d, J = 7.6 Hz, 1H), 7.03–6.97 (m, 2H), 3.66 (br s, 1H), 3.51–3.48 (m, 5H), 3.38–3.37 (br s, 1H), 3.33–3.32 (m, 1H), 2.26 (d, J = 1.6 Hz, 3H), 2.26 (d, 2.4 Hz, 6H), 2.13–2.10 (m, 2H). MH+ 479 (–HCl).

5.2.40. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-1-ethyl-2-methyl-1*H*-pyrrole-3-carboxamide hydrochloride (54)

Compound **54** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.43–7.41 (m, 2H), 7.36–7.34 (m, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.99–6.95 (m, 2H), 3.95 (q, J = 6.8 Hz, 2H), 3.64 (d, J = 10.0 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H), 3.33–3.28 (m, 2H), 3.26–3.16 (m, 6H), 2.59 (d, J = 2.0 Hz, 3H), 2.25 (s, 6H), 2.10–2.07 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H). MH+ 493 (–HCl).

5.2.41. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-2-methyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (55)

Compound **55** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.43–7.41 (m, 2H), 7.35–7.32 (m, 2H), 7.10–7.05 (m, 1H), 6.99–6.95 (m, 2H), 3.89 (t, J = 7.6 Hz, 2H), 3.64 (d, J = 10.8 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 3.36–3.17 (m, 6H), 2.59 (s, 3H), 2.25 (s, 6H), 2.12–2.05 (m, 2H), 1.52–1.46 (m, 2H), 0.71 (t, J = 7.2 Hz, 3H). MH+ 507 (–HCl).

5.2.42. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1-ethyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxamide (56)

Compound **56** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H), 7.14 (dd, J = 8.4, 1.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.66 (dd, J = 8.0, 1.6 Hz, 1H), 6.34 (s, 1H), 3.91 (q, J = 7.2 Hz, 2H), 3.53 (dd, J = 11.2, 5.6 Hz, 2H), 3.06 (m, 4H), 2.67 (s, 3H), 2.61 (t, J = 6.0 Hz, 2H), 1.83–1.73 (m, 3H), 1.37–1.25 (m, 2H), 1.19 (t, J = 7.6 Hz, 3H). MH+ 499.

5.2.43. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-1*H*-pyrrole-3-carboxamide hydrochloride (57)

Compound **57** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.53 (d, J = 8.4 Hz, 2H), 7.35–7.28 (m, 3H), 7.18 (dd, J = 6.4, 3.2 Hz, 2H), 3.68 (d, J = 12.0 Hz, 2H), 3.37 (d, J = 13.2 Hz, 2H), 3.50 (t, J = 6.0 Hz, 2H), 3.36–3.18 (m, 5H), 2.26 (s, 3H), 2.13–2.07 (m, 2H). MH+ 505 (–HCl).

5.2.44. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (58)

Compound **58** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (br s, 1H), 7.32–7.21 (m, 5H), 7.13 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.82 (s, 1H), 6.55 (br s, 1H), 3.67–6.64 (m, 3H), 3.50–3.43 (m, 1H), 3.44 (s, 3H), 3.33–3.31 (m, 4H), 3.14 (br s, 2H), 2.56 (s, 3H), 2.31 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 148.8, 137.2, 134.1, 133.4, 133.2, 130.7, 130.2, 128.7, 127.8, 127.5, 126.0, 119.2, 108.1, 54.6, 52.5, 48.0, 37.5, 32.0, 23.9, 12.2. MH+ 519.

5.2.45. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1-ethyl-2-methyl-1*H*-pyrrole-3-carboxamide hydrochloride (59)

Compound **59** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.43–7.41 (m, 2H), 7.36–7.34 (m, 2H), 7.30–7.29 (m, 2H), 7.18–7.16 (m, 2H), 3.95 (q, J = 6.8 Hz, 2H), 3.67 (d, J = 12.0 Hz, 2H), 3.54 (d, J = 12.4 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.34–3.17 (m, 6H), 2.60 (s, 3H), 2.10–2.06 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 170.0, 150.8, 136.6, 135.2, 134.8, 133.6, 133.0, 131.9, 129.9, 129.5, 128.7, 127.2, 120.7, 114.4, 55.5, 53.5, 40.0, 37.4, 25.7, 16.4, 11.9. MH+ 534 (–HCl).

5.2.46. 5-(4-Chlorophenyl)-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-1-propyl-1*H*-pyrrole-3-carboxamide hydrochloride (60)

Compound **60** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.43–7.41 (m, 2H), 7.34–7.32 (m, 2H), 7.30–7.26 (m, 2H), 7.20–7.16 (m, 1H), 3.89 (t, J = 7.6 Hz, 2H), 3.67 (d, J = 11.6 Hz, 2H), 3.54 (d, J = 12.4 Hz, 2H), 3.47 (t, J = 6.0 Hz, 2H), 3.34–3.17 (m, 4H), 2.59 (s, 3H), 2.11–2.07 (m, 2H), 1.54–1.44 (m, 2H), 0.71 (t, J = 7.2 Hz, 3H). MH+ 547 (–HCl).

5.2.47. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-5-(pyridin-2-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride (61)

Compound **61** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.55 (dd, J = 8.0, 6.0 Hz, 1H), 8.45 (dt, J = 1.6, 8.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.68 (dt, J = 1.2, 7.2 Hz, 1H), 7.59–7.56 (m, 1H), 7.31–7.28 (m, 2H), 7.15–7.10 (m, 1H), 3.70 (d, J = 12.0 Hz, 2H), 3.54 (d, J = 13.6 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 3.37–3.31 (m, 4H), 3.21 (d, J = 12.4 Hz, 2H), 2.46 (s, 3H), 2.14–2.11 (m, 2H). MH+ 472 (–2HCl).

5.2.48. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-(pyridin-2-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride (62)

Compound **62** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.74 (d, J = 6.0 Hz, 1H), 8.58 (dt, J = 1.6, 8.0 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 6.4 Hz, 1H), 7.31–7.28 (m, 2H), 7.26–7.25 (m, 1H), 7.18–7.15 (m, 1H), 3.73 (s, 3H), 3.68 (d, J = 12.0 Hz, 2H), 3.53 (d, J = 12.4 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 3.33–3.28 (m, 2H), 3.23–3.19 (m, 2H), 2.65 (s, 3H), 2.13–2.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 152.2, 151.0, 148.8, 137.2, 136.5, 134.0, 131.3, 127.3, 124.5, 121.8, 120.7, 118.4, 115.2, 108.5, 58.4, 53.5, 51.3, 39.7, 32.5, 25.0, 11.3. MH+ 486 (–2HCl).

5.2.49. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-1-propyl-5-(pyridin-2-yl)-1*H*-pyrrole-3-carboxamide dihydrochloride (63)

Compound **63** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.77 (dd, J = 1.2, 6.0 Hz, 1H), 8.61 (dt, J = 1.6, 8.4 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.94 (dt, J = 1.2, 7.2 Hz, 1H), 7.31–7.28 (m, 2H), 7.26–7.25 (m, 1H), 7.18–7.15 (m, 1H), 4.14 (t, J = 7.2 Hz, 2H), 3.79 (d, J = 12.4 Hz, 2H), 3.54 (d, J = 13.6 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 3.33–3.28 (m, 2H), 3.21 (d, J = 12.0 Hz, 2H), 2.45 (s, 3H), 2.12–2.10 (m, 2H), 1.59–1.56 (m, 2H), 0.76 (t, J = 7.2 Hz, 3H). MH+ 514 (–2HCl).

5.2.50. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-(pyridin-3-yl)-1*H*-pyrrole-3-carboxamide (64)

Compound **64** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 1.6 Hz, 1H), 8.55 (dd, J = 1.2, 4.8 Hz, 1H), 7.62 (td, J = 2.0, 8.0 Hz, 1H), 7.26–7.24 (m, 1H), 7.16–7.13 (m, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.65 (dd, J = 1.2, 8.0 Hz, 1H), 6.44 (s, 1H), 3.55–3.52 (m, 3H), 3.51 (s, 3H), 3.04 (br s, 4H), 2.67 (br s, 2H), 2.65 (s, 3H), 2.61 (t, J = 5.6 HZ, 2H), 1.83–1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.46 150.9, 149.5, 148.2, 135.9, 135.8, 133.9, 129.5, 128.8, 127.5, 124.6, 123.3, 118.3, 115.4, 107.5, 77.3, 58.1, 53.5, 51.3, 39.4, 31.7, 25.1, 11.4. MH+ 486.

5.2.51. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-1-propyl-5-(pyridin-3-yl)-1*H*-pyrrole-3-carboxamide (65)

Compound **65** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 2.0 Hz, 1H), 8.57 (dd, J = 1.6, 4.8 Hz, 1H), 7.60 (td, J = 2.0, 8.0 Hz, 1H), 7.26–7.22 (m, 1H), 7.14 (dd, J = 1.2, 8.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.64 (dd, J = 1.2, 8.0 Hz, 1H), 6.40 (s, 1H), 3.81 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.03 (br s, 4H), 2.67 (br s, 3H), 2.66 (s, 3H), 2.60 (t, J = 6.0 Hz, 2H), 1.83–1.77 (m, 2H), 1.60–1.50 (m, 2H), 0.76 (t, J = 7.2 Hz, 3H). MH+ 514.

5.2.52. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-5-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide (66)

Compound **66** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 1.2 Hz, 1H), 8.55 (dd, J = 1.6, 4.8 Hz, 1H), 7.61 (td, J = 2.0, 8.0 Hz, 1H), 7.26–7.24 (m, 1H), 7.14 (dd, J = 2.8, 6.8 Hz, 1H), 7.02 (t, J = 8.4 Hz, 1H), 6.65 (dd, J = 1.2, 8.0 Hz, 1H), 6.43 (s, 1H), 3.55–3.51 (m, 2H), 3.51 (s, 3H), 3.04 (br s, 4H), 2.67 (br s, 2H), 2.65 (s, 3H), 2.61 (t, J = 6.4 Hz, 2H), 1.83–1.77 (m, 2H). MH+ 486.

5.2.53. *N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-1-propyl-5-(pyridin-4-yl)-1*H*-pyrrole-3-carboxamide (67)

Compound **67** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 1.2 Hz, 1H), 8.56 (dd, J = 1.6, 4.8 Hz, 1H), 7.60 (td, J = 2.0, 7.6 Hz, 1H), 7.26–7.24 (m, 1H), 7.14 (dd, J = 1.2, 8.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.64 (dd, J = 1.2, 8.0 Hz, 1H), 6.40 (s, 1H), 3.81 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.03 (br s, 4H), 2.67 (br s, 4H), 2.66 (s, 3H), 2.60 (t, J = 6.0 Hz, 2H), 1.81–1.78 (m, 2H), 1.58–1.52 (m, 2H), 0.76 (t, J = 7.2 Hz, 3H). MH+ 514.

5.2.54. 5-*tert*-Butyl-*N*-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)ethyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (68)

Compound **68** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, J = 7.6 Hz, 1H), 6.93–6.89 (m, 2H), 6.31 (br s, 1H), 6.01 (s, 1H), 3.59(s, 3H), 3.51 (q, J = 5.2 Hz, 2H), 2.92 (br s, 4H), 2.65 (br s, 4H), 2.63 (q, J = 6.0 Hz, 2H), 2.54 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 1.37 (s, 9H). MH+ 410.

5.2.55. 5-*tert*-Butyl-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (69)

Compound **69** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, J = 7.6 Hz, 1H), 6.93–6.87 (m, 2H), 6.02 (s, 1H), 3.58 (s, 3H), 3.50–3.42 (m, 2H), 2.94(br s, 4H), 2.64 (br s, 4H), 2.57 (t, J = 6.0 Hz, 2H), 2.55 (s, 3H), 2.26 (s, 2H), 2.21(s, 3H) 1.80–1.77 (m, 2H), 1.35 (s, 9H). MH+ 424.

5.2.56. 5-*tert*-Butyl-*N*-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide hydrochloride (70)

Compound **70** was obtained by repeating the procedure of compound **5a**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.28–7.26 (m, 2H), 7.17–7.14 (m, 1H), 3.80 (d, J = 12.4 Hz, 2H), 3.72 (t, J = 5.2 Hz, 2H), 3.56 (d, J = 13.6 Hz, 2H), 3.42 (t, J = 5.6 Hz, 2H), 3.39–3.18 (m, 3H), 2.48 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 169.1, 149.3, 140.7, 135.8, 133.7, 128.0, 127.2, 125.6, 119.2, 110.8, 57.4, 52.4, 52.4, 31.9, 31.3, 29.1, 10.3. MH+ 450 (–HCl).

5.2.57. 5-*tert*-Butyl-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)-propyl)-2-methyl-1*H*-pyrrole-3-carboxamide hydrochloride (71)

Compound **71** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.19–7.10 (m, 2H), 6.99 (br s, 1H), 6.93 (dd, J = 2.4, 2.0 Hz, 1H), 5.98 (d, J = 2.8 Hz, 1H), 3.50 (q, J = 6.0 Hz, 2H), 3.13 (br s, 4H), 2.69 (br s, 4H), 2.59 (t, J = 6.4 Hz, 2H), 2.54 (s, 3H), 1.82–1.76 (m, 2H), 1.23 (s, 9H). MH+ 451 (–HCl).

5.2.58. 5-*tert*-Butyl-*N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (72)

Compound **72** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.10 (m, 2H), 6.92 (dd, J = 2.0, 2.4 Hz, 1H), 6.87 (br s, 1H), 5.99 (s 1H), 3.58 (s, 3H), 3.49 (q, J = 5.6 Hz, 2H), 3.11 (br s, 4H), 2.68 (br s, 4H), 2.58 (t, J = 6.8 Hz, 2H), 2.55 (s, 3H), 1.80–1.77 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 151.0, 140.2 134.8, 134.0, 127.3, 127.3, 124.5, 118.5, 112.9, 102.1, 58.1, 53.5, 51.3, 39.2, 32.6, 31.7, 30.3, 25.6, 11.2. MH+ 465.

5.2.59. 5-*tert*-Butyl-*N*-(2-(4-(3-chloro-2-methylphenyl)piperazin-1-yl)ethyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (74)

Compound **74** was obtained by repeating the procedure of compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.06 (m, 2H), 6.95–6.92 (m, 1H), 6.25 (br s, 1H), 6.00 (s, 1H), 3.59 (s, 3H), 3.51 (q, J = 6.4 Hz, 2H), 2.92 (t, J = 4.4 Hz, 4H), 2.67–2.62 (m, 6H), 2.54 (s, 3H), 2.34 (s, 3H), 1.36 (s, 9H). MH+ 431.

5.3. Biology

5.3.1. Measurement of binding affinity for serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors

Receptor binding affinities of the compounds for serotonin receptors were measured by the method described in the litera-

ture.[18] For serotonin 5-HT_{2A} binding, an aliquot of human recombinant serotonin 5-HT_{2A} receptor (PerkinElmer Life and Analytical Sciences, USA) expressed in CHO-K1 cells (5 μg/well) and 1 nM [^{3}H]Ketanserin (PerkinElmer) were used in the presence of mianserin (20 μM) as nonspecific. The reaction mixture was incubated for 60 min at 27 °C using 50 mM Tris–HCl (pH 7.4) buffer containing 4 mM $CaCl_2$ and 0.1% ascorbic acid, and harvested through filtermate A glass fiber filter (Wallac, Finland) presoaked in 0.5% polyethyleneimine (PEI) by microbeta filtermate-96 harvester (PerkinElmer) to terminate the reaction, and then washed with ice cold 50 mM Tris–HCl buffer solution (pH 7.4). The filter was then covered with MeltiLex, sealed in a sample bag, dried in an oven. The radioactivity retained in the filter was finally counted using MicroBeta Plus (Wallac). The binding affinity (IC_{50}) of a compound for the receptor was calculated by computerized nonlinear regression analysis (GraphPad Prism Program, San Diego, USA) using 7–8 varied concentrations of the compound run in duplicate tubes.

For serotonin 5-HT_{2C} binding, frozen membranes from stable CHO-K1 cell line expressing the human recombinant 5-HT_{2C} receptor (PerkinElmer, 4 μg/well), [^{3}H]Mesulergine (Amersham, 1.3 nM) and test compounds were added into 50 mM Tris–HCl (pH 7.4) buffer containing 0.1% ascorbic acid and 4 mM $CaCl_2$. Nonspecific binding was determined using 100 μM mianserin. The incubations were performed for 60 min at 27 °C, and these were terminated by rapid filtration through filtermate. A glass fiber filter presoaked in 0.5% PEI.

5.3.2. Measurement of binding affinity for serotonin transporter

For serotonin transporter binding assays, a reaction mixture with a final volume of 0.25 ml was prepared by mixing a test compound, human serotonin transporter membrane expressed in HEK-293 cells (PerkinElmer, 5 μg/well), [^{3}H]Imipramine (PerkinElmer, 2 nM) and 50 mM Tris–HCl (pH 7.4) buffer containing 120 mM NaCl and 5 mM KCl. The reaction mixture was incubated for 30 min at 27 °C, and harvested through filtermate. A glass fiber filter presoaked in 0.5% PEI with ice cold 50 mM Tris–HCl buffer (pH 7.4) containing 0.9% NaCl.

5.3.3. [^{3}H] Astemizole binding to hERG potassium ion channel

For hERG K+ channel binding, an aliquot of frozen membrane from HEK293 cell line expressing the recombinant human ether-a-go-go related gene (hERG) (Millipore Coorperation, MA, USA) and [^{3}H] Astemizole 3 nM (PerkinElmer Life and Analytical Sciences, USA) were mixed in the presence of astemizole (10 μM) as nonspecific. The reaction mixture was incubated for 60 min at 27 °C using 10 mM Hepes (pH 7.4) buffer containing 130 mM NaCl, 5 mM KCl, 0.8 mM MgCl2, 1 mM NaEGTA, 10 mM glucose, 0.1% BSA, and harvested through Filtermat A glass fiber filter presoaked in 0.3% PEI using 25 mM Tris (pH 7.4) washing buffer containing 130 mM NaCl, 5 mM KCl, 0.8 mM $CaCl_2$ and 0.1% BSA.

5.3.4. Measurement of antidepressants activity in forced swimming test

To evaluate the antidepressants activity of the compounds, the inhibitory effects on immobility in forced swimming test in mice were measured according to the methods described by Porsolt et al.[20] Each mouse was placed in a 25-cm glass cylinder (10 cm diameter) containing 15 cm of water maintained at 22 ± 1 °C, and was forced to swim for 10 min. Twenty-four hours later, the mouse was replaced into the cylinder and the total duration of immobility was recorded during the last 5 min of the 6-min testing period. Mice are judged immobile when they float in an upright position and make only small movements to keep their head above water. Test drugs were suspended in 3% Tween 80 solution, and administered orally (po) 60 min before the testing.

5.3.5. Measurement of locomotor activity (for Figure 4)

One day before the test, mice were placed in transparent polycarbonate cages located in activity chambers and were allowed to habituate for 20 min. For locomotor activity test, compound was suspended in 3% tween80 solution, and administered orally 60 min before the test. Spontaneous locomotor activity was recorded every 10 min for 30 min using Activity Analyzer (AM1052 Activity Monitor, Benwick, UK). Unit is count/30 min.

5.3.6. Measurement of locomotor activity (for Tables 7 and 8)

We measured using an automated video tracking system (Noldus Information Technology, Wagenin, the Netherlands) to examine locomotor patterns. Mice was treated with test compounds (25 mg/kg B.W., po) and acclimated to the test chamber for 10 min before starting the experiment. Locomotor activity was then measured for 30 min. The distance travelled in centimeters by the animals in horizontal locomotor activity was analyzed. Data were collected and analyzed between 09:00 and 17:00 h.

Acknowledgments

We are grateful to Dr. Eun Chul Huh for his leadership at R&D operation, Green Cross Corporation (GCC). This work is in part supported by Korea Ministry of Knowledge Economy.

References and notes

1. Murray, C. J.; Lopez, A. D. *Lancet* **1997**, *a;349*, 1436.
2. *5-Hydroxyltryptamine Mechanisms in Primary Headaches*; Olesen, J., Saxena, P., Eds., 1st ed.; Raven Press: New York, 1992.
3. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Disease, Injuries and Risk Factors in 1990 and Projected to 2020*; Murray, C. J. L., Lopez, A. D., Eds.; Harvard University Press: Cambridge, MA, 1996; p 38.
4. WHO *The World Health Report 2001, Mental Health: New Understanding, New Hope*, Fact Sheet No. 265.
5. Blier, P.; Bergeron, R. *J. Clin. Psychiatr.* **1998**, *59*, 16.
6. Katz, M. M.; Tekell, J. L.; Bowden, C. L.; Brannan, S.; Houston, J. P.; Berman, N.; Frazer, A. *Neuropsychopharmacology* **2004**, *29*, 566. and references cited therein.
7. (a) Morphy, R.; Kay, C.; Rankovic, Z. *Drug Discovery Today* **2004**, *9*, 641. and reference cited therein; (b) Pacher, P.; Kecskemeti, V. *Curr. Med. Chem.* **2004**, *11*, 925.
8. Ballesteros, J.; Callado, L. F. *J. Affect. Disord.* **2004**, *79*, 137. and reference cited therein.
9. Romeo, L.; Arigas, F. *J. Neurochem.* **1997**, *68*, 2593.
10. Berman, R. M.; Anand, A.; Cappiello, A.; Miller, H. L.; Xu, X. S.; Oren, D. A.; Charney, D. S. *Biol. Psychiatry* **1999**, *45*, 1170.
11. Pullar, I. A.; Carney, S. L.; Colvin, E. M.; Lucaites, V. L.; Nelson, D. L.; Wedley, S. *Eur. J. Pharmacol.* **2000**, *407*, 39.
12. Hatanaka, K.; Nomura, T.; Hidaka, K.; Takeuchi, H.; Yatsugi, S.; Fujii, M.; Yamaguchi, T. *Neuropharmacology* **1997**, *35*, 1621.
13. (a) Rush, A. J.; Armitage, R.; Gillin, J. C.; Yonkers, K. A.; Winokur, A.; Moldofsky, H.; Vogel, G. W.; Kaplita, S. B.; Fleming, J. B.; Montplaisir, J.; Erman, M. K.; Albala, B. J.; McQuade, R. D. *Biol. Psychiatry* **1998**, *44*, 3; (b) Avila, A.; Vardona, X.; Martin-Baranera, M.; Maho, P.; Sastre, F.; Bello, J. *J. Clin. Psychopharmacol.* **2003**, *23*, 509; (c) Greene, D.; Barbhaiya, R. H. *Clin. Pharmacokinet.* **1997**, *33*, 260; (d) Kent, J. M. *Lancet* **2000**, *355*, 911.
14. (a) Lawler, C. P.; Prioleau, C.; Lewis, M. M.; Mak, C.; Jian, D.; Schetz, J. A.; Gonzalez, A. M.; Sibley, D. R.; Mailman, R. B. *Neuropsychopharmacology* **1999**, *20*, 612; (b) Burstein, e. S.; Ma, J.; Wong, S.; Gao, Y.; Pahrm, E.; Knapp, A. E.; Nash, N. R.; Olsson, R.; Davis, R. E.; Hacksell, U.; Weiner, D. M.; Brann, M. R. *J. Pharmacol. Exp. Ther.* **2005**, *315*, 1278.
15. Kang, S. Y.; Park, E.-J.; Park, W.-K.; Kim, H. J.; Jeong, D.; Jung, M. E.; Song, K.-S.; Lee, S. H.; Seo, H. J.; Kim, M. J.; Lee, M.; Han, H.-K.; Son, E.-J.; Pae, A. N.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1705.
16. Vanotti, E.; D'alessio, R.; Tibolla, M.; Varasi, M.; Montagnoli, A.; Santocanale, C.; Martina, K.; Menichincheri, M. WO2005/013986, 2005.
17. Robarge, M. J.; Husbans, S. M.; Kieltyka, A.; Brodbeck, R.; Thurkauf, An.; Newman, A. H. *J. Med. Chem.* **2001**, *44*, 3175.
18. Park, W.-K.; Jeong, D.; Cho, H.; Lee, S. J.; Cha, M. Y.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kong, J. Y. *Pharmacol. Biochem. Behav.* **2005**, *82*, 361.
19. Kerns, E. H.; Di, D. *Drug-like Properties: Concepts, Structure Design and Methods: From ADME to Toxicity Optimization*; Academic Press: Burlington, MA, 2008.

20. Porsolt, R. D.; Bertin, A.; Jalfre, M. *Eur. J. Pharmacol.* **1978**, *51*, 291.
21. (a) Cryan, J. F.; Valentino, R. J.; Lucki, I. *Neurosci. Biobehav. Rev.* **2005**, *29*, 547; (b) Kulkarni, S. K.; Dhir, A. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2007**, *31*, 1248; (c) Bymaster, F. P.; Lee, T. C.; Knadler, M. P.; Detke, M. J.; Itengar, S. *Curr. Pharm. Des.* **2005**, *11*, 1475.
22. Although spontaneous locomotor activity of compound **64** was not measured by Activity Analyzer, hyperactivity was observed by its behavior such as climbing strongly, etc. during forced swimming test.
23. Dierk, T.; Gut, B.; Wendt-Nordahl, G.; Kiehn, J. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 543.