An Interactive SAR Approach to Discover Novel Hybrid Thieno Probes as Ligands for D2-Like Receptors with Affinities in the Subnanomolar Range

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A series of [(phenylpiperazinyl)alkyl]-isoindole-1,3-dione derivatives was synthesized to serve as probes for dopaminergic receptors. Among this series, compound **6a** showed the highest affinity towards D4 and D3 receptors with K_i values in the low nanomolar range, and D2/D4- and D2/D3-selectivity indices of 72 and 20, respectively. Optimization rounds were adopted and led to the D4-selective ligand thiophene-2-carboxamide **9a** with a K_i(D4) value of 0.62 nM, and to its butyl analog, **10a**, with K_i(D4) and K_i(D3) values of 0.03 and 0.26 nM, respectively. Docking experiments revealed the importance of the unique D4 residue Arg186 in manipulating the ligands' D4-subtype-receptor selectivity.

1. Introduction. – Psychosis is a mental illness referred to as the disease of mind and soul, and featured by radical changes, impairment in personality and functioning, as well as a state of nonexistent sense of objective reality [1]. Abnormalities in brain chemistry manifested as singular rise in dopamine brain levels have been shown to be linked to this disorder [2][3]. This can be counteracted through blocking the dopamine neurotransmission *via* antagonizing its action mainly at the different D2-like receptor subtypes [4]. This family of receptors includes D2, D3, and D4 receptor subtypes, and differs from the D1-like family receptors in their molecular structure and the signaling cascade occurring upon stimulation [5–7]. The stimulation of D1-like receptors including D1 and D5 receptor subtypes leads to activation of Adenylate Cyclase (AC) that provokes the production of cAMP and hence Protein Kinase A (PKA) activation, while the stimulation of D2-like family members leads to negative regulation of the production of cAMP and accordingly to a decrease in PKA activity [8][9].

Among the well-known D2-like family antagonists, the butyrophenone derivative *Haloperidol* (**1**) is one of the most commonly marketed typical antipsychotic agents [10]. These typical agents are characterized by their ability to block the D2-like receptor subtypes unselectively, and, though being useful in curing the positive symptoms of psychosis, they possess marked Extra Pyramidal *Parkinson*'s like adverse effects [11]. This undesired propensity is thought to be a result of blocking D2 receptor subtype that is mainly concentrated in striatal areas of the brain [12]. On the contrary, atypical antipsychotic agents relieve both positive and negative signs of psychosis showing much lower incidence of the undesired *Parkinson*'s like symptoms [13]. This special behavior of atypical antipsychotic agents is believed to be either due to their

ability to block D3/D4 receptor subtypes selectively over D2 ones [14], or due to their loose binding and their rapid dissociation off D2 receptor subtype [15]. Recent studies have linked this special pharmacological behavior of atypical agents to their cross-interaction with 5-HT2A receptors [16].

Among these atypical agents, the benzamide derivative sulpiride (**2**) and the thienobenzodiazepine derivative olanzapine (**3**) are commonly used. Ketanserine (**4**) is another ligand characterized by its moderate interaction with D2 receptor subtype, while exhibiting much higher binding affinity to D4 and 5-HT2A receptors. Unfortunately, the use of atypical antipsychotic agents is still limited because of their many adverse effects, including increased risk of brain stroke, cardiovascular diseases, metabolic and diabetic complications, weight gain, and impaired sexual function, leaving the field in need of newer probes [17].

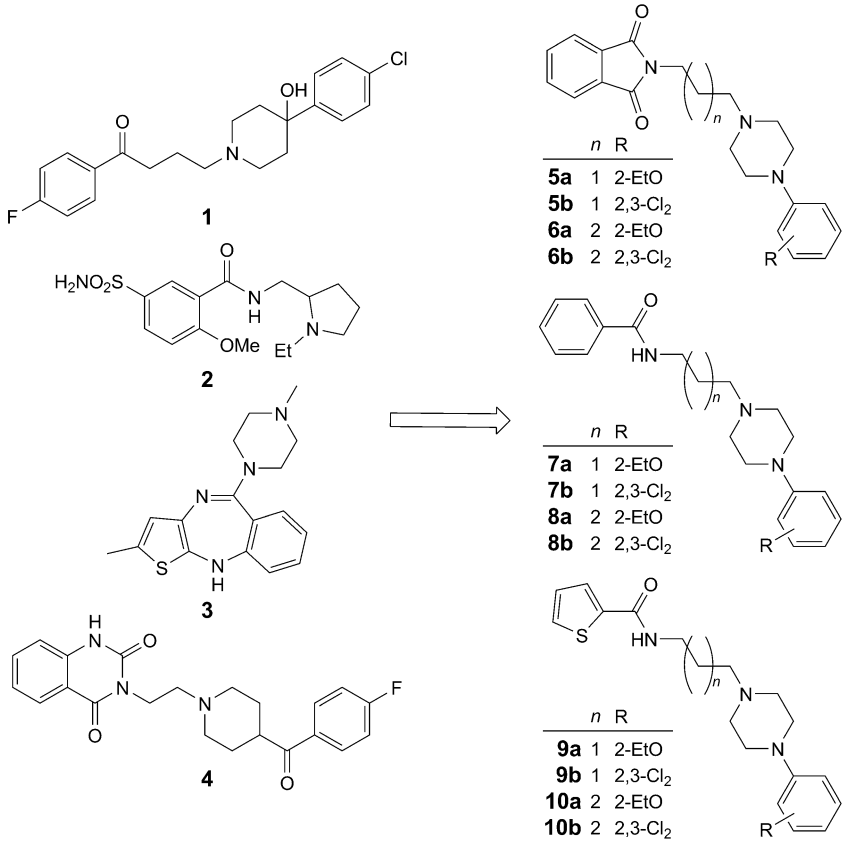
Trying to develop novel selective D3 and/or D4 ligands, some probes were designed to serve as hybrids bearing combined structural features from both the typical and atypical lead compounds haloperidole, sulpiride, olanzapine, and ketanserine (**1**–**4**, resp.; *Scheme 1*). The designed probes bear a scaffold in which the aromatic ring appendage and the basic N-atom of the phenylpiperazine are separated with an amidoalkyl linker and thus would keep the primary recognition elements that have been proved to be necessary for fitting into the binding pockets of the target dopaminergic receptors [18][19].

2. Results and Discussion. – 2.1. *Chemistry.* The synthesis of the [(phenylpiperazinyl)propyl]-isoindole-1,3-dione derivatives as outlined in *Scheme 2* started with a reaction of phthalic anhydride (**11**) with 3-chloropropylamine hydrochloride salt to afford 2-(3-chloropropyl)isoindole-1,3-dione (**12**), which in turn was subjected to a nucleophilic substitution reaction with the corresponding 1-phenylpiperazine to furnish the desired derivatives [20]. Due to the non-availability of the 4-chlorobutylamine hydrochloride salt, the synthesis of the [(phenylpiperazinyl)butyl]-isoindole-1,3-dione derivatives was conducted by adopting *Gabriel* synthesis [21] in which the phthalimide potassium salt (**13**) was *N*-alkylated with 1,4-dibromobutane to give 2-(4-bromobutyl)-isoindole-1,3-dione (**14**), which was again subjected to a nucleophilic substitution reaction with the corresponding 1-phenylpiperazine to yield the desired compounds (*Scheme 3*).

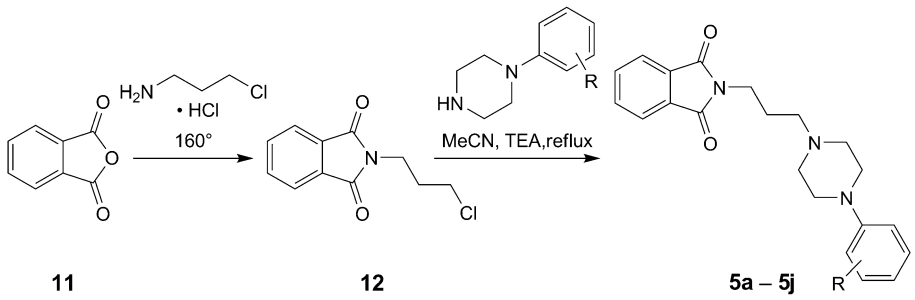
The syntheses of the benzamides and thienoamides as depicted in *Scheme 4* were carried out starting from the corresponding previously synthesized [(phenylpiperazinyl)alkyl]-isoindole-1,3-dione derivatives by adopting *Ing–Mansk* reaction [22] that involves refluxing the [(phenylpiperazinyl)alkyl]-isoindole-1,3-dione derivative with aqueous hydrazine in 95% EtOH to afford the corresponding [(phenylpiperazinyl)alkyl]amine derivatives, **15a**–**15j** and **16a**–**16j**, which in turn were immediately reacted with either benzoyl chloride (**17**) or thiophene-2-carbonyl chloride (**19**) in presence of Et_3N (TEA) to furnish the corresponding amide derivatives [22]. The commercially non-available thiophene-2-carbonyl chloride (**19**) was prepared by reaction of thiophene-2-carboxylic acid (**18**) with $SOCl_2$ [23].

2.2. *Pharmacology.* The final target compounds were screened for their binding affinities towards human cloned dopamine receptor subtypes D1, D2, D3, D4, and D5 utilizing radioligand binding assay according to our previously published protocol [24].

Scheme 1. *Design of Hybrid Dopaminergic Probes Based on Marketed Typical and Atypical Antipsychotic Agents*

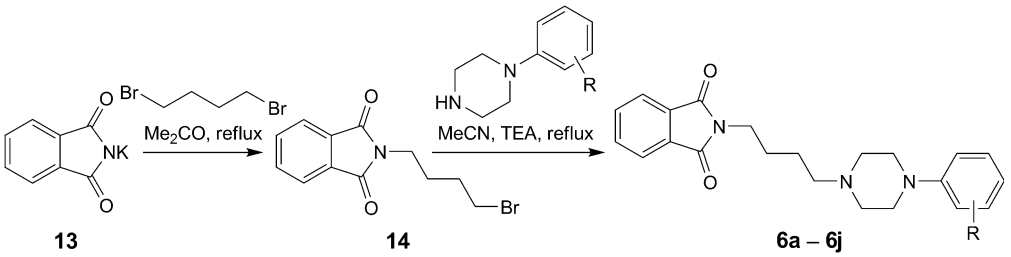


Scheme 2. *Synthesis of [(Phenylpiperazinyl)propyl]-isoindole-1,3-dione Derivatives*

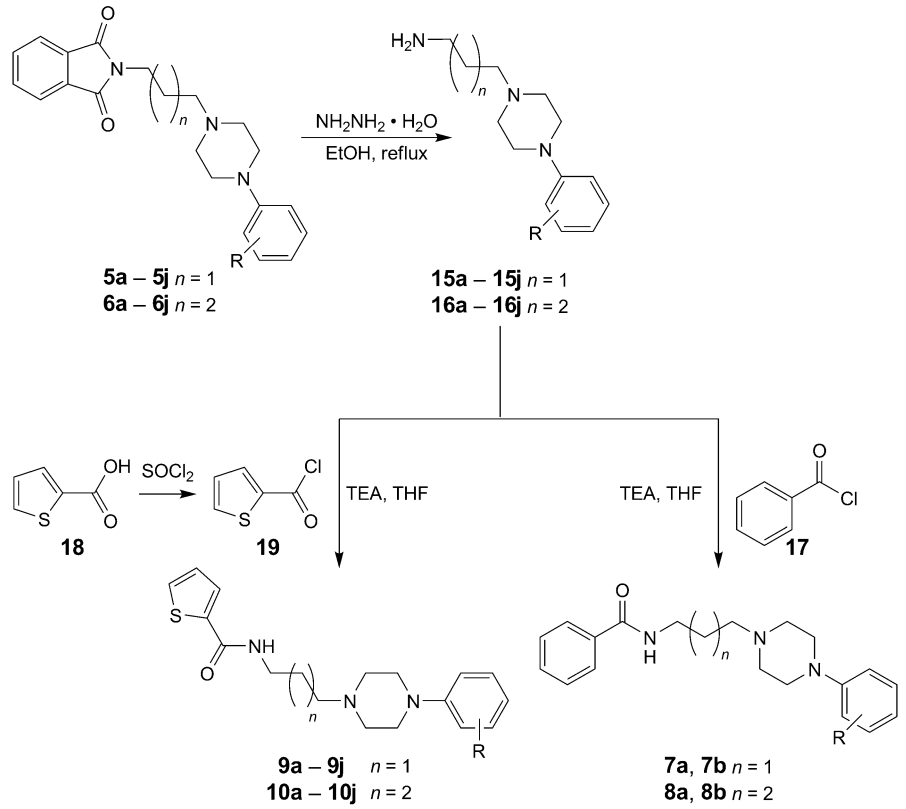


[^{3}H]SCH23390 was used as radioligand for the D1-like family receptors, while [^{3}H]spiperone was the radioligand used for the D2-like family receptors. Incubations at 27° were terminated after 90 min by rapid filtration with a *Perkin-Elmer Mach III*

Scheme 3. *Synthesis of [(Phenylpiperazinyl)butyl]-isoindole-1,3-dione Derivatives*



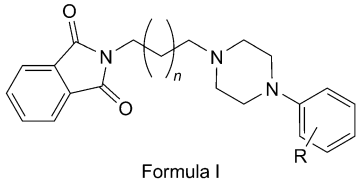
Scheme 4. *Synthesis of Benzamide and Thienoamide Derivatives*



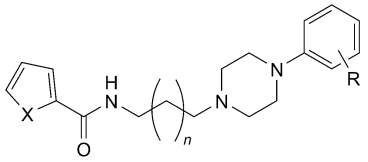
harvester. At least two independent experiments were carried out, each in triplicate. The designed compounds have exhibited functional activities towards D2-like family receptor subtypes ranging from partial agonists to full antagonists in fluorescent Ca^{2+} assay [24].

2.3. *Structure–Activity Relatioship.* The K_i affinity binding data compiled in *Table 1* show that our designed probes lack the affinity towards D1-like family receptor

Table 1. *Binding Affinity Data of the Synthesized Probes towards the Five Subtypes of Human Cloned Dopaminergic Receptors.* At least two independent experiments were carried out in triplicate each.



Formula I



Formula II

Compound	Structure				$K_i \pm$SEM [nM]				
	Formula	*n*	X	R	D1	D2	D3	D4	D5
5a	I	1	–	2-EtO	>10000	1095 ± 28	810 ± 4	118 ± 1	>10000
5b	I	1	–	2,3-Cl_2	>10000	1393 ± 40	806 ± 12	124 ± 10	>10000
6a	I	2	–	2-EtO	>10000	770 ± 4	39 ± 0.5	10.7 ± 0.2	>10000
6b	I	2	–	2,3-Cl_2	>10000	793 ± 2	40 ± 1.5	11 ± 2	>10000
7a	II	1	HC=CH	2-EtO	>10000	185 ± 9	797 ± 16	0.75 ± 0.02	>10000
7b	II	1	HC=CH	2,3-Cl_2	>10000	273 ± 24	780 ± 20	7.3 ± 0.1	>10000
8a	II	2	HC=CH	2-EtO	>10000	29.5 ± 0.7	0.93 ± 0.01	0.64 ± 0.02	>10000
8b	II	2	HC=CH	2,3-Cl_2	>10000	34 ± 1	1.5 ± 0.2	0.66 ± 0.1	>10000
9a	II	1	S	2-EtO	>10000	138 ± 6	765 ± 13	0.62 ± 0.04	>10000
9b	II	1	S	2,3-Cl_2	>10000	147 ± 4	754 ± 13	6.5 ± 0.3	>10000
9c	II	1	S	2-F	>10000	253 ± 2	851 ± 8	14.7 ± 1.5	>10000
9d	II	1	S	2-Cl	>10000	309 ± 27	805 ± 3	14.1 ± 0.3	>10000
9e	II	1	S	2-OH	>10000	591 ± 26	1027 ± 9	13.8 ± 3.5	>10000
9f	II	1	S	4-F	>10000	850 ± 45	1028 ± 10	63.2 ± 2.8	>10000
9g	II	1	S	4-Cl	>10000	637 ± 3	872 ± 23	62.3 ± 0.7	>10000
9h	II	1	S	3,4-Cl_2	>10000	290 ± 9	770 ± 14	60.1 ± 1.3	>10000
9i	II	1	S	4-OH	>10000	618 ± 25	900 ± 12	60.9 ± 0.8	>10000
9j	II	1	S	H	>10000	253 ± 9	907 ± 4	15.1 ± 0.4	>10000
10a	II	2	S	2-EtO	>10000	28.5 ± 0.4	0.26 ± 0.02	0.03 ± 0.01	>10000
10b	II	2	S	2,3-Cl_2	>10000	27.2 ± 0.2	0.5 ± 0.01	0.54 ± 0.01	>10000
10c	II	2	S	2-F	>10000	34 ± 0.2	1.04 ± 0.02	6.6 ± 1.2	>10000
10d	II	2	S	2-Cl	>10000	29 ± 1	0.7 ± 0.01	5.9 ± 0.6	>10000

Table 1 (cont.)

Compound	Structure				$K_i \pm$SEM [nM]				
	Formula	*n*	X	R	D1	D2	D3	D4	D5
10e	II	2	S	2-OH	>10000	54±1	0.53±0.03	6±0.1	>10000
10f	II	2	S	4-F	>10000	53±2	33±3	31.6±0.5	>10000
10g	II	2	S	4-Cl	>10000	38±0.4	20±1	30.9±0.1	>10000
10h	II	2	S	3,4-Cl_2	>10000	40±0.5	9.6±0.4	29.3±1.2	>10000
10i	II	2	S	4-OH	>10000	65±5	1.07±0.03	30.4±0.6	>10000
10j	II	2	S	H	>10000	33±0.7	1±0.01	6.8±0.3	>10000
1					3.93±1.7	0.28±0.2	0.18±0.03	3.53±0.9	4.17±0.3

subtypes, while exhibiting appreciable binding affinity towards D2-like family receptors showing diverse affinity and selectivity patterns.

Starting with the propyl linker-bearing compounds, it is obvious that the isoindole-1,3-dione derivatives **5a** and **5b** have shown the lowest affinity to all the D2-like receptors. The benzamide analogs **7a** and **7b** and the thienoamide analogs **9a** and **9b** have displayed improvement in affinity towards D2 receptor subtypes, marked selectivity to D4 receptor subtypes (view selectivity indices in *Table 2*), but still with low affinity to D3 subtypes.

Table 2. *D2/D3 and D2/D4 Data of Isoindole-1,3-dione, Benzamide, and Thienoamide Derivatives*

Compound	D2/D3	D2/D4	Compound	D2/D3	D2/D4
5a	1.3	9	**8b**	23	50
5b	1.7	11	**9a**	0.2	222
6a	20	72	**9b**	0.2	23
6b	20	72	**10a**	110	950
7a	0.23	247	**10b**	54	50
7b	0.35	37	**1**	1.5	0.08
8a	32	46			

Moving to the butyl-linker-bearing compounds, benzamide derivatives **8a** and **8b** and thienoamide derivatives **10a** and **10b** have exhibited great improvement in affinity to D2, D3, D4 subtypes with marked selectivities to D3 and D4 over D2 subtypes (see the selectivity indices in *Table 2*). The isoindole-1,3-dione analogs **6a** and **6b** exhibited the least binding affinities within this set of compounds.

From the obtained binding data, we can discuss the effect of three major factors on the affinity and selectivity pattern of the synthesized compounds.

2.3.1. *Effect of the Spacer's Length.* In the whole series, compounds bearing the butyl linker have shown better affinities to the D2-like receptors than their propyl analogs. In terms of affinity, the length of the spacer could have prominent effect on the pK_a value of the basic N-atom of the 1-phenylpiperazine unit that is reported to be involved in a key salt-bridge interaction with Asp 3.32 residue of the target receptors [18][25][26]. The calculated pK_a values of the basic piperazin N-atom range from 6.8 to 7.8 in the compounds with the propyl linker, while they range from 7.3 to 8.3 in their butyl-linker-bearing analogs. This could enable the compounds bearing the butyl linker to afford better salt-bridge interaction with Asp 3.32 residue explaining their better affinity to the target receptors compared to their propyl linker-bearing counterparts.

In terms of selectivity, the length of the spacer could play a crucial role in enabling the ligand's aromatic appendage to come into contact and then afford hydrophobic interaction with certain amino acid residues reported to figure the D2/D3 subtype receptor selectivity. These amino acid residues are located in the extracellular side EL2 of the binding pockets of D2 and D3 receptor subtypes, and include Glu 181 and Ile 183 in D2 that face Val 180 and Ser 182, respectively, in D3 [18]. This will be discussed thoroughly later in the docking section.

2.3.2. *Effect of the Ligand's Aromatic Appendage.* It is worth considering the nature of the aromatic appendage responsible for the hydrophobic interaction with the target

receptors. Among the whole series, compounds with thiophene system have shown the highest binding affinities at all the D2-like receptor subtypes, followed by those with the benzene ring, and finally came the largest-in-size isoindole-1,3-dione system with the least binding affinity. The superiority of the thiophene system relative to the benzene may be a function of better hydrophobic interaction at the binding pocket. This is mainly due to the fact that the thiophene system is richer in electrons, as the lone pair of electrons in the p orbital of the S-atom contributes to the *Hückel* aromatic sextet and pushes high electron density toward the ring C-atoms that accordingly acquire partial negative charge. Thus, it was suggested that the large atomic polarizability of the S-atom and the electron-rich thiophene system would provide higher dispersion forces compared to benzene, leading to better π–π stacking and/or *Van der Waals* interaction [27] with the hydrophobic residues lining the hydrophobic pocket of the target receptors.

2.3.3. *Effect of the Nature of the Substituent at the Phenylpiperazine Moiety.* To investigate the impact of changing the nature and the position of the substituent in the phenylpiperazine moiety on the affinity and selectivity, compounds **9c**–**9j** and **10c**–**10j** were synthesized and biologically evaluated. In *Table 1*, the binding affinity data of these compounds towards the human cloned dopamine receptor subtypes are collected.

It is noticeable that the propyl-linker-bearing ligands **9c**–**9j** exhibited appreciable affinities to D4 receptor subtypes. The best affinity was observed with compounds with *ortho*-oxygenated and dihalogenated substituents, followed by those with *ortho*-monohalogenated substituents. The affinity of the synthesized ligands displayed four- to ten-fold decrease, when the substituent was shifted to the *para* position, as deduced from the comparison of the K_i values of compounds **9b**, **9c**, **9d**, and **9e** with those of their *para*-substituted analogs **9h**, **9f**, **9g**, and **9i**. This indicated the importance of an *ortho*-substituted phenylpiperazine moiety with a specific electrostatic potential to regulate affinity towards D4 receptor subtypes.

All of the butyl-linker-bearing ligands, **10c**–**10j**, have shown superior affinities to both D3 and D4 receptor subtypes, relative to D2 ones. Again the nature and position of the substituent in the phenylpiperazine moiety determined the affinity of these derivatives in a similar fashion exhibited by their propyl counterparts.

2.4. In silico *Docking Experiments.* Docking experiments were carried out to configure the binding fashion of the synthesized compounds to the target receptor subtypes. All compounds have been docked to the human D3 model (PDB ID: 3PBL), and the validated D2 and D4 homology models developed before [28]. MOE Software [29] has been used for this purpose.

Compound **9a** with the highest selectivity to D2 over D3 among all derivatives bearing the propyl linker was docked to the D2 receptor homology model and showed the contact between the ligand's arene and Ile 183 residue. Docking the same compound to D3 receptor model revealed the contact between the ligand's arene and the Ser 182 in the EL2 of the binding site of the D3 receptors that is occupied with the more hydrophobic Ile 183 in the D2 receptor subtype, ensuring better hydrophobic interaction with the target receptors. This confirms that these amino acid residues manipulate the ligands' selectivity towards D2/D3. The other propyl-linker-bearing compounds, **7a**, **7b**, and **9b**, have been also docked to D2 and D3 receptor models, and over-relayed compound **9a** in the binding site of the target receptors (*Fig. 1*).

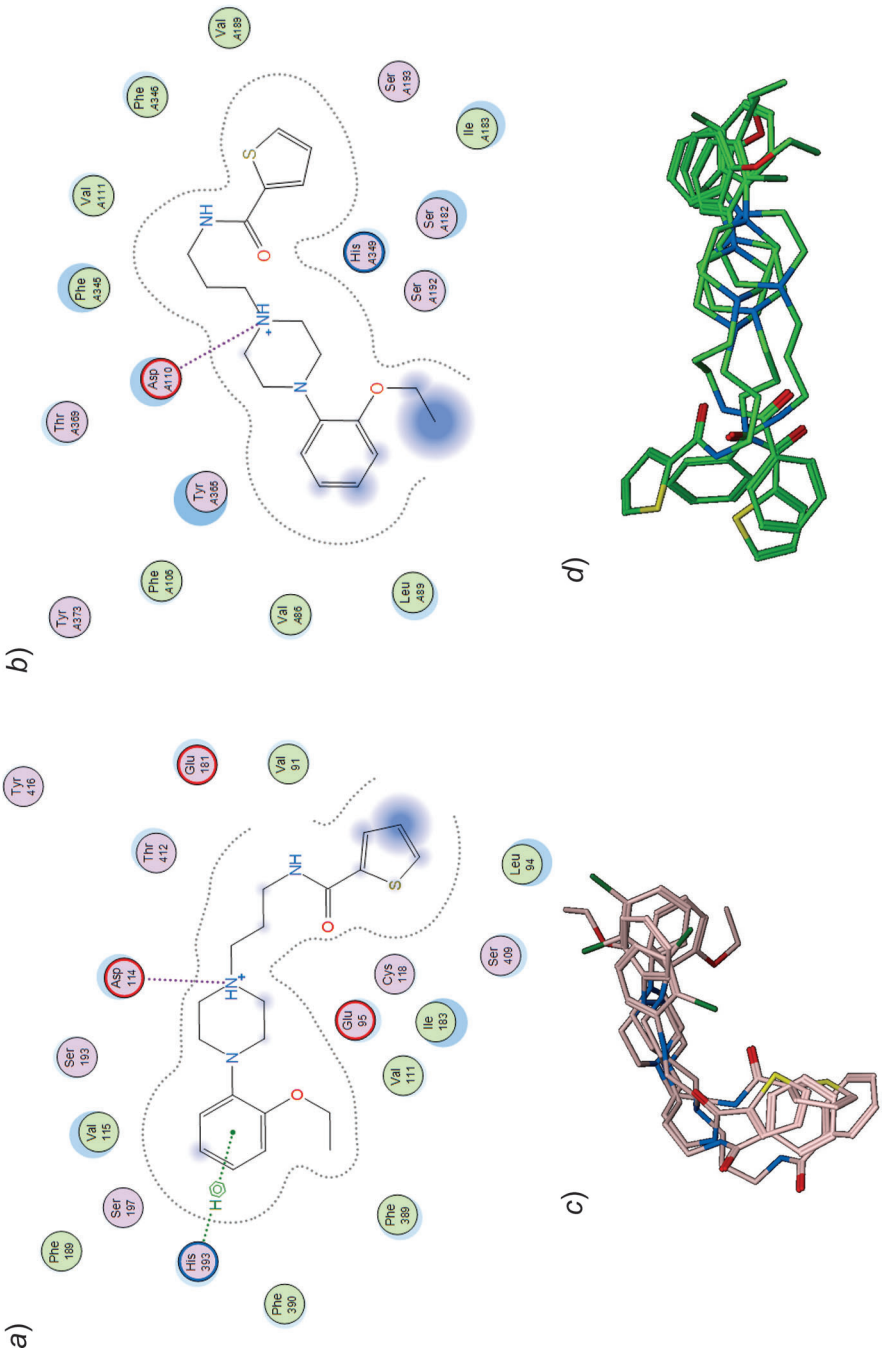


Fig. 1. a) *and* b) *2D Interactions of compound* **9a** *docked to human D2 and D3 model, respectively, showing the key salt-bridge interaction with Asp 3.32* (Asp 114) *and the ligands' aromatic appendage in contact to Ile 183 in EL2.* c) *and* d) *Compounds* **7a**, **7b**, *and* **9b** *over-relayed compound* **9a** *in the binding site of D2 and D3 receptor model, respectively.* The H-atoms of the ligands and the amino acid residues have been removed for clarity.

Compound **10a** with the highest selectivity to D3 over D2 among all the derivatives bearing the butyl linker has been docked to both D2 and D3 models. The docking revealed that the butyl spacer enables the ligands' arene contact with the Glu 181 that is conserved in the binding site of the D2 subtype and faces the more hydrophobic Val 180 in D3. Although Val 180 is conserved in the binding site of D3 receptor subtypes, the 2D interactions of compound **10a** with D3 receptor model did not show this residue in the binding site. The other butyl linker-bearing compounds **8a**, **8b**, **10b** have been also docked to D2 and D3 models and over-relayed compound **10b** in the binding site of the target receptors (*Fig. 2*).

As for D4 receptor subtypes, docking both compounds **9a** and **10a** that were among the compounds with the highest D4 affinity in the whole series have emphasized that the unique D4 amino acid residue Arg 186 turned out to be involved in the H-bond interaction with the C=O moiety of the synthesized ligands. The other propyl-linker-bearing compounds **7a**, **7b**, and **9b**, and the butyl-linker-bearing compounds **8a**, **8b**, and **10b** have been also docked to D4 model and showed to over-relay compounds **9a** and **10a**, respectively, in the binding site of the target receptor (*Fig. 3*).

It is remarkable that the generally enhanced binding affinity of all the butyl-linker-bearing candidates towards all the D2-like members emphasizes the role of the butyl linker in enabling the compound to afford a specific folded conformation stabilized by an intramolecular H-bond between the amide C=O and the protonated piperazin N-atom. This conformation is assumed to possess the optimum distance between the pharmacophore elements leading to optimum binding affinity to the target receptor subtypes [30].

3. Conclusions. – Novel chemical probes bearing three different chemical scaffolds have been designed and synthesized, and their binding affinities to the five subtypes of dopamine receptors were determined. It turned out that the C_4 linker separating the two pharmacophore elements (aromatic appendage and phenylpiperazine unit) of the synthesized probes is crucial to enhance the affinity to all D2-like receptors with marked selectivity towards D3 and D4 over D2 subtypes, giving rise to potential atypical antipsychotic agents. Docking experiments confirmed the rule of certain amino acid residues in the second extra-cellular loop of the target receptors in manipulating subtype-receptor selectivity. These residues include Glu 181 and Ile 183 in D2 receptors, Val 180 and Ser 182 in D3 receptors, and finally Arg 186 in D4 receptors. These findings are important for understanding the interactions with such G-protein-coupled receptors (GPCRs) and for the discovery of highly specific ligands.

Experimental Part

1. *General.* All reactions were performed with commercially available reagents, and they were used without further purification. Solvents were dried by standard methods and stored over molecular sieves. TLC: silica gel *F254* plates (*Merck*); detection of compounds was made by short UV light. Column chromatography (CC): mainly silica gel *60* (SiO_2; 63–200 μm (*Baker*). M.p.: in open cap. tubes, with a *Gallenkamp* melting-point apparatus; uncorrected. FT-IR Spectra: *Nicolet Avatar 380* spectrometer. ^{1}H-NMR spectra: *Bruker Advance 250* spectrometer (250 MHz). MS Data: determined by GC/MS, using a *Hewlett-Packard GCD-Plus* (*G1800C*) apparatus (*HP-5 MS* column; *J&W Scientific*). Elemental analyses were performed on a *Heraeus Vario EL* apparatus in Organic chemistry institute, Friedrich

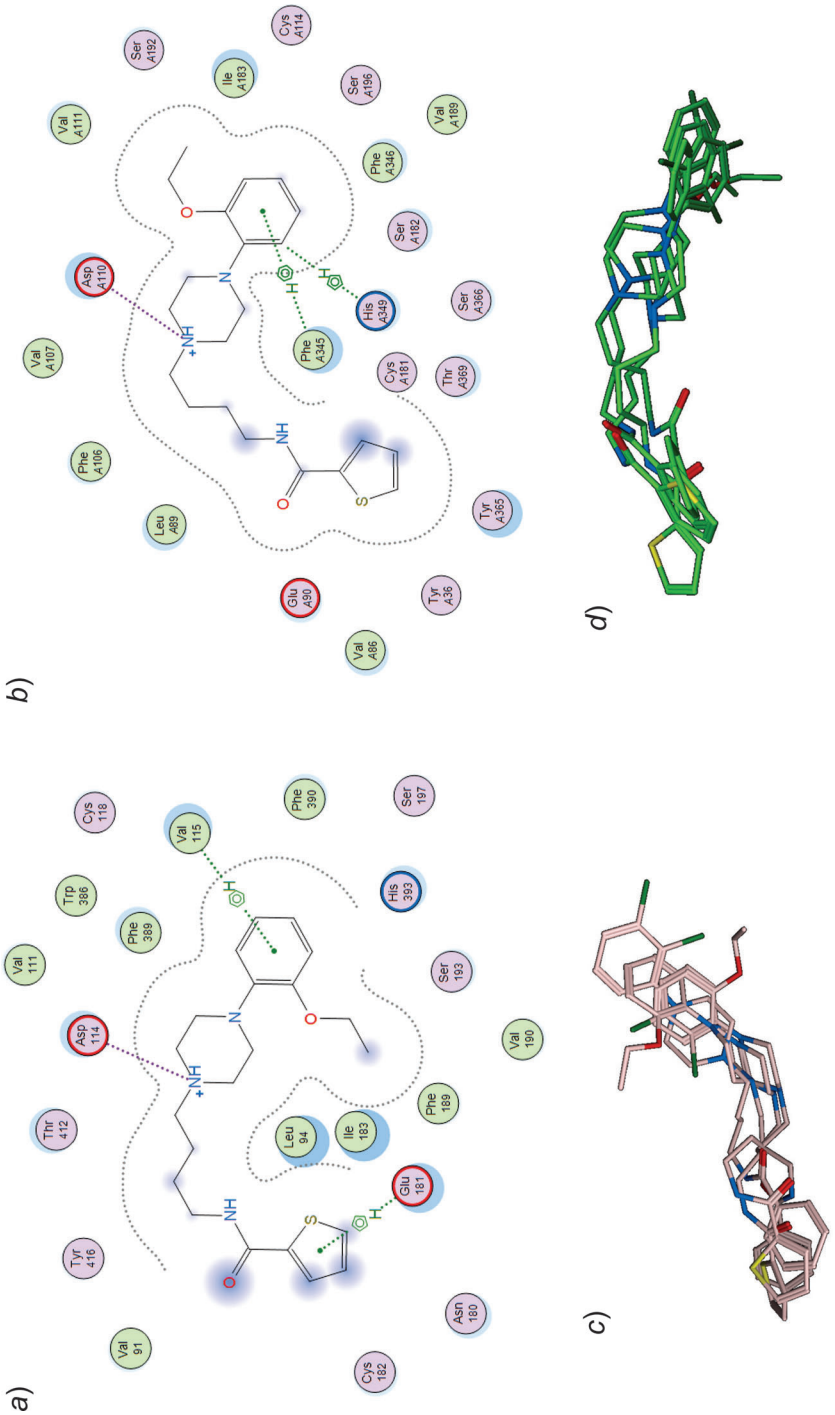


Fig. 2. a) *and* b) *2D Interactions of compound* **10a** *docked to human D2 and D3 model, respectively, showing the key salt-bridge interaction with Asp 3.32* (Asp 114) *and the ligands' aromatic appendage in contact to Glu 181 in EL2.* c) *and* d) *Compounds* **8a**, **8b**, *and* **10b** *over-relayed compound* **10a** *in the binding site of D2 and D3 receptor model, respectively.* The H-atoms of the ligands and the amino acid residues have been removed for clarity.

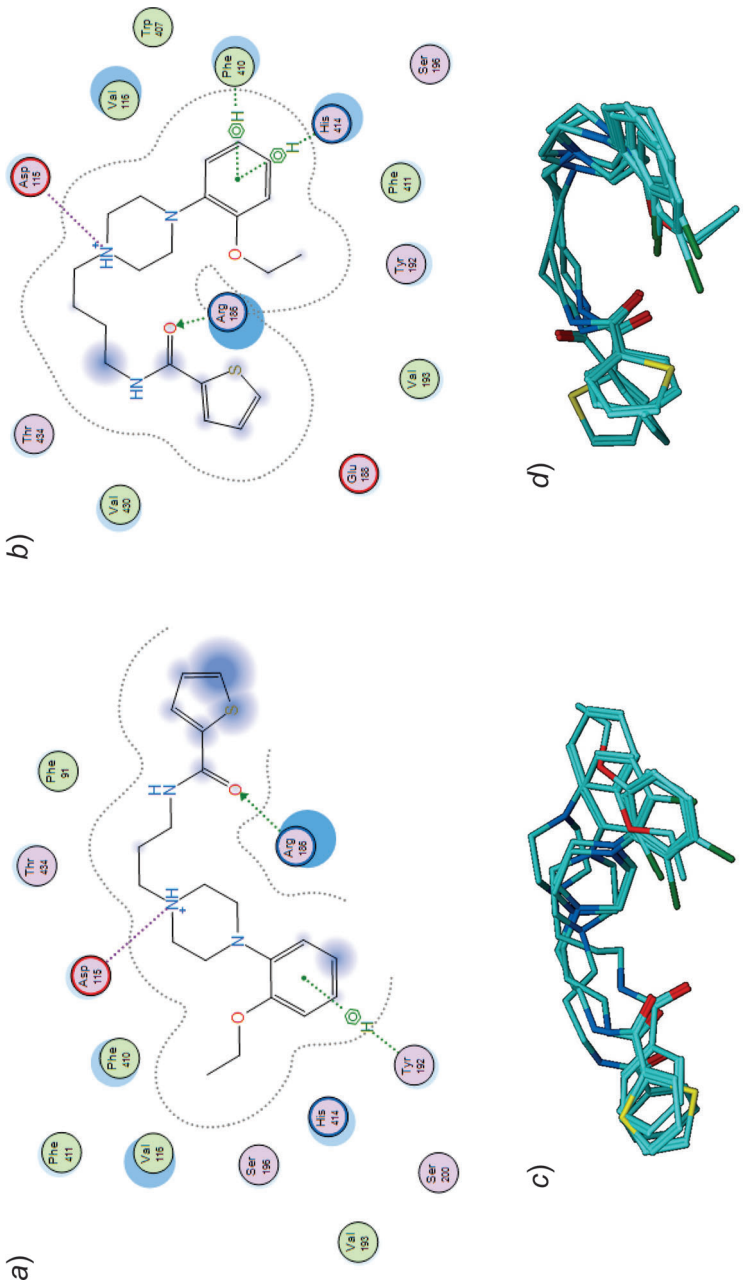


Fig. 3. *2D Interactions of compounds* **9a** (*a*) *and* **10a** (*b*) *docked into human D4 model showing the key salt-bridge interaction with Asp 3.32* (Asp 115), *and the H-bond interaction between the ligand's C=O and the unique D4 residue Arg 186.* c) *Compounds* **7a**, **7b**, *and* **9b** *over-relayed compound* **9a** *in the binding site of D4 receptor model.* The H-atoms of the ligands and the amino acid residues have been removed for clarity. d) *Compounds* **8a**, **8b**, *and* **10b** *over-relayed compound* **10a** *in the binding site of D4 receptor model.* The H-atoms of the ligands and the amino acid residues have been removed for clarity.

Schiller University, Jena; found values were within ±0.4% of the theoretical ones. The pK_a values were calculated using Marvin Sketch software.

*Preparation of 2-(3-Chloropropyl)-1*H*-isoindole-1,3(2*H*)-dione* (**12**). *Phthalic anhydride* (**11**; 1.48 g, 10 mmol) and 3-chloropropylamine hydrochloric salt (1.43 g, 11 mmol) were heated in an oil bath at 160°. The reaction mixture was maintained at the same temp. for 15 min. Then, it was cooled to r.t., and 30 ml H_2O were added just before formation of a slurry. The product was filtered, washed twice with H_2O, and purified by CC (SiO_2; CH_2Cl_2) to afford pure **12** (1.7 g, 75%). White crystals. M.p. 69–71°. ^{1}H-NMR ($CDCl_3$): 2.11–2.22 (*m*, $CH_2(2')$); 3.54–3.59 (*t*, $CH_2(3')$); 3.82–3.87 (*t*, $CH_2(1')$); 7.70–7.91 (*m*, 4 arom. H). GC/MS: 63 (25), 76 (95), 104 (75), 133 (25), 160 (100), 188 (20), 223 (5, M^+).

General Procedure for the Preparation of 2-[3-(4-Arylpiperazin-1-yl)propyl]isoindole-1,3-diones. To a soln. of **12** (1.0 g, 4.5 mmol) in 40 ml of dry MeCN was added the corresponding 1-phenylpiperazine (4.5 mmol) and Et_3N (TEA; 1.5 g, 15 mmol). The mixture was allowed to reflux under inert atmosphere for 48 h, and then left to cool to r.t. The org. solvent was removed under reduced pressure, and the residue was subjected to CC (SiO_2; CH_2Cl_2/MeOH 100:2).

*2-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5a**). Yield: 1.3 g (71%). Yellow crystals. M.p. 109–111°. IR: 1708, 1737 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.42 (*t*, $J = 7$, Me); 1.89–1.95 (*m*, $CH_2(2')$); 2.5 (*t*, $J = 6.9$, $CH_2(3')$); 2.59 (br. *s*, 2 CH_2); 2.96 (br. *s*, 2 CH_2); 3.78 (*t*, $J = 6.9$, $CH_2(1')$); 4.03 (*q*, $J = 7$, MeCH_2); 6.78–6.96 (*m*, 4 arom. H); 7.68–7.82 (*m*, 4 arom. H). GC/MS: 77 (10), 104 (5), 130 (10), 191 (60), 219 (90), 378 (40), 393 (100, M^+). Anal. calc. for $C_{23}H_{27}N_3O_3$ (393.48): C 70.21, H 6.92, N 10.68; found: C 69.84, H 7.08, N 10.89.

*2-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5b**) [31]. Yield: 1.3 g (70%). Yellowish white crystals. M.p. 103–105°. IR: 1711, 1766 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.88–1.96 (*m*, $CH_2(2')$); 2.50 (*t*, $J = 6.9$, $CH_2(3')$); 2.57 (br. *s*, 2 CH_2); 2.90 (br. *s*, 2 CH_2); 3.79 (*t*, $J = 6.9$, $CH_2(1')$); 6.80–7.15 (*m*, 3 arom. H); 7.70 (*dd*, $J = 3, 5.5$, 2 arom. H); 7.84 (*dd*, $J = 3, 5.5$, 2 arom. H). GC/MS: 77 (20), 104 (100), 130 (40), 174 (10), 243 (80), 269 (20), 417 (90, M^+), 419 (55, $[M+2]^+$), 421 (20, $[M+4]^+$). Anal. calc. for $C_{21}H_{21}Cl_2N_3O_2$ (418.32): C 60.30, H 5.06, N 10.05; found: C 60.44, H 4.90, N 9.98.

*2-{3-[4-(2-Fluorophenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5c**). Yield: 1.2 g (71%). Yellow crystals. M.p. 96–98°. IR: 1709, 1765 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.84–1.95 (*m*, $CH_2(2')$); 2.48 (*t*, $J = 6.8$, $CH_2(3')$); 2.56 (*t*, $J = 4.8$, 2 CH_2); 2.94 (*t*, $J = 4.8$, 2 CH_2); 3.79 (*t*, $J = 6.8$, $CH_2(1')$); 6.79–7.05 (*m*, 4 arom. H); 7.67–7.72 (*m*, 4 arom. H); 7.67–7.72 (*m*, 4 arom. H). GC/MS: 77 (80), 104 (100), 130 (20), 193 (60), 352 (10), 368 (30, M^+). Anal. calc. for $C_{21}H_{22}FN_3O_2$ (367.42): C 68.65, H 6.04, N 11.44; found: C 69.02, H 6.11, N 11.41.

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5d**). Yield: 1.1 g (66%). Yellow crystals. M.p. 127–129°. IR: 1714, 1779 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.84–1.95 (*m*, $CH_2(2')$); 2.49 (*t*, $J = 6.85$, $CH_2(3')$); 2.56 (br. *s*, 2 CH_2); 2.89 (br. *s*, 2 CH_2); 3.79 (*t*, $J = 6.85$, $CH_2(1')$); 6.87–7.20 (*m*, 4 arom. H); 7.26–7.72 (*m*, 4 arom. H). GC/MS: 77 (35), 104 (100), 130 (20), 209 (85), 348 (20), 383 (35, M^+), 385 (10, $[M+2]^+$). Anal. calc. for $C_{21}H_{22}ClN_3O_2$ (383.87): C 65.71, H 5.78, N 10.95; found: C 65.32, H 5.41, N 10.76.

*2-{3-[4-(2-Hydroxyphenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5e**). Yield: 1.0 g (60%). Yellow crystals. M.p. 135–137°. IR: 3220 (–OH), 1712, 1769 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.88–1.93 (*m*, $CH_2(2')$); 2.49 (*t*, $J = 6.7$, $CH_2(3')$); 2.53 (br. *s*, 2 CH_2); 2.70 (br. *s*, 2 CH_2); 3.81 (*t*, $J = 6.7$, $CH_2(1')$); 6.81–7.04 (*m*, 4 arom. H); 7.74 (*dd*, $J = 3, 5.4$, 2 arom. H); 7.87 (*dd*, $J = 3, 5.4$, 2 arom. H). GC/MS: 77 (20), 104 (10), 163 (100), 217 (95), 230 (40), 350 (30), 365 (20, M^+). Anal. calc. for $C_{21}H_{23}N_3O_3$ (365.43): C 69.02, H 6.34, N 11.50; found: C 68.78, H 6.32, N 11.24.

*2-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5f**) [32]. Yield: 1.2 g (72%). Brown crystals. M.p. 103–105°. IR: 1712, 1769 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.76–1.95 (*m*, $CH_2(2')$); 2.47 (*t*, $J = 6.9$, $CH_2(3')$); 2.53 (*t*, $J = 4.8$, 2 CH_2); 2.95 (*t*, $J = 4.8$, 2 CH_2); 3.79 (*t*, $J = 6.9$, $CH_2(1')$); 6.76–6.96 (*m*, 4 arom. H); 7.68 (*dd*, $J = 3, 5.5$, 2 arom. H); 7.83 (*dd*, $J = 3, 5.5$ 2 arom. H). GC/MS: 77 (90), 104 (100), 130 (50), 193 (30), 352 (15), 368 (35, M^+). Anal. calc. for $C_{21}H_{22}FN_3O_2$ (367.42): C 68.65, H 6.04, N 11.44; found: C 68.70, H 5.80, N 11.07.

*2-{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione* (**5g**). Yield: 1.2 g (72%). Pale-yellow crystals. M.p. 119–121°. IR: 1701, 1774 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.84–1.95

(*m*, CH_2(2′)); 2.46 (*t*, *J* = 7, CH_2(3′)); 2.52 (*t*, *J* = 5.1, 2 CH_2); 2.98 (*t*, *J* = 5.1, 2 CH_2); 3.79 (*t*, *J* = 7, CH_2(1′)); 6.75 (*d*, *J* = 4.7, 2 arom. H); 7.16 (*d*, *J* = 4.7, 2 arom. H); 7.66–7.84 (*m*, 4 arom. H). GC/MS: 77 (40), 104 (100), 130 (10), 209 (90), 348 (15), 383 (50, M^+), 385 (15, $[M+2]^+$). Anal. calc. for $C_{21}H_{22}ClN_3O_2$ (383.87): C 65.71, H 5.78, N 10.95; found: C 65.83, H 5.68, N 11.37.

*2-{3-[4-(3,4-Dichlorophenyl)piperazin-1-yl]propyl}-1*H-*isoindole-1,3(2*H*)-dione* (**5h**). Yield: 1.3 g (67%). Yellow crystals. M.p. 88–90°. IR: 1713, 1760 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.83–1.94 (*m*, CH_2(2′)); 2.46 (*t*, *J* = 6.8, CH_2(3′)); 2.51 (*t*, *J* = 5.2, 2 CH_2); 2.99 (*t*, *J* = 5.2, 2 CH_2); 3.79 (*t*, *J* = 6.8, CH_2(1′)); 6.67 (*dd*, *J* = 2.85, 9, 1 arom. H); 6.85 (*d*, *J* = 2.85, 1 arom. H); 7.23 (*d*, *J* = 9, 1 arom. H); 7.67–7.83 (*m,* 4 arom. H). GC/MS: 77 (50), 104 (100), 130 (10), 174 (20), 243 (90), 269 (15), 417 (90, M^+), 419 (55, $[M+2]^+$), 421 (20, $[M+4]^+$). Anal. calc. for $C_{21}H_{21}Cl_2N_3O_2$ (418.32): C 60.30, H 5.06, N 10.05; found: C 60.20, H 4.95, N 9.99.

*2-{3-[4-(4-Hydroxyphenyl)piperazin-1-yl]propyl}-1*H-*isoindole-1,3(2*H*)-dione* (**5i**). Yield: 1.0 g (62%). Brown crystals. M.p. 145–147°. IR: 3209 (–OH), 1704, 1759 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.85–1.96 (*m*, CH_2(2′)); 2.51 (*t*, *J* = 6.9, CH_2(3)); 2.55 (*t*, *J* = 4.7, 2 CH_2); 2.90 (*t*, *J* = 6.7, 2 CH_2); 3.78 (*t*, *J* = 6.9, CH_2(1′)); 6.69–7.77 (*m*, 4 arom. H); 7.69 (*dd*, *J* = 3, 5.5, 2 arom. H); 7.83 (*dd*, *J* = 3, 5.5, 2 arom. H). GC/MS: 77 (20), 104 (10), 163 (100), 217 (80), 230 (50), 350 (40), 365 (25, M^+). Anal. calc. for $C_{21}H_{23}N_3O_3$ (365.43): C 69.02, H 6.34, N 11.50; found: C 68.71, H 6.24, N 11.62.

*2-[3-(4-Phenylpiperazin-1-yl)propyl]-1*H-*isoindole-1,3(2*H*)-dione* (**5j**) [33]. Yield: 1.2 g (76%). Yellow crystals. M.p. 105–107°. IR: 1703, 1760 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.86–1.97 (*m*, CH_2(2′)); 2.50 (*t*, *J* = 7, CH_2(3′)); 2.56 (*t*, *J* = 5, 2 CH_2); 3.06 (*t*, *J* = 5, 2 CH_2); 3.80 (*t*, *J* = 7, CH_2(1′)); 6.80–7.26 (*m*, 5 arom. H); 7.68 (*dd*, *J* = 3, 5.4, 2 arom. H); 7.84 (*dd*, *J* = 3, 5.4, 2 arom. H). GC/MS: 77 (95), 104 (100), 130 (50), 160 (60), 175 (30), 349 (10, M^+). Anal. calc. for $C_{21}H_{23}N_3O_2$: C 72.18, H 6.63, N 12.03; found: C 72.09, H 6.67, N 11.98.

*Preparation of 2-(4-Bromobutyl)-1*H-*isoindole-1,3(2*H*)-dione* (**14**). *Phthalimide potassium salt* (**13**; 1.85 g, 10 mmol) was added slowly to a soln. of 1,4-dibromobutane (2.40 g, 11 mmol) in 60 ml acetone. The mixture was refluxed for 24 h, and the precipitate was filtered. The filtrate was evaporated under reduced pressure, and the resulting pale-yellow oil was subjected to CC (SiO_2; CH_2Cl_2) to afford pure creamy white crystals of **14** (2.0 g, 75%). M.p. 67–68°. ^{1}H-NMR ($CDCl_3$): 1.75–1.99 (*m*, CH_2(2′), CH_2(3′)); 3.2 (*t*, *J* = 6.9, CH_2(4′)); 3.71 (*t*, *J* = 6.9, CH_2(1′)); 7.32–7.91 (*m*, 4 arom. H). GC/MS: 77 (60), 105 (50), 133 (100), 160 (95), 202 (98), 336 (10), 281 (20, $[M-2]^+$), 283 (20, M^+).

General Procedure for the Preparation of 2-[4-(4-Arylpiperazin-1-yl)butyl]isoindole-1,3-diones. To a soln. of (**14**; 1.2 g, 4.5 mmol) in 40 ml of dry MeCN, were added the corresponding 1-phenylpiperazine (4.5 mmol) and TEA (1.5 g, 15 mmol). The mixture was allowed to reflux under inert atmosphere for 48 h and then left to cool to r.t. The org. solvent was removed under reduced pressure, and the residue was subjected to CC (SiO_2; CH_2Cl_2/MeOH 100:2).

*2-{4-[4-(2-Ethoxyphenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6a**). Yield: 1.2 g (68%). Orange resin. IR: 1705, 1741 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.44 (*t*, *J* = 7, Me); 1.64–1.74 (*m*, CH_2(2′), CH_2(3′)); 2.44 (*t*, *J* = 7.2, CH_2(4′)); 2.64 (br. *s*, 2 CH_2); 3.11 (br. *s*, 2 CH_2); 3.73 (*t*, *J* = 7.2, CH_2(1′)); 4.05 (*q*, *J* = 7, MeCH_2); 6.82–6.92 (*m*, 4 arom. H), 7.70 (*dd*, *J* = 3, 5.5, 2 arom. H); 7.84 (*dd*, *J* = 3, 5.5, 2 arom. H). GC/MS: 70 (40), 104 (20), 130 (70), 160 (100), 172 (30), 407 (15, M^+). Anal. calc. for $C_{24}H_{29}N_3O_3$ (407.51): C 70.74, H 7.17, N 10.31; found: C 71.03, H 7.42, N 9.96.

*2-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6b**) [31]. Yield: 1.3 g (69%). Yellow crystals. M.p. 119–121°. IR: 1710, 1744 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.57–1.77 (*m*, CH_2(2′), CH_2(3′)); 2.44 (*t*, *J* = 7, CH_2(4′)); 2.61 (br. *s*, 2 CH_2); 3.04 (br. *s*, 2 CH_2); 3.73 (*t*, *J* = 7, CH_2(1′)); 6.92–6.14 (*m*, 3 arom. H); 7.69–7.83 (*m*, 4 arom. H). GC/MS: 70 (60), 104 (30), 130 (50), 160 (100), 172 (30), 243 (50), 432 (5, M^+). Anal. calc. for $C_{22}H_{23}Cl_2N_3O_2$ (432.34): C 61.12, H 5.36, N 9.72; found: C 60.73, H 5.42, N 9.93.

*2-{4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6c**). Yield: 1.2 g (72%). Yellowish-white crystals. M.p. 120–122°. IR: 1703, 1746 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.51–1.79 (*m*, CH_2(2′), CH_2(3′)); 2.43 (*t*, *J* = 7, CH_2(4′)); 2.61 (*t*, *J* = 4.7, 2 CH_2); 3.09 (*t*, *J* = 4.7, 2 CH_2); 3.73 (*t*, *J* = 7, CH_2(1′)); 6.87–6.07 (*m*, 4 arom. H); 7.70 (*dd*, *J* = 3, 5.5, 2 arom. H); 7.81 (*d*, *J* = 4, 2 arom. H). GC/MS: 70 (90), 104 (30), 122 (90), 160 (100), 193 (80), 366 (5), 381 (10, M^+). Anal. calc. for $C_{22}H_{24}FN_3O_2$ (381.44): C 69.27, H 6.34, N 11.02; found: C 69.43, H 6.03, N 10.95.

*2-{4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6d**). Yield: 1.3 g (74%). Pale-yellow crystals. M.p. 141–143°. IR: 1704, 1745 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.57–1.77 (*m*, CH_2(2′), CH_2(3′)); 2.45 (*t*, *J* = 7.1, CH_2(4′)); 2.62 (br. *s*, 2 CH_2); 3.06 (br. *s*, 2 CH_2); 3.73 (*t*, *J* = 7.1, CH_2(1′)); 6.92–6.35 (*m*, 4 arom. H); 7.71 (*dd*, *J* = 3, 5.5, 2 arom. H); 7.83 (*d*, *J* = 3, 2 arom. H). GC/MS: 70 (50), 104 (30), 138 (50), 160 (100), 209 (70), 382 (2), 397 (5, M^+). Anal. calc. for $C_{22}H_{24}ClN_3O_2$ (397.90): C 66.41, H 6.08, N 10.56; found: C 66.20, H 6.02, N 10.43.

*2-{4-[4-(2-Hydroxyphenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6e**). Yield: 1.0 g (63%). Yellowish-white crystals. M.p. 118–120°. IR: 3215 (–OH), 1716, 1741 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.57–1.75 (*m*, CH_2(2′), CH_2(3′)); 2.45 (*t*, *J* = 7.3, CH_2(4′)); 2.61 (br. *s*, 2 CH_2); 2.91 (br. *s*, 2 CH_2); 3.73 (*t*, *J* = 7.3, CH_2(1′)); 6.81–6.17 (*m*, 4 arom. H); 7.70–7.86 (*m*, 4 arom. H). GC/MS: 70 (50), 104 (35), 120 (100), 160 (90), 191 (20), 364 (5), 379 (5, M^+). Anal. calc. for $C_{22}H_{25}N_3O_3$ (379.45): C 69.64, H 6.64, N 11.07; found: C 69.31, H 6.83, N 10.89.

*2-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6f**) [32]. Yield: 1.3 g (76%). Pale-yellow crystals. M.p. 116–118°. IR: 1717, 1776 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.53–1.80 (*m*, CH_2(2′), CH_2(3′)); 2.43 (*t*, *J* = 7.1, CH_2(4′)); 2.58 (*t*, *J* = 5.1, 2 CH_2); 3.10 (*t*, *J* = 5.1, 2 CH_2); 3.73 (*t*, *J* = 7.3, CH_2(1′)); 6.82–6.98 (*m*, 4 arom. H); 7.71 (*dd*, *J* = 3, 5.5 2 arom. H); 7.81 (*d*, *J* = 4, 2 arom. H). GC/MS: 70 (80), 104 (30), 122 (80), 160 (100), 193 (70), 366 (5), 381 (10, M^+). Anal. calc. for $C_{22}H_{24}FN_3O_2$ (381.44): C 69.27, H 6.34, N 11.02; found: C 69.48, H 6.01, N 10.92.

*2-{4-[4-(4-Chlorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6g**). Yield: 1.4 g (77%). Yellow crystals. M.p. 149–151°. IR: 1707, 1755 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.56–1.77 (*m*, CH_2(2′), CH_2(3′)); 2.42 (*t*, *J* = 7.3, CH_2(4′)); 2.57 (*t*, *J* = 4.8, 2 CH_2); 3.14 (*t*, *J* = 4.8, 2 CH_2); 3.73 (*t*, *J* = 7.3, CH_2(1′)); 6.82 (*d*, *J* = 9, 2 arom. H); 7.19 (*d*, *J* = 9, 2 arom. H); 7.71 (*dd*, *J* = 3, 5.5, 2 arom. H); 7.84 (*dd*, *J* = 3, 5.5, 2 arom. H). GC/MS: 70 (60), 104 (30), 138 (40), 160 (100), 209 (50), 382 (5), 397 (15, M^+). Anal. calc. for $C_{22}H_{24}ClN_3O_2$ (397.90): C 66.41, H 6.08, N 10.56; found: C 66.14, H 6.04, N 10.43.

*2-{4-[4-(3,4-Dichlorophenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6h**). Yield: 1.4 g (72%). Yellow crystals. M.p. 125–127°. IR: 1711, 1742 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.56–1.77 (*m*, CH_2(2′), CH_2(3′)); 2.41 (*t*, *J* = 7.3, CH_2(4′)); 2.55 (*t*, *J* = 5.25, 2 CH_2); 3.14 (*t*, *J* = 5.25, 2 CH_2); 3.73 (*t*, *J* = 7.3, CH_2(1′)); 6.72 (*dd*, *J* = 2.75, 9, 1 arom. H); 6.93 (*d*, *J* = 2.75, 1 arom. H); 7.25 (*d*, *J* = 9, 1 arom. H); 7.71 (*dd*, *J* = 3, 5, 2 arom. H); 7.84 (*dd*, *J* = 3, 5, 2 arom. H). GC/MS: 70 (50), 104 (35), 130 (60), 160 (100), 172 (60), 243 (50), 432 (15, M^+). Anal. calc. for $C_{22}H_{23}Cl_2N_3O_2$ (432.34): C 61.12, H 5.36, N 9.72; found: C 61.16, H 5.49, N 10.17.

*2-{4-[4-(4-Hydroxyphenyl)piperazin-1-yl]butyl}-1*H-*isoindole-1,3(2*H*)-dione* (**6i**). Yield: 1.0 g (62%). Pale-yellow crystals. M.p. 151–153°. IR: 3217 (–OH), 1712, 1748 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.65–1.78 (*m*, CH_2(2′), CH_2(3′)); 2.40 (*t*, *J* = 7, CH_2(4′)); 2.57 (br. *s*, 2 CH_2); 3.01 (br. *s*, 2 CH_2); 3.64 (*t*, *J* = 7, CH_2(1′)); 6.68 (*d*, *J* = 9, 2 arom. H); 6.78 (*d*, *J* = 9, 2 arom. H); 7.68–7.76 (*m*, 4 arom. H). GC/MS: 70 (15), 104 (5), 120 (20), 160 (25), 191 (100), 364 (20), 379 (90, M^+). Anal. calc. for $C_{22}H_{25}N_3O_3$: C 69.64, H 6.64, N 11.07; found: C 69.84, H 7.03, N 10.79.

*2-[4-(4-Phenylpiperazin-1-yl)butyl]-1*H-*isoindole-1,3(2*H*)-dione* (**6j**) [32]. Yield: 1.2 g (73%). Yellow crystals. M.p. 137–139°. IR: 1710, 1756 (2 C=O). ^{1}H-NMR ($CDCl_3$): 1.54–1.80 (*m*, CH_2(2′), CH_2(3′)); 2.43 (*t*, *J* = 7, CH_2(4′)); 2.59 (*t*, *J* = 5, 2 CH_2); 3.18 (*t*, *J* = 5, 2 CH_2); 3.73 (*t*, *J* = 7, CH_2(1′)); 6.81–6.93 (*m*, 3 arom. H); 7.22–7.28 (*m*, 2 arom. H); 7.69–7.84 (*m*, 4 arom. H). GC/MS: 77 (95), 104 (100), 130 (40), 160 (80), 175 (70), 348 (5), 363 (15, M^+). Anal. calc. for $C_{22}H_{25}N_3O_2$ (363.45): C 72.70, H 6.93, N 11.56; found: C 72.41, H 6.96, N 11.53.

Procedure for the Preparation of Thiophene-2-carbonyl Chloride (**19**) [23]. To a 100-ml round-bottom flask containing thiophene-2-carboxylic acid (**18**; 0.5 g, 4 mmol) was added slowly and with continuous stirring 10 ml of $SOCl_2$. After complete addition, the mixture was allowed to reflux for 6 h. The flask was then cooled to r.t., 50 ml of H_2O was added, and the desired org. product was extracted with CH_2Cl_2 (2 × 50 ml). The org. layers were collected, dried (Na_2SO_4), and evaporated under reduced pressure. The final product was retrieved in form of brownish-black oil (0.42 g, 72%) and was used for the further reaction without additional purification.

General Procedure for the Preparation of the Amide Derivatives. A soln. of a isoindole-1,3-dione derivative (2 mmol) and $NH_2NH_2 \cdot H_2O$ (80%, 0.25 g, 6 mmol) in 20 ml of EtOH (95%) was heated to reflux for 5 h. After cooling to r.t., any insoluble material was filtered off, washed with EtOH 95% (2 ×

20 ml), and the filtrate was evaporated under reduced pressure. The product was extracted with $CHCl_3$ (2×30 ml), and the desired amines obtained, **15a**–**15j** and **16a**–**16j** were introduced to the following reaction without further purification, where a soln. of *benzoyl chloride* (**17**; 0.28 g, 2 mmol) or **19** (0.30 g, 2 mmol) in 10 ml of dry THF was added slowly to the soln. of the previously obtained corresponding amine derivative (2.3 mmol) and TEA (0.5 g, 5 mmol) in dry THF (30 ml) at 0°. The mixture was then stirred at r.t. for 5 h. The mixture was then poured into 30 ml of H_2O and extracted with CH_2Cl_2 ($2 \times$ 40 ml). The org. layers were collected, dried (Na_2SO_4), and evaporated to yield a residue of the desired product that was purified by CC (SiO_2; CH_2Cl_2/MeOH 200:3).

N-*{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}benzamide* (**7a**). Yield: 0.53 g (72%). Yellow crystals. M.p. 121–123°. IR: 1637 (C=O). ^{1}H-NMR ($CDCl_3$): 1.44 (*t*, *J* = 7, Me), 1.80–1.87 (*m*, $CH_2(2')$); 2.64 (*t*, *J* = 5.75, $CH_2(3')$); 2.71 (br. *s*, 2 CH_2); 3.11 (br. *s*, 2 CH_2); 3.59 (*q*, *J* = 5.5, $CH_2(1')$); 4.05 (*q*, *J* = 7, MeCH_2); 6.84–6.99 (*m*, 4 arom. H); 7.35–7.50 (*m*, 3 arom. H); 7.74–7.83 (*m*, 2 arom. H); 8.31 (br. *s*, NH). GC/MS: 77 (100), 105 (95), 120 (95), 219 (20), 352 (15), 367 (10, M^+). Anal. calc. for $C_{22}H_{29}N_3O_2$ (367.48): C 71.90, H 7.95, N 11.43; found: C 71.58, H 7.74, N 10.84.

N-*{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}benzamide* (**7b**). Yield: 0.60 g (78%); Pale-yellow crystals. M.p. 112–114°. IR: 1640 (C=O). ^{1}H-NMR ($CDCl_3$): 1.81–1.86 (*m*, $CH_2(2')$); 2.65 (*t*, *J* = 6.25, $CH_2(3')$); 2.70 (br. *s*, 2 CH_2); 3.04 (br. *s*, 2 CH_2); 3.59 (*q*, *J* = 5.75, $CH_2(1')$); 6.86–6.90 (*m*, 1 arom. H); 7.12–7.20 (*m*, 2 arom. H); 7.37–7.51 (*m*, 3 arom. H); 7.81–7.85 (*m*, 2 arom. H); 8.11 (br. *s*, NH). GC/MS: 77 (80), 105 (100), 219 (30), 375 (15), 392 (10, M^+). Anal. calc. for $C_{20}H_{23}Cl_2N_3O$ (392.32): C 61.23, H 5.91, N 10.71; found: C 60.96, H 5.84, N 10.47.

N-*{4-[4-(2-Ethoxyphenyl)piperazin-1-yl]butyl}benzamide* (**8a**). Yield: 0.50 g (66%). Pale-yellow crystals. M.p. 106–108°. IR: 1641 (C=O). ^{1}H-NMR ($CDCl_3$): 1.44 (*t*, *J* = 7, Me); 1.60–1.71 (*m*, $CH_2(2')$, $CH_2(3')$); 2.30 (*t*, *J* = 6.75, $CH_2(4')$); 2.70 (br. *s*, 2 CH_2); 3.12 (br. *s*, 2 CH_2); 3.48 (*q*, *J* = 6.2, $CH_2(1')$); 4.06 (*q*, *J* = 7, MeCH_2); 6.82–6.97 (*m*, 4 arom. H, NH); 7.38–7.48 (*m*, 3 arom. H); 7.76–7.87 (*m*, 2 arom. H). GC/MS: 77 (60), 105 (100), 120 (30), 219 (20), 297 (10), 366 (10), 382 (5, M^+). Anal. calc. for $C_{23}H_{31}N_3O_2$ (381.51): C 72.41, H 8.19, N 11.01; found: C 71.87, H 7.98, N 10.87.

N-*{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}benzamide* (**8b**) [34]. Yield: 0.64 g (80%). Yellowish-white crystals. M.p. 128–130°. IR: 1643 (C=O). ^{1}H-NMR ($CDCl_3$): 1.62–1.72 (*m*, $CH_2(2')$, $CH_2(3')$); 2.46 (*t*, *J* = 6.9, $CH_2(4')$); 2.62 (br. *s*, 2 CH_2); 3.02 (br. *s*, 2 CH_2); 3.48 (*q*, *J* = 6.25, $CH_2(1')$); 6.69 (br. *s*, NH), 6.87–6.91 (*m*, 1 arom. H); 7.09–7.17 (*m*, 2 arom. H); 7.38–7.51 (*m*, 3 arom. H); 7.74–7.82 (*m*, 2 arom. H). GC/MS: 77 (100), 105 (95), 172 (80), 205 (70), 243 (60), 410 (5, $[M+4]^+$). Anal. calc. for $C_{21}H_{25}Cl_2N_3O$ (406.35): C 62.07, H 6.20, N 10.34; found: C 61.84, H 6.66, N 10.34.

N-*{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9a**). Yield: 0.50 g (68%). Yellow resin. IR: 1631 (C=O). ^{1}H-NMR ($CDCl_3$): 1.45 (*t*, *J* = 7, Me); 1.76–1.86 (*m*, $CH_2(2')$); 2.62 (*t*, *J* = 6, $CH_2(3')$); 2.71 (br. *s*, 2 CH_2); 3.17 (br. *s*, 2 CH_2); 3.57 (*q*, *J* = 5.6, $CH_2(1')$); 4.07 (*q*, *J* = 7, MeOH_2); 6.84–7.04 (*m*, 5 arom. H); 7.40 (*dd*, *J* = 1.05, 5, 1 arom. H); 7.56–7.58 (*m*, 1 arom. H); 7.79 (br. *s*, NH). GC/MS: 77 (20), 111 (35), 168 (30), 219 (70), 358 (100), 372 (50, M^+). Anal. calc. for $C_{20}H_{27}N_3O_2S$ (373.51): C 64.31, H 7.29, N 11.25; found: C 64.72, H 7.25, N 11.25.

N-*{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9b**). Yield: 0.52 g (65%). Yellow resin. IR: 1639 (C=O). ^{1}H-NMR ($CDCl_3$): 1.80–1.87 (*m*, $CH_2(2')$); 2.64 (*t*, *J* = 6, $CH_2(3')$); 2.71 (br. *s*, 2 CH_2); 3.11 (*t*, *J* = 4.8, 2 CH_2); 3.57 (*q*, *J* = 5.6, $CH_2(1')$); 6.91–6.95 (*m*, 1 arom. H); 7.05 (*dd*, *J* = 3.6, 5, 1 arom. H); 7.12–7.20 (*m*, 2 arom. H); 7.43 (*dd*, *J* = 1.15, 5, 1 arom. H); 7.57 (*dd*, *J* = 1.15, 3.6, 1 arom. H); 7.85 (br. *s*, NH). GC/MS: 77 (20), 111 (80), 168 (80), 197 (100), 381 (20), 398 (10, M^+). Anal. calc. for $C_{18}H_{21}Cl_2N_3OS$ (398.35): C 54.27, H 5.31, N 10.55; found: C 54.11, H 5.36, N 10.52.

N-*{3-[4-(2-Fluorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9c**). Yield: 0.48 g (69%). Brown resin. IR: 1643 (C=O). ^{1}H-NMR ($CDCl_3$): 1.79–1.84 (*m*, $CH_2(2')$); 2.63 (*t*, *J* = 6, $CH_2(3')$); 2.70 (*t*, *J* = 4.8, 2 CH_2); 3.16 (*t*, *J* = 4.8, 2 CH_2); 3.57 (*q*, *J* = 5.5, $CH_2(1')$); 6.90–7.06 (*m*, 5 arom. H); 7.40–7.56 (*m*, 2 arom. H); 7.98 (br. *s*, NH). GC/MS: 77 (15), 111 (100), 122 (80), 193 (40), 331 (40), 347 (10, M^+). Anal. calc. for $C_{18}H_{22}FN_3OS$ (347.45): C 62.22, H 6.38, N 12.09; found: C 62.47, H 6.29, N 12.07.

N-*{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9d**). Yield: 0.45 g (63%). Yellow resin. IR: 1634 (C=O). ^{1}H-NMR ($CDCl_3$): 1.78–1.96 (*m*, $CH_2(2')$); 2.60 (*t*, *J* = 6, $CH_2(3')$); 2.91 (br. *s*, 2 CH_2); 3.25 (br. *s*, 2 CH_2); 3.61 (*q*, *J* = 5.5, $CH_2(1')$); 6.99–7.28 (*m*, 4 arom. H); 7.35–7.68 (*m*, 3

arom. H); 8.09 (br. *s*, NH). GC/MS: 77 (25), 111 (85), 168 (100), 197 (95), 347 (40), 364 (10, $[M+2]^+$). Anal. calc. for $C_{18}H_{22}ClN_3OS$ (363.90): C 59.41, H 6.09, N 11.55; found: C 59.56, H 6.04, N 11.52.

N-*{3-[4-(2-Hydroxyphenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9e**). Yield: 0.47 g (68%). Yellow resin. IR: 3208 (–OH), 1647 (C=O). ^{1}H-NMR ($CDCl_3$): 1.78–1.85 (*m*, $CH_2(2')$); 2.63 (*t*, *J* = 6, $CH_2(3')$); 2.66 (br. *s*, 2 CH_2); 2.97 (br. *s*, 2 CH_2); 3.57 (*q*, *J* = 5.5, $CH_2(1')$); 6.88–7.61 (*m*, 7 arom. H); 7.95 (br. *s*, NH). GC/MS: 77 (15), 111 (75), 168 (80), 197 (100), 330 (10), 345 (15, M^+). Anal. calc. for $C_{18}H_{23}N_3O_2S$ (345.46): C 62.58, H 6.71, N 12.16; found: C 62.51, H 6.78, N 12.24.

N-*{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9f**). Yield: 0.48 g (70%). Yellowish-white crystals. M.p. 103–105°. IR: 1648 (C=O). ^{1}H-NMR ($CDCl_3$): 1.79–1.86 (*m*, $CH_2(2')$); 2.61 (*t*, *J* = 6, $CH_2(3')$); 2.66 (*t*, *J* = 5.1, 2 CH_2); 3.16 (*t*, *J* = 5.1, 2 CH_2); 3.58 (*q*, *J* = 5.6, $CH_2(1')$); 6.84–7.03 (*m*, 5 arom. H); 7.38–7.53 (*m*, 2 arom. H); 7.82 (br. *s*, NH). GC/MS: 77 (20), 111 (100), 122 (50), 197 (90), 331 (60), 347 (20, M^+). Anal. calc. for $C_{18}H_{22}FN_3OS$ (347.45): C 62.22, H 6.38, N 12.09; found: C 62.65, H 6.52, N 12.30.

N-*{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9g**). Yield: 0.54 g (74%). Pale-yellow crystals. M.p. 144–146°. IR: 1641 (C=O). ^{1}H-NMR ($CDCl_3$): 1.79–1.86 (*m*, $CH_2(2')$); 2.60 (*t*, *J* = 6, $CH_2(3')$); 2.64–2.68 (*t*, *J* = 5, 2 CH_2); 3.20 (*t*, *J* = 5, 2 CH_2); 3.58 (*q*, *J* = 5.7, $CH_2(1')$); 6.83 (*d*, *J* = 9, 2 arom. H); 6.0 (*dd*, *J* = 3.7, 5, 1 arom. H); 7.13 (*d*, *J* = 9, 2 arom. H); 7.38–7.52 (*m*, 2 arom. H); 7.78 (br. *s*, NH). GC/MS: 77 (20), 111 (55), 168 (70), 197 (100), 347 (35), 362 (20, M^+). Anal. calc. for $C_{18}H_{22}ClN_3OS$ (363.90): C 59.41, H 6.09, N 11.55; found: C 59.45, H 6.21, N 11.62.

N-*{3-[4-(3,4-Dichlorophenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9h**). Yield: 0.58 g (73%). Pale-yellow crystals. M.p. 107–109°. IR: 1649 (C=O). ^{1}H-NMR ($CDCl_3$): 1.76–1.86 (*m*, $CH_2(2')$); 2.58 (*t*, *J* = 6, $CH_2(3')$); 2.64 (*t*, *J* = 5.2, 2 CH_2); 3.20 (*t*, *J* = 5.2, 2 CH_2); 3.56 (*q*, *J* = 5.7, $CH_2(1')$); 6.72 (*dd*, *J* = 2.8, 8.8, 1 arom. H); 6.94 (*d*, *J* = 2.8, 1 arom. H); 7.02 (*dd*, *J* = 3.6, 5, 1 arom. H); 7.27 (*d*, *J* = 8.8, 1 arom. H); 7.40 (*dd*, *J* = 1, 5, 1 arom. H); 7.51 (*d*, *J* = 3.6, 1 arom. H); 7.78 (br. *s*, NH). GC/MS: 77 (20), 111 (55), 168 (70), 197 (100), 381 (30), 398 (15, M^+). Anal. calc. for $C_{18}H_{21}Cl_2N_3OS$ (398.35): C 54.27, H 5.31, N 10.55; found: C 54.20, H 5.29, N 10.57.

N-*{3-[4-(4-Hydroxyphenyl)piperazin-1-yl]propyl}thiophene-2-carboxamide* (**9i**). Yield: 0.51 g (74%). Creamy-white crystals. M.p. 156–158°. IR: 3217 (–OH), 1639 (C=O). ^{1}H-NMR ($CDCl_3$): 1.77–1.87 (*m*, $CH_2(2')$); 2.70 (*t*, *J* = 6, $CH_2(3')$); 2.75 (*t*, *J* = 4.9, 2 CH_2); 3.23 (*t*, *J* = 4.9, 2 CH_2); 3.58 (*q*, *J* = 5.5, $CH_2(1')$); 6.97–7.38 (*m*, 7 arom. H); 8.00 (br. *s*, NH). GC/MS: 77 (20), 111 (35), 168 (40), 197 (100), 330 (70), 345 (80, M^+). Anal. calc. for $C_{18}H_{23}N_3O_2S$ (345.46): C 62.58, H 6.71, N 12.16; found: C 62.46, H 6.80, N 12.17.

N-*[3-(4-Phenylpiperazin-1-yl)propyl]thiophene-2-carboxamide* (**9j**). Yield: 0.50 g (76%). Creamy-white crystals. M.p. 162–164°. IR: 1635 (C=O). ^{1}H-NMR ($CDCl_3$): 1.77–1.87 (*m*, $CH_2(2')$); 2.61 (*t*, *J* = 6, $CH_2(3')$); 2.67 (*t*, *J* = 5, 2 CH_2); 3.25 (*t*, *J* = 5, 2 CH_2); 3.57 (*q*, *J* = 5.6, $CH_2(1')$); 6.85–7.02 (*m*, 4 arom. H); 7.25–7.40 (*m*, 3 arom. H); 7.55–7.56 (*m*, 1 arom. H); 7.97 (br. *s*, NH). GC/MS: 77 (95), 111 (100), 132 (40), 175 (30), 197 (25), 314 (15), 329 (10, M^+). Anal. calc. for $C_{18}H_{23}N_3OS$ (329.46): C 65.62, H 7.04, N 12.75; found: C 65.61, H 6.89, N 12.57.

N-*{4-[4-(2-Ethoxyphenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10a**). Yield: 0.57 g (74%). Orange resin. IR: 1641 (C=O). ^{1}H-NMR ($CDCl_3$): 1.45 (*t*, *J* = 7, Me); 1.67–1.85 (*m*, $CH_2(2')$, $CH_2(3')$); 2.47 (*t*, *J* = 6.7, $CH_2(4')$); 2.65 (br. *s*, 2 CH_2); 3.12 (br. *s*, 2 CH_2); 3.46 (*q*, *J* = 5.8, $CH_2(1')$); 4.05 (*q*, *J* = 7, MeCH_2); 6.46 (br. *s*, NH); 6.82–7.07 (*m*, 5 arom. H); 7.43–7.49 (*m*, 2 arom. H). GC/MS: 70 (30), 111 (100), 121 (40), 134 (20), 219 (20), 372 (5), 387 (5, M^+). Anal. calc. for $C_{21}H_{29}N_3O_2S$ (387.54): C 65.08, H 7.54, N 10.84; found: C 64.78, H 7.28, N 10.47.

N-*{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10b**). Yield: 0.58 g (71%). Yellowish-brown resin. IR: 1637 (C=O). ^{1}H-NMR ($CDCl_3$): 1.77–1.94 (*m*, $CH_2(2')$, $CH_2(3')$); 2.95 (*t*, *J* = 6.8, $CH_2(4')$); 3.12 (br. *s*, 2 CH_2); 3.36 (br. *s*, 2 CH_2); 3.52 (*q*, *J* = 6.2, $CH_2(1')$); 6.96 (br. *s*, H); 7.13–7.43 (*m*, 4 arom. H); 7.46 (*d*, *J* = 3, 1 arom. H); 7.50 (*d*, *J* = 2.3, 1 arom. H). GC/MS: 70 (50), 130 (60), 160 (100), 174 (40), 243 (40), 397 (5), 412 (5, M^+). Anal. calc. for $C_{19}H_{23}Cl_2N_3OS$ (412.38): C 55.34, H 5.62, N 10.19; found: C 55.44, H 5.62, N 9.94.

N-*{4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10c**). Yield: 0.51 g (71%). Creamy-white crystals. M.p. 135–137°. IR: 1634 (C=O). ^{1}H-NMR ($CDCl_3$): 1.60–1.65 (*m*, $CH_2(2')$, $CH_2(3')$); 2.45 (*t*, *J* = 6.8, $CH_2(4')$); 2.62 (*t*, *J* = 4.9, 2 CH_2); 3.10 (*t*, *J* = 4.9, 2 CH_2); 3.47 (*q*, *J* = 6.3,

$CH_2(1')$); 6.44 (br. *s*, NH); 6.89–7.07 (*m*, 5 arom. H); 7.44 (*d*, *J* = 4.3, 1 arom. H); 7.50 (*d*, *J* = 3.6, 1 arom. H). GC/MS: 70 (50), 111 (100), 122 (60), 193 (40), 211 (20), 346 (10), 361 (5, M^+). Anal. calc. for $C_{19}H_{24}FN_3OS$ (361.48): C 63.13, H 6.69, N 11.62; found: C 62.84, H 6.72, N 12.03.

N-*{4-[4-(2-Chlorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10d**). Yield: 0.53 g (71%). Yellowish-brown resin. IR: 1649 (C=O). ^{1}H-NMR ($CDCl_3$): 1.67–1.80 (*m*, $CH_2(2')$, $CH_2(3')$); 2.47 (*t*, *J* = 6.8, $CH_2(4')$); 2.65 (br. *s*, 2 CH_2); 3.08 (br. *s*, 2 CH_2); 3.44 (*q*, *J* = 6, $CH_2(1')$); 6.39 (br. *s*, NH); 6.93–7.46 (*m*, 7 arom. H). GC/MS: 70 (70), 111 (100), 138 (50), 194 (10), 211 (40), 362 (5), 377 (5, M^+). Anal. calc. for $C_{19}H_{24}ClN_3OS$ (377.93): C 60.38, H 6.40, N 11.12; found: C 60.01, H 6.39, N 10.79.

N-*{4-[4-(2-Hydroxyphenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10e**). Yield: 0.46 g (64%). Reddish-brown resin. IR: 3225 (OH), 1635 (C=O). ^{1}H-NMR ($CDCl_3$): 1.66–1.69 (*m*, $CH_2(2')$, $CH_2(3')$); 2.51 (*t*, *J* = 6.7, $CH_2(4')$); 2.68 (br. *s*, 2 CH_2); 2.93 (*t*, *J* = 4.75, 2 CH_2); 3.44 (*q*, *J* = 5.8, $CH_2(1')$); 6.56 (br. *s*, NH); 6.82–6.95 (*m*, 2 arom. H); 7.04–7.14 (*m*, 3 arom. H); 7.45 (*d*, *J* = 4.8, 1 arom. H); 7.54 (*d*, *J* = 3.8, 1 arom. H). GC/MS: 70 (40), 111 (50), 148 (25), 199 (40), 211 (100), 355 (10), 359 (5, M^+). Anal. calc. for $C_{19}H_{25}N_3O_2S$ (359.49): C 63.48, H 7.01, N 11.69; found: C 63.11, H 6.95, N 11.72.

N-*{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10f**). Yield: 0.53 g (74%). Greysh-white crystals. M.p. 143–145°. IR: 1644 (C=O). ^{1}H-NMR ($CDCl_3$): 1.61–1.67 (*m*, $CH_2(2')$, $CH_2(3')$); 2.46 (*t*, *J* = 6.7, $CH_2(4')$); 2.61 (*t*, *J* = 5, 2 CH_2); 3.12 (*t*, *J* = 5, 2 CH_2); 3.44 (*q*, *J* = 6.3, $CH_2(1')$); 6.40 (br. *s*, NH); 6.83–7.06 (*m*, 5 arom. H); 7.44 (*d*, *J* = 4.9, 1 arom. H); 7.50 (*d*, *J* = 3.8, 1 arom. H). GC/MS: 70 (35), 111 (100), 122 (35), 193 (20), 211 (15), 346 (5), 361 (5, M^+). Anal. calc. for $C_{19}H_{24}FN_3OS$ (361.48): C 63.13, H 6.69, N 11.62; found: C 62.94, H 6.83, N 11.35.

N-*{4-[4-(4-Chlorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10g**). Yield: 0.57 g (76%). Creamy-white crystals. M.p. 158–160°. IR: 1649 (C=O). ^{1}H-NMR ($CDCl_3$): 1.66–1.74 (*m*, $CH_2(2')$, $CH_2(3')$); 2.46 (*t*, *J* = 6.8, $CH_2(4')$); 2.60 (*t*, *J* = 4.8, 2 CH_2); 3.16 (*t*, *J* = 4.8, 2 CH_2); 3.44 (*q*, *J* = 6, $CH_2(1')$); 6.29 (br. *s*, NH); 6.82 (*d*, *J* = 9, 2 arom. H); 7.05 (*m*, 1 arom. H); 7.19 (*d*, *J* = 9, 2 arom. H); 7.44–7.48 (*m*, 2 arom. H). GC/MS: 70 (70), 111 (100), 140 (35), 196 (10), 211 (45), 362 (5), 377 (5, M^+). Anal. calc. for $C_{19}H_{24}ClN_3OS$ (377.93): C 60.38, H 6.40, N 11.12; found: C 60.72, H 6.55, N 10.82.

N-*{4-[4-(3,4-Dichlorophenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10h**). Yield: 0.62 g (76%). Pale-yellow crystals. M.p. 132–134°. IR: 1641 (C=O). ^{1}H-NMR ($CDCl_3$): 1.65–1.74 (*m*, $CH_2(2')$, $CH_2(3')$); 2.43 (*t*, *J* = 6.7, $CH_2(4')$); 2.57 (*t*, *J* = 5, 2 CH_2); 3.16 (*t*, *J* = 5, 2 CH_2); 3.47 (*q*, *J* = 6.2, $CH_2(1')$); 6.28 (br. *s*, NH); 6.72 (*dd*, *J* = 3, 8.8, 1 arom. H); 6.93 (*d*, *J* = 3, 1 arom. H); 7.06 (*d*, *J* = 8.8, 1 arom. H); 7.24–7.47 (*m*, 3 arom. H). GC/MS: 70 (80), 130 (40), 160 (100), 174 (30), 243 (50), 397 (5), 416 (5, $[M+4]^+$). Anal. calc. for $C_{19}H_{23}Cl_2N_3OS$ (412.38): C 55.34, H 5.62, N 10.19; found: C 55.54, H 5.67, N 10.15.

N-*{4-[4-(4-Hydroxyphenyl)piperazin-1-yl]butyl}thiophene-2-carboxamide* (**10i**). Yield: 0.46 g (64%). Buff crystals. M.p. 139–141°. IR: 3236 (OH), 1633 (C=O). ^{1}H-NMR ($CDCl_3$): 1.66–1.69 (*m*, $CH_2(2')$), $CH_2(3')$); 2.52 (*t*, *J* = 6.7, $CH_2(4')$); 2.68 (br. *s*, 2 CH_2); 2.95 (br. *s*, 2 CH_2); 3.47 (*q*, *J* = 5.8, $CH_2(1')$); 6.56 (br. *s*, NH); 6.82–7.55 (*m*, 7 arom. H). GC/MS: 70 (60), 111 (90), 148 (30), 199 (45), 211 (100), 355 (20), 359 (10, M^+). Anal. calc. for $C_{19}H_{25}N_3O_2S$ (359.49): C 63.48, H 7.01, N 11.69; found: C 63.87, H 6.65, N 11.75.

N-*[4-(4-Phenylpiperazin-1-yl)butyl]thiophene-2-carboxamide* (**10j**). Yield: 0.50 g (73%). Creamy-white crystals. M.p. 115–117°. IR: 1641 (C=O). ^{1}H-NMR ($CDCl_3$): 1.65–1.68 (*m*, $CH_2(2')$, $CH_2(3')$); 2.47 (*t*, *J* = 6.8, $CH_2(4')$); 2.63 (*t*, *J* = 5, 2 CH_2); 3.21 (*t*, *J* = 5, 2 CH_2); 3.46 (*q*, *J* = 6.2, $CH_2(1')$); 6.42 (br. *s*, NH); 6.83–7.45 (*m*, 8 arom. H). GC/MS: 70 (30), 104 (40), 111 (50), 132 (60), 211 (100), 328 (50), 343 (30, M^+). Anal. calc. for $C_{19}H_{25}N_3OS$ (343.49): C 66.44, H 7.34, N 12.23; found: C 66.56, H 7.36, N 12.07.

2. *Molecular Modeling.* 2.1. *Energy Minimization and Conformational Search Procedure.* The compounds were drawn using ChemDraw with the basic piperazin N-atom protonated and saved as mol file. The latter were subjected to energy minimization using Force Field MMFF94x by Molecular Operating Environment (MOE) software, *MOE*, *Chemical Computing Group Inc.* http://www.chemcomp/com.

2.2. *Source of Target Proteins.* The crystal structure of human D3 receptors complexed with its antagonist eticlopride (PDB ID code: 3PBL) was downloaded from the Protein Data Bank and opened with MOE software. The homology model of human D4 receptor was downloaded from the *Supporting Information* of the article published in American Chemical Society Publications [29].

2.3. *Docking Procedure of D3 Receptors.* The co-crystallized compound was selected, and the binding site was identified according to residues in 4-Å proximity to those interacted with the co-crystallized antagonist eticlopride. Ligand interactions were computed for the X-ray co-crystallized compound, eticlopride, to reveal the different types of interaction as a validation for the docking procedure. Default settings of MOE-Dock were used, including 'Rotate Bonds' option in order to allow flexible ligand–rigid receptor docking. The scoring function was London dG with a replacement of Triangle Matcher. Thirty poses of each ligand docked to the identified binding site were retained and ranked in order of increasing scoring function. The 2D ligand–receptor interactions of these poses were viewed using the 'compute ligand interaction' option of MOE.

2.4. *Docking Procedure of D4 Receptors.* The binding site was isolated off the validated homology model using the default settings of the site finder panel option of MOE. Again, the default settings of MOE-Dock were used, including 'Rotate Bonds' option in order to allow flexible ligand–rigid receptor docking. The scoring function was London dG with a replacement of Triangle Matcher. Thirty poses of each ligand docked to the identified binding site were retained and ranked in order of increasing scoring function. The 2D ligand–receptor interactions of these poses were viewed using the 'compute ligand interaction' option of MOE.

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Received June 24, 2013