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Original article

Synthesis and structural investigation of some pyrimido[5,4-*c*]quinolin-4(3*H*)-one derivatives with a long-chain arylpiperazine moiety as potent 5-HT$_{1A/2A}$ and 5-HT$_7$ receptor ligands

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ABSTRACT

A series of new pyrimido[5,4-*c*]quinolin-4(3*H*)-ones with variable length of the spacer between amide and 4-arylpiperazine moiety were prepared to further explore the role of a terminal portion in the serotonergic activity. The majority of compounds demonstrated high *in vitro* affinity for 5-HT$_{1A}$ receptor, and moderate-to-low affinity for 5-HT$_{2A}$ and 5-HT$_7$ receptors. X-ray analysis, two-dimensional NMR, conformational studies and docking into the 5-HT$_{1A}$ receptor model were conducted to investigate conformational preferences of selected 5-HT$_{1A}$ receptor ligands in different environments. The extended conformation of tetramethylene derivatives was found in a solid state, in DMSO (for a protonated form) and as a global energy minimum during conformational analysis in simulated water environment. Ligand geometry in top-scored complexes, obtained by docking to a set of 100 receptor models, were either fully extended or with central spacer torsion in synclinal conformation.

1. Introduction

5-Hydroxytryptamine (5-HT, serotonin) is one of the major neurotransmitters in central nervous system (CNS) [1,2]. A plethora of studies shows its involvement in many physiological processes such as the regulation of mood, appetite, sleep, muscle contraction, thermoregulation, cardiovascular function, and some cognitive functions including learning and memory. Malfunctioning serotonin system has been linked to various psychiatric diseases, including anxiety, depression, alcoholism and others [3–5]. There are fourteen known serotonin receptor subtypes (divided into seven subfamilies) based on amino acid sequence, signal transduction mechanism, and pharmacological function [6,7]. Thirteen of them (5-HT$_3$ receptor is a ligand-gated cation channel) belong to G-protein-coupled receptor (GPCR) superfamily. 5-HT$_{1A}$ subtype is one of the most extensively studied because of its early discovery and postulated involvement in anxiety and depression [8,9]. There are numerous potent 5-HT$_{1A}$ receptor ligands, which can be subdivided into different chemical classes: aminotetralines, arylpiperazines, ergolines, indolylalkylamines, aporphines and more, showing diverse pharmacological properties [10]. The most promising group of 5-HT$_{1A}$ receptor ligands are Long-Chain Aryl-Piperazines (LCAPs) with several successfully developed drugs (buspirone, tandospirone, aripiprazole) or pharmacological tools (NAN-190, flexinoxan, WAY 1000135, WAY 1000635). This undoubtedly high prodrug potential of LCAPs resulted in various SAR studies focusing on all three main structural parts: the aryl group at N1 of the piperazine ring, the aliphatic chain at N4 position, and terminal fragment (the most often having amide or imide moiety). Although the influence of the aryl substituent types, as well as the length of the alkyl spacer, on 5-HT$_{1A}$ affinity is relatively well established, the function of the terminal amide/imide moiety is less clear [11]. It is postulated that this part of the ligand is located in a large pocket formed by helices IV–VI, but the limit of hydrophobic pocket capacity has not been determined [12]. Therefore, many research groups have been interested in designing of LACPs with different terminal fragment, as 5-HT$_{1A/2A}$ receptor ligands.

Due to highly flexible linker (usually 2–4 methylene units) various attempts, using diverse experimental and modeling techniques, were conducted to determine the bioactive conformation of LCAPs. Assuming that active conformations of LCAPs are closely related to those in solutions or in solid state, two-dimensional NMR [13–16] and crystallographic methods [13,17–24] were often

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applied. The 2D NMR studies indicated that compounds with tetramethylene spacer can adopt extended, bent or folded conformations [13,15,16]. On the other hand, analysis of Cambridge Structural Database showed that linear geometries predominated (Table 1; see Supplementary Materials). Also molecular modeling studies (conformational analysis, docking, dynamics), provided with structural investigations or conducted separately, gave equivocal results suggesting the possibility of different bioactive conformations of LCAPs.

Looking at the structure–affinity relationships of quinazolin-4(3*H*)-ones [25], we decided to apply all the above mentioned techniques to investigate a new series of LCAP derivatives with a terminal heterocyclic fragment of pyrimido[5,4-*c*]quinolone and variable length of the spacer as serotonin receptors ligands. Diversified structural approaches along with thorough analysis of existing data allowed us to formulate some general conclusions.

2. Chemistry

All compounds investigated in this research were obtained through the synthetic pathway given in Scheme 1. The starting pyrimido[5,4-*c*]quinolin-4(3*H*)-ones were prepared by published procedures [26,27]. Their N-alkylation with 1-bromo-2-chloroethane, 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane in *tert*-butanol in presence of potassium fluoride/aluminium oxide carried to respective 3-(ω-chloroalkyl)pyrimido[5,4-*c*]quinolin-4(3*H*)-one [28]. The reaction temperature was kept at 75 °C and its progress was monitored by the TLC. The final products were obtained by condensation of the appropriate 1-arylpiperazine with above-described chloroalkyl derivatives in acetonitrile at reflux for 24 h, in the presence of potassium carbonate and potassium iodide. The structure of the synthesized compounds was confirmed by physical constants, elemental analysis and NMR spectroscopy. The correlation study COSY $^{1}H-^{1}H$ and HETCOR $^{1}H-^{13}C$ allowed the identification and assignment of all protonated carbons. The remainder was deduced from an HSQC experiment. For biological experiments, free bases (**10**–**67**) were converted into hydrochloride salts, and their molecular formulas and molecular weights were established on the basis of an elemental analysis.

The structural investigation of representative LCAPs were conducted in a solid state (X-ray analysis) and in solutions (2D NMR experiments) to get more information about conformational preferences of studied compounds. Crystals of hydrochlorides of **14**, **23**, **38** and **42**, suitable for X-ray studies, were crystallized from ethanol/methanol mixture (or DMF for **42**) by slow evaporation of respective solvent. Appropriate crystal data are summarized in Supplementary Materials (Table 2), while final coordinates and details of measurements, solutions and refinements have been deposited with Cambridge Crystallographic Data Center No. 794185–794188.

The ROESY experiments of tetramethylene derivatives **35**, **38** and **42** (both free bases and hydrochlorides) were curried out in DMSO and $CDCl_3$ solutions and their results were presented on Fig. 1 in this manuscript and in Supplementary Materials (Fig. 1).

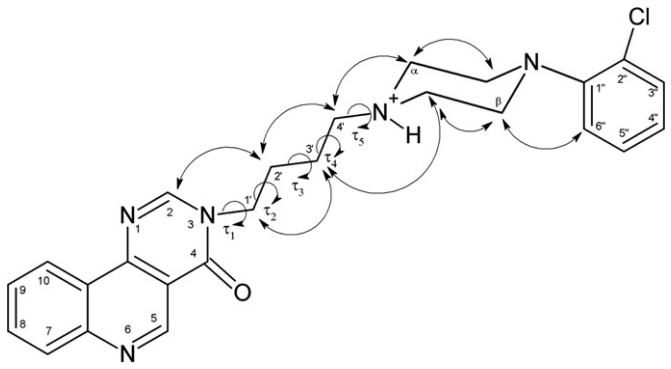


Fig. 1. Significant ROSY signals of 35 (as hydrochloride) in deuterated dimethylsulfoxide solution at 300 K. Also shown is numbering system used in NMR and X-ray analysis.

3. Pharmacology

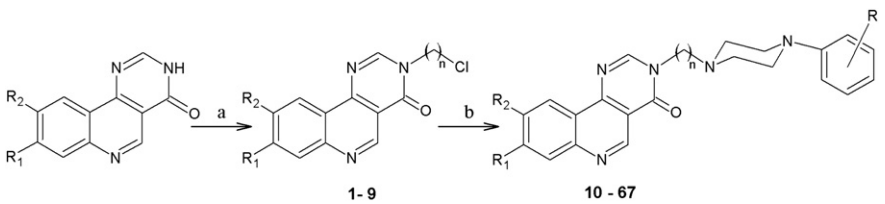
In order to determine activity for 5-HT_{1A} and 5-HT_{2A} receptors, all compounds were assayed *in vitro* radioligand binding experiments according to previously published procedures [29].

At first, the whole set of synthesized derivatives were prescreened at 1 μM concentration, and those inhibited min. 85% of radioligand binding were further examined in full competition experiments to determine K_i value. Since a long-chain arylpiperazines (LCAPs) are also recognized by 5-HT_7 receptor, a set of derivatives with tetramethylene spacer was also examined at this target (Table 1,2).

4. Molecular modeling

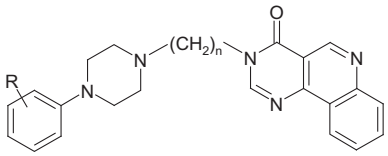
Six compounds with different spacer length were selected for detailed molecular modeling studies **11**, **14**, **23**, **35**, **38** and **42**. For each molecule conformational analysis was performed using Systematic Search module of Tripos SYBYL 8.0 package with the step of 120° for each rotatable bond. Due to sterical clashes total number of returned conformers has been reduced to 48 for 23, 19 for **11** and **14** and 114 for **35**, **38** and **42**. For each set of structures geometry optimization with OpenMopac 2007 was performed. Speed and accuracy of calculations decided on picking semi-empirical methods for all the computations. PM6 Hamiltonian was used and jobs were run for both vacuum and solvent (COSMO algorithm) models. In parallel, flexible docking to hundred 5-HT_{1A} receptor models was performed to predict bioactive conformations of investigated compounds. BioSolveIT FlexX 2.0.3 software was used for docking, and results were scored with CScore module of SYBYL 8.0.

Results of geometry optimizations show that extended conformations are preferred for solvent simulations, whereas in vacuum bent geometries dominated. Results for **35** are presented in Supplementary Materials (Fig. 2a,b). To approximate spacer angulation a distance between nitrogen atoms at both ends of the linker



Scheme 1. Reagents and conditions: (a) alkyldihalides, *tert*-butanol, KF/Al_2O_3; (b) arylpiperazines, CH_3CN, K_2CO_3, KI.

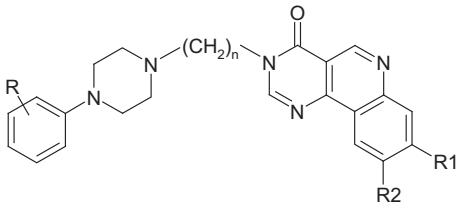
Table 1
5-HT_{1A}, 5-HT_{2A} and 5-HT_7 binding data for compounds **10**–**45**.



No	R	n	5-HT_{1A}		5-HT_{2A}	5-HT_7
			% Inhib[a]	K_i [nM][b]	% Inhib[a]	K_i [nM][b]
10	H	2	66	–	26	–
11	2-Cl	2	90	78	17	–
12	3-Cl	2	93	55	22	–
13	4-Cl	2	11	–	4	–
14	2-OMe	2	93	42	36	–
15	3-OMe	2	82	–	11	–
16	4-OMe	2	6	–	28	–
17	2-F	2	47	–	25	–
18	4-F	2	40	–	14	–
19	2-Me	2	84	514	34	–
20	3-CF_3	2	89	160	36	–
21	4-Py	2	10	–	29	–
22	H	3	95	47	66	–
23	2-Cl	3	87	93	41	–
24	3-Cl	3	91	80	63	–
25	4-Cl	3	42	–	67	–
26	2-OMe	3	97	20	8	–
27	3-OMe	3	89	120	26	–
28	4-OMe	3	0	–	23	–
29	2-F	3	92	55	27	–
30	4-F	3	85	129	73	–
31	2-Me	3	81	–	32	–
32	3-CF_3	3	85	243	44	–
33	4-Py	3	92	48	0	–
34	H	4	93	28	76	612
35	2-Cl	4	92	17	72	153
36	3-Cl	4	96	34	84	184
37	4-Cl	4	54	–	79	328
38	2-OMe	4	97	6	64	276
39	3-OMe	4	90	31	76	484
40	4-OMe	4	11	–	48	>10 000
41	2-F	4	96	63	79	739
42	4-F	4	75	–	82	404
43	2-Me	4	96	52	82	296
44	3-CF_3	4	89	127	61	418
45	4-Py	4	82	–	17	5800

[a] % of Inhibition at 10^{-6} M.
[b] Values are means of three experiments run in triplicate, SEM ≤ 21%.

Table 2
5-HT_{1A} and 5-HT_{2A} binding data for methyl derivatives **46**–**67**.



No	R	R^1	R^2	n	5-HT_{1A}		5-HT_{2A}
					% Inhib[a]	K_i [nM][b]	% Inhib[a]
46	2-OMe	Me	H	2	96	14	19
48	4-OMe	Me	H	2	9	–	9
50	3-CF_3	Me	H	2	88	241	8
52	H	Me	H	3	86	125	44
54	3-Cl	Me	H	3	73	–	40
56	2-OMe	Me	H	3	92	31	18
58	4-F	Me	H	3	68	–	45
60	3-Cl	Me	H	4	85	172	62
62	2-OMe	Me	H	4	99	20	43
64	2-F	Me	H	4	90	83	45
66	4-F	Me	H	4	60	–	57
47	2-OMe	H	Me	2	88	82	11
49	4-OMe	H	Me	2	5	–	4
51	3-CF_3	H	Me	2	82	–	8
53	H	H	Me	3	86	128	28
55	3-Cl	H	Me	3	77	–	44
57	2-OMe	H	Me	3	93	26	5
59	4-F	H	Me	3	67	–	39
61	3-Cl	H	Me	4	91	67	57
63	2-OMe	H	Me	4	99	8	48
65	2-F	H	Me	4	94	97	34
67	4-F	H	Me	4	72	–	56

[a] % of Inhibition at 10^{-6} M.
[b] Values are means of three experiments run in triplicate, SEM ≤ 19%.

was used. All compounds were bound into receptor models in a way similar to that described previously [30]. Phenyl substituent interacted with phenylalanine buried deep in binding pocket (Phe6.51, Phe6.52), protonated piperazine nitrogen was anchored by aspartic acid (Asp3.32) and terminal part was in contact with phenylalanine and/or tyrosine (Tyr2.64, Phe3.28, Tyr7.43) residues. Top scored poses of all investigated ligands are presented on Fig. 2.

5. Results and discussion

New derivatives of pyrimido[5,4-*c*]quinolin-4(3*H*)-one **10**–**67** with 2–4 methylene spacer between amide and 4-arylpiperazine moiety as quinazolidin-4-one analogous [25] were prepared. Compounds **46**–**67** were characterized by the presence of the methyl group located at the C8 or C9 position of the pyrimido[5,4-*c*]quinolin-4(3*H*)-one system, whereas compounds **10**–**45** had no additional substituent in the terminal fragment. At first, the whole set of synthesized derivatives were pre-screened at 1 μM concentration, and those inhibited min. 85% of radioligand binding were further examined in full competition experiments to determine K_i value.

As expected, the combination of arylpiperazine pharmacophore, standard alkylene linkers and pyrimido[5,4-*c*]quinolone as a terminal fragment, resulted in a set of 5-HT_{1A} receptor ligands with well defined SAR. The results of binding experiments, expressed as K_i values varied from 6 nM for **38** to 514 nM for **19** (Table 1) and showed classical LCAPs affinity pattern for 5-HT_{1A} receptors. Generally,

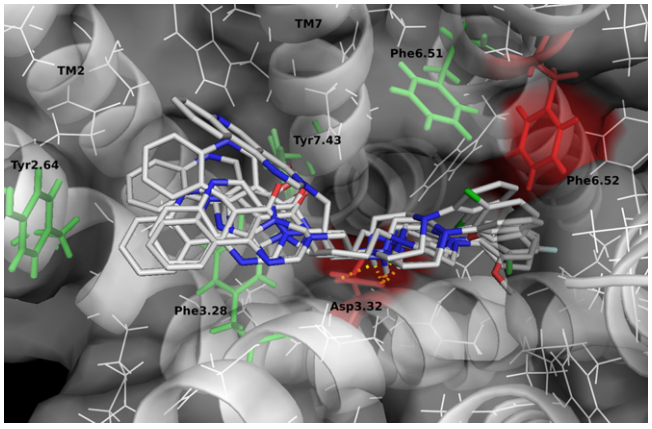


Fig. 2. Top scored poses of investigated compounds docked into binding pocket of 5-HT_{1A} receptor model. Aminoacids in red were used as pharmacophore constraints. Green color indicates residues interacting with ligands. Hydrogen bond between protonated piperazine nitrogen and aspartic acid 3.32 visualized with yellow dashed line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ortho- substituted phenylpiperazine derivatives displayed the highest K_i values and the methoxy group was the most favorable. Unsubstituted phenylpiperazines and *meta*-substituted ones were slightly less active, whereas compounds with substituents in *para*-position as well as pyrimidine–piperazine analogs always presented the lowest affinity.

Elongation of the spacer also had predictable influence on 5-HT_{1A} activity since, besides some derivatives with two unit spacer (i.e. **12**, **14**) which showed comparable K_i values to tetramethylene analogs **34**–**45**, the latter compounds were more active than corresponding "shorter" analogs.

The analysis of the influence of substituent at the non-pharmacophore portion on K_i values revealed that introduction of a methyl group into a complex terminal amide system has no importance for 5-HT_{1A} affinity. All derivatives **46**–**67** showed moderate-to-high K_i values (from 8 nM to 241 for **63** and **50**, respectively) which generally followed structure–activity relationships described above (Table 2).

As regards 5-HT_{2A} receptors, none of the examined compounds displaced more than 85% of radioligand binding from the rat cortex homogenate, and the highest activities were observed for derivatives with tetramethylene linker and unsubstituted terminal amide. With the exception of *para*-substituted phenylpiperazines, all compounds were usually less active at 5-HT_{2A} than 5-HT_{1A} receptors (Table 1,2).

The methyl group substitution at the terminal amide (**46**–**67**), decreased 5-HT_{2A} binding and even usually active *meta*-Cl-phenyl derivatives presented moderate-to-low activity which indicates that compounds with complex terminal amide are not optimally accommodated within 5-HT_{2A} binding site.

As it comes from the affinity data for 5-HT_7 receptors, additionally obtained for the subset of tetramethylene derivatives **34**–**45**, examined compounds displayed moderate-to-low activity (K_i = 153–>10 000 nM). Like in the case of 5-HT_{1A} binding, the most active ligands were *ortho*- substituted phenylpiperazines, whereas *para*-methoxyphenyl derivative was practically inactive at 5-HT_7 receptors.

In the next step of our investigation, several selected agents were used for extensive structural studies to predict their potentially bioactive conformation. Special attention was focused on tetramethylene derivatives due to their significant flexibility and similarity to compounds with therapeutic potential. The four new crystallographic structures obtained (**14**, **23**, **38** and **42**) are very close to protonated analogoues of alkylarylpiperazines deposited in the Cambridge Structural Database (Table 1; see Supplementary Materials). In crystal structures **14**, **23**, **42** (as monohydrochlorides) and **38** (as dihydrochloride) the proton essential for binding with receptor Asp3.32 residue was localized at the piperazine nitrogen linked to the alkyl chain. The piperazine ring was in a common chair conformation (with the two N-substituents in equatorial positions) as indicated by deviations of nitrogen atoms in opposite directions from the plane defined by the ring carbons. Resulting distances were 0.69 and 0.67 Å for **14**, 0.72 and 0.64 Å for **23**, 0.69 and 0.68 Å for **38**, and 0.63 and 0.69 Å for **42**, respectively, with the second values referring to the protonated piperazine nitrogen, substituted equatorially by the alkyl linker. The two aromatic systems, both phenyl from arylpiperazine and pyrimido[5,4-*c*]quinolin-4(3*H*)-one as terminal fragment, were essentially planar with atomic deviation from their least-squares planes no greater than 0.2 Å. In all investigated structures, the alkyl chain (dimethylene in **14**, trimethylene in **23** and tetramethylene in **38**, **42**) was in an antiperiplanar conformation as indicated by the values of appropriate torsion angles (Table 2; see Supplementary Materials).

Due to a limited number of compounds with shorter linkers (only one structure with dimethylene and two with trimethylene groups) structures of **14** and **23** are important to confirm that only antiperiplanar configuration of chain torsional angles are observed. In the case of butyl derivatives **38** and **42**, they fit to the most populated, fully extended conformation (8 structures), characterized by an average N^+–N distance of 6.25 Å. The second cluster, with synclinal conformation of a central C2′–C3′ bond (which shorten an average N^+–N distance to 5.76 Å), consists of 5 structures. There are only 2 (out of 16) folded conformations, as indicated by visibly smaller N^+–N distances: 5.4 and 5.00 Å for two and three synclinal torsions, respectively. More thorough analysis of Table 1 (Supplementary Materials) resulted in further observations: – conformation along C3′–C4′ is always antiperiplanar; C4′–N^+ – synclinal (one exception), C1′–C2′ – antiperiplanar (two exceptions).

The packing of molecules in the studied crystals (**14**, **23**, **38** and **42**) was determined by two important types of intermolecular interactions. The first one was hydrogen bonds network, comprising in all cases N–H···Cl^-···H–O–H hydrogen bonds with inclusion of at least one water molecule from used solvents. The other important interaction was stacking (except for **42**), observed only for planar pyrimido[5,4-*c*]quinolin-4(3*H*)-one systems which may also play a role in binding to the studied receptors.

While the inspection of CSD proved strong preferences of extended conformations of LCAPs in a solid state, our 2D NMR studies in solutions revealed significant influence of a solvent and protonation state.

Since the chemical shift and multiplicity of two methylene groups (2′ and 3′) in the tetramethylene bridging units can provide information about the conformational preferences of tested compounds, at first ^{1}H NMR studies for 3-[4-(4-arylpiperazin-1-ylo)butyl]pyrimido[5,4-*c*]quinolin-4(3*H*)-ones (both free bases and hydrochlorides) were performed. In general, the ^{1}H NMR spectra of compounds **38**, **42** (as free bases), analyzed both in DMSO and $CDCl_3$ solutions, were characterized by two multiple peaks separated by 0.27/0.26 ppm respectively, assigned to the two central methylene groups (2′ and 3′) of the butyl chain. It might suggest the bent conformation advantage, which is in agreement with previous observations [13].

The ^{1}H NMR spectra analysis (in DMSO) of tetramethylene derivatives with the protonated N1 piperazine nitrogen showed a broad cluster, probably associated with the domination of an extended conformation, whereas in $CDCl_3$ solution, two close connected multiplets separated only by 0.08 ppm were present. It suggested that the extended conformation of the structures were in equilibrium with the bent conformation. The above assignments were confirmed by the Overhauser effect. This experimental evidence for the conformations in solution of compounds **35**, **38**, **42** (as free bases and as hydrochlorides) were given by the ROESY experiments which were conducted both in DMSO and $CDCl_3$. In DMSO spectra for protonated form the characteristic cross-peaks from the methylene protons of alkyl chain were assigned for extended conformation (Fig. 1). The lack of interactions between the aromatic protons of the terminal portion and the phenylpiperazine protons or the methylene protons of the alkyl chain excluded the folded geometry of tested compound. The results of the ROESY experiment conducted in a non-polar solvent ($CDCl_3$) were significantly different. The appearance of the weak interactions between H_5–H_β, and H_5–H_{NH} protons, H_5–$H_{5''}$, H_5–$H_{6''}$, besides well-defined cross-peaks from the methylene protons of alkyl chain and H_2–$H_{1'}$, $H_{3'}$–H_α, $H_{4'}$–H_α, indicated the possibility of equilibrium both the bent and the extended conformation. However, the lack of interactions between the aromatic terminal portion ($H_{7,8,9,10}$) and the phenyl protons (from arylpiperazine) definitely excluded the folded conformation of compounds and stacking interaction (Fig. 1; see Supplementary Materials).

The tetramethylene derivatives of free bases were characterized by the bent geometry. The results of the ROESY experiment for **35**, **38**, **42** conducted both in DMSO and $CDCl_3$ showed interactions between H_5—H_β, H_5—H_{NH}, H_5—$H_{5'',6''}$, H_5—$H_{3',4'}$ protons. The lack of interactions between H_2—$H_{1',2'}$ protons also confirmed the bent conformation.

The above results are generally in agreement with those described by Norman et al. [13], but interestingly, they are not fully consistent with those of Lopez-Rodriguez et al. [15], who observed NOE signals between diphenylmethylene-2,5-pyrrolidinedione terminal and piperazine hydrogens for protonated tetramethylene compound in DMSO. Moreover, Nishimura et al. [14] found more folded conformations of tandospirone in aqueous solution than in $CDCl_3$. It thus seems that apart from solvent polarity and protonation the structure of terminal part may also influence the conformational behavior of LCAPs in solution.

The results of *in silico* conformation analysis are in line with our 2D NMR studies. The distance between nitrogen atoms at both ends of a linker represented simplified spacer geometry. Calculations run in vacuum (more similar to non-polar solvent) for **11**, **14**, **23**, **35**, **38** and **42** clearly showed the advantage of bent conformations (with the amide carbonyl oxygen pointing toward the protonated nitrogen atom), whereas in simulated water solution (COSMO algorithm) the lowest energy geometries were fully extended and corresponded with conformation in a solid state. Similar results were obtained by Siracusa et al. [16], though for a free base of *orto*-methoxyphenylpiperazine with thiopropyl linker and benzoxazole terminal. In previous reports [13,15] showing bent or folded conformations as global energy minima, calculations were carried out in a vacuum. Obtained results showing relation between spacer angulation (represented by N—N distance) and relative energy for geometry optimization of **35** run in solvent and in vacuum were presented in Fig. 2a,b (in the Supplementary Materials section).

To complete our studies on the conformational preferences of investigated derivatives **11**, **14**, **23**, **35**, **38** and **42**, flexible docking to hundred 5-HT_{1A} receptor models was performed. Taking into consideration docking results, in top-scored complexes the crucial arylpiperazine moiety was located deep inside the receptor, between TMHs 3, 5, and 6, and the terminal imide was oriented toward TMHs 1, 2 and the extracellular side (Fig. 2a,b; Supplementary Materials). An alternative binding orientation (i.e. opposite, suggested by others) was seldom found, and in lower-ranked complexes only. It has to be stressed that ligands were consequently docked in their fully extended conformations or with synclinal C2′—C3′ torsion which further support our hypothesis about bioactive linear geometries of LCAPs.

6. Conclusions

The present paper has reported the preparation, pharmacological results and conformational studies of new pyrimido[5,4-*c*]quinolin-4(3*H*)-ones **10**—**67** with variable length of the spacer between amide and 4-arylpiperazine moiety. Three different linkers and various substituted arylpiperazines have been employed for this study. Generally, K_i values showed that, most compounds (especially with four methylene spacer) had nanomolar *in vitro* affinity for 5-HT_{1A} receptor and much lower affinity for 5-HT_{2A} and 5-HT_7 receptors. It indicated that compounds with pyrimido[5,4-*c*]quinolin-4(3*H*)-one as terminal system were not optimally accommodated within 5-$HT_{2A,7}$ binding site.

In addition, the analysis of the effect of substituent at the terminal amide system on 5-$HT_{1A/2A}$ binding activity showed that the introduction of a methyl group into a complex terminal amide system has no importance for 5-HT_{1A} affinity but decreased 5-HT_{2A} binding.

The conformational studies (X-ray analysis, 2D NMR experiments) of the polimethylene, especially tetramethylene chain of LCAPs, were discussed. Representative LCAPs **14**, **23**, **38** and **42** demonstrated preferences for extended conformations in a solid state whereas in solutions spatial arrangement of derivatives **35**, **38**, **42** revealed significant influence of a solvent and protonation state.

The above observations were compatible with molecular modeling study performed for **11**, **14**, **23**, **35**, **38** and **42**. Results of geometry optimizations indicated preference for extended conformations in the aqueous medium, whereas bent geometries were dominating in vacuum. The data constituted the basis for molecular modeling and prediction of the ligands binding orientation to a receptor binding site.

Docking analysis of tested compounds showed that all LCAPs were consequently docked in their fully extended conformations or with synclinal C2′-C3′ torsion and bind to 5-HT_{1A} receptor in a similar way.

Our structural investigations organize the knowledge in this topic and show that potentially bioactive conformations can be predicted by X-ray spectrometry and calculating using appropriate solvent simulated semiempirical methods.

7. Experimental protocols

7.1. Chemistry

Reagents and solvents were purchased from common commercial suppliers. The purity of the products were routinely confirmed by the TLC on Marck plates (Kieselgel 60 F_{254}); the appropriate solvents were used, and spots were visualized under the UV light. The catalyst (KF/Al_2O_3) was prepared according to Yamawaki et al. [31]. The melting points were measured on an electrothermal apparatus in open capillaries and are uncorrected. Elemental analyses were carried out with a Perkin—Elmer series II. CHNS/O Analyzer 2400 and were within ±0.4% of the theoretical values. IR spectra were recorded in KBr using a Mattson Infinity Series FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury (300 MHz) spectrophotometer in $CDCl_3$/DMSO-d_6 solutions with TMS as an internal standard. The spectra data of new compounds refer to their free bases. Chemical shifts were expressed in δ (ppm) and the coupling constants J in hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: s (single), d (doublet), t (triplet), m (multiplet). Two-dimensional NMR COSY, ROESY experiments were performed on a Bruker Avance II Plus 700 MHz spectrometer in DMSO at 298 K. The pulse sequences, acquisition, and processing parameters were taken from the standard Bruker software library.

X-ray data were collected on a Bruker SMART diffractometer with CCD area detector APEX for **14** and **38** structure and Kuma4CCD κ-axis diffractometer for **23**, using the graphite monochromated MoK radiation. Data reductions were performed by means of Bruker package of programs [32] and CrysAlis RED [33]. Structures were solved by direct methods using SHELXTL [34] and refinement by full-matrix least squares [35]. Final coordinates and details of measurements, solutions and refinements have been deposited with Cambridge Crystallographic Data Center (No. 794185—794188). All detailes of the crystal data may be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html or from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.

7.1.1. General procedure for the preparation of compounds ***1***—***9***

A mixture of appropriate pyrimido[5,4-*c*]quinolin-4(3*H*)-one (1 mmol), 1-bromo-2-chloroethane, 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane (2.5 mmol),KF/Al_2O_3 catalyst (*ca.*

5 mmol kF) and catalytic amount of KI in *tert*-butanole (20 mL) was stirred at 75 °C, monitored progress of reaction by the TLC. Then the inorganic precipitate was filtered off, solvent was evaporated under reduced pressure to one-half volume and left to crystallization. The crude product was pure by analytical standards. The following products were synthesized using this procedure:

*7.1.1.1. 3-(2-Chloroethyl)pyrimido[5,4-c]quinolin-4(3H)-one (**1**).* Yield: 64%, m.p. 223.7–224.1 °C; IR (KBr, cm^{-1}) ν: 1682 (C=O), 1613–1506 (C=N, C=C); ^{1}H NMR (DMSO-d_6) δ_H: 4.04 (t, J = 6.0 Hz, 2H, C-2′H_2), 4.43 (t, J = 6.0 Hz, 2H, C-1′H_2), 7.80 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.96 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.13 (d, J = 8.4, 1.1 Hz, 1H, C-7H), 8.78 (dd, J = 8.2, 1.1 Hz, 1H, C-10H), 8.85 (s, 1H, C-2H), 9.43 (s, 1H, C-5H) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 159.32, 153.11, 151.32, 149.06, 148.05, 132.13, 129.00, 127.65, 123.97, 122.89, 112.40, 47.91, 41.94 ppm. Anal ($C_{13}H_{10}ClN_3O$) C, H, N.

*7.1.1.2. 3-(2-Chloroethyl)-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**2**).* Yield: 66%, m.p. 203.8–205.3 °C; IR (KBr, cm^{-1}) ν: 1674 (C=O), 1599–1557 (C=N, C=C); ^{1}H NMR (DMSO-d_6) δ_H: 2.62 (s, 3H, CH_3), 4.03 (t, J = 5.7 Hz, 2H, C-2′H_2), 4.41 (t, J = 5.6 Hz, 2H, C-1′H_2), 7.62 (dd, J = 8.4, 1.6 Hz, 1H, C-9H), 7.92 (s, 1H, C-7H), 8.65 (d, J = 8.4 Hz, 1H, C-10H), 8.80 (s, 1H, C-2H), 9.39 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.22, 152.20, 151.06, 150.31, 148.77, 143.24, 129.80, 128.90, 124.23, 121.44, 112.39, 49.46, 42.04, 22.32 ppm. Anal ($C_{14}H_{12}ClN_3O$) C, H, N.

*7.1.1.3. 3-(2-Chloroethyl)-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**3**).* Yield: 68%, m.p. 201.6 (dec) °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1601–1555 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.53 (s, 3H, CH_3), 3.88 (t, J = 5.7 Hz, 2H, C-2′H_2), 4.30 (t, J = 5.6 Hz, 2H, C-1′H_2), 7.61 (dd, J = 8.5, 1.9 Hz, 1H, C-8H), 7.97 (d, J = 8.5 Hz, 1H, C-7H), 8.30 (s, 1H, C-2H), 8.44 (s, 1H, C-10H), 9.43 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 159.99, 151.82, 151.05, 150.82, 147.94, 147.36, 138.08, 134.38, 128.85, 123.43, 112.80, 49.38, 41.98, 22.00 ppm. Anal ($C_{14}H_{12}ClN_3O$) C, H, N.

*7.1.1.4. 3-(3-Chloropropyl)pyrimido[5,4-c]quinolin-4(3H)-one (**4**).* Yield: 79%, m.p. 155.4–156.1 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1600–1506 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.33–2.41(m, 2H, C-2′H_2), 3.62 (t, J = 6.5 Hz, 2H, C-3′H_2), 4.29 (t, J = 6.5 Hz, 2H, C-1′H_2), 7.74 (ddd, J = 8.3, 7.09, 1.3 Hz, 1H, C-9H), 7.91 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.20 (d, J = 8.4 Hz, 1H, C-7H), 8.44 (s, 1H, C-2H), 8.84 (dd, J = 8.3, 1.2 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 159.46, 152.91, 151.23, 148.93, 148.13, 131.88, 128.93, 127.46, 123.89, 122.95, 112.55, 44.52, 42.54, 31.09 ppm. Anal. ($C_{14}H_{12}ClN_3O$) C, H, N.

*7.1.1.5. 3-(3-Chloropropyl)-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**5**).* Yield: 72%, m.p. 155.5–157.2 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1621–1556 (C=N, C=C); ^{1}H NMR (DMSO-d_6) δ_H: 2.19–2.28 (m, 2H, C-2′H_2), 2.58 (s, 3H, CH_3), 3.74 (t, J = 6.5 Hz, 2H, C-3′H_2), 4.18 (t, J = 6.6 Hz, 2H, C-1′H_2), 7.63 (dd, J = 8.4, 1.6 Hz, 1H, C-9H), 7.92 (s, 1H, C-7H), 8.65 (d, J = 8.4 Hz, 1H, C-10H), 8.77 (s, 1H, C-2H), 9.39 (s, 1H, C-5H) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 159.40, 152.69, 151.05, 149.15, 148.08, 142.14, 129.24, 128.08, 123.57, 120.71, 111.97, 44.41, 42.50, 31.08, 21.41ppm. Anal. ($C_{15}H_{14}ClN_3O$) C, H, N.

*7.1.1.6. 3-(3-Chloropropyl)-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**6**).* Yield: 69%, m.p. 149.1–150.6 °C; IR (KBr, cm^{-1}) ν: 1672 (C=O), 1598–1555 (C=N, C=C); ^{1}H NMR (DMSO-d_6) δ_H: 2.17–2.29 (m, 2H, C-2′H_2), 2.58 (s, 3H, CH_3), 3.75 (t, J = 6.6 Hz, 2H, C-3′H_2), 4.19 (t, J = 6.6 Hz, 2H, C-1′H_2), 7.78 (dd, J = 8.5, 1.8 Hz, 1H, C-8H), 8.01 (d, J = 8.5 Hz, 1H, C-7H), 8.54 (s, 1H, C-2H), 8.79 (s, 1H, C-10H), 9.35 (s, 1H, C-5H) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 159.39, 152.41, 150.61, 147.37, 146.98, 137.06, 133.54, 128.60, 122.75, 122.72, 112.43, 44.45, 42.53, 31.08, 21.31 ppm. Anal. ($C_{15}H_{14}ClN_3O$) C, H, N.

*7.1.1.7. 3-(4-Chlorobutyl)pyrimido[5,4-c]quinolin-4(3H)-one (**7**).* Yield: 76%, m.p. 160.5–161.9 °C; IR (KBr, cm^{-1}) ν: 1688 (C=O), 1600–1559 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.86–1.9 (m, 2H, C-2′H_2), 1.99–2.17 (m, 2H, C-3′H_2), 3.62 (t, J = 7.2 Hz, 2H, C-4′H_2), 4.14 (t, J = 7.2 Hz, 2H, C-1′H_2), 7.72 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.90 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.4 Hz, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.5 Hz, 1H, C-10H), 9.64 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.22, 152.13, 150.66, 149.95, 148.94, 132.18, 129.58, 127.65, 124.44, 123.65, 113.04, 46.74, 44.32, 29.65, 27.16 ppm. Anal. ($C_{15}H_{14}ClN_3O$) C, H, N.

*7.1.1.8. 3-(4-Chlorobutyl)-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**8**).* Yield: 78%, m.p. 146.3–147.7 °C; IR (KBr, cm^{-1}) ν: 1671 (C=O), 1600–1559 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.84–1.95 (m, 2H, C-2′H_2), 1.97–2.07 (m, 2H, C-3′H_2), 2.61 (s, 3H, CH_3), 3.60 (t, J = 6.5 Hz, 2H, C-4′H_2), 4.14 (t, J = 76.5 Hz, 2H, C-1′H_2), 7.51 (dd, J = 8.4, 1.5 Hz, 1H, C-9H), 7.93 (s, 1H, C-7H), 8.33 (s, 1H, C-2H), 8.63 (d, J = 8.4 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.14, 151.84, 150.52, 150.03, 148.85, 142.91, 129.59, 128.75, 123.99, 121.30, 112.40, 46.57, 44.25, 29.56, 27.06, 22.20 ppm. Anal. ($C_{16}H_{16}ClN_3O$) C, H, N.

*7.1.1.9. 3-(4-Chlorobutyl)-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**9**).* Yield: 82%, m.p. 161.3–162.9 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1600–1553 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.86–1.95 (m, 2H, C-2′H_2), 1.97–2.17 (m, 2H, C-3′H_2), 2.61 (s, 3H, CH_3), 3.61 (t, J = 6.6 Hz, 2H, C-4′H_2), 4.13 (t, J = 6.5 Hz, 2H, C-1′H_2), 7.71 (dd, J = 8.5, 1.5 Hz, 1H, C-8H), 8.06 (d, J = 8.5 Hz, 1H, C-7H), 8.36 (s, 1H, C-2H), 8.54 (s, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.21, 151.51, 150.37, 148.37, 147.86, 137.87, 134,14, 129.22, 123.39, 123.33, 113.00, 46.47, 44.28, 29.60, 27.10, 22.02 ppm. Anal. ($C_{16}H_{16}ClN_3O$) C, H, N.

*7.1.2. General procedure for the preparation of compounds **10**–**67***

A mixture of the appropriate 1-arylpiperazine (1.2 mmol) and chloroalkyl derivative of (**1**–**9**) (1 mmol) in acetonitrile (25 mL) was refluxed on stirring for about 24 h, in presence of anhydrous K_2CO_3 (1.5 mmol) and catalytic amount of KI. The completion time of reaction was assigned chromatographically (TLC). Then the reaction mixture was filtered off, and the solvent was evaporated to give a crude product, which was purified by crystallization.

Free bases **10**–**67** were converted into hydrochlorides by dissolving the corresponding base in chloroform and treating with diethyl ether saturated with HCl. The precipitate was filtered off and purified by crystallization.

*7.1.2.1. [2-(4-Phenylpiperazin-1-yl)ethyl]pyrimido[5,4-c]quinolin-4(3H)-one (**10**).* Yield: 64%, m.p. 194.6–195.8 °C; IR (KBr, cm^{-1}) ν: 1675 (C=O), 1598–1503 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.57–2.70 (m, 4H, piperazine 2CH_2), 2.76 (t, J = 5.4 Hz, 2H, C-2′H_2), 3.07–3.16 (m, 4H, piperazine 2CH_2), 4.13 (t, J = 5.5 Hz, 2H, C-1′H_2), 6.71–6.86 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.13–7.22 (cluster, 2H, C-3″H, C-5″H), 7.62 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.80 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.10 (d, J = 8.4 Hz, 1H, C-7H), 8.32 (s, 1H, C-2H), 8.74 (dd, J = 8.3, 1.0 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.27, 152.27, 151.52, 151.04, 149.93, 149.00, 132.14, 129.57, 129.18, 127.58, 124.53, 123.74, 120.03, 116.23, 113.04, 56.42, 53.46, 49.30, 44.09 ppm. 10 · 2HCl · 1.5H_2O: Anal ($C_{23}H_{23}N_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.2. 3-{2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**11**).* Yield: 58%, m.p. 184.5–185.9 °C; IR (KBr, cm^{-1}) ν: 1691 (C=O), 1596–1557 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H:

2.64–2.70 (m, 4H, piperazine $2CH_2$), 2.77 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 2.92–3.04 (m, 4H, piperazine $2CH_2$), 4.14 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.82–6.97 (cluster, 2H, C-4″H, C-6″H), 7.12 (ddd, $J = 8.2$, 7.8, 1.5 Hz, 1H, C-5″H), 7.26 (dd, $J = 7.9$, 1.5 Hz, 1H, C-3″H), 7.64 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H, C-9H), 7.81 (ddd, $J = 8.4$, 6.9, 1.5 Hz, 1H, C-8H), 8.11 (d, $J = 8.4$ Hz, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.75 (dd, $J = 8.2$, 1.0 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.25, 152.25, 151.58, 149.93, 149.06, 148.99, 132.12, 130.69, 129.59, 128.80, 127.64, 127.56, 124.50, 123.88, 123.74, 120.49, 113.07, 56.51, 53.63, 51.32, 44.05 ppm. 11 · 2HCl · 1.5H_2O: Anal ($C_{23}H_{22}ClN_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.3. 3-{2-[4-(3-Chlorophenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**12**).* Yield: 52%, m.p. 199.9–200.7 °C; IR (KBr, cm^{-1}) ν: 1685 (C═O), 1600–1561 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.57–2.65 (m, 4H, piperazine $2CH_2$), 2.76 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 3.06–3.14 (m, 4H, piperazine $2CH_2$), 4.13 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.65–6.82 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.06 (t, $J = 8.1$ Hz, 1H, C-5″H), 7.60–7.67 (m, 1H, C-9H), 7.73–7.89 (m, 1H, C-8H), 8.11 (d, $J = 8.3$ Hz, 1H, C-7H), 8.32 (s, 1H, C-2H), 8.74 (dd, $J = 8.3$, 0.9 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.26, 152.26, 152.07, 151.46, 149,92, 148.98, 134.97, 132.17, 130.10, 129.56, 127.61, 124.52, 123.72, 119.60, 115.94, 114.06, 113.03, 56.37, 53.25, 48.84, 44.10 ppm. 12 · 2HCl · H_2O: Anal. ($C_{23}H_{22}ClN_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.4. 3-{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**13**).* Yield: 56%, m.p. 212.5–213.0 °C; IR (KBr, cm^{-1}) ν: 1670 (C═O), 1598–1510 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.61–2.72 (m, 4H, piperazine $2CH_2$), 2.80 (t, $J = 5.5$ Hz, 2H, C-2′H_2), 3.03–3.15 (m, 4H, piperazine $2CH_2$), 4.17 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.67–6.78 (cluster, 2H, C-2″H, C-6″H), 7.06–7.14 (cluster, 2H, C-3″H, C-5″), 7.63 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H, C-9H), 7.81 (ddd, $J = 8.4$, 6.9, 1.5 Hz, 1H, C-8H), 8.11 (d, $J = 8.0$ Hz, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.74 (dd, $J = 8.3$, 1.0 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.29, 152.28, 151.45, 149.94, 149.57, 148.96, 132.21, 129.58, 129.05, 127.64, 124.95, 124.53, 123.72, 117.47, 113.01, 56.32, 53.30, 49.21, 44.02 ppm. 13 · 2HCl · 1.5H_2O: Anal. ($C_{23}H_{22}ClN_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.5. 3-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**14**).* Yield: 60%, m.p. 161.6–162.0 °C; IR (KBr, cm^{-1}) ν: 1676 (C═O), 1596–1498 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.63–2.71 (m, 4H, piperazine $2CH_2$), 2.77 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 2.94–3.06 (m, 4H, piperazine $2CH_2$), 3.71 (s, 3H, OCH_3), 4.13 (t, $J = 5.7$ Hz, 2H, C-1′H_2), 6.69–6.98 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.62 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H, C-9H), 7.80 (ddd, $J = 8.4$, 6.9, 1.5 Hz, 1H, C-8H), 8.10 (d, $J = 8.3$ Hz, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.74 (dd, $J = 8.1$, 1.1 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.22, 152.21, 152.16, 151.57, 149.86, 148.99, 140.92, 132.07, 129.51, 127.51, 124.47, 123.69, 123.14, 121.00, 118.27, 113.01, 111.26, 56.49, 55.53, 53.66, 50.65, 43.94 ppm. 14 · HCl · 2.5H_2O: Anal. ($C_{24}H_{25}N_5O_2$ · HCl · 2.5H_2O) C, H, N.

*7.1.2.6. 3-{2-[4-(3-Methoxyphenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**15**).* Yield: 55%, m.p. 143.8–144.6 °C; IR (KBr, cm^{-1}) ν: 1686 (C═O), 1613–1555 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.53–2.66 (m, 4H, piperazine $2CH_2$), 2.73 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 3.02–3.20 (m, 4H, piperazine $2CH_2$), 3.69 (s, 3H, OCH_3), 4.11 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.25–6.37 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.07 (t, $J = 7.9$ Hz, 1H, C-5″H), 7.56–7.69 (m, 1H, C-9H), 7.74–7.88 (m, 1H, C-8H), 8.10 (d, $J = 8.3$ Hz, 1H, C-7H), 8.31 (s, 1H, C-2H), 8.74 (d, $J = 8.3$, 1.0 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.55, 160.26, 152.48, 152.27, 151.55, 149.91, 149.02, 132.13, 129.85, 129.55, 127.58, 124.52, 123.74, 113.05, 108.95, 104.71, 102.66, 56.45, 55.37, 53.42, 49.27, 44.14 ppm. 15 · 2HCl · 1.25H_2O: Anal. ($C_{24}H_{25}N_5O_2$ · 2HCl · 1.25H_2O) C, H, N.

*7.1.2.7. 3-{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**16**).* Yield: 53%, m.p. 185.7–186.1 °C; IR (KBr, cm^{-1}) ν: 1681 (C═O), 1602–1509 (C═N, C═C), 1239 (OCH_3); ^{1}H NMR ($CDCl_3$) δ_H: 2.62–2.72 (m, 4H, piperazine $2CH_2$), 2.79 (t, $J = 5.4$ Hz, 2H, C-2′H_2), 2.97–3.07 (m, 4H, piperazine $2CH_2$), 3.73 (s, 3H, OCH_3), 4.15 (t, $J = 5.5$ Hz, 2H, C-1′H_2), 6.68–6.86 (cluster, 4H, C-2″H, C-2″H, C-5″H, C-6″H), 7.63 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H, C-9H), 7.81 (ddd, $J = 8.4$, 6.9, 1.5 Hz, 1H, C-8H), 8.11 (d, $J = 8.2$ Hz, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.74 (dd, $J = 8.3$, 1.2 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 154.00, 152.26, 151.54, 149.89, 148.99, 145.25, 132.17, 129.55, 127.61, 124.51, 123.71, 118.42, 114.49, 113.02, 56.35, 55.73, 53.52, 50.72, 43.99 ppm. 16 · 2HCl · 3H_2O: Anal. ($C_{24}H_{25}N_5O_2$ · 2HCl · 3H_2O) C, H, N.

*7.1.2.8. 3-{2-[4-(2-Fluorophenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**17**).* Yield: 61%, m.p. 173.5–173.9 °C; IR (KBr, cm^{-1}) ν: 1690 (C═O), 1597–1499 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.70–2.78 (m, 4H, piperazine $2CH_2$), 2.84 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 3.04–3.15 (m, 4H, piperazine $2CH_2$), 4.21 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.88–7.09 (cluster 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.72 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H, C-9H), 7.90 (ddd, $J = 8.4$, 6.9, 1.5 Hz, 1H, C-8H), 8.19 (d, $J = 7.9$ Hz, 1H, C-7H), 8.42 (s, 1H, C-2H), 8.84 (dd, $J = 8.2$, 1.2 Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 155.91 (157.31, 154.05 $J_{C-F} = 245.6$ Hz), 152.27, 151.57, 149.94, 149.06, 139.86 (139.91, 139.80 $J_{C-F} = 8.6$ Hz), 132.15, 129.60, 129.78, 127.59, 124.53 (124.55, 124.51 $J_{C-F} = 3.4$ Hz), 123.75, 122.70 (122.75, 122.65 $J_{C-F} = 8.0$ Hz), 119.03 (119.05, 119.01 $J_{C-F} = 3.2$ Hz), 116.21 (116.35, 116.08 $J_{C-F} = 20.6$ Hz), 113.08, 56.50, 53.55, 50.66, 44.05 ppm. 17 · 2HCl · 0.5H_2O: Anal. ($C_{23}H_{22}FN_5O$ · 2HCl · 0.5H_2O) C, H, N.

*7.1.2.9. 3-{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**18**).* Yield: 52%, m.p. 190.8–191.8 °C; IR (KBr, cm^{-1}) ν: 1676 (C═O), 1598–1509 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.63–2,73 (m, 4H, piperazine $2CH_2$), 2.81 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 3.05–3.12 (m, 4H, piperazine $2CH_2$), 4.18 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.76–7.02 (cluster, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.70 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H, C-9H), 7.88 (ddd, $J = 8.4$, 7.0, 1.5 Hz, 1H, C-8H), 8.17 (d, $J = 8.4$ Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.81 (dd, $J = 8.2$, 1.2 Hz, 1H, C-10H), 9.64 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.26, 157.22 (158.80, 155.64 $J_{C-F} = 238.5$ Hz), 152.26, 151.54, 149.93, 149.04, 147.76, 132.16, 129.58, 127.60, 124.51, 123.74, 117.94 (117.99, 117.89 $J_{C-F} = 7.7$ Hz), 115.60 (115.75, 115.46 $J_{C-F} = 22.0$ Hz), 113.06, 56.42, 53.48, 50.35, 44.14 ppm. 18 · 2HCl · 1.5H_2O: Anal. ($C_{23}H_{22}FN_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.10. 3-{2-[4-(2-Methylphenyl)piperazin-1-yl]ethyl}pyrimido[5,4-c]quinolin-4(3H)-one (**19**).* Yield: 82%, m.p. 188.3–189.6 °C; IR (KBr, cm^{-1}) ν: 1692 (C═O), 1597–1494 (C═N, C═C); ^{1}H NMR ($CDCl_3$) δ_H: 2.20 (s, 3H, CH_3), 2.60–2.68 (m, 4H, piperazine $2CH_2$), 2.77 (t, $J = 5.6$ Hz, 2H, C-2′H_2), 2,81–2.88 (m, 4H, piperazine $2CH_2$), 4.13 (t, $J = 5.6$ Hz, 2H, C-1′H_2), 6.83–6.96 (cluster, 2H, C-4″H, C-6″H), 7.03–7.12 (cluster, 2H, C-3″H, C-5″H), 7.63 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H, C-9H), 7.80 (ddd, $J = 8.4$, 7.0, 1.5 Hz, 1H, C-8H), 8.10 (d, $J = 8.3$ Hz, 1H, C-7H), 8.34 (s, 1H, C-2H), 8.76 (dd, $J = 8.2$, 1.1 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.26, 152.26, 151.20, 151.13, 149.90, 149.02, 132.59, 132.11, 131.11, 129.56, 127.56, 126.62, 124.51, 123.73, 123.35, 119.10, 113.04, 56.54, 53.99, 51.76, 44.04, 18.11 ppm. 19 · 2HCl · H_2O: Anal. ($C_{24}H_{25}N_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.11. 3-(2-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}ethyl)pyrimido[5,4-c]–quinolin-4(3H)-one (**20**).* Yield: 52%, m.p. 155.3–155.8 °C; IR (KBr, cm^{-1}) ν: 1682 (C═O), 1613–1507 (C═N, C═C); ^{1}H NMR

($CDCl_3$) δ_H: 2.64–2.70 (m, 4H, piperazine $2CH_2$), 2.83 (t, J = 5.6 Hz, 2H, C-2′H_2), 3.18–3.26 (m, 4H, piperazine $2CH_2$), 4.20 (t, J = 5.6 Hz, 2H, C-1′H_2), 6.98–7.12 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.33 (dt, J = 8.3, 8.2, 0.7 Hz, 1H, C-5″H), 7.66 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.89 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.4 Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.3 Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 152.28, 151.49, 151.22, 149.94, 149.02, 132.18, 131.44 (131.65, 131.23 J_{C-F} = 31.8 Hz), 129.63, 129.58, 127.62, 124.36 (126.16, 122.56 J_{C-F} = 272.0 Hz), 124.53, 123.74, 118.91, 116.12 (116.14, 116.09 J_{C-F} = 4.0 Hz), 113.05, 112.30 (112.32, 112.27 J_{C-F} = 4.0 Hz), 56.41, 53.27, 48.92, 44.17 ppm. 20 · 2HCl · 1.5H_2O: Anal. ($C_{24}H_{22}F_3N_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.12. 3-[2-(4-Pyrimidin-2-ylpiperazin-1-yl)ethyl]pyrimido[5,4-c] quinolin-4(3H)-one (**21**).* Yield: 64%, m.p. 192.3–192.9 °C; IR (KBr, cm^{-1}) ν: 1672 (C=O), 1588–1487 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.57–2.65 (m, 4H, piperazine $2CH_2$), 2.82 (t, J = 5.6 Hz, 2H, C-2′H_2), 3.78–3.86 (m, 4H, piperazine $2CH_2$), 4.22 (t, J = 5.6 Hz, 2H, C-1′H_2), 6.49 (t, J = 4.7 Hz, 1H, C-6″H), 7.73 (ddd, J = 8.2, 5.1, 1.2 Hz, 1H, C-9H), 7.90 (ddd, J = 8.4, 5.1, 1.5 Hz, 1H, C-8H), 8.20 (d, J = 8.3 Hz, 1H, C-7H), 8.30 (d, J = 4.7 Hz, 2H, C-3″H, C-5″H), 8.45 (s, 1H, C-2H), 8.85 (dd, J = 8.2, 1.3 Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 161.61, 160.23, 157.74, 152.33, 151.58, 149.96, 149.06, 132.19, 129.60, 127.64, 124.54, 123.78, 113.11, 110.18, 56.63, 53.39, 44.18, 43.89 ppm. 21 · 2HCl · 4H_2O: Anal ($C_{21}H_{21}N_7O$ · 2HCl · 4H_2O) C, H, N.

*7.1.2.13. 3-[3-(4-Phenylpiperazin-1-yl)propyl]pyrimido[5,4-c]quinolin-4(3H)-one (**22**).* Yield: 78%, m.p. 128.2–129.5 °C; IR (KBr, cm^{-1}) ν: 1685 (C=O), 1597–1505 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.04–2.18 (m, 2H, C-2′H_2), 2.47 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.53–2.60 (m, 4H, piperazine $2CH_2$), 3.15–3.25 (4H, piperazine $2CH_2$), 4.22 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.78–6.97 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.18–7.26 (cluster, 2H, C-3″H, C-5″H), 7.65–7.76 (m, 1H, C-9H), 7.90 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.20 (d, J = 8.3 Hz, 1H, C-7H), 8.49 (s, 1H, C-2H), 8.84 (dd, J = 8.3, 1.0 Hz, 1H, C-10H), 9.67 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.32, 152.18, 151.61, 151.16, 149.86, 148.92, 132.05, 129.53, 129.11, 127.53, 124.45, 123.68, 119.83, 116.11, 113.09, 54.37, 53.08, 49.35, 45.74, 25.22 ppm. 22 · 2HCl · 2H_2O: Anal. ($C_{24}H_{25}N_5O$ · 2HCl · 2H_2O) C, H, N.

*7.1.2.14. 3-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**23**).* Yield: 68%, m.p. 150.6–151.2 °C; IR (KBr, cm^{-1}) ν: 1689 (C=O), 1599–1555 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.03–2.14 (m, 2H, C-2′H_2), 2.53 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.61–2.71 (m, 4H, piperazine $2CH_2$), 2.93–3.10 (4H, piperazine $2CH_2$), 4.21 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.81–6.92 (cluster, 2H, C-4″H, C-6″H), 7.10 (dd, J = 8.2, 1.5 Hz, 1H, C-5″H), 7.26 (dd, J = 7.8, 1.4 Hz, 1H, C-3″H), 7.63 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.82 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.11 (d, J = 8.4 Hz, 1H, C-7H), 8.45 (s, 1H, C-2H), 8.75 (dd, J = 8.2, 1.0 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.46, 152.28, 151.62, 149.93, 148.97, 148.82, 132.16, 130.68, 129.60, 128.85, 127.69, 127.63, 124.50, 124.05, 123.73, 120.48, 113.14, 54.64, 53.24, 50.94, 45.82, 25.05 ppm. 23 · HCl · 0.25H_2O: Anal. ($C_{24}H_{24}ClN_5O$ · HCl · 0.25H_2O) C, H, N.

*7.1.2.15. 3-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**24**).* Yield: 67%, m.p. 122.4–123.7; IR (KBr, cm^{-1}) ν: 1670 (C=O), 1596–1559 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.01–2.13 (m, 2H, C-2′H_2), 2.46 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.53–2.63 (m, 4H, piperazine $2CH_2$), 3.05–3.20 (4H, piperazine $2CH_2$), 4.13 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.61–6.79 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.06 (t, J = 8.1 Hz, 1H, C-5″H), 7.60–7.62 (m, 1H, C-9H), 7.77–7.86 (m, 1H, C-8H), 8.10 (d, J = 8.2 Hz, 1H, C-7H), 8.41 (s, 1H, C-2H), 8.72 (dd, J = 8.3, 1.2 Hz, 1H, C-10H), 9.55 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.36, 152.21, 151.98, 151.50, 149,88, 148.89, 134.95, 132.16, 130.10, 129.55, 127.62, 124.45, 123.66, 119.66, 115.97, 114.09, 113.07, 54.44, 52.82, 48.64, 45.70, 25.11 ppm. 24 · 2HCl · 1.75H_2O: Anal. ($C_{24}H_{24}ClN_5O$ · 2HCl · 1.75H_2O) C, H, N.

*7.1.2.16. 3-{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**25**).* Yield: 69%, m.p. 175.3–176.3 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1597–1497 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.96–2.14 (m, 2H, C-2′H_2), 2.42 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.50–2.56 (m, 4H, piperazine $2CH_2$), 3.02–3.10 (4H, piperazine $2CH_2$), 4.12 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.64–6.76 (cluster, 2H, C-2″H, C-6″H), 7.05–7.12 (cluster, 2H, C-3″H, C-5″), 7.62 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.80 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.10 (d, J = 8.0 Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.72 (dd, J = 8.3, 1.0 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.39, 152.23, 151.57, 149.92, 149.72, 148.94, 132.14, 129.58, 128.99, 127.61, 124.75, 124.46, 123.69, 117.36, 113.12, 54.48, 52.93, 45.80, 44.96, 25.20 ppm. 25 · 2HCl · H_2O: Anal. ($C_{24}H_{24}ClN_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.17. 3-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**26**).* Yield: 62%, m.p. 154.6–156.0 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1596–1498 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.02–2.16 (m, 2H, C-2′H_2), 2.49 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.59–2.68 (m, 4H, piperazine $2CH_2$), 3.02–3.11 (4H, piperazine $2CH_2$), 3.86 (s, 3H, OCH_3), 4.22 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.81–7.07 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.72 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, C-9H), 7.90 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H, C-8H), 8.20 (d, J = 8.2 Hz, 1H, C-7H), 8.52 (s, 1H, C-2H), 8.85 (dd, J = 8.1, 1.1 Hz, 1H, C-10H), 9.67 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.38, 152.22, 152.18, 151.75, 149.83, 148.96, 140.96, 132.08, 129.52, 127.55, 124.44, 123.69, 123.04, 120.97, 118.17, 113.13, 111.27, 55.50, 54.44, 53.28, 50.81, 45.83, 25.13 ppm. 26 · 2HCl · 2.5H_2O: Anal. ($C_{25}H_{27}N_5O_2$ · 2HCl · 2.5H_2O) C, H, N.

*7.1.2.18. 3-{3-[4-(3-Methoxyphenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**27**).* Yield: 57%, m.p. 91.2–92.3 °C; IR (KBr, cm^{-1}) ν: 1670 (C=O), 1599–1556 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.93–2.07 (m, 2H, C-2′H_2), 2.38 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.47–2.54 (m, 4H, piperazine $2CH_2$), 3.16–3.23 (4H, piperazine $2CH_2$), 3.70 (s, 3H, OCH_3), 4.12 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.30–6.48 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.09 (dt, J = 8.3, 8.4, 4.8 Hz, 1H, C-5″H), 7.64 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.81 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.11 (d, J = 8.4 Hz, 1H, C-7H), 8.41 (s, 1H, C-2H), 8.75 (dd, J = 8.3, 1.1 Hz, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.54, 160.49, 152.52, 152.41, 151.66, 149.82, 149.02, 132.13, 129.94, 129.81, 127.60, 124.45, 123.68, 113.10, 108.90, 104.62, 103.01, 55.39, 54.33, 53.04, 49.17, 45.27, 25.20 ppm. 27 · 2HCl · 2.5H_2O: Anal. ($C_{25}H_{27}N_5O_2$ · 2HCl · 2.5H_2O) C, H, N.

*7.1.2.19. 3-{3-[4-(4-Methoxyphenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**28**).* Yield: 65%, m.p. 156.4–157.5 °C; IR (KBr, cm^{-1}) ν: 1682 (C=O), 1599–1503 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.03–2.14 (m, 2H, C-2′H_2), 2.50 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.59–2.67 (m, 4H, piperazine $2CH_2$), 3.00–3.11 (4H, piperazine $2CH_2$), 3.68 (s, 3H, OCH_3), 4.15 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.69–6.84 (cluster, 4H, C-2″H, C-2″H, C-5″H, C-6″H), 7.63 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.81 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.11 (d, J = 8.2 Hz, 1H, C-7H), 8.44 (s, 1H, C-2H), 8.74 (dd, J = 8.3, 1.2 Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.43, 154.06, 152.24, 151.57, 149.90, 148.92, 145.24, 132.15, 129.57, 127.62, 124.48, 123.69, 118.53, 114.50, 113.09, 55.74, 54.43, 53.14, 50.53, 45.67, 25.07 ppm. 28 · HCl · 1.75H_2O: Anal. ($C_{25}H_{27}N_5O_2$ · HCl · 1.75H_2O) C, H, N.

*7.1.2.20. 3-{3-[4-(2-Fluorophenyl)piperazin-1-yl]propyl}pyrimido [5,4-c]quinolin-4(3H)-one (**29**).* Yield: 61%, m.p. 115.9–116.9 °C; IR (KBr, cm^{-1}) ν: 1688 (C=O), 1599–1499 (C=N, C=C); ^{1}H NMR ($CDCl_3$)

δ_H: 2.03–2.15 (m, 2H, C-2′H_2), 2.49 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.59–2.66 (m, 4H, piperazine 2CH_2), 3.04–3.11 (4H, piperazine 2CH_2), 4.22 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.82–7.09 (cluster 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.70–7.79 (m, 1H, C-9H), 7.88–7.96 (m, 1H, C-8H), 8.20 (d, J = 7.9 Hz, 1H, C-7H), 8.51 (s, 1H, C-2H), 8.84 (dd, J = 8.2, 1.2 Hz, 1H, C-10H), 9.70 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.42, 155.72 (157.35, 154.10 J_{C-F} = 245.6 Hz), 152.27, 151.69, 149.92, 149.01, 140.01 (140.06, 139.95 J_{C-F} = 8.6 Hz), 132.13, 129.60, 129.78, 127.60, 124.52 (124.54, 124.49 J_{C-F} = 4.0 Hz), 123.73, 122.62 (122.67, 122.57 J_{C-F} = 8.0 Hz), 118.97 (118.99, 118.95 J_{C-F} = 3.2 Hz), 116.18 (116.32, 116.05 J_{C-F} = 20.9 Hz), 113.20, 54.50, 53.18, 50.73, 45.88, 25.19 ppm. 29 · 2HCl · 2H_2O: Anal. ($C_{24}H_{24}FN_5O$ · 2HCl · 2H_2O) C, H, N.

*7.1.2.21. 3-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}pyrimido[5,4-c]quinolin-4(3H)-one (**30**).* Yield: 52%, m.p. 137.9–139.0 °C; IR (KBr, cm^{-1}) ν: 1681 (C=O), 1599–1510 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.00–2.13 (m, 2H, C-2′H_2), 2.46 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.61–2.65 (m, 4H, piperazine 2CH_2), 3.04–3.12 (4H, piperazine 2CH_2), 4.20 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.74–7.05 (cluster, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.70–7.79 (m, 1H, C-9H), 7.86–7.92 (m, 1H, C-8H), 8.20 (d, J = 8.4 Hz, 1H, C-7H), 8.45 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.2 Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.25, 157.22 (158.78, 155.66 J_{C-F} = 238.5 Hz), 152.27, 151.53, 149.92, 149.06, 147.76, 132.15, 129.60, 127.61, 124.53, 123.74, 117.96 (117.99, 117.93 J_{C-F} = 7.7 Hz), 115.61 (115.76, 115.46 J_{C-F} = 22.0 Hz), 113.08, 54.52, 53.20, 50.74, 45.86, 25.20 ppm. 30 · 2HCl · 3.5H_2O: Anal. ($C_{24}H_{24}FN_5O$ · 2HCl · 3.5H_2O) C, H, N.

*7.1.2.22. 3-{3-[4-(2-Methylphenyl)piperazin-1-yl]propyl}pyrimido[5,4-c]quinolin-4(3H)-one (**31**).* Yield: 72%, m.p. 135.7–136.7 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1598–1505 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.02–2.15 (m, 2H, C-2′H_2), 2.27 (s, 3H, CH_3), 2.48 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.54–2.61 (m, 4H, piperazine 2CH_2), 2.81–2.92 (4H, piperazine 2CH_2), 4.21 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.83–7.02 (cluster, 2H, C-4″H, C-6″H), 7.07–7.20 (cluster, 2H, C-3″H, C-5″H), 7.67 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.86 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.3 Hz, 1H, C-7H), 8.51 (s, 1H, C-2H), 8.84 (dd, J = 8.2, 1.1 Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.46, 152.29, 151.79, 151.31, 149.91, 149.03, 132.65, 132.12, 131.08, 129.61, 127.60, 126.60, 124.49, 123.75, 123.25, 118.99, 113.20, 54.57, 53.61, 51.91, 45.93, 25.11. 18.11 ppm. 31 · 2HCl · 3.25H_2O: Anal. ($C_{25}H_{27}N_5O$ · 2HCl · 3.25H_2O) C, H, N.

*7.1.2.23. 3-(3-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}propyl)pyrimido[5,4-c]quinolin-4(3H)-one (**32**).* Yield: 51%, m.p. 221.0–223.4 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1598–1507 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.02–2.13 (m, 2H, C-2′H_2), 2.47 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.61–2.66 (m, 4H, piperazine 2CH_2), 3.06–3.11 (4H, piperazine 2CH_2), 4.20 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.96–7.12 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.35 (dt, J = 8.3, 8.2, 0.7 Hz, 1H, C-5″H), 7.67 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.88 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.4 Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.81 (dd, J = 8.2, 1.3 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.26, 152.25, 151.46, 151.12, 149.89, 149.04, 132.20, 131.42 129.42, 129.58, 127.57, 124.37 (126.17, 122.57 J_{C-F} = 272.0 Hz), 124.53, 123.74, 118.90, 116.01 (116.04, 115.98 J_{C-F} = 4.0 Hz), 113.06, 112.29 (112.31, 112.27 J_{C-F} = 4.0 Hz), 54.55, 53.59, 51.86, 45.90, 25.10 ppm. 32 · 2HCl · 3H_2O: Anal. ($C_{25}H_{24}F_3N_5O$ · 2HCl · 3H_2O) C, H, N.

*7.1.2.24. 3-[3-(4-Pyrimidin-2-ylpiperazin-1-yl)propyl]pyrimido[5,4-c]quinolin-4(3H)-one (**33**).* Yield: 67%, m.p. 184.4–185.4 °C; IR (KBr, cm^{-1}) ν: 1674 (C=O), 1588–1497 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.03–2.14 (m, 2H, C-2′H_2), 2.41–2.51 (cluster, 2H, C-3′H_2 + 4H, piperazine 2CH_2), 3.78–3.83 (4H, piperazine 2CH_2), 4.21 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.47 (t, J = 4.7 Hz, 1H, C-6″H), 7.71 (ddd, J = 8.2, 5.1, 1.2 Hz, 1H, C-9H), 7.88 (ddd, J = 8.4, 5.1, 1.5 Hz, 1H, C-8H), 8.18 (d, J = 8.2 Hz, 1H, C-7H), 8.28 (d, J = 4.8, 2H, C-3″H, C-5″H), 8.49 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.3 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 161.57, 160.42, 157.72, 152.25, 151.63, 149.94, 148.99, 132.13, 129.62, 127.61, 124.50, 123.72, 113.14, 110.04, 54.62, 53.06, 45.85, 43.86, 25.25 ppm. 33 · 2HCl · 2H_2O: Anal. ($C_{22}H_{23}N_7O$ · 2HCl · 2H_2O) C, H, N.

*7.1.2.25. 3-[4-(4-Phenylpiperazin-1-yl)butyl]pyrimido[5,4-c]quinolin-4(3H)-one (**34**).* Yield: 77%, m.p. 174.4–175.5 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1600–1560 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.57–1.71 (m, 2H, C-2′H_2). 1.83–1.99 (m, 2H, C-3′H_2), 2.46 (t, J = 7.2 Hz, 2H, C-4′H_2), 2.52–2.65 (m, 4H, piperazine 2CH_2), 3.09–3.24 (4H, piperazine 2CH_2), 4.13 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.78–6.95 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.19–7.26 (cluster, 2H, C-3″H, C-5″H), 7.65–7.76 (m, 1H, C-9H), 7.89 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.2 Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.3 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.20, 152.12, 151.21, 150.82, 149.87, 148.98, 132.13, 129.55, 129.12, 127.61, 124.40, 123.64, 119.75, 116.06, 113.09, 57.96, 53.45, 49.29, 47.43, 27.67, 24.18 ppm. 34 · 2HCl · 2H_2O: Anal. ($C_{25}H_{27}N_5O$ · 2HCl · 2H_2O) C, H, N.

*7.1.2.26. 3-{4-[4-(2-Chlorophenylpiperazin-1-yl)butyl]pyrimido[5,4-c]quinolin-4(3H)-one (**35**).* Yield: 72%, m.p. 151.4–151.9 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1595–1555 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.60–1.72 (m, 2H, C-2′H_2), 1.85–1.99 (m, 2H, C-3′H_2), 2.49 (t, J = 7.2 Hz, 2H, C-4′H_2), 2.55–2.72 (m, 4H, piperazine 2CH_2), 2.96–3.16 (4H, piperazine 2CH_2), 4.14 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.89–7.06 (cluster, 2H, C-4″H, C-6″H), 7.20 (t, J = 7.7 Hz, 1H, C-5″H), 7.34 (d, J = 7.8 Hz, 1H, C-3″H), 7.72 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.90 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.19 (d, J = 8.4 Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.0 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.21, 152.12, 150.84, 149.86, 149.15, 148.99, 148.819, 132.13, 130.63, 129.55, 128.73, 127.62, 124.40, 123.72, 123.64, 120.38, 113.09, 57.96, 53.56, 51.33, 47.48, 27.67, 24.19 ppm. 35 · 2HCl · 0.75H_2O: Anal. ($C_{25}H_{26}ClN_5O$ · 2HCl · 0.75H_2O) C, H, N.

*7.1.2.27. 3-{4-[4-(3-Chlorophenylpiperazin-1-yl)butyl]pyrimido[5,4-c]quinolin-4(3H)-one (**36**).* Yield: 75%, m.p. 159.5–160.3 °C; IR (KBr, cm^{-1}) ν: 1676 (C=O), 1595–1559 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.75 (m, 2H, C-2′H_2). 1.84–1.98 (m, 2H, C-3′H_2), 2.46 (t, J = 7.2 Hz, 2H, C-4′H_2), 2.53–2.65 (m, 4H, piperazine 2CH_2), 3.07–3.28 (4H, piperazine 2CH_2), 4.13 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.71–6.80 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.14 (t, J = 8.1 Hz, 1H, C-5″H), 7.66–7.77 (m, 1H, C-9H), 7.83–7.85 (m, 1H, C-8H), 8.19 (d, J = 8.2 Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.82 (dd, J = 8.2, 1.2 Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.20, 152.21, 151.11, 150.81, 149,87, 148.97, 134.90, 132.15, 130.04, 129.56, 127.63, 124.40, 123.64, 119.28, 115.72, 113.87, 113.08, 57.88, 53.20, 48.76, 47.40, 27.64, 24.13 ppm. 36 · 2HCl · H_2O: Anal. ($C_{25}H_{26}ClN_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.28. 3-{4-[4-(4-Chlorophenylpiperazin-1-yl)butyl]pyrimido[5,4-c]quinolin-4(3H)-one (**37**).* Yield: 68%, m.p. 175.8–177.0 °C; IR (KBr, cm^{-1}) ν: 1681 (C=O), 1597–1499 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.65–1.72 (m, 2H, C-2′H_2). 1.89–1.98 (m, 2H, C-3′H_2), 2.47 (t, J = 7.2 Hz, 2H, C-4′H_2), 2.57–2.66 (m, 4H, piperazine 2CH_2), 3.04–3.28 (4H, piperazine 2CH_2), 4.14 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.62–6.77 (cluster, 2H, C-2″H, C-6″H), 7.01–7.13 (cluster, 2H, C-3″H, C-5″), 7.68 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, C-9H), 7.86 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, C-8H), 8.16 (d, J = 8.0 Hz, 1H, C-7H), 8.37 (s, 1H, C-2H),

8.82 (dd, $J = 8.3, 1.0$ Hz, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 152.20, 151.67, 149.88, 149.76, 148.84, 132.04, 129.48, 128.91, 127.65, 124.74, 124.42, 123.63, 117.32, 113.09, 57.98, 53.37, 49.26, 47.45, 27.64, 24.16 ppm. **37** · 2HCl · $2H_2O$: Anal. ($C_{25}H_{26}ClN_5O$ · 2HCl · $2H_2O$) C, H, N.

*7.1.2.29. 3-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**38**).* Yield: 87%, m.p. 137.8–138.6 °C; IR (KBr, cm^{-1}) ν: 1688 (C=O), 1599–1498 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.56–1.74 (m, 2H, C-2′H_2). 1.83–1.99 (m, 2H, C-3′H_2), 2.48 (t, $J = 7.2$ Hz, 2H, C-4′H_2), 2.56–2.73 (m, 4H, piperazine 2CH_2), 2.94–3.21 (4H, piperazine 2CH_2), 3.85 (s, 3H, OCH_3), 4.13 (t, $J = 7.3$ Hz, 2H, C-1′H_2), 6.79–7.04 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.72 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H, C-9H), 7.90 (ddd, $J = 8.2, 6.8, 1.4$ Hz, 1H, C-8H), 8.19 (d, $J = 8.2$ Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.82 (dd, $J = 8.1, 1.1$ Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.20, 152.19, 152.11, 150.83, 149.87, 148.99, 141.22, 132.10, 129.55, 127.59, 124.40, 123.65, 122.96, 120.98, 118.20, 113.09, 111.15, 58.06, 55.49, 53.64, 50.80, 47.49, 27.68, 24.19 ppm. **38** · 2HCl · $3.5H_2O$: Anal. ($C_{26}H_{29}N_5O_2$ · 2HCl · $3.5H_2O$) C, H, N.

*7.1.2.30. 3-{4-[4-(3-Methoxyphenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**39**).* Yield: 76%, m.p. 142.5–143.2 °C; IR (KBr, cm^{-1}) ν: 1687 (C=O), 1597–1498 (C=N, C=C); ^{1}H NMR ($CDCl_3$): δ 1.56–1.74 (m, 2H, C-2′H_2). 1.83–1.99 (m, 2H, C-3′H_2), 2.48 (t, $J = 7.2$ Hz, 2H, C-4′H_2), 2.56–2.73 (m, 4H, piperazine 2CH_2), 2.94–3.21 (4H, piperazine 2CH_2), 3.85 (s, 3H, OCH_3), 4.13 (t, $J = 7.3$ Hz, 2H, C-1′H_2), 6.33–6.57 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.16 (t, $J = 8.2$ Hz, 1H, C-5″H), 7.72 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H, C-9H), 7.90 (ddd, $J = 8.3, 7.0, 1.5$ Hz, 1H, C-8H), 8.19 (d, $J = 8.3$ Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.82 (dd, $J = 8.2, 1.1$ Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.50, 160.22, 152.62, 152.13, 150.83, 149.88, 149.00, 132.14, 129.79, 129.57, 127.62, 124.41, 123.66, 113.10, 108.88, 104.48, 102.52, 57.96, 55.34, 53.41, 49.21, 47.44, 27.67, 24.19 ppm. **39** · 2HCl · $3.5H_2O$: Anal. ($C_{26}H_{29}N_5O_2$ · 2HCl · $3.5H_2O$) C, H, N.

*7.1.2.31. 3-{4-[4-(4-Methoxyphenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**40**).* Yield: 57%, m.p. 170.9–171.5 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1597–1513 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.54–1.73 (m, 2H, C-2′H_2). 1.83–1.99 (m, 2H, C-3′H_2), 2.46 (t, $J = 7.2$ Hz, 2H, C-4′H_2), 2.54–2.67 (m, 4H, piperazine 2CH_2), 3.00–3.17 (4H, piperazine 2CH_2), 3.75 (s, 3H, OCH_3), 4.12 (t, $J = 7.3$ Hz, 2H, C-1′H_2), 6.85 (q, $J = 9.2$ Hz, 4H, C-2″H, C-2″H, C-5″H, C-6″H), 7.71 (dd, $J = 8.2, 1.2$ Hz, 1H, C-9H), 7.88 (dd, $J = 8.4, 1.5$ Hz, 1H, C-8H), 8.19 (d, $J = 8.3$ Hz, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.81 (d, $J = 8.3$, Hz, 1H, C-10H), 9.64 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.60, 154.15, 152.52, 151.24, 150.27, 149.39, 146.03, 132.53, 129.96, 128.01, 124.81, 124.05, 118.60, 114.86, 113.50, 58.37, 56.12, 53.96, 51.17, 47.85, 28.08, 24.60 ppm. **40** · HCl · $2H_2O$: Anal. ($C_{26}H_{29}N_5O_2$ · HCl · $2H_2O$) C, H, N.

*7.1.2.32. 3-{4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**41**).* Yield: 61%, m.p. 169.3–170.2 °C; IR (KBr, cm^{-1}) ν: 1696 (C=O), 1600–1499 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.75 (m, 2H, C-2′H_2). 1.82–2.05 (m, 2H, C-3′H_2), 2.55 (t, $J = 7.3$ Hz, 2H, C-4′H_2), 2.39–2.71 (m, 4H, piperazine 2CH_2), 3.09–3.18 (4H, piperazine 2CH_2), 4.13 (t, $J = 7.3$ Hz, 2H, C-1′H_2), 6.84–7.12 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.72 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H, C-9H), 7.90 (ddd, $J = 8.4, 7.0, 1.5$ Hz, 1H, C-8H), 8.19 (d, $J = 8.1$ Hz, 1H, C-7H), 8.40 (s, 1H, C-2H), 8.82 (dd, $J = 8.3, 1.1$ Hz, 1H, C-10H), 9.64 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.22, 155.67 (157.30, 154.05 $J_{C-F} = 245.3$ Hz), 152.14, 150.85, 149.88, 149.00, 140.07 (140.12, 140.02 $J_{C-F} = 8.3$ Hz), 132.14, 129.57, 127.62, 124.50 (124.52, 124.48 $J_{C-F} = 3.7$ Hz), 124.42, 123.66, 122.49 (122.55, 122.44 $J_{C-F} = 8.0$ Hz), 118.94 (118.96, 118.92 $J_{C-F} = 3.1$ Hz), 116.13 (116.27, 115.99 $J_{C-F} = 20.6$ Hz), 113.11, 57.98, 53.49, 50.67, 47.47, 27.67, 24.18 ppm. **41** · 2HCl: Anal. ($C_{25}H_{26}FN_5O$ · 2HCl) C, H, N.

*7.1.2.33. 3-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**42**).* Yield: 53%, m.p. 179.4–180.0 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1600–1510 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.76 (m, 2H, C-2′H_2). 1.82–2.05 (m, 2H, C-3′H_2), 2.46 (t, $J = 7.3$ Hz, 2H, C-4′H_2), 2.53–2.69 (m, 4H, piperazine 2CH_2), 2.99–3.19 (4H, piperazine 2CH_2), 4.13 (t, $J = 7.2$ Hz, 2H, C-1′H_2), 6.90 (dt, $J = 13.7, 9.1$ Hz, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.63–7.78 (m, 1H, C-9H), 7.84–7.99 (m, 1H, C-8H), 8.19 (d, $J = 8.3$ Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.81 (d, $J = 8.2$ Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.23, 157.12 (158.70, 155.54 $J_{C-F} = 238.2$ Hz), 152.14, 150.84, 149.88, 148.99, 147.92, 132.16, 129.57, 127.65, 124.42, 123.66, 117.83 (117.88, 117.78 $J_{C-F} = 7.7$ Hz), 115.55 (115.70, 115.41 $J_{C-F} = 22.0$ Hz), 113.10, 57.92, 53.44, 50.31, 47.44, 27.68, 24.19 ppm. **42** · 2HCl: Anal. ($C_{25}H_{26}FN_5O$ · 2HCl) C, H, N.

*7.1.2.34. 3-{4-[4-(2-Methylphenyl)piperazin-1-yl]butyl}pyrimido[5,4-c]quinolin-4(3H)-one (**43**).* Yield: 72%, m.p. 132.7–133.8 °C; IR (KBr, cm^{-1}) ν: 1677 (C=O), 1595–1494 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.75 (m, 2H, C-2′H_2). 1.85–1.97 (m, 2H, C-3′H_2), 2.45 (s, 3H, CH_3), 2.47 (t, $J = 7.3$ Hz, 2H, C-4′H_2), 2.56–2.63 (m, 4H, piperazine 2CH_2), 3.08–3.04 (4H, piperazine 2CH_2), 4.13 (t, $J = 7.2$ Hz, 2H, C-1′H_2), 6.75–6.96 (cluster, 4H, C-4″H, C-6″H, C-3″H, C-5″H), 7.67 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H, C-9H), 7.90 (ddd, $J = 8.4, 7.0, 1.5$ Hz, 1H, C-8H), 8.19 (d, $J = 8.3$ Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.82 (dd, $J = 8.2, 1.0$ Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.20, 152.13, 151.39, 150.87, 149.87, 148.99, 132.57, 132.13, 131.06, 129.55, 127.61, 126.58, 124.41, 123.66, 123.15, 118.98, 113.12, 58.07, 53.95, 51.84, 47.46, 27.70, 24.21, 18.12 ppm. **43** · 2HCl · H_2O: Anal. ($C_{26}H_{29}N_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.35. 3-(4-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}butyl)pyrimido[5,4-c]quinolin-4(3H)-one (**44**).* Yield: 55%, m.p. 194.3–195.2 °C; IR (KBr, cm^{-1}) ν: 1682 (C=O), 1613–1560 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.59–1.72 (m, 2H, C-2′H_2). 1.86–1.97 (m, 2H, C-3′H_2), 2.47 (t, $J = 7.3$ Hz, 2H, C-4′H_2), 2.55–2.63 (m, 4H, piperazine 2CH_2), 3.17–3.28 (4H, piperazine 2CH_2), 4.14 (t, $J = 7.3$ Hz, 2H, C-1′H_2), 7.00–7.12 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.33 (t, $J = 8.3$ Hz, 1H, C-5″H), 7.69–7.76 (m, 1H, C-9H), 7.87–7.94 (m, 1H, C-8H), 8.20 (d, $J = 8.4$ Hz, 1H, C-7H), 8.39 (s, 1H, C-2H), 8.83 (dd, $J = 8.2, 1.3$ Hz, 1H, C-10H), 9.66 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.27, 152.17, 151.32, 150.84, 149.92, 149.02, 132.20, 131.40 (131.61, 131.19 $J_{C-F} = 31.5$ Hz), 129.62, 129.59, 127.68, 124.39 (126.19, 122.59 $J_{C-F} = 272.0$ Hz), 124.43, 123.68, 118.72, 115.88 (115.91, 115.85 $J_{C-F} = 4.0$ Hz), 113.12, 112.18 (112.20, 112.15 $J_{C-F} = 4.0$ Hz), 57.90, 53.24, 48.82, 47.45, 27.68, 24.19 ppm. **44** · HCl · $1.25H_2O$: Anal. ($C_{26}H_{26}F_3N_5O$ · HCl · $1.25H_2O$) C, H, N.

*7.1.2.36. 3-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]pyrimido[5,4-c]quinolin-4(3H)-one (**45**).* Yield: 59%, m.p. 184.5–185.6 °C; IR (KBr, cm^{-1}) ν: 1695 (C=O), 1588–1490 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.57–1.76 (m, 2H, C-2′H_2). 1.85–1.99 (m, 2H, C-3′H_2), 2.33–2.61 (cluster, 2H, C-4′H_2 + 4H, piperazine 2CH_2), 3.78–3.87 (4H, piperazine 2CH_2), 4.14 (t, $J = 7.2$ Hz, 2H, C-1′H_2), 6.47 (t, $J = 4.7$, 1H, C-6″H), 7.72 (ddd, $J = 8.3, 5.1, 1.2$ Hz, 1H, C-9H), 7.90 (ddd, $J = 8.4, 5.1, 1.5$ Hz, 1H, C-8H), 8.19 (d, $J = 8.3$ Hz, 1H, C-7H), 8.30 (d, $J = 4.7$, 2H, C-3″H, C-5″H), 8.40 (s, 1H, C-2H), 8.82 (d, $J = 8.2$ Hz, 1H, C-10H), 9.65 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 161.57, 160.23, 157.69, 152.15, 150.84, 149.88, 148.99, 132.16, 129.59, 127.64, 124.42, 123.66, 113.11, 109.97, 58.07, 53.32, 45.85, 43.79, 27.67, 24.15 ppm. **45** · 2HCl · $2.5H_2O$: Anal. ($C_{23}H_{25}N_7O$ · 2HCl · $2.5H_2O$) C, H, N.

*7.1.2.37. 3-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**46**).* Yield: 59%, m.p. 183.2–184.1 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1602–1497 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.62 (s, 3H, CH_3), 2.71–2.77 (m, 4H, piperazine $2CH_2$), 2.83 (t, J = 5.7 Hz, 2H, C-2′H_2), 3.03–3.11 (m, 4H, piperazine $2CH_2$), 3.85 (s, 3H, OCH_3), 4.19 (t, J = 5.7 Hz, 2H, C-1′H_2), 6.82–7.03 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.54 (dd, J = 8.4, 1.5 Hz, 1H, C-9H), 7.96 (s, 1H, C-7H), 8.40 (s, 1H, C-2H), 8.70 (d, J = 8.4, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.30, 152.18, 152.11, 151.52, 150.15, 149.10, 142.88, 141.04, 129.58, 128.87, 124.15, 123.09, 121.52, 121.00, 118.26, 112.56, 111.24, 56.61, 55.53, 53.70, 50.78, 43.97, 22.28 ppm. 46 · 2HCl · 0.5H_2O: Anal ($C_{25}H_{27}N_5O_2$ · 2HCl · 0.5H_2O) C, H, N.

*7.1.2.38. 3-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**47**).* Yield: 57%, m.p. 167.2–168.3 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1601–1500 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.64 (s, 3H, CH_3), 2.71–2.80 (m, 4H, piperazine $2CH_2$), 2.86 (t, J = 5.7 Hz, 2H, C-2′H_2), 3.05–3.14 (m, 4H, piperazine $2CH_2$), 3.87 (s, 3H, OCH_3), 4.23 (t, J = 5.7 Hz, 2H, C-1′H_2), 6.81–7.08 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.73 (dd, J = 8.5, 1.7 Hz 1H, C-8H), 8.10 (d, J = 8.5 Hz 1H, C-7H), 8.44 (s, 1H, C-2H), 8.63 (s, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.36, 152.19, 151.74, 151.31, 148.45, 147.97, 140.73, 137.84, 134.15, 129.29, 123.54, 123.49, 123.33, 121.06, 118.37, 113.04, 111.29, 56.38, 55.58, 53.68, 50.40, 43.78, 22.05 ppm. 47 · 2HCl · H_2O: Anal. ($C_{25}H_{27}N_5O_2$ · 2HCl · H_2O) C, H, N.

*7.1.2.39. 3-{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**48**).* Yield: 61%, m.p. 203.7–204.2 °C; IR (KBr, cm^{-1}) ν: 1675 (C=O), 1597–1508 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H:2.61 (s, 3H, CH_3), 2.66–2.72 (m, 4H, piperazine $2CH_2$), 2.80 (t, J = 5.5 Hz, 2H, C-2′H_2), 3.03–3.10 (m, 4H, piperazine $2CH_2$), 3.75 (s, 3H, OCH_3), 4.17 (t, J = 5.5 Hz, 2H, C-1′H_2), 6.76–6.91 (cluster, 4H, C-2″H, C-2″H, C-5″H, C-6″H), 7.53 (dd, J = 8.4, 1.5 Hz, 1H, C-9H), 7.95 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.68 (d, J = 8.4 Hz, 1H, C-10H), 9.60 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.32, 153.86, 152.12, 151.48, 150.16, 149.09, 145.46, 142.17, 129.63, 128.87, 124.17, 121.52, 118.30, 114.47, 112.55, 56.49, 55.73, 53.58, 50.80, 44.04, 22.30 ppm. 48 · 2HCl · 2.25H_2O: Anal. ($C_{25}H_{27}N_5O_2$ · 2HCl · 2.25H_2O) C, H, N.

*7.1.2.40. 3-{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**49**).* Yield: 67%, m.p. 179.2–179.9 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1598–1511 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.60 (s, 3H, CH_3), 2.71–2.85 (m, 4H, piperazine $2CH_2$), 2.90 (t, J = 5.5 Hz, 2H, C-2′H_2), 3.08–3.17 (m, 4H, piperazine $2CH_2$), 3.75 (s, 3H, OCH_3), 4.25 (t, J = 5.5 Hz, 2H, C-1′H_2), 6.73–6.93 (cluster, 4H, C-2″H, C-2″H, C-5″H, C-6″H), 7.69 (dd, J = 8.5, 1.9 Hz 1H, C-8H), 8.05 (d, J = 8.5 Hz 1H, C-7H), 8.42 (s, 1H, C-2H), 8.56 (s, 1H, C-10H), 9.56 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.31, 154.09, 151.70, 151.24, 148.41, 147.91, 145.08, 137.82, 134.13, 129.25, 123.50, 123.46, 118.49, 114.50, 113.00, 56.25, 55.71, 53.46, 50.60, 43.85, 22.02 ppm. 49 · 2HCl · 3H_2O: Anal ($C_{25}H_{27}N_5O_2$ · 2HCl · 3H_2O) C, H, N.

*7.1.2.41. 3-(2-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**50**).* Yield: 60%, m.p. 183.3–184.5 °C; IR (KBr, cm^{-1}) ν: 1672 (C=O), 1598–1497 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.62 (s, 3H, CH_3), 2.65–2.75 (m, 4H, piperazine $2CH_2$), 2.83 (t, J = 5.7 Hz, 2H, C-2′H_2), 3.17–3.27 (m, 4H, piperazine $2CH_2$), 4.20 (t, J = 5.7 Hz, 2H, C-1′H_2), 6.99–7.13 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.33 (t, J = 7.9 Hz, 1H, C-5″H), 7.54 (dd, J = 8.4, 1.5 Hz, 1H, C-9H), 7.97 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.69 (d, J = 8.4 Hz, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.36, 152.16, 151.39, 151.24, 150.24, 149.09, 143.03, 131.47 (131.68, 131.26 J_{C-F} = 31.7 Hz), 129.69, 129.63, 128.92, 124.37 (126.17, 122.57 J_{C-F} = 272.0 Hz), 124.21, 121.55, 118.94, 116.13 (116.16, 116.11 J_{C-F} = 3.7 Hz), 112.57, 112.32 (112.35, 112.29 J_{C-F} = 4.0 Hz), 56.46, 53.29, 48.93, 44.14, 22.31 ppm. 50 · 2HCl · H_2O: Anal. ($C_{25}H_{24}F_3N_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.42. 3-(2-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**51**).* Yield: 56%, m.p. 187.3–187.7 °C; IR (KBr, cm^{-1}) ν: 1677 (C=O), 1600–1559 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.52 (s, 3H, CH_3), 2.69–2.77 (m, 4H, piperazine $2CH_2$), 2.81 (t, J = 5.7 Hz, 2H, C-2′H_2), 3.10–3.26 (m, 4H, piperazine $2CH_2$), 4.16 (t, J = 5.7 Hz, 2H, C-1′H_2), 6.90–7.03 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.24 (t, J = 7.8 Hz, 1H, C-5″H), 7.62 (dd, J = 8.5, 1.8 Hz, 1H, C-8H), 7.98 (d, J = 8.5 Hz, 1H, C-7H), 8.33 (s, 1H, C-2H), 8.48 (s, 1H, C-10H), 9.49 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.34, 151.76, 151.22, 151.07, 148.40, 147.92, 137.93, 134.23, 131.45 (131.66, 131.24 J_{C-F} = 31.7 Hz), 129.66, 129.26, 124.32 (126.12, 122.52 J_{C-F} = 272.0 Hz), 123.51, 123.58, 119.04, 116.04, 113.02, 112.42 (112.45, 112.40 J_{C-F} = 3.7 Hz), 56.25, 53.21, 48.74, 43.98, 22.05 ppm. 51 · 2HCl · 0.5H_2O: Anal. ($C_{25}H_{24}F_3N_5O$ · 2HCl · 0.5H_2O) C, H, N.

*7.1.2.43. 3-[3-(4-Phenylpiperazin-1-yl)propyl]-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**52**).* Yield: 72%, m.p. 161.1–161.8 °C; IR (KBr, cm^{-1}) ν: 1679 (C=O), 1620–1501 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.04–2.12 (m, 2H, C-2′H_2), 2.46 (t, J = 6.5 Hz, 2H, C-3′H_2), 2-57-2.62 (cluster, 4H, piperazine $2CH_2$, 3H, CH_3), 3.14–3.19 (4H, piperazine $2CH_2$), 4.18 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.83–6.91 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.22–7.28 (cluster, 2H, C-3″H, C-5″H), 7.53 (dd, J = 8.5, 1.6 Hz, 1H, C-9H), 7.96 (s, 1H, C-7H), 8.44 (s, 1H, C-2H), 8.68 (d, J = 8.5 Hz, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.39, 152.04, 151.49, 151.16, 150.12, 148.97, 142.83, 129.55, 129.10, 128.85, 124.12, 121.47, 119.79, 116.09, 112.59, 54.40, 53.08, 49.34, 45.66, 25.27, 22.24 ppm. 52 · 2HCl · 2.5H_2O: Anal. ($C_{25}H_{27}N_5O$ · 2HCl · 2.5H_2O) C, H, N.

*7.1.2.44. 3-[3-(4-Phenylpiperazin-1-yl)propyl]-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**53**).* Yield: 71%, m.p. 154.3–154.9 °C; IR (KBr, cm^{-1}) ν: 1685 (C=O), 1600–1505 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H:2.05–2.14 (m, 2H, C-2′H_2), 2.47 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.58–2.62 (cluster, 4H, piperazine $2CH_2$, 3H, CH_3), 3.17–3.20 (4H, piperazine $2CH_2$), 4.21 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.83–6.92 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.22–7.29 (cluster, 2H, C-3″H, C-5″H), 7.71 (dd, J = 8.5, 1.8 Hz, 1H, C-8H), 8.09 (d, J = 8.5 Hz, 1H, C-7H), 8.47 (s, 1H, C-2H), 8.59 (s, 1H, C-10H), 9.59 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.40, 151.67, 151.36, 151.15, 148.39, 147.93, 137.79, 134.07, 129.26, 129.11, 123.51, 123.40, 119.85, 116.13, 113.13, 54.38, 53.08, 49.34, 45.71, 25.20, 22.01 ppm. 53 · 2HCl · H_2O: Anal. ($C_{25}H_{27}N_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.45. 3-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**54**).* Yield: 58%, m.p. 149.3–150.3 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1596–1487 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.04–2.15 (m, 2H, C-2′H_2), 2.48 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.55–2.60 (m, 4H, piperazine $2CH_2$), 2.64 (s, 3H, CH_3), 3.12–3.20 (4H, piperazine $2CH_2$), 4.21 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.69–6.86 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.56 (t, J = 8.1 Hz, 1H, C-5″H), 7.56 (d, J = 8.5 Hz, 1H, C-9H), 7.98 (s, 1H, C-7H), 8.46 (s, 1H, C-2H), 8.71 (d, J = 8.5, 1H, C-10H), 9.63 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.46, 152.10, 152.05, 151.43, 150.15, 148.95, 142.99, 134.96, 130.09, 129.68, 128.87, 124.13, 121.48, 119.61, 115.94, 114.09, 112.59, 54.52, 52.84, 48.67, 45.69, 25.21, 22.28 ppm. 54 · 2HCl · 1.5H_2O: Anal. ($C_{25}H_{26}ClN_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.46. 3-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**55**).* Yield: 61%, m.p. 155.3–155.9 °C; IR (KBr, cm^{-1}) ν: 1678 (C=O), 1595–1554 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.05–2.16 (m, 2H, C-2′H_2), 2.53 (s, 3H, CH_3), 2.57 (t, J = 6.6 Hz, 2H, C-3′H_2), 2.62–2.70 (m, 4H, piperazine 2CH_2), 3.13–3.23 (4H, piperazine 2CH_2), 4.15 (t, J = 6.6 Hz, 2H, C-1′H_2), 6.62–6.87 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.07 (t, J = 8.1 Hz, 1H, C-5″H), 7.62 (dd, J = 8.5, 1.9 Hz, 1H, C-8H), 7.97 (d, J = 8.5 Hz, 1H, C-7H), 8.43 (s, 1H, C-2H), 8.47 (s, 1H, C-10H), 9.47 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.49, 151.82, 151.69, 151.23, 148.39, 147.84, 137.92, 134.99, 134.20, 130.15, 129.26, 123.46, 123.41, 119.87, 116.08, 114.21, 113.06, 54.48, 52.76, 48.41, 45.58, 25.02, 22.07 ppm. 55 · 2HCl · 1.25H_2O: Anal. ($C_{25}H_{26}ClN_5O$ · 2HCl · 1.25H_2O) C, H, N.

*7.1.2.47. 3-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-8-methylpyrimido[5,4-c]-quinolin-4(3H)-one (**56**).* Yield: 59%, m.p. 152.9–153.5 °C; IR (KBr, cm^{-1}) ν: 1677 (C=O), 1603–1499 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.01–2.15 (m, 2H, C-2′H_2), 2.48 (t, J = 6.3 Hz, 2H, C-3′H_2), 2.62–2.76 (cluster, 4H, piperazine 2CH_2 + 3H, CH_3), 2.94–3.16 (4H, piperazine 2CH_2), 3.84 (s, 3H, OCH_3), 4.19 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.81–7.06 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.53 (d, J = 8.5 Hz, 1H, C-9H), 7.96 (s, 1H, C-7H), 8.47 (s, 1H, C-2H), 8.68 (d, J = 8.5 Hz, 1H, C-10H), 9.61 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.40, 152.19, 152.06, 151.61, 150.08, 148.99, 142.83, 141.12, 129.56, 128.82, 124.10, 122.99, 121.48, 120.96, 118.17, 112.61, 111.18, 55.49, 54.47, 53.28, 50.81, 45,74, 25.20, 22.25 ppm. 56 · 2HCl · H_2O: Anal. ($C_{26}H_{29}N_5O_2$ · 2HCl · H_2O) C, H, N.

*7.1.2.48. 3-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-9-methylpyrimido[5,4-c]-quinolin-4(3H)-one (**57**).* Yield: 63%, m.p. 152.7–153.5 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1607–1501 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.10–2.19 (m, 2H, C-2′H_2), 2.53 (t, J = 6.5 Hz, 2H, C-3′H_2), 2.62 (s, 3H, CH_3), 2.72–2.81 (m, 4H, piperazine 2CH_2), 3.06–3.11 (4H, piperazine 2CH_2), 3.85 (s, 3H, OCH_3), 4.22 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.82–7.02 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.70 (dd, J = 8.5, 1.9 Hz, 1H, C-8H), 8.05 (d, J = 8.5 Hz, 1H, C-7H), 8.50 (s, 1H, C-2H), 8.57 (s, 1H, C-10H), 9.57 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.47, 152.19, 151.71, 151.38, 148.42, 147.93, 140.83, 137.82, 134.11, 129.29, 123.52, 123.43, 123.24, 121.02, 118.29, 113.12, 11.22, 55.53, 54.49, 53.25, 50.41, 45.67, 25.02, 22.04 ppm. 57 · 2HCl · 4H_2O: Anal. ($C_{26}H_{29}N_5O_2$ · 2HCl · 4H_2O) C,H, N.

*7.1.2.49. 3-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**58**).* Yield: 54%, m.p. 146.3–147.7 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1601–1509 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.01–2.08 (m, 2H, C-2′H_2), 2.42 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.51–2.54 (cluster, 3H, CH_3, 4H, piperazine 2CH_2), 2.99–3.05 (4H, piperazine 2CH_2), 4.11 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.70–6.93 (cluster, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.44 (dd, J = 8.5, 1.6 Hz, 1H, C-9H), 7.87 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.60 (d, J = 8.5 Hz, 1H, C-10H), 9.523 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.45, 157.21 (158.79, 155.63 J_{C-F} = 238.5 Hz), 152.17, 151.49, 150.15, 148.99, 147.78, 142.95, 129.64, 128.87, 124.12, 121.49, 117.95 (118.00, 117.90 J_{C-F} = 7.7 Hz), 115.76 (115.83, 115.70 J_{C-F} = 22.0 Hz), 112.62, 54.47, 53.07, 50.29, 45.74, 25.23, 22.26 ppm. 58 · 2HCl · 2H_2O: Anal. ($C_{25}H_{26}FN_5O$ · 2HCl · 2H_2O) C, H, N.

*7.1.2.50. 3-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**59**).* Yield: 59%, m.p. 153.5–154.6 °C; IR (KBr, cm^{-1}) ν: 1680 (C=O), 1601–1508 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 2.01–2.08 (m, 2H, C-2′H_2), 2.43 (t, J = 6.4 Hz, 2H, C-3′H_2), 2.52–2.56 (cluster, 3H, CH_3, 4H, piperazine 2CH_2), 2.99–3.04 (4H, piperazine 2CH_2), 4.11 (t, J = 6.5 Hz, 2H, C-1′H_2), 6.71–6.89 (cluster, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.62 (dd, J = 8.5, 1.9 Hz, 1H, C-8H), 7.97 (d, J = 8.5 Hz, 1H, C-7H), 8.38 (s, 1H, C-2H), 8.47 (s, 1H, C-10H), 9.47 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.45, 157.23 (158.81, 155.65 J_{C-F} = 238.5 Hz), 151.69, 151.34, 148.41, 147.92, 147.73, 137.85, 134.13, 129.29, 123.49, 123.40, 117.99 (118.04, 117.94 J_{C-F} = 7.4 Hz), 115.57 (115.72, 115.43 J_{C-F} = 22.0 Hz), 113.13, 54.41, 53.04, 50.23, 45.72, 25.11, 22.04 ppm. 59 · 2HCl · 1.5H_2O: Anal. ($C_{25}H_{26}FN_5O$ · 2HCl · 1.5H_2O) C, H, N.

*7.1.2.51. 3-{4-[4-(3-Chlorophenylpiperazin-1-yl)butyl]-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**60**).* Yield: 57%, m.p. 154.9–156.0 °C; IR (KBr, cm^{-1}) ν: 1690 (C=O), 1599–1555 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.57–1.72 (m, 2H, C-2′H_2), 1.83–1.98 (m, 2H, C-3′H_2), 2.48 (t, J = 7.5 Hz, 2H, C-4′H_2), 2.62 (s, 3H, CH_3), 2.53–2.65 (m, 4H, piperazine 2CH_2), 3.04–3.21 (m, 4H, piperazine 2CH_2), 4.14 (t, J = 7.5 Hz, 2H, C-1′H_2), 6.71–6.83 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.18 (t, J = 8.2 Hz, 1H, C-5″H), 7.56 (dd, J = 8.5, 1.6 Hz, 1H, C-9H), 7.94 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.65 (d, J = 8.5 Hz, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.36, 152.16, 152.05, 151.37, 150.05, 148.87, 142.76, 134.93, 130.11, 129.71, 128.89, 124.12, 121.48, 119.57, 115.84, 114.13, 112.49, 57.91, 53.24, 50.28, 47.40, 27.69, 24.21, 22.28 ppm. 60 · 2HCl · 1.25H_2O: Anal. ($C_{26}H_{28}ClN_5O$ · 2HCl · 1.25H_2O) C, H, N.

*7.1.2.52. 3-{4-[4-(3-Chlorophenylpiperazin-1-yl)butyl]-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**61**).* Yield: 71%, m.p. 196.1–196.73 °C; IR (KBr, cm^{-1}) ν: 1674 (C=O), 1597–1554 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H:1.55–1.72 (m, 2H, C-2′H_2). 1.82–1.97 (m, 2H, C-3′H_2), 2.45 (t, J = 7.2 Hz, 2H, C-4′H_2), 2.53–2.58 (m, 4H, piperazine 2CH_2), 2.62 (s, 3H, CH_3), 3.10–3.22 (4H, piperazine 2CH_2), 4.12 (t, J = 7.2 Hz, 2H, C-1′H_2), 6.68–6.89 (cluster, 3H, C-2″H, C-4″H, C-6″H), 7.14 (t, J = 8.1 Hz, 1H, C-5″H), 7.71 (d, J = 8.5 Hz, 1H, C-9H), 8.08 (d, J = 8.5 Hz, 1H, C-7H), 8.36 (s, 1H, C-2H), 8.57 (s, 1H, C-10H), 9.58 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 152.25, 151.61, 150.55, 148.43, 147.99, 137.90, 134.92, 134.17, 130.05, 129.31, 123.49, 123.37, 119.30, 115.74, 113.89, 113.13, 57.91, 53.24, 48.80, 47.40, 27.66, 24.18, 22.07 ppm. 61 · 2HCl · 1.25H_2O: Anal. ($C_{26}H_{28}ClN_5O$ · 2HCl · 1.25H_2O) C, H, N.

*7.1.2.53. 3-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-8-methylpyrimido[5,4-c]quinolin-4(3H)-one (**62**).* Yield: 83%, m.p. 144.9–145.7 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1601–1498 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.59–1.73 (m, 2H, C-2′H_2). 1.85–1.98 (m, 2H, C-3′H_2), 2.51 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.63 (s, 3H, CH_3), 2.65–2.68 (m, 4H, piperazine 2CH_2), 3.04–3.17 (4H, piperazine 2CH_2), 3.85 (s, 3H, OCH_3), 4.13 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.82–7.06 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.56 (d, J = 8.4 Hz, 1H, C-9H), 7.98 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.70 (d, J = 8.4 Hz, 1H, C-10H), 9.62 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 152.20, 152.01, 150.74, 150.14, 149.05, 142.96, 141.12, 129.67, 128.87, 124.04, 123.04, 121.46, 121.00, 118.25, 112.59, 111.18, 58.01, 55.50, 53.60, 50.65, 47.38, 27.68, 24.06, 22.26 ppm. 62· fumarate · 2H_2O: Anal. ($C_{27}H_{31}N_5O_2$ · fumarate · 2H_2O) C, H, N.

*7.1.2.54. 3-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-9-methylpyrimido[5,4-c]quinolin-4(3H)-one (**63**).* Yield: 84%, m.p. 159.2–160.4 °C; IR (KBr, cm^{-1}) ν: 1684 (C=O), 1601–1499 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.56–1.74 (m, 2H, C-2′H_2). 1.83–1.98 (m, 2H, C-3′H_2), 2.48 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.57–2.73 (cluster, 4H, piperazine 2CH_2 + 3H, CH_3), 2.98–3.18 (4H, piperazine 2CH_2), 3.85 (s, 3H, OCH_3), 4.13 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.80–7.04 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.71 (d, J = 8.5 Hz, 1H, C-9H), 8.08 (d, J = 8.5 Hz, 1H, C-7H), 8.36 (s, 1H, C-2H), 8.58 (s, 1H, C-10H), 9.59 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.24, 152.19, 151.58, 150.56,

148.39, 147.98, 141.21, 137.82, 134.10, 129.27, 123.46, 123.35, 122.95, 120.98, 118.19, 113.12, 111.14, 58.05, 55.49, 53.64, 50.79, 47.45, 27.68, 24.19, 22.04 ppm. 63 · 2HCl · $3H_2O$: Anal. ($C_{27}H_{31}N_5O_2$ · 2HCl · $3H_2O$) C, H, N.

*7.1.2.55. 3-{4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl}-8-methyl-pyrimido[5,4-c]quinolin-4(3H)-one (**64**).* Yield: 66%, m.p. 174.6–175.8 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1600–1501 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.74 (m, 2H, C-2′H_2). 1.85–2.00 (m, 2H, C-3′H_2), 2.47 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.56–2.65 (cluster, 4H, piperazine 2CH_2 + 3H, CH_3), 3.04–3.14 (4H, piperazine 2CH_2), 4.12 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.85–7.09 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.54 (dd, J = 8.4, 1.6 Hz, 1H, C-9H), 7.96 (s, 1H, C-7H), 8.37 (s, 1H, C-2H), 8.68 (d, J = 8.4 Hz, 1H, C-10H), 9.61 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 155.69 (157.32, 154.07 J_{C-F} = 245.3 Hz), 152.01, 150.76, 150.15, 149.06, 142.97, 140.08 (140.14, 140.03 J_{C-F} = 8.3 Hz), 129.68, 128.89, 124.51 (124.53, 124.48 J_{C-F} = 3.7 Hz), 124.09, 122.49 (122.54, 122.44 J_{C-F} = 7.7 Hz), 121.47, 118.95 (118.97, 118.93 J_{C-F} = 2.9 Hz), 116.14 (116.28, 116.00 J_{C-F} = 20.6 Hz), 112.61, 57.99, 53.49, 50.71, 47.41, 27.69, 24.19, 22.28 ppm. 64 · 2HCl · H_2O: Anal. ($C_{26}H_{28}FN_5O$ · 2HCl · H_2O) C, H, N.

*7.1.2.56. 3-{4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl}-9-methyl-pyrimido[5,4-c]quinolin-4(3H)-one (**65**).* Yield: 64%, m.p. 160.7–161.6 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1600–1500 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.58–1.71 (m, 2H, C-2′H_2). 1.87–1.97 (m, 2H, C-3′H_2), 2.48 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.56–2.68 (cluster, 4H, piperazine 2CH_2 + 3H, CH_3), 3.04–3.14 (4H, piperazine 2CH_2), 4.13 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.86–7.01 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.71 (d, J = 8.5 Hz, 1H, C-9H), 8.08 (d, J = 8.5 Hz, 1H, C-7H), 8.36 (s, 1H, C-2H), 8.58 (s, 1H, C-10H), 9.58 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.26, 155.66 (157.29, 154.04 J_{C-F} = 245.3 Hz), 151.59, 150.57, 148.39, 147.98, 140.06 (140.12, 140.01 J_{C-F} = 8.6 Hz), 137.86, 134.13, 129.27, 124.49 (124.51, 124.47 J_{C-F} = 3.4 Hz), 123.48, 123.37, 122.48 (122.53, 122.43 J_{C-F} = 7.7 Hz), 118.93 (118.95, 118.91 J_{C-F} = 2.9 Hz), 116.12 (116.26, 115.98 J_{C-F} = 20.9 Hz), 113.13, 57.91, 53.47, 50.701, 47.43, 27.65, 24.17, 22.04 ppm. 65 · 2HCl · $2H_2O$: Anal. ($C_{26}H_{28}FN_5O$ · 2HCl · $2H_2O$) C, H, N.

*7.1.2.57. 3-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-8-methyl-pyrimido[5,4-c]quinolin-4(3H)-one (**66**).* Yield: 71%, m.p. 199.6–200.1 °C; IR (KBr, cm^{-1}) ν: 1672 (C=O), 1600–1506 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.55–1.70 (m, 2H, C-2′H_2). 1.85–1.97 (m, 2H, C-3′H_2), 2.46 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.53–2.67 (m, 4H, piperazine 2CH_2), 2.60 (s, 3H, CH_3), 3.04–3.14 (4H, piperazine 2CH_2), 4.12 (t, J = 7.2 Hz, 2H, C-1′H_2), 6.78–7.02 (cluster, 4H, C-2″H, C-3″H, C-5″H, C-6″H), 7.54 (dd, J = 8.5, 1.7 Hz, 1H, C-9H), 7.96 (s, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.68 (d, J = 8.4 Hz, 1H, C-10H), 9.61 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.28, 157.12 (158.70, 155.54 J_{C-F} = 238.2 Hz), 152.01, 150.73, 150.16, 149.05, 147. 94, 142.98, 129.69, 128.89, 124.09, 121.46, 117.84 (117.87, 117.77 J_{C-F} = 7.4 Hz), 115.55 (115.69, 115.40 J_{C-F} = 22.0 Hz), 112.60, 57.93, 53.44, 50.31, 47.37, 27.69, 24.20, 22.28 ppm. 66 · HCl · H_2O: Anal. ($C_{26}H_{28}FN_5O$···HCl · H_2O) C, H, N.

*7.1.2.58. 3-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-9-methyl-pyrimido[5,4-c]quinolin-4(3H)-one (**67**).* Yield: 77%, m.p. 175.2–175.8 °C; IR (KBr, cm^{-1}) ν: 1686 (C=O), 1597–1508 (C=N, C=C); ^{1}H NMR ($CDCl_3$) δ_H: 1.53–1.69 (m, 2H, C-2′H_2). 1.82–1.97 (m, 2H, C-3′H_2), 2.45 (t, J = 7.3 Hz, 2H, C-4′H_2), 2.53–2.65 (cluster, 4H, piperazine 2CH_2 + 3H, CH_3), 3.02–3.14 (4H, piperazine 2CH_2), 4.12 (t, J = 7.3 Hz, 2H, C-1′H_2), 6.75–7.01 (cluster, 4H, C-3″H, C-4″H, C-5″H, C-6″H), 7.71 (dd, J = 8.5, 1.7 Hz, 1H, C-9H), 8.07 (d, J = 8.5 Hz, 1H, C-7H), 8.35 (s, 1H, C-2H), 8.56 (s, 1H, C-10H), 9.58 (s, 1H, C-5H) ppm. ^{13}C NMR ($CDCl_3$) δ_C: 160.24, 157.08 (158.66, 155.50 J_{C-F} = 238.2 Hz), 151.57, 150.53, 148.40, 147.96, 147.92, 137.85, 134.12, 129.27, 123.46, 123.35, 117.78 (117.83, 117.73 J_{C-F} = 7.7 Hz), 115.51 (115.66, 115.37 J_{C-F} = 22.0 Hz), 113.11, 57.89, 53.41, 50.28, 47.38, 27.64, 24.18, 22.03 ppm. 67 · HCl · H_2O: Anal. ($C_{26}H_{28}FN_5O$ · HCl · H_2O) C, H, N.

7.2. In vitro radioligand binding assays

Radioligand studies with native 5-HT_{1A} and 5-HT_{2A} receptors were conducted according to the methods previously described. Briefly, the following were used: for 5-HT_{1A} assays, rat hippocampal membranes, [^{3}H]-8-OH-DPAT (170 Ci/mmol, Perkin–Elmer), and 5-HT (10 μM) for non-specific binding; [^{3}H]-ketanserin (88.0 Ci/mmol, Perkin–Elmer) and methysergide (1 μM) for non-specific binding.

For 5-HT_7 binding assay, membranes from HEK-293 cells, stably expressing human 5-HT_{7b} receptor and [^{3}H]-5-CT (93.0 Ci/mmol, Hartmann) as radioligand were used [36].

In the screening procedure one compound concentrations at 1 μM was tested, whereas in full binding experiments 7–9 sample concentrations, each run in triplicate, were used to determine inhibition constant (K_i).

7.3. Molecular modeling

For each of selected molecules conformational analysis and docking were performed. Systematic Search module from Tripos SYBYL 8.0 suite was used for generating geometries. Step of 120° was set for each rotatable bond within spacer, VdW General = 0.5 and VdW 1–4 = 0.2.

For each so created conformer geometry optimization in vacuum and in solvent (COSMO algorithm) using OpenMopac 2007 was run [37,38]. For all calculations with OpenMopac PM6 Hamiltonian was used along with dielectric constant of 78 (keyword EPS = 78), number of geometric segments equal 60 (NSPA = 60) and Van der Waals radius of solvent 1 (RSOLV = 1 keyword) for COSMO computations.

Docking (using BioSolveIT FlexX 2.0.3) was set up with 100 5-HT1A receptor models with pharmacophore restraints on Asp3.32 and Phe6.52 as shown previously [39,40]. Results were scored using CScore module of SYBYL 8.0.

Authors' contributions

WL participated in the design of the study, preparing the manuscript, and carried out the synthesis of the compounds. WL was involved in the interpretation of spectral, analytical data and 2D NMR analysis of obtained compounds. AB took the lead on performing biological study, data interpretation and preparing the manuscript. MS, AO and MG participated in the structural investigations of selected compounds and writing the manuscript. SM contributed to conformational analysis and docking of selected molecules. AS acquired funding for the project and worked on the design of the study. All authors read and approved the final manuscript.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.04.060.

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