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Chemical puzzles in the search for new, flexible derivatives of lurasidone as antipsychotic drugs

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ABSTRACT

In the pharmacotherapy of schizophrenia, there is a lack of effective drugs, and currently used agents cause a large number of side effects. The D_2, 5-HT_{1A}, 5-HT_{2A} receptors are among the most important receptor targets in the treatment of schizophrenia, but antagonism at 5-HT_6 and 5-HT_7 receptors may bring about additional improvement of cognitive functions. However, doubt exists regarding the importance of 5-HT_7R in the pharmacotherapy. In 2010, lurasidone (with high affinity for D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 receptors) was approved for the treatment of schizophrenia. Due to the efficacy of the mentioned drug and doubts related to the role of 5-HT_7R, we decided to obtain compounds with an activity profile similar to that of lurasidone, but with the reduced affinity for 5-HT_7R and increased affinity for 5-HT_6R. For this purpose, we chose a flexible hexyl derivative of lurasidone (2-(6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione **1a**) as a *hit* structure. After molecular modeling, we modified it, in the area of the arylpiperazine and imide group, using the moieties found in other known CNS drugs. We received the compounds in accordance with the previously developed method of ecological synthesis in the microwave radiation field. Among the obtained compounds, *N*-(6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexyl)naphthalene-sulfonamides **1v** and **1w** were distinguished as multifunctional ligands showing increased affinity for 5-HT_6R, and 2-(6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3(2H)-one **1i** – a multifunctional ligand showing moderate affinity for 5-HT_6R and threefold lower for 5-HT_7R. In the paper, we discuss some of the observed dependencies regarding 5-HT_6/5-HT_7R affinity using molecular docking methods.

1. Introduction

Currently, there is still a lack of effective drugs in the pharmacotherapy of schizophrenia and the existing drugs have many side effects. The minimization of negative and cognitive symptoms seems to be a particularly difficult problem. Therefore, new drug candidates are still being sought, with a goal of achieving higher efficacy and minimized side effects.[1] The most important receptor targets in the treatment of schizophrenia include the dopamine D_2 receptors.[2] Some reports suggest that an effective antipsychotic drug should possess 5-HT_{2A} serotonin receptor antagonist profile in addition to the blockade of dopamine D_2R, due to the synergistic effect of the D_2/5-HT_{2A} antagonists.[3,4] In mitigating the symptoms of schizophrenia, the effect of partial 5-HT_{1A}R agonism is also beneficial, resulting in the reduction of aggressive behaviors and depressive states,[5] but also antagonism at 5-HT_6[6] and 5-HT_7 receptors,[7] because of improvement of cognitive functions and antidepressant effect. However, the existing studies on the role of 5-HT_7 receptors are contradictory and there is no clear evidence of their importance and the effectiveness of their ligands in the treatment of psychiatric conditions.[8] In search of antipsychotics, one of the leading strategies is to look for multifunctional ligands with high affinity for several receptor targets.[9] An example of a multifunctional antipsychotic drug is lurasidone, long chain arylpiperazine (LCAP) compound, introduced to the US market in 2010 (Fig.1). This drug is characterized by high affinity for D_2, D_3, 5-HT_{1A}, 5HT_{2A}, 5-HT_7 receptors.[10] In current studies, it has been shown that it is highly effective in the treatment of schizophrenia and certain types of depression, including bipolar depression. In addition, this drug does not cause a large number of side effects.[11]

There is no data on significant lurasidone binding with 5-HT_6R in the literature. Due to the efficacy of the lurasidone pharmacological profile in the treatment of schizophrenia and role of 5-HT_6R in relieving

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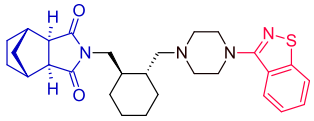


Fig. 1. The structure of lurasidone.

cognitive symptoms, it seems reasonable to search for ligands exhibiting a similar receptor profile as lurasidone, while simultaneously binding strongly with 5-HT$_6$R. Moreover, considering the ambiguities associated with the role of 5-HT$_7$R in the treatment of schizophrenia, it seems interesting to design a compound with a similar pharmacological profile as lurasidone, which does not bind to 5-HT$_7$R. This type of approach can help determine the role of the 5-HT$_7$R in the treatment of schizophrenia.

Previous research on derivatives of lurasidone described the influence of the used carbon linker on the affinity of the drug analogs for D$_2$/5-HT$_{2A}$R. Compounds having C3-C5 carbon chains were tested. It turned out that a butyl chain has optimal length of the alkyl chain, while its stiffening with the cyclohexyl ring increases the selectivity towards the D$_2$/5-HT$_{2A}$ receptors. A group of amide and imide derivatives of 3-(4-butylpiperazin-1-yl)-1,2-benzothiazole was also tested. The arylpiperazine and imide fragments were chosen because of their fitting for the D$_2$ receptor binding pocket and the binding inhibition (%) D$_2$/5-HT$_{2A}$.[12] On the basis of the reference literature and the structures of other antipsychotic drugs perospirone and ziprasidone[13] (Fig. 2), it can be concluded that the strong binding of these compounds toward many serotonin receptors (in particular 5-HT$_{2A}$R and 5-HT$_7$R) and the dopamine D$_2$R is influenced by the benzo[*d*]isothiazol-3-yl)piperazine group (red marked, Fig. 1).

Other studies have described the pharmacological profile of a large group of aryl sulfonamide LCAP derivatives, having a fragment of benzo[*d*]isothiazol-3-ylpiperazine (red marked, Fig.1) in the structure. These compounds were tested for binding toward the 5-HT$_{2A}$, 5-HT$_6$, 5-HT$_7$ and D$_2$ receptors.[14] Most compounds showed high affinity for all of the listed targets. However, none of the tested compounds showed high binding to the 5-HT$_{2A}$, 5-HT$_6$ and D$_2$ receptors in the absence of affinity for 5-HT$_7$R.[15] In consideration of the previous research findings, a good fit of the benzo[*d*]isothiazol-3-ylpiperazine moiety for the 5-HT$_6$R binding pocket was associated with high affinity to 5-HT$_6$R, however it was also related with strong binding toward 5-HT$_7$R.

To build on previous research, we chose a compound with moiety's derived from the lurasidone as a basic structure (*hit*), i.e. (3aR,4S,7R,7aS)-3a,7a-dimethylhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (blue marked, Fig.1) and 3-(piperazin-1-yl)-1,2-benzothiazole (red marked, Fig.1). Bearing in mind the interesting properties of LCAP with a hexyl carbon chain, in particular their high affinity for 5-HT$_{1A}$R, as previously published,[15–17] we decided to choose a hexyl chain as a linker. In our study, we focused on the search for ligands with a similar binding profile to lurasidone, however, with the increased affinity for 5-HT$_6$R and reduced affinity toward 5-HT$_7$R.

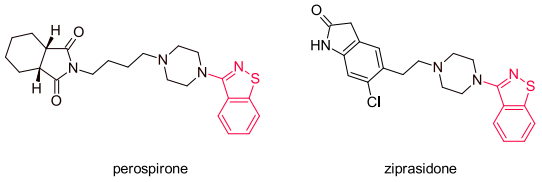


Fig. 2. The structure of perospirone and ziprasidone.

2. Results and discussion

The aim of the study was to synthesize lurasidone derivatives, showing the increased affinity for 5-HT$_6$R and reduced toward 5-HT$_7$R. The biological activity of the compounds (affinity for D$_2$, 5-HT$_{1A}$, 5-HT2$_A$, 5-HT$_6$, 5-HT$_7$ receptors) was determined in *in vitro* radioreceptor assays. In the context of the interesting properties of LCAP having hexyl carbon linker[15–17] as the *hit,* we chose the structure **1a** (3aR,4S,7R,7aS)-3a,7a-dimethylhexahydro-1H-4,7-methano-isoindole-1,3(2H)-dione (shown in Fig.3). As we showed in our previous publications, a change in the length of the carbon chain can lead to a change in the activity profile. This compound is a derivative of lurasidone with a flexible, elongated linker. We also planned modifications of the chosen *hit* **1a** structure, after molecular modeling, using structural fragments from other known drugs or drug candidates (trazodone, aripiprazole,[18] fliibanserin,[19] NAN-190,[20] fananserin[21]), and groups derived from them. The compounds were obtained according to the previously developed, universal method of microwave assisted synthesis, using phase transfer catalysts (PTC).[15–17,22,23]

The *hit* compound **1a** was obtained as a result of a two-step

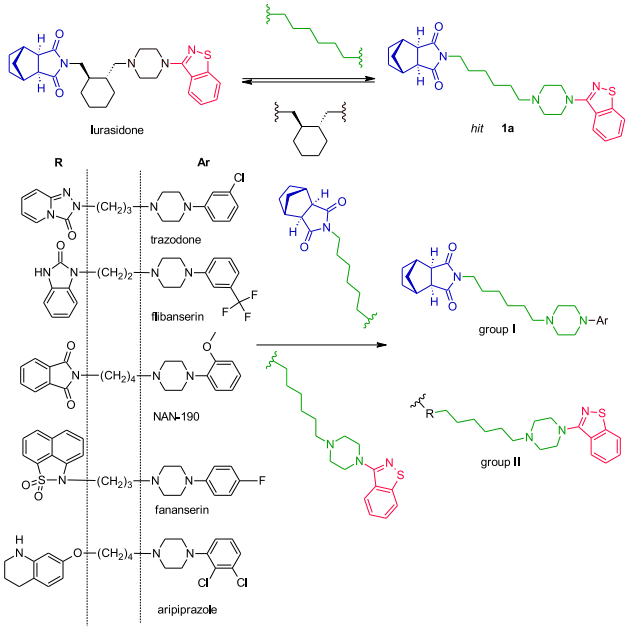
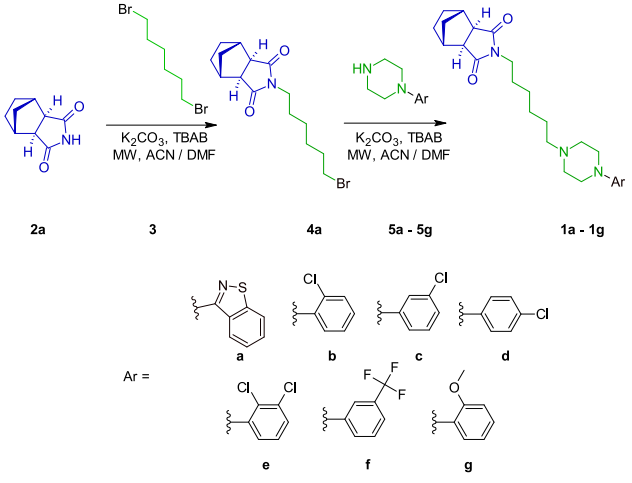


Fig. 3. Modification plan of the *hit* structure **1a**.



Scheme 1. Preparation of I group of compounds.

synthesis (scheme 1), including *N*-alkylation of (3aR,4S,7R,7aS)-3a,7a-dimethylhexahydro-1H-4,7-methanoisoindole-1,3(2H)dione (**2a**) by 1,6-dibromohexane (**3**). In the next step, the resulting intermediate (**4a**) was condensed with 3-(piperazin-1-yl)-1,2-benzothiazole (**5a**). The reactions were carried out in the presence of microwave radiation, using K_2CO_3 as a basic agent, tetra-*n*-butylammonium bromide (TBAB) as PTC, and a small amount of dimethylformamide (DMF).

The *hit* compound **1a** showed a similar activity profile compared to lurasidone (Table 1). The compound had a slightly lower affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors, with an increased affinity toward D_2R. The compound **1a** showed a relatively low affinity for the 5-HT_6R.

Molecular docking for D_2R (pdb ID: 6CM4), and homology models of 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 receptors (Fig. 4) and 5-HT_6R (Fig. 5) were performed to identify the binding mode of the compound **1a**. For all receptors, the presence of a salt bridge between the protonated basic nitrogen atom in the piperazine ring and the residues Asp3.32 were observed. The next interactions emerging in all cases were the π-π interactions between the 1,2-benzothiazole group and the Phe6.51 and Phe6.52 residues. The arrangement of this part of the ligand is very well suited to the size of the binding pocket and consistent with the data presented in the previous publication.[24]

Table 1
Affinity of lurasidone[10] and obtained derivatives (I group) for the tested receptors, K_i [nM]. Each compound was tested in triplicate at 8 different concentrations (10^{-4} to 10^{-11} M).

No.	Ar	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_6	5-HT_7
	lurasidone[10]	1.68 ± 0.09	6.75 ± 0.97	2.03 ± 0.46	–	0.5 ± 0.09
1a		1 ± 0.2	27 ± 4	4 ± 1	486 ± 86	9 ± 2
1b		35 ± 4	12 ± 2	541 ± 69	1641 ± 213	198 ± 29
1c		225 ± 38	18 ± 4	81 ± 5	1142 ± 136	39 ± 5
1d		370 ± 41	55 ± 7	73 ± 6	3028 ± 299	202 ± 31
1e		55 ± 7	32 ± 4	161 ± 22	536 ± 62	117 ± 9
1f		168 ± 17	22 ± 3	189 ± 23	2205 ± 251	53 ± 4
1g		41 ± 5	4 ± 1	785 ± 151	4874 ± 627	146 ± 18

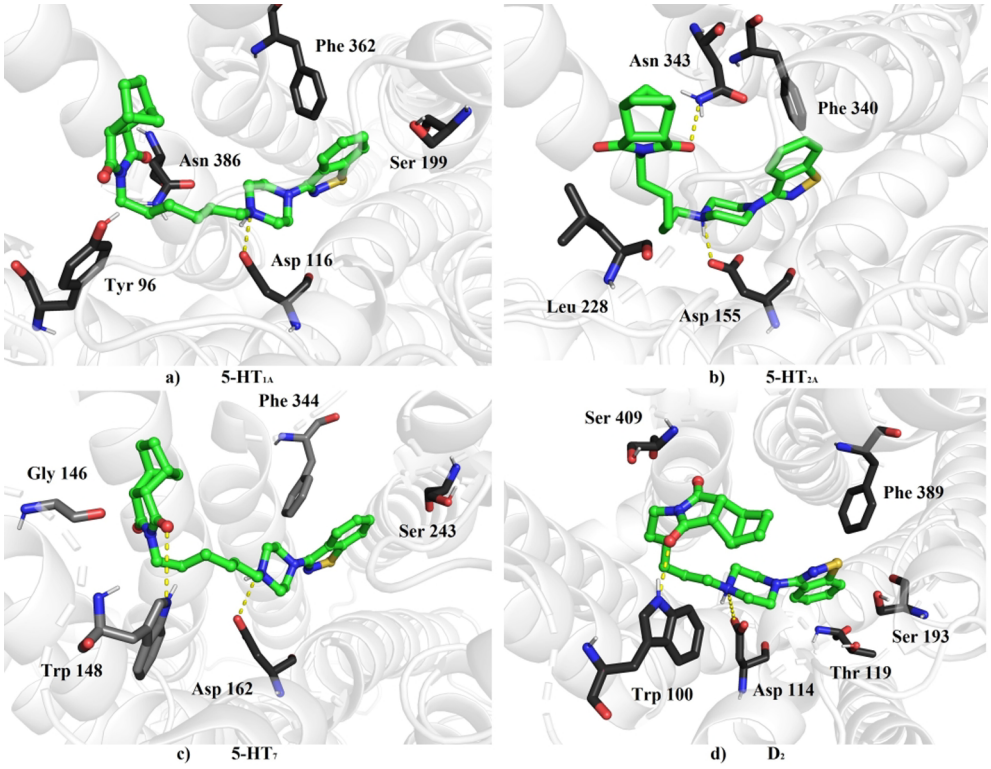


Fig. 4. Docking of **1a** to the receptors: (a) 5-HT_{1A}, (b) 5-HT_{2A}, (c) 5-HT_7, (d) D_2. The yellow lines indicate the hydrogen bonds. Nitrogen – blue, sulfur – yellow, oxygen – red, green – **1a**.

The differences appear in the bending of the alkyl chain and the terminal imide group. In the structure of lurasidone, a straight arrangement of the alkyl chain was described, where the imide group was directed towards helix 1 and 2. In *hit* **1a**, the bending of the imide group towards helix 6 and 7 was observed. Ligand **1a** had a slightly lower affinity for 5-HT_{1A}R than 5-HT_{2A}, 5-HT_7 and D_2 receptors. This can be explained by the occurrence of additional hydrogen bonds, in which imide carboxylic groups are involved (5-HT_{2A}, 5-HT_7, D_2 receptors).

In the case of the 5-HT_6R, **1a** binding mode was compared with lurasidone and a phthalimide analogue. Interestingly, in the case of compounds having no aromatic rings in the terminal part, a different conformation of the 1,2-benzothiazole groups were observed. Moreover, in the *hit* structure, there was a different bending of the imide moiety in the terminal part of the binding pocket (similar arrangement was noted for other *hit* analogues, without aromatic group in the terminal part, e.g. hexyl perospirone analog). Straight binding modes were observed for the compounds with shorter linkers, or aromatic imides in the terminal part. However, lurasidone (and other compounds with short linkers), showed repulsive interactions with Asn86 residue.

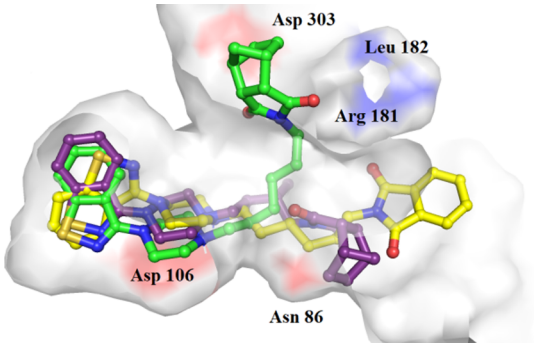


Fig. 5. Docking of **1a** (green), lurasidone (purple) and phthalimide analogue (yellow) to the receptor 5-HT_6. Nitrogen – blue, sulfur – yellow, oxygen – red. Receptor surface – blue represents a positive charge, red – negative charge.

Based on the conducted molecular modeling, it was found that the aromatic group in the terminal part may be used to increase the affinity of flexible, hexyl derivatives for 5-HT_6R. In the second part of the study, we decided to investigate two groups of hexyl lurasidone analogs. Structural modifications were performed as shown in Fig.3, using the compound **1a** as the base structure, whereas the fragments introduced in the modifications were derived from known LCAP compounds (trazodone, flibanserin, NAN-190, fananserin, aripiprazole) and from related moieties. In the first group, several analogs of the compound **1a** were obtained, with the selected arylpiperazine fragments. The common part is marked in blue. Modifications in the arylpiperazine moiety were introduced to assess whether the 1,2-benzothiazole group was crucial in the context of the multifunctionality of the hexyl derivatives of lurasidone.

The compounds **1b-g** were prepared according to the procedure analogous to the compound **1a**, including *N*-alkylation of (3aR,4S,7R,7aS)-3a,7a-dimethylhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**2a**) by 1,6-dibromohexane (**3**) and condensation of the resulting intermediate (**4a**) with the selected arylpiperazine (**5b-5 g**) in the presence of microwave radiation (Scheme 1).

In the first group, the compounds were distinguished by a markedly higher selectivity, as compared to the *hit* **1a**, in particular toward the 5-HT_{1A} receptors (Table 1). The compounds with a substituent on the aryl group in 2nd position showed the highest affinity for the D_2R (**1b**, **1e**, **1g**). The placement of the substituent at the 3rd position in the aromatic ring resulted in an increased affinity for the 5-HT_7R (**1c**, **1e**, **1f**). Substitution in the 4th (**1d**) or 3rd (**1c**) position resulted in the highest

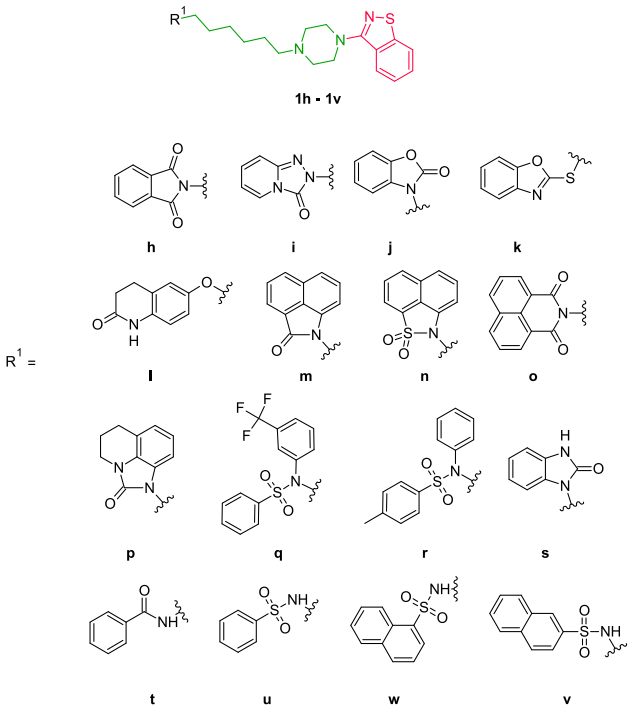
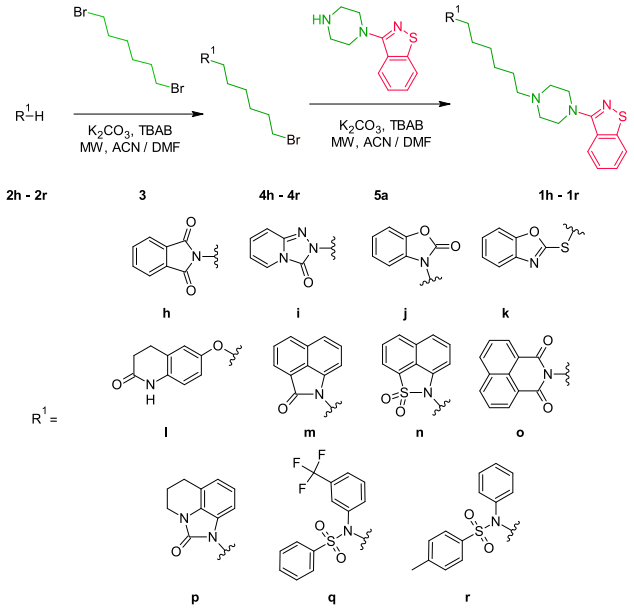


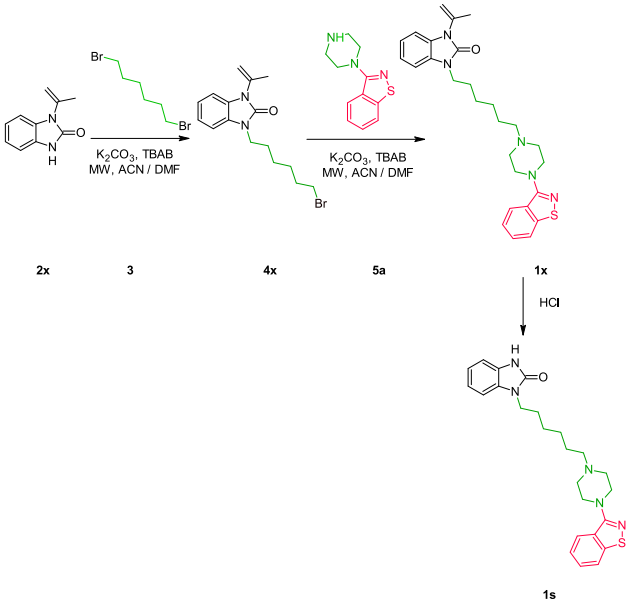
Fig. 6. The second group of compounds.

affinity for the 5-HT_{2A}R. Interestingly, the profile of activity changed very clearly and regularly, when the position of the substituent in the aryl part was changed. In the presented group, two dual ligands for 5-HT_{1A}/D_2 receptors (**1b**, **1g**) and two dual 5-HT_{1A}/5-HT_7R ligands (**1c**, **1f**) were distinguished. However, the compound **1a** showed the highest (albeit relatively low) affinity for 5-HT_6R. Therefore, in the next part of the work, we decided to synthesize a group of 3-(4-hexylpiperazin-1-yl)-1,2-benzothiazole derivatives, as shown in Fig.6. The planned compounds had aromatic moieties in the terminal part due to the high affinity for 5-HT_6R, which was previously determined in molecular modeling.

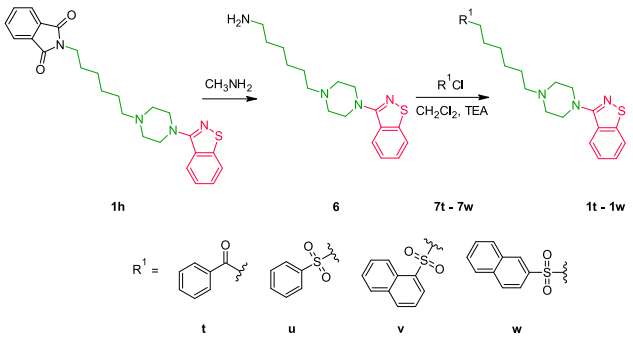
The compounds **1h-1r** were obtained as a result of a two-step



Scheme 2. Preparation of compounds **1 h-1r** from group II.



Scheme 3. Preparation of compound **1 s** from group II.



Scheme 4. Preparation of compounds **1 t-1w** from group II.

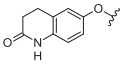
synthesis (scheme 2), including the *N*-alkylation, *O*-alkylation or *S*-alkylation of the corresponding heterocycles (**2h**-**2p**) or sulfonamides (**2q**, **2r)** with 1,6-dibromohexane (**3**). The next step was condensation of the resulting intermediate (**4h**-**4r**) with 3-(piperazin-1-yl)-1,2-benzothiazole (**5a**). The reactions were carried out in the presence of microwave radiation, using K_2CO_3 as a basic agent, TBAB as a PTC and small additions of DMF or acetonitrile (ACN).

The compound **1s** was obtained as a result of a three-step synthesis[26] (Scheme 3), including *N*-alkylation of 1-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-one (**2x**) by 1,6-dibromohexane (**3**). The next step was condensation of the resulting intermediate (**4x**) with 3-(piperazin-1-yl)-1,2-benzothiazole (**5a**). In the final step, deprotection of the protected 1,3-dihydro-2H-benzimidazol-2-one derivative (**1x**) by adding 4 M HCl in dioxane was performed.

The compounds numbered **1t-1w** were obtained from compound **1h** by a two-step reaction (scheme 4), involving the preparation of amine **6** in the Gabriel reaction using methylamine[27] followed by condensation of the resulting amine with the corresponding arylsulfochloride (**7u-7w**) or arylacylchloride (**7t**) in the presence of triethylamine.[28]

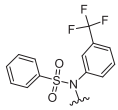
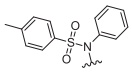
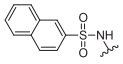
The substitution of the group (3aR,4S,7R,7aS)-3a,7a-dimethylhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione with another imide group (**1h**, **1o**) resulted in a decrease in 5-HT_7R affinity with a simultaneous increase of the affinity for 5-HT_6R, which was desirable in the context of this work. A much more favorable profile was exhibited by **1h**, which had a small decrease in the affinity for 5-HT_{2A}R and D_2R as compared to **1a**. The use of amide groups (**1m)** caused lower affinity for all receptors, without changing the activity profile. The compound with a benzamide moiety in the terminal part (**1t**) showed the increased affinity for 5-HT_6R. Very interesting properties were exhibited by the compounds having in their structure cyclic urea moieties (**1i**, **1p**, **1s**). The compounds **1p** and **1s** showed a similar activity profile compared to **1a**, with a small increase in 5-HT_6R affinity (Table 2).

Table 2
Affinity of obtained compounds (II group) for the tested receptors, K_i [nM]. Each compound was tested in triplicate at 8 different concentrations (10^{-4} to 10^{-11} M).

No.	R^1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_6	5-HT_7
1h		10 ± 2	18 ± 3	24 ± 2	160 ± 33	114 ± 17
1i		9 ± 2	11 ± 3	5 ± 1	252 ± 43	747 ± 93
1j		16 ± 1	5 ± 2	6 ± 2	189 ± 35	7 ± 2
1k		33 ± 4	10 ± 3	13 ± 4	302 ± 81	72 ± 9
1l		39 ± 5	20 ± 6	20 ± 3	805 ± 97	387 ± 61
1m		56 ± 8	71 ± 6	55 ± 4	568 ± 117	36 ± 8
1n		18 ± 3	63 ± 8	32 ± 5	158 ± 18	105 ± 14
1o		59 ± 7	86 ± 12	53 ± 3	110 ± 20	118 ± 22
1p		1 ± 0.3	44 ± 7	12 ± 2	379 ± 47	16 ± 3

(*continued on next page*)

Table 2 (*continued*)

No.	R^1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_6	5-HT_7
1q		164 ± 12	42 ± 5	65 ± 8	1103 ± 141	193 ± 32
1r		106 ± 9	32 ± 3	26 ± 2	772 ± 82	54 ± 6
1s		16 ± 1	16 ± 3	6 ± 1	189 ± 35	7 ± 2
1t		14 ± 3	22 ± 4	4 ± 3	221 ± 42	99 ± 8
1u		31 ± 7	8 ± 1	15 ± 7	317 ± 23	37 ± 6
1v		31 ± 2	39 ± 8	63 ± 15	52 ± 7	30 ± 4
1w		27 ± 4	73 ± 11	44 ± 9	57 ± 4	31 ± 6

The compound **1i** was particularly interesting, as it exhibited a very close affinity (compared to **1a**) for the 5-HT_{1A}, D_2 and 5-HT_{2A} receptors and an almost twofold increase in the affinity for 5-HT_6R, with a very low binding with 5-HT_7R compared to **1a**.

Among the naphthyl sulfonamide derivatives **1n**, **1v**, **1w**, some decrease in the affinity for the D_2, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors can be observed. The compounds remain active in the said region, but also showed a much higher affinity for the 5-HT_6R compared to the **1a**. Interestingly, the use of a stiffened naphthalene sulfonamide moiety (**1n**) caused a threefold decrease in 5-HT_6R affinity in comparison with other naphthalenesulfonamide derivatives (**1v**, **1w**). Phenyl sulfonamide derivatives (**1q**, **1u**, **1r**) are characterized by a decrease in the binding towards D_2 and 5HT_7 receptors, as well as a significant decrease in the affinity for 5-HT_6R (except for **1u**). **1j** shows an increase in 5-HT_{1A}R, 5-HT_6R and 5-HT_7R affinity compared to **1a**, with a decrease in binding toward D_2R. The compound **1l** showed a high affinity for 5-HT_{1A}R, 5-HT_{2A}R and D_2R with a low affinity for 5-HT_6R and 5-HT_7R. In the second group, 12 compounds with an increased affinity for 5-HT_6 receptors were obtained in comparison to *hit* **1a**. In the context of high binding for 5-HT_6R, while maintaining a high affinity for other receptors, **1v** and **1w** had the most beneficial properties. The compound **1i** appears to be particularly interesting in the context of this work, showing a similar activity profile compared to the **1a**, while at the same time strongly reducing the affinity for 5-HT_7R and moderate increase in the affinity for 5-HT_6 R.

In the context of binding for 5-HT_6R, the best results were obtained for naphthalenesulfonamide compounds **1v** and **1w**. Interestingly, **1n**, with the stiffened naphthalene sulfonamide fragment showed a significant decrease in the affinity for the 5-HT_6R. Its imide analog, **1o**, showed a slightly higher affinity for 5-HT_6R. We decided to investigate this with molecular docking methods (Fig.7). We performed docking using the homology 5-HT_6 receptor model (template 5-HT_{2A}, pdb ID: 6A94).

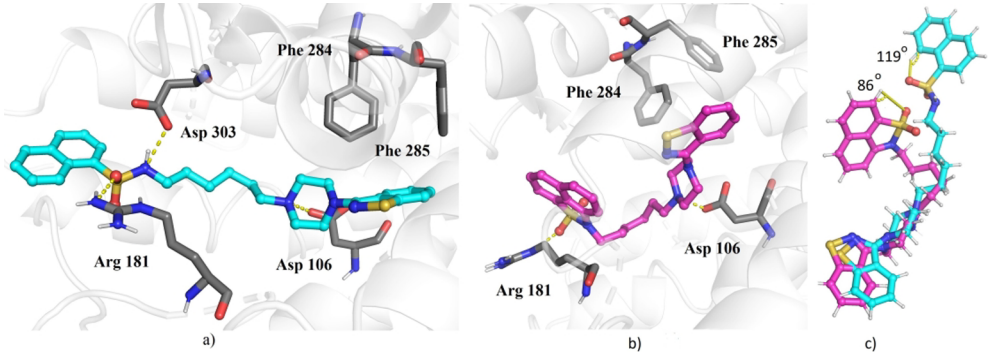


Fig. 7. Docking of a) **1v**, b) **1n,** for 5-HT_6R and a comparison of binding modes and the possibility of occurrence of intramolecular hydrogen bonds in **1v** and **1n**. The yellow lines indicate the hydrogen bonds. Nitrogen – blue, sulfur – yellow, oxygen – red, turquoise – **1v,** violet – **1n**.

For the naphthalenesulfonamide **1v** (Fig.7a) and the stiffened **1n** (Fig.7b), a similar arrangement of the arylpiperazine moiety in the 5-HT_6R binding pocket was observed. In both cases, the ligands showed the ability to form a salt bridge between the nitrogen atom in the piperazine structure and the residue Asp106. Interestingly, both compounds were involved in the formation of π-π interactions in the 3-(piperazin-1-yl)-1,2-benzothiazole part with the residues Phe284 and Phe285. The differences between the ligands were found in the bending of the naphthalenesulfonamide group. In the case of the compound **1v**, this group was arranged in the direction of helices 1 and 2, while in **1n** it bent towards the helix 6. Both ligands demonstrated the ability to form a hydrogen bond of the sulphonyl group with Arg181. In **1v**, an additional hydrogen bond was observed between the NH group in the sulfonamide structure and Asp303. The ability to form intramolecular hydrogen bonds in the arylsulfonamide fragment may also affect the affinity of 5-HT_6R.[25] In **1v**, the probability of occurrence of this type of binding was much greater than in the case of **1n**, which was confirmed by the geometry of the hypothetical hydrogen bond (Fig.7c.). These observations are consistent with the theory presented previously.[25]

Most of the compounds in group II showed a high or moderate affinity for 5-HT_7R. The exception here was the compound **1i**, which was particularly interesting in the context of this work. The molecular docking to the 5-HT_7 receptor (homology modeling, template 5-HT_{1B}; pdb ID: 6G79) was performed to compare the binding mode of active compounds (**1a** – bright green, **1m** – blue, **1p** – pink, **1s** – brown) and inactive (**1i** – dark green) (Fig.8).

In the arylpiperazine fragment, all compounds exhibited similar alignment as previously described for the compound **1a**. In the compound **1i**, the piperazine nitrogen atom was the furthest away from Asp162, which could reduce the possibility of hydrogen bonding. The biggest differences were observed in the bending of the terminal groups. For the active compounds, the arrangement of the terminally located groups were identical. Polar interactions (hydrogen bonds) with Trp148 were observed. The inactive compound strongly bent towards helices 2 and 3, which may explain its low binding with 5-HT_7R.

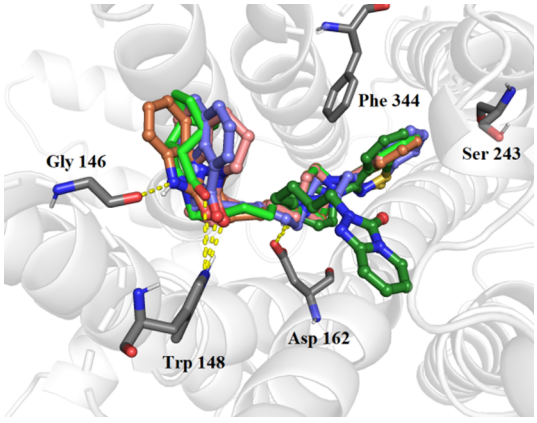


Fig. 8. Docking of selected ligands, for 5-HT_7R. The yellow lines indicate the hydrogen bonds. Nitrogen – blue, sulfur – yellow, oxygen – red, **1a** – bright green, **1 m** – blue, **1p** – pink, **1 s** – brown, **1i** – dark green.

3. Conclusion

In summary, the *hit* compound, which was a flexible, hexyl analog of lurasidone, had a similar binding profile to the mentioned drug. In **1a**, high binding for D_2 and 5-HT_{2A} receptors was maintained with a small decrease in the affinity for 5-HT_{1A} and 5-HT_7 receptors. The studies focused on the search for lurasidone analogs with the increased affinity for 5-HT_6R and reduced to 5-HT_7R. Unfortunately, no compound was obtained that showed complete reversal of 5-HT_6/5-HT_7R activity. However, compounds with partial reversal of activity were obtained, and the relation between this effect and the structural modifications create a field for further studies.

In the context of the binding toward 5-HT_6R, the *hit* showed relatively low affinity. The presence of the 1,2-benzothiazole moiety proved to be crucial for the binding toward this receptor. In the group of derivatives of the aforementioned arylpiperazine, the most active compounds turned out to be the ones with a naphthalenesulfonamide fragment (**1v** and **1w**) in their structure, while the use of a stiffened naphthalenesulfonamide fragment (sultam; **1n**) caused a three-fold decrease in affinity. High binding with this type of compounds may result from the good alignment of the said arylpiperazine for the 5-HT_6R binding pocket, hydrogen bonds stabilizing the receptor-ligand complex, but also the possibility of intramolecular hydrogen bonds in the naphthalenesulfonamide fragment. The latter fact may explain the higher affinity of **1v** and **1w** compounds compared to **1n**, and also remains in accordance with previously published reports.[25] Interestingly, the 1,2-benzothiazole group was also of key importance in the context of the binding toward 5-HT_7R. Among the tested compounds, one (**1i**) was found which, despite the presence of the said moiety, showed a low affinity for 5-HT_7R, with moderate affinity for 5-HT_6R. In this compound, the affinities for the D_2, 5-HT_{1A} and 5-HT_{2A} receptors remained at a very high level. Low binding with the 5-HT_7R was discussed, emphasizing the different bending of the triazolopyridinone group, as compared to the conformations of the active compounds. All compounds were obtained using the previously developed ecological method of the synthesis in the microwave radiation field, which confirmed its versatility in obtaining differentiated LCAP libraries. The development of the new analogs of currently used drugs with an altered activity profile may help to assess the actual importance of some receptor targets in the treatment of CNS disorders.

4. Experimental section

4.1. Chemistry

The microwave-assisted reactions were carried out in the CEM Discover microwave reactor (100 W). All chemicals were purchased from Sigma Aldrich and all solvents used in the synthesis were from POCH. Thin-layer chromatography (TLC) was preformed using chloroform:methanol as an eluent, in the ratio of 9:1, on Sigma Aldrich sheets (silica gel on aluminium, with fluorescent indicator 254 nm, 200 μm layer thickness, 60 Å pore diameter, 8.0–12.0 μm particle size) and UV light with a wavelength of 254 nm was used for the analysis. High-performance liquid chromatography (HPLC) was performed on a Perkin Elmer Series 200 HPLC (XTerra RP C-18, 3.5 μm seed size, 4.6 × 150 mm) column and MeOH:H_2O 1:1 eluent acidified with 0.1% formic acid. The melting points were measured using a Boëtius apparatus. IR spectra were taken on an FTS-165 spectrometer. ^{1}H NMR

spectra were recorded on Bruker Avance 400 MHz spectrometer, using TMS as an internal reference. The LC-MS system consisted of a Waters Acquity UPLC system coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole). The analyses were carried out using an Acquity UPLC BEH C18, 1.7, 2.1 × 100 mm column.

4.1.1. Synthesis of intermediates 4a, 4h-4r

A mixture of heterocycle **2a**, **2h-2p, 2x** or sulfonamide **2q**, **2r** (0.001 mol) with 0.414 g of K_2CO_3 (0.003 mol) and 0.032 g of TBAB (0.0001 mol) were triturated in a mortar. The triturated mixture was transferred to a round bottom flask, after which 0.46 cm^3 (0.003 mol) of 1,6-dibromohexane (**3**) and 0.2 cm^3 of ACN or DMF was added. The reactions were carried out for 30 s in a CEM Discover microwave reactor at 100 W output power. After the reaction had been completed, 40 cm^3 of water was added to the mixture and extracted with methylene chloride. After the distillation of methylene chloride, the product was macerated in 20 cm^3 of hexane to get rid of the excess 1,6-dibromohexane (**3**). The reaction yields for each product were calculated on the basis of the weight of the obtained product.

4.1.1.1. (3aR,4S,7R,7aS)-2-(6-bromohexyl)-3a,7a-dimethylhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 4a. Molecular formula: $C_{15}H_{22}BrNO_2$, ^{1}H NMR (400 MHz, DMSO) δ 3.51 (t, J = 6.7 Hz, 2H, CONCH), 3.40 (s, 2H, $BrCH_{Aliph}$), 3.32 (t, J = 7.3 Hz, 2H, CH_{Aliph}), 2.65–2.57 (m, 2H, CH_{Aliph}), 2.53–2.46 (m, 4H, CH_{Aliph}), 1.81–1.71 (m, 2H, CH_{Aliph}), 1.65–1.49 (m, 2H, CH_{Aliph}), 1.48–1.11 (m, 5H, CH_{Aliph}), 1.00–0.90 (m, 1H, CH_{Aliph}), FT-IR: 3034 (C—H, Ar, Str), 2934; 2857 (C—H Aliph, Str), 1692 (C═O, Str), 1491; 1436 (C═C Ar, Str), 1342 (C—N, Str), HPLC: R_t = 5.41 min, P = 99%, TLC: R_f = 0.91, m_p = oil, Y = 79%.

4.1.1.2. 2-(6-bromohexyl)isoindoline-1,3-dione 4h. Molecular formula: $C_{14}H_{16}BrNO_2$, m_p = 55–57 °C, HPLC: R_t = 7.14 min, P = 99%, TLC: R_f = 0.90, Y = 79%.

4.1.1.3. 2-(6-bromohexyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one 4i. Molecular formula: $C_{12}H_{16}BrN_3O$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, J = 5.5, 3.3, 2.2 Hz, 1H, ArH), 7.15–7.07 (m, 2H, ArH), 6.51 (ddd, J = 7.2, 4.4, 3.0 Hz, 1H, ArH), 4.02 (t, J = 7.1 Hz, 2H, CONCH), 3.42–3.96 (dd, J = 8.0, 5.6 Hz, 2H, $BrCH_{Aliph}$), 1.89 (ddd, J = 10.3, 7.3, 3.4 Hz, 4H, CH_{Aliph}), 1.55–1.48 (m, 2H, CH_{Aliph}), 1.46–1.39 (m, 2H, CH_{Aliph}), FT-IR: 3066 (C—H Ar, Str), 2942; 2854 (C—H Aliph, Str), 1703 (C═O, Str), 1641 (C═N, Str), 1593; 1491 (C═C, Str), 1376 (C—N, Str), HPLC: R_t = 7.31 min, P = 91%, TLC: R_f = 0.96, m_p = oil, Y = 79%.

4.1.1.4. 3-(6-bromohexyl)benzo[d]oxazol-2(3H)-one 4j. Molecular formula: $C_{13}H_{16}BrNO_2$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–6.84 (m, 4H, ArH), 3.83 (dt, J = 17.0, 8.5 Hz, 2H, CONCH), 3.42 (t, J = 6.7 Hz, 2H, $BrCH_{Aliph}$), 1.97–0.96 (m, 8H, CH_{Aliph}), FT-IR: 2969; 2931; 2860 (C—C Aliph, Str), 1743 (C═O, Str), 1615 (N—H, Str), 1484 (C═C, Str), 1371 (C—N,Str), 750 (C-Br, Str), HPLC: R_t = 3.20 min, P = 90%, TLC: R_f = 0.89, m_p = 55 °C, Y = 71%.

4.1.1.5. 2-((6-bromohexyl)thio)benzo[d]oxazole 4 k. Molecular formula: $C_{14}H_{16}BrNOS$, ^{1}H NMR (400 MHz, DMSO) δ 7.74–7.50 (m, 2H, ArH), 7.40–7.19 (m, 2H, ArH), 3.65–3.20 (m, 2H, SCH_{Aliph}), 2.67–2.39 (m, 2H, $BrCH_{Aliph}$), 1.96–0.84 (m, 8H, CH_{Aliph}), FT-IR: 3090 (C—H Ar, Str), 2970; 2934; 2856 (C—C Aliph), 1738 (C═O, Str), 1589; 1491 (C═C Ar, Str), 1380 (C—N, Str), HPLC: R_t = 3.83 min, P = 99%, m_p = 76 °C, Y = 67%.

4.1.1.6. 6-((6-bromohexyl)oxy)-3,4-dihydroquinolin-2(1H)-one 4l. Molecular formula: $C_{15}H_{20}BrNO_2$, ^{1}H NMR (400 MHz, CDCl3) δ 9.11 (s, 1H, NH), 6.89–6.60 (m, 3H, ArH), 3.93 (t, J = 6.4 Hz, 2H, OCH_{Aliph}), 3.44 (t, J = 6.8 Hz, 2H, $BrCH_{Aliph}$), 3.02–2.88 (m, 2H, CONCH), 2.63 (dd, J = 8.4, 6.7 Hz, 2H, CH_{Aliph}), 2.01–1.40 (m, 8H, CH_{Aliph}), FT-IR: 3176 (N—H Amine, Str), 3030 (C—H Ar, Str), 2969; 2936; 2858 (C—C Aliph, Str), 1747 (C═O, Str), 1502; 1485 (C═C Ar, Str), 1366 (C—N, Str), UPLC-MS: 329.17 (M + 1, 20) 328.17 (M, 100), 327.17 (M − 1, 23), 326.17 (M − 2, 97), HPLC: R_t = 12.18 min, P = 100%, TLC: R_f = 0.90, m_p = 115 °C, Y = 90%.

4.1.1.7. 1-(6-bromohexyl)benzo[cd]indol-2(1H)-one 4m. Molecular formula: $C_{17}H_{18}BrNO$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.0 Hz, 1H, ArH), 8.07–8.01 (m, 1H, ArH), 7.76–7.72 (m, 1H, ArH), 7.56 (d, J = 8.4 Hz, 1H, ArH), 7.52–7.46 (m, 1H, ArH), 6.94 (d, J = 6.9 Hz, 1H, ArH), 3.99–3.93 (m, 2H, CONCH), 3.44–3.40 (m, 2H, $BrCH_{Aliph}$), 1.89–1.80 (m, 4H, CH_{Aliph}), 1.50–1.41 (m, 4H, CH_{Aliph}), FT-IR: 3055 (C—H Ar Str), 2932; 2857 (C—H Aliph, Str), 1694 (C═O, Str), 1602; 1495 (C═C Ar, Str), 1373 (C—N, Str), 773 (C-Br, Str), HPLC: R_t = 4.05 min, P = 88%, TLC: R_f = 0.90, m_p = oil, Y = 78%.

4.1.1.8. 2-(6-bromohexyl)–2H-naphtho[1,8-cd]isothiazole1,1-dioxide 4m. Molecular formula: $C_{16}H_{18}BrNOS$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.00 (m, 1H, ArH), 7.98–7.91 (m, 1H, ArH), 7.77–7.72 (m, 1H, ArH), 7.62–7.51 (m, 1H, ArH), 7.46 (t, J = 9.4 Hz, 1H, ArH), 6.75–6.68 (m, 1H, ArH), 3.86 (t, J = 7.3 Hz, 2H, SONCH), 3.44 (t, J = 6.7 Hz, 2H, $BrCH_{Aliph}$), 1.95–1.86 (m, 4H, CH_{Aliph}), 1.61–1.53 (m, 4H, CH_{Aliph}), FT-IR: 3060 (C—H Ar, Str), 2933; 2856 (C—H, Aliph, Str), 1591; 1492 (C═C Ar, Str), 1371 (C—N, Str), 1348 (S═O, Str), 851 (N—S, Str), 756 (C-Br, Str), HPLC: R_t = 4.12 min, P = 95%, TLC: R_f = 0.90, Y = 67%.

4.1.1.9. 2-(6-bromohexyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione 4o. Molecular formula: $C_{18}H_{18}BrNO_2$, ^{1}H NMR (400 MHz, DMSO) δ 8.48–8.40 (m, 4H, ArH), 7.91–7.79 (m, 2H, ArH), 4.07–4.01 (m, 2H, CONCH), 3.53 (t, J = 6.7 Hz, 2H, $BrCH_{Aliph}$), 1.87–1.75 (m, 2H, CH_{Aliph}), 1.64 (dd, J = 14.7, 7.3 Hz, 2H, CH_{Aliph}), 1.40–1.33 (m, 4H, CH_{Aliph}), FT-IR: 3061 (C—H Ar Str), 2933; 2855 (C—H Aliph, Str), 1692 (C═O, Str), 1587; 1461 (C═C Ar, Str), 1361 (C—N, Str), 779 (C-Br, Str), HPLC: R_t = 3.85 min, P = 99%, TLC: R_f = 0.90, Y = 87%.

4.1.1.10. 1-(6-bromohexyl)-5,6-dihydro-1H-imidazo[4,5,1-ij]quinolin-2(4H)-one 4p. Molecular formula: $C_{16}H_{21}BrN_2O$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.91 (m, 2H, ArH), 6.85–6.77 (m, 1H, ArH), 4.39 (d, J = 12.4 Hz, 2H, CONCH), 3.44–3.40 (m, 2H, $BrCH_{Aliph}$), 3.15 (s, 2H, CH_{Aliph}), 2.84 (t, J = 6.0 Hz, 2H, CH_{Aliph}), 2.12–2.05 (m, 2H, CH_{Aliph}), 1.90– 1.85 (m, 2H, CH_{Aliph}), 1.84–1.74 (m, 2H, CH_{Aliph}), 1.40– 1.38 (m, 4H, CH_{Aliph}), FT-IR: 3059 (C—H Ar Str), 2928; 2852 (C—H Aliph, Str), 1703 (C═O, Str), 1599; 1486 (C═C Ar, Str), 1373 (C—N, Str), 780 (C-Br, Str), HPLC: R_t = 4.17 min, P = 96%, TLC: R_f = 0.90, m_p = oil, Y = 79%.

4.1.1.11. N-(6-bromohexyl)-N-(3-(trifluoromethyl)phenyl) benzenesulfonamide 4q. Molecular formula: $C_{19}H_{21}BrF_3NO_2S$, ^{1}H NMR (400 MHz, DMSO) δ 7.72–7.66 (m, 2H, ArH), 7.62–7.53 (m, 5H, ArH), 7.40 (d, J = 8.2 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 3.66–3.57 (m, 2H, SONCH), 3.47 (t, J = 6.7 Hz, 2H, $BrCH_{Aliph}$), 1.71 (dd, J = 13.5, 6.9 Hz, 2H, CH_{Aliph}), 1.31–1.25 (m, 5H, CH_{Aliph}), 1.20 (s, 1H, CH_{Aliph}), FT-IR: 3063 (C—H Ar, Str), 2937; 2855 (C—H Aliph, Str), 1491 (C═C Ar, Str), 1370 (C—N, Str), 1326 (S═O, Str), 1232 (C-F, Str), 786 (C-Br, Str), 690 (S—N, Str), 651 (C—S, Str), HPLC: R_t = 7.15 min, P = 99%, TLC: R_f = 0.95, m_p = 57–58 °C, Y = 81%.

4.1.1.12. N-(6-bromohexyl)-4-methyl-N-phenylbenzenesulfonamide 4r. Molecular formula: $C_{19}H_{24}BrNO_2S$, ^{1}H NMR (400 MHz, DMSO) δ 7.43 (dd, J = 8.2, 6.2 Hz, 2H, ArH), 7.40–7.35 (m, 3H, ArH), 7.35–7.31 (m, 2H, ArH), 7.08–6.98 (m, 2H, ArH), 3.51 (d, J = 6.2 Hz, 2H, SONCH), 3.47 (t, J = 6.7 Hz, 2H, $BrCH_{Aliph}$), 1.71 (dd, J = 13.6, 6.8 Hz, 2H, CH_{Aliph}), 1.51–1.44 (m, 3H, CH_{Aliph}) 1.29–1.20 (m, 5H, CH_{Aliph}), 1.18 (s, 1H, CH_{Aliph}), FT-IR: 3030 (C—H Ar, Str), 2926; 2863 (C—H Aliph, Str), 1489 (C═C Ar, Str), 1384 (C—N, Str), 1342 (S═O,

Str), 744 (C-Br, Str), 695 (S—N, Str), 655 (C—S, Str), HPLC: R_t = 7.80 min, P = 91%, TLC: R_f = 0.95, m_p = 54–55 °C, Y = 72%.

4.1.1.13. 1-(6-bromohexyl)-3-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2(3H)-one 4x. Molecular formula: $C_{16}H_{21}BrN_2O$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–6.96 (m, 4H, ArH), 5.41–5.15 (m, 2H, isopropenyl-CH_2), 3.96–3.81 (m, 2H, CONCH), 3.40 (dt, J = 13.5, 6.8 Hz, 2H, $BrCH_{Aliph}$), 2.28–2.18 (s, 3H, isopropenyl-CH_3), 1.93–1.73 (m, 4H, CH_{Aliph}), 1.57–1.34 (m, 4H, CH_{Aliph}), FT-IR: 3062 (C—H Ar, Str), 2956; 2935; 2854 (C—C Aliph, Str), 1624; 1485 (C═C, Str), 1402; 1377; 1363 (C—N, Str), P = 95%, TLC: R_f = 0.85, m_p = 75 °C, Y = 40%.

4.1.2. Synthesis of compounds (1a-1r)

A mixture of 6-bromohexylated derivative **4a/4r-4h** (0.001 mol), arylpiperazine **4a-g** (0.00095 mol), 0.414 g of K_2CO_3 (0.003 mol) and 0.032 g of TBAB (0.0001 mol) were triturated in a mortar. The triturated mixture was transferred to a round bottom flask, and 0.2 cm^3 of ACN, or DMF was added. The reactions were carried out for 60 s in a CEM Discover microwave reactor at 100 W output power. The progress of the reaction was monitored by TLC. After the reaction had been completed, 40 cm^3 of water was added to the mixture and placed in the refrigerator overnight. After cooling, the crude product was filtered off. In the absence of the required purity, the crude product was crystallized from methanol or methanol—water. After obtaining a minimum of 95% purity, the compounds were dissolved in acetone, then converted to hydrochlorides by 4 M HCl in dioxane. The reaction yields for individual compounds were calculated on the basis of the weight of the obtained hydrochloride.

4.1.2.1. (3aR,4S,7R,7aS)-2-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1a. Molecular formula: $C_{26}H_{34}N_4O_2S$, ^{1}H NMR (400 MHz, DMSO) δ 7.42–7.35 (m, 2H, ArH), 7.15–7.11 (m, 2H, ArH), 4.24 (d, J = 12.9 Hz, 2H, CONCH), 3.68–3.52 (m, 4H, CH_{Pip}), 3.33–3.24 (m, 2H, CH_{Pip}), 3.12–3.06 (m, 4H, CH_{Pip}), 2.65 (s, 2H, CH_{Aliph}), 1.52–1.44 (m, 8H, CH_{Aliph}), 1.31–1.26 (m, 6H, CH_{Aliph}), 1.16 (d, J = 9.7 Hz, 1H, CH_{Aiph}), 0.96 (d, J = 9.9 Hz, 1H, CH_{Aliph}), FT-IR: 3034 (C—H Ar, Str), 2941; 2870 (C—H Aliph, Str), 1686 (C═O Str), 1630 (C═N, Str), 1477; 1430 (C═C Ar, Str), 1371 (C—N, Str), 693 (S—N, Str), 624 (C—S, Str), UPLC-MS: 468.32 (M + 2, 5), 467.39 (M + 1, 35), 466.24 (M, 100), HPLC: R_t = 5.80 min, P = 96%, TLC: R_f = 0.73, m_p = 169–172 °C, Y = 67%.

4.1.2.2. (3aR,4S,7R,7aS)-2-(6-(4-(2-chlorophenyl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1b. Molecular formula: $C_{25}H_{34}ClN_3O_2$, ^{1}H NMR (400 MHz, DMSO) δ 7.46–7.40 (m, 1H, ArH), 7.37–7.31 (m, 1H, ArH), 7.21–7.18 (m, 1H, ArH), 7.12–7.08 (m, 1H, ArH), 3.57 (d, J = 5.8 Hz, 2H, CONCH), 3.41 (d, J = 9.1 Hz, 2H, CH_{Pip}), 3.34 (t, J = 7.2 Hz, 2H, CH_{Pip}), 3.22–3.06 (m, 6H, CH_{Pip}, CH_{Aliph}), 2.69–2.64 (m, 2H, CH_{Aliph}), 2.50 (s, 2H, CH_{Aliph}), 1.74–1.69 (m, 2H, CH_{Aliph}), 1.57 (d, J = 8.0 Hz, 2H, CH_{Aliph}), 1.48 (dd, J = 14.4, 7.2 Hz, 2H, CH_{Aliph}), 1.38–1.21 (m, 6H, CH_{Aliph}), 1.16 (d, J = 10.7 Hz, 1H, CH_{Aliph}), 0.97 (d, J = 10.8 Hz, 1H, CH_{Aliph}), FT-IR: 3036 (C—H Ar, Str), 2936; 2875 (C—H Aliph, Str), 1692 (C═O Str), 1470; 1455 (C═C Ar, Str), 1362 (C—N, Str), 764 (C-Cl, Str), HPLC: R_t = 2.73 min, P = 95%, TLC: R_f = 0.76, m_p = 189–191 °C, Y = 63%.

4.1.2.3. (3aR,4S,7R,7aS)-2-(6-(4-(3-chlorophenyl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1c. Molecular formula: $C_{25}H_{34}ClN_3O_2$, ^{1}H NMR (400 MHz, DMSO) δ 7.27–7.19 (m, 1H, ArH), 7.09–7.03 (m, 1H, ArH), 6.97 (d, J = 8.1 Hz, 1H, ArH), 6.88 (d, J = 7.8 Hz, 1H, ArH), 3.88 (d, J = 12.6 Hz, 2H, CONCH), 3.74–3.61 (m, 8H, CH_{Pip}), 3.54 (d, J = 10.2 Hz, 2H, CH_{Pip}), 3.34 (t, J = 7.2 Hz, 1H, CH_{Aliph}), 3.22–3.05 (m, 6H, CH_{Aliph}), 2.66 (s, 1H, CH_{Aliph}), 1.72–1.69 (m, 2H, CH_{Aliph}), 1.57 (d, J = 7.7 Hz, 1H, CH_{Aliph}), 1.49–1.44 (m, 1H, CH_{Aliph}), 1.37–1.25 (m, 4H, CH_{Aliph}), 1.16 (d, J = 10.8 Hz, 1H, CH_{Aliph}), 1.04–0.83 (m, 1H, CH_{Aliph}), FT-IR: 3051 (C—H Ar, Str), 2939; 2870 (C—H Aliph, Str), 1689 (C═O Str), 1475; 1455 (C═C Ar, Str), 1375 (C—N, Str), 787 (C-Cl, Str), HPLC: R_t = 2.63 min, P = 94%, TLC: R_f = 0.65, m_p = 184–186 °C, Y = 71%.

4.1.2.4. (3aR,4S,7R,7aS)-2-(6-(4-(4-chlorophenyl)piperazin-1-yl)hexyl)qhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1d. Molecular formula: $C_{25}H_{34}ClN_3O_2$, ^{1}H NMR (400 MHz, DMSO) δ 7.29 (d, J = 9.0 Hz, 2H, ArH), 7.02 (d, J = 9.1 Hz, 2H, ArH), 3.80 (d, J = 10.2 Hz, 2H, CONCH), 3.59–3.48 (m, 2H, CH_{Pip}), 3.34 (t, J = 7.2 Hz, 2H, CH_{Pip}), 3.23–2.99 (m, 6H, CH_{Pip}, CH_{Aliph}), 2.71–2.63 (m, 2H, CH_{Aliph}), 2.38–2.29 (m, 1H, CH_{Aliph}), 2.09 (s, 1H, CH_{Aliph}), 1.70 (s, 2H, CH_{Aliph}), 1.57 (d, J = 7.8 Hz, 2H, CH_{Aliph}), 1.47 (dd, J = 14.3, 7.2 Hz, 2H, CH_{Aliph}), 1.41–1.19 (m, 6H, CH_{Aliph}), 1.16 (d, J = 10.7 Hz, 1H, CH_{Aliph}), 0.97 (d, J = 10.9 Hz, 1H, CH_{Aliph}), FT-IR: 3057 (C—H Ar, Str), 2944; 2874 (C—H Aliph, Str), 1693 (C═O Str), 1491; 1455 (C═C Ar, Str), 1364 (C—N, Str), 711 (C-Cl, Str), HPLC: R_t = 3.39 min, P = 96%, TLC: R_f = 0.64, m_p = 146–149 °C, Y = 70%.

4.1.2.5. (3aR,4S,7R,7aS)-2-(6-(4-(2,3-dichlorophenyl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1e. Molecular formula: $C_{25}H_{33}Cl_2N_3O_2$, ^{1}H NMR (400 MHz, DMSO) δ 7.42–7.33 (m, 2H, ArH), 7.23 (dd, J = 7.4, 2.1 Hz, 1H, ArH), 3.61 (t, J = 6.6 Hz, 2H, CONCH), 3.57–3.49 (m, 2H, CH_{Pip}), 3.45 (d, J = 12.1 Hz, 2H, CH_{Pip}), 3.21–3.14 (m, 4H, CH_{Pip}), 1.74–1.70 (m, 2H, CH_{Pip}), 1.68–1.64 (m, 2H, CH_{Aliph}, 1.56–1.50 (m, 4H, CH_{Aliph}), 1.46–1.41 (m, 2H, CH_{Aliph}), 1.40–1.35 (m, 2H, CH_{Aliph}), 1.31–1.28 (m, 4H, CH_{Aliph}), 1.24 (d, J = 7.0 Hz, 2H, CH_{Aliph}), 1.15 (d, J = 10.7 Hz, 1H, CH_{Aliph}), 1.00–0.95 (m, 1H, CH_{Aliph}), FT-IR: 3049 (C—H Ar, Str), 2937; 2873 (C—H Aliph, Str), 1693 (C═O Str), 1486; 1452 (C═C Ar, Str), 1373 (C—N, Str), 776 (C-Cl, Str), HPLC: R_t = 3.55 min, P = 95%, TLC: R_f = 0.63 m_p = oil, Y = 66%.

4.1.2.6. (3aR,4S,7R,7aS)-2-(6-(4-(3-trifluoromethylphenyl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1f. Molecular formula: $C_{26}H_{34}F_3N_3O_2$, ^{1}H NMR (400 MHz, DMSO) δ 7.48 (t, J = 8.0 Hz, 1H, ArH), 7.30 (d, J = 13.2 Hz, 2H, ArH), 7.17 (d, J = 7.7 Hz, 1H, ArH), 3.97 (d, J = 10.2 Hz, 2H, CONCH), 3.60–3.49 (m, 4H, CH_{Pip}), 3.34 (t, J = 7.2 Hz, 2H, CH_{Pip}), 3.15–3.07 (m, 6H, $CH_{Pip,}$, CH_{Aliph}), 2.70–2.64 (m, 2H, CH_{Aliph}), 2.39–2.30 (m, 1H, CH_{Aliph}), 1.72 (d, J = 27.7 Hz, 2H, CH_{Aliph}), 1.57 (d, J = 7.6 Hz, 2H, CH_{Aliph}), 1.53–1.41 (m, 2H, CH_{Aliph}), 1.41–1.24 (m, 5H, CH_{Aliph}), 1.16 (d, J = 10.9 Hz, 1H, CH_{Aliph}), 0.97 (d, J = 10.9 Hz, 1H, CH_{Aliph}), FT-IR: 3045 (C—H Ar, Str), 2933; 2871 (C—H Aliph, Str), 1695 (C═O Str), 1471; 1455 (C═C Ar, Str), 1372 (C—N, Str), 1170 (C-F, Str), HPLC: R_t = 3.01 min, P = 95%, TLC: R_f = 077, m_p = 190–191 °C, Y = 65%.

4.1.2.7. (3aR,4S,7R,7aS)-2-(6-(4-(2-methoxyphenyl)piperazin-1-yl)hexyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 1g. Molecular formula: $C_{26}H_{37}N_3O_3$, ^{1}H NMR (400 MHz, DMSO) δ 7.04–6.97 (m, 2H, ArH), 6.93–6.88 (m, 2H, ArH), 3.80 (s, 3H, OCH), 3.51–3.47 (m, 4H, CH_{Pip}), 3.34 (t, J = 7.2 Hz, 2H, CONCH), 3.28–2.93 (m, 8H, $CH_{Pip,}$ CH_{Aliph}), 2.71–2.62 (m, 2H, CH_{Aliph}), 1.72 (d, J = 18.5 Hz, 2H, CH_{Aliph}), 1.57 (d, J = 7.8 Hz, 2H, CH_{Aliph}), 1.47–1.44 (m, 2H, CH_{Aliph}), 1.30–1.21 (m, 6H, CH_{Aliph}), 1.16 (d, J = 10.8 Hz, 1H, CH_{Aliph}), 0.97 (d, J = 10.8 Hz, 1H, CH_{Aliph}), FT-IR: 3054 (C—H Ar, Str), 2940; 2867(C—H Aliph, Str), 1696 (C═O Str), 1453 (C═C Ar, Str), 1375(C—N, Str), 1261; 1029 (C—O, Str), UPLC-MS: 442.28 (M + 3, 5), 441.35 (M + 2, 40), 440.46 (M+, 100), HPLC: R_t = 1.92 min, P = 97%, TLC: R_f = 0.73, m_p = 147–150 °C, Y = 54%.

4.1.2.8. 2-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)isoindoline-1,3-dione 1h. Molecular formula: $C_{25}H_{28}N_4O_2S$, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dt, J = 10.2, 3.8 Hz, 4H, ArH), 7.75–7.66 (m, 2H, ArH), 7.51 (td, J = 8.2, 7.0, 1.1 Hz, 1H, ArH), 7.40 (td, J = 8.0, 7.0, 1.1 Hz, 1H, ArH), 4.24–4.03 (m, 4H, CH_{Pip}), 3.67 (t, J = 7.1 Hz, 2H, CONCH), 3.50 (d, J = 11.2 Hz, 2H, CH_{Pip}), 3.13 (dd, J = 20.2, 8.1 Hz, 2H, CH_{Pip}), 3.03–2.91 (m, 2H CH_{Pip}), 1.95 (m, 2H, CH_{Aliph}), 1.76–1.65 (m, 2H, CH_{Aliph}), 1.61–1.35 (m, 4H, CH_{Aliph}), FT-IR: 3037 (C—H Ar, Str),

2936; 2861 (C—H Aliph, Str), 1770, 1709 (C═O Str), 1612, 1591; 1560 (C═C Ar, Str), 1397, 1366 (C—N, Str), 796, 776, 743 (S—N, Str), 717, 710, 675 (C—S, Str), HPLC: R_t = 5.06 min, P = 98%, TLC: R_f = 0.56, m_p = 179–185 °C, Y = 44%.

4.1.2.9. 2-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-[1,2,4] triazolo[4,3-a]pyridin-3(2H)-one 1i. Molecular formula: $C_{23}H_{28}N_6OS$, ^{1}H NMR (300 MHz, DMSO) δ 8.12 (t, J = 7.5 Hz, 2H, ArH), 7.84 (d, J = 7.1 Hz, 1H, ArH), 7.63–7.55 (m, 2H, ArH), 7.47 (t, J = 7.6 Hz, 1H, ArH), 7.22 (d, J = 3.2 Hz, 1H, ArH), 6.61 (t, J = 7.2 Hz, 1H, ArH), 4.06 (d, J = 13.7 Hz, 2H, CONCH), 3.90 (t, J = 6.8 Hz, 2H, CH_{Pip}), 3.58–3.51 (m, 2H, CH_{Pip}), 3.26—3.14 (m, 4H, CH_{Pip}), 3.12–3.08 (m, 2H, CH_{Pip}), 1.77–1.63 (m, 4H, CH_{Aliph}), 1.34–1.28 (s, 4H, CH_{Aliph}), FT-IR: 3037 (C—H Ar, Str), 2940; 284 (C—H Aliph, Str), 1708 (C═O, Str), 1640 (C═N, Str), 1539; 1476 (C═C, Str), 1371 (C—N, Str), 692 (S—N, Str), 665 (C—S, Str), HPLC: R_t = 8.12 min, P = 97%, TLC: R_f = 0.63, m_p = 62–64 °C (oiled), Y = 51%.

4.1.2.10. 3-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)benzo[d] oxazol-2(3H)-one 1j. Molecular formula: $C_{24}H_{28}N_4O_2S$, ^{1}H NMR (400 MHz, DMSO) δ 8.12 (t, J = 8.4 Hz, 2H, ArH), 7.60 (dd, J = 11.5, 4.4 Hz, 1H, ArH), 7.48 (t, J = 7.6 Hz, 1H, ArH), 7.35 (d, J = 7.9 Hz, 2H, ArH), 7.24 (td, J = 7.8, 1.0 Hz, 1H, ArH), 7.14 (td, J = 7.8, 1.2 Hz, 1H, ArH), 4.05 (d, J = 13.4 Hz, 2H, CONCH), 3.83 (dd, J = 13.6, 6.6 Hz, 2H, CH_{Pip}), 3.60–3.55 (m, 2H, CH_{Pip}), 3.50 (t, J = 13.0 Hz, 2H, CH_{Pip}), 3.24 (dd, J = 21.2, 9.3 Hz, 2H, CH_{Pip}), 3.12 (dt, J = 10.6, 5.3 Hz, 2H, CH_{Pip}), 1.74 (d, J = 6.6 Hz, 4H, CH_{Aliph}), 1.37 (s, 4H, CH_{Aliph}), FT-IR: 3030 (C—H Ar, Str), 2970; 2929; 2857 (C—H Aliph, Str), 1591 (C═C Ar, Str), 1365 (C—N, Str), 752 (S—N, Str), 677 (C—S, Str), HPLC: R_t = 5.21 min, P = 96%, TLC: R_f = 0.71, m_p = 170–172 °C, Y = 47%.

4.1.2.11. 2-((6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)thio) benzo[d]oxazole 1k. Molecular formula: $C_{24}H_{28}N_4OS_2$ ^{1}H NMR (400 MHz, DMSO) δ 8.13 (t, J = 8.5 Hz, 1H, ArH), 7.68–7.64 (m, 1H, ArH), 7.60 (t, J = 7.5 Hz, 1H, ArH), 7.48 (t, J = 7.6 Hz, 1H, ArH), 7.34–7.31 (m, 1H, ArH), 7.28 (d, J = 7.4 Hz, 1H, ArH), 7.18–7.01 (m, 1H, ArH), 6.85 (m, 1H, ArH), 4.06 (d, J = 13.5 Hz, 2H, CONCH), 3.70–3.45 (m, 4H, CH_{Pip}), 3.39–3.23 (m, 2H, CH_{Pip}), 3.14 (m, 2H, CH_{Pip}), 3.04–2.76 (m, 2H, CH_{Pip}), 1.88–1.27 (m, 8H, CH_{Aliph}), FT-IR: 3290 (N—H amine, Str), 3024 (C—H Ar, Str), 2994, 2969; 2938; 2856 (C—H Aliph, Str), 1591 (C═C Ar, Str), 1379 (C—N, Str), 742 (S—N, Str), 677 (C—S, Str), UPLC-MS: 455.18 (M + 3, 15), 454.25 (M + 2, 40), 453.25 (M + 1, 100), HPLC: R_t = 6.06 min, P = 97%, TLC: R_f = 0.82, m_p = 164 °C, Y = 40%.

4.1.2.12. 6-((6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)oxy)-3,4-dihydroquinolin-2(1H)-one 1l. Molecular formula: $C_{26}H_{32}N_4O_2S$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 22.1 Hz, 1H, ArH), 7.86 (dd, J = 10.9, 6.1 Hz, 1H, ArH), 7.53 (dd, J = 14.5, 7.1 Hz, 1H, ArH), 7.42 (dd, J = 14.4, 7.4 Hz, 1H, ArH), 6.78–6.67 (m, 4H, ArH), 4.15 (m, 2H, CONCH), 3.93 (dd, J = 13.2, 6.7 Hz, 2H, CH_{Pip}), 3.57 (t, J = 6.7 Hz, 2H, CH_{Pip}), 3.10 (dd, J = 50.5, 10.1 Hz, 2H, CH_{Pip}), 2.98–2.89 (m, 2H, CH_{Pip}), 2.67–2.57 (m, 2H, CH_{Pip}), 2.13–1.43 (m, 12H, CH_{Aliph}), FT-IR: 3343 (N—H, Str), 3056 (C—H Ar, Str), 2926; 2855, 2812 (C—H Aliph, Str), 1700 (C═O Str), 1655 (C═N, Str), 1591; 1559 (C═C Ar, Str), 1391, 1379 (C—N, Str), 771, 771, 734 (S—N, Str), 679 (C—S, Str), HPLC: R_t = 4.86 min, P = 96%, TLC: R_f = 0.69, m_p = 159–161 °C, Y = 53%.

4.1.2.13. 1-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)benzo[cd] indol-2(1H)-one 1 m. Molecular formula: $C_{28}H_{30}N_4OS$ ^{1}H NMR (400 MHz, DMSO) δ 8.20 (d, J = 8.1 Hz, 1H, ArH), 8.13 (d, J = 8.2 Hz, 2H, ArH), 8.07 (d, J = 6.9 Hz, 1H, ArH), 7.82–7.77 (m, 1H, ArH), 7.66 (d, J = 8.4 Hz, 1H, ArH), 7.59–7.51 (m, 2H, ArH), 7.49 (d, J = 8.0 Hz, 1H ArH), 7.24 (d, J = 7.0 Hz, 1H ArH), 4.05 (s, 2H, CONCH), 3.93 (t, J = 6.9 Hz, 2H, CH_{Pip}), 3.58–3.50 (d, J = 10.9 Hz, 2H, CH_{Pip}), 3.45–3.36 (m, 4H, CH_{Pip}), 3.16–3.03 (m, 2H, CH_{Pip}), 1.73–1.63 (m, 4H, CH_{Aliph}), 1.39–1.29 (m, 4H, CH_{Aliph}), FT-IR: 3037 (C—H Ar, Str), 2945; 2842 (C—H Aliph, Str), 1708 (C═O, Str), 1642 (C═N, Str), 1540; 1471 (C═C, Str), 1371 (C—N, Str), 692 (S—N, Str), 660 (C—S, Str), UPLC-MS: 473.19 (M + 3, 10), 472.26 (M + 2, 50), 471.20 (M+, 100), HPLC: R_t = 11.16 min, P = 95%, TLC: R_f = 0.82, m_p = 193–194 °C, Y = 36%.

4.1.2.14. 2-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)–2H-naphtho [1,8-cd]isothiazole 1,1-dioxide 1n. Molecular formula: $C_{27}H_{30}N_4O_2S_2$ ^{1}H NMR (400 MHz, DMSO) δ 8.31 (d, J = 8.1 Hz, 1H, ArH), 8.25 (d, J = 7.2 Hz, 1H, ArH), 8.17–8.10 (m, 2H, ArH), 7.93–7.88 (m, 1H, ArH), 7.64–7.57 (m, 3H, ArH), 7.48 (t, J = 7.2 Hz, 1H, ArH), 7.11 (d, J = 6.6 Hz, 1H, ArH), 4.09 (d, J = 12.8 Hz, 2H, SONCH), 3.87 (t, J = 7.3 Hz, 2H, CH_{Pip}), 3.61–3.53 (m, 2H, CH_{Pip}), 3.39–3.30 (m, 2H, CH_{Pip}), 3.27–3.20 (m, 2H, CH_{Pip}), 3.19–3.09 (m, 2H, CH_{Pip}), 1.90–1.85 (m, 2H, CH_{Aliph}), 1.73–1.66 (m, 2H, CH_{Aliph}), 1.55–1.47 (m, 2H, CH_{Aliph}), 1.43 (d, J = 7.3 Hz, 2H, CH_{Aliph}), FT-IR: 2978 (C—H Ar, Str), 2939, 2884 (C—H, Aliph, Str), 1639 (C═N, Str), 1594, 1476 (C═C Ar, Str), 1376 (C—N, Str), 1298 (S═O, Str), 687 (S—N, Str), HPLC: R_t = 8.97 min, P = 100%, TLC: R_f = 0.87, m_p = 117–121 °C, Y = 45%.

4.1.2.15. 2-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione 1o. Molecular formula: $C_{29}H_{30}N_4O_2S$ ^{1}H NMR (400 MHz, DMSO) δ 8.50–8.41 (m, 4H, ArH), 8.16–8.08 (m, 2H, ArH), 7.88 (d, J = 7.7 Hz, 2H, ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.47 (t, J = 7.4 Hz, 1H, ArH), 3.64 (t, J = 19.2 Hz, 2H, CONCH), 3.59 (t, J = 12.1 Hz, 2H, CH_{Pip}), 3.47 (t, J = 12.3 Hz, 2H, CH_{Pip}), 3.37–3.20 (m, 4H, CH_{Pip}), 3.16–3.10 (s, 2H, CH_{Pip}), 1.73 (d, J = 19.2 Hz, 2H, CH_{Aliph}), 1.69–1.53 (m, 2H, CH_{Aliph}), 1.41–1.33 (m, 4H, CH_{Aliph}), FT-IR: 3062 (C—H Ar, Str), 2942, 2874 (C—H, Aliph, Str), 1693 (C═O, Str), 1656 (C═N, Str), 1589, 1493 (C═C Ar, Str), 1354 (C—N, Str), 697 (S—N, Str), UPLC-MS: 501.11 (M + 3, 15), 500.24 (M + 2, 40), 499.25 (M+, 100), 158.24 (5) HPLC: R_t = 5.83 min, P = 100%, TLC: R_f = 0.47, m_p = 201–203 °C, Y = 47%.

4.1.2.16. 1-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-5,6-dihydro-1H-imidazo[4,5,1-ij]quinolin-2(4H)-one 1p. Molecular formula: $C_{27}H_{33}N_5OS$ ^{1}H NMR (400 MHz, DMSO) δ 8.12 (t, J = 8.6 Hz, 2H, ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.48 (t, J = 7.2 Hz, 1H, ArH), 7.00 (d, J = 7.6 Hz, 1H, ArH), 6.93 (dd, J = 9.5, 5.8 Hz, 1H, ArH), 6.83 (d, J = 7.4 Hz, 1H, ArH), 4.05 (d, J = 13.7 Hz, 2H, CONCH), 3.78–3.65 (m, 4H, CH_{Pip}), 3.58–3.44 (m, 4H, CH_{Pip}), 3.31–3.21 (m, 2H, CH_{Pip}), 3.11–3.03 (m, 2H, CH_{Pip}), 2.79 (t, J = 5.8 Hz, 2H, CH_{Aliph}), 2.02–1.98 (m, 2H, CH_{Aliph}), 1.69–1.60 (m, 4H, CH_{Aliph}), 1.35 (d, J = 3.6 Hz, 4H, CH_{Aliph}), FT-IR: 3067 (C—H Ar, Str), 2935; 2859 (C—H Aliph, Str), 1672 (C═O Str), 1642 (C═N, Str), 1589; 1498 (C═C Ar, Str), 1379 (C—N, Str), 677 (S—N, Str), 656 (C—S, Str), HPLC: R_t = 4.54 min, P = 97%, TLC: R_f = 0.80, m_p = 55–58 °C, (oiled), Y = 67%.

4.1.2.17. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-N-(3-(trifluoromethyl)phenyl)benzenesulfonamide 1q. Molecular formula: $C_{30}H_{33}F_3N_4O_2S_2$ ^{1}H NMR (400 MHz, DMSO) δ 8.12–8.08 (m, 2H, ArH), 7.73 (d, J = 7.2 Hz, 2H, ArH), 7.66–7.52 (m, 6H, ArH), 7.48–7.45 (m, 1H, ArH), 7.42 (d, J = 7.5 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 3.67–3.61 (m, 2H, SONCH), 3.21–3.14 (m, 8H, CH_{Pip}), 1.74–1.69 (m, 2H, CH_{Pip}), 1.56–1.40 (m, 4H, CH_{Aliph}), 1.33–1.21 (vm, 4H, CH_{Aliph}), FT-IR: 3063 (C—H Ar, Str), 2937; 2854 (C—H Aliph, Str), 1490 (C═C Ar, Str), 1370 (C—N, Str), 1326 (S═O, Str), 1233 (C-F, Str), 690 (S—N, Str), 654 (C—S, Str), HPLC: R_t = 7.82 min, P = 92%, TLC: R_f = 0.88, m_p = 217–220 °C, Y = 54%.

4.1.2.18. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-4-methyl-N-phenylbenzenesulfonamide 1r. Molecular formula: $C_{30}H_{36}N_4O_2S_2$ ^{1}H NMR (400 MHz, DMSO) δ 8.17–8.09 (m, 3H, ArH), 7.61 (t, J = 7.5 Hz, 2H, ArH), 7.51–7.44 (m, 3H, ArH), 7.42 (s, 1H, ArH), 7.41–7.32 (m, 3H, ArH), 7.08–7.05 (m, 1H, ArH), 4.08 (d, J = 13.5 Hz, 2H, SONCH), 3.44 (d, J = 14.5 Hz, 2H, CH_{Pip}), 3.36–3.24 (m, 4H,

CH_{Pip}), 3.21–3.14 (m, 2H, CH_{Pip}), 1.80–1.71 (m, 2H, CH_{Pip}), 1.62 (d, J = 39.1 Hz, 2H, CH_{Aliph}), 1.55–1.44 (m, 3H, CH_{Aliph}), 1.38 (d, J = 19.4 Hz, 2H, CH_{Aliph}), 1.36–1.28 (m, 4H, CH_{Aliph}), FT-IR: 3067 (C—H Ar, Str), 2932; 2833 (C—H Aliph, Str), 1590, 1484 (C═C Ar, Str), 1380 (C—N, Str), 1361 (S═O, Str), 691 (S—N, Str), 653(C—S, Str), HPLC: R_t = 6.29 min, P = 91%, TLC: R_f = 0.88, m_p = 128–130 °C, Y = 63%.

4.1.3. Synthesis of compound 1s

A mixture of 6-bromohexylated derivative **4x** (0.002 mol), arylpiperazine **5a** (0.002 mol), 0.76 g of K_2CO_3 (0.006 mol) and 0.06 g of TBAB (0.0002 mol) were triturated in a mortar. The triturated mixture was transferred to a round bottom flask, and 0.5 cm^3 of DMF was added. The reactions were carried out for 60 s in a CEM Discover microwave reactor at 100 W output power. The progress of the reaction was monitored by TLC. After completion of the reaction, 50 cm^3 of water was added to the mixture and placed in the refrigerator overnight. After cooling, the crude product (**1x**) was filtered off. In the absence of the required purity, the crude product was purified by column chromatography using chloroform:methanol 9:1 eluent as mobile phase. After obtaining a minimum of 95% purity, the product (**1x**) was dissolved in acetone, then converted to hydrochloride by 4 M HCl in dioxane resulting in the desired compound (**1s**). The reaction yield for 1-(6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexyl)-1H-benzo[*d*]imidazol-2(3H)-one (**1s**) was calculated on the basis of the weight of the obtained hydrochloride.

4.1.3.1. 1-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)-1H-benzo[d]imidazol-2(3H)-one 1s. Molecular formula: $C_{24}H_{28}N_5OS$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H, NH), 7.85 (t, J = 8.8 Hz, 2H, ArH), 7.53 (t, J = 7.4 Hz, 1H, ArH), 7.41 (t, J = 7.5 Hz, 1H, ArH), 7.09 (dt, J = 21.7, 7.5 Hz, 3H, ArH), 6.99 (d, J = 7.8 Hz, 1H, ArH), 4.14 (d, J = 28.7 Hz, 4H, CH_{Pip}), 3.89 (t, J = 6.7 Hz, 2H, CONCH), 3.54 (dd, J = 7.9, 4.5 Hz, 2H, CH_{Pip}), 3.12 (s, 2H, CH_{Pip}), 3.01 (d, J = 4.3 Hz, 2H, CH_{Pip}), 1.99 (m, 4H, CH_{Aliph}), 1.43 (m, 3H, CH_{Aliph}), FT-IR: 3398 (N—H amine, Str), 3030 (C—H Ar, Str), 2931; 2856 (C—H Aliph, Str), 1758; 1708 (C═O, Str), 1612; 1590 (C═C Ar, Str), 1364 (C—N, Str), 742 (S—N, Str), 650 (C—S, Str), UPLC-MS: 439,43 (M + 4, 5), 438,36 (M + 3, 10), 437,43 (M + 2, 32), 436,37 (M + 1, 100), 177,18 (5); HPLC: R_t = 4.86 min, P = 96%, TLC: R_f = 0.58, m_p = 134–135 °C, Y = 20%.

4.1.4. Synthesis of amine 6

A mixture of 0.35 g of 2-(6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexyl)isoindoline-1,3-dione **1h** (0.003 mol) and 15 ml of 40% aqueous solution of methylamine was stirred at room temperature for 48 h. After this time, 15 ml 20% aqueous solution of NaOH was added to the mixture and the mixture was stirred for another 24 h. Then, the resulting solution was mixed with 10 cm^3 of brine and extracted with 2 × 30 cm^3 methylene chloride. Organic layer was washed with water and dried over anhydrous magnesium sulphate. After the evaporation of methylene chloride under reduced pressure, the desired product (**6**) was obtained. The reaction yield for 6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)hexan-1-amine (**6**) was calculated on the basis of the weight of the obtained product (**6**).

4.1.4.1. 6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexan-1-amine 6. Molecular formula: $C_{17}H_{26}N_4S$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.66 (m, 2H, ArH), 7.57–7.19 (m, 2H, ArH), 3.79–3.35 (m, 4H, CH_{Pip}), 3.11 (dd, J = 13.5, 8.7 Hz, 2H, CH_{Aliph}), 2.83–2.60 (m, 4H, CH_{Pip} 2.55–2.31 (m, 2H, amine-NH_2), 1.79–1.14 (m, 10*H*, CH_{Aliph}), FT-IR: 3342 (N—H amine,Str), 3054 (C—H Ar, Str), 2926, 2846, 2812, 27,69 (C—H Aliph, Str), 1633, 1590, 1559 (C═C Ar, Str), 1258, 1147, 1130, (C—N, Str), 773, 734 (S—N, Str), 679 (C—S, Str); HPLC: R_t = 1.39 min, P = 99%, TLC: R_f = 0.07, m_p = 72–75 °C, Y = 100%.

4.1.5. Synthesis of compounds 1 t-w

A mixture of 1.91 g of 6-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl) hexan-1-amine **6** (0.006 mol), 30 cm^3 of methylene chloride and 0.63 cm^3 of triethylamine was stirred in a round bottom flask. After complete dissolution of substrate (**6**), a benzoyl chloride **7 t** (0.0006 mol) or corresponding arylsulphonyl chloride **7u/v/w** (0.0006 mol**)** was added. The reaction mixture was stirred upon dissolution of chloride and left at room temperature for 3 h. After that time, the remaining solvent was evaporated under reduced pressure and the precipitate was dissolved in 20 cm^3 methylene chloride and washed with 20 cm^3 of 5% $NaHCO_3$ and 20 cm^3 of water. Then, the organic layer was dried over anhydrous magnesium sulphate and the solvent was evaporated. Crude benzamide (**1t**) and sulphonamides (**1u/1v/1w**) were purified by column chromatography using chloroform:methanol 9:1 eluent as mobile phase, and after obtaining min. 95%, the compounds (**1t/1u/1v/1w**) were dissolved in acetone and converted to hydrochloride by 4 M HCl in dioxane. The reaction yields were calculated on the basis of the weight of the obtained hydrochlorides.

4.1.5.1. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl)benzamide 1t. Molecular formula: $C_{24}H_{30}N_4OS$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.79 (m, 3H, ArH), 7.58–7.39 (m, 5H, ArH), 6.57 (m, 1H, ArH), 4.25–4.06 (m, 4H, $CH_{Pip,}$ CONCH), 3.75 (q, J = 7.0 Hz, 1H, NH), 3.50 (d, J = 6.3 Hz, 4H, CH_{Pip}), 3.24–3.07 (m, 2H, CH_{Pip}), 3.04–2.94 (m, 2H, CH_{Pip}), 2.00 (m, 2H, CH_{Aliph}), 1.76–1.67 (m, 2H, CH_{Aliph}), 1.51 (d, J = 3.5 Hz, 2H, CH_{Aliph}), 1.27 (dd, J = 8.6, 5.5 Hz, 2H, CH_{Aliph}), FT-IR: 3288 (N—H amine,Str), 3055 (C—H Ar, Str), 2939, 2856 (C—H Aliph, Str), 1642, 1576 (C═C Ar, Str), 1487 (C—N, Str), 773, 742 (S—N, Str), 677, 669 (C—S, Str), HPLC: R_t = 1.70 min, P = 95%, TLC: R_f = 0.54, m_p = 210 °C, Y = 28%.

4.1.5.2. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl) benzenesulfonamide 1u. Molecular formula: $C_{23}H_{30}N_4O_2S_2$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.91 (m, 2H, ArH), 7.86 (t, J = 8.2 Hz, 2H, ArH), 7.61–7.49 (m, 4H, ArH), 7.42 (t, J = 7.9 Hz, 1H, ArH), 5.79 (s, 1H, NH), 4.26–4.05 (m, 4H, $CH_{Pip,}$ CONCH), 3.65 (d, J = 10.6 Hz, 2H, CH_{Pip}), 3.24–3.04 (m, 4H, CH_{Pip}), 2.99–2.93 (m, 2H, CH_{Pip}), 2.17–1.18 (m, 8H, CH_{Aliph}), FT-IR: 3268 (N—H amine, Str), 3054 (C—H Ar, Str), 2941; 2855 (C—H Aliph, Str), 1589 (C═C Ar, Str), 1380 (C—N, Str), 1317 (S═O, Str), 751 (S—N, Str), 659 (C—S, Str), HPLC: R_t = 1.705 min, P = 96%, TLC: R_f = 0.6, m_p = 164–166 °C, Y = 41%.

4.1.5.3. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl) naphthalene-1-sulfonamide 1v. Molecular formula: $C_{27}H_{32}N_4O_2S_2$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 8.7 Hz, 1H, ArH), 8.29–8.24 (m, 1H, ArH), 8.07 (d, J = 8.3 Hz, 1H, ArH), 7.96 (d, J = 8.1 Hz, 1H, ArH), 7.87 (t, J = 7.4 Hz, 2H, ArH), 7.72 (m, 1H, ArH), 7.64–7.59 (m, 1H, ArH), 7.58–7.52 (m, 2H, ArH), 7.42 (t, J = 7.6 Hz, 1H, ArH), 5.85 (s, 1H, NH), 4.26–4.04 (m, 4H, CH_{Pip}), 3.60 (d, J = 12.2 Hz, 2H, SONCH), 3.17–3.11 (m, 2H, CH_{Pip}), 3.05–2.97 (m, 2H, CH_{Pip}), 2.93 (t, J = 6.4 Hz, 2H, CH_{Pip}), 1.97–1.33 (m, 8H, CH_{Aliph}). FT-IR: 3268 (N—H amine,Str), 3055 (C—H Ar, Str), 2969; 2940; 2855 (C—H Aliph, Str), 1589 (C═C Ar, Str), 1380 (C—N, Str), 1316 (S═O, Str), 751 (S—N, Str), 659 (C—S, Str), HPLC: R_t = 1.91 min, P = 97%, TLC: R_f = 0.67, m_p = 156 °C, Y = 75%.

4.1.5.4. N-(6-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)hexyl) naphthalene-2-sulfonamide 1w. Molecular formula: $C_{27}H_{32}N_4O_2S_2$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, J = 14.1, 8.7 Hz, 3H, ArH), 7.93 (m, J = 6.4 Hz, 1H, ArH), 7.87 (m, J = 7.0 Hz, 1H, ArH), 7.79 (m, J = 11.6, 8.1 Hz, 1H, ArH), 7.65 (m, J = 13.7, 7.7 Hz, 3H, ArH), 7.54 (t, J = 7.4 Hz, 1H, ArH), 7.48–7.42 (m, 1H, ArH), 4.16 (s, 1H, NH), 3.70–3.64 (m, 2H, CONCH), 3.39–3.33 (m, 2H, CH_{Pip}), 3.13 (m, J = 7.3, 4.9 Hz, 4H, CH_{Pip}), 1.84–1.39 (m, 12H, CH_{Pip}, CH_{Aliph}), FT-IR: 3293 (N—H amine,Str), 3092 (C—H Ar, Str), 2942, 2919, 2879, 2862

(C—H Aliph, Str), 1585 (C=C Ar, Str), 1426 (C—N, Str), 1316 (S=O, Str), 773 (S—N, Str), 657 (C—S, Str), HPLC: R_t = 1.91 min, P = 98%, TLC: R_f = 0.65, m_p = 112 °C, Y = 74%.

4.2. In vitro evaluation

4.2.1. Cell culture and preparation of cell membranes for radioligand binding assays

HEK293 cells with stable expression of human 5-HT_{1A}, 5-HT_6, 5-HT_{7b} and D_{2L} receptors were prepared with the use of Lipofectamine 2000. CHO-K1 cells, with plasmid containing the sequence coding for the human serotonin 5-HT_{2A} receptor were prepared using PerkinElmer. The cells were maintained at 37 °C in a humidified atmosphere, with 5% CO_2 and grown in Dulbecco's Modifier Eagle Medium (10% dialyzed fetal bovine serum, 500 μg/ml G418 sulfate). For membrane preparation, the cells were subcultured in 150 cm^2 flasks, grown to 90% confluence and then washed twice with pre-warmed to 37 °C phosphate buffered saline (PBS) and pelleted by centrifugation (using ×200*g*) in PBS containing 0.1 mM EDTA and 1 mM dithiothreitol. The pellets were stored at −80 °C.

4.2.2. Radioligand binding assays

The thawed cell pellets were homogenized in 20 volumes of assay buffer in tissue homogenizer (Ultra Turrax) and then centrifuged twice at 35*g* for 20 min (4 °C), with incubation for 15 min (37 °C) in between rounds of centrifugation. The composition of the assay buffers:

5-HT_{1A} − 50 mM Tris–HCl, 0.1 mM EDTA, 4 mM $MgCl_2$, 10 μM pargyline and 0.1% ascorbate; 5-HT_{2A} − 50 mM Tris–HCl, 0.1 mM EDTA, 4 mM $MgCl_2$, and 0.1% ascorbate; 5-HT_6 − 50 mM Tris–HCl, 0.5 mM EDTA and 4 mM $MgCl_2$; 5-HT_7 − 50 mM Tris–HCl, 4 mM $MgCl_2$, 10 μM pargyline and 0.1% ascorbate; D_2 − 50 mM Tris HCl, 1 mM EDTA, 4 mM $MgCl_2$, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$ and 0.1% ascorbate.

The assays were incubated in a total volume of 200 μl in 96-well microtiter plates for 1 h (37 °C, except for 5-HT_{1A} and 5-HT_{2A}, which were incubated at room temperature). The process of equilibration was terminated by rapid filtration through Unifilter plates (96-well cell harvester, PerkinElmer), and the radioactivity retained on the filters was quantified on a Microbeta plate reader (PerkinElmer).

For displacement studies, the assay samples contained the following as radioligands: 2.5 nM [^{3}H]-8-OHDPAT (187 Ci/mmol) − 5-HT_{1A}; 1 nM [^{3}H]-Ketanserin (53.4 Ci/mmol) − 5-HT_{2A},; 2 nM [^{3}H]-LSD (85 k Ci/mmol) − 5-HT_6; 0.8 nM [^{3}H]-5-CT (39.2 Ci/mmol) − 5-HT_7; 2.5 nM [^{3}H]-raclopride (76.0 Ci/mmol) - D_2. Nonspecific binding was defined with 10 μM of 5-HT (5-HT_{1A}, 5-HT_7). 10 μM of chlorpromazine or 10 μM of methiothepine were used in the 5-HT_{2A}/D_2 and 5-HT_6 assays, respectively.[29] Each compound was tested in triplicate at 8 different concentrations (10^{-4} to 10^{-11} M). The inhibition constants (*K*i) were calculated from the Cheng-Prusoff equation.[30] The results are expressed as the means of at least two separate experiments. The reference compounds: Buspirone for 5-HT_{1A}, Olanzapine for 5-HT_{2A} and 5-HT_6, Clozapine for 5-HT_7 and Risperidone for D_2.

4.3. Molecular modelling

The 3-dimensional structures were prepared using LigPrep 3.7.[31] The appropriate ionization states at pH ¼ 7.4 were assigned using Epik.[32] To assign the bond orders and appropriate amino acid ionization states The Protein Preparation Wizard was used. The grids were generated by centering the grid box of the size of 12 Å on the Asp3.32 with OPLS_2005 force field. Docking was performed by using Glide version 7.0, with the flexible docking option turned on. The poses were optimized with QM/MM approach (functional DFT-B3LYP and LACVP as basis set). QM region was set up on conserved amino acids and ligand.[33] The homology model of the active 5-HT_{1A} (template 5-HT_{1B}; pdb ID: 5V54[34]) and 5-HT_{2A} (template pdb ID: 6BQG[35]) receptor were used, from gpcrdb[36], as well as the crystal structure of the D_2 (pdb ID: 6CM4[37]) receptor in the complex with Risperidone. The homology model of the 5-HT_6R and 5-HT_7R were generated in SWISS-MODEL automated protein structure homology-modelling server,[38] using templates: 5-HT_6 (template 5-HT_{2A}; pdb ID: 6A94[39]) 5-HT_7 (template 5-HT_{1B}; pdb ID: 6G79[40]). Amino acid sequences were taken from Uniprot.[41] For the graphic presentation of selected the structures, PyMOL 3.7[42] software was used. The models were validated using SWISS-MODEL server[38], by QMEAN[43] parameters determination. The percent of residues in favored regions of the Ramachandran plot was also determined.[44] Molecular docking was carried out for a set of ligands with known affinity. The sets of ligands with known activities (K_i < 50 nM) and inactivities (K_i > 500 nM) were retrieved from the ChEMBL database.[45] The selected set contained mainly ligands from the group of long-chain arylpiperazines and arylpiperidines due to the similarity of the binding mode. 25 active and 25 inactive ligands were selected.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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