Table 6: values of the descriptors for individual compounds.

Name of the compound	Molecular surface area (whole molecule)	Verloop B2 (subs 2)	Verloop B4 (subs 3)	KierChiv 4 (subs 3)
4	294.682	2.09779	2.02262	0.383284
5	320.969	2.00424	3.08551	0.383284
6	0	2.5611	3.22968	0.383284
7	339.552	2.42569	2.82775	0.383284
8	327.953	2.37467	1.65	0.383284
9	329.275	2.55983	1.65494	0.383284
15	344.27	2.0588	2.02749	0.621575
16	401.41	2.00014	2.02969	0.545889
17	430.474	2.02243	2.02537	0.698765
18	424.358	2.05526	2.02702	0.698765
19	300.876	2.0185	2.02128	0.621775
20	297.775	2.07737	2.02109	0.545329
21	304.974	2.01965	2.02615	0.613964
22	311.839	2.02691	2.0212	0.654437
23	327.768	2.05954	2.03903	0.807468
27	320.734	2.0564	2.03035	0.383284
28	341.324	2.11945	2.02349	0.621575
29	455.694	1.96899	2.02017	0.698765
30	317.397	1.95878	2.02986	0.545329
31	314.376	2.00834	2.02134	0.613964
32	311.326	1.72337	2.02345	0.613964
33	339.85	2.12043	2.02186	0.807468
34	322.256	1.65852	2.02295	0.807468
43	319.796	1.77131	1.9	0.807468
44	312.548	1.65059	1.8	0.807468
45	321.841	1.73201	1.65	0.807468
46	302.876	1.9402	1.9	0.654437
47	306.878	1.66433	1.8	0.654437
48	300.212	1.65371	1.65	0.654437
49	322.509	1.66649	1.9	0.613964
50	302.523	1.65473	1.8	0.613964
51	300.259	1.66791	1.65	0.613964

Table 7: Depicting values of various parameters constituting Lipinski's rule of five.

Name of the Compound	ADME weight(Whole molecule)	ADME H-bond Acceptors	ADME H-bond donors	ADME log P	ADME violations
4	319.4	4	1	2.1557	0
5	333.43	4	1	2.552	0
6	359.47	4	1	2.721	0
7	387.4	4	1	2.9138	0
8	344.41	5	1	1.896	0
9	343.42	4	1	2.2126	0
15	366.46	4	1	3.2458	0
16	413.53	5	1	2.4939	0
17	430.61	5	1	2.9088	0
18	416.58	5	1	2.5125	0
19	328.41	3	2	2.1816	0
20	341.41	5	1	1.585	0
21	340.42	4	1	2.4978	0
22	340.42	4	1	2.5636	0
23	358.44	4	1	1.6098	0
27	342.45	4	2	2.4641	0
28	389.51	4	2	3.5542	0
29	453.66	5	2	3.2172	0
30	364.46	5	2	1.8934	0
31	363.47	4	2	2.8062	0
32	349.44	4	2	2.6577	0
33	381.49	4	2	1.9182	0
34	367.46	4	2	1.7697	0
43	432.32	4	2	2.0943	0
44	387.87	4	2	1.8205	0
45	378.44	5	2	1.1675	0
46	414.3	4	2	3.0481	0
47	369.85	4	2	2.7743	0
48	360.42	5	2	2.1213	0
49	414.3	4	2	2.9823	0
50	369.85	4	2	2.7085	0
51	360.42	5	2	2.0555	0

In depth analysis of the derived descriptors and their correlation with the structural architecture of the molecules helped in surfacing of the interesting facts. Upon comparison of the least active molecule with that of the most active compound of the selected series we observed that in compound 7 (least active), R_1 is substituted with the methoxy benzene, R_2 with methyl group and R_3 with an ester group all of which increased the shape and volume of the molecule and eventually resulted in enhanced surface area. Whereas in the most active compound, compound 48, methoxy benzene is replaced with a fused heterocyclic substituent and ester group with a triazole ring both of which reduced the width and volume of the molecule, thus, resulting in profound increase in the JNK3 inhibitory activity. Interestingly, both ester and triazole ring have comparable molecular mass and, thus, no additional bulk was introduced to the molecule. Therefore, a simple augmentation in bulk or mass cannot be accounted for an improved activity profile. The possible reason for improved activity, perhaps, could be the flat structure of the triazole ring, which leads to compression in the shape of the molecule, that allows it to conveniently enter into the binding site and align in such a way that it fits snugly with the walls of the active site. The shape of the triazole ring, hence, can be attributed for the better orientation of the molecule that capacitate it to show better interactions with the binding domain. In addition to this, compound 48 has lower molecular mass (360.42) than compound 7 (387.4) that may also be accounted for the discernible augmentation in the activity. Also, the compounds bearing chloro and cyano groups were found to be the most potent and those bearing bromo group exhibited comparatively less potency. The dramatic increase in the biological activity can clearly be attributed to the fact that chloro and cyano groups being highly electronegative, decreased the overall nucleophilicity of the molecule to a greater extent than the bromo group, which is comparatively less electronegative. The decreased nucleophilic character of the molecule eventually capacitated the molecule to accept the electron pairs and make covalent bonds with the receptor binding domain. A point must be made here, that positive correlation of Kier Chiv4 (path/cluster) index at R_1 indicates an increase in bulk at this position would lead to increase in activity but Molecular surface area, which is in negative correlation with the whole molecule predicts the decrease in activity with overall increase in volume or size of the molecule (Figure 10). Therefore, an optimal increase in the bulk or branching only at certain positions will bring about an increase in bioactivity of the molecules. The above results explicitly indicates that all the descriptors that entered the final 2D QSAR model were significant and their correlation with the biological activity concurred well to the substitution present in the structures of the selected series of the JNK3 inhibitors. The in-depth study of these physicochemical parameters has provided substantial insights to design better chemical scaffolds in term of selectivity and efficacy. This model has provided sufficient information to design new molecules and have ignited a hope that through incorporating the appropriate features, deduced to be important through these descriptors, designing of JNK3 inhibitors with a better selectivity profile can be easily achieved.

CONCLUSION

Through the proposed study, an effort has been made to analyse the reported JNK3 inhibitors and to get insight into their structural architecture responsible for their specific JNK3 inhibitory activity, and thereby to suggest the beneficial or detrimental impact of the substitution pattern on the biological activity. The scrupulous evaluation of the chemical structures and the physicochemical descriptors derived from them capacitated us to understand the dependence of the biological activity on the structural architecture of the molecules. The major factor that govern the efficacy of a CNS targeting drug is its ability to cross Blood Brain Barrier (BBB) which in turn depends on optimal logP (partition coefficient), Molecular mass and polar surface area. The developed model explicitly indicated that an introduction of optimal bulk or mass distribution at certain positions, and not at any position, will lead to an increased activity profile of the selected set of compounds. Additionally, the shape of the molecules, that determines the efficacy with which a molecule aligns itself with the binding domain of the active site, was found to be a dominating factor in determining the potency of these JNK3 inhibitors. Also, decreasing the overall nucleophilic character, through replacement of electron donor groups with electronegative groups resulted in overall increase in the activity. Therefore, through this work, we concluded that when molecules are substituted with those groups, at certain positions, that increase the mass of the molecule but compresses its shape, hence, its surface area and those that decreases the nucleophilic character of these molecules can, possibly, contribute positively towards increasing the bioactivity and selectivity and, hence, exhibiting better JNK3 inhibitory activity. The proposed study, capacitated us to gain insights into the structural dependency of the biological activity and thereby to suggest possible replacements that, perhaps, would eventually lead to optimized JNK3 inhibitors with better activity as well as selectivity profile.

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