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Crystallographic structure, activity prediction, and hydrogen bonding analysis of some CSD-based 3,3'-*bis*-indole derivatives: A review

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REVIEW ARTICLE

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ABSTRACT

Herein we report crystallographic comparison of some geometrical and structural features for a series of biologically relevant bis-indole derivatives. Selected bond distances and bond angles of interest in a series of bis-indole derivatives have been discussed in detail. The biological activity of the substances has been correlated with based the structure-activity relationships (SAR) base which provides the different possibility of activity (Pa) and possibility of inactivity (Pi). For a better understanding of the packing interactions existing among these derivatives, an overview of crystal structure analysis with emphasis on the intramolecular hydrogen bonding in some bis-indole derivatives is presented. The role of hydrogen bonding in the crystal structure assembly of bis-indole derivatives has been found to be predominant and this observation reveals significant impact of hydrogen bonding in high value of drug-likeness of these bio-molecules.

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1. Introduction

Indole is the structural core unit of bis-indole derivatives, which are an important class of heterocyclic compounds having a wide variety of biological activities in both research and development of pharmaceuticals. Bis-indolylmethane derivatives (BIMs), mainly consist of two indole moieties connected to each other via heterocyclic units (Figure 1). These class of indole derivatives exhibits a diverse class of biological properties such as antifungal, antibacterial [1], anti-implantation activities [2]. Moreover, BIMs have also been found to be potent anticancer derivatives, and clinical studies have demonstrated that they could be potentially used as chemotherapeutic agents against various forms of cancer. BIM suppresses the proliferation of estrogen dependent reproductive cancers of breast [3], ovarian [4], cervical [5], and prostate [6] but also thyroid [7], neck and head [8], melanoma or blood cells (leukemia) [9]. BIMs is a potent radioprotector against UV and ionizing radiation acting by a unique mechanism of sudden activation of a nuclear kinase which regulates the response to DNA damage, repair, or apoptosis and oxidative stress [10]. Even though the most reactive site for electrophilic attack is 3-position for indole [11] but due to the competitive formation of 1,3-di-alkyl/acylated and/or 1-acylated products, low yields are always encountered because of the ambident nature of the indole ring system.

The current work provides comprehensive account of structural characteristics and packing interactions/hydrogen bonding in bis-indole derivatives. Here, we have identified a series of forty-one derivatives of bis-indole from the literature, for which an online survey of Cambridge Structural Database (CSD) has been performed. The reference code, chemical name, chemical formula, and published reference [12-53] of each molecule is presented in Table 1.

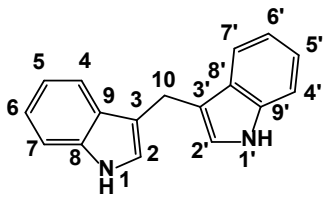

Figure 1. Basic bis-indole molecule with numbering scheme.

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Table 1. CSD codes, chemical name, chemical formula, molecular wt. and reference of Molecule M1-41.

Molecule	CSD code	CCDC code	Chemical name	Chemical formula	Ref.
M1	TAXTAQ	1528295	3,3'-((3,4-Dimethoxyphenyl)methylene)bis(1H-indole)	$C_{25}H_{22}N_2O_2$	[12]
M2A	TEVTIY	633690	3,3'-(4-Bromophenylmethanediyl)bis(5-methoxy-1H-indole)	$C_{25}H_{21}BrN_2O_2$	[13]
M2B	TEVTIY01	1511318	3,3'-[(4-Bromophenyl)methylene]bis(5-methoxy-1H-indole)	$C_{25}H_{21}BrN_2O_2$	[14]
M3	DEFMEH	233333	3,3-Bis(1H-indol-3-yl)indolin-2-one	$C_{24}H_{17}N_3O{\cdot}C_2H_6O_1$	[15]
M4	DOPZIT	1024391	Dimethyl 3,3'-((4-chlorophenyl)methylene)bis(1H-indole-2-carboxylate)	$C_{27}H_{21}Cl_1N_2O_4$	[16]
M5	EHINAM	1408303	5,5''-Dibromo-1,1'-dimethyl-1H,1''H-3,3':3',3''-terindol-2'(1'H)-one	$C_{26}H_{19}Br_2N_3O_1$	[17]
M6	EMIGUE	1029492	5,5''-Difluoro-1H,1''H-3,3':3',3''-terindol-2'(1'H)-one dimethyl sulfoxide solvate	$C_{24}H_{15}F_2N_3O{\cdot}2(C_2H_6OS)$	[18]
M7	EVAKES	834300	4-(Bis(1H-Indol-3-yl)methyl)benzonitrile	$C_{24}H_{17}N_3$	[19]
M8	GIHDUY	950651	2-(2,2-Bis(1H-Indol-3-yl)ethyl)aniline	$C_{24}H_{21}N_3$	[20]
M9	GUCJEV	1017941	5'-Nitro-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one dimethyl sulfoxide solvate	$C_{26}H_{22}N_4O_4S$	[21]
M10	HABWOY	277162	3,3',3''-Methanetriyltris(6-methyl-1H-indole)	$C_{28}H_{25}N_3$	[22]
M11	HODROH	135757	Bis(Indol-3-yl)(p-tolyl)methane	$C_{24}H_{20}N_2$	[23]
M12	HOYPAN	719583	4,4-Bis(1-Benzyl-5-bromo-1H-indol-3-yl)but-3-en-2-onedimethylsulfoxide solvate	$C_{34}H_{26}Br_2O{\cdot}C_2H_6OS$	[24]
M13	IVALEX	802362	3,3'-Ethene-1,1-diylbis(2-phenyl-1H-indole)	$C_{30}H_{22}N_2$	[25]
M14	KEQREE	625021	5,5'-Dimethoxy-3,3'-(3-fluorophenylmethanediyl)-bis(1H-indole)	$C_{25}H_{21}FN_2O_2$	[26]
M15	KIFMES	277582	5,5'-Dimethoxy-3,3'-di-indolyl(4-(phenyl)phenyl)methane	$C_{31}H_{26}N_2O_2$	[27]
M16	LANFIS	1511319	5-Methoxy-3-((5-methoxy-1H-indol-3-yl)(4-methylphenyl)methyl)-1H-indole	$C_{26}H_{24}N_2O_2$	[14]
M17	LAWGEY	1497585	3-((4-Chlorophenyl)(1H-indol-3-yl)methyl)-1H-indole ethyl acetate solvate	$C_{23}H_{17}ClN_2{\cdot}C_4H_8O_2$	[28]
M18	LOKKON	946729	3,3'-(1-Naphthylmethylene)bis-1H-indole dimethylsulfoxide solvate	$C_{27}H_{20}N_2{\cdot}C_2H_6OS$	[29]
M19	MASQAB	1532121	3-[(4-Bromophenyl)(1H-indol-3-yl)methyl]-1-methyl-1H-indole	$C_{24}H_{19}BrN_2$	[30]
M20	MAVCUI	287459	3,3-Bis(1H-Indol-3-yl)indolin-2-one	$C_{24}H_{17}N_3O$	[31]
M21	MEDJEK	140500	1,1-Bis(Indol-3-yl)-1-phenylethane	$C_{24}H_{20}N_2$	[32]
M22	NUQGAJ	1421585	Dimethyl 3,3'-((4-fluorophenyl)methylene)bis(1H-indole-2-carboxylate)	$C_{27}H_{21}FN_2O_4$	[33]
M23	OBABOL	1492901	3-((4-Nitrophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indole	$C_{35}H_{25}N_3O_2$	[34]
M24	OCESAS	807664	3,3'-(Phenylmethylene)bis(5-methoxy-1H-indole)	$C_{25}H_{22}N_2O_2$	[35]
M25	ODAFAD	1408973	3,3'-((4-Methoxyphenyl)methylene)bis(1-methyl-1H-indole)	$C_{26}H_{24}N_2O$	[36]
M26	OYUXUD	1007024	3,3'-(2,2-Dimethylpropane-1,1-diyl)bis(1H-indole)	$C_{21}H_{22}N_2$	[37]
M27	PADKUD	966140	3,3'-((4-Methoxyphenyl)methylene)bis(1-ethyl-1H-indole)	$C_{28}H_{28}N_2O$	[38]
M28	PAHSAV	1038916	3,3'-(Phenylmethylene)bis(1-ethyl-1H-indole)	$C_{27}H_{26}N_2$	[39]
M29	PEMLUP	620698	5,5'-Dimethoxy-3,3'-(3-nitrophenylmethanediyl)bis(1H-indole)	$C_{25}H_{21}N_3O_4$	[40]
M30	PUZCAQ	956470	2,2-Bis(1H-Indol-3-yl)-1-phenylethanone	$C_{24}H_{18}N_2O$	[41]
M31	QINXAO	969227	Dimethyl 3,3'-(phenylmethylene)bis(1H-indole-2-carboxylate)	$C_{27}H_{22}N_2O_4$	[42]
M32	SESMIN	629528	3,3'-(4-Chlorophenylmethanediyl)-bis(5-methoxy-1H-indole)	$C_{25}H_{21}Cl_1N_2O_2$	[43]
M33A	SUVHAS	130877	3,3'-Benzylidenedi-indole	$C_{23}H_{18}N_2$	[44]
M33B	SUVHAS01	215714	3,3'-Benzylidenedi-indole	$C_{23}H_{18}N_2$	[45]
M33C	SUVHAS02	1452420	3,3'-Benzylidenedi-indole	$C_{23}H_{18}N_2$	[46]
M34	TAGQEA	868517	3,3',3''-Methanetriyltris(1H-indole)	$C_{25}H_{19}N_3$	[47]
M35	UNEMOR	1452423	2-Methyl-3-((2-methyl-1H-indol-3-yl)(phenyl)methyl)-1H-indole	$C_{25}H_{22}N_2$	[46]
M36	UKAYIQ	1447737	3-(1H-Indol-3-yl(pyridin-3-yl)methyl)-1H-indole hydrate	$C_{22}H_{17}N_3{\cdot}0.75H_2O$	[48]
M37	UNOPOE	1481317	3-((2-Fluorophenyl)(1H-indol-3-yl)methyl)-1H-indole	$C_{23}H_{17}FN_2$	[49]
M38	VURKIE	1060893	Ethyl bis(1-methyl-1H-indol-3-yl)acetate	$C_{34}H_{22}N_{12}O_8$	[50]
M39A	XADJOE	1050231	3,3'-Ethane-1,1-diylbis(1H-indole)	$C_{18}H_{16}N_2$	[51]
M39B	XADJOE01	1007025	3,3'-Ethane-1,1-diylbis(1H-indole)	$C_{18}H_{16}N_2$	[52]
M40	YOTREF	738233	3,3'-((4-Methoxyphenyl)methylene)bis(1,2-dimethyl-1H-indole)	$C_{28}H_{28}N_2O$	[53]

2. Methodology

2.1. Crystallographic comparison

The precise comparative structural parameters of all bis-indole derivatives as obtained from CSD were analysed for their crystal class, space group, the number of molecules per asymmetric unit cell, the final R-factor and are shown in Table 2. Whereas Table 3 and 4 lists the selected bond distances and bond angles of the identified molecules.

2.2. Biological activity predictions

One of the most important reasons for the synthesis and structural characterization of BIMs is their potent biological and pharmacological activities. The biological activity spectrum provides us with the list of all the biological activity names which is the result of chemical substance's interaction with different biological entities, by comparing the structure of the compound with the well-known substrate already existing in database.

Prediction of Activity Spectra for Substances (PASS) software [54] is a powerful tool which provides the grounds for predicting many activity types for different compounds. The structural formula of the compound is presented as a mol. file and the predictions result us with a list of biological activities on a scale of probability ranging from 0-1. Each activity is computed on the basis of Structure-activity relationship data and knowledge base (SAR), which provides two values: Pa - the probability of the compound being active and Pi - the probability of the compound being inactive for a particular biological activity. All the activities with Pa > Pi are retained as the most probable and predicted ones for a given compound. The Pa and Pi values for the molecules (M1-40) are presented in Table 5.

2.3. Molecular packing interaction analysis

Hydrogen bonds is the most significant interaction having large scale application in the field of material science, crystal engineering and biological recognition due to their distinctive features i.e., strength, flexibility and directionality. In the wake of well-known documentation for strong bonds such as N-H···O and O-H···O, but weak hydrogen bonds such as C-H···N, C-H···O and C-H···X are of quiet interest due to their frequent occurrence in organic crystal structure [55]. The knowledge of such an analysis of interactions helps us to understand the structure of bio-molecules with implication for structure-based drug design. Thus, by accumulating the research data of comparative study, we examined hydrogen-bonded interactions of the type N-H···O, C-H···O, C-H···F, N-H···N, N-H···S, and C-H···N present in bis-indole derivatives.

The Crystallographic Information File (CIF) for each structure was used as an input to Mercury 4.1 software [56] for the computation of all possible hydrogen bonding interactions. Table 6 presents the data of these interactions.

Table 2. Preliminary crystal data for Molecule M-1-41.

Molecule	Crystal system	Space group	R-factor	Z value
M1	Triclinic	*P*-1	4.33	2
M2A	Monoclinic	$P2_1/n$	5.80	4
M2B	Triclinic	*P*-1	5.30	3
M3	Monoclinic	$P2_1/n$	5.84	4
M4	Triclinic	*P*-1	5.70	2
M5	Orthorhombic	$P2_12_12_1$	4.01	4
M6	Monoclinic	$P2_1/n$	5.25	4
M7	Monoclinic	$P2_1/c$	4.10	4
M8	Orthorhombic	$P2_12_12_1$	7.06	4
M9	Monoclinic	$P2_1$	4.14	2
M10	Triclinic	*R*-3	7.63	6
M11	Monoclinic	$P2_1/c$	6.60	4
M12	Monoclinic	$P2_1/n$	5.37	4
M13	Monoclinic	$P2_1/c$	3.72	4
M14	Monoclinic	$P2_1/n$	6.14	4
M15	Monoclinic	$P2_1/n$	5.18	4
M16	Monoclinic	$P2_1/n$	5.73	3
M17	Triclinic	*P*-1	8.61	2
M18	Monoclinic	$P2_1/c$	6.70	4
M19	Monoclinic	$P2_1/n$	6.85	4
M20	Monoclinic	$C2/c$	4.96	8
M21	Triclinic	*P*-1	6.71	4
M22	Triclinic	*P*-1	5.42	2
M23	Triclinic	*P*-1	8.54	2
M24	Monoclinic	$P2_1/n$	4.10	4
M25	Triclinic	*P*-1	4.12	2
M26	Orthorhombic	$Pna2_1$	5.02	4
M27	Monoclinic	$P2_1/c$	4.34	4
M28	Triclinic	*P*-1	5.81	2
M29	Monoclinic	$P2_1/c$	6.08	4
M30	Monoclinic	$P2_1/n$	6.64	4
M31	Monoclinic	$P2_1/c$	6.17	4
M32	Monoclinic	$P2_1/n$	6.12	4
M33A	Monoclinic	$P2_1/c$	5.32	4
M33B	Monoclinic	$P2_1/c$	6.10	4
M33C	Monoclinic	$P2_1/c$	6.26	4
M34	Monoclinic	$P2_1/c$	3.59	8
M35	Monoclinic	$I2/a$	5.75	8
M36	Monoclinic	$P2_1/n$	7.38	4
M37	Monoclinic	$P2_1/c$	3.80	4
M38	Monoclinic	$P2_1/n$	6.74	2
M39A	Triclinic	*P*1	4.94	4
M39B	Orthorhombic	$P2_12_12_1$	3.74	4
M40	Monoclinic	$P2_1/n$	4.41	4

3. Discussion

3.1. Comparative crystallographic analysis

On the basis of crystallographic data as presented in Table 2, the following observations can be made: *i*) Most of the identified structures of bis-indole has been crystallized in monoclinic crystal system (65.90%) followed by triclinic (25.00%), and orthorhombic (9.09%), and the most common space group of identified structure is $P2_1/n$ (31.81%), followed by $P2_1/c$ (27.27%) and *P*1 (22.72%), *ii*) The range of reliability index of identified structure is between 3.80-8.61% which conveys us how accurate a crystal structure is determined, *iii*) Degree of freedom depends on number of molecules per unit cell, $Z = 4$ is observed for 65.90% molecules.

3.2. Bond distance and angles

All molecules undertaken contain substitutional groups at C10 positions. Therefore, it is of interest to investigate the C10-C3, C3-C2, C3-C9, C10-C3', C3'-C2', and C3'-C8' bond distances and C3-C10-C3', C2-C3-C9 and C10-C3'-C8' bond angles and their data is presented in Table 3 and 4. The substitution of groups at C10 position of the bis-indole nucleus causes significant change in the value of bond distances in rings A and A'.

i) The bond distance C10-C3 (sp^3-sp^2) lies in the range 1.480-1.532 Å [Average value of 1.506 Å] and the bond distance C10-C3' (sp^3-sp^2) lies in the range 1.457-1.528 Å [Average value of 1.510 Å]. Whereas the bond distance C3-C2 (sp^2-sp^2) lies in the range 1.343-1.382 Å [average value of 1.361 Å] and the bond distance C3'-C2' (sp^2-sp^2) lies in the range 1.351-1.442 Å [Average value of 1.365 Å]. Moreover, the bond distance C3-C9 (sp^2-sp^2) lies in the range 1.365-1.464 Å [Average value of 1.436 Å]. The bond distance C3'-C8' (sp^2-sp^2) lies in the range 1.364-1.480 Å [Average value of 1.436 Å].

ii) The substitution of a group at C10 (sp^3) position also causes a significant change in the value of bond angle C3-C10-C3'. The bond angle C3-C10-C3' in molecules with a substituent group at the C10 (sp^3) position varies from 108.60 to 114.65° [Average value of 112.81°]. The bond angle C10-C3-C2 and C10-C3'-C2' in molecules with a substituent group at the C10 (sp^3) position varies from 113.18 to 129.36° [Average value of 126.82°] and from 124.58 to 131.09° [Average value of 127.45°]. The bond angle C2-C3-C9 and C2'-C3'-C8' in molecules with a substituent group at the C10 (sp^3) position varies from 104.26 to 108.30° [Average value of 106.24°] and from 103.99 to 107.01° [Average value of 106.20°]. The bond angle C10-C3-C9 and C10-C3'-C8' in molecules with a substituent group at the C10 (sp^3) position varies from 123.52 to 131.37° [Average value of 126.55°] and from 122.48 to 129.00° [Average value of 126.55°]. The deviation of these bond distances and angles may be due to the effect of some functional group located at C10 (sp^3) position which invariably is involved in intra-/inter-molecular interactions.

Table 3. Selected bond distances (Å) for molecules M1-41 *.

Molecule	[C10-C3]	[C10-C3']	[C3-C2]	[C3'-C2']	[C3-C9]	[C3'-C8']
	sp^3-sp^2	sp^3-sp^2	sp^2-sp^2	sp^2-sp^2	sp^2-sp^2	sp^2-sp^2
M1	1.515	1.514	1.368	1.364	1.439	1.442
M2A	1.505	1.503	1.342	1.386	1.464	1.480
M2B	1.503	1.505	1.353	1.360	1.429	1.440
M3	1.506	1.527	1.365	1.363	1.365	1.438
M4	1.521	1.520	1.382	1.383	1.449	1.440
M5	1.494	1.528	1.362	1.359	1.431	1.442
M6	1.510	1.517	1.365	1.371	1.431	1.440
M7	1.502	1.503	1.358	1.356	1.437	1.435
M8	1.493	1.513	1.356	1.358	1.451	1.440
M9	1.510	1.513	1.356	1.369	1.442	1.440
M10	1.509	1.508	1.357	1.357	1.432	1.432
M11	1.522	1.507	1.343	1.442	1.439	1.442
M12	1.472	1.457	1.370	1.365	1.440	1.449
M13	1.480	1.472	1.374	1.376	1.438	1.438
M14	1.511	1.511	1.355	1.367	1.433	1.436
M15	1.505	1.507	1.357	1.354	1.424	1.428
M16	1.515	1.519	1.362	1.358	1.433	1.437
M17	1.514	1.512	1.370	1.361	1.432	1.429
M18	1.515	1.507	1.365	1.357	1.438	1.433
M19	1.532	1.513	1.371	1.349	1.416	1.432
M20	1.516	1.511	1.363	1.359	1.439	1.441
M21I	1.516	1.512	1.379	1.357	1.436	1.459
M21II	1.517	1.540	1.359	1.362	1.455	1.444
M22	1.519	1.513	1.379	1.385	1.443	1.434
M23	1.509	1.528	1.358	1.373	1.435	1.431
M24	1.505	1.506	1.361	1.356	1.433	1.429
M25	1.516	1.513	1.360	1.364	1.435	1.435
M26	1.516	1.510	1.359	1.364	1.443	1.435
M27	1.519	1.505	1.370	1.363	1.432	1.440
M28	1.509	1.502	1.365	1.354	1.432	1.431
M29	1.512	1.504	1.353	1.365	1.442	1.439
M30	1.507	1.511	1.354	1.359	1.435	1.438
M31	1.516	1.510	1.365	1.374	1.450	1.434
M32	1.510	1.512	1.362	1.359	1.436	1.428
M33A	1.349	1.513	1.349	1.359	1.434	1.426
M33B	1.514	1.509	1.358	1.361	1.435	1.441
M33C	1.506	1.508	1.354	1.362	1.434	1.430
M34	1.511	1.505	1.353	1.357	1.434	1.439
M35	1.527	1.510	1.364	1.355	1.452	1.434
M36	1.518	1.519	1.375	1.372	1.425	1.433
M37	1.508	1.511	1.360	1.364	1.443	1.364
M38	1.498	1.514	1.350	1.356	1.435	1.439
M39A	1.497	1.514	1.369	1.351	1.432	1.424
M39B	1.511	1.504	1.359	1.362	1.433	1.436
M40	1.521	1.509	1.366	1.372	1.440	1.432
Average	1.506	1.510	1.361	1.365	1.436	1.436

* A, B, and C refers to polymorphic forms; I and II refers to crystallographic independent molecules.

3.3. Biological activity predictions

The biological-activity relationship as presented in Table 5, the computation of various activities of bis-indole derivatives by using PASS software possesses 5-hydroxytryptamine release stimulant, Aspulvinonedimethylallyl transferase inhibitor, Preneoplastic conditions treatment, Endothelial growth factor antagonist and Lyase inhibitor activities. Majority of the identified molecules exhibit greater probability for 5-hydroxytryptamine release stimulants except [M12]. A comparison of possible activities shows that the molecules M1, M3, M8, M13, M14, M15, M16, M18, M20, M21, M25, M26, M29, M33, M34, M37, M38, and M39 exhibit very high value of positive 5-hydroxytryptamine release stimulant activity while other molecules show high or low/neutral activity. The identified molecules exhibit high biological activity for Aspulvinone dimethylallyl transferase inhibitor except (M7, M9). The probability of very high Aspulvinonedimethylallyl transferase inhibitor activity lies in molecules viz. M2, M13, M25, M27, and M40, whereas the other molecules exhibit almost neutral or low values. Similarly, the most of the identified molecules exhibit greater probability for Preneoplastic conditions treatment except (M5, M7), where molecules M1, M24, M29, M33, and M34 have very high activity. The identified molecules exhibit high biological activity for Endothelial growth factor antagonists except (M38, M40). The Pa > Pi value for Endothelial growth factor antagonist activity shows that it has high positivity value only for molecule M2. Whereas positive Lyase inhibitor activity has been shown by almost all molecule except (M5, M7, M12). It is observed that Lyase inhibitor activity is very high for molecules M1, M8, M9, M10, M11, M15, M16, M18, M21, M24, M26, M33, M34, M35, and M39.

3.4. Molecular packing interactions

Directionality of intermolecular hydrogen bonding plays an important role in molecular packing. And d-θ and D-θ scatter plots have a significant role in analysing the directionality of hydrogen bonds. The plots contain all contacts found in molecule (1-41) with d < 2.85 Å and D < 3.6209 Å at any occurring angle (θ). The d-θ scatter plots have been made for intermolecular hydrogen bonds as shown in Figure 2a and b, respectively.

i) From the pie chart, the frequency of occurrence of N-H···O, C-H···O, C-H···F, N-H···N, N-H···S, and C-H···N intermolecular hydrogen bonds is 67.3, 17.3, 5.7, 5.7, 1.9 and 1.9%, respectively, and are presented in Figure 3. N-H···O is the most preferred intermolecular interaction in bis-indole class.

ii) In case of N-H···O hydrogen bond, the density of spots for d(H···A) = 1.95-2.15 Å; D(X···A) = 2.80-3.00 Å and θ (X–H···A) = 145-165°. Most of the N-H···O contacts belongs to the category of strong hydrogen bond.

Table 4. Selected bond angles (°) for molecules M1-41 *.

Molecule	[C3-C10-C3']	[C2-C3-C9]	[C2'-C3'-C8'a]	[C10-C3-C2]	[C10-C3'-C2']	[C10-C3-C9]	[C10-C3'-C8']
	C10 (sp^3)	C1 (sp^2)	C1' (sp^2)	C1 (sp^3)	C1' (sp^3)	C1 (sp^3)	C1' (sp^3)
M1	114.10	105.94	106.14	127.01	129.18	126.76	124.46
M2A	112.26	107.70	103.99	113.18	129.57	123.84	126.45
M2B	112.49	106.26	106.16	129.04	127.64	124.70	126.20
M3	113.24	106.46	106.81	127.27	127.61	127.04	127.61
M4	112.69	105.55	106.25	123.08	125.38	131.37	128.27
M5	112.87	105.89	106.92	125.90	126.54	128.18	126.34
M6	114.49	106.04	106.16	127.43	125.57	126.22	128.00
M7	113.60	105.91	106.14	128.48	124.97	125.51	124.97
M8	112.85	105.73	105.88	127.21	125.33	125.33	127.21
M9	112.89	107.06	106.51	126.46	125.61	125.83	127.68
M10	112.17	106.44	106.44	127.27	127.29	126.25	126.24
M11	110.89	107.37	105.63	127.10	128.21	125.44	126.00
M12	116.84	105.76	106.12	125.39	125.29	128.73	128.49
M13	120.10	106.75	106.42	128.31	128.49	124.91	125.08
M14	113.08	106.75	106.42	128.78	128.68	124.84	125.19
M15	113.07	106.22	106.65	127.70	127.69	126.08	125.60
M16	110.54	106.32	106.60	126.11	125.49	127.52	127.87
M17	113.21	106.43	106.40	127.03	127.85	126.42	125.64
M18	113.82	105.93	106.34	126.82	129.33	127.16	124.32
M19	112.41	106.33	106.72	125.73	128.24	127.50	125.41
M20	112.29	106.62	106.14	123.37	127.32	129.90	126.30
M21I	111.02	105.84	105.62	125.68	128.29	128.47	125.74
M21II	108.60	104.26	106.90	126.80	126.17	128.52	126.82
M22	113.12	105.94	105.78	123.54	125.89	130.52	128.13
M23	110.58	106.48	106.76	124.20	124.58	129.27	128.12
M24	113.07	105.79	106.27	128.93	128.72	125.20	124.96
M25	112.58	106.28	105.82	128.10	126.36	125.61	127.82
M26	113.35	105.94	105.76	129.31	129.03	124.73	125.21
M27	113.10	106.11	105.75	126.66	128.08	127.08	126.12
M28	112.30	105.67	106.24	127.55	127.79	126.76	125.95
M29	112.52	106.27	105.63	127.73	129.87	126.00	124.37
M30	114.50	105.58	106.00	129.14	128.96	124.19	124.39
M31	112.43	106.66	106.27	124.00	124.66	129.30	129.00
M32	112.23	106.28	106.55	127.56	128.08	126.16	125.36
M33A	111.50	105.80	106.05	128.39	128.17	125.79	125.77
M33B	111.31	106.04	106.75	129.18	127.77	125.77	125.48
M33C	111.24	106.54	106.14	128.03	127.75	125.42	126.10
M34	112.71	106.17	105.75	128.12	128.21	125.35	126.02
M35	113.18	108.30	105.50	126.17	128.85	125.31	125.52
M36	113.75	107.51	106.43	128.94	131.09	123.52	122.48
M37	111.58	106.08	106.33	128.64	128.07	125.27	125.60
M38	114.65	106.26	106.62	128.53	125.52	125.21	127.84
M39A	112.53	104.75	106.25	129.36	127.33	125.87	126.29
M39B	112.33	106.13	105.91	127.28	128.82	126.46	125.21
M40	112.38	106.90	107.01	126.61	125.84	129.49	127.14
Average	112.81	106.24	106.20	126.82	127.45	126.55	126.55

* A, B, and C refers to polymorphic forms; I and II refers to crystallographic independent molecules.

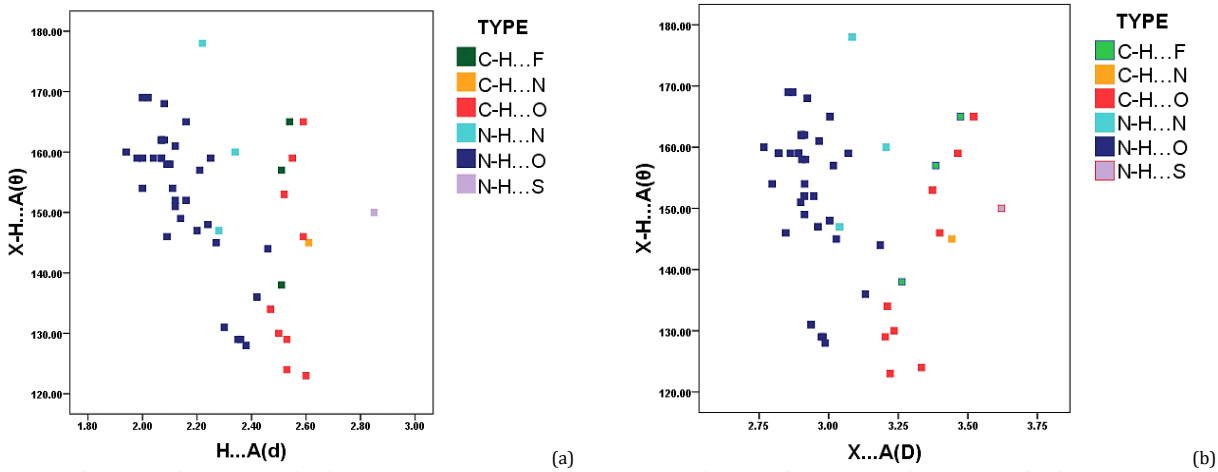

Figure 2. (a) d-θ scatter plot for intermolecular N-H···O, C-H···O, C-H···F, N-H···N, N-H···S and C-H···N; (b) D-θ scatter plot for intermolecular N-H···O, C-H···O, C-H···F, N-H···N, N-H···S and C-H···N.

iii) Density spots of C-H···O type of hydrogen bonds is maximum for range (d(H···A) = 2.52-2.58 Å; D(X···A) = 3.15-3.35 Å and θ(X–H···A) = 125-135°). Most of the C-H···O contacts belongs to the category of weak hydrogen bond.

iv) The range of d(H···A), D(X-H···A) and θ(X–H···A) for all the obtained data of intermolecular hydrogen interactions of the type N-H···O, C-H···O, C-H···F, N-H···N, N-H···S and C-H···N lies between 1.94-2.85 Å, 2.7669-3.6209 Å and 123-178°, respectively.

Table 7 presents all the range for d(H···A), D(X···A) and Θ(X-H···A) of various types of intermolecular bonds in the identified molecules.

Table 5. Pa and Pi values for the molecule 1-41 *.

Molecule	5-Hydroxytryptamine release stimulant	Aspulvinonedimethylallyl transferase inhibitor	Preneoplastic conditions treatment	Endothelial growth factor antagonist	Lyase inhibitor
	$P_a > P_i$	$P_a > P_i$	$P_a > P_i$	$P_a > P_i$	$P_a > P_i$
M1	0.878 > 0.007	0.688 > 0.068	0.816 > 0.003	0.433 > 0.017	0.754 > 0.015
M2A	0.639 > 0.034	0.751 > 0.048	0.599 > 0.024	0.603 > 0.005	0.611 > 0.040
M2B	0.639 > 0.034	0.751 > 0.048	0.599 > 0.024	0.603 > 0.005	0.611 > 0.040
M3	0.722 > 0.023	0.524 > 0.127	0.520 > 0.046	0.367 > 0.029	0.647 > 0.033
M4	0.639 > 0.034	0.751 > 0.048	0.599 > 0.024	0.603 > 0.005	0.611 > 0.040
M5	0.242 > 0.148	0.311 > 0.260	-	0.178 > 0.159	-
M6	0.640 > 0.034	0.311 > 0.260	0.326 > 0.148	0.294 > 0.056	0.366 > 0.112
M7	0.242 > 0.148	-	-	0.178 > 0.159	-
M8	0.719 > 0.023	0.364 > 0.217	0.623 > 0.019	0.394 > 0.023	0.776 > 0.012
M9	0.228 > 0.158	-	0.607 > 0.023	0.252 > 0.082	0.753 > 0.015
M10	0.742 > 0.020	0.580 > 0.105	0.667 > 0.012	0.471 > 0.012	0.741 > 0.017
M11	0.772 > 0.017	0.533 > 0.123	0.614 > 0.021	0.483 > 0.011	0.725 > 0.019
M12	-	0.558 > 0.113	0.256 > 0.217	0.305 > 0.047	-
M13	0.864 > 0.008	0.832 > 0.025	0.550 > 0.037	0.402 > 0.022	0.596 > 0.043
M14	0.864 > 0.008	0.487 > 0.143	0.562 > 0.033	0.386 > 0.025	0.598 > 0.043
M15	0.834 > 0.011	0.613 > 0.093	0.595 > 0.025	0.371 > 0.028	0.717 > 0.020
M16	0.817 > 0.013	0.621 > 0.090	0.655 > 0.014	0.562 > 0.007	0.739 > 0.017
M17	0.618 > 0.036	0.446 > 0.164	0.701 > 0.009	0.482 > 0.014	0.644 > 0.033
M18	0.779 > 0.016	0.645 > 0.082	0.647 > 0.015	0.377 > 0.027	0.764 > 0.014
M19	0.483 > 0.055	0.390 > 0.198	0.330 > 0.145	0.274 > 0.067	0.282 > 0.175
M20	0.722 > 0.023	0.524 > 0.127	0.520 > 0.046	0.367 > 0.029	0.647 > 0.033
M21	0.883 > 0.006	0.668 > 0.074	0.676 > 0.011	0.389 > 0.024	0.803 > 0.009
M22	0.301 > 0.111	0.410 > 0.185	0.456 > 0.071	0.307 > 0.050	0.292 > 0.165
M23	0.326 > 0.100	0.489 > 0.143	0.696 > 0.009	0.271 > 0.069	0.723 > 0.019
M24	0.893 > 0.005	0.730 > 0.054	0.736 > 0.006	0.478 > 0.012	0.794 > 0.010
M25	0.748 > 0.020	0.743 > 0.050	0.478 > 0.061	0.255 > 0.080	0.423 > 0.089
M26	0.867 > 0.008	0.584 > 0.103	0.639 > 0.017	0.370 > 0.029	0.823 > 0.007
M27	0.578 > 0.041	0.716 > 0.058	0.472 > 0.064	0.238 > 0.093	0.424 > 0.088
M28	0.497 > 0.052	0.585 > 0.103	0.401 > 0.098	0.213 > 0.116	0.435 > 0.084
M29	0.468 > 0.057	0.444 > 0.165	0.800 > 0.004	0.334 > 0.039	0.818 > 0.008
M30	0.766 > 0.018	0.585 > 0.103	0.662 > 0.013	0.337 > 0.038	0.730 > 0.018
M31	0.307 > 0.108	0.625 > 0.089	0.614 > 0.021	0.349 > 0.034	0.490 > 0.068
M32	0.692 > 0.027	0.534 > 0.123	0.737 > 0.005	0.526 > 0.009	0.661 > 0.030
M33A	0.863 > 0.008	0.660 > 0.077	0.703 > 0.008	0.411 > 0.020	0.785 > 0.011
M33B	0.863 > 0.008	0.660 > 0.077	0.703 > 0.008	0.411 > 0.020	0.758 > 0.011
M33C	0.863 > 0.008	0.660 > 0.077	0.703 > 0.008	0.411 > 0.020	0.785 > 0.011
M34	0.894 > 0.005	0.697 > 0.065	0.724 > 0.006	0.471 > 0.012	0.815 > 0.008
M35	0.665 > 0.030	0.446 > 0.164	0.648 > 0.015	0.362 > 0.031	0.849 > 0.005
M36	0.589 > 0.040	0.660 > 0.077	0.519 > 0.046	0.558 > 0.007	0.603 > 0.041
M37	0.816 > 0.013	0.446 > 0.164	0.555 > 0.035	0.363 > 0.031	0.603 > 0.036
M38	0.761 > 0.018	0.500 > 0.137	0.411 > 0.092	-	0.315 > 0.145
M39A	0.886 > 0.006	0.667 > 0.074	0.696 > 0.009	0.443 > 0.015	0.795 > 0.010
M39B	0.886 > 0.006	0.667 > 0.074	0.696 > 0.009	0.443 > 0.015	0.795 > 0.010
M40	0.669 > 0.030	0.743 > 0.050	0.397 > 0.100	-	0.352 > 0.120

* "-" indicates the absence of a particular type of biological activity.

Table 6. Geometry of N-H···O, C-H···O, C-H···F, N-H···N, N-H···S and C-H···N inter-molecular interactions.

Molecule [Number of Donors and Accepters]	X-H···A	H···A (Å)	X···A (Å)	∠ X-H···A (°)
M1, TAXTAQ, Donors = 3 Acceptors = 2	N1-H1P···O1	2.24	3.0035	148
	C5-H5···O1	2.52	3.3729	153
	C25-H25A···O2	2.55	3.4640	159
M2A, TEVTIY, Donors = 1 Acceptors = 1	N2-H2A···O1	2.35	2.9730	129
M2B, TEVTIY01, Donors = 2 Acceptors = 2	N3-H3···O4	2.36	2.9793	129
	N4-H4···O2	2.38	2.9872	128
M3, DEFMEH, Donors = 3 Acceptors = 2	N1-H1···O2	1.98	2.8190	159
	N2-H2···O1	2.12	2.9659	161
	N3-H3···O1	2.27	3.0270	145
M4, DOPZIT, Donors = 2 Acceptors = 2	N1-H1A···O3	2.08	2.9229	168
	N2-H2A···O1	2.04	2.8621	159
M5, EHINAM, Donors = 1 Acceptors = 1	N2-H2A···O1	2.00	2.7966	154
M6, EMIGUE, Donors = 5 Acceptors = 4	N1-H1···S2	2.85	3.6209	150
	N1-H1···O2	2.00	2.8201	159
	N11-H11···O1	2.00	2.8541	169
	N21-H21···O1	2.09	2.8453	146
	C31-H20C···O2	2.59	3.5210	165
	C32-H30C···F10	2.54	3.4735	165
M7, EVAKES, Donors = 2 Acceptors = 1	N2-H2A···N1	2.34	3.2063	160
	N3-H3A···N1	2.22	3.0843	178
M8, GIHDUY, Donors = 1 Acceptors = 1	N2-H2···N3	2.28	3.0389	147
M9, GUCJEY, Donors = 3 Acceptors = 2	N1-H1···O22	2.21	3.0166	157
	N10-H10···O101	1.94	2.7669	160
	N23-H23···O22	2.14	2.9130	149
M12, HOYPAN, Donors = 1 Acceptors = 1	C11-H11···O2	2.53	3.2032	129
M14, KEQREE, Donors = 2; Acceptors = 2	N2-H2A···O1	2.16	2.9464	152
	C3-H3A···F	2.51	3.2630	138
M15, KIFMES, Donors = 1; Acceptors = 1	N1-H1···O2	2.46	3.1851	144
M16, LANFIS, Donors = 2; Acceptors = 2	N1-H1···O2	2.25	3.0702	159
	N2-H2···O1	2.10	2.9158	158

Table 6. Continued.

Molecule [Number of Donors and Accepters]	X-H···A	H···A (Å)	X···A (Å)	∠X-H···A (°)
M17, LAWGEY, Donors = 1; Acceptors = 1	N1-H1···O1	2.12	2.9122	152
M18, LOKKON, Donors = 2; Acceptors = 2	N1-H1A···O1A	2.07	2.9016	162
	N1-H1A···O1	2.16	3.0043	165
	N2-H2B···O1A	2.20	2.9610	147
	N2-H2B···O1	2.11	2.9135	154
M19, MAVCUI, Donors = 1; Acceptors = 1	N1-H1···O1	2.08	2.9123	162
M20, MEDJEK, Donors = 2; Acceptors = 2	N1-H1A···O4	2.07	2.9029	162
	N2-H2A···O2	2.07	2.8917	159
M21, NUQGAJ, Donors = 2; Acceptors = 2	N1-H1A···O4	2.07	2.9029	162
	N2-H2A···O2	2.07	2.8917	159
M23, OCESAS, Donors = 1; Acceptors = 1	N1-H1A···O2	2.09	2.9034	158
M28, PEMLUP, Donors = 2; Acceptors = 2	N2-H2A···O1	2.12	2.8995	151
	C1-H1D···O4	2.47	3.2106	134
M29, PUZCAQ, Donors = 2; Acceptors = 1	N3-H9···O1	2.42	3.1318	136
	C13-H11···O1	2.50	3.2348	130
M30, QINXAO, Donors = 2; Acceptors = 4	N2-H2A···O2	2.02	2.8703	169
	C11-H11A···O3	2.60	3.2207	123
	C11-H11B···N1	2.61	3.4425	145
	C11-H11C···O4	2.53	3.3334	124
M31, SESMIN, Donors = 1; Acceptors = 1	N1-H1A···O2	2.30	2.9364	131
M35, UKAYIQ, Donors = 1; Acceptors = 1	C20-H14···O1	2.59	3.3991	146
M36, UNOPOE, Donors = 1; Acceptors = 1	C5-H5···F26	2.51	3.3849	157

Table 7. Range for d (H···A), D (X···A) and Θ (X-H···A) of various types of intermolecular bonds.

Type of hydrogen bond	d(H···A) range (Å)	D (X···A) range (Å)	Θ (X-H···A) range (°)
N-H···O	1.94-2.46	2.7669-3.1851	128-169
C-H···O	2.47-2.60	3.2032-3.521	123-165
C-H···F	2.51-2.54	3.2630-3.4735	138-165
N-H···N	2.22-2.34	3.0389-3.2063	147-178
N-H···S	2.85 *	3.6209 *	150 *
C-H···N	2.61 *	3.4425 *	145*

* Indicates only one bond of this type is present.

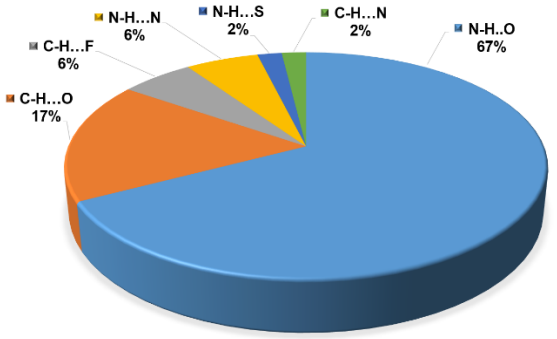

Figure 3. Relative frequency of occurrence (%) for various types of intermolecular hydrogen bonding.

Table 8. Geometrical parameters for very strong, strong and weak hydrogen bonds.

Property	Very strong	Strong	Weak	Present work
D(H···A), Å	1.2-1.5	1.5-2.2	2.0-3.0	1.94-2.85
D(X···A), Å	2.0-2.5	2.5-3.2	3.2-4.0	2.77-3.62
Θ(X-H···A), °	175-180	130-180	90-180	123-178

On the basis of Table 8 which presents a comparison of geometrical parameters for strength of hydrogen bonds [57], the hydrogen bonding strength of the identified molecules is of strong to weak nature.

Among the identified BIMs, all intermolecular bifurcated hydrogen bonding is due to donor N atom and acceptor O and N atoms. The bifurcated hydrogen bonding for donor N atoms are observed in molecule (M6 and M18) and bifurcated hydrogen bonding for accepter O and N atoms are observed in a molecule M1, M3, M6, M7, M9, M18 and M31, respectively. In molecules M1, M3, M6, M7, M9, M18, and M31, the bifurcated hydrogen bonds O and N atoms are involved in hydrogen bonds [N1-H1P···O1/C5-H5···O1, N2-H2···O1/N3-H3···O1, N1-H1···O2/C31-H20C···O2, N11-H11···O1/N21-H21···O1, N2-H2A···N1/N3-H3A···N1, N1-H1···O22/N23-H23···O22, N1-H1A···O1A/N2-H2B···O1A and N3-H9···O1/C13-H11···O1]. The molecule M6 has three bifurcated hydrogen bonding, due to the presence of donor N atom and acceptor O atom. In the present study, majority of bifurcated hydrogen bonds are due to O acceptor site. The bifurcated hydrogen bond donor forms intermolecular bond [N1-H1···S2 and N1-H1···O2] with bifurcated angle 309° in M6.

4. Conclusion

In the present work, the crystallography comparison of bis-indole derivatives has been done along with their biological activity prediction and molecular packing interaction. The biological-activity are characterized by Pa and Pi values which depict that majority of the molecules undertaken for present study have high value of 5-hydroxytryptamine release stimulant inhibitor activity. The analysis of hydrogen bonding is quite interesting due to the nature of substitution at position C10 of bis-indole ring system. Bis-indole derivatives have mostly crystallized in monoclinic crystal system followed by triclinic and orthorhombic crystal system. The deviation of bond distance (C10-C3, C3-C2, C3-C9, C10-C3', C3'-C2', and C3'-C8') and bond angle (C3-C10-C3', C2-C3-C9 and C10-C3'-C8') is due

to the involvement of variety of substituent's at position C10 in hydrogen bonding interactions. On the basis of hydrogen bonding interaction data, it may be concluded that almost all the N-H···O intermolecular interaction belongs to the category of strong hydrogen bonding, whereas majority of C-H···O and C-H···F contacts belongs to weak interaction. The molecules M1, M3, M6, M7, M9, M17 and M30 depict the phenomenon of bifurcated hydrogen bonding and most of these bifurcated hydrogen bonds are due to the O acceptor atom. Most of the H-bonds are based on N-H···O. This show that due to substitution at position C10 of bis-indole ring N donor atom dominates over other atoms in intermolecular hydrogen bond formation. The design of new molecules with desired properties is the future intention of chemists/crystallographers, which requires the clear understanding of intermolecular interactions in crystal packing. Thus, understanding of intermolecular interactions in-depth becomes vital.

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Supporting information

The data of chemical structure of molecule 1-41 data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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Conflict of interests: The authors declare that they have no conflict of interest.
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CRediT authorship contribution statement

Conceptualization: Varun Sharma; Methodology: Varun Sharma; Software: Varun Sharma; Validation: Goutam Brahmachari; Formal Analysis: Goutam Brahmachari; Investigation: Goutam Brahmachari; Resources: Vivek Kumar Gupta; Data Curation: Vivek Kumar Gupta; Writing - Original Draft: Varun Sharma; Writing - Review and Editing: Vivek Kumar Gupta; Visualization: Vivek Kumar Gupta; Funding acquisition: Vivek Kumar Gupta; Supervision: Vivek Kumar Gupta; Project Administration: Vivek Kumar Gupta.

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