International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 07 Issue: 02 | Feb 2020 www.irjet.net p-ISSN: 2395-0072

Insilico Studies of Molecular Property and Bioactivity of Organic Crystalline Compounds using Molinspiration

M. Suganya[1], MadhukarHemamalini[2], S. JoseKavitha[3] & Venkatachalam Rajakannan[4]

[1]Guest faculty, Department of Chemistry, Mother Teresa Women's University, Kodaikanal.
[2]Assistant Professor, Department of Chemistry, Mother Teresa Women's University, Kodaikanal.
[3]Assistant Professor & Head, Department of Chemistry, Mother Teresa Women's University, Kodaikanal.
[4]Assistant Professor Centre of Advanced study in Crystallography and Biophysics, University of Madras, Chennai.

Abstract - *Some organic crystalline compounds were selected for the assessment of molecular property and bio-activity scores using molinspiration software whose crystal structures were obtained from literature. All the ten (I-X) compounds obeyed Lipinski's rule and (II-IX) compounds showed good likeness scores. The crystalline compounds were found to be better drugs and the compounds (I,II,IV,V,VI,VII,VIII & IX) were found to be moderately active as GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor.*

Key Words: *Organic Crystalline Compounds, Lipinski's rule, MiLog P, TPSA and GPCR.*

1. INTRODUCTION

In recent years, the sources of drug leads in the pharmaceutical industry have changed significantly. From about 1970 on, what were considered at that time to be large empirically-based screening programs became less and less important in the drug industry as the knowledge base grew for rational drug design. Drug discovery and development is an iterative process which begins with the identification of lead compounds. In this context, the conventional approach is challenging, time consuming, expensive and requires consideration of many aspects that have negative impact on pharmaceutical industries. The use of computational technology, so-called insilico, in drug discovery and development has now surpassed the conventional approach. The insilico approach estimates potential biological activity and druggability of new leads without having to undergo the costly and tedious wet conventional experiments. Thus, the insilico approach facilitates drug discovery efficiently where the target protein, and thus biological activity, could be predicted at early stage expediting the time required for the discovery process. Sydnone and its derivatives, show various pharmacological activity and antimicrobial properties [1-3]. Particularly thiazolidine ring exhibits bactericidal, antifungal, anticonvulsant, anti-HIV, antituberculotic, non-nucleoside inhibitors of HIV-RT and anti-histaminic agents. Pyrazole and pyrazoline are reported to possess wide range of biological activities such as antiamoebic, analgesic, anti-inflammatory, anti-convulsant, antidepressant, hypotensive, cytotoxic, anticancer and antioxidant. Pyrazoles have been used extensively as ligands in the field of coordination chemistry and catalysis [4-14]. In the present study we have evaluated and discussed about the bioactivity and molecular properties of organic crystalline compounds of sydnone, pyrazole and pyrazoline derivatives.

2. Materials and Methods

By applying computational methods, the various physicochemical features and pharmacokinetic descriptors were calculated for some selected organic crystalline compounds through the online tool Molinspiration Cheminformatics server[15-17]. The structures of all the organic crystalline structures given as Figure 1-10 were taken from the reported literature.

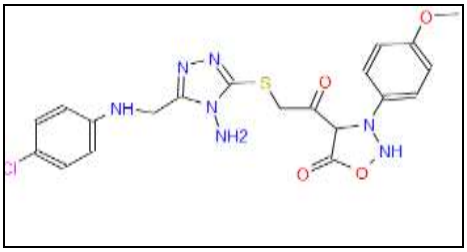

Fig -1 4-({[4-Amino-5-(4-chloroanilinomethyl)-4H-1,2,4-triazol-3-yl]sulfanyl}acetyl)-3-(4-methoxyphenyl)-1,2,3-oxadiazol-3-ium-5-olate

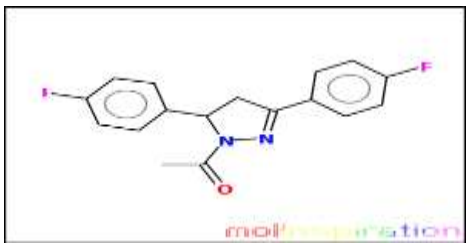

Fig -2 1-[3,5-Bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]ethenone

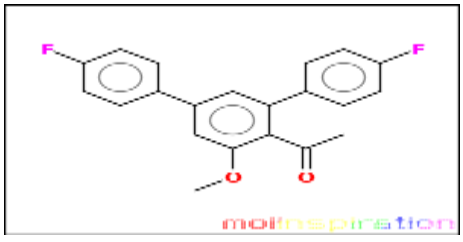

Fig -3 1-(4,4"-Difluoro-5'-methoxy-1,1':3',1"-terphenyl-4'-yl)ethenone

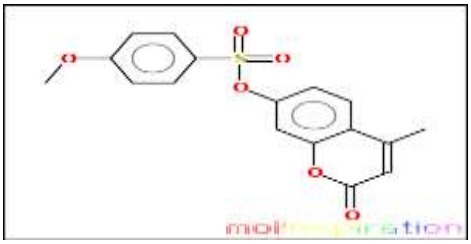

Fig -4 4-Methyl-2-oxo-2H-chromen-7-yl4-methoxybenzenesulfonate

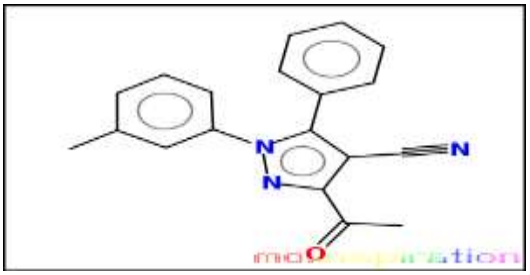

Fig -5 3-Acetyl-1-(3-methylphenyl)-5-phenyl-1H-pyrazole-4-carbonitrile

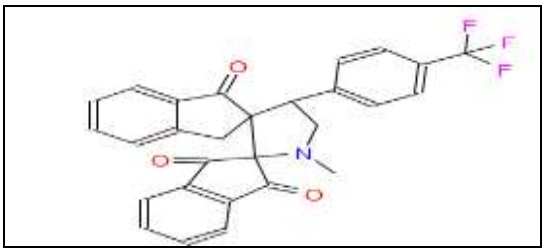

Fig -6 10-Methyl-40-[4-(trifluoromethyl) phen-yl] dispiro[indan-2,20-pyrrolidine-3',2"-indan]-1,3,1"-trione

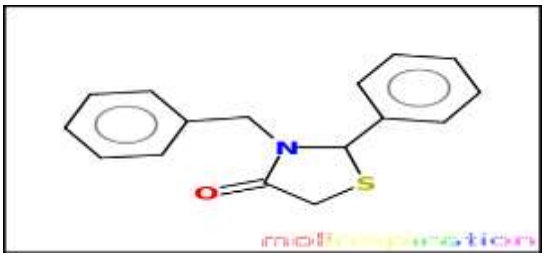

Fig -7 3-Benzyl-2-phenyl-1,3-thiazolidin-4-one

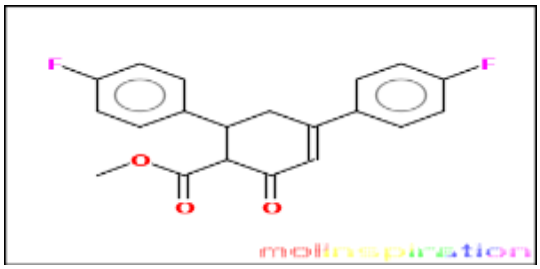

Fig -8 Methyl 4, 6-bis (4-fluorophenyl)-2-oxo-cyclohex-3-ene -1-carboxylate

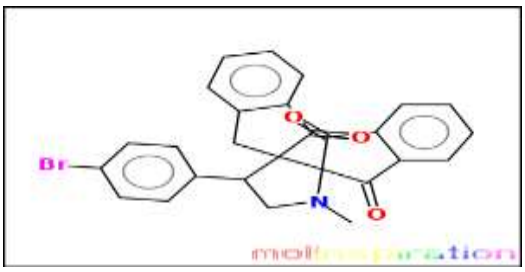

Fig -9 4'-(4-Bromophenyl)-1'-methyldispiro-[indan-2, 2'-pyrrolidine-3', 2"-indan]-1,3,1"-trione

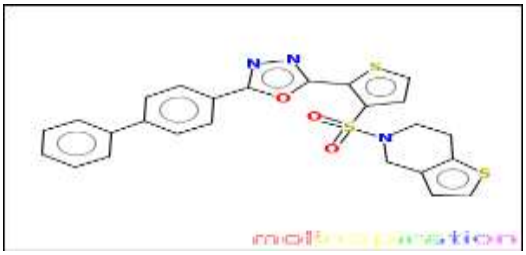

Fig -10 2-(Biphenyl-4-yl)-5-[3-(4,5,6,7-tetra-hydrothieno[3,2-c]pyridine-5-yl-sulfonyl)thiophen-2-yl]-1,3,4-oxadiazole

The drug likeness scores were assessed by considering MiLogP (partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds and volume. The bioactivity scores of these organic crystalline compounds were assessed on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor.

Table 1- Drug likeness score for organic crystalline compounds.

S.No	Compound	miLogP	TPSA	nAtoms	nON	nOHNH	nviolation	rotb	volume	MW
1.	I	2.20	136.64	33	11	4	1	9	396.54	489.94
2.	II	3.25	32.67	22	3	0	0	2	259.69	300.31
3.	III	5.67	26.30	25	2	0	1	4	297.81	338.35
4.	IV	3.39	82.82	24	6	0	0	4	282.52	346.36
5.	V	3.79	58.69	23	4	0	0	3	277.04	301.35
6.	VI	4.92	54.45	35	4	0	0	2	395.37	475.47
7.	VII	3.02	20.31	19	2	0	0	3	244.94	269.37
8.	VIII	4.10	43.38	25	3	0	0	4	295.86	342.34
9.	IX	4.83	54.45	32	4	0	0	1	381.95	486.37
10.	X	5.81	76.30	34	6	0	2	5	408.13	505.65

Table II- Bio Activity scores of organic crystalline compounds

S.No.	Compound	GPCR Ligand	Ion Channel modulator	Kinase Inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	I	-0.58	-0.66	-0.39	-0.75	-0.41	-0.38
2.	II	-0.45	-0.95	-0.70	-0.73	-0.57	-0.41
3.	III	0.03	0.02	0.07	0.12	-0.08	0.01
4.	IV	-0.50	-0.64	-0.47	-0.38	-0.24	-0.07
5.	V	0.07	-0.34	0.13	0.01	-0.42	-0.01
6.	VI	0.31	-0.01	-0.11	0.19	0.12	0.16
7.	VII	-0.32	0.02	-1.20	-1.07	-0.70	-0.32
8.	VIII	-0.19	-0.30	-0.50	0.09	-0.22	-0.16
9.	IX	0.22	-0.13	-0.20	0.00	0.03	0.12
10.	X	-0.17	-0.68	-0.46	-0.62	-0.14	-0.21

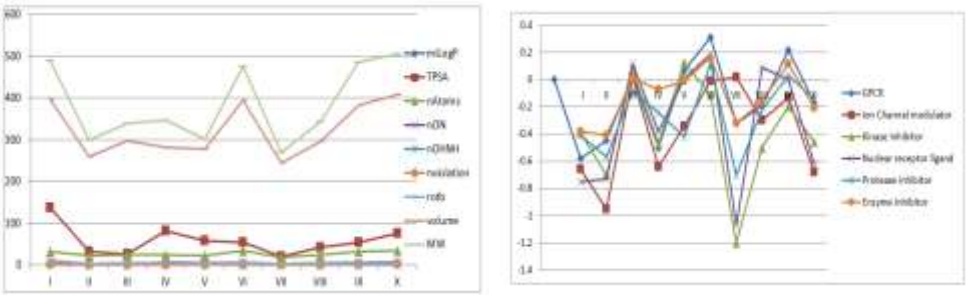

Chart -1 Drug likeness score and Bio Activity scores organic crystalline compounds

miLogP – Logarthim of partition coefficient **TPSA –** Topological Polar Surface Area **nAtoms –** Number of Atoms
nON – Number of hydrogen bond acceptors **rotb -** Number of rotatable bonds **MW –** Molecular Weight

nOHNH - Number of hydrogen bond donors

Results and Discussion

I. Assessment of Drug likeness on the basis of Lipinski rule of five

The drug likeness scores were calculated by considering **(miLogP, TPSA, nAtoms, nON, nOHNH, rotb & MW).** These properties were calculated and discussed on the basis of Lipinski's rule and its component. All the ten (I-X) compounds obeyed Lipinski's rule and showed good likeness scores.

MiLog P

MiLog P values of these compounds were found below 5 showing good permeability across cell membrane.

TPSA

All compounds were found to have TPSA in the range of 20.31-136.64 and were well below 160A^{o2} showing that they are better drugs.

nON & nOHNH

The number of hydrogen bond donors and the number of hydrogen bond acceptor in the nine compounds (II-X) are in accordance with Lipinski's rule of 5 except first compound (I) i.e. less than 5 and 10 respectively.

rotb

Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs.

Molecular Weight

Low Molecular Weight drug molecules (<500) means they are easily transported, diffuse and absorbed as compared to heavy molecules.

n violations

All the crystalline compounds were found to have n violations equal to 0 except I, III and X. N violations equal to 0 means that all the crystalline compounds can easily bind to receptor.

The compounds (I, II, IV, V, VI, VII, VIII and IX) were found to have drug likeness score in the range of 2.20 - 4.92 except the compounds III & X which had drug likeness score in the range of 5.67 & 5.81. These values indicated that these crystalline compounds were found to be better drugs.

II. Bioactivity score of the compounds

The bioactivity scores of the ten crystalline compounds were assessed on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor as given in **Table -II** . The parameters of bioactivity score active if (>0), moderately active if (-5.0-0.0), inactive if the score is (< -5.0). Calculation of drug likeness score towards GPCR ligands showed that the compounds III, V, VI and IX were found to have moderate bioactivity (<0). The compounds III & VII were found to be moderately bioactive (<0) as ion channel modulator. The compounds III & V were found to be moderately active as kinase inhibitor (> -0.5). Nuclear receptor properties of compounds III, VI, VII & IX were moderately active (< 0). The compounds VI & IX were found to have moderate inhibitor activity (<0) towards Protease. The compounds III, VI & IX were found to exhibit (-0.5-0.0) moderate enzyme inhibitor compared to others. Bioactivity scores of the compounds lie in the range (-1.20 to 0.31), so they can function as good drugs.

Conclusion

Among the ten compounds selected for the assessment of the drug likeness score, all the organic crystalline compounds were found to obey the Lipinski's rule and showed good drug likeness score. MiLogP value of eight compounds were found to be better drugs. All the ten compounds were found to be moderately active as GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor as their bioactivity scores lie in the range (-1.20 to 0.31).

REFERENCES

[1] Rai, N. S., Kalluraya, B., Lingappa, B., et al J. Med. Chem. 43, 2008, 1715–1720.

[2] Kalluraya, B., Rahiman, A. et al J. Chem. Sect. B, 41, 1712–1717 (2002).

[3] Hoong-Kun Fun, MadhukarHemamalini, Nithinchandra and BalakrishnaKalluraya "4 ({[4-Amino-5-(4-chloroanilinomethyl)-4H-1,2,4-triazol 3 yl]sulfanyl}acetyl)-3-(4-methoxyphenyl)-1,2,3 oxadiazol-3-ium-5-olate" ActaCryst 2010.

[4] Amir, M., Kumar, H. & Khan, S. A. Bioorg. Med. Chem. Lett. 18, 2008, 918–922.

[5] Dipankar Bardalai et al. / Int. Res J Pharm. App Sci., 2012; 2(3): 1-8.

[6] Sinha, S., Osman, H., Wahab, H. A., Hemamalini, M. & Fun, H.-K. 2011. ActaCryst.

[7] SumanSinh, Hasnah Osman, Habibah A. Waha, MadhukarHemamalini and Hoong-Kun Fun 4-Methyl-2-oxo-2H-chromen-7-yl 4-methoxybenzenesulfonate ActaCryst 2011.

[8] Hatem A. Abdel-Aziz and MadhukarHemamalini et al "3-Acetyl-1-(3-methylphenyl)-5-phenyl- 1H-pyrazole-4-carbonitrile" ActaCryst 2012.

[9] Wei, A. C., Ali, M. A., Ismail, R., Hemamalini, M. & Fun, H. K. ActaCryst 2011.

[10] AngChee Wei, Mohamed Ashraf Ali and MadhukarHemamalini et al "1'-Methyl-4'-[4 (trifluoromethyl)phen- yl]dispiro[indan-2,2'-pyrrolidine-3',2"- indan]-1,3,1"-trione" ActaCryst 2011.

[11] Kumar, R. R., Perumal, S., Senthilkumar, P., Yogeeswari, P. & Sriram, D. (2009). Eur. J. Med. Chem. 44, 3821–3829.

[12] Maheswari, S. U., Balamurugan, K., Perumal, S., Yogeeswari, P. &Sriram, D. Bioorg Med ChemLett. 20, 2010, 7278–7282.

[13] Hoong-Kun Fun, MadhukarHemamalini et al "3-Benzyl-2-phenyl-1,3-thiazolidin-4-one" ActaCryst 2011.

[14] Hoong-Kun Fun, MadhukarHemamalini, et al "Methyl 4, 6-bis(4-fluorophenyl)-2-oxo- cyclohex-3-ene-1-carboxylate" ActaCryst 2010.

[15] MadhukarHemamalini and Hoong-Kun Funb 4'-(4-Bromophenyl)-1'-methyldispiro- [indan-2, 2'-pyrrolidine-3', 2"-indan]- 1,3,1"-trione ActaCryst 2011.

[16] Hoong-Kun Fun, MadhukarHemamalini et al "2-(Biphenyl-4-yl)-5-[3-(4,5,6,7-tetra- hydrothieno[3,2-c]pyridine-5-yl- sulfonyl)thiophen-2-yl]-1,3,4-oxadiazole" ActaCryst 2011.

[17] Sharma CS, Mishra SS, Singh HP, Kumar N. "In silicoADME and Toxicity Study of Some Selected Antineoplastic Drugs". International Journal of Pharmaceutical Sciences and Drug Research, 2016; 8(1):65-7

BIOGRAPHIES

Guest faculty, Department of Chemistry, Mother Teresa Women's University, Kodaikanal

Assistant Professor, Department of Chemistry, Mother Teresa Women's University, Kodaikanal

Assistant Professor, & Head Department of Chemistry, Mother Teresa Women's University, Kodaikanal

Assistant Professor, Centre of Advanced study in Crystallography and Biophysics, University of Madras, Chennai