iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 8 **Issue:** VII **Month of publication:** July 2020

DOI: https://doi.org/10.22214/ijraset.2020.30645

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 8 Issue VII July 2020- Available at www.ijraset.com

Investigation of ADMET Profile of Lead Molecule for COVID-19

Nilesh S. Kadu[1], Atul V. Ingle[2], P. G. Bansod[3], N. D. Gawhale[4], S. B. Suryawanshi[5]
[1]*Department of Chemistry, Bharatiya Mahavidyalaya, Amravati, Maharashtra, India*
[2]*Department of Chemistry, Yeshwantrao Chavan College of Arts, Commerce and Science, Sillod, Tq. Sillod, Dist. Aurangabad, Maharashtra, India*
[3]*Department of Botany, Vidya Bharati Mahavidyalaya, Amravati, Maharashtra, India*
[4]*Department of Chemistry, G. S. Tompe Mahavidyalaya, Chandur Bazaar, Amravati, Maharashtra, India*
[5]*Department of Chemistry, Hutatma Rajguru Mahavidyalaya, Rajgurunagar, Tal. Khed, Pune, Maharashtra, India*

Abstract: ***In the present work, an extensive ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis of α-Ketoamides (peptide-type analogues) 13b, which has been recently reported to possess activity for COVID-19, has been performed. The analysis indicates that this could have severe toxic issues. The analysis indicates that this compound 13b needs a lot of modification to become a drug.***
Keywords: COVID-19, SARS-CoV-2, α-Ketoamides, Peptide-type analogues, ADMET

I. INTRODUCTION

The emergence of COVID-19 has caused many countries to go for lock down. This has resulted in slow down of its spread but the social, economic, and health burden are unprecedented. The high infection rate indicates that there is need to develop a drug at earliest. Recently, Rolf et al synthesized and screened α-Ketoamides (peptide-type analogues) and one of the derivatives 13b revealed activity against SARS-CoV and SARS-CoV-2. This compound was found to have good chemical and biological profile [1,2] . In the present work, we have carried out ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis of α-Ketoamides (peptide-type analogues) 13b. The analysis could be useful for future optimization of this compound as a drug for COVID-19.

II. EXPERIMENTAL METHODOLOGY

The compound 13b was drawn using Chemsketch freeware, followed by its optimization using MMFF94 force field. In the next step, SWISSADME (http://www.swissadme.ch/) [3-5] and LabMol (http://predherg.labmol.com.br/) [6-7] were used to perform ADMET analysis of 13b using default settings.

III. RESULTS AND DISCUSSION

The ADMET analysis of 13b for hERG has been depicted in figure 1. From figure 1, it is clear that the compound 13b could block hERG due to the presence of good number of atoms contributing positively as hERG blockers.

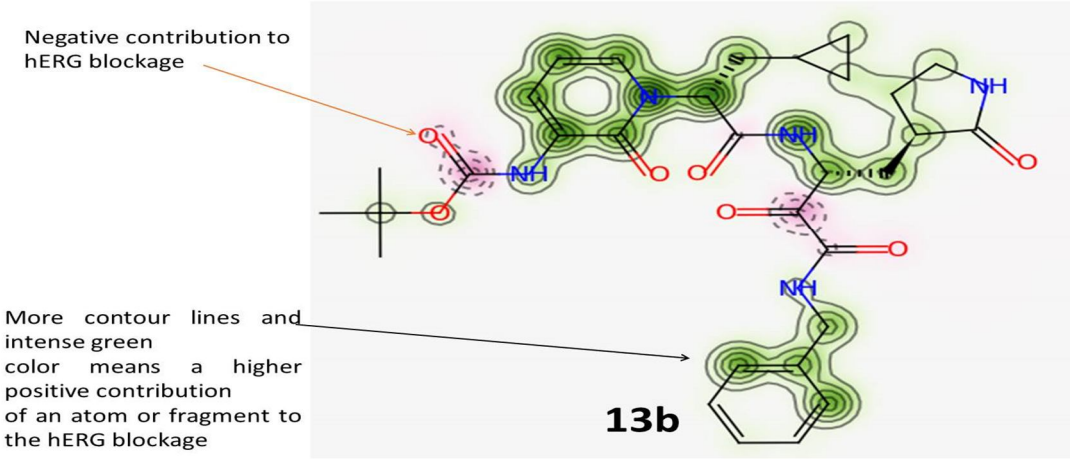

Figure 1. hERG analysis of 13b

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Table 1
The admet analysis obtained through swissadme has been presented in.

Canonical SMILES	O=C(OC(C)(C)C)Nc1ccn(c1=O)[C@@H](C(=O)N[C@@H](C(=O)C(=O)NCc1ccccc1)C[C@H]1CCNC1=O)CC1CC1	Ali Class	Moderately soluble
Formula	C31H39N5O7	Silicos-IT LogSw	-6.96
MW	593.67	Silicos-IT Solubility (mg/ml)	6.49E-05
#Heavy atoms	43	Silicos-IT Solubility (mol/l)	1.09E-07
#Aromatic heavy atoms	12	Silicos-IT class	Poorly soluble
Fraction Csp3	0.48	GI absorption	Low
#Rotatable bonds	17	BBB permeant	No
#H-bond acceptors	7	Pgp substrate	Yes
#H-bond donors	4	CYP1A2 inhibitor	No
MR	162.89	CYP2C19 inhibitor	No
TPSA	164.7	CYP2C9 inhibitor	Yes
iLOGP	3.61	CYP2D6 inhibitor	No
XLOGP3	2.54	CYP3A4 inhibitor	Yes
WLOGP	1.65	log Kp (cm/s)	-8.12
MLOGP	0.76	Lipinski #violations	2
Silicos-IT Log P	2.98	Ghose #violations	3
Consensus Log P	2.31	Veber #violations	2
ESOL Log S	-4.21	Egan #violations	1
ESOL Solubility (mg/ml)	3.70E-02	Muegge #violations	2
ESOL Solubility (mol/l)	6.23E-05	Bioavailability Score	0.17
ESOL Class	Moderately soluble	PAINS #alerts	0
Ali Log S	-5.65	Brenk #alerts	1
Ali Solubility (mg/ml)	1.34E-03	Leadlikeness #violations	2
Ali Solubility (mol/l)	2.26E-06	Synthetic Accessibility	5.32

From table 1, it is clear that the compound has issues with respect to BB (blood brain) permeation, low Gastro-intestinal absorption, violates Veber's, Lipinski's and Brenk rules. Therefore, in future modifications, the molecule 13b should be prioritized using the present analysis.

IV. CONCLUSION

In conclusion, the compound 13b has good activity for COVID-19 but further modifications are necessary to transform it into a drug with optimized ADMET profile. The present analysis highlights some of the key issues which must be addressed before beginning the clinical trials for 13b. Thus, the present work has successfully pointed out toxicity and other issues well in advance.

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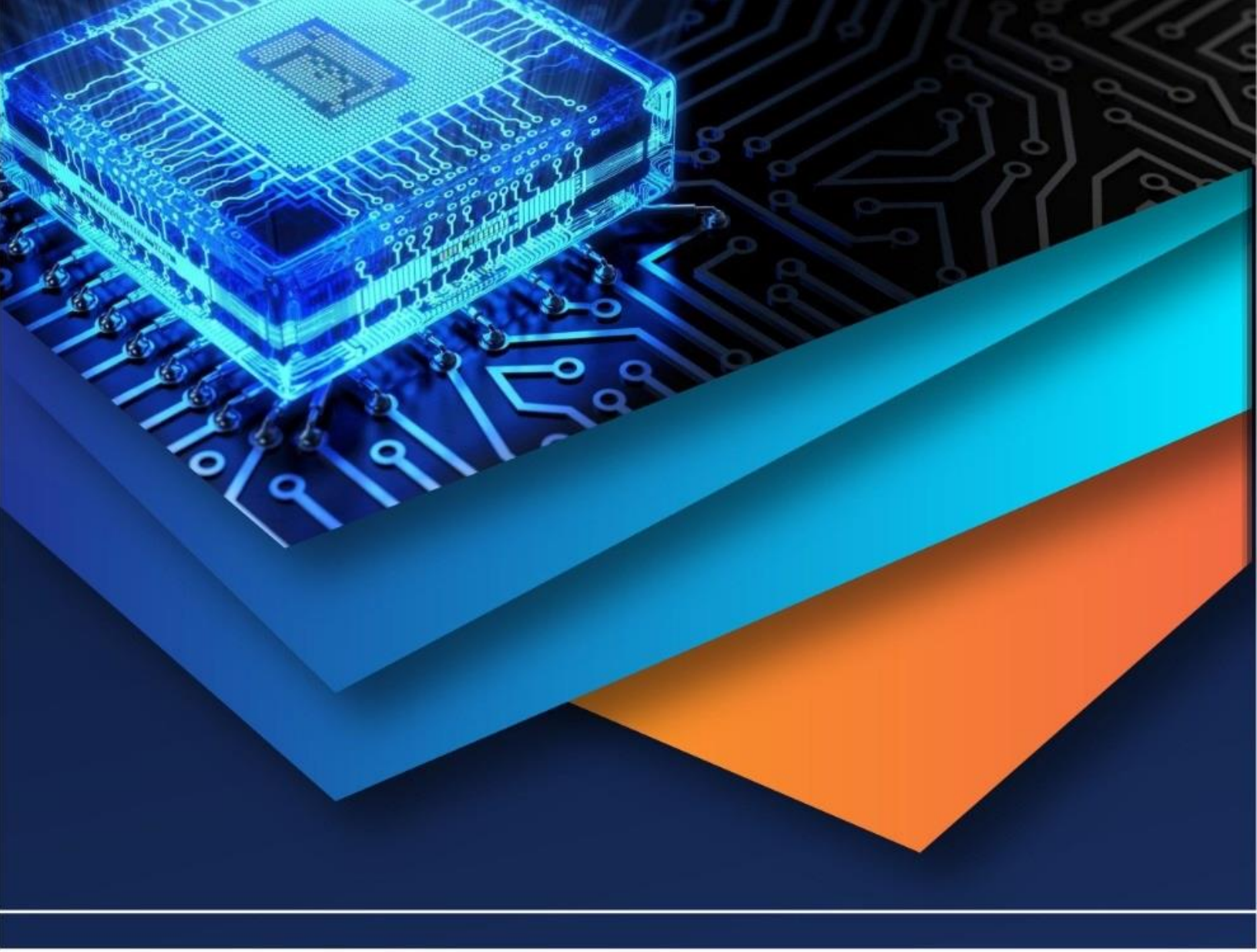

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