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In silico molecular modelling studies of newly synthesized pyrazole derivatives from p-bromo benzoic acid

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Abstract
In silico screening helps to predict whether a compound will shows desired characteristics or activity on the basis of its two dimensional or three dimensional chemical structures (Molecular modelling software was used to develop a 3D molecular structures of new pyrazole derivatives from p-bromo benzoic acid) or its physical properties. In this study the software's like AutoDock, PASS, Molinspiration, ACD LABS, Chem Sketch were used for the determination of different molecular descriptors profile of proposed molecules. Energy minimization is carried out in this 3D structure and then the bond length, bond angle and torsional angle of the proposed new structure is calculated. The software programs were also allows to study the binding site, to design the molecule which will fit to this binding site and drug-likeness of the molecule, molinspiration software helps to calculate different molecular descriptors like log P, polar surface area, number of hydrogen bond donors and acceptors etc of proposed structures. Analysis by Lipinski's rule was done to identify the best molecule. Five derivatives of 1-(4-bromobenzoyl)-3-(4-substituted phenyl)-1H-pyrazole-4-carbaldehyde were identified for synthesis using conventional method.

Keywords: Lipinski's rule, AutoDock version 4.0, PASS, Molinspiration

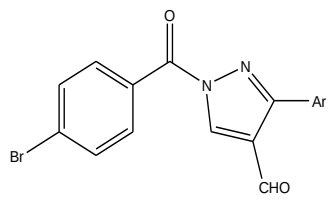
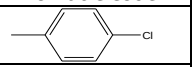
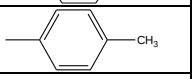
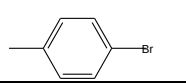
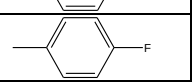
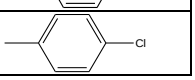
1. Introduction
In silico design of the molecules using different softwares such as ACD LABS 10.0 Chem sketch, PASS and Molinspiration was done, to identify the molecules obeying Lipinski's rule of five for selection of wet lab synthesis. Five derivatives of 1-(4-bromobenzoyl) - 3 - (4 -substituted phenyl)-1H-pyrazole-4-carbaldehyde[4] were selected using the docking studies.

2. Materials
The following Softwares were used for the *In silico* design and docking studies.
ACD Labs Chem sketch 10.00
Chem Draw Ultra 8.0
Chem3D Ultra 8.0
Molinspiration
Molegro Molecular Viewer 2.5
AutoDock 4.0

3. Methodology
Pyrazole a π-excessive heterocycle containing 2 nitrogen atoms adjacent to each other was selected as the lead molecule based on literature survey to synthesize derivatives such as 1-(4-bromobenzoyl) - 3 - (4 -substituted phenyl)-1H-pyrazole-4-carbaldehyde[1,2.]

3.1 Design of 3D structures of new derivatives of pyrazole [3]
The ACD Labs Chem sketch 10.00, Chem Draw Ultra 8.0 and Chem3D Ultra 8.0 were used to design the following structures:
1-(4-bromobenzoyl)-3-(4-methoxy phenyl)-1H-pyrazole-4-carbaldehyde(AV1),
1-(4-bromobenzoyl)-3-(4-methyl phenyl)-1H-pyrazole-4-carbaldehyde(AV2),
1-(4-bromobenzoyl)-3-(4-bromophenyl)-1H-pyrazole-4-carbaldehyde(AV3),
1-(4-bromobenzoyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde(AV4),
1-(4-bromobenzoyl)-3-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde(AV5)

Table 1: Proposed Derivatives

	Compound Code	Aromatic code
	AV1	
	AV2	
	AV3	
	AV4	
	AV5	

3.2 Analysis of Lipinski's rule [5]

The analysis of Lipinski's rule was done using PASS and Molinspiration to identify the best lead molecule for wet lab synthesis.

3.3 Calculation of Molecular Properties

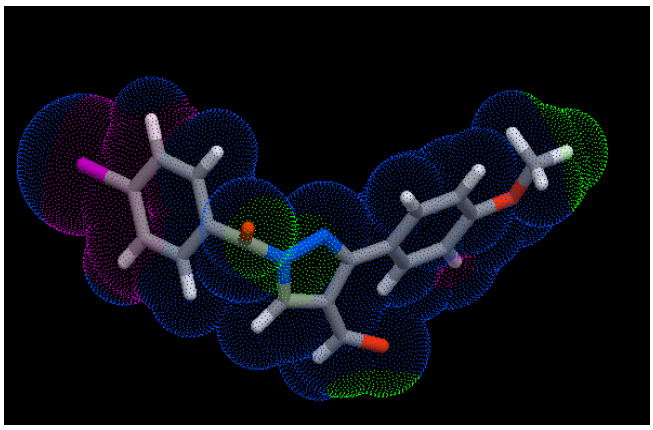
The Molecular properties of the above compounds were determined using AutoDock version 4.0, Molinspiration and PASS.

4. Results & Discussion

4.1 3D structures of new derivatives of pyrazole

The below given are the results given by the ACD Labs Chem sketch 10.00, Chem Draw Ultra 8.0 and Chem3D Ultra 8.0 as well as Molinspiration.

AV1:1-(4-bromobenzoyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde



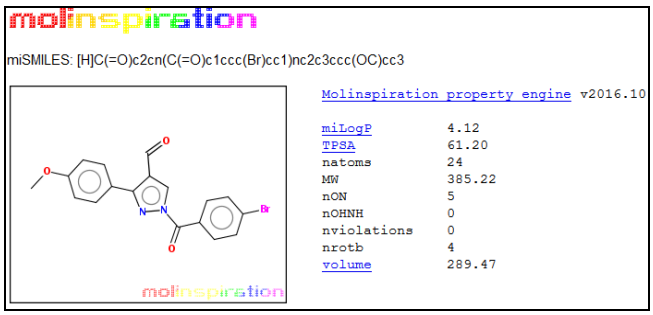
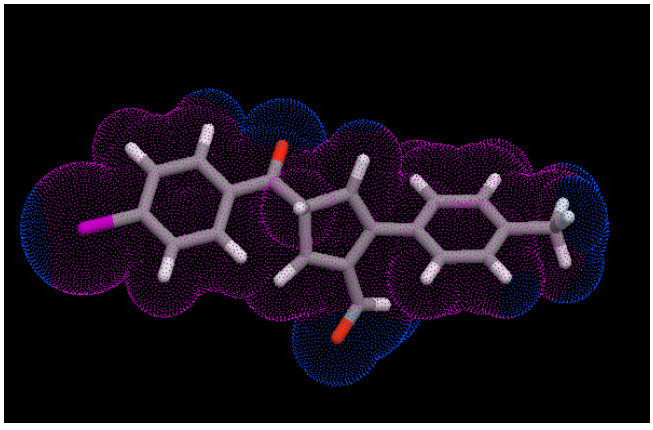


Fig 1: Three Dimensional Structure and Molecular properties of the Analogue (AV1) Using Chem 3D

AV2:1-(4-bromobenzoyl)-3-(4-methylphenyl)-1H-pyrazole-4-carbaldehyde



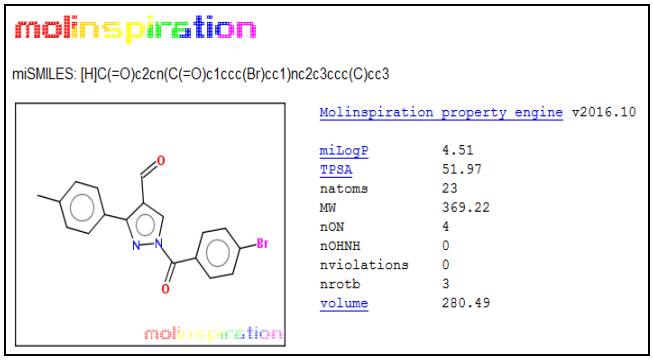
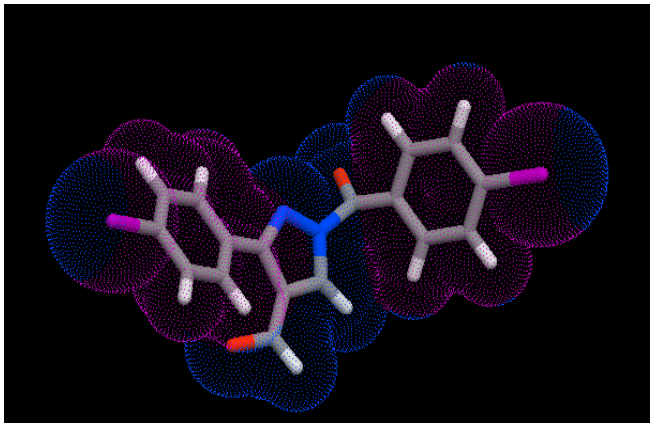


Fig 2: Three Dimensional Structure and Molecular properties of The Analogue (AV2) Using Chem 3D

AV3: 1-(4-bromobenzoyl)-3-(4-bromophenyl)-1H-pyrazole-4-carbaldehyde



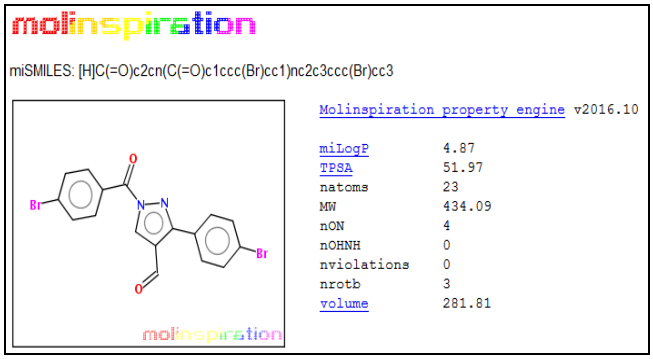
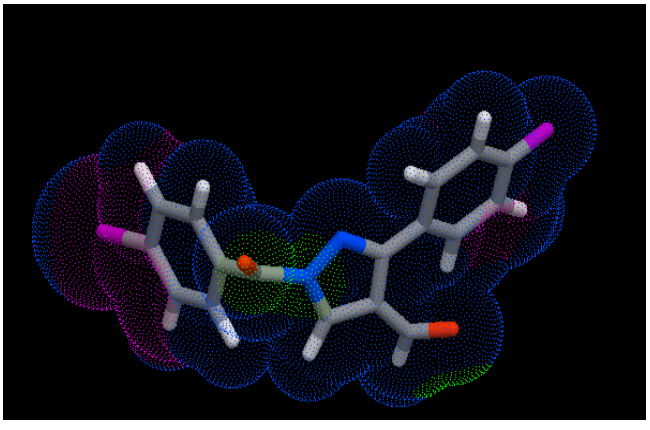


Fig 3: Three Dimensional Structure and Molecular properties of the Analogue (AV3) Using Chem 3D

AV4: 1-(4-bromobenzoyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde



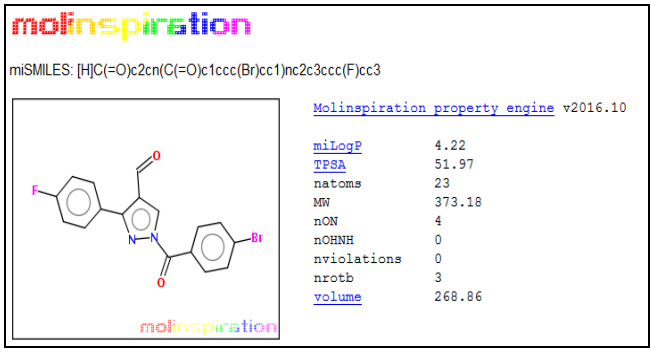


Fig 4: Three Dimensional Structure and Molecular properties of the Analogue (AV4) Using Chem 3D.

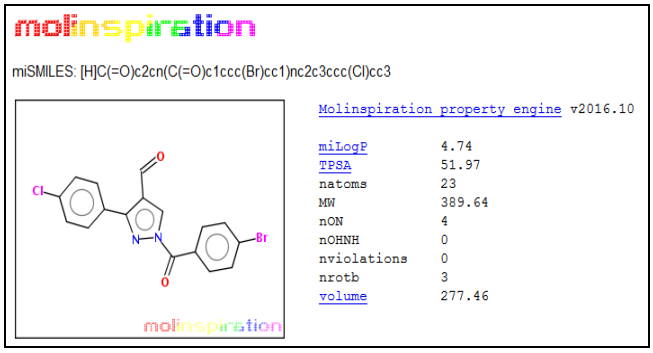
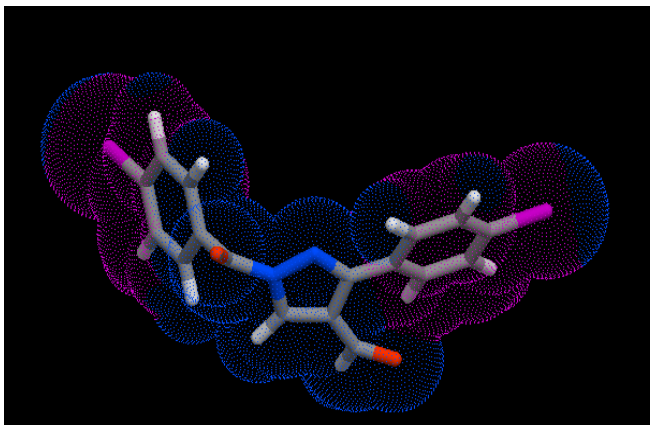


Fig 5: Three Dimensional Structure and Molecular properties of the Analogue (AV5) Using Chem 3D

AV5: 1-(4-bromobenzoyl)-3-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde



All these *In silico* properties are closely compared and evaluated. The analogues with desired physicochemical properties, obeying Lipinski Rule of five are selected for wet lab synthesis.

4.2. Analysis of Lipinski's rule

Below are given the results of the Lipinski's rule analysis of the proposed structures AV1, AV2, AV3, AV4 and AV5. The data shows that AV3 (1-(4-bromobenzoyl)-3-(4-bromophenyl)-1H-pyrazole-4-carbaldehyde) is the best lead molecule.

Table 2: Analysis of Lipinski's rule of five of the proposed analogues

Compound	C log P	MW	Non	NOHNH	Nrotb	NViolations
AV1	4.12	385.21	5	0	4	0
AV2	4.51	369.21	4	0	3	0
AV3	4.87	434.08	4	0	3	0
AV4	4.22	373.18	4	0	3	0
AV5	4.74	389.63	4	0	3	0

Table 3: Drug likeness analysis

Compound Code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear Receptor ligand	Protease inhibitor	Enzyme Inhibitor
AVI	-0.34	-0.45	-0.08	-0.15	-0.35	-0.24
AV2	-0.36	-0.46	-0.09	-0.19	-0.39	-0.26
AV3	-0.32	-0.39	-0.07	-0.18	-0.37	-0.23
AV4	-0.30	-0.40	-0.01	-0.13	-0.35	-0.21
AV5	-0.31	-0.38	-0.04	-0.15	-0.32	-0.19

5. Conclusions

The *In silico* studies performed have identified the probable best lead molecule (AV3 (1-(4-bromobenzoyl)-3-(4-bromophenyl)-1H-pyrazole-4-carbaldehyde) for wet lab synthesis. This study is a stepping stone towards green chemistry.

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7. References

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