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Insilico Design and Synthesis of Novel 4-Arylidene Methyl Phenyl Pyrazol-5-One Derivatives

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ABSTRACT

Novel 4-arylidene methyl phenyl pyrazol-5-one derivatives were designed by using various softwares such as ACD Lab ChemSketch 12.0, Marvin Sketch and Mol inspiration. The designed molecules having required physico-chemical properties, drug likeness and obeying Lipinski's rule of five were selected for the synthesis. The selected derivatives (PCl2, PCl4, PN3, PN4 and PV) were synthesized by conventional method. The synthesized compounds were confirmed based on TLC, melting point determination, IR, 1HNMR and Mass spectroscopic studies.

INTRODUCTION

Pyrazolone derivatives are an important class of heterocyclic compounds that occur in many drugs and synthetic products [1]. The synthesis of pyrazolone and its derivatives have engrossed substantial attention from organic and medicinal chemists for many years as they belong to a class of compounds with proven utility in medicinal chemistry. After the discovery of the natural pyrazole C-glycoside pyrazofurin; 4-hydroxy-3-β-D-ribofuranosyl-1H-pyrazole-5- carboxamide as an antibiotic with broad spectrum of antimicrobial and antiviral activities in addition to being active against several tumor cell lines, there has been a renewed interest in pyrazoles. These compounds exhibit remarkable antitubercular, antifungal, antibacterial, anti-inflammatory, and antitumor activities. Our ongoing investigations have been directed toward the insilico design, synthesis and pharmacological evaluation of some novel 4-arylidene methyl phenyl pyrazol-5-one derivatives [2-9].

MATERIALS AND METHODS

Insilico Molecular Modification

Insilico molecular modification was the most important preliminary step in the rational drug designing of novel drugs. In the present study different proposed derivatives are screened for different physico-chemical properties by using different softwares. ACD Lab Chemsketch 12.0 was used for 3-D drawing, optimizing and calculating various molecular descriptors such as hydrophobicity, lipophilicity, steric and electronic parameters of the proposed molecules. The Mol inspiration software was used for calculating LogP values, Lipinski's rule of five and drug likeness.

The proposed molecules were screened for whether they obey the rule of five or not. The general biological activities of proposed molecules were predicted by using PASS (Prediction of activity spectra for substances) software. Discovery Studio (Libdock score) program was used for the molecular docking of proposed molecules. Five 4-arylidene methyl phenyl pyrazol-5-one derivatives were selected for synthesis with the help of these selection parameters. They are

(4E)-4-(2-chlorobenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-5-one. (PCl2)

(4E)-4-(4-chlorobenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-5-one. (PCl4)

(4E)-5-methyl-4-(4-nitrobenzylidene)-2-phenyl-2,4-dihydro-3H-pyrazol-5-one. (PN4)

(4E)-5-methyl-4-(3-nitrobenzylidene)-2-phenyl-2,4-dihydro-3H-pyrazol-5-one. (PN3)

(4E)-4-(4-hydroxy-3-methoxybenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-5-one. (PV)

Synthesis of Selected Derivatives

The selected compounds were synthesized through a two-step process.

Step-1

Synthesis of 3-methyl phenyl pyrazol-5-one: Ethyl acetoacetate (0.05 mol, 6.2 ml) was mixed with phenyl hydrazine (0.05 mol, 5 ml), followed by addition of 0.5 ml of acetic acid and then heated on a boiling water bath for one hour with occasional stirring. The heavy syrup was allowed to cool and 30-40 ml of ether was added and stirred the mixture vigorously to get crystalline pyrazolone. The product was filtered at the pump and the solid material washed thoroughly with ether and then recrystallized from a small quantity of a mixture of equal volume of water and ethanol. The methyl phenyl pyrazolone was obtained.

Step-2

Synthesis of 4-arylidene-3-methyl phenyl pyrazol-5-one derivatives: A mixture of 1-aryl-3-methyl-5-pyrazolone (0.01 mol, 1.74 g) and substituted aromatic aldehydes (0.012 mol) were heated on oil bath at 150-160°C for 2-4 hrs. The mixture was cooled, triturated with ether (20 ml) and filtered off. The coloured residue was recrystallized from ethanol.

CHARACTERIZATION OF SYNTHESIZED COMPOUNDS BY SPECTRAL STUDY

IR Spectrum

IR spectra were recorded by using KBr pellets in the range of 4000-500 cm^{-1} on Shimadzu FTIR to elucidate the structure of the compounds.

1HNMR spectrum: Proton NMR (400 MHz) spectra were recorded by using Bruker ultra shield model 400 MHz spectrometer using Di methyl sulphoxide as the solvent and tetra methyl silane (TMS) as internal standard.

Mass spectrum: Mass spectra of the synthesized compounds were recorded by FAB+ ionization mode on JEOL JMS 600 instrument.

RESULTS

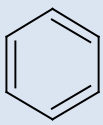
In the present study, insilico molecular modifications of proposed derivatives were done by using different softwares. 3-D drawing, optimizing and calculating various descriptors of proposed derivatives were done by using ACD Lab Chemsketch 12.0 software. The results are shown in **Table 1.**

Table 1. Molecular descriptors of proposed 4-arylidene methyl phenyl pyrazol-5-one derivatives.

Compound	Molar Refractivity (cm^3)	Molar volume (cm^3)	Parachor (cm^3)	Surface tension (dyne/cm)	Polarizability (x10-24cm^3)
PB	80.92 ± 0.5	232.6 ± 7.0	598.3 ± 8.0	43.7 ± 7.0	32.07 ± 0.5
PCl2	85.52 ± 0.5	241.9 ± 7.0	627.2 ± 8.0	45.1 ± 7.0	33.90 ± 0.5
PCl4	85.52 ± 0.5	241.9 ± 7.0	627.2 ± 8.0	45.1 ± 7.0	33.90 ± 0.5
PM4	86.73 ± 0.5	254.3 ± 7.0	648.6 ± 8.0	42.2 ± 7.0	34.38 ± 0.5
PN2	86.58 ± 0.5	237.9 ± 7.0	643.8 ± 8.0	53.5 ± 7.0	34.32 ± 0.5
PN3	86.58 ± 0.5	237.9 ± 7.0	643.8 ± 8.0	53.5 ± 7.0	34.32 ± 0.5
PN4	86.58 ± 0.5	237.9 ± 7.0	643.8 ± 8.0	53.5 ± 7.0	34.32 ± 0.5
PD	93.72 ± 0.5	273.8 ± 7.0	694.6 ± 8.0	41.3 ± 7.0	37.15 ± 0.5
PV	87.58 ± 0.5	251.6 ± 7.0	654.2 ± 8.0	45.7 ± 7.0	34.72 ± 0.5

The mol inspiration software was used to study the LogP values, violation of Lipinski's rule of five and drug likeness by comparing with already existing standard drugs. The results are shown in **Tables 2-4** and **Figure 1.**

Table 2. Smile notations of proposed 4-arylidene methyl phenyl pyrazol-5-one derivatives.

COMPOUND	Ar	SMILES NOTATION
PB		O=C3/C(=C/c1ccccc1)C(C)=NN3c2ccccc2

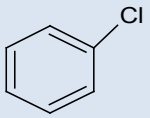
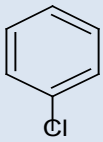
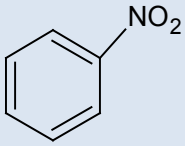
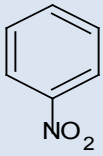
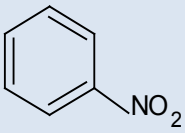
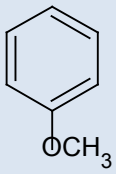
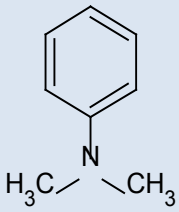
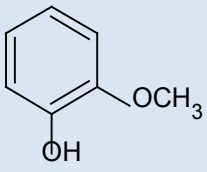
PCl2		Clc3ccccc3/C=C1/C(=O)N(N=C1C)c2ccccc2
PCl4		Clc1ccc(cc1)/C=C2/C(=O)N(N=C2C)c3ccccc3
PN2		[O][N+](=O)c3ccccc3/C=C1/C(=O)N(N=C1C)c2ccccc2
PN4		[O][N+](=O)c1cccc(c1)/C=C2/C(=O)N(N=C2C)c3ccccc3
PN3		[O][N+](=O)c1cccc(c1)/C=C2/C(=O)N(N=C2C)c3ccccc3
PM4		COc3ccccc3/C=C1/C(=O)N(N=C1C)c2ccccc2
PD		CN(C)c1ccc(cc1)/C=C2/C(=O)N(N=C2C)c3ccccc3
PV		Oc1ccc(cc1OC)/C=C2/C(=O)N(N=C2C)c3ccccc3

Table 3. Lipinskis rule analysis of proposed 4-arylidene methyl phenyl pyrazol-5-one derivatives.

CODE	miLogP	MW	nON	nOHNH	nviolations	Nrotb
PB	2.854	262.312	3	0	0	2
PCl2	3.484	296.757	3	0	0	2
PCl4	3.532	296.757	3	0	0	2
PM4	2.911	292.338	4	0	0	3
PN2	2.765	307.309	6	0	0	3
PN3	2.789	307.309	6	0	0	3
PD	2.956	305.381	4	0	0	3
PV	2.193	308.337	5	1	0	3

Table 4. Drug likeness analysis of proposed 4-arylidene methyl phenyl pyrazol-5-one derivatives.

Novel compounds	GPCR Ligands	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
PB	0.05	0.01	0.15	0.29	0.21	0.16
PCl2	-0.81	-1.01	-0.28	-0.55	-0.75	-0.53
PCl4	-0.79	-0.97	-0.28	-0.56	-0.67	-0.47
PM4	-0.78	-1.00	-0.26	-0.50	-0.62	-0.46
PN2	-0.89	-0.94	-0.44	-0.62	-0.65	-0.53
PN3	-0.86	-0.96	-0.35	-0.56	-0.68	-0.54
PN4	-0.85	-0.95	-0.36	-0.56	-0.67	-0.52
PD	-0.78	-0.92	-0.29	-0.44	-0.60	-0.44
PV	-0.70	-0.93	-0.20	-0.41	-0.60	-0.39

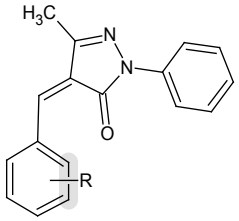


Figure 1. Proposed general structure of pyrazolone derivative.

With the help of these selection parameters five analogues were selected for synthesis. The selected compounds were synthesized by conventional and microwave assisted synthetic methods. The general scheme for the synthesis is presented in **Figure 2.**

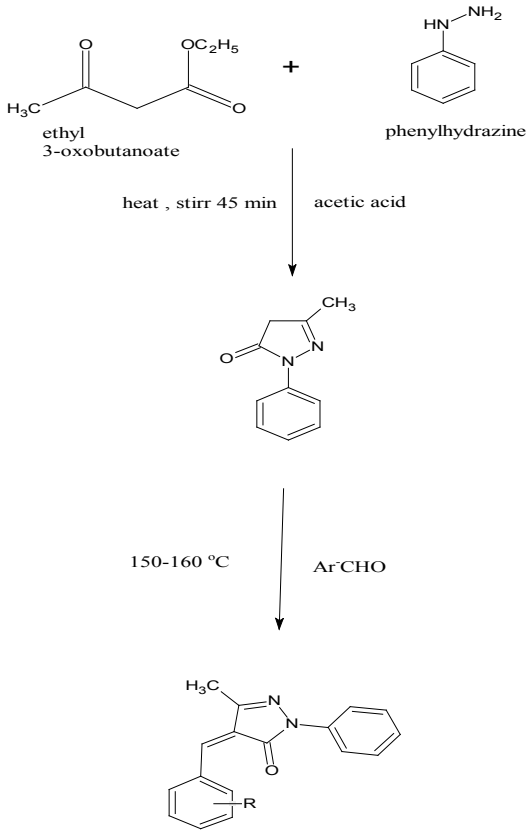


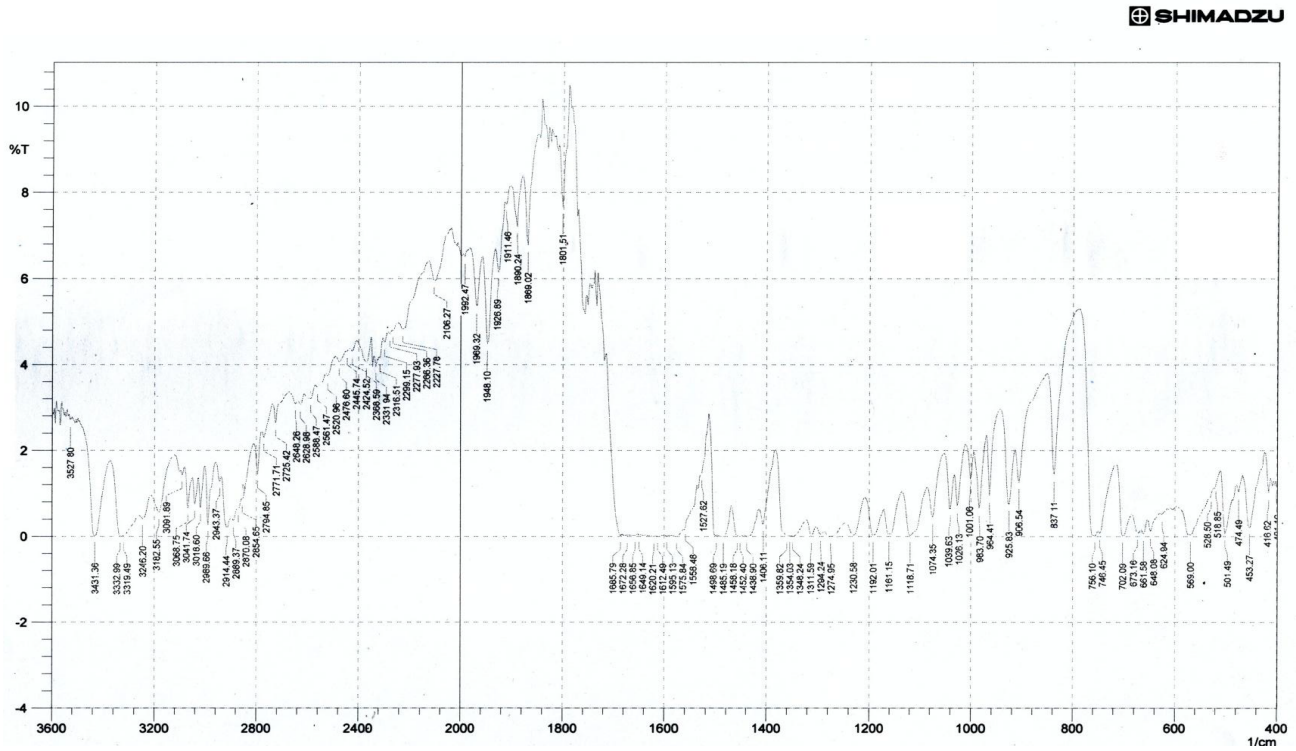
Figure 2. General Scheme for synthesis of 4-arylidene methyl phenyl pyrazol-5-one derivatives.

The various physicochemical parameters like molecular mass, melting point and percentage yield are summarized in **Table 5.**

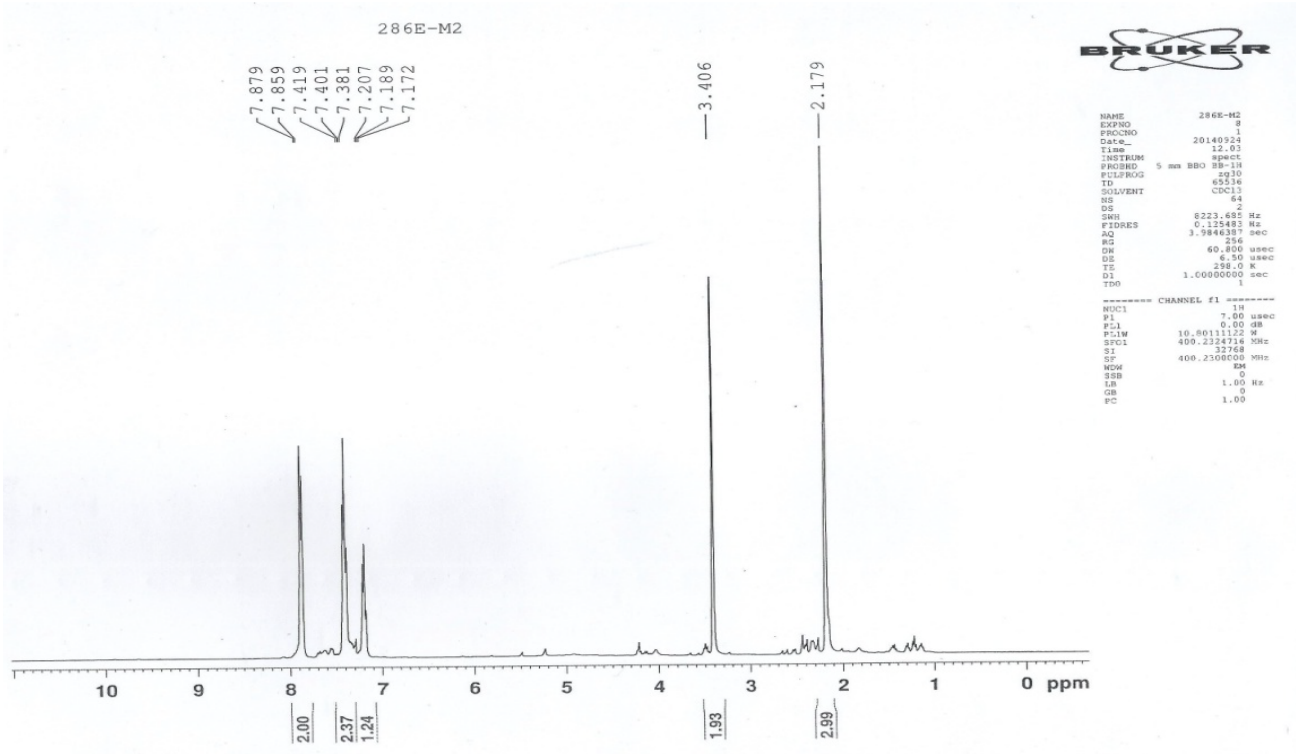
Table 5. Physicochemical parameters proposed 4-arylidene methyl phenyl pyrazol-5-one derivatives.

Compound	Molecular formula	Molecular weight	Melting point	% Yield
PCl2	$C_{17}H_{13}ClN_2O$	296.75	122	76.82
PCl4	$C_{17}H_{13}ClN_2O$	296.75	84	81.8
PN3	$C_{17}H_{13}N_3O_3$	307.3	218	78.9
PN4	$C_{17}H_{13}N_3O_3$	307.3	220	76.29
PV	$C_{18}H_{16}N_2O_3$	308.33	94	78.46

The synthesized compounds were characterized by FTIR AND 1H NMR spectroscopic methods. The FTIR report for the synthesized compound PCL2 is shown in **Graph 1.** 1H NMR report for the compound PCL2 is shown in **Graph 2.**



Graph 1. FT IR report for compound PCl2.



Graph 2. The 1H-NMR report for compound PCl2.

DISCUSSION

In the present study, the insilico molecular modeling studies were carried out for the selection of suitable drug candidates prior to wet lab synthesis. Insilico studies were performed on 26 analogues by means of ACD Lab ChemSketch 12.0, Mol inspiration, PASS, and Discovery studio. Of the proposed 10 analogues, 5 candidates were chosen for wet lab synthesis.

These compounds were synthesized by conventional methods. The synthesized compounds were subjected to TLC, melting point determination, IR, 1 HNMR and Mass spectroscopic studies. All these evaluation ensured the synthesized compounds. Of

course this compound needs further studies such as toxicity and *in vivo* evaluation. So it is clear that further works needed to be done in the future for the development of clinically useful chemotherapeutic agents.

CONCLUSION

In summary, the prime objective of the present work was to design, synthesize and screen some of the 4-arylidene methyl phenyl pyrazol-5-one derivatives. Based on that particular objective, various 4-arylidene methyl phenyl pyrazol-5-one derivatives were designed by preliminary in silico methods using various softwares. Based on the in silico results, five derivatives were synthesized by the conventional method and the purity of the compounds thus synthesized was ascertained by consistency in melting point and characterized by IR and 1H NMR spectroscopy. This analogue can be subjected to further detail pharmacological screening for consideration as drug candidate.

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