DESIGN SYNTHESIS, SPECTRAL CHARACTERIZATION, ANTI MICROBIAL EVALUATION AND ADME PREDICTIONS OF 1 -3-(MORPHOLINO PENYL)-5-ARYL-4,5-DIHYDROPYRAZOL-1-YL)-1-ONE DERIVATIVES

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Abstract: A new series of five bioactive pyrazole compounds (4a-4e) was synthesized from the morpholine substituted chalcone derivative (3a-3e). The synthesized compounds functional groups were unambiguously assigned by FT-IR characterization and the skeleton structure of the target compound 4a was characterized by proton and carbon NMR spectral characterization. The physical characterization like melting point, molecular weight, yield and elemental analysis was carried for the synthesized compounds (4a-4e). Finally, the synthesized compounds biological applications like antimicrobial evaluation were carried using disc diffusion method, all the compounds showed good bacterial activity against all the bacterial strains and except 4a and 4e remaining three compounds showed the better fungal activity against the fungal stains. In silico ADME property of the compounds were identified, all compounds obey the Lipinski's rule of five without any violations.

Key words: **NMR spectral studies, ADME property, antimicrobial activity, Lipinski's rule**

I. INTRODUCTION

Heterocyclic compounds particularly those with oxygen, nitrogen and Sulphur atoms have been identified to have the most comprehensive spectrum of biological activities[1].In the synthesis of heterocyclic compounds, chalcones is used as an intermediate and it should have a good biological activity as well as it plays an important role in medicinal chemistry and drug discovery[2,3,4].The pyrazoline derivatives are the most important classes of heterocyclic compound and it is a versatile lead molecule in agrochemical and pharmaceutical field. The pyrazoline derivatives have various biological activities such as antimicrobial [5], antitumor [6], antibacterial [7], anti-inflammatory [8], anticancer [9], antidiabetic [10], pharmacological [11], free radical scavenging [12,13] activities. Among the reported activities, it is important to note that pyrazoline are not only useful in the treatment of various cancer types, including brain, bone, mouth, esophagus, stomach, liver, bladder, pancreas, cervix, lung, breast, colon, rectum and prostate cancers, but some of them act as cancer chemo preventive agents [14]. Most of the pyrazole compounds have lot of industrial applications and anticorrosive inhibition property [15].

On the other hand, pyrazoline derivatives were carried out of the focus of drug discovery; like the studies drug-ability and bioactivity of the compounds. The concept of drug-ability is defined as the prospect to find a compound with high potency, drug-like properties, as well as measured properties concerning to undesirable side effects, metabolism and intestinal absorption. It was observed that about 30% of oral drug fail in development due to poor pharmacokinetics studies [16]. It is worth to note that lack of *in vivo* effectiveness of a drug candidate might be due to poor physiochemical properties of the drug candidate itself [17].In addition biding activity can be predicted by studying whether the tested compounds are complementary with the binding sites on biological molecules in terms of topology, volume and physiochemical properties[18].That's to say, it is useful to estimate the probability that molecule can bind a given protein with sufficient affinity in order to modify its activity[19]. So, Computation screening of new compounds, ie *in-silico* prediction of drug-likeness and bioactivity, has been proved to be very important in the early stage of drug discovery to subject the most suitable compounds to further optimization, and to find drug candidate for further clinical development [20,21]

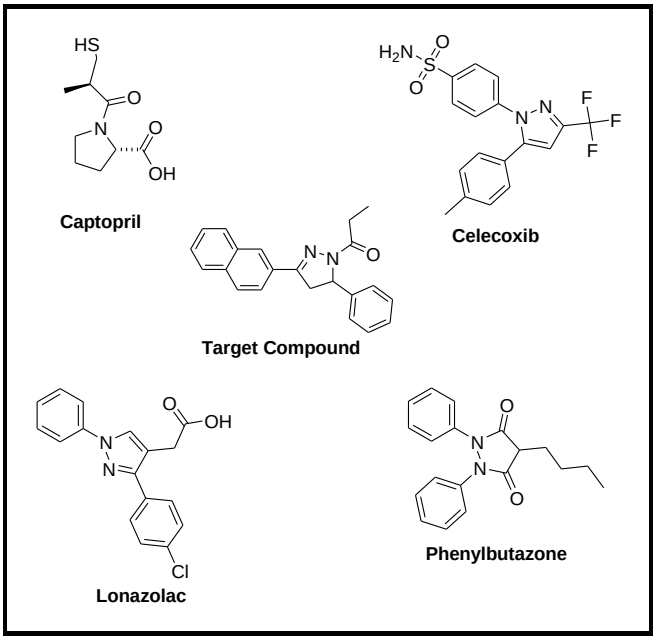

Figure 1 The structure of some drugs bearing the pyrazole moiety

Finally, the synthesized compounds were screened for antimicrobial activity against disc diffusion method. Based on the above study, we need to development of new drugs against the antimicrobial activities. Therefore, we were led to identifying new approaches of pyrazoline derivatives as well as test the antimicrobial.

II. RESEARCH METHODOLOGY

2.1. MATERIALS AND METHODS:

The n-butyric acid (500 mL) was purchased from sigma Aldrich. The melting points of the compounds were determined through open capillary method and values were uncorrected. The FT-IR spectrum (cm^{-1}) was recorded through KBr in a Fourier Transform IR spectrometer (model Shimadzu 8400s) in the range of 400-4000 cm^{-1}. The ^{1}H, ^{13}C NMR spectra and ^{1}H-^{1}H Cosy were recorded by Brucker 400 MHz spectrometer and chemical shifts are recorded in δ value (ppm) with Tetra Methyl Silane (TMS) as internal standard, as well as $CDCl_3$ used as a solvent.

2.1.1. GENERAL PROCEDURE FOR THE PREPARATION OF TLC PLATES:

Analytical TLC was performed on precoated silica gel (Merck, Germany). Silica gel G. 10g was dispersed in 15 ml of distilled water. The resulted homogenous solution was applied on glass plates using an applicator. The plates were allowed to dry in Owen for 30 minutes and activated in an Owen for one hour before use.

2.1.2. PERCENTAGE OF THE PRODUCT:

All the synthesized compounds were purified by recrystallization procedures. The purity of the compound was checked by TLC method. The percentage of yield of the compounds was calculated as shown below.

$$\% \text{ Yield} = \frac{\text{Weight of the product obtained}}{\text{Theoretical weight}} \times 100$$

2.1.3. GENERAL PROCEDURE FOR THE SYNTHESIS OF (E)-1-(4-MORPHOLINOPHENYL)-3-ARYLPROP-2-EN-1-ONE DERIVATIVES: (3a-3e)

One mol of 4-mopholino acetophenone and one mole of various substituted aromatic aldehydes were taken in a beaker and to this approximately added 30 ml of ethanol containing 2g of NaOH pellets. Then the mixture was stirred well for 30 minutes in an ice-cold bath, after it was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The chalcone were precipitated out as solid. Then it was filtered, dried and recrystallized from ethanol. The purity of the compound was checked by TLC by using $CHCl_3$ as a solvent.

2.1.4. GENERAL PROCEDURE FOR THE SYNTHESIS OF 1 -3-(MORPHOLINO PENYL)-5-ARYL-4,5-DIHYDROPYRAZOL-1-YL)-1-ONE DERIVATIVES: 4a-4e

Chalcone (1 mol) and hydrazine hydrate (1 mol) were taken in a 250 ml round bottom flask and approximately added 30 ml of propionoic acid. Then the mixture was refluxed for 14-16 hours. The completion of the reaction was monitored by TLC using 100% $CHCl_3$. After this reaction mixture was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The product was precipitated out as solid. Then it was filtered, dried and recrystallized using ethanol. The purity of the compound was checked by TLC using 9:1 ratio (P. E+ E.A).

2.2. ANTIMICROBIAL EVALUATION

2.2.1. ANTIBACTERIAL SCREENING

The antibacterial screening for synthesized pyrazoline compounds were determined by agar disk diffusion method against gram positive bacterial strains of *Staphylococcus aureus*, *Streptococcus pyogenes* and gram-negative bacterial strains of *Escherichia coli*,

Pseudomonasaeruginosa. The zone of inhibition was measured after 24h incubation at 37 ºC. The biological screening experimental procedure was adopted by the literature survey method [22].

2.2.2. ANTIFUNGAL SCREENING

The antifungal screening for synthesized pyrazoline compounds were determined by agar disk diffusion method against *Candida albicans strain*. The zone of inhibition was measured after 24 h incubation at 37 ºC.

2.2.3.IN SILICO ADME PROPERTIES

Absorption, distribution, metabolism and excretion (ADME) properties of all the synthesized 2-(3-(naphthalene-2-yl)-3-oxo-1-phenylpropyl) cyclohexanone derivatives (2a-2h) were predicted using swissADME online tool about the molecular weight, hydrogen bond acceptor, hydrogen bond donor, octanol water partition co-efficient (log p0/w), solubility (log S), skin-permeation (log Kp), total polar surface area (TPSA), molar refractivity and bioavailability score.

III. RESULTS AND DISCUSSION

3.1. CHEMISTRY

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activity of chalcones. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones bears a very good python so that variety of novel heterocyclic with good pharmaceutical profile can be designed. Morpholino chalcone were prepared from various substituted aromatic aldehydes reacted with 4-acetyl biphenyl in the presence of strong base. The morpholino chalcone were then cyclization with hydrazine hydrate and propionic acid to give 2-pyrazoline derivatives. Claisen-Schmidt condensation method for the synthesis of chalcones is very attractive since it specifically generates the Trans E-isomer.

SCHEME

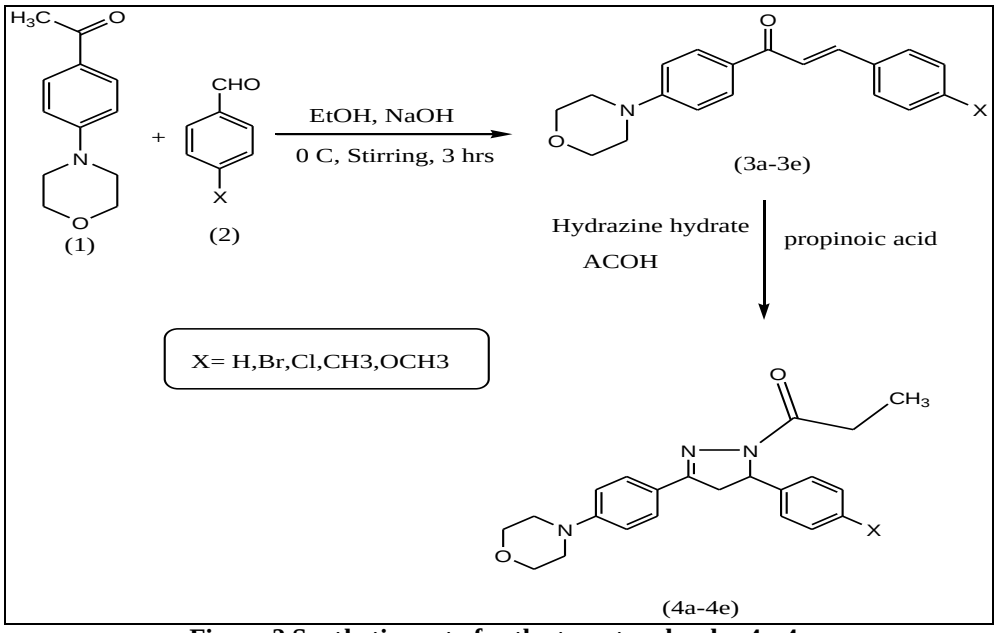

Figure 2 Synthetic route for the target molecules 4a-4e

The IR spectrum supported the data showing the characteristic band for compounds (3a-3e) C=O at 1690 – 1750 cm^{-1}, aromatic CH stretching around at 3000-3100 cm^{-1} and aliphatic CH stretching around at 2900 – 3000 cm^{-1}.

3.1.2. THE PHYSICAL CHARACTERIZATION OF THE COMPOUNDS 4A-4E

The elemental analysis, melting point and yield were observed for the synthesized compounds 4a-4e. The results were given table-1.

TABLE 1 Physical analytical characterization of the compound 4a-4e

Compound	Molecular formula	Yield	Melting point	Elemental analysis	
				Found	Calculated
4a	$C_{22}H_{25}N_3O_2$	88	240-242	C 72.70, H 6.93,N 11.56, O 8.80	C 72.63, H 6.87,N 11.55, O 8.80
4b	$C_{22}H_{24}BrN_3O_3$	82	230	C 59.73, H 5.47Br 18.06,N 9.50, O 7.23	C 59.68, H 5.42,Br 18.31,N 9.49, O 10.85
4c	$C_{22}H_{24}ClN_3O_3$	86	212	C 66.41,H 6.08, Cl 8.91, N 10.56, O 8.04	C 66.34,H 6.03, Cl 8.91, N 10.55, O 12.06
4d	$C_{23}H_{25}N_3O_3$	84	198	C 73.18, H 7.21, N 11.13, O 8.48	C 73.11, H 6.62, N 11.12, O 12.71
4e	$C_{23}H_{27}N_3O_3$	80	210	C 70.21, H 6.92, N 10.68, O 12.20	C 70.14, H 6.86, N 10.67, O 12.19

3.1.3.IR SPECTRAL CHARACTERIZATION

The FT-IR Spectrum of the shows that the characteristic absorption frequency at 1654 cm^{-1} is due to amide carbonyl stretching vibration of pyrazole moiety. The absorption band at 1427 cm^{-1} is attributed to C=N stretching. The absorption frequency around 3060.31 cm^{-1} is assigned to aromatic CH Stretching vibration. The absorption band around 2929 cm^{-1} is assigned to aliphatic CH stretching vibration. From the results skeleton structure of the synthesized compounds functional groups was unambiguously assigned. The IR spectrum of the compound 4a given in the figure-1

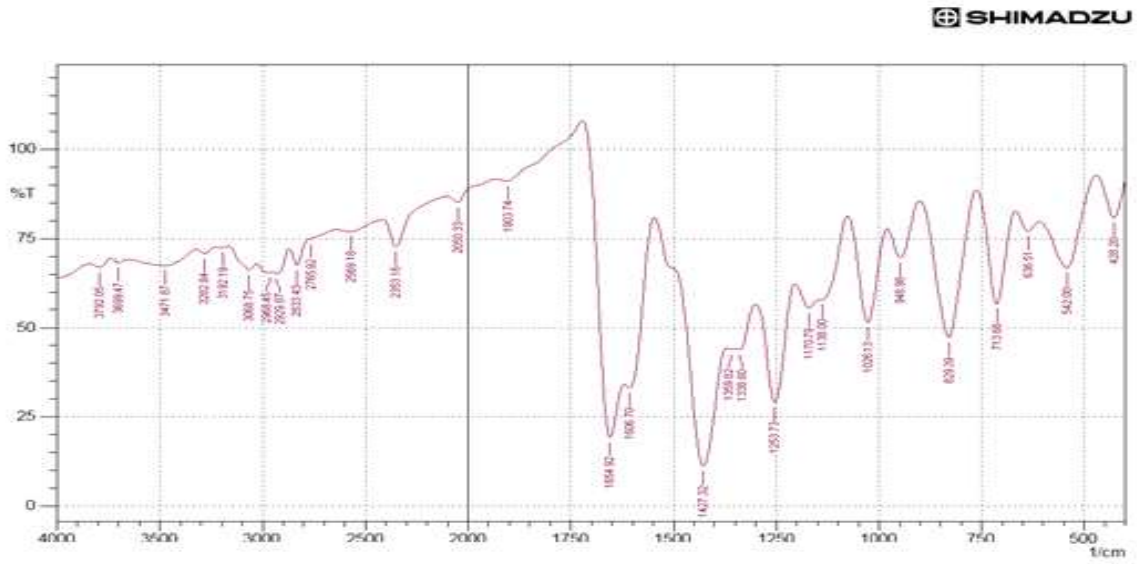

Figure 3 FT-IR spectrum of the compound -4a

3.1.4. ANALYSIS OF ^{1}H NMR SPECTRUM OF COMPOUND-4a

In the ^{1}H NMR spectrum of compound 4a, the methylene protons of (H-4a &H-4e) of the pyrazole moiety appeared as two doublets of doublets due to multiple coupling involving both germinal and vicinal protons. The signal H4-a &H4-e observed at3.29 and 3.88 ppm. The doublet of doublet at 3.29ppm ($J_{4a,5a}$=18 Hz &$J_{4a,4e}$=4 Hz) is assigned to H4a proton of the pyrazoline moiety. Likewise, the doublet of doublet at 3.88 ppm ($J_{4e,4a}$ =18 and $J_{4e,5a}$ =12 Hz) is assigned to H-4e proton of the pyrazoline moiety. Similarly, the methine proton (H-5) of the pyrazole moiety is expected to give signal as a doublet of doublet due to vicinal coupling with the two magnetically nonequivalent protons of the methylene group (H-4a-H4e) of the pyrazoline moiety and the signals are observed at 5.63 ppm ($J_{5a,4a}$= 12 Hz and $J_{5a,4e}$ =4.0 Hz).Also the acetyl methyl protons of pyrazoline moiety gives signal as a singlet at 2.47 ppm. The aromatic protons appear as a multiplet in the range of 7.02-8.11 ppm.

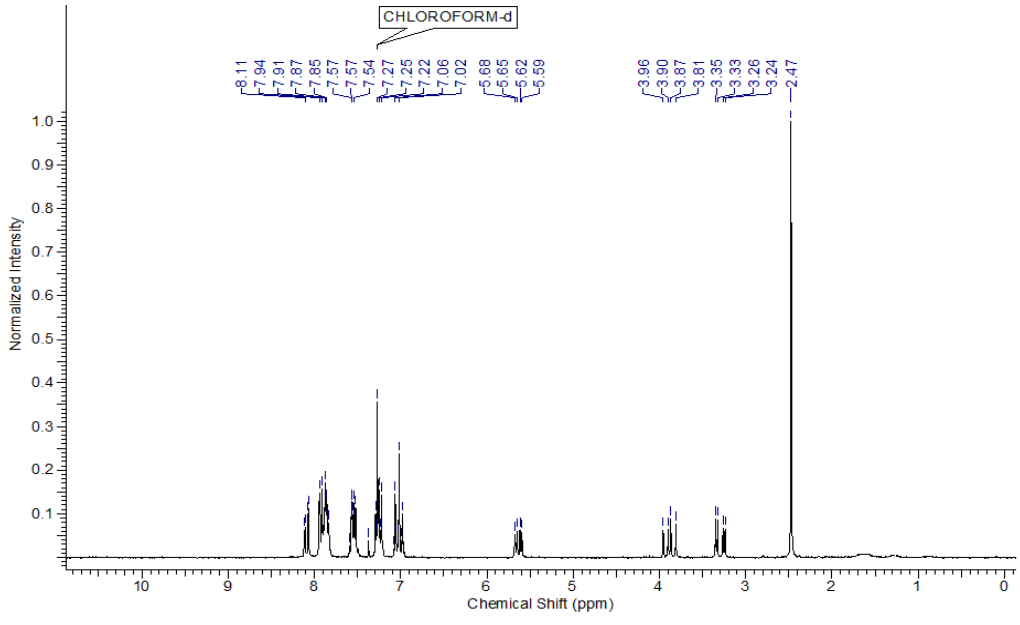

Figure 4 Proton NMR Spectrum of the Compound 4a

3.1.5.ANALYSIS OF ^{13}C NMR SPECTRUM OF COMPOUND-4a

The ^{13}C NMR spectrum of compound is reproduced in Figure-3 .In the ^{13}C NMR spectrum of compound 4a, In the ^{13}C NMR specrum of 1-acetyl-4,5-dihydro-5-phenyl-3-(thiophen-2yl)pyrazoles, ^{13}C resonanceat 59.58 ppm is assigned to C-5 of pyrazole moiety. The ^{13}C resonance observed at 42.23 ppm is due to C-4 of pyrazole moiety. The ^{13}C resonance observed at 153.89 ppm is assigned to C-3 of pyrazole moiety. The aromatic carbons are observed in the region of 114.25-129.09 ppm. The ^{13}C resonance observed at 22.11 ppm is due to acetyl methyl carbon. The remaining ^{13}C signal at 133.15 are 134.02are due to ipso carbon. The ^{13}C NMR chemical shift values are given in Table-4.

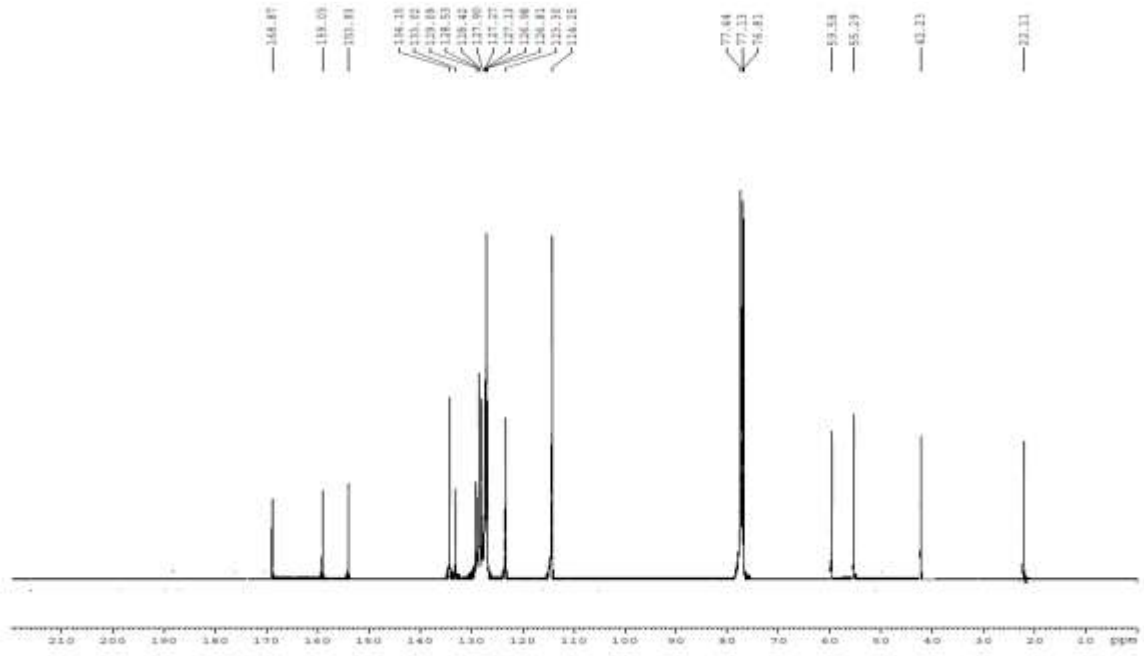

Figure 5 Carbon NMR spectrum of the compound 4a

3.2. ANTIMICROBIAL STUDIES

3.2.1. ANTIBACTERIAL ACTIVITY

Antibacterial screening of synthesized derivatives (4a-5e) against Gram positive bacterial species: *Staphylococcus aureus*, *Streptococcus pyogenes* and gram-negative species *Escherichia coli*, *Pseudomonas aeruginosa*. Antibacterial activity results (Table-6) particularly; compound 4b exhibited good zone of inhibition against *Staphylococcus aureus* and Compound 4d exhibited excellent zone of inhibition as compared with standard drug ciprofloxacin against *Streptococcus pyogenes*. Compound 4b exhibited excellent zone of inhibition as compared with standard drug ciprofloxacin against *E.coli*. Compound 4b have excellent zone of inhibition compared with standard drug against Pseudomonas aeruginosa. Finally, the antibacterial result, the electronegativity group has excellent activity. From the results all the synthesized compounds show good activity against all the bacterial strains. The bacterial activity values are depicted in the Table-2.

Table 2 Antibacterial activity of isolated compound (4a-4e) at 1.0 mg/ml.

Entry	Bacteria(zone of inhibition in mm)			
	Staphylococcus aureus	***Streptococcus pyogenes***	***Escherichia Coli***	***Pseudomonas aeruginosa***
4a	16	20	19	17
4b	21	23	24	24
4c	13	17	15	17
4d	17	25	20	16
4e	17	18	18	-
Ciprofloxacin	**26**	**17**	**19**	**22**

3.2.2. ANTIFUNGAL ACTIVITY

Antifungal screening of synthesized derivatives (4a-4e) against *candida albicans* species was done by agar disk diffusion method. Antifungal results indicated (Table-7) particularly compound 5b shown more promising antifungal activity (15 mm) as compared with standard drug Clotrimazole (24 mm) while other derivatives are moderately active. The electron withdrawing group directly attached with pyrazole ring portion of compound 5b increased the antifungal potential against *C.albicans*. Compound 4a and 4e did not have any promising activity against the fungal strains.The fungal activity was given in the Table-3.

Table 3 Antifungal activity of isolated compound (4a-4e)

Entry	***Candida albicans***
4a	-
4b	15
4c	14

4d	13
4e	-
Clotrimazole	**24**

3.3. ADME STUDIES

3.3.1. In silico ADME property:

Determination of ADME parameters of the synthesized 1-(3-(4-Morpholinophenyl)-5-Phenyl-4,5-Dihydropyrazol-1-Yl) Propan-1-One derivatives (4a-4e) were done using Swiss ADME online software. The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, we have calculated log p0/w, solubility (log S), molecular weight, TPSA (topological polar surface area), drug-likeness, hydrogen bond acceptor, hydrogen bond donor, molar refractivity, drug score and pharmacokinetics study of GI absorption, BBB (blood brain barrier), P-gp substrate, cytochrome P450 family and sub-family members and log Kp (skin permeation), Lipinski's violation, Ghose filter, Veber, Egan, Muegge and Bioavailability score, Pains, Brenk, Lead-likeness and synthetic accessibility were carried using Swiss ADME online tool. Percentage of absorption were carried by the following formula,

% of ABS = 109- Total Polar Surface Area X 0.345

All the compounds (4a-4e) were subjected to ADME property prediction with the help of Swiss ADME online software. This in silico method plays a major role in the pharmacokinetics property of the new molecules. All the target compounds obey the Lipinski rule of five and also exhibit good solubility and absorption values. The synthesized compound 4a-4e exhibits good log P value. The ADME prediction values of other compounds are shown in Table-4.

Table 4 ADME properties of the compounds 4a-4e

Compound		**Molecular formula**	**MW**	**Log $P_{o/w}$[c]**	**n-Hy-A**	**n-Hy-D**	**M. Rfy**	**n-violation of rule of five**	**Log S**	**TPSA in Å**	**Drug likeness**	**% ABS**
4a	H	$C_{22}H_{25}N_3O_2$	363.45	3.01	3	0	117.56	0	-3.93	45.14	3.72	93.43
4b	4-Br	$C_{22}H_{24}BrN_3O_3$	442.35	3.63	3	0	125.26	0	-4.84	45.14	3.77	93.43 .
4c	4-Cl	$C_{22}H_{24}ClN_3O_3$	397.90	3.54	3	0	122.57	0	-4.53	45.14	3.27	93.43
4d	4-Me	$C_{23}H_{25}N_3O_3$	377.48	3.36	3	0	122.53	0	-4.24	45.14	3.83	93.43
4e	4-OMe	$C_{23}H_{27}N_3O_3$	393.48	3.00	4	0	124.06	0	-4.01	54.37	3.82	90.25

The Pharmacokinetics' and Drug-likeness prediction of the synthesized compounds (4a-4e) were carried out by Swiss ADME online tool and the data are given Table-4. According to pharmacokinetic properties, all the synthesized compounds showed high Gastro intestinal absorption. In Blood Brain Barrier (BBB), all the compounds have permeability values. However, most of them 4a-4e showed inhibition to Cytochrome P450 isomers (CYP2C19, CYP2C9, CYP2C6 and CYP3A4). The synthesized compound does not inhibit the CYP1A2 cytochrome P450. Skin permeation values ie log K_p values appeared in the range of -6.21 to -6.65. The drug-likeness prediction was also conducted depending on the selected Lipinski's, Ghose, Veber and Bioavailability score. All the compounds have the similar bioavailability score of 0.55. All the synthesized compounds 4a-4e was obey the Lipinski's rule of five. All of them obey veber rules there is no violation. All the synthesized compounds probably accept the Ghose, Muggee and Egan rules. Medicinal Chemistry Properties also carried out by swissadme software. In this study they have no alert in Pains and Brenk filter, in lead likeness properties all the synthesized compounds 4a-4e showed two violations like Molecular weight >350, and XLOGP3>3.5. All the compounds have the synthetic ability value between 3.72-3.83. From these values of synthetic ability, the compounds (4a-4e) are obeyed the medicinal chemistry property. The values are given in Table-4 and 5.

Table 5: Pharmacodynamics properties of the compounds 4a-4e

Compound	**4a**	**4b**	**4c**	**4d**	**4e**
Pharmacokinetics					
GI absorption	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	Yes
P-gp	Yes	No	No	No	Yes
CYP1A2	No	No	No	No	No
CYP2C19	Yes	Yes	Yes	Yes	Yes
CYP2C9	Yes	Yes	Yes	Yes	Yes
CYP2D6	Yes	Yes	Yes	Yes	Yes
CYP3A4	Yes	Yes	Yes	Yes	Yes
Log K_p (skin permeation)cm/s	-6.44	-6.44	-6.21	-6.27	-6.65
Drug Likeness					
Lipinski	Yes ;0 violation	Yes ;0 violation	Yes ;0 violation	Yes; 0 violation	Yes ;0 violation

Ghose	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55	0.55	0.55
Medicinal Chemistry					
PAINS	0 alert	0 alert	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	0 alert	0 alert	0 alert
Leadlikeness	No:1violation MW>350	No; 2 violation,MW>350, XLOGP3>3.5	No; 2 violation,MW>350, XLOGP3>3.5	No; 1violation,MW>350, XLOGP3>3.5	No;1 violation,MW>350,
Synthetic accessbility	3.72	3.77	3.73	3.83	3.82

IV SUMMARY

Substituted benzaldehydes were reacted with 4-morpholinoacetophenone in the presence of a strong base to yield chalcone derivatives (**3a–3e**). These derivatives were then cyclized with hydrazine hydrate and propionic acid to produce 2-pyrazoline compounds (**4a–4e**). The functional groups of the synthesized compounds were confirmed via FT-IR spectroscopy, while the skeletal structure of the target compound **4a** was characterized using ^{1}H and ^{13}C NMR spectroscopy. Physical properties, including melting point, molecular weight, yield, and elemental analysis, were recorded for all synthesized compounds (**4a–4e**). Finally, the biological applications of the compounds, specifically their antimicrobial potential, were evaluated using the disc diffusion method. All compounds exhibited significant antibacterial activity against the tested strains. Regarding antifungal activity, all compounds except **4a** and **4e** showed enhanced activity against the fungal strains. In silico ADME profiling revealed that all compounds obey Lipinski's rule of five without any violations.

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