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Synthesis characterisation and Biological Studies of Pyridazine Analogues

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Abstract - The findings from a single treatment were presented in the form of a mean graph showing the percentage growth of treated cells. For the One-dose test, the reported value reflects an increase from the baseline number of cells and is also expressed as a percentage relative to the no-drug control.The -NH group that is present in benzimidazole is capable of forming salts due to its ability to be both highly acidic and mildly basic at the same time. The product demonstrated quick prototropictautomerism rather than isomerism. occurs when the group that is connected to the nitrogen atom in the first position is bigger than the hydrogen atom; in this case, tautomerism does not occur. In the current research work, we have synthesised new derivatives of 4H- pyrazolo[3,4-d]pyrimidine by reacting 3-amino-5-(methylthio)-1H-pyrazole-4- carboxamide and various benzaldehyde with propyl phosphonic anhydride (T3P, 50% Ethyl acetate) in acetonitrile solvent at reflux temperature. A result of 0 indicates that there was no overall increase during the duration of the trial. A number of -40 would indicate a lethality level of 40%. A number of -100 signifies all cells are dead. The data from a single dosage mean graph is already accessible for comparative examination.

Keywords - Biological Studies, Synthesis, Pyridazine, growth inhibition.

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INTRODUCTION

Scientists have discovered that nitrogen heterocyclic compounds, such those present in vitamins, nucleic acids, proteins, and so on, play a crucial role in the biology of molecular systems.Imidazole is a heterocyclic ring that has five members and contains two atoms of nitrogen in its structure. As seen in the structure for benzimidazole, the benzoimidazole molecule has a benzene ring that has been fused to an imidazole ring. Because this molecule belongs to an important family of heterocyclic compounds for the creation of novel drugs, it is referred to as benzoimidazole. Benzimidazole has properties that are characteristic of both basic and acidic substances. The -NH group that is present in benzimidazole is capable of forming salts due to its ability to be both highly acidic and mildly basic at the same time. the product demonstrated quick prototropictautomerism rather than isomerism. Isomerization, on the other hand, occurs when the group that is connected to the nitrogen atom in the first position is bigger than the hydrogen atom; in this case, tautomerism does not occur. [1]

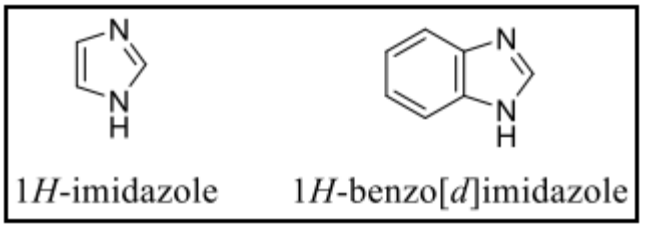


Figure 1: Structure of Imidazole

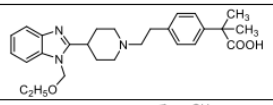
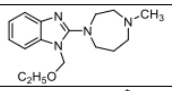
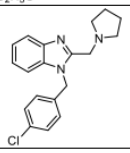
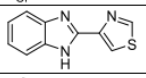
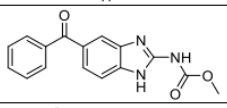
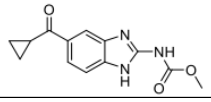
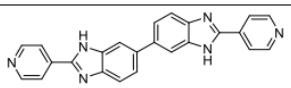
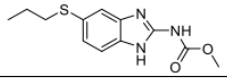
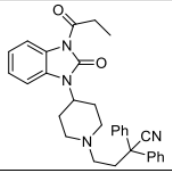
The discovery of the 5,6-dimethyl bezimidazole moiety as part of vitamin B12's chemical structure has piqued scientific interest in benzoimidazole chemistry in recent decades. That's a very special structure in medicinal chemistry, and it serves as a key pharmacophore. Many medical chemistry and pharmaceutical applications rely on molecules with the benzimidazole motif since it is the central unit of these substances' biological activity. [2]

Biological importance:

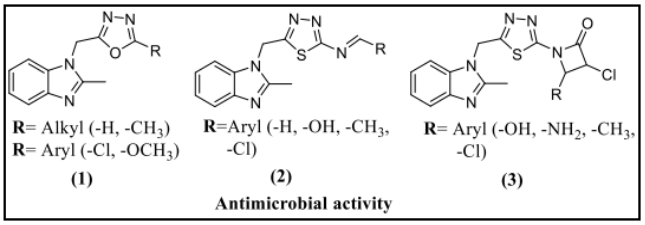
There are two nitrogen atoms linked to the benzene ring at adjacent sites in the bicyclic organic compound known as benzo(a)imidazole. Some of the many biological effects attributed to benzimidazole include antimalarial, antiviral, anticonvulsant, antiinflammatory, antimycobacterial, antiparasitic, antihypertensive, and antineoplastic

properties. When it comes to combating microbial systems, Benz imidazole and its results are among the most useful groups of chemicals. Research into novel amalgams for discussinginfective infections is essential in light of the rise in resistance to currently available antimicrobial medicines. Several different benzimidazole-based medications are now on the market. [3]

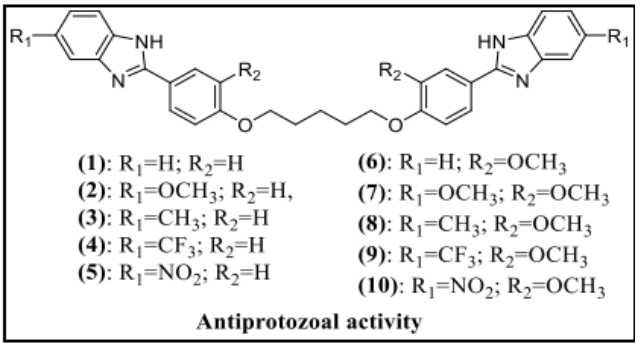
Table 1: There are some significant benzoimidazole-containing medications on the market.

Name of Drug	Chemical structure	Uses
Bilastine		H1-receptor antagonists
Emedastine		
Clemizole		
Thiabendazole		Antifungal agent and Antiparasitic agent
Mebendazole		Antihelmintic activity
Cyclobendazole		Antihelmintic activity
Ridinalazole		*Clostridium difficile* infection Antimicrobial activity
Albendazole		Parasitic worm infestations Antihelminthic agent
Benzitramide		Narcotic analgesic

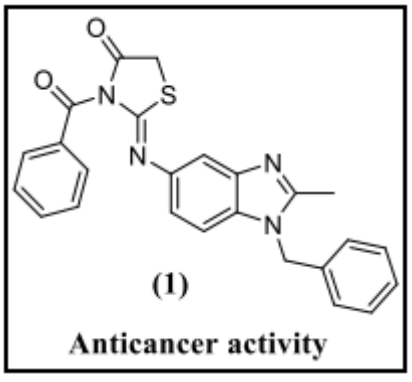
This study involves the synthesis of 2-substituted-1H benzimidazole derivatives and testing them for antibacterial activity against a set of target microorganisms. When compared to the gold standard antibiotics ciprofloxacin, ampicillin, and amphotericin B, compounds (1) containing p-OCH3 and p-Cl groups connected to an aryl ring and a simple alkyl group demonstrated superior antibacterial and antifungal action. In comparison to the gold standard antibiotics ampicillin and amphotericin B, the compounds (2) and (3) with o-Cl, o-CH3, p-OH, and p-NH2 groups in the aryl ring, as well as the compound (2) without substitution, exhibited significant antibacterial activity. [4]



A new class of hybrid compounds derived from pentamidine and benzimidazole were tested in vitro for their effectiveness against the protozoa Entamoebahistolytica, Trichomonasvaginalis, Plasmodium berghei, Giardia lamblia, and Leishmaniamexicana and compared to pentamidine and metronidazole, two common antibiotics. Against the first four protozoa, several substances demonstrated excellent bioactivity in the low M range (IC50 1 M). Comparing compound (2) to pentamidine and metronidazole, two common medications, we found that compound (2) was more effective against G. lamblia. When it came to fighting off T. vaginalis, L. Mexicana, and E. histolytica, this substance was more effective than pentamidine. [5]

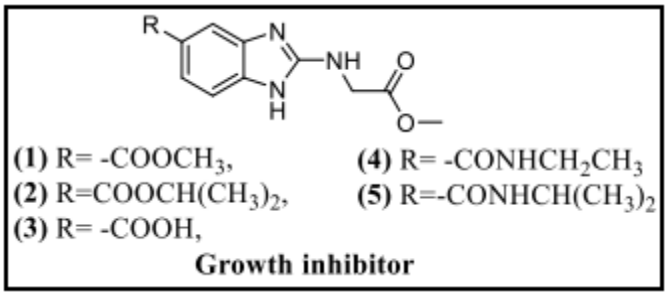


The production of 3-(substituted)-thiazolidines-4-ones and 2-(1-benzyl-2-methyl-1Hbenzimidazol-5-ylimino)-3-(substituted)-thiazolidines-4-ones) (2-methyl-1Hbenzimidazol-5- yl) Epstein-Barr virus antitumor activity was assessed for 2-substituted thiazolidine-4-ones. Compound (1) was discovered to be considerably active, according to the data.

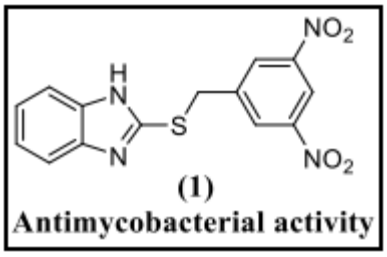


It was determined if a novel series of methyl and ethyl-5- (alkoxy carbonyl)-1H benzimidazole-2-carbamates and methyl 5-carbamoyl-1H benzimidazole2 -carbamates had any anticancer properties. The considerable growth inhibitions linked to mitotic spindle poisoning of compounds (1),

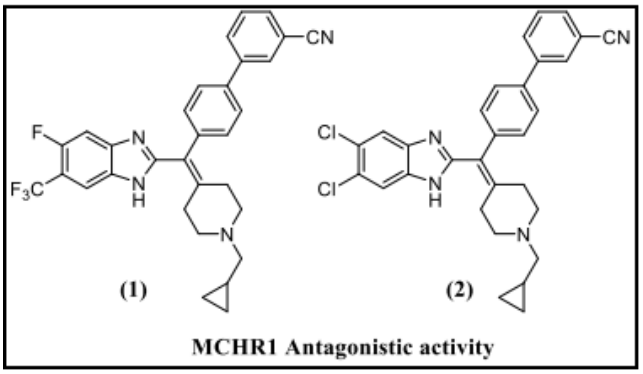
(3), and (5) were assessed. Through the use of a microwave-assisted reaction technique, a new series of benzimidazole-4,7-diones with 2-position substitutions was created. Lung cancer, colon cancer, and breast cancer cell lines were used to test the compounds' cytotoxicity. [6]



the creation of a brand-new class of 2-alkyl sulphanylbenzimidazoles, and testing of their efficacy against M. kansasii and M. avium mycobacteria. In comparison to the conventional medicine isoniazid, the synthesised compound (1) is the most effective compound against M. kansasii and M. avium, while also displaying good action against M. tuberculosis.



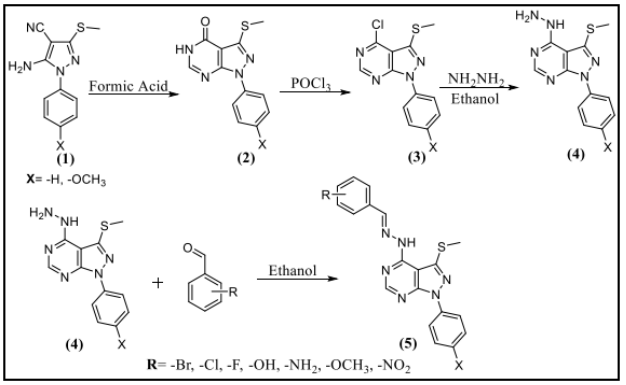
tested for their MCHR1 antagonistic activity were a few fresh benzimidazole variants. In a functional experiment, compounds (1) and (2) having Kb values of 25 nM and 70 nM, respectively, were tested for their potential as MCHR1 antagonists. [7]



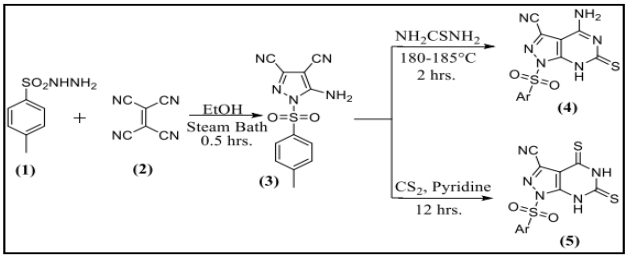
SYNTHETIC ASPECT

The synthesis of pyrazolo pyrimidine derivatives, there are a few described techniques accessible in the literature. In a survey of the literature on the synthesis of the substances, the researchers reported a number of synthetic routes, some of which are shown below.

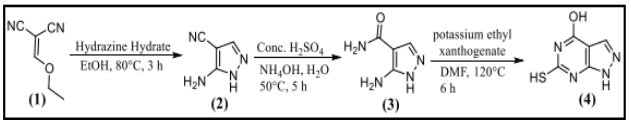
Pyrazole derivatives (1) were cyclized with formic acid to produce pyrazolo[3,4-d]pyrimidin-4-ones (2), which were produced in high yields. The subsequent stage included chlorinating compounds (2) with POCl3, which produced 4-chloro derivatives (3). The later compounds (3) were combined with hydrazine hydrate to produce the appropriate 4-hydrazinyl derivatives (4). By combining 4-hydrazinyl derivatives (4) with the suitable aromatic aldehyde in ethanol and glacial acetic acid, the title compounds (5) were created. [8]



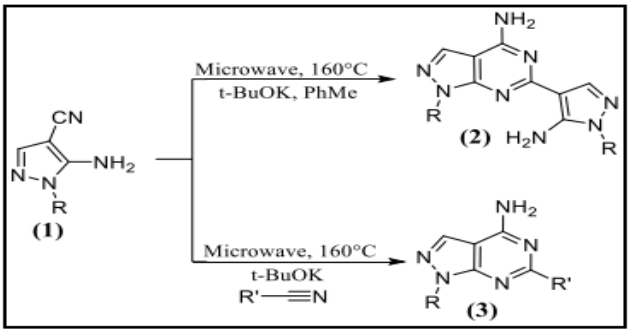
the process of making pyrazolo[3,4-d] Pyrazo[3,4-b] and pyrimidine-3- carbonitrile (4) 5-amino-1-tosyl-1H-pyrazole-3,4-dicarbonitrile (3) was used as a major starting material in a reaction with a variety of electrophilic and nucleophilic reagents to produce pyridine-3-carbonitrile (5) derivatives. [9]



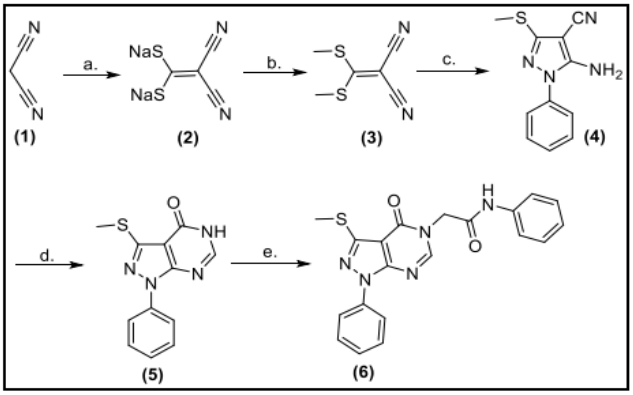
5-amino-3-methyllH-pyrazole-4-carbonitrile (2) was treated with concentrated sulfuric acid to produce a good yield of 5-amino-3-methyll.fipyrazole-4-carboxamide, which was then used to synthesise 3-methyl-6-thioxol,5,6,7- tetrahydropyrazolo[3,4-d]pyrimidin-4-one derivatives (3). Compound (4) was produced in 89% yield by ring closure of compound.[10]



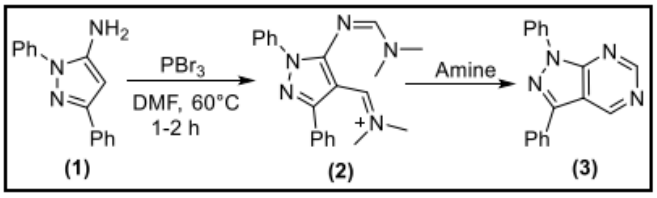
the synthesis of 4-aminopyrazolopyrimidines derivatives, which was a cyclization process by employing microwave heating in neat reagents to access the final product (2), and using different nitrile to give compound (3) in excellent yields (88– 94%) and purities (95%).[11]



The production of pyrazolo[3,4-d]pyrimidine derivatives included the reaction of malononitrile with carbon disulfide in the presence of sodium ethoxide, followed by the methylation of the resulting product with dimethyl sulphate to get 2(bis(methylthio)methylene)malononitrile (3). The resultant chemical (3) was then processed with phenyl hydrazine in ethanol to produce compound (4). Formic acid's action on compound (4) caused it to be cyclized, giving rise to compound (5). The final compounds (6) were created by reacting 2-chloro-N-phenylacetamide or 3-chloro-N-phenylpropanamide derivatives with 3-(methylthio)-1-phenyl-1H- pyrazolo[3,4-d] pyrimidin-4(5H)-one.[12]



thevilsmeier reaction between 5-aminopyrazole (1) and PBr3 in N,N-dimethylformamide (DMF) solution at 60°C is used to create pyrazolo[3,4-d]pyrimidine derivatives. Excellent yield (90%) was achieved in the production of the equivalent 4-(iminomethyl)-1,3-diphenyl-1H-pyrazol-5-yl-formamidine (2). Without isolating the intermediate (2), amine was added to the reaction mixture, and after the solution was heated at reflux for three to five hours, title compounds (3) were produced with good yield.[13]



2,3-dihydroquinazolin-4(1H)-one derivatives were produced using a model reaction between 2-aminobenzamide (1) and benzaldehyde (2) with T3P (50% EtOAc) in acetonitrile, which produced the end product, dihydroquinazolinone (3), in a high yield.[14]

METHODOLOGY

Each synthetic chemical enrolled in the 60 Cell Screening Program at the National Cancer Institute is screened in the NCI 60 Cell Panel at a single extremely high dose (10-5 M). Before the 5-dose experiment, compounds must pass a threshold inhibition test on a particular number of cell lines.

The outcomes from the experiment with one dosage were displayed as a mean graph showing the percentage rise in treated cells. The One-dose test figure shows the growth experienced compared to the no-drug control and the total number of cells at time zero. This stops the organism's development and identifies when it has perished. If the value is 100, this suggests there is no growth inhibition and no growth limitation. A score of forty indicates a 60% growth limit. Zero means that there was no overall development during the trial. It would be the same as having 40% lethality if the value was -40. If the value is zero, then every cell has been removed from the system (-100). This section compares data from a graph representing the mean of a single dose.

RESULT

By heating various benzaldehydes with propyl phosphonic anhydride (T3P, 50% ethyl acetate) and 3-amino-5-(methylthio)-1H-pyrazole-4-carboxamide, new derivatives of 4H-pyrazolo[3,4-d]pyrimidine were synthesised in the present work.

We have demonstrated the presence of the intended pyrazolo pyridine compounds using 1H NMR, 13C NMR, IR, and mass spectrometry analyses. The existence of the NH- group is demonstrated by two peaks in the IR spectra of the compounds, at 3411 cm-1 and 3101 cm-1. The existence of the C=O (amide) group is indicated by a third, prominent signal at 1681–1635 cm1. There is just one proton signal seen in 1H NMR spectra, which peak at 12.44 and 12.29 ppm and 6 and 5.00 ppm. This is because the -NH group of the synthesised molecule includes a proton. A singlet peak of a single proton signal may be observed at 2.56 ppm due to the presence of the -CH3 group. The 13C NMR spectra have validated the chemical structures assigned to the carbon atoms in the synthesised molecules.

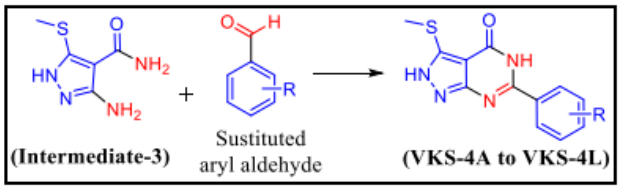
Anti-cancer activity

It was determined in vitro whether or not a select group of synthesised compounds had anti-cancer effects. Data on in-vitro anticancer efficacy shows that VKS-4C is relatively active against HOP-92, a non-small cell lung cancer; nevertheless, some other medications have been demonstrated to be less effective against other cancer cell lines. In terms of its biological impact, that chemical's anti-cancer activity is weaker.

Optimisation Reaction Condition

We have previously reported the very effective use of propylphosphonic anhydride (T3P, 50% Ethyl acetate) in the Fischer indole synthesis, the Pictet-Spengler reaction, and the synthesis of different pyrazolones.

We have experimented with a number of organic solvents and reductants. T3P investigates the interactions of 3-amino-5-(methylthio)-1H-pyrazole-4-carboxamide with a variety of benzaldehydes (50 percent ethyl acetate). There are several polar (protic and aprotic) and non-polar solvents available, including ethanol, methanol, tert-butyl alcohol, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), toluene, and acetonitrile. Even when a simple catalyst was used in catalytic proportions at room temperature under reflux conditions, the yield barely altered. The inclusion of an equamolar quantity of a phosphorus-based cyclic anhydride (T3P, 50% ethyl acetate) catalyst under reflux conditions considerably enhanced the yield and cut the reaction time in half. It was also demonstrated that when the reaction was carried out in a polar aprotic solvent, the yield was greatly increased (Table 3, entries 8 and 9). When one equivalent of T3P (50-50, ethyl acetate) was present, the reaction was completed cleanly after 3-4 hours at reflux temperature.

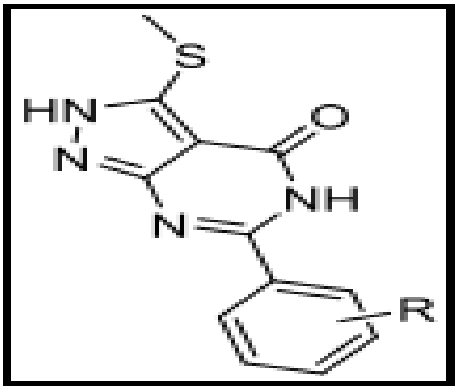


No.	Solvent	Reductant	Temperature	Reaction Time (hrs.)	Yield %
1	Ethanol 99%	K_2CO_3	Room Temperature	12	20
2	Ethanol 95%	-	Reflux	24	25
3	MeOH	K_2CO_3	Reflux	18	38
4	Ethanol 95%	K_2CO_3	Reflux	12	45
5	Toluene	Piperidine	Reflux	15	30
6	*t*-Butanol	Potesium tret-Butoxide	Reflux	12	65
7	DMSO	Diisopropyl Amine	110 °C	24	45
8	**Acetonitrile**	**T3P (50% Ethyl acetate)**	**Room Temperature**	**12**	**75**
9	**Acetonitrile**	**T3P (50% Ethyl acetate)**	**Reflux**	**3**	**85**

Substances and Techniques

All chemicals, reagents, and solvents were purchased and utilised as purchased from spectrochem, sigma-aldrich, and alfa-aesar. The reaction was seen using thin layer chromatography (TLC) on 0.5 mm thick silica gel-G plates, Merck's G60 F254, and the additives aqueous KMnO4, iodine vapour, and ultraviolet light (254 and 365 nm). A ruby thermometer was used to measure the temperature of the reaction. The melting points of all compounds were obtained using the unmodified Buchi B-540 open capillary apparatus. The FT-IR spectrum was captured using a Shimadzu FTIR-8400 S, CE and is shown in cm-1 (KBr). The 1H NMR and 13C NMR spectra were obtained using a BrukerAvance 400 MHz spectrometer with DMSO-d6 as the solvent. Chemical shifts in 1H NMR are expressed in parts per million (ppm) relative to an internal standard known as TMS (). In terms of splitting multiplicities, we give singlet (s), doublet (d), double doublet (dd), triplet (t), triplet (dt), quartet (q), multiplet (m), and wide signal (br). Mass spectra were obtained on ESI (70eV) type mass spectrometers using the direct intake probe method; m/z is provided in atomic units per elementary charge. Because of the lower pressure, solvents were distilled.

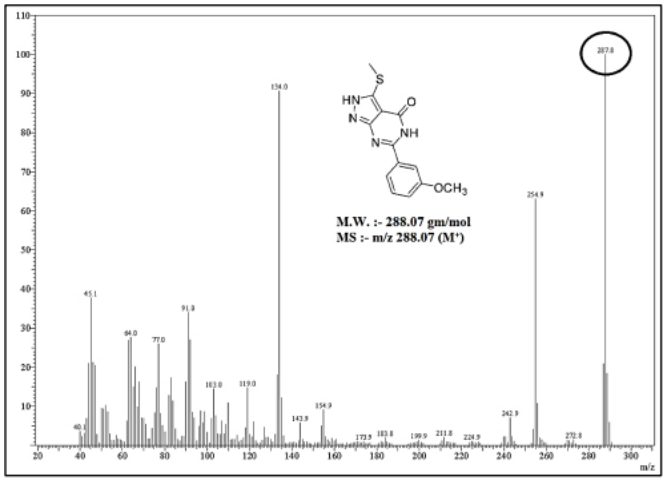
Table 2:- Physical characteristic of 6 (Substituted phenyl) -3-(methylthio) 4,5-dihydro-2,5 pyrazolo[3,4-d] pyrimidin-4-ones (VKS-4A to VKS-4L)



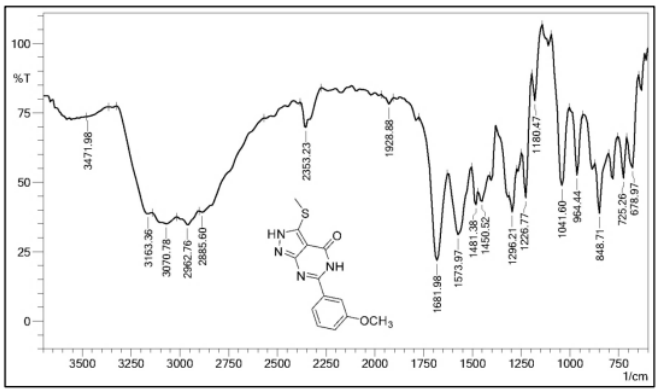
Compound Code	Substituent -R	Molecula formula	M.W. gm/mole	Yield (%)	M.P. °C
4a	3-OCH_3	$C_{13}H_{12}N_4O_2S$	288	88	237-239
4b	4-CH_3	$C_{13}H_{12}N_4OS$	272	92	201-203
4c	4-F	$C_{12}H_9FN_4OS$	276	86	259-261
4d	4-Cl	$C_{12}H_9ClN_4OS$	292	79	249-251
4e	2-H	$C_{12}H_{10}N_4OS$	258	77	190-192
4f	2,4-$(OCH_3)_2$	$C_{14}H_{14}N_4O_3S$	318	80	213-215
4g	4-Br	$C_{12}H_9BrN_4OS$	337	85	207-209
4h	3-NO_2	$C_{12}H_9N_5O_3S$	303	89	229-231
4i	4-$N(CH_3)_2$	$C_{14}H_{15}N_5OS$	301	78	199-201
4j	4-NO_2	$C_{12}H_9N_5O_3S$	303	91	229-231
4k	2,4-$(Cl)_2$	$C_{12}H_8C_{12}N_4OS$	327	83	255-257
4l	2-Cl	$C_{12}H_9ClN_4OS$	292	90	249-251

VKS-4A		6-(3-Methoxyphenyl)-3-(methylthio)-2,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one		
Mol. Formula		$C_{13}H_{12}N_4O_2S$		
Physical Appearance		Off White solid		
M.P.°C		237-239		
Mol. Wt. (gm/mol)		288.07		
Mass (m/z)		288.07 (M^+)		
Ele. Ana.	Value	C	H	N
	Cal.	54.16	4.20	19.43
	Obs.	54.16	4.19	19.42
IR(KBr) (ν_{max}), cm^{-1}		3471 (-NH-, str., amide), 3163 (-NH-, str., cy amine), 3070, 2962 (C-H, str., aromatic), 2885 (C-H, str., alkane), 2090 (-N=C=N-, str.), 1681 (-C=O, str., sec. amide), 1573 (-NH-, bend., sec. amine), 1481, 1450 (C=C, str., aromatic), 1296 (C-H, bend., -CH_3), 1226 (-C-O-, str., acyl), 1041 (C-H, bend., aromatic), 964 (C-S, str., sulfur), 848 (m-disubs. aromatic ring).		
^{1}H NMR (400 MHz, DMSO-d_6) in δ ppm		2.56 (s, 3H), 3.68 (s, 3H), 6.32 (s, 1H), 6.98-6.96 (m, 1H), 7.23-7.17 (m, 2H), 7.64-7.62 (m, 1H), 12.29 (s, 1H).		
^{13}C NMR (101 MHz, DMSO-d_6) in δ ppm		14.40, 56.04, 101.75, 127.61, 127.93, 128.48, 128.65, 131.71, 132.11, 140.23, 158.16, 161.05.		

MASS spectrum of compound VKS-4A:



IR spectrum of compound VKS-4A:



VKS-4B		3-(Methylthio)-6-(p-tolyl)-2,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one		
Mol. Formula		$C_{13}H_{12}N_4OS$		
Physical Appearance		White solid		
M.P.°C		201-203		
Mol. Wt. (gm/mol)		272.07		
Mass (m/z)		272.07 (M^+)		
Ele. Ana.	Value	C	H	N
	Cal.	57.34	4.44	20.57
	Obs.	57.32	4.44	20.56
IR(KBr) (ν_{max}), cm^{-1}		3348 (-NH-, str., amide), 3171 (-NH-, str., cy amine), 3093, 2978 (C-H, str., aromatic), 2885, 2839 (C-H, str., alkane), 2067 (-N=C=N-, str.), 1674 (-C=O, str., sec. amide), 1581 (-NH-, bend., sec. amine), 1504 (C=C, str., aromatic), 1311,1257 (C-H, bend., -CH_3), 1080, 1033 (C-H, bend., aromatic), 941 (C-S, str., sulfur), 840 (p-disubs. aromatic ring).		
^{1}H NMR (400 MHz, DMSO-d_6) in δ ppm		2.55 (s, 3H), 3.85 (s, 3H), 6.51 (s, 1H), 7.16-7.14 (m, 1H), 7.47-7.43 (m, 1H), 7.71-7.69 (d, *J*=8 Hz 2H), 12.28 (s, 1H)		
^{13}C NMR (101 MHz, DMSO-d_6) in δ ppm		14.40, 21.13, 102.75, 126.59, 127.93, 128.48, 128.65, 131.71, 133.11, 140.05, 158.16, 161.05.		

CONCLUSION

Because pyridazine analogues are uncommon in nature, research on these chemicals has just recently begun. Pyridazine analogues are being studied because of the wide range of biological activities they exhibit. We look at the biological impacts of certain newly found pyridazine analogues. This was done in order for the investigation to be completed. Medicinal chemists look at the possible connections between chemical substances and their biological effects. Our goal is to employ the best synthesis approach to attach the pyridazine ring to a variety of anilines while maintaining the biological and pharmacological value of the pyridazine analogues and other moieties in mind. Based on the physicochemical and spectral data, it is possible to infer that the synthetic process was effective in producing the needed intermediates and end products.

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