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Synthesis, *in silico* ADMET study and anti-oxidant action of novel phenyl azetidin-2-one derivatives

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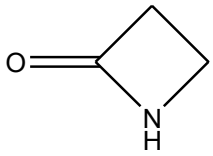
Abstract
In this investigation, we have synthesized novel azetidin-2-one derivatives, 6a-j and performed the in silico ADMET study and in vitro antioxidant study of the molecules. The synthesis of the target compounds was confirmed by spectral analysis. Four compounds ***6c, 6d, 6h*** *and* ***6a*** *were found to possess good antioxidant action. These compounds inhibited DPPH radical by 78%, 64%, 60% and 45% respectively. All studied compounds are expected to exhibit high absorption, strong permeability, and bioavailability, resulting in a favourable drug-likeness profile. The results of our study led us to conclude that phenyl-2-azetidinone nucleus could be easily synthesized and can be computationally optimized to obtain good anti-oxidant compounds.*

Keywords
Azetidinone, anti-oxidant, ADMET, synthesis, inflammation

INTRODUCTION

The World Health Organization (WHO) ranks chronic diseases as the greatest threat to human health. The prevalence of diseases associated with chronic inflammation is anticipated to increase persistently for the next 30 years in the United States. In 2000, nearly 125 million Americans were living with chronic conditions and 61 million (21%) had more than one. In recent estimates by Rand Corporation, in 2014 nearly 60% of Americans had at least one chronic condition, 42% had more than one and 12% of adults had 5 or more chronic conditions. Worldwide, 3 of 5 people die due to chronic inflammatory diseases like stroke, chronic respiratory diseases, heart disorders, cancer, obesity, and diabetes (Tsai et al., 2019). Oxidative stress has been a critical factor contributing to chronic inflammation and other diseases and disorders. Use of anti-oxidants has been proven to be effective in management for inflammation and other critical illness.

The search for a new molecule that could be a potential drug candidate has always been the mainstay of the medicinal chemistry research. Azetidinone nucleus (I) has been widely investigated since decades for its therapeutic potential ever since the discovery of penicillin in 1928. Several antibiotics have been clinically approved for treatment of infectious diseases possessing a azetidinone moiety (Figure 1).



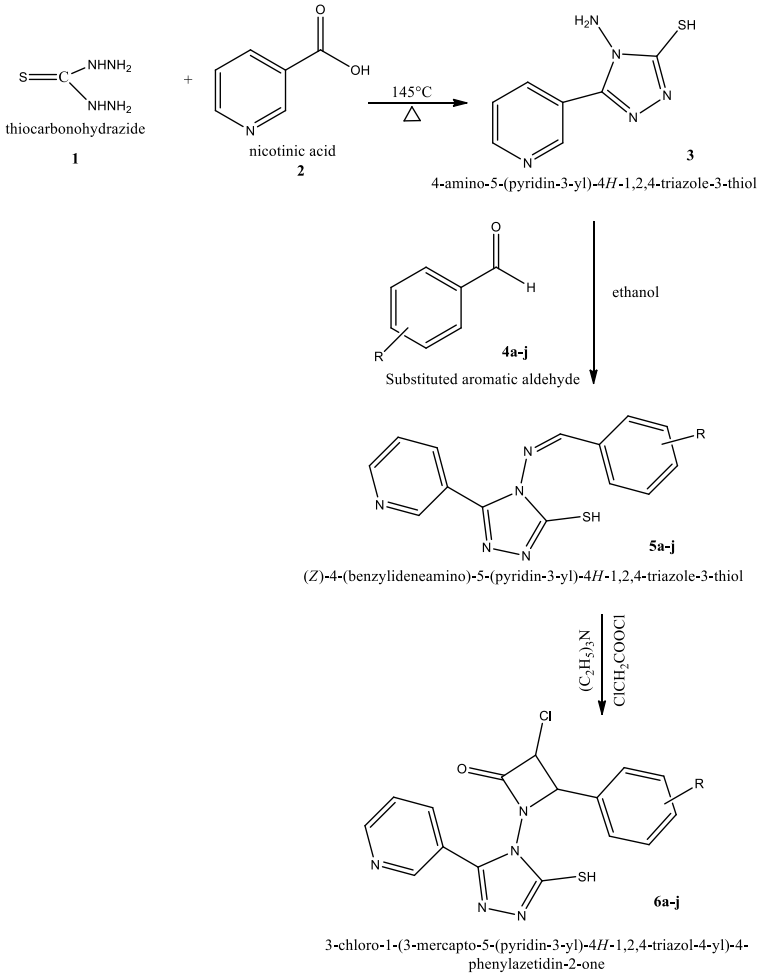
(I)

Azetidin-2-one, a four-membered cyclic lactam (ßlactam) skeleton has been recognized as an attractive target of contemporary organic synthesis of a large number of organic molecules by exploiting the strain energy associated with it. It possesses good pharmacological and biological activities like antimicrobial (Pandya and Desai, 2013), antibacterial (Khan et al, 2018), antifungal (Patel and Mehta, 2006) anti- inflammatory (Rajasekaran et al, 2010), antitubercular (Dubey et al, 2013), anticancer and cytotoxic (Deep et al, 2016). Some attempts to design newer antidepressant molecules using azetidinone have also been reported (Kerzare et al, 2018; Thomas et al, 2016). In the present work we have reported the synthesis of novel azetidinone derivatives with anti-oxidant activity and highlighted the ADMET features of the molecules.

MATERIAL AND METHODS

Melting point were recorded on Biotechnics melting point apparatus, IR were recorded on Shimadzu IR spectrophotometer, 1H NMR was recorded on Bruker NMR and mass spectra were obtained on Jeol Mass spectrophotometer. All reagents and chemical used were procured from Loba Chemie, India.

The synthesis of azetidinone derivatives was accomplished using Scheme 1.



Scheme 1. Synthetic pathway for azetidinone derivatives

Synthesis of thiocarbonohydrazide, 1

The synthesis of 1 was carried out in a 1000 mL four-necked round-bottom flask equipped with a thermometer, a mechanical stirrer, a dropping funnel and a reflux condenser connected to a caustic trap. The whole apparatus was kept in a water bath to maintain the required reaction temperatures. Briefly, a 0.25 mol of 85% aqueous hydrazine hydrate was placed in the flask. The temperature was lowered to 10 °C and the stirring rate was controlled at 800 rpm. 0.1 mL of carbon disulfide were added dropwise over about one hour, while maintaining the temperature below 15 °C. After addition the reaction mixture continued to be agitated for 30 min at room temperature. The resultant mixture was then heated to the 70 °C and refluxed for 6 h. The reaction mixture was thereafter cooled to room temperature and the crystalline precipitate separated from the liquid by filtration. After washing with a minimum amount of cold water, the crystals obtained were dried at 110 ◦C in air for 5 h to obtain **1** (Zhou et al., 2010).

Synthesis of 4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-thiol, 3

Nicotinic acid, 2 (0.006 mol) and thiocarbonohydrazide, 1 (0.006 mol) were dissolved in ethanol (10 mL) and the mixture was refluxed at 145 °C for 3h using oil bath. The product obtained on cooling was treated

with sodium bicarbonate solution (10 mL) to neutralize the unreacted carboxylic acid, if any. It was then washed with water and collected by filtration to obtain **3** (Ahmed et al., 2018).

General method for synthesis of 5a-j

A mixture of **3** (0.01 mol) and appropriate aromatic aldehyde, **4a-j** (0.01 mol) was dissolved in dry benzene (30ml) and to it was added anhydrous zinc chloride (100 mg). The solution was refluxed for 5 to 6 hours. The excess solution was removed by distillation and the product obtained was filtered and washed with little sodium bisulphate solution to remove the unreacted aldehyde. The product was then washed with consecutively with 10% HCl and water. The solid obtained was collected and crystallized from suitable solvent to obtain **5a-j** (Malviya et al., 2021).

General method for synthesis of 6a-j

A mixture of Schiff base, **5a-j** (0.01 mol) and triethylamine (0.02 mol) was dissolved in 1, 4-Dioxane (15 mL). To this, a solution of chloroacetyl chloride (0.02 mol) was added in portions with vigorous shaking at room temperature for 20 min. The reaction mixture was heated under reflux for 3 h and the content was kept at room temperature for 48 h and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then recrystallized from 70% ethanol (Malviya et al., 2021).

3-chloro-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)-4-phenylazetidin-2-one, 6a

Yield: 81%; Melting point (°C): 171; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 359.11 (M+2)

3-chloro-4-(4-hydroxyphenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6b

Yield: 72%; Melting point (°C): 173; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 373.8 (M+)

3-chloro-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)-4-(4-nitrophenyl)azetidin-2-one, 6c

Yield: 79%; Melting point (°C): 185; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 403.15 (M+1)

3-chloro-4-(4-chlorophenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6d

Yield: 74%; Melting point (°C): 175; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 393.01 (M+2)

3-chloro-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)-4-(4-methoxyphenyl)azetidin-2-one, 6e

Yield: 69%; Melting point (°C): 173; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 387.83 (M+)

3-chloro-4-(3,4-dimethoxyphenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6f

Yield: 77%; Melting point (°C): 189; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 418.24 (M+1)

3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6g

Yield: 71%; Melting point (°C): 192; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 403.11 (M+)

3-chloro-4-(2-chlorophenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6h

Yield: 78%; Melting point (°C): 181; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 392.14 (M+1)

3-chloro-4-(2,3-dihydroxyphenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6i

Yield: 72%; Melting point (°C): 178; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 390.01 (M+1)

3-chloro-4-(2,4-dihydroxyphenyl)-1-(3-mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)azetidin-2-one, 6j

Yield: 68%; Melting point (°C): 177; FTIR (cm^{-1}): 3104.67 (Ar/Het C-H Stretch), 2970.38 (Ar C-C Stretch), 1639.00 (C=N Stretch), 1456.90 (N=N Stretch), and 1417.36 (C-N Stretch); m/e: 326.2 (M+); proton NMR (δ, ppm): 8.4; 7.21-7.93 Aromatic protons, 7.5 imine proton, and 7.7-9.3 pyridine H; m/z: 391.03 (M+2)

***In silico* study**

ChemDraw Ultra 12.0 was utilized to create the 2D structures of the ligands, which were then imported into Chem 3D for the generation of their three-dimensional representations. The simplified molecular-input line-entry system, also known as canonical SMILES, was generated using ChemDraw. These structures were then uploaded to the SwissADME and pkCSM online platforms for the purpose of ADMET analysis, prediction of physicochemical parameters, and assessment of drug-likeness in accordance with the Lipinski rule of five. Lipinski's "Rule-of-Five" outlines the relationship between physicochemical and pharmacokinetic factors.

DPPH radical scavenging activity

The free radical scavenging activity of the synthesized molecules was measured in terms of hydrogen donating or radical scavenging ability using the stable radical DPPH. The test samples (10–50 ppm) were prepared in DMSO and were mixed with 1.0 mL of DPPH solution and filled up with methanol to a final volume of 4 mL. Absorbance of the resulting solution was measured at 517 nm in a visible spectrophotometer (Gupta et al., 2023). Ascorbic acid was used as the reference compound. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. Radical scavenging activity was expressed as the inhibition percentage of free radical by the sample and was calculated using the following formula:

$$\%\ DPPH\ Inhibition = \frac{(Acontrol - Atest)}{Acontrol} \times 100$$

RESULTS AND DISCUSSION

Chemical Characterization

The synthesis of the target compounds was achieved by first synthesizing triazole nucleus, followed by the formation of Schiff bases and eventually converting the imine linkage to azetidin-2-one ring by interaction with chloroacetic acid in presence of triethylamine. The synthesized compounds 6a-j were obtained in yield of 69-81% and were partially soluble in chloroform and exhibited the stretching of carbonyl (C=O), thiol (SH), aromatic C-H, C-C, C=C, C-N, C=N, N-N and C-Cl confirming the presence of all the expected functional groups in the molecules. The 1HNMR spectra revealed the presence of protons of pyridine ring (8-9 ppm), aromatic ring (6.6-7.8 ppm), thiol (5-6 ppm) and azetidine methylene (5-6 ppm). The molecule specific peaks like protons of methoxy, and hydroxyl could be found in the corresponding compounds.

***In silico* studies**

The physicochemical properties of the compounds predicted *in silico* by SwissADME are presented in table 1 and the ADMET properties predicted by pkCSM are presented in table 2.

The physicochemical properties of a crucial molecule significantly influence its efficacy, safety, and metabolism. One might foresee the application of Lipinski's rule of five, Veber's rule, or Muegge's rule. The characterization of an orally active pharmaceutical agent is delineated by Lipinski's rule, which ascertains that a compound possesses the following attributes: molecular weight (MW) less than 500 Da; a maximum of 10 hydrogen bond acceptors (HBA); a maximum of 5 hydrogen bond donors (HBD); and a log P (the logarithm of the octanol-water partition coefficient) not exceeding 5. The physical properties include molecular weight, the number of rotatable bonds (NRB), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), molar refractivity (MR, in m3.mol-1), and polar surface area (PSA, in Å). The assessment of lipophilicity and solubility constitutes two additional critical factors that are monitored for the advancement of effective pharmaceuticals.

Table 1 indicates that all compounds adhere to Lipinski's rule of five, fulfilling each of the five criteria. All studied compounds are expected to exhibit high absorption, strong permeability, and bioavailability, resulting in a favourable drug-likeness profile.

Solubility is a crucial factor in regulating absorption. A soluble molecule simplifies various facets of drug development, such as formulation and handling. A compound is deemed insoluble if its solubility characteristic is less than -10. The values range from -10 to greater than zero, corresponding to low solubility and high solubility, respectively. The solubility of weakly soluble chemicals is quantified within the range of -10 to -6. The interval between -6 and -4 is classified as mildly soluble.

A compound's pharmacokinetic profile dictates its ADME (absorption, distribution, metabolism, and excretion) properties. Among other things, the toxicity evaluation (ADMET, T for Toxicity) can predict mutagenicity and carcinogenicity. Toxicological endpoints such as Ames toxicity, hepatotoxicity, and oral rat acute toxicity (LD50) have been selected. To evaluate the degree of a drug's toxicity, the lethal dosage (LD50) was utilized, along with the Globally Harmonized System (GSH) classification of chemical toxicity.

Table 1. Physicochemical properties of 6a-j predicted by SwissADME

Compound Code	Rotatable Bonds	$HB_{acceptor}$	HB_{donor}	Molar Refractivity	Polar Surface Area	Log P	ESOL	GI Absorption	Lipinski violation	Bioavailability score	Leadlikeliness
6a	3	4	0	95.56	102.71	2.18	-3.8	High	0	0.55	No
6b	3	5	1	97.58	122.94	1.75	-3.66	High	0	0.55	No
6c	4	6	0	104.38	148.53	1.43	-3.85	Low	0	0.55	No
6d	3	4	0	100.57	102.71	2.65	-4.39	High	0	0.55	No
6e	4	5	0	102.05	111.94	2.17	-3.86	High	0	0.55	No
6f	5	6	0	108.54	121.17	2.07	-3.94	High	0	0.55	No
6g	4	6	1	104.08	132.17	1.72	-3.72	High	0	0.55	No
6h	3	4	0	100.57	102.71	2.68	-4.39	High	0	0.55	No
6i	3	6	2	99.61	143.17	1.47	-3.51	Low	0	0.55	No
6j	3	6	2	99.61	143.17	1.31	-3.51	Low	0	0.55	No

Table 2. Pharmacokinetic and toxicity of 6a-j predicted by pkCSM

ADMET Parameters	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j
Absorption										
Aqueous solubility	-3.27	-3.488	-3.847	-4.014	-3.756	-3.942	-3.69	-4.029	-3.23	-3.206
$Caco_2$ permeability	0.861	1.01	0.934	0.955	1.057	1.08	0.472	0.964	0.174	0.23
Intestinal absorption	95.564	93.684	93.163	94.641	97.23	98.135	95.766	95.284	91.912	88.965
Skin Permeability	-2.712	-2.795	-2.735	-2.742	-2.761	-2.779	-2.796	-2.743	-2.753	-2.761
Distribution										
VDss (human) (log L/kg)	-0.288	-0.224	-0.284	-0.255	-0.27	-0.432	-0.288	-0.219	-0.008	-0.234
CNS permeability (log PS)	-2.554	-2.788	-2.797	-2.445	-2.787	-3.199	-3.226	-2.442	-3.629	-3.976
Metabolism										
CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Excretion										
Total Clearance (log ml/min/Kg)	0.015	-1.103	-0.085	-0.118	0.046	0.184	0.035	-0.054	-0.004	-0.039
Toxicity										
AMES toxicity	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oral (LD_{50}) (Acute, mol/kg)	2.365	2.667	2.632	2.427	2.575	2.566	2.742	2.424	2.769	2.866

DPPH Scavenging

The anti-oxidant ability of the synthesized compounds was assessed using their ability to scavenge DPPH free radical. It was found that the presence of electron withdrawing group at para position of the aldehydic ring improved the anti-oxidant potential (6c, 6d) whereas same substitution at ortho position was slight less potent (6h). On the other hand molecules substituted with electron donating groups were having negligible anti-oxidant action. The absence of any substitution was having better activity (6a) compared to electron donating group containing compounds (Table 3).

Table 3. DPPH radical scavenging action of 6a-j

	10	20	30	40	50
6a	27.7974	32.0377	35.4535	40.8716	45.2297
6b	3.18021	6.36042	12.3675	14.4876	17.4323
6c	61.4841	66.0777	69.8469	74.2049	78.3274
6d	44.8763	51.119	55.477	59.5995	64.311
6e	14.1343	16.6078	17.6678	19.788	20.8481
6f	19.3168	21.0836	22.1437	22.6148	23.3216
6g	18.4923	19.5524	20.6125	21.0836	21.3192
6h	43.1095	46.2898	51.9435	57.3616	60.5418
6i	2.82686	5.65371	9.89399	13.7809	16.6078
6j	3.53357	7.06714	13.0742	16.0188	18.7279
Ascorbic Acid	83.74558	86.33687	87.27915	88.81037	90.93051

CONCLUSION

The study successfully synthesized azetidinone derivatives with promising antioxidant activity, particularly **6c** and **6d**. While ADMET profiles support drug-likeness, toxicity remains a challenge. Further optimization and preclinical studies are warranted to advance these compounds as therapeutic agents for oxidative stress-related diseases.

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