International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Synthesis and ADMET-Evaluation of Oxadiazole and Pyrazolone Derivatives

Vijay J. Desale

Department of Chemistry, HPT Arts and RYK Science College, Nashik, Maharashtra, India

Abstract: ***Hydrazides and hydrazones are important molecules for synthesizing numerous heterocyclic compounds. These heterocycles show important biological activities. This research work leads to synthesize pyrazolone and oxadiazole derivatives from hydrazides-hydrazones through cyclization reaction using different reagents. These compounds were screened in silico ADMET properties to evaluate their bio-chemical studies by using online mode ADMET Lab 3.0. These in silico ADMET evaluation results suggests that, the compounds show good chemical ADMET properties, indicating their potential for safe and effective use and it also provide a comprehensive toxicity profile needed for development of therapeutic agents.***

Keywords: Hydrazide, hydrazone, pyrazolone, oxadiazole, ADMET properties.

1. Introduction

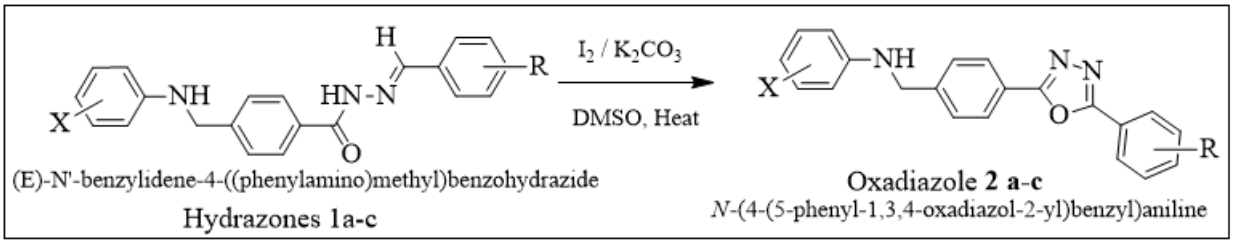
Oxadiazoles and Pyrazoles are the class of five-membered heterocyclic compounds, which belong to the azole family. These compounds have a wide range of pharmaceutical applications, particularly in the development of antimicrobial agents. Sahin et al [1] have been synthesized various oxadiazole derivatives and evaluated their antimicrobial activity against a range of microorganisms, including bacteria and fungi. Hydrazides were treated with aromatic aldehydes in the solvent such as methanol, ethanol to obtain hydrazones. Hydrazones were subsequently converted to 1, 3, 4 Oxadiazoles via oxidative cyclization using I_2 and K_2CO_3. Wenquan Y. et al [2] synthesized series of symmetrical as well as asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. Carbohydrazide were treated with ethyl acetoacetate, triethylamine and refluxed in ethanol. Samshuddin S. et al [3] synthesized pyrazolone and oxadiazoles from hydrazides. Oxadiazoles [4] were prepared by treating carbohydrazides with aromatic carboxylic acids in $POCl_3$. Kumar H. et al [5] synthesized 2-[([1,1′-Biphenyl]-4-yloxy) methyl]-5-phenyl-1,3,4-oxadiazole from 2-([1,1′-biphenyl]-4-yloxy) hydrazide and suitable aromatic carboxylic acid in phosphorus oxychloride. Baciu-Atudosie et al [6] reported a single step synthesis of 5-substituted-2-[2-(2-substituted-phenothiazinyl)-2-oxoethyl]-dihydro-pyrazol-3-one by the reaction of acid hydrazide and ethyl acetoacetate. Manojkumar P. et al [7] reported preparation of 1-(4-methylcoumarinyl-7-oxyacetyl)-3,5-dimethyl-4-(arylazo) pyrazoles from 1,3(diketo, dimethyl)-2-(arylazo) propane and 4-methylcoumarinyl-7-oxyacetic acid hydrazide in glacial acetic acid. This study is significant as it proposes new oxadiazole and pyrazolone derivatives with potential bio-chemical activities.

2. Materials and Methods

The hydrazones, (E)-N'-benzylidene-4-((phenylamino) methyl) benzohydrazide [8] were synthesized from hydrazides are converted to cyclized products [9] such as oxadiazoles and hydrazides are cyclized to pyrazolones using ethyl aceto acetate.

Oxidative cyclization of Hydrazide-hydrazones to Oxadiazoles:

It is a simple oxidative C−O bond formation reaction. It is useful for the synthesis of 1, 3, 4-oxadiazoles. Hydrazide-hydrazones are obtained through the condensation of aldehydes and hydrazides were converted to oxadiazoles [10]. It gives a series of 2, 5-disubstituted 1,3,4-oxadiazoles.



Scheme 1: Oxidative cyclization of hydrazones

Experimental procedure:

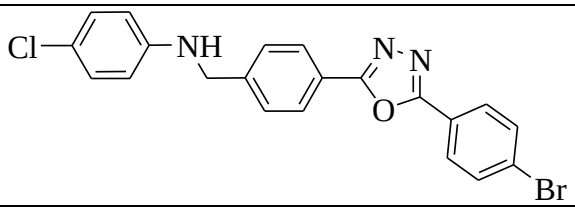
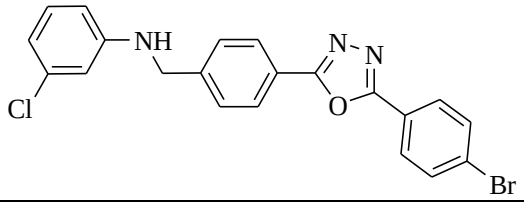
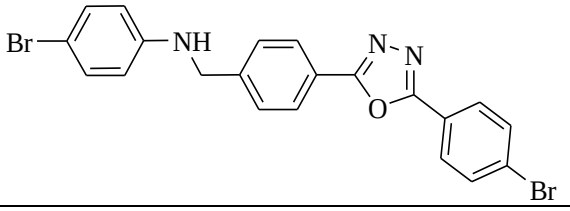
As depicted in **Scheme** 1.0 mmol Hydrazone (substituted (E)-N'-benzylidene-4-[(phenylamino) methyl) benzohydrazide] (1a-1c) was dissolved in 5 ml dimethyl sulphoxide (DMSO). Then 3.0 mmol of K_2CO_3 was added and stirred it. Added 1.2 mmol I_2 slowly in small quantities to the reaction mixture Then reaction mixture was stirred for 4 to 6 hours at 100^0C. Reaction progress was checked on TLC. On completion of reaction, it was cooled to RT then treated with 5% sodium thiosulphate solution to neutralize unreacted Iodine present in reaction mixture. Solid product was filtered and dried. (**Table 1**).

Purification of Oxadiazole:

Purification of oxadiazole products were performed using SiO_2 column chromatography. Silica gel used for the

preparation of column was 60-120 mesh size. Percentage yield and M.P. of oxadiazole products were recorded. (**Table 1**).

Table 1: Synthesis of oxadiazoles

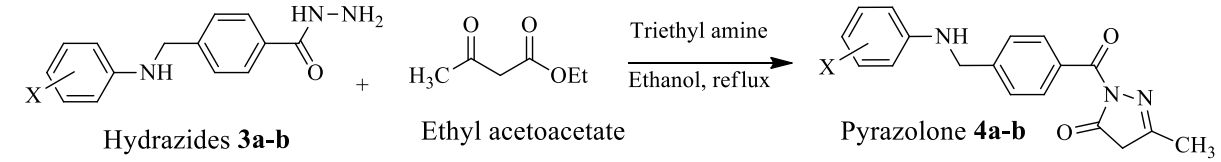
Code	Name	Structure	Yield	M.P.°C
2a	*N*-({4-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]phenyl}methyl)-4-chloroaniline		65%	158-160
2b	*N*-({4-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]phenyl}methyl)-3-chloroaniline		64%	140-142
2c	*N*-({4-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]phenyl}methyl)-4-bromoaniline		62%	164-166

Synthesis of Pyrazolones: Reaction of hydrazide with Ethyl aceto acetate

Hydrazide reacted with Ethyl aceto acetate undergoes cyclization and gave heterocyclic compound Pyrazolone. Amino group -NH_2 is nucleophilic in nature and attacks on carbonyl group of Ethyl aceto acetate followed by cyclization to give pyrazolones.

3. Experimental Procedure

As depicted in **Scheme 2,** 1.0 mmol Hydrazide (3a-b: 4-((phenylamino)methyl) benzohydrazide) taken in ethanol, followed by addition of 1.0 mmol ethyl acetoaceate, 2 mmol triethyl amine then reaction mixture was refluxed for 4-6 hours to give solid product pyrazolone **(4a-b)**. Product was isolated, dried and purified. Recorded their physical constants.

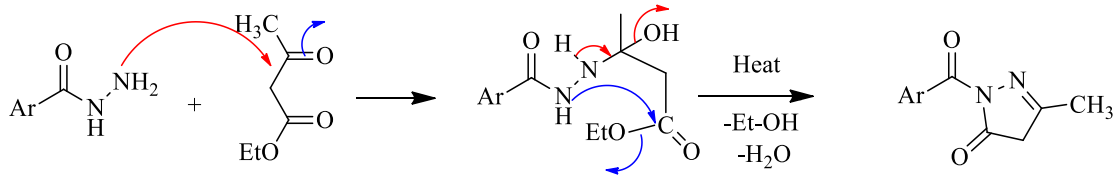


Hydrazides **3a-b** Ethyl acetoacetate Pyrazolone **4a-b**

4-((phenylamino)methyl)benzohydrazide

3-methyl-1-(4-((phenylamino)methyl)benzoyl)-1*H*-pyrazol-5(4*H*)-one

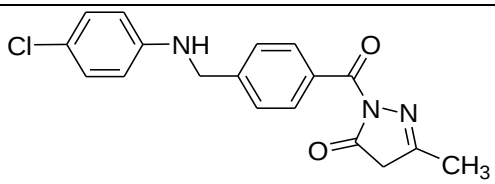
Scheme 2: Synthesis of pyrazolones

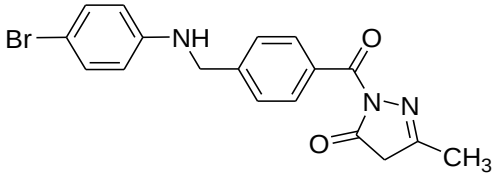


Hydrazides Ethyl acetoacetate Pyrazolone

In above figure, mechanism of pyrazolone synthesis have shown from benzohydrazides and ethyl aceto acetate.

Table 2: Synthesis of Pyrazolones

Code	*Name*	Structure	Yield	M.P.°C
4a	2-{4-[(4-chloroanilino)methyl] benzoyl}-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one		65%	88-90

4b	2-{4-[(4-bromoanilino)methyl] benzoyl}-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one		68%	102-104

Characterization of Oxadiazole and Pyrazolone:
Oxadiazoles and pyrazolones are synthesized as shown in Table 1 and 2. Oxadiazole and pyrazolone derivatives were characterized using proton NMR spectroscopy. Signals of hydrazones between 11 and 12 δ, ppm (s, -NH-CO), whereas signal between 8 and 9 δ, ppm (s, -N=CH-) were disappeared/ vanished after the oxidative cyclization of hydrazones and information of protons present in compound appropriate in terms of signals confirms the completion of cyclization.

In Silico Prediction of Chemical ADMET Properties Evaluation:
It is widely recognized that, evaluating the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of chemicals at early stage [11]. To evaluate the ADMET comprehensively and physicochemical properties of molecules, upgraded platform ADMETlab 3.0 [12] used. It significantly helps in accelerating the drug development process.

1) Absorption:

Compounds	**2a**	**2b**	**2c**	**4a**	**4b**	**ADMET Evaluation Comment**
Property	Value	Value	Value	Value	Value	
Caco-2 Permeability	-4.812	-4.83	-5.019	-4.678	-4.795	Optimal: higher than -5.15 Log unit
MDCK Permeability	-4.663	-4.694	-4.669	-4.691	-4.591	low permeability: < 2 × 10-6 cm/s Medium permeability: 2-20 × 10^{-6} cm/s High passive permeability >20 × 10^{-6}
PAMPA	0.002	0.01	0.002	0.019	0.017	Molecules with log Peff values Below 2.0 low-permeability. Exceeding 2.5: high-permeability
Pgp-inhibitor	0.997	0.994	0.998	0.568	0.684	Category 1: Inhibitor; Category 0: Non-inhibitor;
Pgp-substrate	0.0	0.001	0.0	0.002	0.002	Category 1: substrate; Category 0: Non-substrate;
HIA	0.0	0.0	0.0	0.0	0.0	Human Intestinal Absorption Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA >= 30%)
$F_{20\%}$	0.0	0.002	0.0	0.0	0.0	20% Bioavailability
$F_{30\%}$	0.001	0.01	0.0	0.0	0.0	30% Bioavailability
$F_{50\%}$	0.014	0.034	0.007	0.055	0.027	50% Bioavailability

2) Distribution:

Property	2a	2b	2c	4a	4b	Comment
PPB	99.166	99.21	98.604	98.265	98.425	Plasma Protein Binding Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VDss	-0.05	0.092	0.147	-0.716	-0.387	Volume Distribution Optimal: 0.04-20L/kg
BBB	1.0	1.0	1.0	0.999	0.999	Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-
Fu	0.549	0.524	1.115	0.996	1.244	The fraction unbound in plasms Low: <5%; Middle: 5~20%; High: > 20%
OATP1B1 inhibitor	0.893	0.912	0.934	0.943	0.962	Category 0: Non-inhibitor; Category 1: inhibitor.
OATP1B3 inhibitor	0.709	0.856	0.838	0.905	0.946	Category 0: Non-inhibitor; Category 1: inhibitor.
BCRP inhibitor	0.016	0.1	0.013	0.001	0.001	Category 0: Non-inhibitor; Category 1: inhibitor.
MRP1 inhibitor	0.466	0.552	0.569	0.292	0.407	Category 0: Non-inhibitor; Category 1: inhibitor.

3) Metabolism:

Property	2a	2b	2c	4a	4b	Comment
CYP1A2 inhibitor	0.456	0.696	0.11	0.986	0.859	Category 1: Inhibitor; Category 0: Non-inhibitor;
CYP1A2 substrate	0.005	0.0	0.0	0.954	0.789	Category 1: Substrate; Category 0: Non-substrate
CYP2C19 inhibitor	0.014	0.023	0.016	0.999	0.998	Category 1: Inhibitor; Category 0: Non-inhibitor;
CYP2C19 substrate	0.0	0.0	0.0	0.006	0.102	Category 1: Substrate; Category 0: Non-substrate
CYP2C9 inhibitor	0.999	0.999	1.0	0.987	0.988	Category 1: Inhibitor; Category 0: Non-inhibitor
CYP2C9 substrate	0.147	0.006	0.131	0.001	0.001	Category 1: Substrate; Category 0: Non-substrate;
CYP2D6 inhibitor	0.0	0.0	0.0	0.0	0.0	Category 1: Inhibitor; Category 0: Non-inhibitor
CYP2D6 substrate	0.009	0.001	0.047	0.0	0.0	Category 1: Substrate; Category 0: Non-substrate
CYP3A4 inhibitor	0.957	0.574	0.846	0.636	0.55	Category 1: Inhibitor; Category 0: Non-inhibitor
CYP3A4 substrate	0.329	0.003	0.016	0.936	0.13	Category 1: Substrate; Category 0: Non-substrate
CYP2B6 inhibitor	0.008	0.001	0.0	0.0	0.0	Category 1: Inhibitor; Category 0: Non-inhibitor
CYP2B6 substrate	0.0	0.0	0.0	0.0	0.0	Category 1: Substrate; Category 0: Non-substrate;
CYP2C8 inhibitor	1.0	1.0	1.0	0.995	1.0	Category 1: Inhibitor; Category 0: Non-inhibitor
HLM Stability	0.0	0.0	0.0	0.218	0.162	Human liver microsomal (HLM) stability Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM < 30 min).

4) Excretion:

Property	2a	2b	2c	4a	4b	Comment
CL_{plasma}	2.291	2.243	1.784	0.995	0.767	>15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance.
$T_{1/2}$	1.065	1.024	1.15	1.418	1.573	Ultra-short half-life drugs: 1/2 < 1 h. Short half-life drugs: T1/2 between 1-4 h Intermediate short: T1/2 between 4-8 h Long half-life drugs: T1/2 > 8 h.

5) Toxicity:

Property	**2a**	**2b**	**2c**	**4a**	**4b**	**Comment**
hERG Blockers	0.699	0.664	0.602	0.4	0.302	Molecules with IC50 ≤10μM or 50% inhibition at 10 μM: hERG+(Category 1), IC50 >10μM or < 50% (Category 0).
hERG Blockers10um	0.769	0.734	0.713	0.702	0.638	Molecules: IC50 <10 μM hERG+ Molecules: IC50 > 10μM: hERG-
DILI	0.994	0.994	0.995	0.848	0.863	Drug Induced Liver Injury. Category 1: drugs with a high risk of DILI; Category 0: with no risk of DILI.
AMES Mutagenicity	0.329	0.334	0.272	0.654	0.59	Category 1: Ames positive(+); Category 0: Ames negative(-)
Rat Oral Acute Toxicity	0.441	0.403	0.497	0.222	0.263	Category 0: low-toxicity, > 500 mg/kg Category 1: high-toxicity; < 500 mg/kg
FDAMDD	0.786	0.779	0.907	0.286	0.519	FDA Maximum Daily Dose. Category 1: FDAMDD (+); Category 0: FDAMDD (-)
Skin Sensitization	0.918	0.94	0.942	0.736	0.803	Category 1: Sensitizer; Category 0: Non-sensitizer.
Carcinogenicity	0.401	0.388	0.447	0.512	0.559	Category 1: carcinogens; Category 0: non-carcinogens;
Eye Corrosion	0.0	0.0	0.0	0.0	0.0	Category 1: corrosives; Category 0: noncorrosives
Eye Irritation	0.693	0.769	0.889	0.231	0.515	Category 1: irritants; Category 0: nonirritants
Respiratory	0.161	0.166	0.153	0.33	0.319	Category 1: respiratory toxicants; Category 0: non-respiratory toxicants.
Human	0.679	0.696	0.632	0.72	0.675	Category 1: H-HT positive(+);

Hepatotoxicity						Category 0: H-HT negative(-);
Drug-induced Nephrotoxicity	0.628	0.539	0.389	0.83	0.647	Category 0: non-nephrotoxic (-); Category 1: nephrotoxic (+).
Ototoxicity	0.485	0.436	0.362	0.537	0.41	Category 0: non-ototoxicity (-); Category 1: ototoxicity (+).
Hematotoxicity	0.114	0.114	0.08	0.406	0.314	Category 0: non-hematotoxicity (-); Category 1: hematotoxicity (+).
Genotoxicity	0.998	0.998	1.0	1.0	1.0	Category 0: non-Genotoxicity (-); Category 1: Genotoxicity (+).
RPMI-8226 Immunitoxicity	0.058	0.062	0.06	0.014	0.015	Category 0: non-cytotoxicity (-); Category 1: cytotoxicity (+).
A549 Cytotoxicity	0.886	0.851	0.781	0.07	0.033	Category 0: non-cytotoxicity (-); Category 1: cytotoxicity (+).
Hek293 Cytotoxicity	0.807	0.757	0.615	0.629	0.394	Category 0: non-cytotoxicity (-); Category 1: cytotoxicity (+)
Drug-induced Neurotoxicity	0.475	0.403	0.39	0.892	0.854	Category 0: non-neurotoxic (-); Category 1: neurotoxic (+).

6) Environmental toxicity:

Property	2a	2b	2c	4a	4b	Comment
Bioconcentration Factors	2.16	2.303	2.15	0.925	0.953	Bioconcentration used for considering secondary poisoning potential, assessing risks to human health.
IGC_{50}	4.815	4.704	4.887	3.705	3.702	Tetrahymena pyriformis 50 percent growth inhibition conc.
$LC_{50}FM$	5.587	5.456	5.251	4.59	4.537	96-hour fathead minnow 50 % lethal concentration.
$LC_{50}DM$	6.23	6.082	5.83	5.071	5.06	48-hour daphnia magna 50 % lethal concentration.

ADMET Parameters Evaluation:

1) **Parameters of Absorption**: Caco-2 Permeability makes use of human colon adenocarcinoma cell lines to estimate intestinal absorption and indicate drug absorption. In a similar manner, MDCK (Madin-Darby Canine Kidney) cells assess the permeability of the membrane. Passive membrane diffusion is measured by the Parallel Artificial Membrane Permeability Assay (PAMPA). P-glycoprotein (Pgp) parameters define whether or not compounds are substrates or inhibitors of this vital efflux transporter. Human Intestinal Absorption (HIA) together with bioavailability measures (F20%, F30%, F50%) indicate the percentage of the drug that reaches systemic circulation.
2) **Distribution Parameters:** Plasma Protein Binding (PPB) demonstrates the extent to which drug binds to proteins in blood. Volume of distribution (VDss) reflects the extent of drug tissue distribution. Blood Brain Barrier (BBB) penetration indicates CNS exposure. The concentration of the free drug is shown by the fraction unbound (Fu). Drug distribution and interactions are altered by a number of transporter inhibition parameters (OATP1B1/1B3, BCRP, and MRP1).
3) **Parameters of metabolism:** The compound's status as substrates or inhibitors of other significant drug breakdown enzymes is determined by the parameters of the CYP enzyme. Metabolic stability can be predicted using HLM (Human Liver Microsome) Stability.
4) **Parameters for Excretion**: Plasma clearance (CLplasma) and half-life (T1/2) describe drug elimination rates.
5) **Toxicity Parameters:** These include a number of toxicity endpoints: Heart (heart blockers) DILI, or Drug-Induced Liver Injury, affects the liver. Genetic (AMES mutational potency) Acute toxicity (rat oral), Toxicity to specific tissues (nephro, oto, hemato, and neuro) Toxicity of cell lines (RPMI-8226, A549, and HEK293) Environmental impact (bioconcentration, IGC50, LC50).
6) **Impact on the environment**: Measures how much a substance accumulates in organisms compared to environment. IGC50 - Growth inhibition concentration (50%) for aquatic organisms. LC50 Measures: Lethal concentration for 50% of fish and DM (Daphnia Mortality).

These parameters are crucial for drug development and optimization, helps to predict both therapeutic potential and safety concerns early in development. These ADMET results shows various parameters aid in the evaluation of drug candidates for the Drug-likeness and bioavailability and it also provide a comprehensive toxicity profile needed for drug development and environmental safety assessment. The specific concentrations and protocols for each assay would need to be standardized for proper comparison of compounds.

4. Conclusion

The synthesis of novel oxadiazole and pyrazolones derivatives from hydrazone and hydrazides. They characterized using spectroscopic techniques. The derivatives were screened in silico for ADMET properties through ADMET 3.0. Overall, in silico evaluations suggests that the compounds shows good chemical ADMET properties, indicating their potential for safe and effective use. These results are highly encouraging and synthesized derivatives may lead as a possible therapeutic agents in future.

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