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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLE

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ABSTRACT

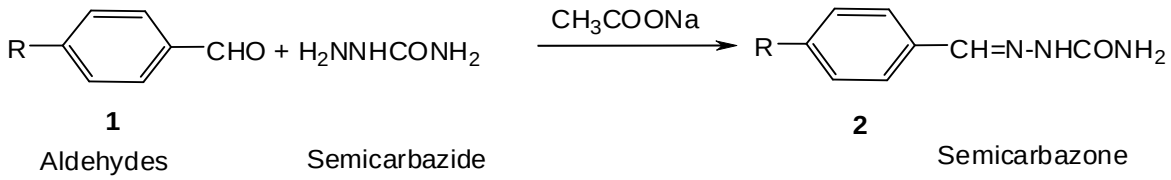
Oxadiazole is the heterocyclic compounds having one oxygen and two nitrogen atoms in a five membered ring. Their derivatives were containing antimicrobial activity against all the selected microbial strains. Oxadiazole ring named as azoxime (1,2,4-oxadiazole), Furazan (1,2,5-oxadiazole) has gained acceptance, as a consequence, the literature is full of the multiplicity of the name for this nucleus. The present work reports the synthesis and biological activities of some novel 1,3,4-oxadiazoles with the following prototype structure. Physicochemical properties perform a useful and resulting role for the logical study of a chemical moiety and help in the determination of melting point, boiling point and determination of pH of a compound, we have done all these studies for oxadiazole derivative. For the synthesis of 1,3,4-oxadiazole, we use two step method in the first step we synthesize semicarbazone by semicarbazide and in second step Cyclization of semicarbazones to synthesize 5-Substituted oxadiazoles.1,3,4-Oxadiazole, the heterocyclic nucleus selected for the present study has been established to possess the varied type of biological activity like sedative, hypnotic, anticonvulsant, anticancer, antibacterial, antifungal, antiviral activities, etc. We have also performed antibacterial, anti-fungal, and anti-convulsant activity which has been produced well desire result. The present results have revealed that synthesized 2-amino-5-aryl-1,3,4-oxadiazole analogues exhibited better antibacterial activity than antifungal activity.

KEYWORD: 1,3,4-Oxadiazole, Antimicrobial activity, Oxadiazolines, azoxime, CADD, QSAR.

INTRODUCTION

Basic research is an attempt to search for a novel and better drug. Approach of group substitution, in which the fundamental portion of the molecule is being kept constant while the remainder is modified quite extensively, also play an important role in the search of newer molecule. For example development of synthetic sulfonamides from sulfanilamide. Compounds containing hetero-cyclic ring are not only essential to life but also shows a wide variety of pharmacological activity. Heterocyclic compounds are those cyclic compounds whose ring contains besides carbon, one or more atom of other elements (heteroatoms). The most common heteroatoms are nitrogen, sulphur and oxygen. 1,3,4-Oxadiazoles have a wide variety of uses, in particular as biologically active compounds in medicine and in agriculture, asdyestuffs, UV absorbing and fluorescent materials, heat- resistant polymers and scintillators.

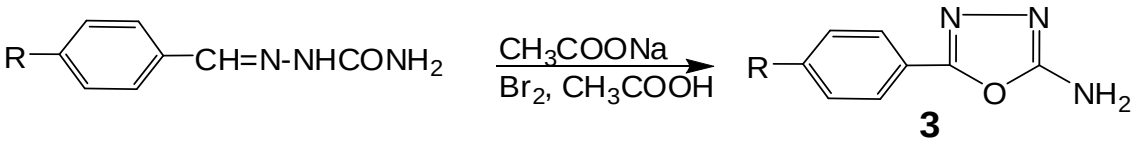
Semicarbazide Hydrochloride (0.1M) and sodium acetate (0.2M) was added and dissolved in 15-20mL of distilled water placed in flat-bottomed flask. In a separate beaker containing required aromatic aldehyde (1) (0.1M) was dissolved in aldehyde free alcohol. This ethanolic aromatic aldehyde solution was added slowly to the solution of semicarbazide hydrochloride. The precipitate, which gets separated, was filtered, dried and recrystallised from 95% hot ethanol.



Step 1: Synthesis of m-substituted and p-substituted benzaldehyde semicarbazone.

Table 1: Physical properties of synthesized semicarbazones.

S. No.	R	Mol. Wt.	% Yield	M.P.
a	*m*-chloro	197.50	94.3 %	228-230^{0}C
b	*p*-chloro	197.50	95.0%	250-254^{0}C
c	*m*-bromo	241.00	95.3%	228-230^{0}C
d	*p*-bromo	241.00	96.05%	234-237^{0}C
e	*m*-methoxy	193.00	90.0%	228-230^{0}C
f	*p*-methoxy	193.00	93.0%	215-217^{0}C
g	*m*-nitro	208.00	96.0%	270-274^{0}C
h	*p*-nitro	208.00	95.90%	218-220^{0}C



Semicarbazone Oxadiazole

Step 2: Synthesis of 2-Amino-5-aryl-1,3,4-oxadiazoles[55]

Semicarbazone (2) (0.1M) and sodium acetate (0.2M) was dissolved in 300-400 mL of glacial acetic acid with continuous stirring. Bromine (7 mL in 50 mL of GAA) was added slowly to it. Solution was stirred for an hour and then poured on crushed ice. The resulting solid was separated, dried and recrystallized from hot ethanol (95%).

Table. 2: Quantity of substituted semicarbazones taken for the synthesis.

S. No.	Semicarbazones	Mol. Wt.	Quantity taken in g
a	*m*-chlorobenzaldehyde semicarbazone	197.5	19.75
b	*p*- chlorobenzaldehyde semicarbazone	197.5	19.75
c	*m*-bromobenzaldehyde semicarbazone	241.0	24.10
d	*p*-bromobenzaldehyde semicarbazone	241.0	24.10
e	*m*-methoxybenzaldehyde semicarbazone	193.0	19.30
f	*p*-methoxybenzaldehyde semicarbazone	193.0	19.30
g	*m*-nitrobenzaldehyde semicarbazone	208.0	20.80
h	*p*-nitrobenzaldehyde semicarbazone	208.0	20.80

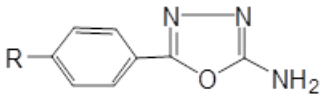


Table 3: Physical properties of synthesized oxadiazoles.

S. No.	R	Mol. Wt.	% Yield	M.P.	Nitrogen Estimation	
					Quantitative	Qualitative
a	*m*-chloro	195.5	73.06%	237-240^{0}C	21.48%	++
b	*p*-chloro	195.5	75.04%	288-290^{0}C	21.48%	++
c	*m*-bromo	240.0	83.06%	238-240^{0}C	17.5%	++
d	*p*-bromo	240.0	81.4%	259-260^{0}C	17.5%	++
e	*m*-methoxy	191.0	62.4%	256-258^{0}C	21.99%	++
f	*p*-methoxy	191.0	86.03%	232^{0}C	21.99%	++
g	*m*-nitro	206.0	83.0%	245-247^{0}C	27.18%	++
h	*p*-nitro	206.0	78.78%	260-262^{0}C	27.18%	++

++ = Nitrogen present

The synthesized compounds were subjected to qualitative and quantitative elemental analysis. IR spectra were recorded on Perkin Elmer Spectrum RX1 in KBr pellets, 1 H-NMR spectra

were recorded on Bruker DRX-300 spectrometer and were recorded at 300 MHZ, using DMSO as the solvent. Chemical shifts are reported in parts per million (ppm) using trimethyl silane (TMS) as an internal standard. Elemental analysis was undertaken with elem-entar vario ELIII carlo Erba 1108 elemental analyzer. Mass spectra were recorded on Micromass Quattro II by chemical ionization (CI) method, using DMSO as the solvent. Solubility of the synthesized compounds was checked in diffe-rent solvents at room temperature (28-30 0 C).

Table 4: Solubility data of synthesized compounds.

comp.	Cool Water	Hot Water	Methanol	Ethanol	Hot Ethanol	DMF	Chlorof-orm	DMSO
3a	__	__	+	+	+++	+++	__	+++
3b	__	__	+	+	+++	+++	__	+++
3c	__	__	+	+	+++	+++	__	+++
3d	__	__	+	+	+++	+++	__	+++
3e	__	__	+	+	+++	+++	__	+++
3f	__	__	+	+	+++	+++	__	+++
3g	__	__	+	+	+++	+++	__	+++
3h	__	__	+	+	+++	+++	__	+++

- Practically insoluble, + Slightly soluble, ++ Soluble, +++ Freely soluble

Anticonvulsant Activity

The term epilepsy, based on the Greek word epilambaein (meaning to seize), has been first mentioned by Hippocrates. It is characterized by abnormal and excessive electroence-phalographic discharge and a disturbance or loss of consciousness.

Anticonvulsant activity was determine by maximal electro shock (MES) induced method.

Albino mice of either sex weighing 25-30 g were divided into different group for different synthesized compound, control and stan-dard. The animal of all group were treated with 100 mg/Kg in susp-ension of Tween-80 (8%) by i.p. route. Except control group which received plain Tween-80 (8%), standard group received (Diphenyl hydntoin) 25 mg/Kg body weight by i.p. route. The effect of drug was observed after 30 min and 4h of the drug treatment.

Seizure was produced in mice by “Biocraft” convulsometer by delivering a current of 50 mA through the corneal electrodes for a period of 0.2 seconds. The animal was placed on the table and its head was fixed. The electrodes were dipped in normal saline and placed gently on the cornea. The shock was delivered by putting on the switch of the instrument. The animals were observed for the following parameters.

a. Tonic phases

- Flexion phase (towards the upper extremities)

- Extensor phase (extended the lower extremities)

b. Clonic phase (intermediate jerking of the limbs)

c. Stupor (unconsciusness)

d. Recovery/ Death

Time for each phase was noted by stop watch. Drug treated animals, were observed for presence or absence of extensor and flexor component of tonic phase during seizures. The observation repres ented on Table.13:, Table.14:

Table 5: Effect of synthesized Compounds by Maximal Electro shock method on Albino mice. (at 100 mg/Kg dose after 30 min)

Code No.	Time (Sec) in various phase of convulsion				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery/ Death
3a	1.79 ± 0.34	abs	8.5 ± 0.30	90.3 ±9.07	Recovery
3b	1.29 ± 0.09	abs	4.8 ±1.07	61.6 ±10.40	Recovery
3c	1.58 ± 0.39	4.06 ± 3.6	Abs	75 ± 10.0	Recovery
3d	1.44 ± 0.33	3.43 ± 0.86	2.3 ± 3.98	87 ± 2.64	Recovery
3e	1.70 ± 0.45	9.40 ± 1.0	11.12 ±1.37	46.6± 20.81	Recovery
3f	1.84 ± 0.56	5.6 ± 1.27	Abs	53.3±16.07	Recovery
3g	1.33 ± 0.33	10.55±2.03	9.81±6.84	91.6± 2.51	Recovery
3h	0.82± 0.1	abs	Abs	72.3±15.69	Recovery
C	1.93 ± 0.05	13.93±0.46	11.5 ±1.04	109± 2.40	Recovery
Sd	abs	4 ±0.7	0.8 ±0.3	86± 1.8	Recovery

Table 6: Effect of synthesized Compounds by Maximal Electro shock method on Albino mice. (at 100 mg/Kg dose after 4hrs).

Code No.	Time (Sec) in various phase of convulsion				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery/ Death
3a	1.79 ± 0.34	Abs	8.5 ± 0.30	90.3 ±9.07	Recovery
3b	1.29 ± 0.09	Abs	4.8 ±1.07	61.6 ±10.40	Recovery
3c	1.18 ± 0.21	2.30 ± 3.98	abs	67.3 ±11.01	Recovery
3d	1.32 ± 0.29	2.48 ± 0.48	1.9 ± 3.40	77.3 ±6.42	Recovery
3e	1.79 ± 0.54	10.4 ±1.45	11.8 ±1.69	53.3 ±23.0	Recovery
3f	1.95 ± 0.61	6.53 ± 1.19	7.76 ±2.15	58.3 ±16.07	Recovery
3g	1.30 ± 0.1	3.93 ±0.81	6.63 ±1.52	97.6 ± 2.51	Recovery
3h	0.82 ± 0.1	Abs	abs	72.3 ±15.69	Recovery
C	1.93 ± 0.05	13.9 ±0.46	11.5 ±1.04	109 ± 2.40	Recovery
Sd	abs	04 ± 0.7	0.8 ±0.3	86 ± 1.8	Recovery

- C = Control
- Sd = Standard (phenytoin)
- abs = Absence of activity
- SE = Standard Error

Phenytoin was selected as standard drug for anticonvulsant activity. The anticonvulsant evaluation of synthesized compound 3b, 3a, 3h shows seizure protection at 100mg/kg dose after 30 min and 4hrs, so they have good onset of action as quickly reach brain. And have prolonged action reveal that compound metabolized slowely. The compound 3e, 3f and 3g shows decease in activity after 4hrs shows that they metabolise at high rate then other compounds. The synthesized compound 3c, 3d shows increase in activity after 4 hrs, reveals that they cross blood brain barrier slowly.

Antimicrobial Activity of Synthesised Compounds

Bacteria are very small (0.5-1.0 µm in diameter) unicellular, prokaryotic organism with rigid cell wall. Bacteria are of different nutritional types like saprophytic, parasitic, phototrophic and autot-rophic. They can be non-motile or motile with simple flagella, axial filament or gliding motility.

Table. 7: MICs of 2-Amino-5-aryl-1,3,4-Oxadiazoles for Antibacterial activity

Compounds	**Antibacterial activity in (µg/mL) (Mean[a] ± SE[b])**			
R	*S. aureus*	*B. Subtilis*	*P.aeruginosa*	*E.coli*
3a	26 ± 0.2	24 ± 0.	28 ± 0.2	30 ± 0.2
3b	20 ± 0.2	22 ± 0.2	24 ± 0.2	28 ± 0.2
3c	30 ± 0.2	30 ± 0.2	34 ± 0.4	36 ± 0.2
3d	28 ± 0.2	28 ± 0.2	30 ± 0.4	36 ± 0.2
3e	42 ± 0.8	46 ± 0.8	48 ± 0.8	50 ± 0.2
3f	38 ± 0.8	42 ± 0.8	46 ± 0.8	44 ± 0.2
3g	36 ± 0.6	42 ± 0.6	54 ± 0.6	56 ± 0.4
3h	34 ± 0.6	40 ± 0.6	52 ± 0.6	52 ± 0.4
Norfloxacin	6 ± 0.6	8 ± 0.2	8 ± 0.2	4 ± 0.2

- a = Average of triplicate
- b = Denotes the standard error (S.E.)

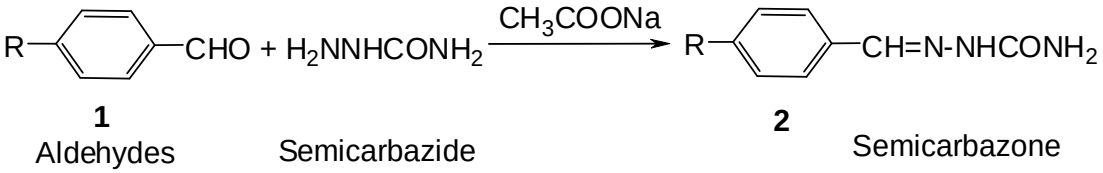
All the synthesized compounds were more active against Gram +ve strain as compare to Gram-ve strain. Substitution of electron withdrawing group at *p*-position of aromatic ring generated more active compounds. Compound 3b was found to be most active compound in the synthesized analogues.

SUMMARY AND CONCLUSION

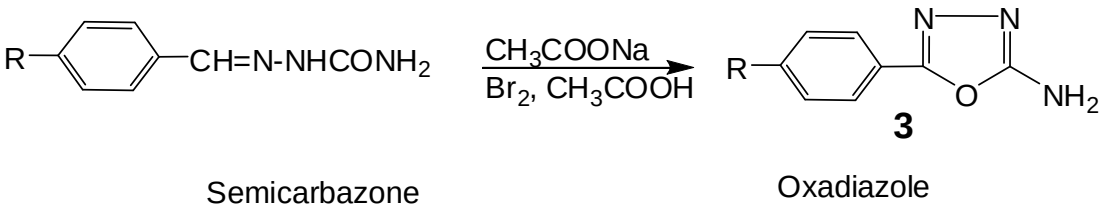
The practice of medicinal chemistry is devoted to the discovery and development of new agents for treated disease. Most of the activity in this discipline is directed to the new natural or synthetic organic compounds, organic compounds have a major place in therapy and they being with increasingly specific. Pharmacological activities are clearly the dominant force. Hundreds of thousands of organic chemicals are prepared annually throughout the world, and many of them enter into pharmacological screening to determine if they have useful biological activity. Among these organic chemicals, heterocyclic nucleus containing compounds occupy a major portion.[111]

1,3,4-Oxadiazole, the heterocyclic nucleus selected for the present study has been established to possess varied type of biologi-cal activity like sedative, hypnotic, anticonvulsant, anticancer, anti-bacterial, antifungal, antiviral activities etc.

Synthesis of title compound (3a-3h) was carried out by following steps



Step.1: Synthesis of *m*-substituted and *p*-substituted benzaldehyde semicarbazone



Step 2: Synthesis of 2-Amino-5-aryl-1,3,4-oxadiazoles.

Table 15: List of title compounds synthesized.

S.No.	Com-pounds	Chemical Name	R	% Yield
a	3a	2-Amino-5-(3-chloro)phenyl-1,3,4-Oxadiazole	*m*-chloro	73.06%
b	3b	2-Amino-5-(4-chloro)phenyl-1,3,4-Oxadiazole	*p*-chloro	75.04%
c	3c	2-Amino-5-(3-Bromo)phenyl-1,3,4-Oxadiazole	*m*-bromo	83.06%
d	3d	2-Amino-5-(4-Bromo)phenyl-1,3,4-Oxadiazole	*p*-bromo	81.4%
e	3e	2-Amino-5-(3-Methoxy)phenyl-1,3,4-Oxadiazole	*m*-methoxy	62.4%
f	3f	2-Amino-5-(4-Methoxy)phenyl-1,3,4-Oxadiazole	*p*-methoxy	86.03%
g	3g	2-Amino-5-(3-Nitro)phenyl-1,3,4-Oxadiazole	*m*-nitro	83.0%
h	3h	2-Amino-5-(4-Nitro)phenyl-1,3,4-Oxadiazole	*p*-nitro	78.78%

The purity of compounds was checked by TLC. Melting points were determined by melting point apparatus in open capillary tubes. All of the synthesized compounds were subjected to qualitative, quantitative and spectral analysis. These include quantitative eleme-ntal analysis, spectral analysis by U.V., I.R., ^{1}H-NMR & Mass spectroscopy.

The synthesized 1,3,4-Oxadiazole analogues 3a-3h was scree-ned for their antimicrobial activity by serial dilution method for evaluating minimum inhibitory concentration and Pharmacological activity for evaluating anticonvulsant activity by maximal electro-shock method.

Antibacterial activity

Antibacterial activity was done using the following bacteria:

a) *Bacillus subtilis (MTCC-619)*
b) *Pseudomonas aeruginosa (MTCC-424)*
c) *Staphyloccocus aureus (MTCC-96)*
d) *Escherichia coli (MTCC-40)*

The standard drug used was Norfloxacin. The MIC of Norfl-oxacin was found to be 4.33-8 µg/mL. The MIC of synthesized compounds was found to be in the range of 20-56µg/mL.Out of eight synthesized compound code no. 3b was found most effective.

Antifungal activity

Anti fungal studies were carried out using the following fungal species.

a) *Aspergillus niger (MTCC-282)*
b) *Candida Albicans (MTCC-227)*

Clotrimazole was selected as the standard drug for antifungal studies. The MIC of standard drug was found to be 6-8.66µg /mL. The MIC of synthesized compound was found to be in the range of 42-78µg/mL. Out of eight synthesized compound code no.3b was found most effective.

Anticonvulsant activity

Phenytoin was selected as standard drug for anticonvulsant evaluation. The anticonvulsant evaluation of synthesized compound 3b,3a,3h shows seizure protection at 100mg/kg dose after 30 min and 4hrs. The compound 3e,3f and 3g shows decease in activity after 4hrs. The synthesized compound 3c,3d shows increase in activity after 4 hrs.

Compound 3b was found to be most active compound of the prepared series. All active compounds should better antibacterial activity than antifungal activity in the range of 20µg/mL-78µg/mL. In conclusion the present results have revealed that synthesized 2-amino-5-aryl-1,3,4-oxadiazole analogues exhibited better antibacterial activity than antifungal activity.

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