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Synthesis, Characterization and Insilco Study of New 1,3-Oxazolone-5-(4-Cl)-one and - Oxazolone-5-(4-NO₂)-one Derivatives

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Abstract:

In this study two new compounds are prepared 1,3-Oxazolone-5-(4-Cl)-one and Oxazolone-5-(4-NO₂)-one derivatives by a reaction of glycine with sebacoyl chloride. The two compounds were identified and characterized by CHN, IR and ¹H-NMR Spectroscopy. Both derivatives show different biological activity according to the program.

Keyword: Oxazolone Derivatives, Insilco.

Introduction

Oxazolones have five membered heterocyclic compound containing an oxygen and nitrogen as hetero atoms (Fig .1). The C-4 and C-2 position are characterized for their different biological activates (1).

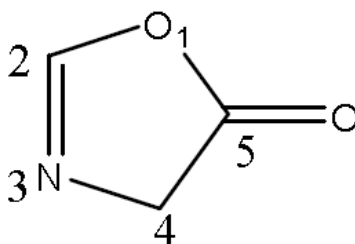
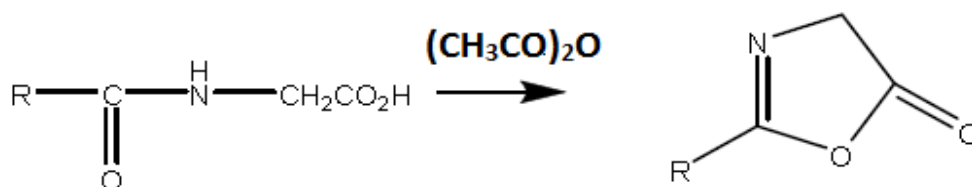


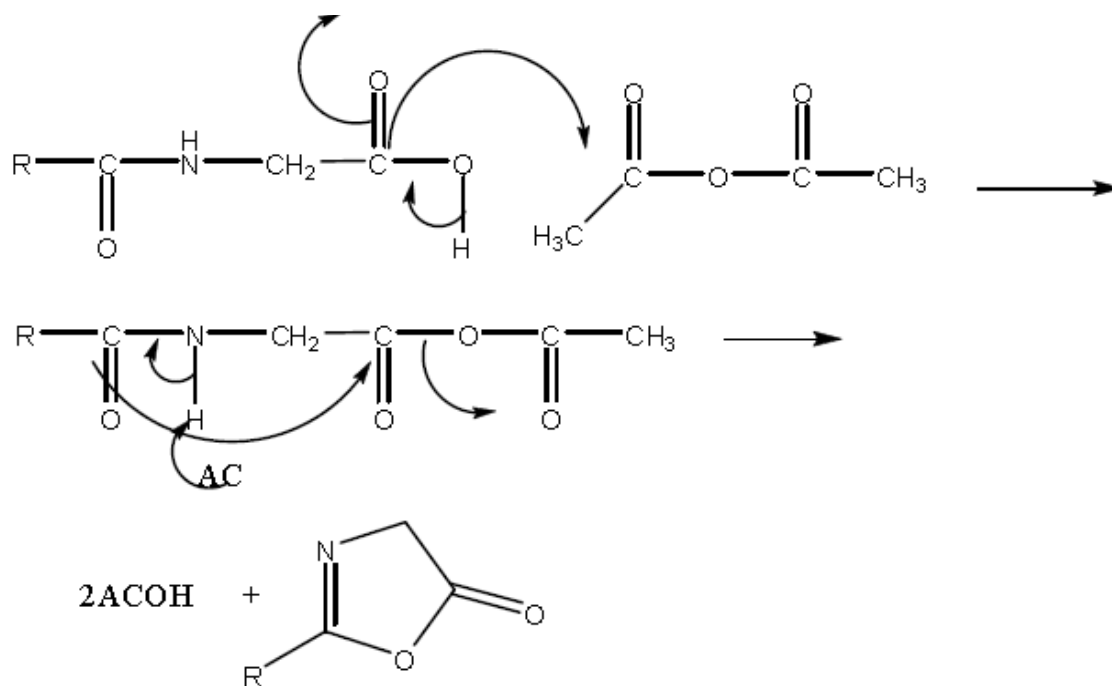
Fig. 1: The structure of oxazolone

Various derivatives of Oxazolones show pharmacological activity, for example: anti-cancer (5) anti-diabetic (6), antifungal (7) , anti-inflammatory (8) and immunomodulatory activity (9). In addition, oxazolones uses as intermediate for synthesis of many compounds such as amino acid (10) dyes (10) and alcohols (11).

The prepare of Oxazolone consisting the intermolecular condensation (Perkin Condensation Reaction) of N-acetyl 2-amino acid with aromatic aldehyde in the existent of acetic anhydride is well-known as Erlemeyer–Plochi oxazolone synthesis (1-5).

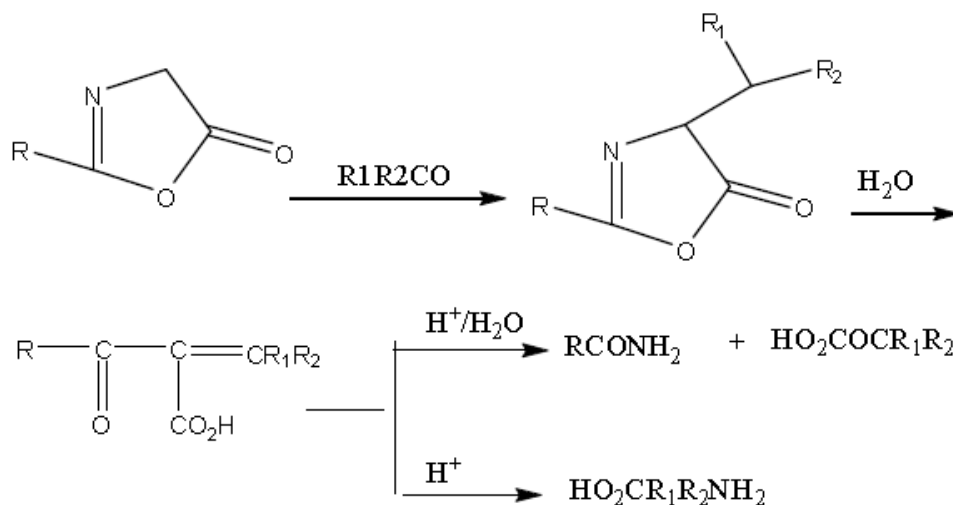


The Mechanism of the Reaction



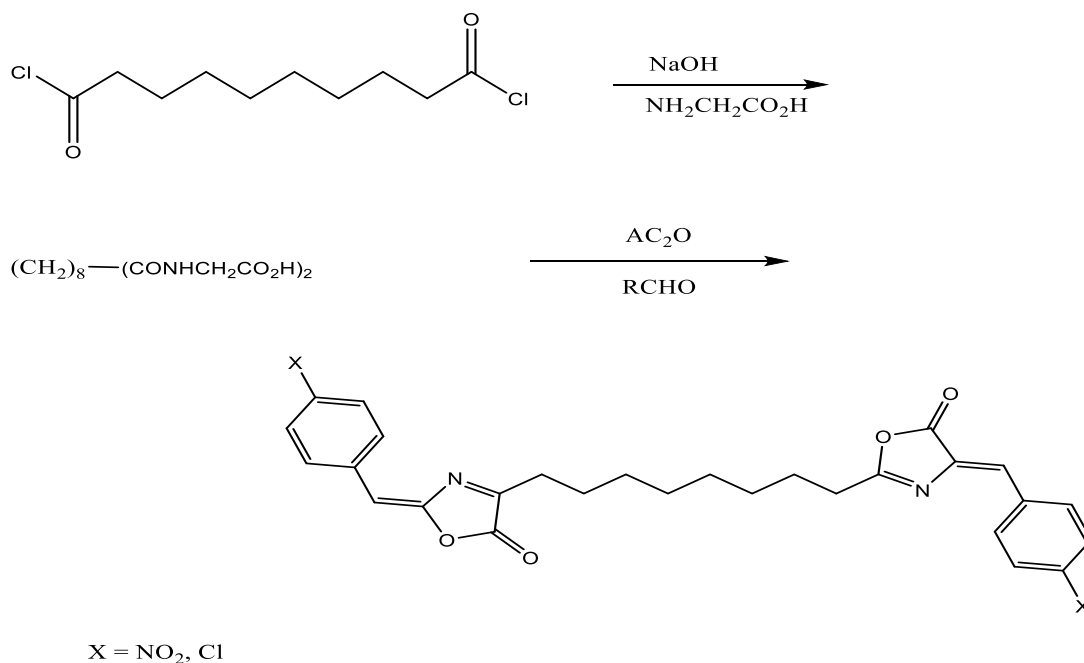
Eq.1 Erlemeyer-plochi Oxazalone Snthesis

This is an important way to prepare 2-amino acid and related compound (2). The aldol condensation reaction of oxazolons with carbonyl compound is accurately often followed by hydrolysis to provide unsaturated alpha amino acid, while drastic hydrolysis gives alpha oxa acid (4)



In the previous studies show various method to synthesis oxazolone (12,13) involve used zinc oxide (14) sodium acetate (15) and Calcium acetate (16) . When oxazolone substituted at C-2 and C-4 position s demonstrate various activity. (17)

The present work include the synthesis , characterization and biological study of two new oxazolone derivative by reaction Sebasoyl chloride with glycine as show in equation :



Experimental

A- Preparation of bis (2-acetamido acetic acid octane compound A)

A solution of glycine (1 mg, 0.02 mole) and sodium hydroxide (1 ml, 10 % solution), Sebacoyl chloride (0.01 mole) was added, then the reaction mixture was shaken vigorously for an hour, then a few grams of ice was added with string, after that, the solution was acidified with concentrated HCl and the product was collected and recrystallized from ethanol, the yield was 70 %, mp (236-238 °C).

B- Preparation (4-Cl-benzylidene)sebasoyl bis 1,3-oxazol-5-(4H)-one compound or (4-NO₂-benzylidene) sebasoyl bis(1,3-oxazol-5-(4H)-one) compound 2:

A mixture of 0.01 mole acetic acid, 5 ml of acetic anhydride and 20ml of p-chloro-benzaldehyde (0.02) mole or p-nitro-benzaldehyde (0.02) mole was added to compound A. The temperature of the reaction kept to 70 °C for 10 minutes. The mixture was poured into crushed ice and stirred for 32 minutes, the product was collected and recrystallized from ethanol to give the product. Table (1) shows the physical properties of the two compounds.

Table. 1 The physical properties of colored compound

No.	X	M.W.	Yield %	Color
1	P-NO ₂	546.536	70	Yellow
2	P-Cl	525.432	70	White

Result and Discussion

1. Elemental analysis

The structure of the synthesized compounds were confirmed that elemental analysis as in Table (2), the difference between the elemental analysis data and the calculated value of C, H and N elements were situated with range and this confirmed the validity of the structures of synthesized compound.

Table 2. : CHN results of prepared compounds

No.	X	Molecular	Calculate			Observed		
			C%	H%	N%	C%	H%	N%
1	NO ₂	C ₂₈ H ₂₆ N ₄ O ₈	61.53	4.7952	10.251	61.3421	4.5952	10.1120
2	Cl	C ₂₈ H ₂₆ Cl ₂ N ₂ O ₄	64.0059	4.9878	5.331	64.0051	4.9810	5.2320

Table 3. ^1H NMR of prepared compounds

No	X	Haro.	Hb	Hg	Ha	Hc
1	NO ₂	7.01-7.04	1.7-1.8m	8.75	1.21	2.1-2.3t
2	Cl	6.5-7.5	1.7-1.8m	8.95	1.24	2.3-2.5 t

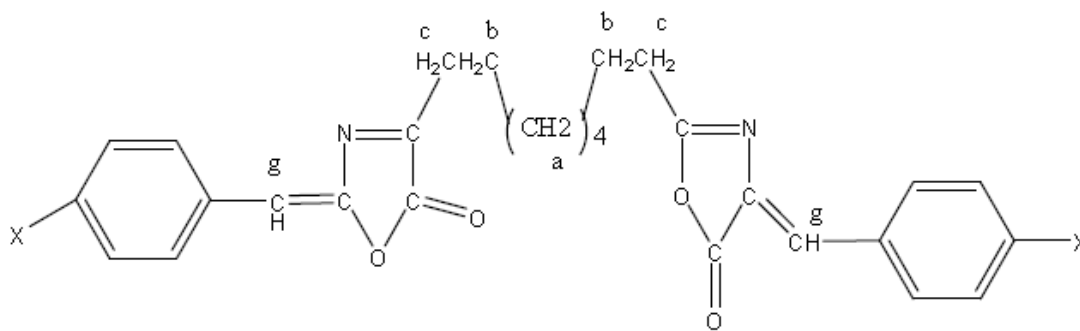


Fig 2. The structure of prepared compound (NO₂) and (Cl)

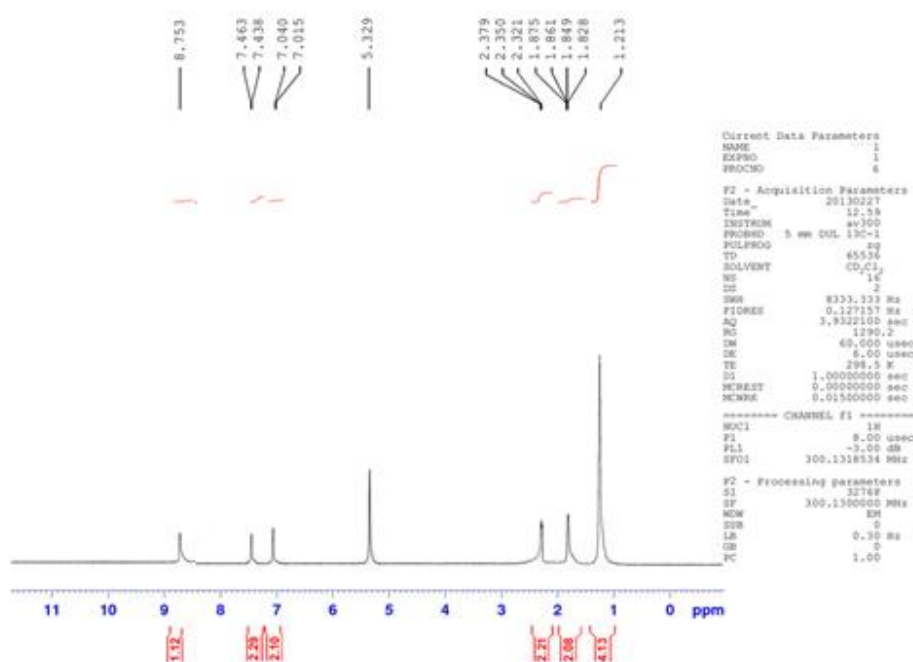
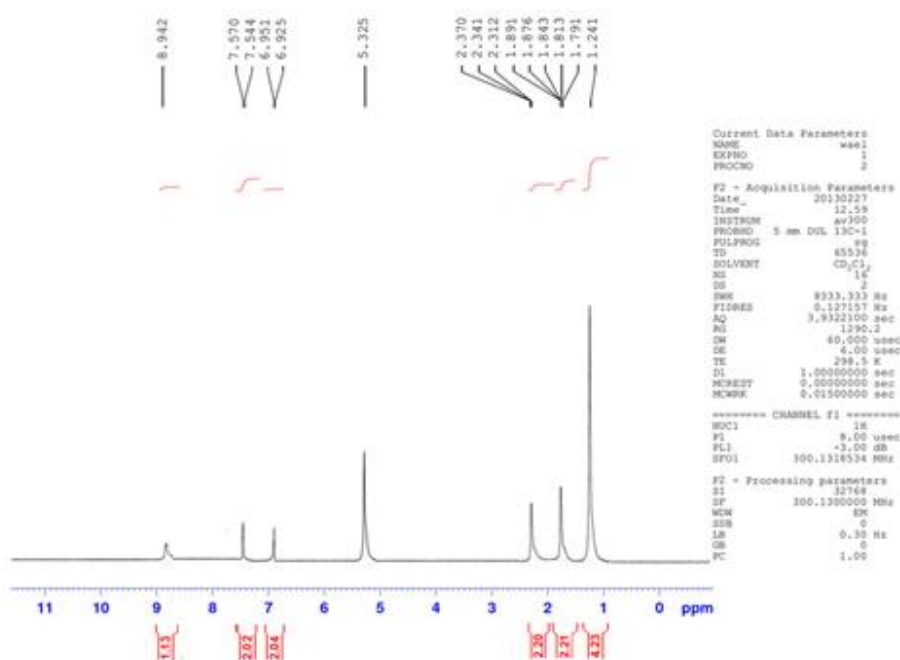


Fig .3 the ^1H NMR of compound 4-NO₂**Fig .4 The ^1H NMR of compound 4- Cl**

3. FT-IR Spectra.

The spectra of compound have common strong absorption in the region $1700\text{--}1710\text{ cm}^{-1}$ due to C=O of oxazol 5 (4H)one .

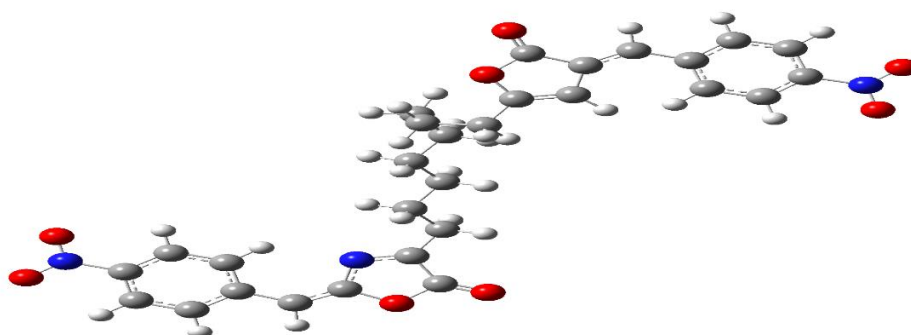
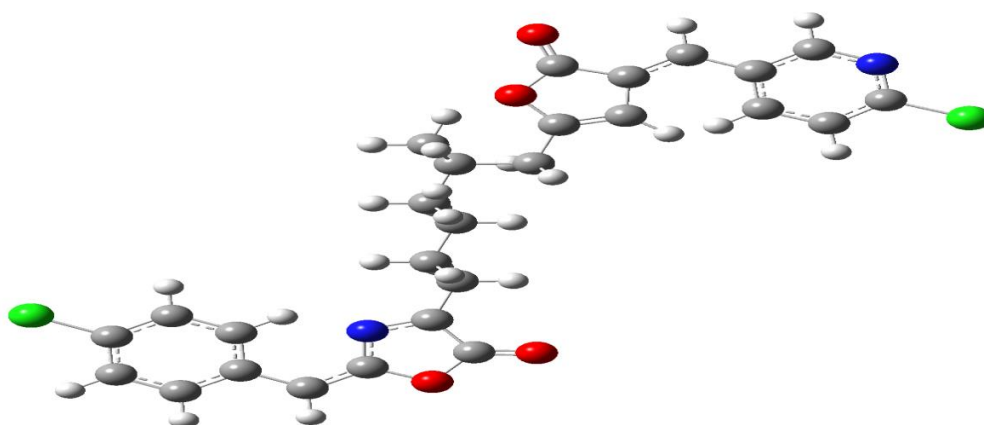
The two strong peaks can be indicated to aromatic double bond C=C ($1600\text{--}1585\text{ cm}^{-1}$), while C=N appears at $1510\text{--}1500\text{ cm}^{-1}$. ν C-H of linic appears at $3090\text{--}3095\text{ cm}^{-1}$.

4. Theoretical study

Theoretical study were done by using Am1 semi-empirical method to calculate E Homo , E Lumo and dipole moment (Table4), by using Hyper Chem 80, the figures show the ball and stick model for new compounds .

Table4, theoretical results for prepared compounds

NO.	E Homo (eV)	E Lumo (eV)	energy (au)	Dipole moment (Debye)
1	-0.32149	0.99582	-1865.233326600	1.4156
2	-0.299921	-0.00161	-2389.938	3.1041

Ball and stick for NO₂ compound

Ball and stick for Cl compound

5. Physical Measurement

IR spectra with KBr disc in the range (200-4000) cm^{-1} were recorded on a pye-Unicam SP3-300s IR spectrometer. Electronic spectra recorded on Pye-Unicam SP8-100 spectrophotometer. ^1H NMR spectra in CDCl_3 solvent were recorded in Joel EX-90FT using TMS as an internal standard. Melting point was measured on Gallenkam melting point apparatus and uncorrected. The carbon hydrogen analysis was carried out with Perkin-Elmer 240M element analyzer.

6. Evaluation Biological activity of compounds;

6.1 Derivative has chlorine group.

Two theoretical methods used to measure the biological activity using Insilco Study of the two compounds.

The Oral toxicity prediction results of (Cl) compound using Toxicity Model Computation show LOD50 of the compound equal to 2800 mg /Kg and this show the lower toxicity of compound. Also the class of toxicity is 5 class and result a comparison with 54.26 of accuracy and the results in Fig. 5 and Table 5.

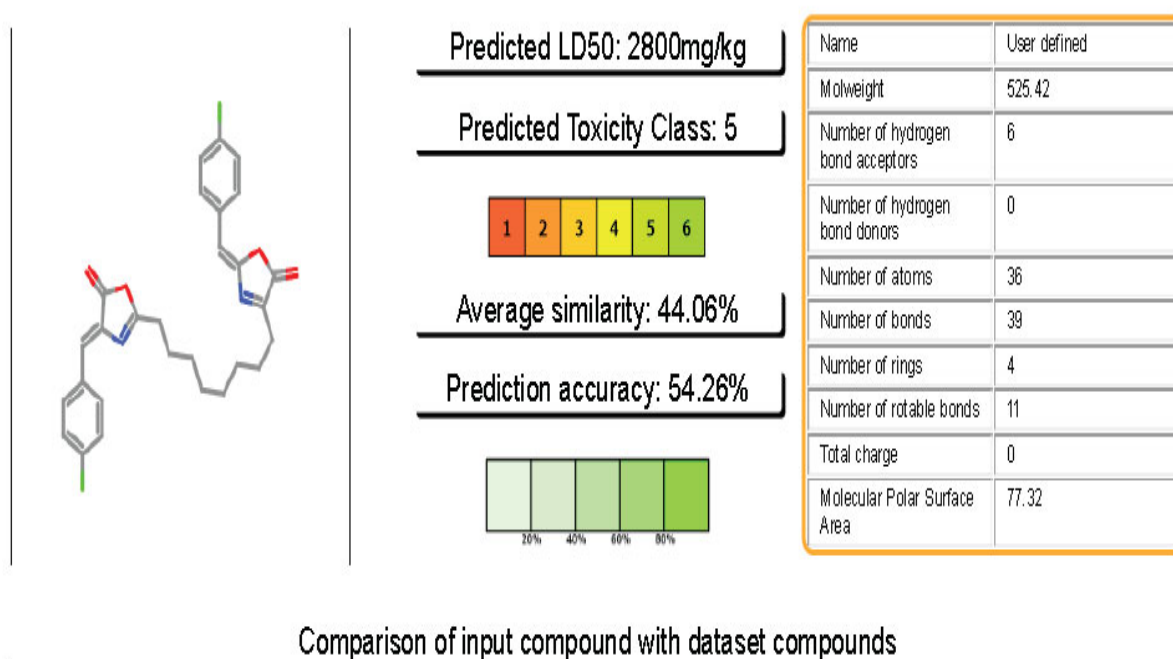


Fig .5 comparison of input compound (Cl) with dataset compounds

Table.5 Toxicity model Report.

Classification	Target	shorthand	Predication	Probability
Organ toxicity	Hepatotoxicity	Dil.	inactive	0.55
Toxicity end points	Carcinogenicity	Carcinogen	active	0.52
Toxicity end points	Immunotoxicity	immune	inactive	0.85
Toxicity end points	Mutagenicity	Mutagen	active	0.67
Toxicity end points	Cytotoxicity	cyto	inactive	0.67

6.2 Derivative of Nitro group.

The Oral toxicity prediction results for (NO₂) compound using Toxicity Model Computation show LOD50 of the compound equal to 2800 mg /Kg and this show the lower toxicity of compound . Also the class of toxicity is 5 class and result a comparison with 54.26 of accuracy and the results in Fig. 6 and Table.6.

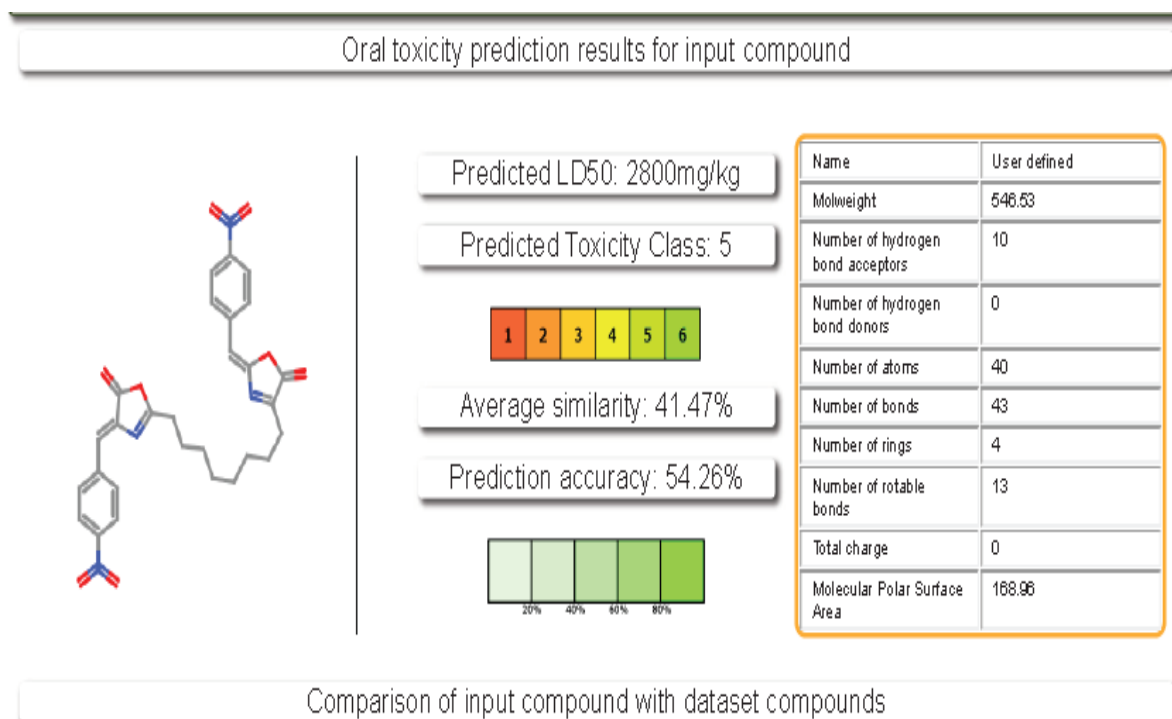


Fig .6 comparison of input compound (NO₂) with dataset compounds

Table.6 Toxicity model Report.

Classification	Target	shorthand	Predication	Probability
Organ toxicity	Hepatotoxicity	Dil.	inactive	0.56
Toxicity end points	carcinogenicity	Carcinogen	active	0.52
Toxicity end points	immunotoxicity	immune	inactive	0.85
Toxicity end points	mutagenicity	Mutagen	active	0.67
Toxicity end points	cytotoxicity	cyto	inactive	0.67

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