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NOVEL 4-OXO-[1, 3-THIAZOLIDINE-3-YL] BENZAMIDE AND ITS DERIVATIVES AS POTENT ANTIPROTOZOAL FERREDOXIN MARKER INTERACTION WITH LIGANDS: DISCOVERY OF NEW DRUG

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Abstract:

In this paper, we synthesized the compound N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboximide(IV) were synthesized. . The chosen ligands have conformational stability and structural diversity in relation to the bound ligands of the N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboximide (IV) crystal structure. The ligand structures used in docking were obtained from Pubchem compound database. Ligands were identified as per the pharmacokinetic parameter and solubility. The active site i.e. ferredoxin enzyme in the protein interacts with ligands of the substrate and gives rise to the catalytic activity to test ligands that helps in determining the binding pattern of the ligands to the active site of ferredoxin enzyme. The pharmacological study was undertaken to evaluate the effects of substituents on the antiprotozoal activity. The synthesized compounds exhibited better antiprotozoal activity towards Paramecium caudatum, Vorticella campanula, it can be inferred that as the OCH3, SH, NH group substitution on the ring causes an increase in the intensity of the activity against Paramecium caudatum, Vorticella campanula , Opalina ranarum and have potent antiprotozoal activity.

Key words: *Thiazolidinones, molecular docking and antiprotozoal activity.*

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INTRODUCTION:

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. The growing potent literature of recent years demonstrates that the thiazole derivatives exhibit better pharmacological properties. The bioactive molecule mostly which shows presence of heteroatom such as sulphur, nitrogen becomes wide area of interest for chemist for reasearch. Thiazolidinones are a potent thiazolidine derivative which shows the presence of heteroatom sulphur at position 1, nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. Its recognition in nature was confirmed through it's presence in penicillin [1, 2]. On Literature review it was revealed that thiazolidine derivatives such as 1, 3-thiazolidin-4-ones, 4- thiazolidinone have been subjected to extensive study in the recent years. It has featured in a number of clinically used drugs due to presence and position of heteroatom in its scaffold [4-6]. They have different Pharmacological activites such as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agent [7,8].

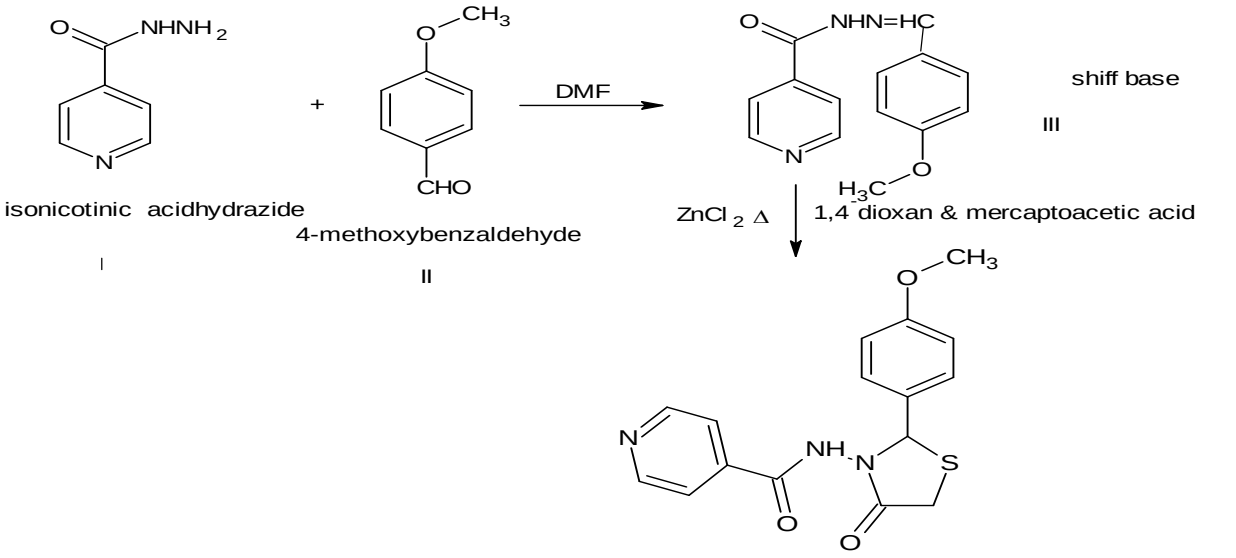
Regarding this, I design for compounds with high specificity towards potent antiprotozoal has been developed by means of a structure-based drug design approach. Computational chemistry has developed into an important contributor towards rational drug design. Quantitative structural activity relationship (QSAR) modeling results in a quantitative correlation between chemical structure and biological activity. QSAR analyses of potent antiprotozoal as ferredoxin enzyme in the protein interacts with ligands of the substrate and gives rise to the catalytic activity to test ligands that helps in determining the binding pattern of the ligands to the active site of ferredoxin enzyme which shows good result in docking studies. Characterization of all compounds by modern analytical tools such as IR, 1H NMR and Mass. And potent antiprotozoal as ferredoxin marker interaction with ligands screening of compound.

MATERIAL AND METHODS:

All the required chemicals were purchased from Merck and Aldrich Chemical Company (USA). Precoated aluminium sheets (silicagel 60 F254, Merck Germany) were used for thin- layer chromatography (TLC) and spots were visualized under UV light. Elemental analysis was carried out on CHNS Elementar (Vario EL-III, Germany) and the results were within ±0.3% 0f theoretical values. IR spectra were recorded on Bruker FTIR spectrophotometer. 1 H NMR and 13C NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz using $CDCl_3$ or DMSO as a solvent and trimethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; m, multiplet. Chemical shift values were given in ppm. The FAB mass spectra of the compounds were recorded on JEOL SX 102/DA-6000 mass spectrometer using Argon/Xenon (6 KV, 10 Ma) as the FAB gas and m-nitro benzyl alcohol (NBA) was used in the matrix.

It has been felt worthwhile to synthesize some new N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboxamide and to evaluated them for them for their possible biological and pharmacological properties. For this purpose, the is nicotinic acidhydrazide (I) has been condensed with 4-methoxy Benz aldehyde heating under reflux in DMF containing traces of glacial acetic acid. The resultant product has been purified by recrystallization and characterized as the respective N-[(4-methoxyphenyl) benzylidene] pyridine-4-carboximide (III).

Then, this Schiff base (III) has been subjected to a polar cycloaddition using mercaptoacetic acid by heating in presence of anhydrous zinc chloride. Their analytical and spectral studies have helped in characterizing as N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV). Synthesis of the tittle compounds has been effected as per unambiguous synthetic routes specified in Scheme-I.



Scheme 1. **Synthesis of N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV).**

The Molecular structure *of* N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboxamide is shown in *Fig.1*.

Fig.1: Molecular structure of N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboxamide.

General Procedure for Schiff base:
A mixture of isoniazid (0.01mol), different substituted aromatic aldehydes (0.01mol) in dry DMF (30ml) was refluxed for 24 hr. and the excess DMF (dimethyl formamide) was removed by distillation. Then the mixture was poured into crushed ice with stirring. The solid mass obtained was filtered and recrystallized from ethanol.

General Methods of Synthesis of *N*-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide:
To a mixture of Schiff base (0.01mol) and thioglycolic acid (0.01mol) dissolved in 1,4 dioxane (20ml), anhydrous zinc chloride (0.004 mol) was added and refluxed for 8h. The reaction
Absolute ethanol.

Physical and Spectral Data of Synthesized Compounds.

***N*-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboxamide**
$C_{16}H_{15}N_3O_3S$, mp-245-250°C, IR(KBr pellets,cm-1) 2925-2850(C-H Str), 1578 (C=O), 784(C-S-C), 1HNMR δ(DMSO) 3.09 (d, 2H,S-CH2-CO), 2.4 (d, 2H, N-CH2), 6.8-7.05 (m, 4H, Ar-H), Ms (m/z): 329 (M+).

It is believed that the strong lipophilic character of the molecule plays an essential role for antiprotozoal activity. These N-[(4-methoxyphenyl)benzylidene]pyridine-4-carboximide(III) may act via reduction of the nitro group via ferredoxin in the same way metronidazole acts, but not as inhibitors of tubulin polymerization as albendazole does, since the metronidazole-resistant line was not susceptible to these compounds. This is what is expected of drugs with a similar mechanism of action to metronidazole.

MOLECULAR DOCKING
In silico screening
500 compounds from different chemical databases were screened, including the PubChem & ChemBank. They were docked into the binding pocket of reduction of the nitro group via ferredoxin in the same way metronidazole acts, but not as inhibitors of tubulin polymerization is an enzyme structure using the program AutoDock4.

Substrate selection
500 structures most 2D-similar to N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) were chosen based on screening from the PubChem. The chosen ligands have conformational stability and structural diversity in relation to the bound ligands of the N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) crystal structure. The ligand structures used in docking were obtained from PubChem compound database. Ligands were

identified as per the pharmacokinetic parameter and solubility. The active site i.e. ferredoxin enzyme in the protein interacts with ligands of the substrate and gives rise to the catalytic activity to test ligands that helps in determining the binding pattern of the ligands to the active site of ferredoxin enzyme shown in *Fig.2*

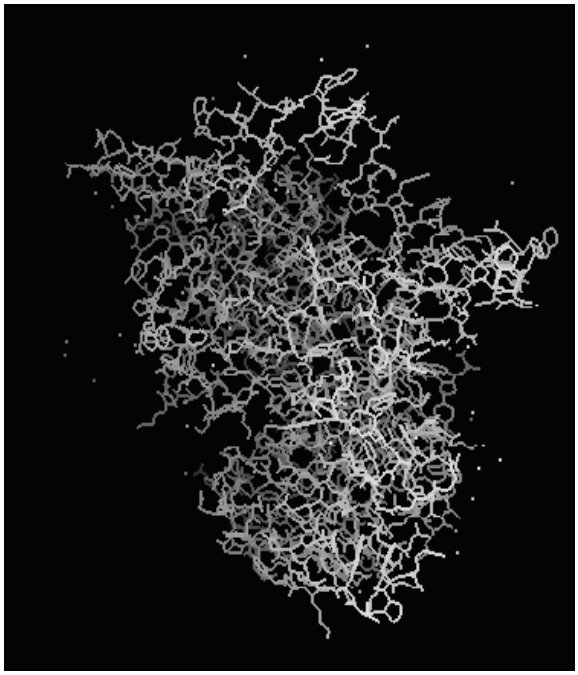


Fig.2: Autodock window showing grid parameters options.

ANTIPROTOZOAL EVALUATION

Antiprotozoal activity of synthesized compounds were tested by using microscopic count method The in vitro antiprotozoal activity was performed against Paramecium caudatum, Vorticella campanula, Rectal ciliates, Opalina ranarum and, Nyctotherus cordiformis.. Known Antiprotozoal like Albendazole and Metronidazole were used as a Standard.Strong lipophilic character of the molecule plays an essential role for antiprotozoal activity. These N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) may act via reduction of the nitro group via ferredoxin in the same way metronidazole acts, but not as inhibitors of tubulin polymerization as albendazole does, since the metronidazole-resistant line was not susceptible to these compounds. This is what is expected of drugs with a similar mechanism of action to metronidazole.

Preparation of the culture media for free-living protozoa

Undefined complex medium was used to culture protozoa. In this method, few leaves of submerged weeds from a pond were collected and kept in a 1-liter jar having distilled water. It was covered and allowed to rot. Within a few days large numbers of protozoa appeared. In order to grow them, hay infusion was prepared by autoclaving hay in tap water and then the supernatant was collected. A few grains of wheat were added to it and were kept undisturbed for four days, in order to get bacterial growth that serves as a source for protozoal nutrition. Then about 5 ml of the inoculum was transferred to the infusion and incubated for two days. This was used for testing the antiprotozoal activity.

Antiprotozoal test

It was made by microscopic count method. 1 ml of aqueous solution of acetonic extract was added to 4ml of protozoal inoculum, to get a final concentration of 4 mg/ml. After two minutes, 0.02 ml was transferred onto a glass slide. In control experiment, only 1 ml of distilled water, instead of aqueous extract, was added to the 4ml of inoculum. Both the test and control samples were examined under a compound microscope and motile and non-motile organisms were counted. Non-motile organisms were considered as non-viable due to its susceptibility towards the extract and motile were considered as resistant to the extracts. Tests were repeated four times and the average number of motile/non-motile organisms was recorded.

RESULTS AND DISCUSSION:

The thiazolidine derivatives N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) is characterized with thin layer chromatography and spectral analysis like IR and NMR spectra. Some of the synthesized compounds tested were endowed with a medium activity against Nyctotherus cordiformis. The compounds with OCH3, SH, NH group substitution on the ring showed better activity against Paramecium caudatum. For Opalina ranarum, the tested compounds showed low to moderate antiprotozoal activity which is shown in *Table. 1.*

Table 1: Antiprotozoal effect of synthesized compound against fresh water protozoa.

Compound	Observation of protozoa after 2 min for sensitivity/resistance		Total no of protozoa counted			
			a	***b***	***c***	***d***
	No. of motile/ resistant organisms	**No. of non-motile Sensitive organisms**				
IV	0	All	8 ± 2	7 ±1	9±2	7±2
Std (Metronidazole)	All	0	10 ± 1	12 ± 2	12±1	10±1

Where, a. *Paramecium caudatum,* b.Vorticella *campanula,* c. *Opalina ranarum* and d. *Nyctotherus cordiformis.*

CONCLUSION:

In conclusion, the compound N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) were synthesized. . The chosen ligands have conformational stability and structural diversity in relation to the bound ligands of the N-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl] pyridine-4-carboximide (IV) crystal structure. The ligand structures used in docking were obtained from PubChem compound database. Ligands were identified as per the pharmacokinetic parameter and solubility. The active site i.e. ferredoxin enzyme in the protein interacts with ligands of the substrate and gives rise to the catalytic activity to test ligands that helps in determining the binding pattern of the ligands to the active site of ferredoxin enzyme. The pharmacological study was undertaken to evaluate the effects of substituents on the antiprotozoal activity. The synthesized compounds exhibited better antiprotozoal activity towards Paramecium caudatum, Vorticella campanula, it can be inferred that as the OCH3, SH, NH group substitution on the ring causes an increase in the intensity of the activity against Paramecium caudatum, Vorticella campanula , Opalina ranarum and have potent antiprotozoal activity.

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