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Research Article

NOVEL MANNICH BASES OF 4-THIAZOLIDINONE DERIVATIVES AS ANTITUBERCULAR AGENTS

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ABSTRACT

A series of novel 2, 3-substituted-5-(morpholin-4-ylmethyl)-1, 3-thiazolidin-4-ones were selected by *in silico*design and were prepared by treating 2, 3-substituted-4-thiazolidinones with formaldehyde and morpholine by Mannich reaction. 2, 3-substituted-4-thiazolidinones in turn, were synthesised from a series of Schiff bases by reaction with thioglycolic acid. Structures of the newly synthesized compounds were assigned on the basis of elemental analysis, IR, 1H NMR and mass spectral studies. The newly synthesized compounds were tested for their *in vitro*antitubercular activity against *Mycobacterium tuberculosis* by alamar blue assay method.

Keywords: Schiff base,Mannich base, 4-thiazolidinones,antitubercular.

INTRODUCTION

Tuberculosis is a common and an infectious disease which is caused by bacteria called *"Mycobacterium tuberculosis" (M. tuberculosis)* and seven very closely related mycobacterial species (*M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti*and*M. mungi*) together comprise what is known as the *M. tuberculosis* complex. Most, but not all, of these species have been found to cause disease in humans. In the United States, the majority of TB cases are caused by *M. tuberculosis*.

Tuberculosis (TB) remains as a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immune deficiency virus (HIV). The latest estimates included in WHO's report are; there were almost 9 million new cases and 1.4 million TB deaths in 2012(990 000 among HIV negative people and 430 000 HIV-associated TB deaths). Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s. The World Health Organization (WHO) declared TB a global public health emergency in 1993. Starting in the mid-1990s, efforts to improve TB care and control intensified at national and international levels. Globally, 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB. In 2010, the treatment success rate was 85% among all new TB cases and 87% among new cases of sputum smear-positive pulmonary TB (the most infectious cases). Improvement in treatment outcomes is needed in the European Region, where the treatment success rate in 2010 was 74% and 67% for new cases and new smear positive cases respectively. The provision of diagnosis and treatment according to the DOTS/Stop TB Strategy has resulted in major achievements in TB care and control. Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the DOTS/Stop TB Strategy, saving 20 million lives. In countries reporting age-disaggregated data, most cases (88%) were aged 15–64 years. Children (aged <15 years) accounted for 6% of notified cases. The

male:female ratio was 1.7 globally, ranging from 1.1 to 2.2 among WHO six regions.

There are more than twenty drugs that are currently used for the treatment of TB and almost all of them were developed some years ago. The drugs are used in differing combinations in different circumstances, so that for example some TB drugs are only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs. There are other drugs that are only used for the treatment of drug resistant TB.

The basic TB drugs (1st line drugs)

5 basic or 1st line TB drugs are;

- Ethambutol is EMB or E,
- Isoniazid is INH or H,
- Pyrazinamide is PZA or Z,
- Rifampicin is RMP or R,
- Streptomycin STM or S

All the other TB drugs are generally referred to as “second line” or reverse TB drugs.

Classical drug discovery was solely based on observation of natural phenomena and consequences of relieved distress. Latest scientific technologies have helped to understand the drug action mechanism. Likewise the drug discovery procedures have changed.

Computational chemistry and molecular modelling have become an essential part and an emerging tool for research and drug development process.The process of drug discovery is very complex and requires an interdisciplinary effort to design effective and commercially feasible drugs. The objective of drug design is to find a chemical compound that can fit to a specific cavity on a protein target both geometrically and chemically.

Molecular docking

Molecular docking is a computer simulation procedure to predict theconformation of a receptor-ligand complex, where the receptor is usually a protein ora nucleic acid molecule (DNA or RNA) and the ligand is either a small molecule oranother protein. It can also be defined as a simulation process where a ligand positionis estimated in a predicted or pre-defined binding site. The aim is to achieve anoptimized conformation for both the protein and the ligand and relative orientationbetween them such that the free energy of the overall system is minimized. The twomain stages of molecule docking are: a search stage that configures a certain numberof possible binding of given protein and ligand and a scoring stage that estimatesbinding affinity for given protein, ligand, pose and conformations.

Lead compound

The objective of this drug discovery phase is to synthesize lead compounds.A lead compound in drug discovery is a chemical compound thathas pharmacological or biological activity and whose chemical structure is used as astarting point for chemical modifications in order to improve potency, selectivity,or pharmacokinetic parameters.

Two types of investigational activities of lead include:

a) ***Exploration of Leads***, which involves the search for a new lead ; and

b) ***Exploitation of Leads***, which requires the assessment, improvement and extension of the lead.

Heterocyclic compounds as lead

Heterocyclic compounds have a wide range of applications. Their applications in pharmaceutics are because of their specific chemical reactivity. Organic chemists synthesize hundreds of new heterocyclic compounds every week. In most cases the chemist has specific reasons for synthesizing a particular compound, usually based on theoretical considerations, medicinal chemistry, biological mechanisms or a combination of all three. The heterocyclic compounds are very widely distributed in nature and are very essential to living organisms. They play a vital role in the metabolism of all the living cells.

Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant specially those containing oxygen or sulphur due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity. Majority of the large number of drugs being introduced in pharmacopoeias in recent year are heterocyclic compounds. Various studies showed that heterocyclic ring with electron donating group increases the anti-TB activity.

Thiazolidinone as lead

4-Thiazolidinone, a saturated form of thiazole with carbonyl group on fourthcarbon, has been considered as a magic moiety which possesses almost all types ofbiological activities. This diversity in the biological response profile has attracted theattention of many researchers to explore this skeleton to its multiple potential againstseveral activities.

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds

containingsulphur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities.Thiazolidinones, which belong to an important group of heterocyclic compounds, have been extensively explored for their application in the field of medicine. Thiazolidinones, with a carbonyl group at position 2-(a), 4-(b), on 5-(c) have been subjects of extensive study in the field of 4-Thiazolidinones.

Mannich bases as lead

A Mannich base is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde (or an aldehyde) and a carbon acid.Many Mannich bases have been synthesized and have been reported to possess various activities that include anti tubercular, antidepressant activity, anticonvulsant activity anti-cancer and antimicrobial properties.The Mannich reaction is also used in the synthesis of medicinal compounds.

MATERIALS AND METHODS

Materials

*In silico*molecular modelling studies were carried out on various softwares like Schrodinger, ACDLABS ChemSketch and Molinspiration.

The chemicals and reagents used in the present work were of AR and LR grade, procured from Merck, Spectrum, Hi-Media, Nice and Sigma-Aldrich. All the chemicals were dried and purified wherever necessary. The melting points of the synthesized compounds were determined by Thiels melting point apparatus (open capillary tube method) and all the compounds gave sharp melting points and were uncorrected.Purity of the compounds was ascertained by thin layer chromatography. The IR spectra of the synthesized compounds were recorded on IR affinity-1 FTIR spectrophotometer Shimadzu in the range of 400-4000.The NMR Spectra of the characteristic compound was recorded by NMR 400 MHZ Spectrophotometer Brucker.The mass spectrum of the characteristic compound was recorded by JOEL GC mass spectrometer using electron ionisation method.

Methods

***In silico*design procedure**

The 3-D structure of the protein was obtained from PDB using their specific PDB ID (4DRE). The protein structure was prepared using the protein preparation wizard in the Schrodinger software graphical user interface Maestro v9.3. A set of derivatives of Mannich bases of thiazolidinone were selected as ligands and their structures weredrawn using the workspace of Maestro and were converted to 3D form for the docking studies. The collected ligands were prepared for docking. Then the prepared ligands were docked into the generated grid in the prepared protein.The best docked pose with lowest Glide score value was recorded for each ligand. Extra precision (XP) was performed using the module Induced Fit Docking of Schrödinger-Maestro v9.3 (2012). Best derivatives with good docking score were selected and their ADME properties were checked using QIKPROP which is a tool available in Schrodinger under Maestro. The Lipinski's rule of five and drug likeness analysis of selected derivatives are also calculated.

Procedure for synthesis

Synthesis of Schiff base: Equimolar quantities of substituted benzaldehydes and substituted anilines dissolved in ethanol are taken in a round bottom flask. To this added 2 drops of glacial acetic acid and was refluxed for 3 hours and the completion of reaction monitered by TLC. Then the reaction mixture was poured into crushed ice. The precipitate obtained was filtered and washed with cold water to obtain compound 1a-5a. Dried product was recrystallized from ethanol (Table 1).

Synthesis of thiazolidinones

0.01 mol of Schiff base (1a-5a) in dry benzene was taken in a round bottom flask. To this added 0.015 mol of thioglycolic acid and a pinch of $ZnCl_2$and was cnnected to a dean stark water seperator. Then it was refluxed for 16-24 hours, during the course of reaction the water was removed continously. The completion of reaction was monitered by TLC. Then the excess of solvent was removed under presure and the concentrated solution was washed with saturated solution of $NaHCO_3$ followed by water. The solid product obtained was filtered, washed repeatedly with water, dried and recrystallzed from benzene to obtain compound 1b-5b (Table 2).

Synthesis of Mannich bases

The prepared 4-Thiazolidinone derivatives were treated with equimolar quantities of various aromatic amines and formaldehyde 37%, refluxed for 2 hours in presence of DMF, completion of reaction was monitored by TLC.

The products (1c-5c) were recrystallized from alcohol and benzene (Table 3).

Table 1: Physicochemical parameters of different Schiff bases

Compound	Molecular Formula	Mole-cular weight	Appea-rance	Melting Point (°C)	Rf value	% yield
1a	$C_{13}H_9Cl_2N$	250	Crystalline yellow	168	0.824	90
2a	$C_{14}H_{12}ClNO$	245	Crystalline white	154	0.812	89
3a	$C_{13}H_9ClN_2O_2$	260	Crystalline yellow	158	0.796	85
4a	$C_{13}H_9Cl_2N$	250	Crystalline yellow	163	0.845	92
5a	$C_{13}H_9ClFN$	233	Crystalline Greenish yellow	146	0.782	87

Table 2: Physicochemical parameters of different 4-thiazolidinones

Compound	Molecular Formula	Mole-cular weight	Appea-rance	Melting Point (°C)	Rf value	% yield
1b	$C_{15}H_{11}Cl_2NOS$	324	Crystalline Yellow	231	0.624	78
2b	$C_{16}H_{14}ClNO_2S$	320	Crystalline White	235	0.712	76
3b	$C_{15}H_{11}ClN_2O_3S$	345	Crystalline White	228	0.654	75
4b	$C_{15}H_{11}Cl_2NOS$	324	Crystalline Yellow	231	0.751	72
5b	$C_{15}H_{11}ClFNOS$	308	Crystalline Yellow	238	0.619	74

Table 3: Physicochemical parameters of different mannich bases of 4-thiazolidinones

Compound	Molecular formula	Mole-cular Weight	Appea-rance	Melting Point (°C)	Rf value	% yield
1c	$C_{20}H_{20}Cl_2N_2O_2S$	423	Crystalline white	168	0.524	69
2c	$C_{21}H_{23}ClN_2O_3S$	419	Crystalline white	190	0.562	70
3c	$C_{20}H_{20}ClN_3O_4S$	434	Crystalline white	185	0.604	67
4c	$C_{20}H_{20}Cl_2N_2O_2S$	423	Crystalline white	201	0.531	71
5c	$C_{20}H_{20}ClFN_2O_2S$	407	Crystalline yellow	179	0.499	65

Scheme

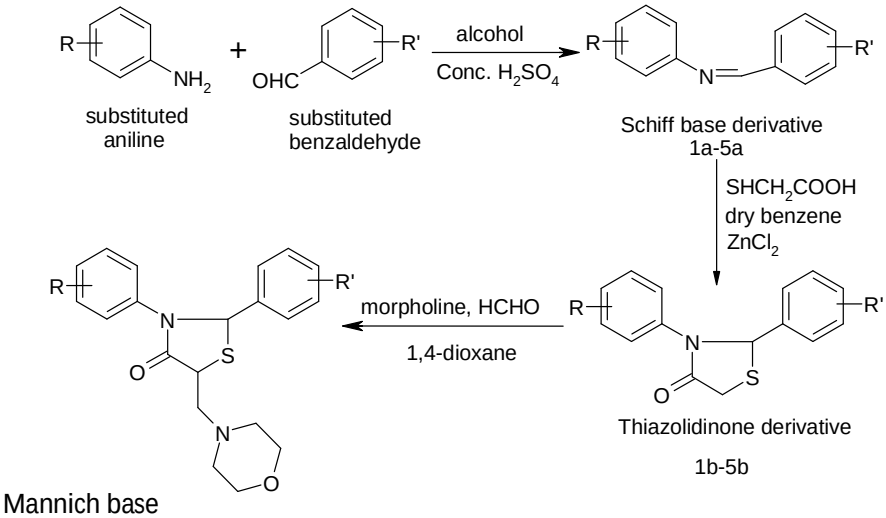

Table 4: substituent details in synthesized compounds

COMPOUND	R	R'
1a, 1b, 1c	4-Cl	4-Cl
2a, 2b, 2c	4-Cl	4-OCH_3
3a, 3b, 3c	4-Cl	3-NO_2
4a, 4b, 4c	4-Cl	2-Cl
5a, 5b, 5c	4-F	2-Cl

RESULTS AND DISCUSSION

The current research revealed the significance of rational designing for the development of novel Mannich base derivative of 4-thiazolidinones. The newly synthesized Mannich base derivatives were anticipated as promising leads having many biological activities. Keeping this view in mind, the new analogues were designed, synthesized and evaluated for antitubercular activity.

In silico design

Docking result

Glide scores of designed analogues of Mannich base of thiazolidinones and corresponding thiazolidinone for antitubercular activity (Table 5).

Analysis of Lipinski's rule of five

Lipinski's rule of the synthesized compound: All the synthesised derivatives obey Lipinski's rule of five and the values are given in table 6

Drug likeness analysis

Drug likeness analysis parameters of selected derivatives for synthesis were compared to standard anti TB drugs and are given in tables 7 and 8.

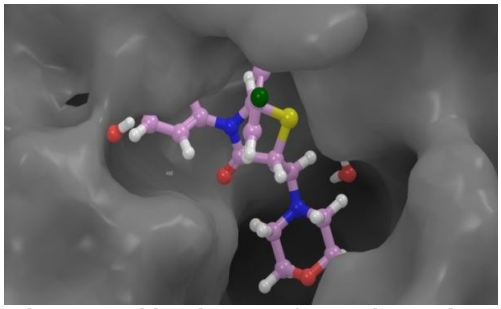

Fig. 1: Docking image of mycobacterium tuberculosis protein enoyl ACP reductase

Table 5: Docking score of Mannich base derivatives

S. No:	Compound	Docking score
1	1c	-7.724
2	2c	-5.694
3	3c	-6.269
4	4c	-7.460
5	5c	-6.995

Table 6: Parameters and its values in Lipinski's rule of five

Compound	Log P	Mol.wt	nHDon	nHAcc	nrotb	Lipinski's rule alert index
1c	4.536	423.356	3	6	4	0
2c	3.914	418.946	2	7	5	0
3c	3.793	433.917	4	6	5	0
4c	4.488	423.365	3	6	4	0
5c	3.731	406.91	2	7	4	0

Table 7: Drug likeness analysis of antitubercular drugs

Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand
Isonicotinic acid hydrazide(INH)	-1.39	-1.45	-1.05	-2.33
Pyrazinamide	-1.97	-1.45	-1.71	-2.87
Streptomycin	-0.30	-0.16	-0.44	-0.68
p-amino salicylic acid	-1.21	-0.45	-1.06	-1.38

Table 8: Drug likeness analysis of synthesized compounds

Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand
1c	-0.16	-0.39	-0.58	-0.58
2c	-0.20	-0.44	-0.59	-0.56
3c	-0.29	-0.41	-0.67	-0.61
4c	-0.09	-0.46	-0.54	-0.52
5c	-0.09	-0.48	-0.51	-0.49

Characterisation

2,3-bis(4-chlorophenyl)-5-(morpholin-4-ylmethyl)-1,3-thiazolidin-4-one, 1c:- Yield 69%; M.P 168^{0}C; IR: 1686 (C=O), 1354 (C-N), 1193 (C-O-C),606 (C-S), 835 (C-Cl), 3067 (C-H Stretching hetero aromatic); ^{1}H NMR: 7.122-8.170 (m, Aromatic 8H), 6.199 (s, 1H in N-CH-S of thiazolidinone), 3.905-4.031(m, 4H in CH_2 and 4H in CH_2O of morpholine), 1.614 (d,2H in CH_2 of methylene bridge), 3.705(t, 1H in C_5-CH of thiazolidinone); MS: molecular ion peak is 423.5137 and base peak is 249.5412.

2-(4-methoxyphenyl)-3-(4-chlorophenyl)-5-(morpholin-4-ylmethyl)-1,3-thiazolidin-4-one, 2c:- Yield 70%; M.P 190^{0}C, IR: 1679 (C=O), 1329 (C-N), 1193 (C-O-C), 609 (C-S), 825 (C-Cl), 3061 (C-H Stretching hetero aromatic); ^{1}H NMR: 7.176-8.181 (m, Aromatic 8H), 6.175 (s, 1H in N-CH-S of thiazolidinone), 3.905-4.031(m, 4H in CH_2 and 4H in CH_2O of morpholine), 1.613 (d, 2H in CH_2 of methylene bridge), 3.765(t, 1H in C_5-CH of thiazolidinone).

2-(3-nitrophenyl)-3-(4-chlorophenyl)-5-(morpholin-4-ylmethyl)-1,3-thiazolidin-4-one, 3c:- Yield 67%67%; M.P 185^{0}C; IR: 1680 (C=O), 1337 (C-N), 1192 (C-O-C), 609 (C-S), 835 (C-Cl), 3138 (C-H Stretching hetero aromatic); ^{1}H NMR: 7.215-8.172 (m, Aromatic 8H), 6.129 (s, 1H in N-CH-S of thiazolidinone), 3.895-4.0510m, 4H in CH_2 and 4H in CH_2O of morpholine), 1.625 (d,2H in CH_2 of methylene bridge), 3.703 (t, 1H in C_5-CH of thiazolidinone).

2-(2-chlorophenyl)-3-(4-chlorophenyl)-5-(morpholin-4-ylmethyl)-1,3-thiazolidin-4-one, 4c:- Yield70%; M.P 201^{0}C; IR: 1687 (C=O), 1354 (C-N), 1217 (C-O-C), 613 (C-S), 835 (C-Cl), 3125 (C-H Stretching hetero aromatic); ^{1}H NMR: 7.122-8.170 (m, Aromatic 8H), 6.199 (s, 1H in N-CH-S of thiazolidinone), 3.912-4.031(m, 4H in CH_2 and 4H in CH_2O of morpholine), 1.607 (d, 2H in CH_2 of methylene bridge), 3.690 (t, 1H in C_5-CH of thiazolidinone).

2-(2-chlorophenyl)-3-(4-fluorophenyl)-5-(morpholin-4-ylmethyl)-1,3-thiazolidin-4-one, 5c:- Yield 67%; M.P 185^{0}C; IR: 1681 (C=O), 1354 (C-N), 613 (C-S), 851 (C-Cl), 3120 (C-H Stretching hetero aromatic); ^{1}H NMR: 7.125-8.172 (m, Aromatic 8H), 6.201 (s, 1H in N-CH-S of thiazolidinone), 3.923-4.132(m, 4H in CH_2 and 4H in CH_2O of morpholine), 1.562 (d,2H in CH_2 of methylene bridge), 3.705 (t, 1H in C_5-CH of thiazolidinone)

Antitubercular activity

The synthesised analogue 1c, 2c and 3cwas selected for antitubercular activity. *Mycobacterium tuberculosis* H37Rv maintained in Lowenstein Jensen mediumwas used as the test organism for antimycobacterial screening studies.The bacterial cultures were grown till mid-log phase in the Middle brook 7H9 broth for *Mycobacterium tuberculosis* H37Rv. Stock solutions of the test compounds were prepared at a concentration of 2 mg/ml. 50 µL of the mid-log phase culture was added to 150µL of the media taken in microtitre plates. From the stock solution of the compounds 1c, 2c and 3c was added to the wells to final concentration of 100, 250, 500 µg/ml. The control wells contained culture without any compound. All the tests were done in duplicates. The plates were then incubated at 37°C for 7 days. After incubation 20µL of Resazurin dye was added and change of colour, if any was noted. The control wells showed no change of colour from pink. Those compounds which prevented the change of colour of the dye from blue to pink were considered to be inhibitory. It was found that all the selected mannich base derivatives are active against *Mycobacterium tuberculosis* and from which 1c is more active than 2c and 3c. The MIC was defined as of the compounds were given in table 9

Table9: MIC values (µg/ml) of 1c, 2c and 3c

Sl no:	Compound	MIC value (µg/ml)
1	1c	25
2	2c	50
3	3c	50

CONCLUSION

This research was focused on the rational approach in design and development of Mannich derivatives of thiazolidinone for novel antitubercular agents.The present research work involved the preliminary *in silico* designing, synthesis, characterisation and biological screening.Mannich base derivative of thiazolidinone showed a better binding character than thiazolidinones.Out of the results obtained, it may be concluded that the analogues of Mannich base derivative of thiazolidinone, obtained from *p*-chloro substituted aniline and *p*-chloro substituted aldehyde (1c) shows good receptor binding with the selected target and good biological activity.From these results it can be concluded that electronegative substitution increases the activity.

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