

9223

**DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF
SOME NOVEL AZOLE AND SEMICARBAZONE
ANALOGUES**

Summary
**Synopsis of thesis submitted to
NIMS University
for the award of degree of**

DOCTOR OF PHILOSOPHY

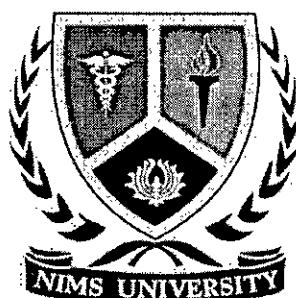
in

Pharmaceutical Science

By

**MD JAWED AHSAN
M. PHARM**

**UNDER THE SUPERVISION OF
Prof. (Dr.) JEYABALAN GOVINDASAMY**



**NIMS UNIVERSITY
Shobha Nagar, Jaipur 303 121
Rajasthan (India)
2012**

Plan of work

Step 1: Design and synthesis of semicarbazone and azole analogues

Step 2: Synthesis of the compounds

Step 3: Chemical characterization of synthesized compounds on the basis of:

IR spectroscopy

^1H NMR and ^{13}C NMR spectroscopy

Mass spectroscopy

Step 4: Biological evaluation of synthesized compounds

Anticonvulsant screening

Anticancer screening

Antimycobacterial screening

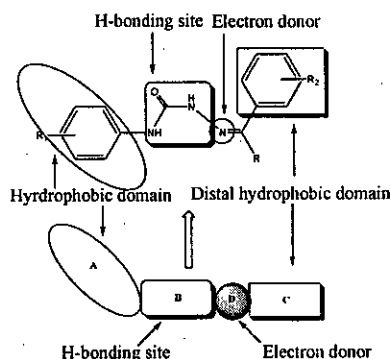
Antimicrobial screening

Molecular docking study

Step 1: Rationale based drug design

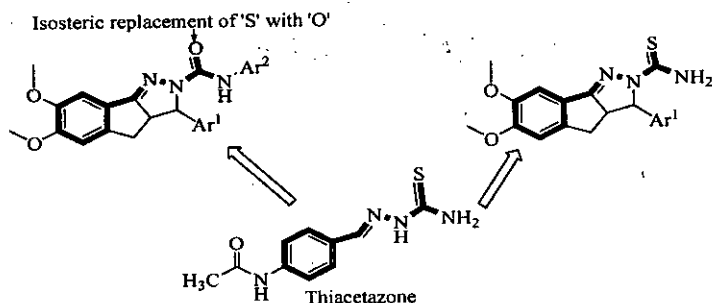
Design of anticonvulsant agents

The general pharmacophore for anticonvulsant agents include an aryl center or the lipophilic group (R), an electron donor group (D), a hydrogen bond acceptor (HA), and a hydrogen bond donor (HD).



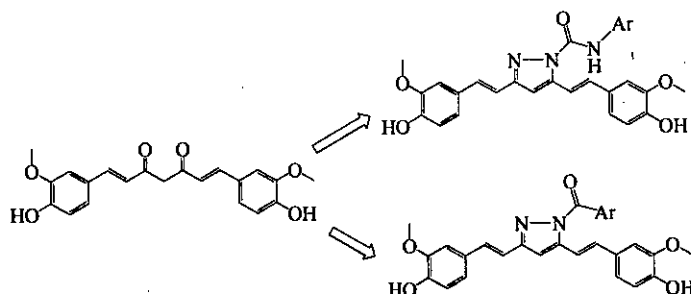
Design of antimycobacterial agents

All the pyrazoline derivatives have been designed based on the structure of existing antitubercular agent, thiacetazone in which 'S' was replaced by isosteric 'O'.



Design of anticancer agents

Curcumin, a major yellow pigment and active component of turmeric, has been shown to possess anti-inflammatory and anticancer activities. In some countries, curcumin was consumed in the diet up to 4 g per adult/day, which appears to lower the incidence rate of colorectal cancer. In a study curcumin showed autophagic and apoptotic death of K562 cell line (leukemia).



Molecular properties prediction of the compounds (By MolSoft 2007 & Molinspiration)

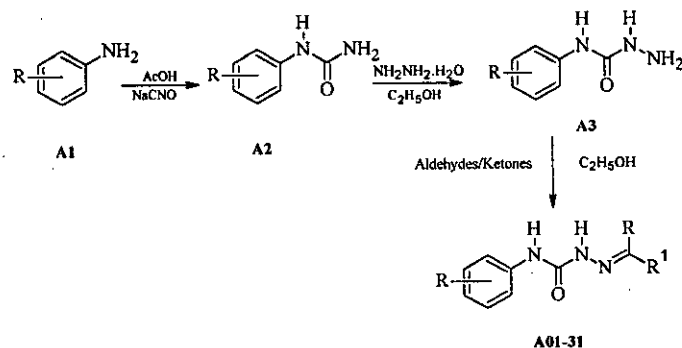
Lipophilicity

Solubility

Absorption, Polar surface area, and "Rule of five" properties

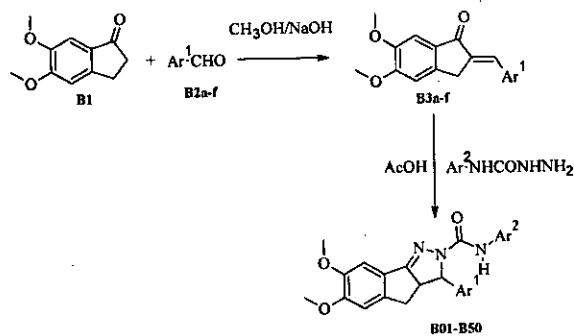
Step 2: Synthesis of compounds

Scheme 1



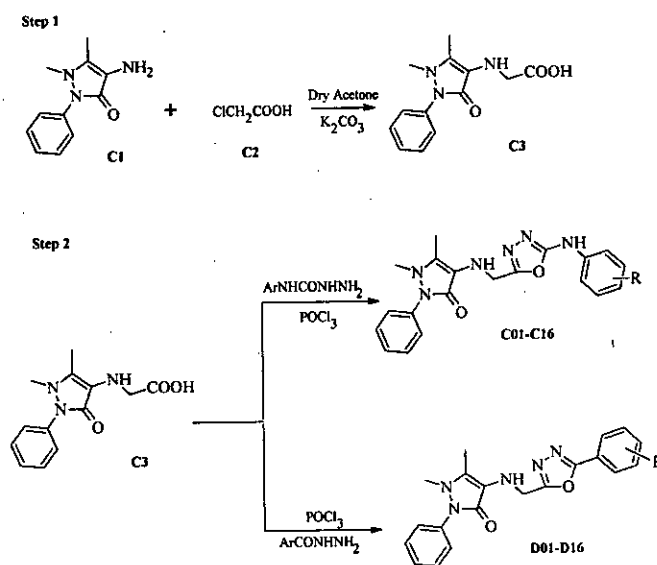
Scheme 1. Protocol for synthesis of semicarbazones

Scheme 2



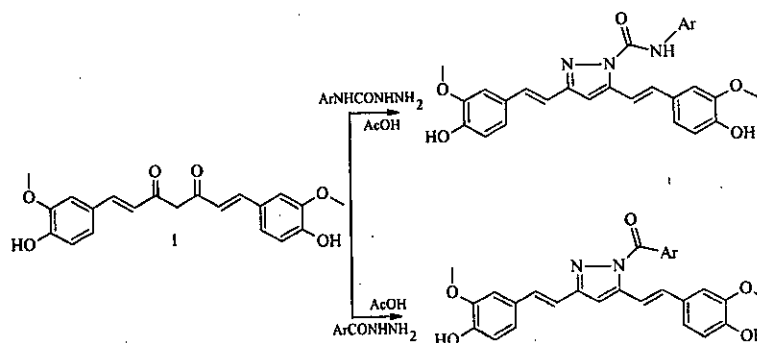
Scheme 2. Protocol for the synthesis of pyrazolines

Scheme 3



Scheme 3. Protocol for the synthesis of oxadiazoles

Scheme 4



Scheme 5. Protocol for the synthesis of pyrazole analogues.

Molecular docking study

Step 3: Characterization of synthesized compounds

IR Spectroscopy

¹H NMR and ¹³C NMR Spectroscopy

Mass Spectroscopy

Step 4: Biological evaluation of synthesized compounds

Anticonvulsant screening

Anticancer screening

Antimycobacterial screening

Antimicrobial screening

Results and Discussion

Semicarbazone analogues (A01-A31)

A series of 31 semicarbazone analogues were synthesized involving three steps in good yields. 16 compounds were evaluated for antimicrobial screening and 15 compounds were evaluated for anticonvulsant screening. In anticonvulsant screening we have observed that aryl semicarbazone with electronegative group substitution such as 2-chloro, 4-chloro, 2,4-dichloro and electron releasing group such as 2-hydroxy and 3-hydroxy in the distal hydrophobic aryl domain showed decreased activity in MES screening while electron releasing group such as 4-hydroxy, 4-methoxy and 3,4-dimethoxy group showed increased activity in MES screening. 4-Hydroxy group present on distal hydrophobic aryl domain showed maximum activity in 6 Hz psychomotor seizure test without any toxicity. Also semicarbazone analogue with cyclohexyl group showed significant activity. For antimicrobial screening we have observed that the electron releasing group such as -OH and electronegative group such as -NO₂ on phenyl ring at position 4 showed good antibacterial activity while electron releasing group such as -OCH₃ on phenyl ring at position 4 showed moderate antifungal activity. Further it was also observed that antimicrobial activity was more pronounced if imine H was present on the semicarbazones.

3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide analogues (B01-B50)

A series of 50 pyrazoline analogues were synthesized in good yields involving two steps. All the synthesized compounds were evaluated for their anticonvulsant, anticancer,

antimycobacterial and antimicrobial activity. It was observed that, the compound having 3-aryl substitution with 4-fluorophenyl, 3,4-dimethoxyphenyl, phenyl and 4-methoxyphenyl group showed good to moderate anticonvulsant activity, while electron withdrawing groups such as 2-chlorophenyl, 4-fluorophenyl and electron releasing group on *N*-aryl substitution enhanced anticancer activity. The anticancer activity was more pronounced if the electron releasing group, 2,6-dimethylphenyl was present on the *N*-aryl group. For antitubercular activity the 3-substituted compounds with electron withdrawing groups such as 4-fluorophenyl, 4-pyridyl produced more inhibitory and 2-chlorophenyl produced moderate inhibitory activity while the electron releasing groups such as 4-methoxyphenyl, 3,4-dimethoxyphenyl showed less inhibitory activity. The 4-fluorophenyl substitution on *N*-aryl group showed maximum inhibitory followed by 4-chlorophenyl and 2-chlorophenyl activity as compared to 4-bromophenyl 3-chloro-4-fluorophenyl, 2,4-dimethylphenyl and 2,6-dimethylphenyl substitution. In the pyrazoline analogues (B37-B48), C_3 aryl group influenced the antimicrobial activities. The 3-substituted compounds with electronegative group such as 4-fluorophenyl had more inhibitory activity than 2-chlorophenyl and 4-pyridinyl group against bacterial strains, while the electron releasing group 4-methoxyphenyl showed more activity than 3,4-dimethoxyphenyl against fungal strains.

1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3H-pyrazol-3-one analogues (C01-C16)

A series of sixteen 1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3H-pyrazol-3-one analogues (C01-C16) were synthesized and evaluated for antimycobacterial activity. The substitution on *N*-aryl group influenced the antitubercular activity. The electron withdrawing groups such as 4-fluorophenyl, 4-nitrophenyl, 4-sulphamyl produced more inhibitory and 4-chlorophenyl and 4-bromophenyl produced moderate inhibitory activity while the electron releasing groups such as 4-methylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,4-dimethoxyphenyl showed less inhibitory activity.

1,5-dimethyl-2-phenyl-4-[(5-aryl-1,3,4-oxadiazol-2-yl)methylamino]-1,2-dihydro-3H-pyrazol-3-one analogues (D01-D14)

A series of fourteen 1,5-dimethyl-2-phenyl-4-[(5-aryl-1,3,4-oxadiazol-2-yl)methylamino]-1,2-dihydro-3H-pyrazol-3-one analogues were synthesized and evaluated for antimycobacterial and antimicrobial activity. The *N*-aryl with electronegative group

substitution showed maximum activity, in which 4-pyridinyl group had maximum inhibition when compare to 2-chlorophenyl, 4-chlorophenyl and 4-aminophenyl group substitution. The electron releasing group such as 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl etc. showed less inhibition. The *N*-aryl with 2-hydroxyphenyl, 4-methylphenyl and 2-methylphenyl group substitution showed maximum antifungal activity than electronegative group substitution. When the biological activities were related with computational calculated drug-likeness score model it was found out that the compound, **D01** with maximum drug-likeness score model (0.95) showed maximum antibacterial activity. The compounds, **D09** and **D11** showed maximum antifungal activity have drug-likeness score model of 0.93 and 0.69 respectively.

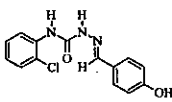
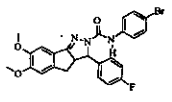
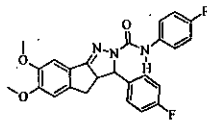
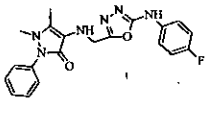
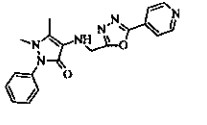
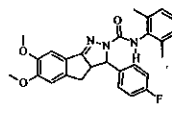
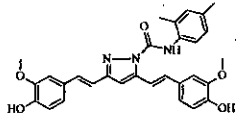
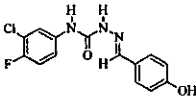
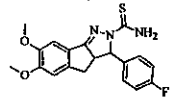
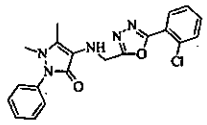
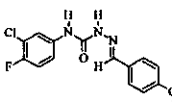
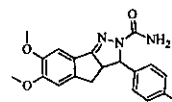
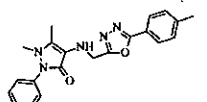
Pyrazole carboxamide/methanone (E01-E10)

A series of 10 novel prazole analogues were synthesized starting from curcumin and evaluated for their anticancer activity. The compound **E07** showed maximum activity on SK-MEL-5 (Colon Cancer), RXF 393 (Renal Cancer) and SK-OV-3 (Ovarian Cancer) with GP - 83.44, -65.55 and -63.58 respectively, with mean GP -19.19. Pyrazoline carboxamide is more active than pyrazoline methanone. No clear-cut SAR was developed with the screening data obtained.

Summary and conclusion

The main aim of the present study was to synthesize better biological and therapeutical agents. For this purpose, syntheses of four different series of compounds were undertaken which includes the synthesis of semicarbazone, pyrazoline carboxamide/carbothioamide oxadiazole and pyrazole carboxamide/methanone (curcumin analogues) derivatives. Most of the compounds followed the Lipinski "Rule of five". These compounds were successfully synthesized, having good yields. The compounds were characterized by their IR, ¹H NMR & ¹³C NMR and mass spectral data and further evaluated for different biological activities. The list of the most potent synthesized compounds is given in **Table 1**

Table 1: List of the most active compounds.

S. No.	Biological activity	Scheme 1	Scheme 2	Scheme 3	Scheme 4
1.	Anticonvulsant activity			-	-
2.	Antitubercular activity	-		 	-
3.	Anticancer activity	-		-	
4.	Antibacterial activity				-
5.	Antifungal activity				-

List of papers published (08)

1. Synthesis and anticonvulsant activity of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Ahsan, M. J.; Habibullah, K.; Samy, G. J.; Stables, J. P. *J. Enz. Inh. Med. Chem.* (March, 2012). Impact factor: 1.56
2. Discovery of novel antitubercular 1,5-dimethyl-2-phenyl-4-((5-(arylamino)-1,3,4-oxadiazol-2-yl)methyl)amino)-1,2-dihydro-3H-pyrazol-3-one analogues. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Nomani, M. S.; Krit. C. *Bioorg Med Chem Lett.* 2012, 22, 969-972. Impact factor: 2.65
3. Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Nomani, M. S.; Saraswat, P.; Gaur, R.; Singh, *Bioorg Med Chem Lett.* 2011, 21, 7246-7250. (Most Downloaded Paper in BMCL). Impact factor: 2.65
4. Synthesis and antimycobacterial evaluation of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide analogues. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Bakht, M. A.; Hassan, M. Z. *Eur. J. Med. Chem.* 2011, 46, 5694-5697. Impact factor: 3.13
5. Synthesis and antimicrobial activity of N¹-(3-Chloro-4-fluorophenyl)-N⁴-substituted semicarbazone derivatives. Ahsan, M. J.; Amir, M.; Samy, G. J.; Nomani, M. S.; Hasan, M. Z. *Arabian J. Chem.* (In press)
6. Discovery of novel antitubercular 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Ahsan, M. J.; Samy, G. J.; Soni, S.; Jain, N.; Kumar, L.; Sharma, L. K.; Yadav, H.; Saini, L.; Kalyansing, R. G.; Devenda, N. S.; Prasad, R.; Jain, C. B. *Bioorg Med Chem. Lett.* 2011, 21, 5259-5261. Impact factor: 2.65
7. Design, synthesis and antimycobacterial evaluation of novel 3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide analogues. Ahsan, M. J.; Samy, G. J.; Dutt, K. R.; Agrawal, U. K.; Yadav, B. S.; Vyas, S.; Kaur, R.; Yadav, G. *Bioorg Med Chem. Lett.* 2011, 21, 4451-4453. Impact factor: 2.65
8. Semicarbazone Analogues: A Review. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Nomani, M. S. *Der Pharmacia Sinica.* 2011, 6, 107-113.

List of papers accepted (02)

9. Molecular properties prediction and synthesis of novel pyrazoline carboxamide analogs as antitubercular agents. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Krit, C. R.; Soni, S. *Anti-infective Agents.* (Accepted Manuscript). Impact factor: 0.96
10. 1,3,4-Oxadiazole: A Biologically Active Scaffold. Khalilullah, H.; Khan, S.; Ahsan, M. J.; Ahmed, B. Mini-Reviews in Medicinal Chemistry. (Accepted). Impact factor: 2.64

Research articles communicated (03)

1. Synthesis and in vitro antitumor activity of novel curcumin analogues: Search for novel anticancer agents Part I. *Eur. J. Med. Chem.*
2. Synthesis of semicarbazone derivatives with anticonvulsant activity. Ahsan, M. J.; Samy, G. J.; Stables, J. P. *Medicinal Chemistry Research.*
3. Synthesis and anticancer activity of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Ahsan, M. J.; Habibullah, K.; Samy, G. J. *Letters in Drug Design & Development.*

SHORT COMMUNICATION

Synthesis and anticonvulsant activity of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues

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Abstract

A series of fourteen 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues were synthesized and evaluated for anticonvulsant activity according to the Antiepileptic Drug Development Programme (ADD) protocol. Some of the synthesized compounds showed significant activity in minimal clonic seizure model (6 Hz psychomotor seizure test). 3-(4-Fluorophenyl)-N-(4-bromophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide (**4c**) was found to be the most active compound of the series showing 75% (3/4, 0.25-2.0 h) and 50% (2/4, 4.0 h) protection against minimal clonic seizure at 100 mg/kg without any toxicity. 3-(Pyridin-4-yl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide (**4f**) showed protection in maximal electroshock (MES) seizure and subcutaneous metrazol (scMET) seizure at 300 mg/kg.

Keywords: Pyrazolines, 6 Hz psychomotor seizure test, maximal electroshock seizure test, subcutaneous metrazole seizure test, neurotoxicity

Introduction

Epilepsy is a common neurological disorder, affecting 1-2% world's population¹. In recent years, several new drugs such as oxcarbazepine, lamotrigine, topiramate, gabapentine and vigabatrin have been added as therapeutic agents for the treatment of epilepsy. However, there is a significant group of patients (up to 30%) who are resistant to the available antiepileptic drugs (AEDs). Also most of the AEDs have dose related toxicity and idiosyncratic side effects^{2,3}. Hence, there is an urgent need to develop new AEDs that lead to substantial benefit to the patient population in the form of increase seizure control, increase tolerability, and better safety and pharmacokinetic properties. CPP 115 and vigabatrin were found to be effective in 6 Hz minimal clonic seizure test in mice at both 32 mA and 44 mA stimuli (3 s).⁴

Pyrazoline is an important class of heterocyclic compounds, and were found to have various biological

activities including antiamebic, anticonvulsant, anti-cancer, antimicrobial, anti-inflammatory, antiviral, anti-arrhythmic, antidepressant, antidiabetic, antitubercular and more⁵⁻¹³. Hence, it is worth to synthesize such compounds. In the present investigation, we have focussed on the anticonvulsant screening of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Earlier, we have reported the antitubercular activity of pyrazoline analogues¹⁴⁻¹⁶. The proposed pharmacophore model contains three binding site for interaction with a macromolecular complex *in vivo* (Figure 1).

Results and discussion

Chemistry

The 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues (**4a-n**) described in this study are shown in Table 1 and the reaction sequence for the synthesis is summarized in Scheme 1. In the

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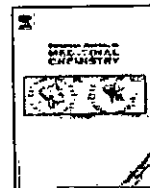
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Short communication

Synthesis and antimycobacterial evaluation of 3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide analogues

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ABSTRACT

In the present investigation, a series of 3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide analogues were synthesized and were evaluated for antitubercular activity by two fold serial dilution technique. All the newly synthesized compounds showed low to good inhibitory activities against *Mycobacterium tuberculosis* H₃₇Rv and multi-drug resistant *M. tuberculosis* (MDR-TB). 3-(4-fluorophenyl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide (4c) was found to be the most promising compound active against *M. tuberculosis*, H₃₇Rv and MDR-TB with minimum inhibitory concentrations 0.83 μM and 3.32 μM respectively.

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1. Introduction

Tuberculosis or TB is a dreadful life threatening disease caused by the bacteria *Mycobacterium tuberculosis* and to a lesser degree by *Mycobacterium Bovis* and *Mycobacterium Africana*. There are one-third of world's population which are currently infected with TB, with about 9.4 million worldwide and 1.6–2.4 million cases in India [1,2]. An estimated 1.7 million people died from TB in 2009 as per WHO survey. There are estimated 1.3 million multi-drug/ extensively drug resistant tuberculosis (M/XDR-TB) cases which will need to be treated between 2010 and 2015 [2]. The development of multi-drug resistant tuberculosis (MDR-TB; resistant to isoniazid and rifampicin) and extensively drug resistant tuberculosis (XDR-TB; resistant to quinolones and also to any one of kanamycin, capreomycin or amikacin) are alarming for the discovery of new drugs to reduce the potential hazards caused by TB. The current strategies to cure the diseases are very complicated as they take several months of chemotherapy to eliminate

persistent bacteria. Also the treatment of TB with the frontline drugs is associated with severe side effects including hepatotoxicity, ocular toxicity, thrombocytopenia, neuropathy, rashes, fever, drug induced hepatitis. Nowadays there is an apparent need for fast acting drugs with less toxicity, which are capable to eliminate infection within a few weeks.

The azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and showed promising activity against resistant TB by inhibiting the biosynthesis of lipids [3,4]. Pyrazoline is an important class of heterocyclic compounds, and were found to have various biological activities including antiamebic, anticonvulsant, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, anticancer, antidiabetic, and antitubercular, etc [5–13]. Earlier we have reported the antimycobacterial activity of diketones and pyrazolines [14,15]. The present investigation is the continuation of the previous work. In this investigation we have focussed on the design and synthesis of some novel 3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide analogues based on the structure of the known antitubercular agent, thiacetazone (Fig. 1) in which the "S" atom of the thiacetazone was replaced with isosteric "O" atom in the title compounds (4a–r). All the synthesized compounds were evaluated for their anti tubercular activity.

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Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents

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Lipinski 'Rule of five'

ABSTRACT

In the present investigation, a series of 1,5-dimethyl-2-phenyl-4-((5-aryl-1,3,4-oxadiazol-2-yl)methylamino)-1,2-dihydro-3H-pyrazol-3-one were subjected to molecular properties prediction, drug-likeness by Molinspiration (Molinspiration, 2008) and MolSoft (MolSoft, 2007) software, lipophilicity and solubility parameters using ALOGPS 2.1 program. The compounds followed the Lipinski 'Rule of five' were synthesized for antimicrobial and antitubercular screening as oral bioavailable drugs/leads. Maximum drug-likeness model score (0.95) was found for compound, 4a. All the synthesized compounds were characterized by IR, NMR and mass spectral analysis followed by antimicrobial and antimycobacterial screening. Among the title compounds, compound 4d showed pronounced activity against *Mycobacterium tuberculosis* H₃₇Rv and isoniazid resistant *M. tuberculosis* (INHR-TB) with minimum inhibitory concentrations (MICs) 0.78 μM and 1.52 μM, respectively. The compound, 4a showed maximum activity against all bacterial strains with MIC 4–8 μg/mL comparable to standard drug ciprofloxacin, while the compounds, 4e and 4k showed maximum antifungal activity with MIC 8–16 μg/mL less active than standard drug fluconazole.

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The pathogenic agent of tuberculosis (TB), *Mycobacterium tuberculosis* (MTB) is responsible for death of 2–3 million people annually.¹ There are estimated 1.3 million multi/extensively drug resistant TB (M/XDR-TB) cases will need to be treated between 2010 and 2015.² Antibacterial resistance is a cause of increased mortality.³ Fungal infections like Candidiasis, Cryptococcosis and Aspergillosis are more common in immuno-compromised patients.⁴ Life threatening infectious disease caused by multi-drug-resistant pathogenic bacteria (Gram-positive/Gram-negative) increased an alarming level around the world. Owing to this increased microbial resistance, new classes of antimicrobial agents with novel mechanisms are today's need to fight against the multidrug-resistant infections.

Oxadiazoles are important classes of compounds which have long attracted attention, owing to their remarkable biological and pharmacological properties, such as antitubercular, antibacterial, antiviral, anti-inflammatory, antifungal and insecticidal activities.^{5–13} Also theazole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and show promising activity against resistant TB by inhibiting the

biosynthesis of lipids.^{14,15} Most of the antitubercular drugs (isoniazid, pyrazinamide, etc.) are inhibitors of mycobacterial cell wall synthesis by inhibiting fatty acid synthetase. In the present investigation it has been tried to design and synthesized such novel compounds which include both the advantage of pyrazole and oxadiazole nucleus in the single molecule. All the title compounds (4a–4n) were subjected to molecular properties prediction by Molinspiration and MolSoft (MolSoft, 2007) software in order to filter the drugs for synthesis and biological screening and to reduce enormous wastage of expensive chemicals and precious time. Earlier we have reported the antimycobacterial activity of diketones and pyrazoline.^{16,17}

A good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. The computed logP values (*P* is the partition coefficient of the molecule in the water/octanol system) are shown in Table 1. The ALOGPS method is part of the ALOGPS 2.1 program used to predict lipophilicity and aqueous solubility of compounds. The lipophilicity calculations within this program are based on the associative neural network approach and the efficient partition algorithm. The Log Kow (Kow-WIN) program estimates the log octanol/water partition coefficient (logP) of organic chemicals and drugs using an atom/fragment contribution method developed at Syracuse Research Corporation. The XLOGP2 is an atom additive method applying corrections. Computed partition coefficients for drugs studied varied

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Discovery of novel antitubercular 1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3H-pyrazol-3-one analogues

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ABSTRACT

In search of potential therapeutics for tuberculosis, we describe herewith the synthesis, characterization and antimycobacterial activity of 1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3H-pyrazol-3-one analogues. Among the synthesized compounds, 4-([5-([4-fluorophenylamino]-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (4a) was found to be the most promising compound active against *Mycobacterium tuberculosis* H₃₇Rv and isoniazid resistant *M. tuberculosis* with minimum inhibitory concentrations, 0.78 and 3.12 µg/mL, respectively, free from any cytotoxicity (>62.5 µg/mL).

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The pathogenic agent of tuberculosis (TB), *Mycobacterium tuberculosis* (MTB) is responsible for death of 2–3 million people annually and for global financial toll of ~12 billion dollar each year.¹ A recent threat to TB is the development of drug resistant strains. The drug resistant TB is classified into two categories such as multidrug resistant tuberculosis (MDR-TB) that is resistant to isoniazid and rifampicin and extensively drug resistant tuberculosis (XDR-TB) that is resistant either to quinolones or to any one of kanamycin, capreomycin or amikacin. There are estimated 1.3 million multi/extensively drug resistant TB (M/XDR-TB) cases will need to be treated between 2010 and 2015.² In spite of major advances that have been made in the drug discovery process, no new drugs have been introduced since the discovery of rifampin.³ As a result, there is an urgent need to develop novel, faster acting chemotherapeutic agents with lower toxicity. Consequently, today, it is clear that vigorous and widespread research on drug design will be necessary to make new advances.

Oxadiazoles are important classes of compounds which have long attracted attention, owing to their remarkable biological and pharmacological properties, such as antitubercular, antibacterial, antiviral, anti-inflammatory, antifungal and insecticidal activities.^{4–12} The azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion

and show promising activity against resistant TB by inhibiting the biosynthesis of lipids.^{13,14} Most of the antitubercular drugs (isoniazid, pyrazinamid, etc.) are inhibitors of mycobacterial cell wall synthesis by inhibiting fatty acid synthetase. In the present investigation it has been tried to design and synthesized such novel compounds which include the advantage of both pyrazole and oxadiazole nucleus in the single molecule. All the title compounds (4a–p) were subjected to molecular properties prediction by Molinspiration and MolSoft (MolSoft, 2007) software in order to filter the drugs for synthesis and biological screening and to reduce enormous wastage of expensive chemicals and precious time. Earlier we have reported the antimycobacterial activity of diketones and pyrazoline.^{15–17}

A computational study for prediction of ADME properties of all molecules was performed and is presented in Table 1. Topological polar surface area (TPSA), that is, surface belonging to polar atoms, is a descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs in the intestines and blood–brain barrier crossing.¹⁸ TPSA and volume are inversely proportional to %ABS. TPSA was used to calculate the percentage of absorption (%ABS) according to the equation: %ABS = 109 ± 0.345 × TPSA, as reported.¹⁹ From all these parameters, it can be observed that all the title compounds exhibited a great %ABS ranging from 66.57% to 84.30%. Good intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and

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Design, synthesis and antimycobacterial evaluation of novel 3-substituted-*N*-aryl-6,7-dimethoxy-3*a*,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogues

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ABSTRACT

In the present investigation, a series of 3-substituted-*N*-aryl-6,7-dimethoxy-3*a*,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogues were synthesized and were evaluated for antitubercular activity by two fold serial dilution technique. All the newly synthesized compounds showed moderate to high inhibitory activities against *Mycobacterium tuberculosis* H₃₇Rv and INH resistant *M. tuberculosis*. The compound *N*,3-bis(4-fluorophenyl)-6,7-dimethoxy-3*a*,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide (4c) was found to be the most promising compound active against *M. tuberculosis* H₃₇Rv and isoniazid resistant *M. tuberculosis* with minimum inhibitory concentration 0.78 μM.

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Now a day's tuberculosis, TB is a major public health problem and over one third of the world population is infected with this dreadful disease caused by *Mycobacterium tuberculosis*.¹ The effective treatment of TB becomes more complicated due to the resistance developed by bacteria, *M. tuberculosis*. More than 1.7 million people died and 9.4 million new cases worldwide in 2009 are reported as per WHO survey. It has been estimated that up to 50 million people are infected with drug-resistant forms of TB. There are estimated 1.3 million multi/extensively drug resistant TB (M/XDR-TB) cases will need to be treated between 2010 and 2015.² The treatment of TB with frontline drugs is associated with severe side effects including hepatotoxicity, thrombocytopenia, itching, rashes, fever, drug induced hepatitis, etc.^{3,4} A recent threat to TB is the development of drug resistant strains. The drug resistant TB is classified into two categories such as multi drug resistant tuberculosis (MDR-TB) that is resistant to isoniazid and rifampicin and extensively drug resistant tuberculosis (XDR-TB) that is resistant either to quinolones or to any one of kanamycin, capreomycin, or amikacin.

In an effort to discover new and effective therapeutic agents, we recently reported the in vitro antimycobacterial activity of novel diketones.⁵ The azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and show promising activity against resistant TB by inhibiting the

biosynthesis of lipids.^{6,7} Most of the antitubercular drugs (isoniazid, pyrazinamid, etc) are inhibitors of mycobacterial cell wall synthesis by inhibiting fatty acid synthetase. Pyrazoline is an important class of heterocyclic compounds, and were found to have various biological activities including antiamebic, anticonvulsant, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, anticancerous, antidiabetic, antitubercular, etc.^{8–17} Hence it is worth to synthesize such compounds. In the current work eighteen novel 3-substituted-*N*-aryl-6,7-dimethoxy-3*a*,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogues were designed and synthesized based on the structure of the known antitubercular agent, thiacetazone (Fig. 1). All the synthesized compounds were evaluated for their anti-tubercular activities.

The 3-substituted-*N*-aryl-6,7-dimethoxy-3*a*,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogues (4a–r) described in this study are shown in Table 1 and the reaction sequence for the synthesis is summarised in Scheme 1. In the initial step 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (0.1 mol) and appropriate aromatic aldehydes (0.1 mol) in diluted methanolic sodium hydroxide solution stirred at room temperature giving the (2*E*)-2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one derivatives (3a–f). In the subsequent step 2-substituted-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one derivatives treated with appropriate semicarbazides furnished the titled compounds (4a–r). The substituted phenyl semicarbazides were synthesized as per the reported method.^{18,19} The yields of the titled compounds were ranging from 62% to 88% after recrystallization

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Discovery of novel antitubercular 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues

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ABSTRACT

In the present investigation, a series of 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues were synthesized and were evaluated for antitubercular activity by two fold serial dilution technique. All the newly synthesized compounds showed low to high inhibitory activities against *Mycobacterium tuberculosis* H₃₇Rv and INH resistant *M. tuberculosis*. The compound 3-(4-fluorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carbothioamide (**4o**) was found to be the most promising compound active against *M. tuberculosis* H₃₇Rv and isoniazid resistant *M. tuberculosis* with minimum inhibitory concentration 3.12 μM and 6.25 μM, respectively.

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Mycobacterium tuberculosis infections are responsible for one in four preventable adult deaths in developing countries. The current strategies for the treatment of tuberculosis (TB) are very complicated as it takes several months of chemotherapy to eliminate persistent bacteria. Also widespread non-compliance has contributed to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.^{1,2} There are estimated 1.3 million multi/extensively drug resistant TB (M/XDR-TB) cases will need to be treated between 2010 and 2015.³ Hence there is a need for fast acting drugs that are capable of eliminating an infection just in a few weeks.

In an effort to discover new and effective therapeutic agents, we recently reported the in vitro antimycobacterial activity of novel diketones and pyrazoline derivatives.^{4,5} Pyrazoline is a class of heterocyclic compounds possess significant pharmacological activities including anticancer, antitubercular, anticonvulsant, antiemetic, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, antidiabetic, etc.^{6–15} In the current work we have synthesized eighteen 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues based on the structure of the known antitubercular agent, thiacetazone (Fig 1). All the synthesized compounds were evaluated for their anti-tubercular activities.

The 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues (**4a–r**) described in this study are shown in Table 1 and the reaction sequence for the synthesis is summa-

rised in Scheme 1. In the initial step 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (0.1 mol) and appropriate aromatic aldehydes (0.1 mol) in diluted methanolic sodium hydroxide solution stirred at room temperature giving the (2E)-2-substituted-5,6-dimethoxy-2,3-dihydro-1H-indene-1-one derivatives (**3a–f**). In the subsequent step 2-substituted-5,6-dimethoxy-2,3-dihydro-1H-indene-1-one derivatives treated with appropriate semicarbazides furnished the titled compounds (**4a–r**). The substituted phenyl semicarbazides were synthesized as per the reported method.^{16,17} The yields of the titled compounds were ranging from 66% to 87% after recrystallization with absolute ethanol. The purity of the compounds was checked by TLC using eluant benzene–acetone (9:1) and elemental analyses. Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on TLC plates (silica gel G) using eluants benzene–acetone (9:1), the spots were located under iodine vapours or UV light. The entire chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). IR spectra were obtained on a Shimadzu 8201 PC, FT-IR spectrometer (KBr pellets). ¹H NMR spectra were recorded on a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO. Mass spectra were recorded on a Bruker Esquire LCMS using ESI and elemental analyses were performed on Perkin–Elmer 2400 Elemental Analyzer. Both the analytical and spectral data (IR, ¹H NMR) of all the synthesized compounds were in full accordance with the proposed structures. In general, the IR spectra of the compounds afforded pyrazoline C=N stretching at 1501–1576 cm⁻¹, C–H deformation at 1362–1464 cm⁻¹, C₂–N₁ stretching at 1069–1189 cm⁻¹, and carbamoyl

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Molecular Properties Prediction and Synthesis of Novel Pyrazoline Carboxamide Analogs as Antitubercular Agents

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Abstract: In the present investigation, a series of 3-substituted-*N*-aryl-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogs were synthesized based on the structure of known antitubercular drug thiacetazone and were evaluated for antitubercular activity by two fold serial dilution technique. A computational study was carried out for prediction of pharmacokinetic properties and none of the compounds violated Lipinski "Rule of Five". The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. All the newly synthesized compounds showed low to good activity inhibitory activities against *Mycobacterium tuberculosis* H₃₇Rv (MTB) and isoniazid resistant *M. tuberculosis* (INHR-MTB). 3-(4-fluoromethyl)-*N*-(2-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide (**4e**) was found to be the most promising compound active against *M. tuberculosis* H₃₇Rv and isoniazid resistant *M. tuberculosis* (INHR-MTB) with minimum inhibitory concentration 0.83 and 3.35 μ M respectively.

Keywords: Pyrazolines, claisen schmidt condensation, antitubercular agents, molecular properties prediction, lipophilicity; lipinski "rule of five".

INTRODUCTION

Mycobacterium tuberculosis (MTB) is responsible for life threatening disease, tuberculosis (TB). An estimated 1.7 million people died from TB in 2009 as per WHO survey [1]. The recent strategies for the treatment of TB are complicated; take several months of chemotherapy to eliminate persistent bacteria. In addition, prevalent non compliance contributed to the emergence of multi-drug resistant (MDR) and extensive drug resistant (XRD) TB [2, 3]. There are estimated 1.3 million multi-drug/extensively drug resistant TB (M/XDR-TB) cases will need to be treated between 2010 and 2015 [1]. Also the drugs used to cure TB show potential side effects including thrombocytopenia, neuropathy, rashes, fever, drug induced hepatitis. Therefore search for novel compounds with novel mechanism of actions is today's need to eradicate or combat against MTB.

The azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and showed promising activity against resistant TB by inhibiting the biosynthesis of lipids [4, 5]. Most of the antitubercular drugs (isoniazid, pyrazinamide, etc) are inhibitors of mycobacterial cell wall synthesis by inhibiting fatty acid synthetase. Pyrazoline is an important class of heterocyclic compounds, and were found to have various biological

activities including antiamebic, anticonvulsant, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, anticancer, antidiabetic, antitubercular, etc [6-14]. In the current work fourteen novel 3-substituted-*N*-aryl-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogs were designed and synthesized based on the structure of the known antitubercular agent, thiacetazone (Fig (1)). We have also reported the antimycobacterial activity of diketones and pyrazolines [15-17].

MOLECULAR PROPERTIES PREDICTION

Molecular properties including hydrophobicity, molecular size, flexibility and presence of various pharmacophoric features influence the behavior of molecules in a living organism, including bioavailability. The computational sensitivity analysis and structural analysis have been used to study the candidate drug because good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. Thus in order to achieve good oral drugs we have subjected a series of 3-substituted-*N*-aryl-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogs (**4a-n**) for the prediction of lipophilicity, solubility and Lipinski "Rule of Five" and other properties for filtering compounds for subsequent antimicrobial screening.

LIPOPHILICITY AND SOLUBILITY

The computed log *P* values (*P* is the partition coefficient of the molecule in the water-octanol system) are shown in Table 1. The ALOGPS method is part of the ALOGPS 2.1 program used to predict lipophilicity and aqueous solubility

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ORIGINAL ARTICLE

Synthesis and antimicrobial activity of N^1 -(3-chloro-4-fluorophenyl)- N^4 -substituted semicarbazone derivatives

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KEYWORDS

Semicarbazones;
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Lipinski-Rule of Five

Abstract A series of 16 N^1 -(3-chloro-4-fluorophenyl)- N^4 -substituted semicarbazone derivatives were synthesized and subjected to computational pharmacokinetic studies to predict molecular properties. All the title compounds (4a–p) followed the Lipinski "Rule of Five". The synthesized compounds were characterized by elemental analyses and spectral data and the compounds (4a–p) were evaluated for antimicrobial activities. Among them the compound 2-(4-hydroxybenzylidene)- N -(3-chloro-4-fluorophenyl)hydrazinecarboxamide (4f) was found to be the most active compound that showed good antibacterial inhibition while the compound 2-(4-methoxybenzylidene)- N -(3-chloro-4-fluorophenyl)hydrazinecarboxamide (4g) was moderately active against fungal strains. We have noticed that the compounds, (4f, 4k and 4d) bearing OH and NO₂ groups on the phenyl ring at position 4 exhibited good antibacterial activity while compound (4g) bearing OCH₃ on the phenyl ring at position 4 exhibited moderate antifungal activity.

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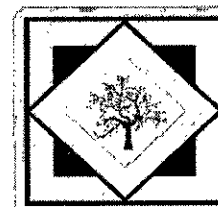
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1. Introduction

A wide variety of antibiotics have been developed to combat against bacterial infections. After years of extensive overuse or misuse of antibiotics, bacteria are becoming antibiotic resistant resulting in growing threat to human health around the world. Antibacterial resistance is a cause of increased mortality (Mohamed et al., 2004). Fungal infections like Candidiasis, Cryptococcosis and Aspergillosis are more common in immunocompromised patients (Spratt, 1994). Life threatening infectious disease caused by multidrug-resistant Gram-positive and -negative pathogenic bacteria increased to an alarming level around the world. Owing to this increased microbial resis-



Semicarbazone analogues: A mini review

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ABSTRACT

Semicarbazones are compounds which are synthesized by the condensation of semicarbazide and aldehydes/ketones. The literature survey revealed that semicarbazones had been emerged as a compound with broad range of activities including anticonvulsant, antitubercular, anticancer and antimicrobial activity. Dimmock *et al.*, reported an extensive series of semicarbazones and reported 4-(4-fluorophenoxy) benzaldehyde semicarbazone as potential anticonvulsant. Preclinical evaluations have been completed and an IND has been filed for this potential compound. In the present study we have focused on the biological activity of semicarbazone analogues.

Keywords: Semicarbazone; Biological activity.

INTRODUCTION

In organic chemistry, semicarbazone is a derivative of semicarbazide which contains an additional ketone functional group. Its structure is given in the Fig. 1.

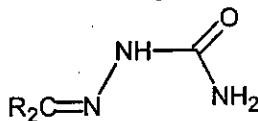


Fig. 1. General Structure of semicarbazone analogues

Dimmock *et al.*, reported an extensive series of semicarbazone [1]. The lead compound among the (aryloxy)aryl semicarbazones was 4-(4-fluorophenoxy) benzaldehyde semicarbazone. Preclinical evaluations have been completed and an (IND) has been filed. The compound is a potent sodium channel blocker (Na⁺) and it is planned to be developed for the treatment of neuropathic pain. Phase I Clinical trials are scheduled in the near future (Fig. 3)