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Relation between Minimum Inhibitory Concentration and Chemical Structure of Heterocyclic Organic Compounds against Mycobacterium

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Abstract

This study aimed to study different derivatives of heterocyclic organic compounds and related antibacterial activities of these compounds which were evaluated against Mycobacterium tuberculosis. This review represents an overview of minimum inhibitory concentration (MIC) of these compounds to find a meaningful relationship between chemical structure of the compounds and the related MIC values. The chemical structures of these compounds have been classified into 11 groups. Among the 100 evaluated compounds in this study, a non-fused heterocyclic compound and fused heterocyclic compound were found to be the most active compound with MIC of 0.06 and 0.003 µg/ml against *Mycobacterium*, respectively. Some chemical properties impact antibacterial activities of these compounds, which depend on the delocalized electrons in the structure of the compounds and the presence of electronegative element such as nitrogen or oxygen in the rings of the compounds.

Keywords: Chemical structure; Minimum inhibitory concentration (MIC); *Mycobacterium*; Delocalized electrons; Heterocyclic organic compounds.

Introduction

People with active tuberculosis have to take several medications for months. Based on the World Health Organization (WHO) estimation, two millions of people die from tuberculosis (TB) each year. During the treatment of TB, the patients receive chemotherapy for 6 months to cure and also promote side effects [1,2]. Isoniazid, streptomycin, rifampin, and pyrazinamide have been used as antituberculosis drugs [3]. On the other hand, some tuberculosis patients do not respond to medication at the beginning of the treatment. If the right drugs chose, the treatment time decrease and subsequently the drug-resistant strains moderate or even eliminate. The clinical trials data for isoniazid and rifampin showed that these drugs were effective and also showed that tolerability for a three month period was sufficient to prevent TB [4]. The results of clinical trials for streptomycin and pyrazinamide showed same results [5].

One of the most important mortality in the developing countries such as in Bangladesh and Africa is TB. Although it is found that mortality decrease by chemotherapy which is insufficient especially in the developing countries [6]. Of course, WHO has estimated that 7% of death in the developing countries occur in adults by single source [7]. In 2007, about 9.2 million people died and also Bangladesh was ranked as one of the highest-rated TB countries [8,9]. Therefore, it is essential to synthesize new chemical compounds with improved effective properties to treat TB. This study aimed to find a significant relationship between the minimum inhibitory concentration (MIC) values and the related chemical structures of heterocyclic organic compounds against *Mycobacterium tuberculosis*. The MIC value is defined as the lowest drug concentration with no visible growth after incubation.

Organic compounds

Table1: Classification of efficiencies based on the related MIC values.

Mean MIC value (µg/ml)	Efficiency
<1	Very potent
01-Oct	Potent
10-100	Medium
>100	Weak

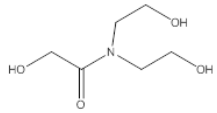
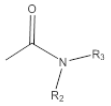
To compare the potential effect of chemical structures on growth of *Mycobacterium tuberculosis*, four types including of very potent, potent, medium and weak in terms of mean MIC values have been shown in Table 1 [10]. The organic compounds could be classified based on their scaffolds into 11 groups mentioned in Table 2. Some of the significant moieties of the mentioned

classifications of organic compounds and related MIC values have been summarized in Table 3. Subsequently the chemical compounds and related MIC values will help the researchers to anticipate the MIC range before experiment.

Table 2: Classification of organic compounds into 11 main groups and their subgroups.

Main group	Subgroup	Number of subgroups	Groups
Chain compounds	-	-	1
Compounds with one 5-membered ring	-	-	2
Compounds with one 6-membered ring	-	-	3
T Compounds with two non-fused rings	Compounds with 5 and 6-membered non-fused rings	2	4
	Compounds with two 6-membered non-fused rings		
Compounds with two fused rings	Compounds with two 5-membered fused rings	3	5
	Compounds with 5 and 6-membered fused rings		
	Compounds with two 6-membered fused rings		
Compounds with three non-fused rings	Compounds with three 5 and 6-membered non-fused rings	2	6
	Compounds with three 6-membered non-fused rings		
Compounds with three fused rings	Compounds with two 5 and 6-membered fused and one 6-membered non-fused rings	2	7
	Compounds with two 6-membered fused and one 6-membered non-fused rings		
Compounds with four rings	Compounds with four non-fused rings	5	8
	Compounds with two non-fused and two fused rings		
	Compounds with two set of two fused rings		
	Compounds with three fused and one non-fused rings		
	Compounds with four fused rings		
Compounds with five rings	Compounds with four fused and one non-fused rings	2	9
	Compounds with three fused and one non-fused rings		
Compounds with six rings	-	-	10
Compounds with seven rings	-	-	11

Table 3: Some important moieties in the chemical structure of 11 groups of heterocyclic organic compounds for classification of these compounds, related MIC values and example of the chemical compounds.

Class	Significant moiety	Example	Typical MIC (µg/ml)	Reference
Substituted acetamide (Chain Compounds) 	-CONRR' 	1	200	[11]

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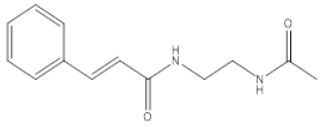
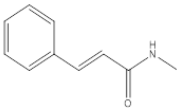
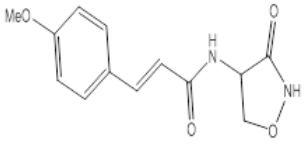
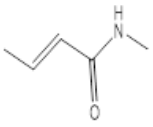
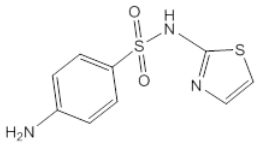
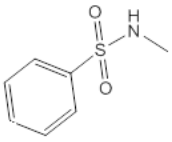
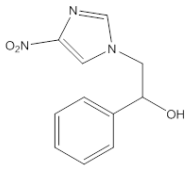
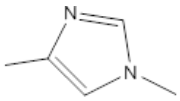
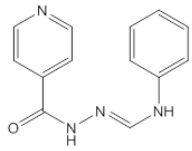
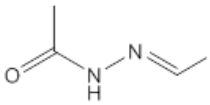
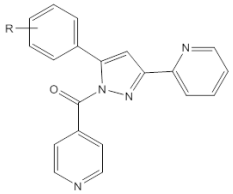
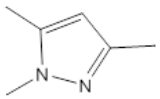
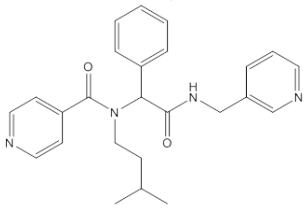
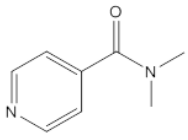
Substituted cinnamide (one 6-membered ring) 	$C_6H_5CH=CHCONHR$ 	5	208	[17]
Substituted acrylamide (two non-fused rings) 	CHR=CHCONHR' 	6	42	[17]
Substituted Benzenesulfonamide (two non-fused rings) 	$C_6H_5SO_2NHR$ 	8	32	[23]
Substituted Imidazole (two non-fused rings) 	$C_3H_2N_2$-RR' 	9	42	[29]
Substituted Hydrazonamide (two non-fused 6-membered rings) 	R'COHNN=CHR 	11	20	[32]
Substituted Pyrazole (four non-fused 5 and 6-membered rings) 	RR'R''-C_3HN_2 	17	0.06	[49]
Substituted Isonicotinamide (three non-fused 6- membered rings) 	$C_5H_4NCONRR'$ 	16	7.6	[43]

The Chain Compounds

Some of chemical structures of the organic compounds illustrate in Figure 1 so that for the 1 containing amide group and OH group, a weak MIC value has been reported [11,12]. However, secondary amine group (R_2-NH) in the structure should be shown a better MIC value compared to the other chemical compounds of this group [13]. Additionally, in this group with more OH groups than amide group, should make the MIC value to be increased to provide weaker antibacterial effects compared to the other chemical compounds of this group. By substitution of a tertiary amine group (R3-N), a better MIC value has been shown

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compared with the substitution of the OH group. In this group, chain structures present a weak MIC value [14]. The mean MIC value for 28 samples of this group has been obtained 200.50 µg/ml in the weak MIC range.

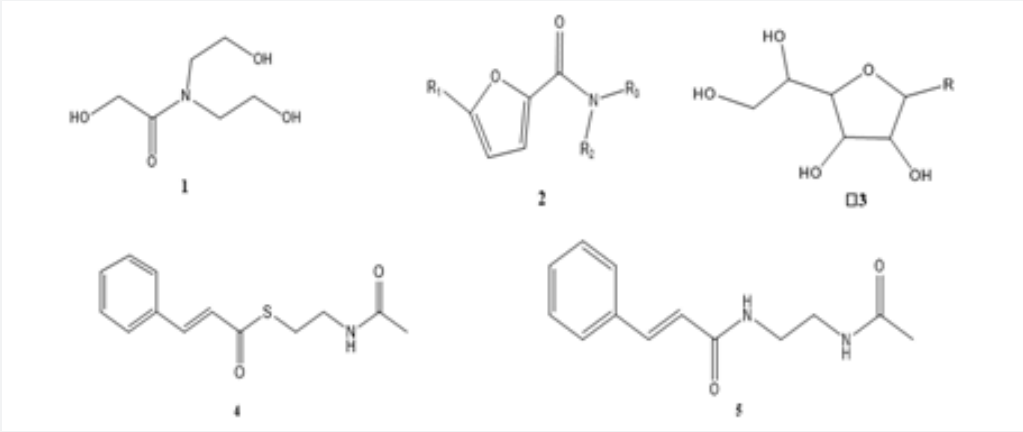

Figure 1: The structures of chemical compounds belonging to groups 1, 2 and 3.

The Compounds with One 5-Membered Ring

In the 2 due to the presence of delocalized electrons, amide group and also heteroatom in cyclic organic compounds shows a more intense MIC value compared with the 3 which does not have delocalized electrons in the structure [15,16]. The mean MIC value for 23 samples of this group has been obtained 0.09 µg/ml which was considered as a very potent MIC value.

The compounds with Two Non-Fused Rings

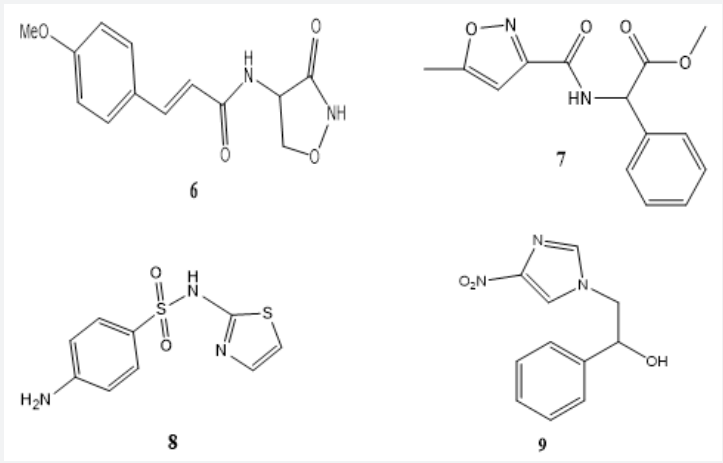

Figure 2: The chemical structures of non-fused compounds belonging to group 4.1.

The compounds with 5 and 6-membered Non-Fused Rings: The compounds of this group containing phenyl group with 5 and 6-membered rings have been presented in Figure 2 so that for 6 weak MIC value related to lack of delocalized electrons in the whole molecule [17]. However, 7 and 8 contain a 5-membered ring consisting nitrogen, oxygen and sulfur heteroatoms with delocalized electrons [18,19]. The related mean MIC value for these compounds has been obtained 32 µg/ml. However, in the 9 absence of delocalized electron in the molecule could be the reason of related weak MIC value. The mean MIC value for 44 samples of this group has been obtained 42.6 µg/ml.

The Compounds with One 6-Membered Ring

In the 4 and 5 consisting one phenyl and one amide group and also presence of sulfur (S) atom in the structure which were considered as a weak MIC value [17-22]. The mean MIC value for this group has been obtained 208.9 µg/ml which was considered as a weak MIC value.

The compounds with two 6-membered non-fused rings: The mean MIC value for 10 consisting two fused amide groups is potent which could be probably due to the presence of delocalized electrons in the whole molecule [18-32]. The 11 shows a potent MIC value due to the presence of tertiary amine group and presence of delocalized electrons in the molecule [18]. The 10, 11 and 12 have been presented in Figure 3 so that for 12 a medium MIC value due to the presence of delocalized electrons in the molecule with four OH groups, which could be able to exchange the protons and essential for the antibacterial activity [28]. The mean MIC value for 62 samples of this group were obtained 20.9 µg/ml which was considered as a medium MIC value.

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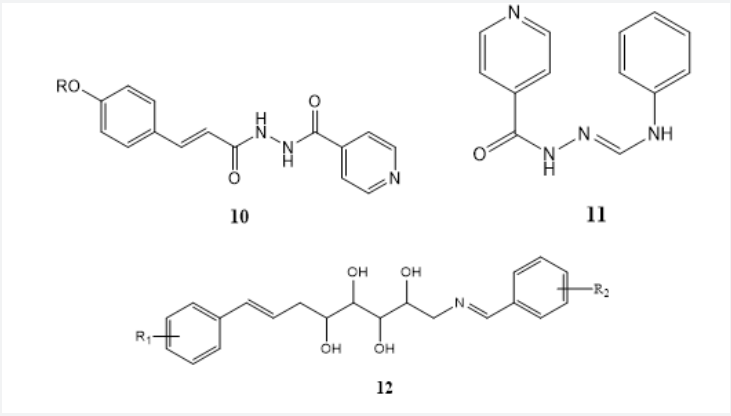

Figure 3: The chemical structures of two 6-membered cyclic compounds belonging to group 4.2.

The Compounds with Two Fused Rings

The compounds with two 5-membered fused rings: The 13 consist of two 5-membered rings which are fused together by two carbon atoms. The mean MIC value for seven samples of this group has been obtained 20.5 μg/ml and could be due to the absence of conjugated systems [33].

The compounds with 5 and 6-membered fused rings: This group presents a potent MIC value which could be due to the presence of tertiary amine and carbonyl functional groups in the chemical structure such as thiosemicarbazone derivatives [34]. The mean MIC value for 60 samples of this group has been obtained 9.4 μg/ml.

The compounds with two 6-membered fused rings: In this group, the structures have been presented in Figure 4 so that the 14 shows a better MIC value due to the presence of delocalized electrons in the whole molecule [35-37]. The mean MIC values for 66 samples of this group have been obtained 43.4 μg/ml which was considered as a medium MIC value.

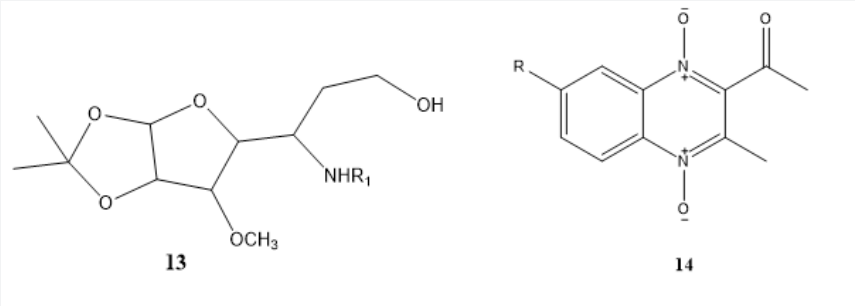

Figure 4: The chemical structures of fused heterocyclic compounds belonging to group 5.

The Compounds with Three Non-Fused Rings

The compounds with three 5 and 6-membered non-fused rings: All the compounds in this group contain two phenyl groups and a 5-membered ring which is different in type and numbers of heteroatoms. The mean MIC value for 49 samples of this group has been obtained 33.5 μg/ml which was considered in the medium range [38,39].

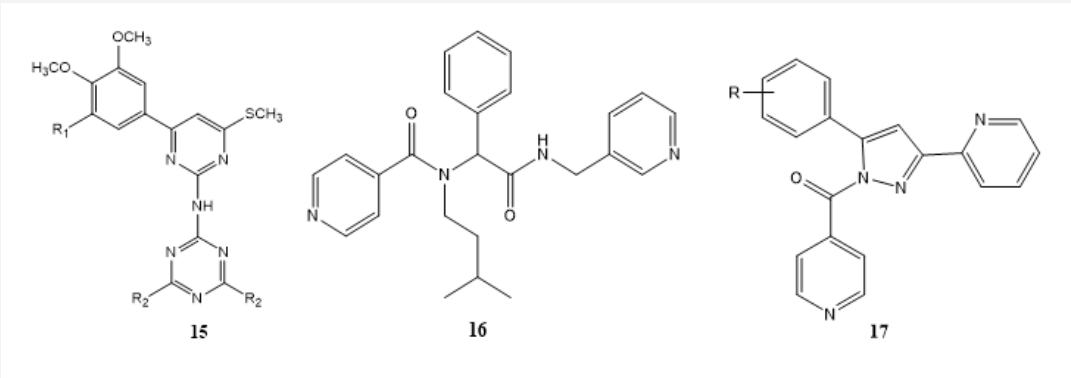

Figure 5: The chemical structures of non-fused heterocyclic compounds belonging to group 6.

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The compounds with three 6-membered non-fused rings: The compounds of this group contain three non-fused rings [40-43]. The 15 which has been presented in Figure 5, shows a medium MIC value probably due to the presence of electron donating groups such as methoxy (OCH_3) group and decreases related MIC [31]. In the 16 due to the presence of two amide groups and conjugated systems in the molecule could be changed MIC value to 7.66 µg/ml. The mean MIC value for 32 samples of this group has been obtained 14.9 µg/ml which was considered as a medium MIC value.

The Compounds with Three Fused Rings

The compounds with two 5 and 6-membered fused and one 6-membered non-fused rings: These compounds consist of three rings and one of them is non-fused ring [18]. The mean MIC value for 18 samples of this group has been obtained 76.8 µg/ml which was in the weak range of MIC value [44-46].

The compounds with two 6-membered fused and one 6-membered non-fused rings: The mean MIC value for 54 chemical compounds of this group has been calculated for 7.1 µg/ml [47,48].

The Compounds with Four Rings

The compounds with four non-fused rings: The chemical structures of 17 present a very potent MIC value due to the presence of conjugated systems and heteroatoms in non-fused rings [49,50]. The mean MIC value for 23 samples of this group has been obtained 0.06 µg/ml.

The compounds with two non-fused and two fused rings: The mean MIC value for 52 samples of this group has been obtained 24.4 µg/ml [47-52].

The compounds with two set of two fused rings: The 18 shows a very potent MIC value due to the presence of conjugated systems in the molecule and also the presence of amide group and carbonyl group in the chemical structure [53]. The mean MIC value for five samples of this group has been obtained 0.4 µg/ml.

The compounds with three fused and one non-fused rings: The mean MIC value for 19 samples of this group has been obtained 81.6 µg/ml which was in the medium range [17,54].

The compounds with four fused rings

The mean MIC value for 18 samples of this group has been obtained 34.3 µg/ml [55].

The Compounds with Five Rings

The compounds with four fused and one non-fused rings: The 19 shows a very potent MIC value due to the presence of conjugated systems in the molecule which has been presented in Figure 6 and also have an electronegative atom such as bromine (Br) in the chemical structure. The mean MIC value for 17 samples of this group has been obtained 0.003 µg/ml [56].

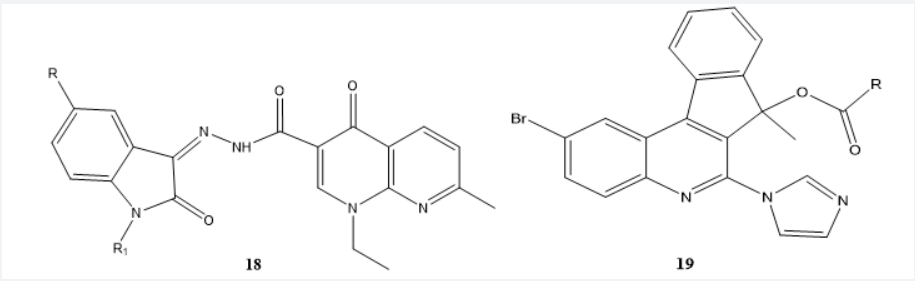

Figure 6: The chemical structures of fused heterocyclic compounds belonging to groups 8 and 9.

The compounds with three fused and two non-fused rings: The mean MIC value for 19 samples of this group has been obtained 81.6 µg/ml [17,57].

The Compounds with Six Rings

The mean MIC value for 24 samples of this group has been obtained 0.24 µg/ml [47,58,59].

The Compounds with Seven Rings

These synthetic seven cyclic compounds contain fewer number of fused and non-fused rings compared to the other compounds in this study. The mean MIC value has been obtained 99.8 µg/ml which was considered as weak MIC value [56- 66].

Chemistry

Along with comparing different chemical structure of the heterocyclic organic compounds with related MIC data, an algorithm containing the ring numbers and fused or non-fused rings was considered. Some chemical properties such as presence of delocalized electrons in the whole molecule, number of heteroatoms in the heterocyclic organic compounds and also the presence of electronegative substitutions in the compounds were found which affect antibacterial activities of these compounds. These chemical properties could be helped medicinal chemists to synthesize novel chemical compounds with better predicted characteristics and more antibacterial activities of drugs.

Pharmacology

Among the mentioned chemical compounds, the 19 with four fused and one non-fused rings have all characteristics which has been found to affect the potency against Mycobacterium and has presented very potent MIC value. The toxicity for this compound was shown a selectivity index higher than 4, therefore the 19 could be considered as potential candidate as well.

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Conclusion

In this study, it has been tried to find a significant relationship between the MIC values of the heterocyclic organic compounds and their chemical structures. The most significant factor to improve the MIC values has been observed to be the presence of delocalized electrons in the whole structure of the compound [9,24,25,51]. The second important factor to improve the MIC values has been found to be the presence of electronegative substitutions such as bromine which would lead to a better potential MIC values in the mentioned groups [17,23,53]. The third factor affect the MIC values has been shown the presence of heteroatom such as nitrogen and sulfur in the rings of the heterocyclic compounds. Also the presence of fused rings in the compounds leads to a better MIC values [21,34,51]. Among the 100 evaluated compounds in this study, 17 and 19 were found to be the most active compound with MIC of 0.06 and 0.003 μg/ml against Mycobacterium, respectively. The presence of amide and tertiary amine groups could improve the MIC values in addition to the factors mentioned [61-66]. Although, this study reviews the effects of chemical structure on potency of these heterocyclic compounds that present Antimycobacterial effects to give idea for future therapeutic approaches.

Declaration of Interest

The authors declare no conflict of interest.

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