6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020
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Design, synthesis and biological screening of 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones as potential antitubercular and antiproliferative agents

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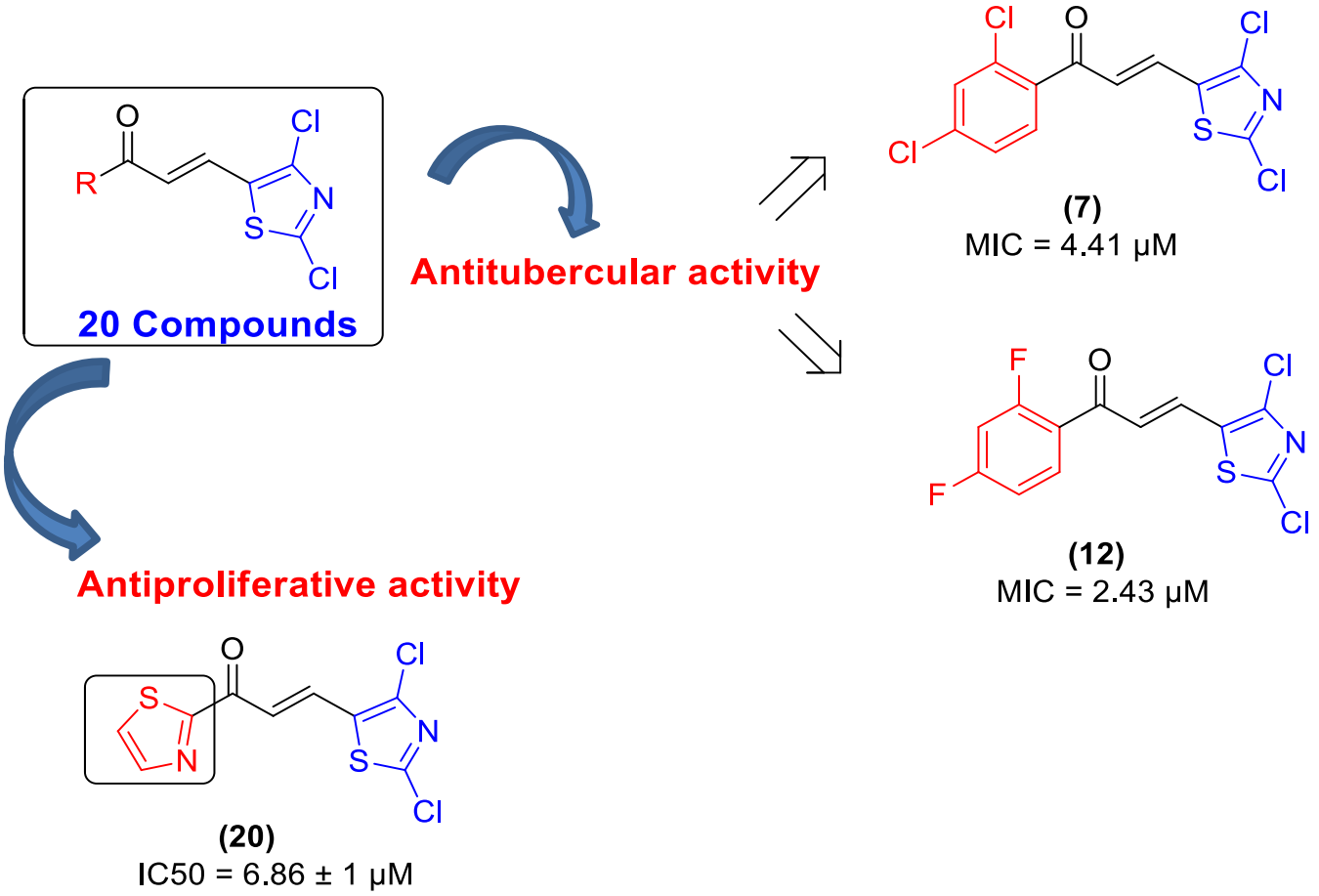
Design, synthesis and biological screening of 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones as potential antitubercular and antiproliferative agents

Graphical Abstract



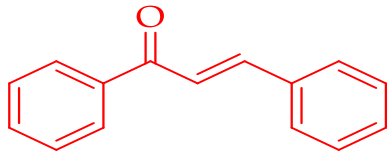
Abstract: Compounds containing thiazole and chalcone privileged scaffolds were reported to possess excellent antitubercular and anticancer activities. Considering the potential activities of these privileged structures, in the present study, we designed, synthesized and characterized a novel series of 2,4-dichlorothiazole-5-carboxaldehyde-derived chalcones (**1-20**) and evaluated them for antitubercular and antiproliferative activities by employing standard protocols.

Among the twenty compounds, chalcones **12** and **7** containing 2,4-difluoro and 2,4-dichloro groups showed potential antitubercular activity higher than the standard pyrazinamide (MIC = 25.34 μM) with MICs **2.43 and 4.41 μM** respectively. Chalcone **20** containing heteroaryl 2-thiazolyl moiety exhibited promising antiproliferative activity against the prostate cancer cell line DU-145 higher than the standard methotrexate (IC_{50} = 11 ± 1 μM) with an IC_{50} value of **6.86 ± 1** μM. All the compounds were further evaluated for their cytotoxicity against normal human liver cell lines L02 and were found to be non-toxic. Potential activity and non-toxic nature of these compounds advocate that the lead compounds emerged out of this study, pave the way for the development of novel drugs against tuberculosis infections and prostate cancer.

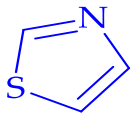
Keywords: antiproliferative activity; antitubercular activity; chalcones; cytotoxic activity; thiazole.

Introduction

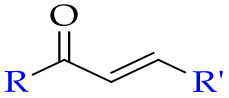
Chalcone and thiazole derivatives are privileged scaffolds with antimicrobial, anticancer, cytotoxic, antitubercular, antioxidant and antifinflammatory activities



Chalcone

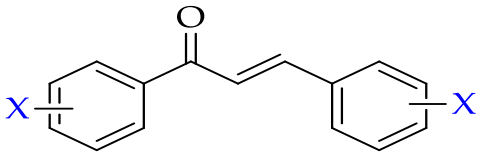


Thiazole



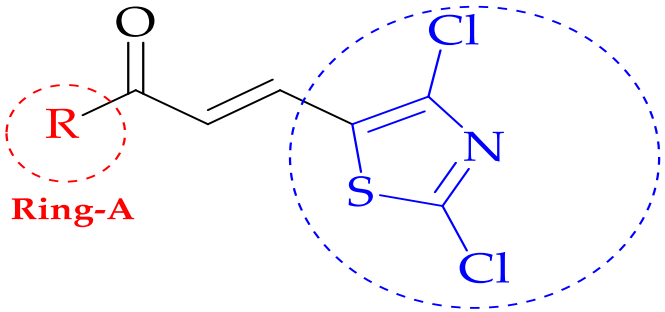
Heteroaryl Chalcones

R and R'=Heteroaryl rings



Halogenated Chalcone

X = F, Cl, Br, I



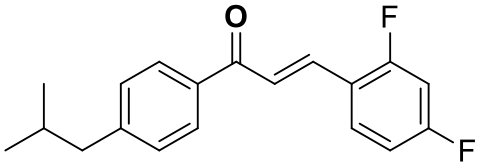
Ring-A

Ring-B

Heteroaryl and halogenated chalcones possess improved antitubercular and antiproliferative properties

Introduction

Some of our previously reported potential antitubercular and antiproliferative halogenated and heterocyclic chalcones



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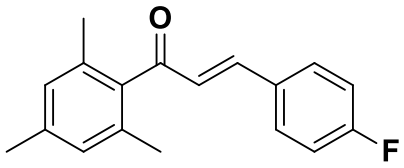

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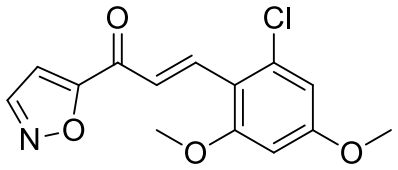

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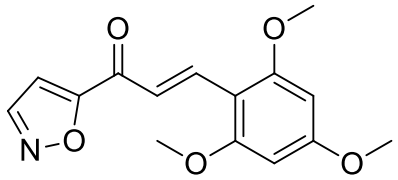

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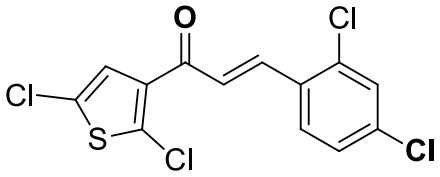

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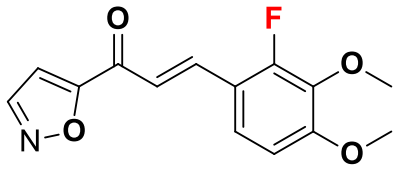

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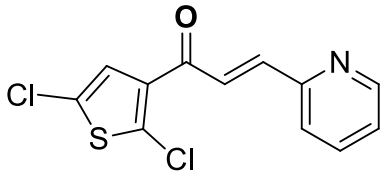

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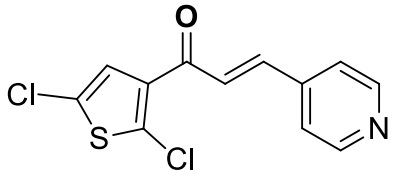

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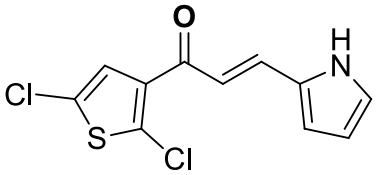
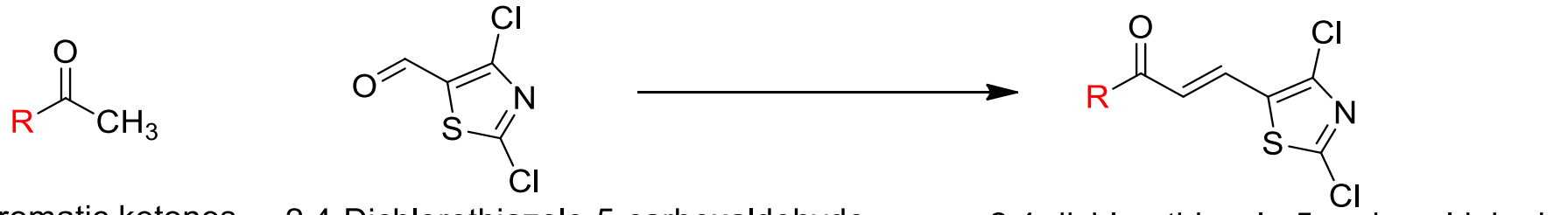


9

Considering the potential activity of heteroaryl and halogenated chalcones and thiazole derivatives, in the present study, we designed, synthesized and evaluated the antitubercular and antiproliferaative activities of 20 new 2,4-dichlorothiazole-5-carboxaldehyde-derived chalcones.

Results and discussion: Chemistry



Aromatic ketones

2,4-Dichlorothiazole-5-carboxaldehyde

2,4-dichlorothiazole-5-carboxaldehyde derived chalcones (**21-40**)

R

1. 2-chlorophenyl; 2.3-chlorophenyl; 3. 4-chlorophenyl; 4. 2,3-dichlorophenyl; 5. 2,6-dichlorophenyl; 6. 2,5-dichlorophenyl; 7. 2,4-dichlorophenyl; 8. 3,4-dichlorophenyl; 9. 2-fluorophenyl; 10. 3-fluorophenyl; 11. 4-fluorophenyl; 12. 2,4-difluorophenyl; 13. 2,5-difluorophenyl; 14. 2,6-difluorophenyl; 15. 3,4-difluorophenyl; 16. 3-fluorophenyl; 17. 2-pyridinyl; 18. 3-pyridinyl; 19. 4-pyridinyl; 20. 2-thiazolyl

2,4-dichlorothiazole-5-carboxaldehyde derived chalcones were synthesized by condensing a variety of aromatic ketones with 2,4-dichloro-5-carboxaldehyde in the presence of glacial acetic acid and hydrochloric acid mixture as shown above to isolate compounds (**1-20**) in 75-91% yields. The synthesized chalcones were pale yellow coloured compounds with solubility in chloroform, methanol and DMSO. All the compounds were well characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry.

Results and discussion: Chemistry

- In the FT-IR spectrum of all the compounds two diagnostic stretching absorption bands of C=O and C=C were seen around the wave numbers 1651-1698 cm^{-1} and 1506-1520 cm^{-1} respectively.
- The ^{1}H NMR spectra showed two doublet signals characteristic of the α- and β-protons of the propenone linkage resonating between the chemical shift values 7.27-7.89 ppm and 7.66-8.16 ppm. The coupling constant value, *J*, for these doublets ranged between 15-17 Hz. These large coupling constant values confirmed the *trans* geometry of the olefinic bond present in the chalcone scaffolds.
- ^{13}C-NMR spectrum of the compounds displayed the signals at δ 181–196 (C1), 122–130 (C-2), and 133–146 (C-3).
- The molecular ion peak in the mass spectrum further confirmed the formation of chalcones.

Results and discussion: Biological studies

Table 1. Antitubercular, antiproliferative and cytotoxic evaluation of 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones

Entry	*Mt* (H_{37}Rv strain) (MIC in μM)[a]	Prostate cancer cell line (DU-145) (IC_{50} in μM)[b]	Normal liver cell line (L02) (IC_{50} in μg/ml)[b]
1	78.46	100.43 ± 2	>70
2	313.87	1607.03 ± 2	>70
3	78.46	401.75 ± 1	>70
4	141.62	181.28 ± 1	>70
5	35.40	90.64 ± 1	>70
6	141.62	2900.52 ± 2	>70
7	**4.41**	181.28 ± 1	>70
8	141.62	1450.26 ± 1	>70
9	**20.68**	52.95 ± 2	>70
10	165.48	847.28 ± 2	>70
11	**20.68**	423.64 ± 2	>70
12	**2.43**	99.95 ± 1	>70
13	39.04	3198.70 ± 2	>70
14	**9.74**	24.98 ± 2	>70
15	39.04	799.67 ± 1	>70
16	156.18	3198.70 ± 1	>70
17	350.70	14.02 ± 1	>70
18	701.40	28.05 ± 1	>70
19	350.70	14.02 ± 1	>70
20	343.45	**6.86 ± 1**	>70
Pyrazinamide	25.34	-	>70
Methotrexate	-	11 ± 1	>70

[a]MIC's are mean of three independent experiments; [b]Data presented as mean ± SD (n=3). All the compounds and the standard dissolved in DMSO, diluted with culture medium containing 0.1% DMSO. The control cells were treated with culture medium containing 0.1% DMSO.

Results and discussion: Biological studies

- All the compounds were evaluated for their antitubercular and antiproliferative activities by MABA and MTT assays respectively. The 20 target compounds were partitioned into three categories based on the nature of ring-A in 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones i.e., chloro-substituted aryl derivatives (**1-7**), fluoro-substituted aryl derivatives (**9-16**) and unsubstituted heteroaryl derivatives (**17-20**).
- Amongst the 20 compounds, the halogen substituted (**1-16**) chalcones showed potential antitubercular activity whereas the compounds containing unsubstituted heteroaryl scaffold (**17-20**) exhibited potential antiproliferative activity.
- The compounds 7, 9, 11, 12 and 14 showed antitubercular activity greater than pyrazinamide (MIC = 25.34 μM) with different potencies. For instance, compounds **12** and **7** bearing halogen atoms in both *ortho* and *meta* positions i.e., 2,4-difluorophenyl (MIC = 2.43 μM) and 2,4-dichlorophenyl (MIC = 4.41 μM) showed potencies 10.42 and 5.74 times more than the standard whereas the monofluorinated compounds **9** and **11** bearing fluorine atom at *ortho* and *para* positions, showed activity at MIC 20.68 μM which is 0.81 times greater than pyrazinamide. The chalcone **14** (MIC = 9.74 μM) containing 2,6-difluorophenyl scaffold was 2.6 times more active than the standard.

Results and discussion: Biological studies

- The above results indicate that the ring-A portion if substituted with halogens (Cl/F) at both ortho and meta positions make the 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones potential antitubercular agents. And among the two halogens more electronegative fluorine atom is crucial for the activity.
- Among the unsubstituted heteroaryl derivatives (**17-20**), chalcone **20** containing 2-thiazolyl moiety as ring-A component showed the highest antiproliferative activity than methotrexate with IC_{50} value of 6.86 μM. This activity was 1.6 more than the standard.
- Compounds 17 and 19 containing 2-pyridinyl and 4-pyridinyl scaffolds exhibited IC50 value close to methotrexate. The activity of these compounds is 1.27 times less than methotrexate.
- The above results strongly indicate that a five-membered heterocyclic scaffold at ring-A portion is vital for the activity of 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones.

Conclusions

- In the present study we designed and synthesized 20 new 2,4-dichlorothiazole-5-carboxaldehyde derived chalcones and tested all the compounds for antitubercular, antiproliferative and cytotoxic activities. We identified five potential antitubercular chalcones and one promising antiproliferative chalcones. The potent compounds derived from these studies are the lead compounds for the development of useful drug candidates against tuberculosis and prostate cancers.

- Further, we are working towards elucidating the mode of action for the proposed activities.