Synthesis of Certain Heterocyclic Compounds Chemically Related to Antituberculous Drugs.

Thesis presented by

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Abstract

The present thesis comprises a survey covering antimycobacterial drugs with known and unknown mode of action.

The study involves the synthesis of ethyl benzothiazole-2-carboxylate **(I)**. Hydrazinolysis of the ester **I** resulted in the hydrazide **II**. Condensation of the latter with some aromatic aldehydes afforded the arylidene derivatives **IIIa-d**. Cyclization of **IIIa-d** with acetic anhydride yielded substituted 1,3,4-oxadiazoles **IVa-d.** Also, reaction of the hydrazide **II** with isatin and certain acid anhydrides led to substituted indolin-3-ylidene **V** and amide derivatives **VI** & **VII** respectively.

The investigation also involves the reaction of *o*-phenylenediamine with succinic anhydride to give 2-aminophenylamidosuccinic acid **(VIII)** which, on boiling under reflux for 3 hours in absolute ethanol, gave 3-(1*H*-benzimidazol-2-yl) propanoic acid **(IX)**. Esterification with ethanol led to the corresponding ethyl ester **X** which upon reaction with hydrazine gave the hydrazide **XI**. Condensation of the latter with isatin led to indolin-3-ylidene derivative **XII.** Also, cyclization of the hydrazide **XI** with some aromatic acids afforded 2,5-disubstitued-1,3,4-oxadiazoles **XIIIa-c**. Cyclization of the hydrazide **XI** with acetylacetone yielded compound **XIV**.

Moreover, 3-(1*H*-benzimidazol-2-yl) propanoic acid hydrazide **(XI)** was reacted with some aromatic aldehydes yielding arylidene derivatives **XVa-e**, which upon cyclization with acetic anhydride yielded substituted-1,3,4-oxadiazoles **XVIa-d.** In addition, reaction of the

hydrazide **XI** with certain acid anhydrides led to substituted amide derivatives **XVII** & **XVIII**.

On the other hand, ethyl (and/or phenyl) thiosemicarbazides **XIXa&b** were synthesized *via* reaction of the hydrazide **XI** with the corresponding isothiocyanate. The substituted thiosemicarbazides were then cyclized in presence of conc. H_2SO_4 to give 2,5-disubstituted-1,3,4-thiadiazol derivatives **XXa&b,** while cyclization of these substituted thiosemicarbazides in the presence of piperidine/H_2O led to 1,2,4-triazoles **XXIa&b** which, upon alkylation with different alkyl and/or aryl halides, gave **XXIIa-f.** While cyclizayion of ethyl(and/or phenyl) thiosemicarbazides **XIXa&b** with chloroacetic acid afforded thiazolidinone derivatives **XXIIIa&b.**

5-Substituted-1,3,4-oxadiazole-2-thiol **XXIV** was prepared by heating the hydrazide **XI** with CS_2 in the presence of alcoholic KOH. Alkylation of **XXIV** with different alkyl or aryl halides gave **XVa-c**.

When **XXIV** was subjected to Mannich reaction conditions, by reacting it with formaldehyde and different secondary amines in ethanol, it gave the corresponding 3-substituted aminomethyl-5-substituted-1,3,4-oxadiazole-2-thiones **XXVIa-e.**

Accordingly, this work comprises the synthesis of the following unavailable starting materials, reactants and reported intermediates:

1) Ethyl benzothiazole-2-carboxylate **(I)**.
2) Benzothiazole-2-carboxylic acid hydrazide **(II)**.
3) 2-Aminophenylamidosuccinic acid **(VIII)**.
4) 3-(1*H*-Benzimidazol-2-yl) propanoic acid **(IX)**.
5) Ethyl 3-(1*H*-Benzimidazol-2-yl) propanoate **(X)**.
6) 3-(1*H*-Benzimidazol-2-yl) propanoic acid hydrazide **(XI)**.
7) 1-[3-(1*H*-Benzimidazol-2-yl) propanoyl]-4-ethyl(and/or phenyl)-3-thiosemicarbazides **(XIXa&b)**.
8) 5-[2-(1*H*-Benzimidazol-2-yl) ethyl]-4- phenyl-4*H*-1,2,4-triazole-3- thiol **(XXIb)**.

In addition, this study involves the syntheses of the following new compounds:

1) *N*′-Arylidene benzothiazole-2-carbohydrazide **IIIa-d**.
2) 1-[(5-Benzothiazol-2-yl)-2-(substituted phenyl)-1,3,4-oxadiazol-3(2*H*)-yl] ethanones **IVa-d**.
3) *N*′-(2-Oxo-indolin-3-ylidene) benzothiazole-2-carbohydrazide **(V)**.

4) *N*-(1,3-Dioxo-isoindolin-2-yl) benzothiazole-2- carboxamide **(VI)**.

5) *N*-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl) benzothiazole-2- carboxamide **(VII)**.

6) 3-(1*H*-Benzimidazol-2-yl) propanoic acid-*N´*-(2-oxo-indolin-3-ylidene)hydrazide **(XII)**.

7) 2-[2-(1*H*-Benzimidazol-2-yl) ethyl]-5-(substituted phenyl)-1,3,4-oxadiazoles **XIIIa-c**.

8)1-[3-(1*H*-Benzimidazol-2-yl) propanoyl]-3,5-dimethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole **(XIV)**.

9) 3-(1*H*-Benzimidazol-2-yl)-*N´*-arylidene propanoic acid- hydrazides **XVa-e**.

10) 1-{5-[2-(1*H*-Benzimidazol-2-yl) ethyl]}-2-(substituted phenyl)-1,3,4-oxadiazol-3(2*H*)-yl]- ethanones **XVIa-d**.

11) 3-(1*H*-Benzimidazol-2-yl)-*N*-(1,3-dioxo-isoindolin-2-yl)propanamide **(XVII)**.

12) 3-(1*H*-Benzimidazol-2-yl)-*N*-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanamide **(XVIII)**.

13)*N*-{5-[2-(1*H*-Benzimidazol-2yl) ethyl]-1,3,4-thiadiazol-2-yl} ethyl-(and/or phenyl)amines **(XXa&b)**.

14) 5-[2-(1*H*-Benzimidazol-2-yl) ethyl]-4- ethyl-4*H*-1,2,4-triazole-3-thiol **(XXIb)**.

15) 3-[2-(1*H*-Benzimidazol-2-yl) ethyl]-4-ethyl (and/or phenyl)-4*H*-5- substitutedthio-1,2,4-triazoles **XXIIa-f**.

16) 3-(1*H*-Benzimidazol-2-yl)-*N´*-[3-ethyl (and/or phenyl)-4-oxo-thiazolidin-2-ylidene] propanoic acid hydrazides **(XXIIIa&b)**.

17) 5-[2-(1*H*-Benzoimidazol-2-yl) ethyl]-1,3,4-oxadiazole-2-thiol **(XIV)**.

18) 2-[2-(1*H*-Benzimidazol-2-yl) ethyl]-5-substitutedthio-1,3,4-oxadiazoles **XXVa-c**.

19) 5-[2-(1*H*-Benzoimidazol-2-yl) ethyl]-3-subtituted aminomethyl-1,3,4 -oxadiazole-2(3*H*)-thiones **XXVIa-e**.

The structural elucidation of the new synthesized compounds was supported by element analysis, IR, ^{1}H-NMR as well as mass spectral data.

The antimycobacterial activity of eighteen selected novel compounds was performed at the department of Microbiology and Immunology, Faculty of Pharmacy, Beni-Suef University. Some of the selected compounds showed antimycobacterial activity.

رئيس قسم الكيمياء العضوية الصيدلية

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