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Synthesis of Phenyl Substituted Thiosemicarbazone as Antituberculosis Agent

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ABSTRACT

Thiosemicarbazone (TSC) & it derivatives have raised considerable interest in chemistry and biology due to their different antigenic property and activities specialy for anti- tubercular drug. Two compounds of hydrazinecarbothioamide were synthesized via three steps starting from hydrazine hydrate and carbon disulfide using the state of art approaches (substructural approach based on the pattern recognition).

KEYWORDS :

Introduction:

Tuberculosis caused by Mycobacterium tuberculosis takes the leading place in the reports of incidence and mortality among populations of developed countries.[1] The infection can affect the respiratory system, central nervous system, lymphatic system, genitourinary system, bones, and even skin.[2] In 1990, there were over 6 million new cases, and in 2007 this figure rose to 9.2 million.[3] Furthermore, new multidrug-resistant tuberculosis strains (***MDR-TB***) are appearing at an alarming speed. The cure of multidrug-resistant tuberculosis requires a longer treatment period, and the success rate is only 52% in newly diagnosed patients, and 29% among previously treated patients.[4] Tuberculosis is one of the opportunistic infections in ***AIDS*** patients. For this reason, it represents a serious threat for this group of individuals. Immune deficiency increases vulnerability incidence to tuberculosis up to 50%. At the same time there is only a small number of effective antitubercular chemotherapeutics. Among them isoniazid ***(INH***) and pyrazinamide ***(PZA***) belong to the most commonly administrated drugs (Fig. 1). Unfortunately, the most effective chemotherapeutics, as well as antibiotics such as rifampicin (RMP), rapidly induce multidrug resistance (***MDR***) and cause serious side effects, like hepatotoxicity, neurotoxicity, acute pancreatitis and hypersensitivity reactions.[5,6] Therefore, the search for new antitubercular drugs active against resistant strains of M. tuberculosis should be one of the priority tasks of medicinal chemistry.

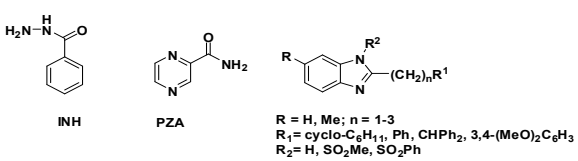


Figure 1. Structures of some tuberculostatic drugs and benzimidazoles of tuberculostatic activity.

MTb produces two series of structurally related peptidic siderophores known as the mycobactins and carboxymycobactins that vary by the appended lipid residue. Mycobactins have emerged as attractive targets for the development of anti-TB agent because of their critical role in the growth and virulence of MTb.[7–9] Thus the development of species resistance against anti-TB drugs in mycobacterium species are forcing for the development of novel drugs as anti-TB agents. Thiosemicarbazone (***TSC***) & it derivatives have raised considerable interest in chemistry and biology due to their different antigenic property and activities. It shows anti-cancer (anti-tumor), anti-microbial, anti-malarial, anti-bacterial, antineoplastic, and antiviral activities.[10] Moreover, it is very much important for their parasiticidal action against Plasmodium falciparum, Tripanosoma cruzi, Toxoplasma gondii, Leismania amazonensis, Herpes simplex virus(*HSV*), Human immunodefiency virus(*HIV*) etc. In view of the above and activity associated with hydrazinecarbothioamide,[10-11] we have designed and modification of molecule of novel substituted hydrazinecarbothioamide using the state of art approaches (**substructural approach based on the pattern recognition**). These molecules have been synthesized . The common structure formula of the synthesized titles compounds is shown in Figure 2.

Substituted hydrazinecarbothioamide as potent antitubercular agents

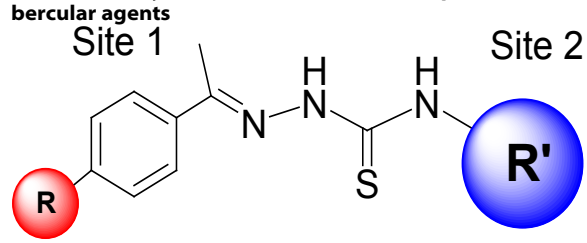
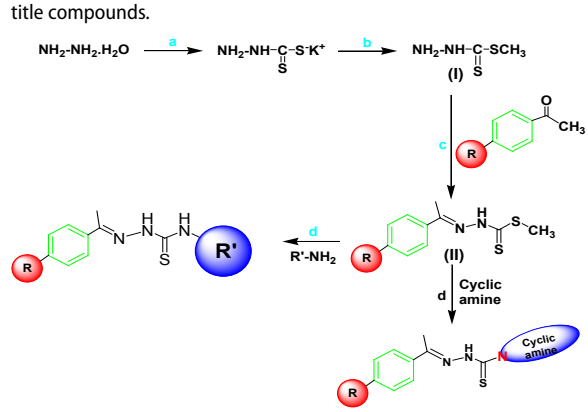


Figure 2. The common structural formula of the title compounds with encircled portions indicate the modification sites viz. site 1 and 2.

Results and discussion:

Chemistry

The general synthesis of the novel substituted hydrazinecarbothioamides is outlined in Scheme 1.[10] The first step involves the reaction of hydrazine hydrate with carbon disulfide in the presence of KOH at 0–10 ^{0}C. The next step involves the dropwise addition of methyl iodide to the ice-cooled reaction mixture over nearly 2 h. During this process, the colour of the reaction mixture changes from yellow to white (*colourless*) which indicates the formation of intermediate I, methyl hydrazinecarbodithionate. The third step involves the addition of the substituted acetophenone to the solution of I in 2-propanol to afford the intermediate II. The last step involves the reaction of the intermediate II with the substituted/unsubstituted amines to afford the title compounds.



Scheme 1: Synthesis of substituted hydrazinecarbothioamides. Reagents and conditions: (a) CS_2 (3 mol), KOH (3 mol), 0–10 ^{0}C; (b) CH_3I (3 mol), rt; (c) 2-propanol, rt; (d) ethanol, rt.

Mechanism:

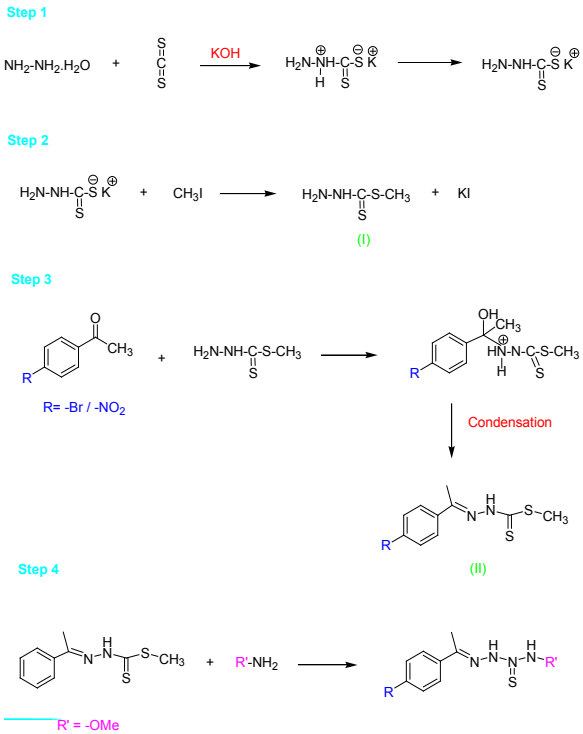
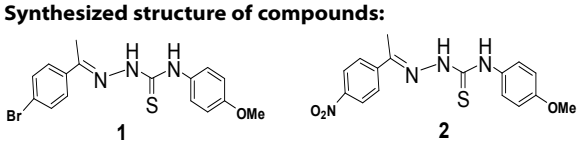


Table 1: Preparation of substituted hydrazinecarbodithionates

Compound	R	R′	Yield (%)
1	-Br	-OMe	94.5
2	-NO_2	-OMe	92

Synthesized structure of compounds:



Experimental Section:

Synthesis of intermediate I: The CS_2 (2.5 mL) was added dropwise to a ice-cooled mixture of hydrazine hydrate (85%, 2 mL) in aqueous .KOH (3 mol) and 2-propanol (10 mL) for 1–2 h at 0–10°C. The stirring was continued for 1 h with precipitated yellow solid, followed by dropwise addition of iodomethane (2.5 mL) leading to the colourless (white) solution. The colourless mixture was stirred for an additional 1–2 h and the white precipitate was filtered and washed with cold water. The crude product was recrystallized with dichloromethane to afford colourless methyl hydrazinecarbodithionate, I (86.5%).

Synthesis of methyl 2-(1-(4-bromophenyl) ethylidene) hydrazine carbo- dithionate (Intermediate IIa): The equimolar solution of methyl hydrazine carbo- dithionate (I) and 4-bromo acetophenone in 2-propanol was stirred for about half an hour. The reaction mixture turned into yellow precipitate. This was stirred for additional 2–3 h and kept as such overnight. The separated crystals were filtered, washed with cold 2-propanol and air dried to yield the intermediate product **IIa** (59.2%).

Synthesis of methyl 2-(1-(4-nitrophenyl) ethylidene) hydrazinecarbo- dithionate (Intermediate IIb): The equimolar solution of methyl hydrazinecarbo- dithionate (I) and 4-nitro acetophenone in 2-propanol was stirred for about half an hour. The reaction mixture turned into yellow precipitate. This was stirred for additional 2–3 h and kept as such overnight. The separated crystals were filtered, washed with cold 2-propanol and air dried to yield the intermediate product **IIb** (61%).

Synthesis of the title compound 1: The 4-methoxyaniline (1.23 g, 0.01 mol) was added to a warm solution of the methyl 2-(1-(4-bromophenyl)ethylidene) hydrazine carbo- dithioate (3 g, 0.01 mol) in warm ethanol. The reaction mixture was refluxed overnight. The resulted solid was filtered and recrystallized in absolute ethanol to yield the title compound **1** (94.5%).

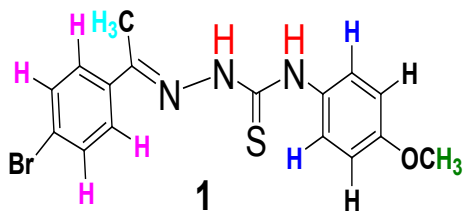
Synthesis of the title compound 2:

The 4-methoxyaniline (1.23 g, 0.01 mol) was added to a warm solution of the methyl 2-(1-(4-nitrophenyl)ethylidene)-hydrazinecarbodithioate (2.7 g, 0.01 mol) in warm ethanol. The reaction mixture was refluxed overnight. The resulted solid was filtered and recrystallized in absolute ethanol to yield the title compound **2**(92%).

Spectral Analysis:

(a) Compound 1: Chemical formula: **$C_{16}H_{16}BrN_3OS$**; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d^6): d 1.76 (s, 3H), 3.12 (s, 3H), 6.21 (d, 2H, *J* = 6.87), 6.76 (d, 2H, *J* = 6.93), 7.63-8.41(m, 4 H), *9.68 (s, 1H), 9.69 (s, 1H)*.

IR (KBr) cm^{-1}:676, 740, 1246, 2947,3188, 3451.



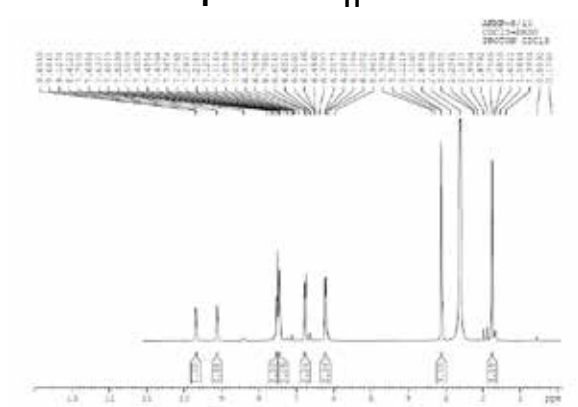
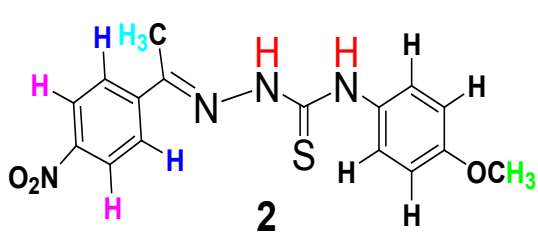


Figure 3. ^{1}H NMR NMR (300 MHz, $CDCl_3$ + DMSO-d^6) for compound (**1**)

(b) Compound 2: Chemical formula: **$C_{16}H_{16}N_4O_3S$**; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d^6): d 2.08 (s, 3H), 3.45 (s, 3H), 6.39 (s, 1H), 6.88 (s, 1H), 6.93 (s, 1H), 7.03 (s, 1H), 7.84-7.87 (m, 2H), 7.67-7.73 (m, 2H), *9.30 (s, 1H), 9.80 (s, 1H)*.

IR (KBr) cm^{-1}:676, 740, 1246, 2947,3188, 3451.



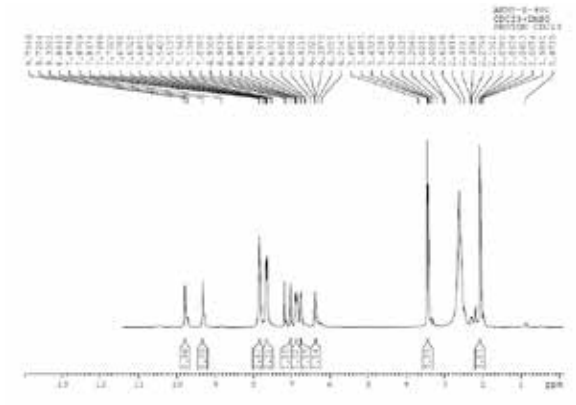


Figure 4. ^{1}H NMR NMR (300 MHz, $CDCl_3$ + DMSO-d^6) for compound (**2)**

Conclusion:

Nowadays TB drug discovery is a challenge. Absence of efficacy, resistance, poor compliance and comorbidities are some factors that difficult TB treatment. The molecular modification is an important and promising tool to discovery new antitubercular drugs, this fact can be perceived in the current pipeline TB drugs in clinical trial that almost of them were obtained using this strategy.

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