Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β-D-ribofuranosyl) thiosemicarbazones

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Abstract

A novel synthesis of eleven heteroaromatic aldehyde / ketone of 2- (2,3,5- Tri-O-benzoyl-β-D-ribofuranosyl) thiosemicarbazones derivatives (4) have been synthesized by condensation of 2-( 2,3,5- Tri-O-benzoyl-β-D-ribofuranosyl)thiosemicarbazide( 2) with an heteroaromatic aldehyde or ketone (3) ,and then debenzoylated of the resulting product to produce 2-(β-D-ribofuranosyl) thiosemicarbazone (5). The synthesis was carried out in ethanol at reflux temperature either by modified domestic microwave oven irradiation or conventional heating (heating mental). Microwave technique gave improved yield in less reaction time All compounds (5a-k) were elucidated by FTIR , 1H-NMR , and elemental analysis .The antibacterial activity of these compounds were tested in vitro by the disk diffusion assay against Escherichia coli as Gram-negative bacteria and Staphylococcus aureus as Gram-positive bacteria. Compounds display remarkable antibacterial activity as compared to amoxicillin.

Keywords: Ribofuranosyl thiosemicarbazone, Microwave-assisted method, Heteroaromatic aldehyde, Heteroaromatic ketone.
Introduction

Thiosemicarbazones and its derivatives are a class of special important compounds because of their versatile biological and pharmacological activities. They exhibit various biological activities such as antituberculoss\(^1\), antimicrobial\(^2\), anti-inflammatory\(^3\), anticonvulsant \(^4\), antihypertensive \(^5\), local anesthetic\(^6\), hypoglycemic \(^7\). It have been also evaluated over the last 50 years as antiviral and anticancer therapeutics, as well as for their parasitical action against Plasmodium falciparum and Trypanasoma cruzi which are the causative agents of malaria and chagas's disease, respectively \(^8\). In addition thiosemicarbazone derivatives have found application in drug development for the treatment of central nervous system disorders, as well as analgesic and antiallergic agent \(^9\).
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The chemistry of coordination metal complexes of thiosemicarbazone ligands have been receiving considerable attention primarily because of their bioinorganic relevance\cite{10}. It is well authenticated that a NS bidentate system is present in most of the thiosemicarbazones, so they can bond to metals through sulphur and the hydrazinic nitrogen atoms to form complexes. Heterocyclic thiosemicarbazones showed higher activity compared with aromatic thiosemicarbazones \cite{11}. For example, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (also called Triapine) is a substance that was studied in the treatment of cancer. It belong to the family of drugs called ribonucleotide reductase inhibitors \cite{12}. These compounds are generally synthesized by condensation reaction of thiosemicarbazides and suitable aldehydes or ketones.

It is known that the introduction of carbohydrate moiety into the structure of biologically active substances leads to an increase in their solubility in water and to decrease in their toxicity. It is also possible to expect some selectivity in the action of carbohydrate-containing biologically active substances \cite{13, 14}. There were several researches have been published on aldehyde / ketone (β-D-glucopyranosyl) thiosemicarbazones synthesis \cite{15-18}. It has been studded as antioxidant and anti-dyslipidemic agents. A group of 15 aromatic aldehyde 4-(β-D-glucopyranosyl) thiosemicarbazones have been synthesized and evaluated as inhibitors of rabbit muscle glycogen phosphorylase b (G Pb) \cite{19}. The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic studies, because it is a new enabling technology for drug discovery and development. By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of the time required by classical thermal methods \cite{20}.

We were interested to synthesis a new series of (β-D-ribofuranosyl) thiosemicarbazones, with this view we have reported here a systematic study for the synthesis and spectral characterization of a series of heterocyclic ketones and aldehydes ribofuranosyl thiosemicarbazones using condensation reaction by conventional and microwave assisted methods.
Experimental

Materials: Most of the chemicals used in this work were purchased from either Fluka Chemicals Ltd. or BDH Ltd with high degree of purity and they were used without purification. All the solvents were dried by the methods explained in Vogel practical organic chemistry textbook. Compound 1 (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl thiosemicarbazide) was prepared from D-ribose sugar according to well known methods. Piperonal(3,4-Methylenedioxybenzaldehyde), Imidazole-2-carboxaldehyde, 2-Thiazole carboxaldehyde were purchased from Fluka Chemicals Ltd. and Sigma – Aldrich Cheme, while other aldehydes and ketones were prepared as described below.

Apparatus: A domestic microwave oven (Shownic, Model:MW-GA 38GSC9), multi-mode microwave device with 2.45 GHz frequency (38 L capacity) and rated microwave power 1000 W was purchased from the local market and modified to carryout chemical reaction. The modification included, reflux condenser mounted through hole in the roof of the cavity, a remote IR sensor (Pyrometer) through hole inside of the cavity was inserted for temperature reaction measurement, and magnetic stirrer was fixed down the cavity of the oven.

1H NMR spectra were recorded on a Bruker 300MH instrument, using DMSO as solvent and chemical shifts were given relative to tetra methyl silane (TMS). Multiplicities of proton resonances are designated as singlet (s), doublet(d), triplet(t), quartet(q), multiplet(m), and broad(br). FT-IR spectra were recorded on ABB Spectrolap MB 3000 England, transform infrared (FT-IR) spectrometer. Vibration transition frequencies were reported in wave number between 500-4000cm⁻¹. The band intensity was classified as weak (w), medium (m), shoulder (sh), strong(s), and broad (br).

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl thiosemicarbazide (2): It was synthesized according the reported method with slightly modification:

Compound 1 (0.01mol.) was dissolved in methylene dichloride (50 ml) and cooled the solution to 15°C under exclusion of moisture. A thin stream of hydrazine hydrate (99%) (0.015 mol.) was added to this solution. The mixed solution was allowed to stand at room
temperature with stirring for 24 hr until the spot of the initial compound on the TLC chromatogram was disappeared using benzene / acetone (2:1) as developing solvents. The solution was evaporated under vacuum at 40°C. The residue was dissolved in dry benzene and reprecipitated with dry light petroleum ether. The resulting product was recrystallized from methanol to give compound 2. Yield 89%, m.p.183-185°C, Anal. Calc. for C$_{27}$H$_{23}$N$_{3}$O$_{7}$S, Mwt: 535, C (60.56%), H (4.67%), N (7.85%), O (22.80%), S(5.98%). Found: C (60.05%), H (4.70%), N (7.79%). FTIR(KBr): $\nu$cm$^{-1}$, 3342(s), 3280(s), 3190(m), 3080 (w), 1736(s), 1645(m), 1600(s), 1560(m), 1474(m) 1376(s) 1280(m), 1240(m), 1118(s), 1044(s), 820(s).

**Synthesis of heteroaromatic carboxaldehydes (3a-d)** (24)

**General procedure**

**Benzothiophene - 2 - carboxaldehyde (3a) and Benzoferan - 2 - carboxaldehyde (3b):**

To a solution of benzoferan or benzothiophene (8.5 mmol) in dry THF (40 ml), was added drop wise n-BuLi (6.0ml, 1.42M in hexane) at -78°C under liquid nitrogen. The mixture was stirred at -78°C for 1hr and then DMF (1.24 g, 17.0 mmol) was added. After 4h, the mixture was poured into aqueous HCl (4.5% w/v, 80ml) and stirred at 0°C for 0.5 h. The organic phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$. After removal of the solvent under vacuum, the residue was purified by column chromatography with hexane / EtOAc(3:1) as eluent to give 3a or 3b.

**Benzothiophene - 2 - carboxaldehyde (3a):** Pale yellow liquid, Yield 60%, Anal. Calcd. C$_9$H$_6$O$_2$, Mwt: 146, C (73.97%), H (4.11%), O (21.92%). Found: C (74.67%), H (4.07%). FTIR(KBr): $\nu$ cm$^{-1}$, 3055(w), 2871(w), 2760(w), 1650(m),1620(s),1540(m), 1464(m), 1268(s),1097(m),944(m),790(s) .

**Benzoferan - 2 - carboxaldehyde (3a):** off white crystals, Yield 70 %, m.p. 34-35°C, Anal.Calcd.C$_{9}$H$_{6}$OS, Mwt: 162, C (66.66%), H (3.70%)O(9.88),S(19.75). Found: C (66.00 %), H (3.74%). FTIR(KBr): $\nu$ cm$^{-1}$,3070(w),2840 (w), 2770 (w),1660 (s), 1620 (s) ,1610 (m),1560(m),1490(m),1110 (m), 980(w), 770 (s) , 670(w) .
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β-D-ribofuranosyl) thiosemicarbazones
Hussein Ismael Khalaf

10 - Methylphenothiazine - 4 - carboxaldehyde (3c):
The same above procedure was used except dry ether and TMEDA (3.0ml) was added in staid of dry THF to dissolve 10-Methylphenothiazine (2.0g, 9.4 mmol). Yellow crystals, Yield 37 %, m.p. 111-113°C, Anal. Calcd. C_{14}H_{11}NSO, Mwt: 241, C (69.70 %), H (4.56 %), N(5.81%), S(13.28%), O(6.64%). Found: C (70.21 %), H (4.52 %), N (5.74%). FTIR(KBr) : v cm⁻¹, 3072(w), 2960(w), 2920(w), 2820(w), 2740(w), 1705(m), 1601(s), 1570(m), 1480(m), 1430(m), 1377(m), 790(s), 670(w).

10 - Methyl phenol - thiazine - 3 - carboxaldehyde 3d:
Sodium hydroxide (4.9 g, 123mmol) was dissolved in glacial acetic acid (300ml) under nitrogen. 10-Methylphenothiazine (40mmol) was added, followed by chloroform (50ml). Bromine (6.7g, 40mmol) in glacial acetic acid (40ml) was added drop wise during 2h at (5-10)°C. The suspension was stirred at room temperature for 2h and then evaporated to dryness. The residue was dissolved in 10% NaHCO₃ and CH₂Cl₂. The aqueous phase was separated and extracted with CH₂Cl₂. The combined organic phase was dried over Na₂SO₄. After removal of the solvent under vacuum, the residue was separated by column chromatography with hexane / EtOAc (3:1) as eluent to give 3-Bromo-10- methylphenothiazine. To a solution of this intermediate (6.0mmol) in dry THF (40 ml), was added drop wise n-BuLi (6.0ml, 1.42M in hexane) at-78°C under liquid nitrogen. The procedure was completed as above general procedure to obtain 10-Methyl pheno- thiazine -3-carboxaldehyde 3d. Colorless crystals, Yield 51 %, m.p:84-86°C, Anal. Calcd. C_{14}H_{11}NSO, Mwt: 241, C (69.64 %), H (4.56 %), N(5.81%), S(13.28%), O(6.64%). Found: C (70.11 %), H (4.54 %) N (5.77%). FTIR(KBr) : v cm⁻¹, 3062(w), 2980(w), 2940(w), 2810(w), 2750(w), 1705(m), 1601(s), 1570(m), 1480(m), 1430(m), 1377(m), 790(s), 670(w).

Synthesis of 4 - acetyl / benzoyl - 2 - pyrazoline - ones (3h-k):
General procedure (25,26).
3-Methyl-1-phenyl-2-pyrazoline-5-one (5.8g, 0.033 mol) was dissolved in hot dioxane (25 ml) in a flask equipped with a stirrer, separating funnel and reflux condenser. Calcium hydroxide (4.92g, 0.2 mol) was added to this solution, followed by acetyl chloride (4ml) added drop...
wise with precaution, as this reaction was exothermic. During this addition the whole mass converted into a thick paste. After the complete addition, the reaction mixture was refluxed for 2hr and then it was poured into cold dilute hydrochloric acid (70ml, 2M). The colored crystals thus obtained were separated by filtration, washed with water and dried.

4 - Acetyl - 3 - methyl - 1 - phenyl - 2 - pyrazoline - 5 - one (3h): yellow powder, Yield 55%, m.p 61°C, Anal. Calcd.C_{12}H_{12}N_{2}O_{2}, Mwt: 216, C (66.66%), H (5.55%), N (12.96%), O (14.81%) Found: C (70.11%), H (4.53%) N (12.88%). FTIR (KBr): 3080(w), 2967(w), 2924(w), 1635(s), 1600(w), 1552(s), 1510(m), 1441(s), 1374(m), 1364(m), 800(s), 640(m).

4 - Benzoyl - 3 - methyl - 1 - phenyl - 2 - pyrazoline - 5 - one (3i): Yellow powder, Yield 80%, m.p 93°C, Anal. Calcd.C_{17}H_{14}N_{2}O_{2}, Mwt: 278, C (73.38), H (5.03), N (10.07), O (11.51%). Found: C (74.11%), H (4.99%) N (11.65%). FTIR (KBr): 3070(m), 2980(w), 2930(w), 1655(s), 1610(w), 1595(m), 1540(s), 1512(m), 1451(s), 1380(s), 1370(m), 805(s), 690(m), 667(m).

4 - Acetyl - 3 - methyl - 1 - (4'-methyl phenyl) - 2 - pyrazoline - 5 - one (3j): Yellow powder, Yield 73%, m.p 76°C, Anal. Calcd.C_{13}H_{14}N_{2}O_{2}, Mwt: 230, C (67.82%), H (6.09%) N (12.17%), O (13.91%). Found: C (67.00%), H (6.02%) N (11.99%). FTIR(KBr): 3084(w), 2985(w), 2935(w), 1640(s), 1610(w), 1565(m), 1545(s), 1510(m), 1451(s), 1379(s), 780(s), 680(m).

4 - Benzoyl - 3 – methyl - 1 - (4'-methyl phenyl) - 2 - pyrazoline - 5 - one (3k): Yellow powder, Yield 73%, m.p 105°C, Anal. Calcd.C_{18}H_{16}N_{2}O_{2}, Mwt: 292, C (73.97%), H (5.48%), N (9.59%). Found: C (74.50%), H (5.51%) N (9.70%). FTIR(KBr): 3077(w), 2984(w), 2940(w), 1663(s), 1620(m), 1570(m), 1540(s), 1510(m), 1445(s), 1376(s), 786(s), 675(m).
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones
Hussein Ismael Khalaf

General procedure for synthesis of 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl thiosemicarbazones (17).

Method A (microwave irradiation):
A suspension mixture of compound 2 (5mmol) and corresponding aldehyde or ketone 3 (5mmol) and glacial acetic acid (0.3 ml) in absolute methanol (20 ml) was irradiated with reflux for 10 min. in microwave oven (200 W). The suspension mixture became clear solution after irradiating in 3 minutes. The mixture was cooled to room temperature to produce the precipitate. Recrystallization was done from ethanol/toluene to yield the corresponding aldehyde or ketone (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl) - thiosemi- carbazones 4.

Method B (conventional heating):
The procedure of method A was applied with refluxing by conventional heating for 5 hr, and completed to obtain the final thiosemicarbazones 4.

Benzofurancarboxaldehyde - 2 - (2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) thiosemicarbazone (4a): light yellow powder, Yield 85% , m.p 230°C, Anal. Calcd. C_{36}H_{29}N_{3}O_{8}S, Mwt: 663, C (65.16%), H (4.37%), N (6.33%), O (19.30%), S (4.83%). Found: C (65.60%), H (4.31%), N (6.26%).

FTIR(KBr): 3350 (m), 3290 (m), 3087 (w), 2870 (w), 2830 (w), 1740 (s), 1647 (m), 1620 (s), 1590 (m), 1530 (m), 1480 (s), 1445 (m), 1380 (m), 1282 (m), 1250 (m), 1125 (s), 1040 (s) 820 (m), 780 (s), 670 (m).

Benzothiophenecarboxaldehyde - 2 - (2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) - thiosemicarbazone(4b): Light yellow powder, Yield 90%, m.p 210°C, Anal. Calcd. C_{36}H_{29}N_{3}O_{7}S_{2}, Mwt: 679, C (63.62%), H (4.27%), N (6.18%), O (16.49%), S (4.71%). Found: C (63.11%), H (4.22%), N (6.11%).

FTIR(KBr): 3370 (m), 3274 (m), 3066 (w), 2879 (w), 2845 (w), 1733 (s), 1660 (m), 1625 (s), 1586 (m), 1523 (m), 1482 (s), 1430 (m), 1378 (m), 1288 (m), 1254 (s), 1125 (s), 1040 (s), 820 (m), 792 (s), 674 (m), 665 (m).

Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones
Hussein Ismael Khalaf

C_{41}H_{34}N_{4}O_{7}S_{2} Mwt: 758, C (64.90%), H (4.48%), N (7.38%), O (14.77%), S (8.44 %).
Found: C (65.31 %), H (4.43%), N (7.29%).
FTIR(KBr) : 3388 (m), 3280(m), 3065(w),2963(w), 2879 (w),2845(w),1736(s), 1650(m), 1625(s),1600(m), 1586 (m),1530(m), 1472(s), 1430 (m), 1376(m),1284(m), 1246(s), 1115(s), 1050(s),817(m),788(s),670(m), 671(m).

10-Methylphenothiazinecarboxaldehyde - 3 - (2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl)- thiosemicarbazone(4d): yellow powder ,Yield 89% ,m.p 274°C,
Anal.Calcd.C_{41}H_{34}N_{4}O_{7}S_{2},Mwt: 758, C (64.90%), H (4.48%), N (7.38%),O(14.77%),S( 8.44 %).Found : C (64.40 %), H (4.44%), N (7.29%).
FTIR(KBr) : 3383 (m), 3284(m), 3069(w),2970(w),2882(w),2845(w), 1730(s),1667(m), 1620(s),1597(m), 1586 (m),1540(m), 1470(s), 1440 (m), 1382(m),1278(m), 1250(s), 1121(s),1070(s),820(m),790(s),669(m), 671(m).

3,4 - Methylenedioxybenzaldehyde - 1 - (2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl) thiosemicarbazone (4e): light yellow powder ,Yield 87% ,m.p 197°C , Anal.
Calcd.C_{35}H_{29}N_{3}O_{9}S, Mwt: 667, C (62.97%), H (4.35%), N (6.29%), O (21.59%), S (4.80 %).Found: C (62.37%), H (4.30%), N (6.35%).
FTIR(KBr) : 3360 (m), 3280(m),3077(w),2874(w),2839(w),1736(s),1649(m),1616(s),1584(m),1532(m), 1467(s), 1429 (m), 1383(m),1278(m), 1255(s),1118(s), 1070(s), 824(m),785(s),668(m).

Imidazol carboxaldehyde - 2 - (2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl) thiosemicarbazone (4f): yellow powder ,Yield 87% ,m.p 200°C , Anal. Calcd.C_{31}H_{27}N_{5}O_{5}S,
Mwt: 613, C (60.68%), H (4.40%), N (11.42%), O (18.27%), S (5.22 %).Found: C (61.00%), H (4.37%), N (11.34%).
FTIR(KBr) : 3387 (m), 3274(m),3100(w),2884(w),2850(w),1727(s),1655(m),1622(s),1580(m),1529(m), 1460(s), 1419 (m), 1375(m),1273(m), 1249(s),1118(s), 1066 (s), 819(m).

Thiazole carboxaldehyde - 2 - (2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl) thiosemicarbazone (4g): Off white ,Yield 84% ,m.p 205°C , Anal. Calcd.C_{31}H_{26}N_{4}O_{7}S_{2}, Mwt: 630, C (59.05%), H (4.13%), N (8.88%), O (17.77%), S (10.16 %).Found: C (59.45%), H (4.10%), N (8.80%)
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

FTIR(KBr) : 3370 (m), 3280(m),3091(w),2875(w),2835(w),1725(s),1644(m),1624(s),1586(m),1533(m),1462(s),1423(m),1377(m),1281(m),1252(s),1123(s),1089(s),840(S),660(w).

4 - Acetyl - 3 - methyl - 1- phenyl - 2 - pyrazoline -5 - one - 4 - (2,3,5-tri-O-benzoyl - β- D - ribofuranosyl)thiosemicarbazone (4h): Yellow powder ,Yield 77% ,m.p 255°C , Anal. Calcd. C_{39}H_{34}N_{5}O_{8}S, Mwt: 732, C (63.93%), H (4.65%), N (9.56%), O (17.48%), S (4.37%). Found: C (64.51%), H (4.70%), N (9.62%).

FTIR(KBr) : 3400 (m), 3290(m),3080(w),2972(w), (w),2885(w),2856(w),1730(s), 1654(m), 1619(s) ,1580(m) ,1534(m), 1460(s), 1423(m), 1382(m),1281(m), 1253(s), 1120(s),1094(s),819(m),680(s).

4 - Benzoyl - 3 - methyl - 1- phenyl - 2 - pyrazoline - 5 - one - 4 - (2,3,5 - tri - O - benzoyl- β-D-ribo - furanosyl)thiosemicarbazone (4i): Yellow powder ,Yield 78% ,m.p 264°C , Anal. Calcd. C_{44}H_{36}N_{5}O_{8}S, Mwt: 794, C (66.50%), H (4.53%), N (8.81%), O (16.12%), S (4.03 %). Found: C (67.11%), H (4.50%), N (8.74%).

FTIR(KBr) : 3375 (m), 3269(m),3078(w),2970(w), (w),2880(w),2858(w),1734(s), 1658(m), 1621(s) ,1582(m) ,1539(m), 1464(s), 1420(m), 1385(m),1284(m), 1253(s), 1125(s),1090(s),1122(s),1084(s),810(m),690(s).

4 - Acetyl - 3 - methyl - 1- (4' - methylphenyl) - 2 - pyrazoline - 5 - one - 4 - (2,3,5 - tri - O - benzoyl- β-D-ribofuranosyl)thiosemicarbazone (4j): Yellow powder ,Yield 75% ,m.p 262°C , Anal. Calcd. C_{40}H_{36}N_{5}O_{8}S, Mwt: 746, C (64.34%), H (4.82%), N (9.38%), O (17.16%), S (4.29%).Found: C (65.00%), H (4.76%), N (9.27%).

FTIR(KBr) : 3389 (m), 3288(m),3086(w),2972(w), (w),2880 (w),2860(w), 17 27(s) , 1660(m), 1621(s) ,1582(m) ,1530(m), 1455(s), 1420(m), 1381(m),1281(m), 1257(s),1118(s),1085(s),830(m),690(s).

4 - Benzoyl - 3 - methyl - 1- (4' - methylphenyl) - 2 - pyrazoline - 5 - one - 4 - (2,3,5 - tri - O - benzoyl- β-D-ribofuranosyl) thiosemicarbazone (4k): Yellow powder ,Yield 79% ,m.p 270°C , Anal. Calcd. C_{45}H_{38}N_{5}O_{8}S, Mwt: 808, C (66.83%), H (4.70%), N (8.66%), O (15.84%), S (3.96 %).Found: C (67.00%), H (4.75%), N (8.60%).
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β - D - ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

FTIR(KBr) : 3380 (m), 3272(m),3073(w),2976(w), (w),2884(w),2850(w), 1732(s ), 1650(m), 1625(s) ,1587(m) ,1543(m), 1460(s), 1410(m), 1381(m),1280(m), 1250(s),
1122(s),1078(s),835(s)794(m) ,690(s).

Debenzoylation of 2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl thiosemicarbazones (4a-k):
A solution of each 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl thiosemicarbazone in saturated methanolic ammonia (30ml) was stirred at room temperature overnight .The solvent was removed under vacuum and the residue was purified on silica gel column eluting with CHCl₃-MeOH(92:8) to afford the debenzoylated analogous compound (5a-k).

Benzofuran carboxaldehyde - 2 - (β - D - ribofuranosyl) thiosemicarbazone (5a):
White solid powder, Yield 65%. Anal. Calcd.C₁₅H₁₇N₃O₅S, Mwt: 351, C (51.28%), H (4.84%), N (11.96%), O (22.79%), S (9.12 %).Found: C (50.87%), H (4.89%), N (12.11%)
FTIR(KBr) : 3420(s),3360 (m), 3270(m) , 3066(w), 2876(w),2840(w), ,1650(m),1615(s)
,1580(m) ,1534(m ), 1460(s),1420 (m), 1376(m),1277(s), ,1125(s), 820(m), 780(s), 670 ( m ) .
¹H-NMR(DMSO-d6):δ ppm,[3.54(m,2H,H-5’),3.79(t,1H,H- 4’),,4.11(t,1H,H-3’), 4.25 ( t,1H,H-
2’)5.80(d,1H,H-1’),4.92(s,1H,OH-3’),5.22(t,1H, OH-5’), 5.54(d,1H, OH-2’)ribose] ,
[7.18(s,1H,H-1),7.32-7.58(m,4H) benzofuran],[6.6(s,1H),8.85(d,1H,H-4’”),11.04(s,1H, H-
2”)thioamide].

Benzo thiophene carboxaldehyde - 2 - (β - D - ribofuranosyl) thiosemicarbazone (5b):
White solid powder, Yield 66%. Anal. Calcd.C₁₅H₁₇N₃O₄S₂, Mwt: 367, C (49.04%), H (4.63%), N (11.44%), O (17.44%), S (17.44 %). Found: C (49.60%), H (4.59%), N (11.38%)
FTIR(KBr) : 3405(s),3377 (m), 3266(m), 3069(w),2873(w),2841(w), 1654(m),1618(s)
,1581(m) ,1513(m), 1470(s), 1430 (m), 1373(m),1281(m), 1233(s),1120(s), ,817(m) , 789(s)
,670(m),667(m).
¹H-NMR(DMSO-d6):δ ppm,[3.41(m,2H,H-5’),3.80(t,1H,H- 4’),,4.15(t,1H,H-3’), 4.30 ( t,1H,H-2’),5.90(d,1H,H-1’),4.95(s,1H,OH-3’),5.25(t,1H, OH-5’), 5.58(d,1H, OH-2’)ribose] ,
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β- D-ribofuranosyl) thiosemicarbazones
Hussein Ismael Khalaf

[7.89(s,1H,H-1),7.39-7.79(m,4H) benzothiophene],[6.77(s,1H),8.80(d,1H,H-4″),10.98 (s, 1H, H-2″)thioamide].

10 - Methylphenothiazine carboxaldehyde - 4 - (β - D - ribofuranosyl) thiosemi-carbazone (5c): white foam , Yield 70% , Anal.Calcd.C_{20}H_{22}N_{4}O_{4} S_{2}, Mwt: 446, C (53.81%), H (4.93%), N (12.56%),O(14.35%),S( 14.35 %).Found: C (54.14%), H (5.00%), N (12.40%).
FTIR(KBr) :3440(s) 3381 (m), 3275(m), 3070(w),2960(w),2873(w),2840(w), 1650(m), 1625(s) ,1602(m), 1586 (m),1527(m), 1470(s), 1434 (m), 1376(m),1281(m), 1251(s), 1101(s), 813(m),782(s),671(m).

1H-NMR(DMSO-d6):δppm, [3.45(m,2H,H-5′),3.78(t,1H,H- 4′), 4.20(t,1H,H-3′), 4.29 (t, 1H,H-2′)5.94(d,1H,H-1′),4.92(s,1H,OH-3′),5.21(t,1H, OH-5′), 5.55(d,1H, OH-2′)ribose] , [2.92(s,3H,CH_{3})), 6.77-7.40(m,7H) 10-methylphenothiazine], [6.80(s,1H),8.82(d,1H,H-4″),11.10 (s, 1H, H-2″)thioamide].

10 - Methylphenothiazine carboxaldehyde – 3 - (β - D-ribofuranosyl) thiosemi-carbazone (5d ) : white foam ,Yield 65% , Anal.Calcd.C_{20}H_{22}N_{4}O_{4} S_{2}, Mwt: 446, C (53.81%), H (4.93%), N (12.56%),O(14.35%),S( 14.35 %).Found: C (54.40%), H (5.00%), N (12.41%).
FTIR(KBr) :3460(s), 3375 (m), 3274(m), 3073(w),2972(w),2885(w),2845(w), 1662(m) , 1622(s) ,1597(m), 1581(m),1533(m), 1462(s), 14290 (m), 1378(m),1256(m), 1111(s), 822(m),782(s),664(m) , 673(m).

1H-NMR(DMSO-d6):δppm, [3.50(m,2H,H-5′),3.82(t,1H,H- 4′), 4.15(t,1H,H-3′), 4.29 (t, 1H,H-2′)5.94(d,1H,H-1′),4.92(s,1H,OH-3′),5.21(t,1H, OH-5′), 5.55(d,1H, OH-2′)ribose] , [3.34(s,3H,CH_{3})), 6.74-7.59(m,7H) 10-methylphenothiazine], [6.74(s,1H),8.84(d,1H,H-4″),11.05 (s, 1H, H-2″)thioamide].

3, 4 - Methylene dioxybenzaldehyde - 1 - (β - D- ribofuranosyl) thiosemicarbazone (5e): white powder, Yield 56%, Anal. Calcd.C_{14}H_{17}N_{3}O_{6}S, Mwt: 355, C (47.32%), H (4.79%), N (11.83%), O (27.04%), S (9.01 %).Found: C (46.80%), H (4.72%), N (11.70%).
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

FTIR(KBr) :3430(s) 3373(m), 3260(m), 3070(w), 2872(w),2833(w), 1649(m),1620(s), 1580(m),1531(m), 1460(s), 1438 (m), 1380(m), 1278 (m), 1251(s),1118(s),1030(s), 810(m), 780(s),664(m) .

1H-NMR(DMSO-d6):δppm, [3.55(m,2H,H-5’),3.80(t,1H,H- 4’), ,4.31(t,1H,H-3’), 4.12 (t, 1H,H-2’)] 5.96(d,1H,H-1’),4.92(s,1H,OH-3’),5.22(t,1H, OH-5’), 5.54(d,1H, OH-2’)ribose] , [7.32(s,1H),7.40(d,1H),6.94(d,1H), 3.8(s,2H) 3,4-Methylene dioxybenzene], [6.44(s,1H), 8.82(d,1H,H-4’”),11.03 (s, 1H, H-2”’thioamide].

Imidazol carboxaldehyde - 2 - (β - D - ribofuranosyl) thiosemicarbazone (5f):
White powder, Yield 71%, Anal. Calcd.C_{10}H_{15}N_{5}O_{4}S, Mwt: 301, C (39.87%), H (4.98%), N (23.26%), O (21.26%), S (10.63 %).Found: C (39.37%), H (4.92%), N (23.00%).

FTIR(KBr) :3449 (s),3390 (m), 3281(m),3088(w),2880(w),2843(w), 1651(m),1623(s) ,1557(m) , 1462(s), 1422(m), 1379(m),1263(m), 1250(s),1114(s), 819(m) .

1H-NMR(DMSO-d6):δppm, [3.54(m,2H,H-5’),3.82(t,1H,H- 4’), ,4.20(t,1H,H-3’), 4.33 (t, 1H,H-2’)] 6.01(d,1H,H-1”), 4.93(s,1H,OH-3’),5.20(t,1H, OH-5’), 5.53(d,1H, OH-2”)ribose] , [7.40(d,1H),7.60(d,1H),10.6(s,N-H) Imidazol], [6.60(s,1H), 8.80(d,1H,H-4’”),11.00 (s, 1H, H-2”’thioamide].

Thiazole carboxaldehyde - 2 - (β - D - ribofuranosyl) thiosemicarbazone (5g):
White foam, Yield 64%, Anal. Calcd.C_{10}H_{14}N_{4}O_{4}S_{2}, Mwt: 318, C (37.74%), H (4.40%), N (17.61%), O (20.13 %), S (20.13 %).Found: C (37.45%), H (4.45%), N (17.40%)

FTIR(KBr) : 3470(s),3390 (m), 3283(m),3040(w),2871(w),2830(w), 1644(m),1621(s) , (m) ,1550(m), 1459(s), 1370(m),1282(m), 1246(s),1113(s), 999(s),833 (s) , 671(w) .

1H-NMR(DMSO-d6):δppm, [3.56(m,2H,H-5’),3.80(t,1H,H- 4’), ,4.12(t,1H,H-3’), 4.33 (t, 1H,H-2’)] 5.82(d,1H,H-1”), 4.91(s,1H,OH-3’),5.22(t,1H, OH-5’), 5.54(d,1H, OH-2”)ribose] , [7.50(d,1H),7.30(d,1H), Thiazole], [6.50(s,1H), 8.81(d,1H,H-4””),10.99 (s, 1H, H-2”’thioamide].

4 - Acetyl -3 - methyl -1- phenyl - 2- pyrazoline - 5 - one - 4 - (β - D - ribofuranosyl) - thiosemicarbazone (5h): light Yellow powder, Yield 67%, Anal. Calcd. C_{18}H_{22}N_{5}O_{5}S, Mwt: 420, C (51.43%), H (5.24%), N (16.66%), O (19.05%), S (7.62%).Found: C (50.81%), H (5.30%), N (16.53%)
Microwave-Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β- D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

FTIR(KBr) : 3460(s), 3390(m), 3273(m),3072(w),2966(w), (w),2875(w),2844(w), 1657(m), 1621(s), 1580(m), 1538(m), 1454(s), 1423(m), 1377(m),1279(m), 1247(s), 1120(s), 823(m), 684(s).

\[ ^1 \text{H-NMR(DMSO-d6):} \delta \text{ppm, } [3.50(m,2H,H-5'),3.79(t,1H,H- 4'), ,4.09(t,1H,H-3'), 4.29 (t, 1H,H-2')5.68(d,1H,H-1'),4.90(s,1H,OH-3'),5.21(t,1H, OH-5'), 5.52(d,1H, OH-2')ribose] , [2.31(s,3H,CH3),7.22-7.53(m,5H,ph),3-methyl-1-phenyl-2-pyrazoline-5-one],[2.42 (s,3H,CH3) , 8.84(d,1H,H-4"),11.08 (s, 1H, H-2")thioamide].

4 -Benzoyl - 3 - methyl - 1 - phenyl - 2 - pyrazoline - 5 - one - 4 - (β - D-ribofuranosyl) - thiosemicarbazone (5i): Yellow powder, Yield 70%, Anal. Caled. C_{23}H_{24}N_{5}O_{5}S, Mwt: 482, C (57.26%), H (4.98%), N (14.52%), O (16.60%), S (6.64 %). Found: C (58.01%), H (5.02%), N (14.38%).

FTIR(KBr) : 3440(s)3365(m), 3260(m),3067(w),2970(w), (w),2875(w),2844(w), 1660(m), 1624(s), 1580(m), 1532(m), 1469(s), 1423(m), 1380(m),1279(m), 1247(s), 1120(s), 1084(s), 819(m), 693(s).

\[ ^1 \text{H-NMR(DMSO-d6):} \delta \text{ppm, } [3.55(m,2H,H-5'),3.83(t,1H,H- 4'), ,4.11(t,1H,H-3'), 4.33 (t, 1H,H-2')5.85(d,1H,H-1'),4.92(s,1H,OH-3'),5.22(t,1H, OH-5'), 5.54(d,1H, OH-2')ribose] , [2.36(s,3H,CH3),7.30-7.62(m,10H,2ph),3-methyl-1-phenyl-2-pyrazoline-5-one],[8.86(d, 1H , H-4"),11.04 (s, 1H, H-4")thioamide].

4 -Acetyl - 3 - methyl - 1- (4'-methylphenyl) -2 - pyrazoline - 5 - one - 4 - (β - D - ribofuranosyl) thiosemicarbazone (5j): Yellow powder, Yield 65%, Anal. Caled.
C_{19}H_{24}N_{5}O_{5}S, Mwt: 434, C (52.53%), H (5.53%), N (16.13%), O (18.43%), S (7.37%). Found: C (51.85%), H (5.60%), N (16.00%)

FTIR(KBr) : 3451(s), 3380 (m), 3281(m),3067(w),2969(w), (w),2875 (w),2834(w), 1662(m), 1617(s), 1580(m), 1534(m), 1451(s), 1434(m), 1376(m),1279(m), 1250(s), 1110(s), 833(m), 691(s).

\[ ^1 \text{H-NMR(DMSO-d6):} \delta \text{ppm, } [3.55(m,2H,H-5'),3.81(t,1H,H- 4'), ,4.11(t,1H,H-3'), 4.30 (t, 1H,H-2')5.81(d,1H,H-1'),4.92(s,1H,OH-3'),5.21(t,1H, OH-5'), 5.54(d,1H, OH-2')ribose] , [2.31(s,3H,CH3), 2.40(s,3H,CH3), 2.51 (s,3H,CH3),7.20-7.55(m,4H,ph), 3-methyl-1-(4'-}
Microwave-Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde/Ketone- (β-D-ribofuranosyl) thiosemicarbazones
Hussein Ismael Khalaf

methylphenyl) -2-pyrazoline-5-one], [2.42(s,3H,CH₃), 8.82(d,1H,H-4”),11.03 (s, 1H, H-2”)thioamide].

4 - Benzoyl - 3 - methyl - 1 - (4' - methyl phenyl) -2 - pyrazoline - 5 - one -4 - (β -D - ribofuranosyl) thiosemicarbazone (5k): Yellow powder, Yield 64%, Anal. Calcd.
C₂₄H₂₆N₅O₅S, Mwt: 496, C (58.06%), H (5.24%), N (14.11%), O (16.13%), S (6.45 %). Found: C (57.35%), H (5.31%), N (14.09%).

FTIR(KBr) : 3451(s), 3374 (m), 3266(m),3065(w), 2976(w), (w),2870(w),2843(w), 1660(m),
1625(s), 1581(m), 1540(m), 1454(s), 1421(m), 1380(m),1276(m), 1244(s), 1118(s),
840(s)790(m),684(s).

1H-NMR(DMSO-d6):δppm, [3.53(m,2H,H-5’),3.82(t,1H,H- 4’), 4.12(t,1H,H-3’), 4.35 (t, 1H,H-2’)5.90(d,1H,H-1’),4.90(s,1H,OH-3’),5.22(t,1H, OH-5’), 5.52(d,1H, OH-2’)ribose] ,
[2.24(s,3H,CH₃), 2.36(s,3H,CH₃)7.22-7.52(m,9H,2ph), 3-methyl-1-(4'-methylphenyl) -2-
pyrazoline-5-one], [8.80(d,1H,H-4”),10.98 (s, 1H, H-2”)thioamide].

Antimicrobial Activities
The standardized disc-agar diffusion method(27) was followed to determine the activity of the synthesized compounds against the sensitive organisms Staphylococcus aureus as Gram-positive bacteria and Escherichia coli as Gram-negative bacteria. Amoxicillin (30µg) was used as standard drug (positive control). A DMSO-wetted disk was used as negative control. The tested compounds were dissolved in dimethyl sulfoxide [(DMSO) which has no inhibition activity] to get concentration of 2 mg /ml. The test was performed on medium potato dextrose agar (PDA) . Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10µL, 20 µg) from the specific concentration of dissolved test compounds and placed on incubated agar surface.

The susceptibility of the bacteria to the test compounds was determined by the formation of an inhibitory zone after 18h of incubation at 36°C . Table 1 reports the inhibition zones (mm) of each compound.
Results and discussion

The starting material compound 1 (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate) was freshly prepared as yellow syrup from D-ribose sugar and confirmed by FTIR spectrum (strong stretching vibration at 2060 cm\(^{-1}\), due to the formation of (N = C = S bond)\(^{(23)}\). Compound 2 (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl thiosemicarbazide) was synthesized by condensation reaction of compound 1 and hydrazine hydrate in dry methylene chloride at 15°C, as shown below. The IR spectrum showed the characteristic stretching vibration for the NH and NH\(_2\) groups in the thiosemicarbazide moiety (NH-(C=S)-NH-NH\(_2\)) at 3342 cm\(^{-1}\),3280 cm\(^{-1}\) and 3190 cm\(^{-1}\), in addition to characteristic bands, \(\nu(C=S)\) at 1290 cm\(^{-1}\) and \(\delta(C=S)\) at 820 cm\(^{-1}\). Stretching vibrations of ribosyl moiety appeared at 1736 cm\(^{-1}\), 1240 cm\(^{-1}\) and 1048 cm\(^{-1}\) for the ester groups (benzoate).

Benzofuran-2-carboxaldehyde (3a) and benzothiophene-2-carboxaldehyde (3b) were synthesized by the direct lithiation (n-BuLi) of benzofuran and benzothiophene respectively, and subsequent formulation with DMF. While, 10-methylphenothiazine-4-carboxaldehyde (3c) was synthesized from 10-methylphenothiazine using the same procedure except dry ether and TMEDA as catalyst was added\(^{(24)}\). 10-Methylphenothiazine-carboxaldehyde was synthesized by brominating of 10-methylphenothiazine followed by lithium-bromine exchange and formulation with DMF. Column chromatography was used to obtain a pure 3-bromo-10-methylphenothiazine. 4-Acetyl / benzoyl-2-pyrazoline - ones (3h-k) were synthesized according to reported method\(^{(25, 26)}\). Elemental analysis, melting points
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone - (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

and FTIR results for synthesized compounds (3a-k) were compared with the available literature (25, 26). All these prepared compounds (3a-k) gave satisfactory elemental analysis, which are in close agreement with the empirical formula of the respective heteroaromatic aldehydes and ketones. FTIR spectra of compounds(3a-d) showed weak bands ranged of 2820 – 2871 cm⁻¹, 2740-2760 cm⁻¹ and strong bands ranged of 1650 – 1705 cm⁻¹ which are characteristic bands of carboxaldehyde group, while FTIR spectra of compounds(3h-k) showed the characteristic band ranged 1635-1663 cm⁻¹ related to carbonyl group.

The synthesis of (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl) thiosemicarbazones(4a-k) is outlined next, through condensation reaction of 2,3,5-Tri-O-benzoyl-β-D-ribo-furanosyl thiosemicarbazide 2 with several heteroaromatic aldehydes or heteroaromatic ketones (3a-k). The synthesis was carried out in ethanol at reflux temperature either by modified domestic microwave oven irradiation or conventional heating (heating mental). It was observed that all the reactions under microwave irradiation were done within 10 min., and yield reached 90% for aldehyde and 79% for ketones, whereas similar reactions under conventional heating at reflux gave less yields (not exceed than 75% for aldehyde and 65% for ketones) after much longer reaction time (5h). These results indicated that microwave technique gave improved yield in less reaction time than conventional heating method. This is because microwave ray couple directly with the molecules of the reactants in the mixture leading to a rapid rise in temperature(super heating)(28).
Microwave-Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf
The FTIR spectra of the synthesized thiosemicarbazones (4a-k) showed generally, characteristic absorptions in the range of 3350-3400 cm\(^{-1}\) and 3269-3290 cm\(^{-1}\) which are assigned to \(\nu (N-H)\). Strong bands in the region 1273-1288 cm\(^{-1}\) and 810-840 cm\(^{-1}\) due to \(\nu (C=S)\) and \(\delta (C=S)\) respectively and absence of any band in the region 2500-2600 cm\(^{-1}\) due to \(\nu (C-SH)\) suggested that all the thiosemicarbazones remain in their thion form. Another characteristic band proved the formation of thiosemicarbazones is the strong band arranged of 1619 -1625 cm\(^{-1}\) due to \(\nu (C=N)\) stretching of the azomethine linkage. The bands at 1727 - 1740, 1246 – 1212 cm\(^{-1}\) and 1040 – 1090 cm\(^{-1}\) is characteristic bands of ester group (benzoate).

The debenzyolation of compounds (4a-k) was attempted using methanolic ammonia in dry methanol. As a result deblocked β-D-ribofuranosyl thiosemicarbazones (5a-k) were obtained in moderate yields (60-73%). Most of these compounds get decomposed on heating therefore, their melting points were not very sharp. All these compounds (5a-k) were purified by column chromatography and their purity checked by thin layer chromatography on silica gel plates with fluorescent-254nm using solvent system (Methanol: Chloroform 9:1).

The FTIR spectra of all the debenzzoylated β-D-ribofuranosyl thiosemicarbazones (5a-k) showed a broad band centered at 3500-3250 cm\(^{-1}\) due to the overlap of the stretching vibrations of N-H and O-H groups. In addition, any signal due to carbonyl stretching vibrations of benzoyl group was lacked. The remaining IR spectral data was found, more or less the same as for the benzoylated compounds. Figure 1. Shows an exampling of FTIR for compound 5a.

\(^1\)H-NMR spectra of a debenzyolated β-D- ribofuranosyl thiosemicarbazones (5a-k) showed resonating peaks related to the protons (H-1’, H-2’, H-3’, H-4’, H-5’) for ribose moiety. Anomeric proton (H-1’) of ribose moiety which resonated in the region (5.8-6.01)ppm showed doublets peaks. It means, clear indication of diaxial orientation of H-1’ and H-2’, hence confirming the β-configuration in these compounds.

N-H protons (H-2’&H-4’) of thioamide functionality appeared at 10.98-11.10 ppm as single for H-2” and doublet for H-4” at8.82-8.86 ppm. In addition, protons of heterocyclic parts were
Microwave-Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

clearly appeared in the expected positions in spectra. Figure 2 shows an exampleing $^1$H-NMR spectrum of compound 5a.
The invitro antibacterial activity of the synthesized β-D-ribofuranosyl thiosemicarbazones (5a-k) were assayed by the diffusion method using culture of Staphylococcus aureus as Gram-positive bacteria and Escherichia coli as Gram-negative bacteria Amoxicillin (30µg) was used as the standard drug, whereas DMSO-wetted disk was used as negative control. results showed good antibacterial activity compared to the standard drug.

![Figure 1. FTIR Spectrum of Compound 5a](image-url)
Microwave-Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

Figure 2. $^1$H-NMR Spectrum of Compound 5a
Table 1. Antibacterial activity of the synthesized β-D-ribo-furanosyl thiosemicarbazones (5a-k), measured by the Halo Zone Test (unit, mm).

<table>
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<th>Compound</th>
<th>E.coli</th>
<th>S.aureus</th>
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<tr>
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<tr>
<td>5b</td>
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Conclusion

The modified domestic microwave oven can be use efficiently in the synthesis of thiosemicarbazone derivatives. Polar organic solvent (MeOH) was a suitable absorber for microwave energy. The method is simple, fast and give high yield. The ribofuranosyl moiety in the synthesized thiosemicarbazone derivatives of hetero aromatic aldehydes or ketones (5a-k) enhances the antibacterial activity for these compounds.
Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone- (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

References

Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone – (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf

Microwave – Assisted Synthesis and Characterization of New Heteroaromatic Aldehyde / Ketone – (β-D-ribofuranosyl) thiosemicarbazones

Hussein Ismael Khalaf