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Efficient synthesis and anti-bovine viral diarrhea virus evaluation of 5-(aryldiazo)salicylaldehyde thiosemicarbazone derivatives

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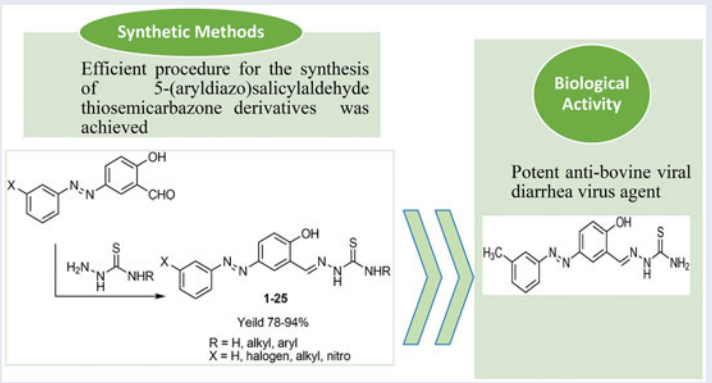
ABSTRACT

An efficient procedure for the synthesis of 5-(aryldiazo)salicylaldehyde thiosemicarbazone derivatives 1-25 was achieved via the condensation of 5-(aryldiazo)salicylaldehyde derivatives I–V with *N*-(4)-substituted thiosemicarbazide derivatives. Antiviral activity of the synthesized compounds was carried out. From the obtained results, it was noticed that compound 11 has a strong antiviral activity.

GRAPHICAL ABSTRACT



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Introduction

Thiosemicarbazone derivatives were reported as interesting moiety where they displayed a wide range of biological activities such as antibacterial, antifungal, antiprotozoal, anti-tumor, and antiviral activities (Figure 1).[1–4]

In 1972, D. J. Bauer stated that the first true antiviral agents discovered were the thiosemicarbazones.[5] In 1950, *p*-aminobenzaldehyde thiosemicarbazone was found as the first antiviral agent to be active against vaccinia virus infection in mice and fertile

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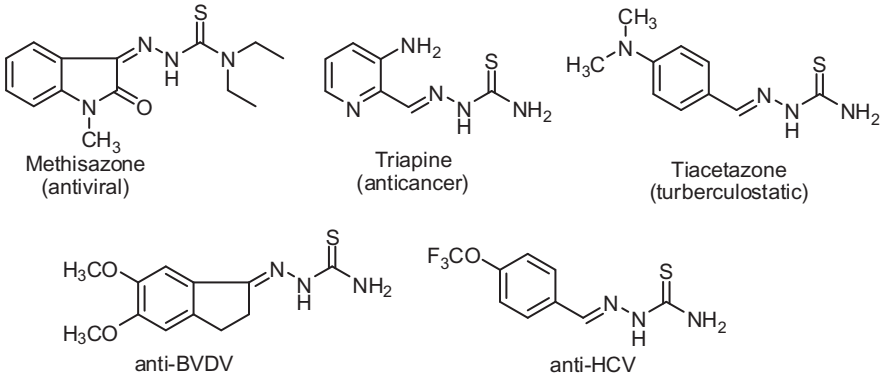


Figure 1. Some of the known biologically active thiosemicarbazone derivatives.

eggs.[6,7] Then, a wide range of thiosemicarbazones were discovered from which isatin 3-thiosemicarbazone (methisazone) was emerged (Figure 1). Methisazone was used for man where it had tentative efficacy in the treatment and prophylaxis of smallpox.[8]

Some thiosemicarbazone derivatives (Figure 1) showed potent anti-bovine viral diarrhea virus activity. The thiosemicarbazones have the potentiality as antiviral agents for the treatment of infections caused by other highly related members of Flaviviridae family such as hepatitis C virus.[9] Therefore, thiosemicarbazone-related compounds (Figure 1) being strong inhibitors of HCV replicon replication.[10]

Owing to their versatile chemistry, researches have been progressed to design and synthesize broad spectrum of thiosemicarbazone derivatives. Also, thiosemicarbazone derivatives are versatile scoffed for the syntheses of biologically active heterocyclic compounds.[11]

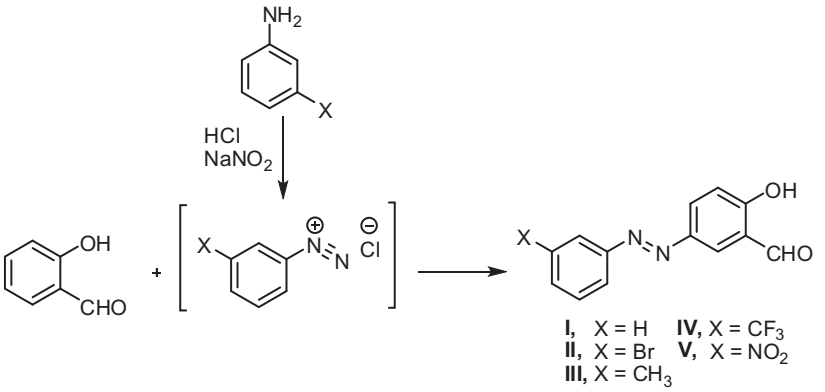
Today, the chemists, especially the synthetic organic chemists are faced with development of new procedures or improvement of old procedures with environmental concerns where energy/cost-effective preparations and minimal waste production should be taken into consideration.[12–14]

Therefore, the aim of the present work was directed for synthesizing several newer thiosemicarbazone derivatives and bear structural similarities to the well-known potent anti-HCV agents.

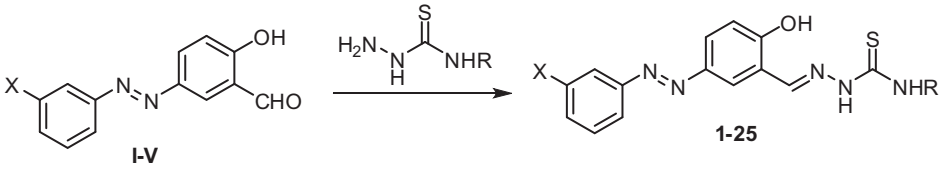
Result and discussion

The present investigation was directed for synthesizing a new series of 5-(aryldiazo)-salicylaldehyde thiosemicarbazone derivatives bearing various substituents at aryldiazo and *N*-(4)-substituted thiosemicarbazone moieties. The aryldiazo-salicylaldehyde derivatives **I–V** precursors are not commercially available, as far as we are aware and were prepared. Thus, 5-(3-substituted-phenyldiazo)-salicylaldehyde derivatives **I–V** were prepared according to the previously reported procedures via reacting salicylaldehyde with the appropriate 3-substituted-phenyldiazonium chloride (Scheme 1).[15–19] Structural elucidation of compounds **I–V** was accomplished by careful inspection of their spectral data.

Many trails were carried out for synthesizing the desired thiosemicarbazone derivatives. Generally, the *N*-(4)-substituted thiosemicarbazone derivatives **1–25** were synthesized via



Scheme 1. Synthesis of 5-(3-substituted-phenyldiazo)-salicylaldehyde derivatives I–V.



1 X = H R = H
2 X = H R = CH_3
3 X = H R = C_2H_5
4 X = H R = C_6H_5
5 X = H R = $C_6H_4OCH_3$-4
6 X = Br R = H
7 X = Br R = CH_3
8 X = Br R = C_2H_5
9 X = Br R = C_6H_5
10 X = Br R = $C_6H_5OCH_3$-4
11 X = CH_3 R = H
12 X = CH_3 R = CH_3
13 X = CH_3 R = C_2H_5
14 X = CH_3 R = C_6H_5
15 X = CH_3 R = $C_6H_4OCH_3$-4
16 X = CF_3 R = H
17 X = CF_3 R = CH_3
18 X = CF_3 R = C_2H_5
19 X = CF_3 R = C_6H_5
20 X = CF_3 R = $C_6H_4OCH_3$-4
21 X = NO_2 R = H
22 X = NO_2 R = CH_3
23 X = NO_2 R = C_2H_5
24 X = NO_2 R = C_6H_5
25 X = NO_2 R = $C_6H_4OCH_3$-4

Scheme 2. Synthesis of 5-(3-substituted-phenylazo)-salicylaldehyde thiosemicarbazones 1–25.

reacting the 5-(3-substituted-phenylazo)-salicylaldehydes **I–V** with the desired thiosemicarbazide derivative (Scheme 2).

Structure of the *N*-(4)-substituted thiosemicarbazones **1–25** was investigated through careful study of their spectral data as well as their elemental analyses. IR spectra showed ν(OH) in the region 3468–3409 cm^{-1} as characteristic intense bands due tothe phenolic group. The spectra showed other bands in the region 3300–3100 cm^{-1} attributed to NH groups. IR spectra revealed also the presence of bands in 1618–1614 cm^{-1} and 1281–1223 cm^{-1} regions for CH = N and C = S diagnostic groups, respectively, for thiosemicarbazones with the disappearance of carbonyl group bands.

^{1}H NMR spectra of **1–25** were characterized, generally, by the presence of broad signals integrating as one proton at about $\delta = 10.90$ ppm (D_2O-exchangeable) assigned to the OH protons. The spectra of the 4-amino derivatives showed NH_2 proton signals at: δ about 8.20 ppm. For other substituted products, NH-R proton signals appeared at δ about 8.60 and 10.20 ppm for alkyl and aryl substituents, respectively. The spectra revealed also signals due to NH–N = protons at δ in the region 11.86–11.48 ppm (D_2O-exchangeable) beside the other characteristic signals. ^{13}C NMR spectral assignments

depended on characteristic signals, where the signals resonated in the deshielded region about 160 and 177 ppm are assigned to C = N and C = S, respectively.

Anti-viral screening of the new synthesized compounds

Preliminary anti-viral screening of selected examples from the synthesized products was carried out on the bovine viral diarrhea virus (BVDV), which is a single positive RNA stranded virus classified as a member of the same family of hepatitis C Virus (HCV), i.e. flaviviridae. Some of the synthesized compounds were subjected to *in vitro* testing of antiviral activity. Viral infectivity assay was carried out using the plaque formation method.[20] A plaque is a localized focus of virus-infected cells which under optimal conditions originates from a single infectious virus particle. Counting of these foci for serial dilution of virus suspension is a highly quantitative method for assay of viral infectivity. Under these conditions, reduction in virus plaque counts provides a very sensitive mean for measuring the antiviral activity of a potential antiviral. The results of the plaque reduction assay are summarized in Table 1. The antiviral effect obtained for the synthesized compounds suggested that the tested thiosemicarbazone derivatives have no antiviral activity or have a toxic effect on the cells.

From the results obtained from the Table 1, it was noticed that compound **11** has a strong antiviral activity. Compounds **9** and **25** have a toxic effect on the cells. The activity of thiosemicarbazone derivative **11** may be attributed to the presence of the methyl group at 5-(arylazo)salicylaldehyde moiety and free amino group at N-(4)-thiosemicarbazone moiety. The presence of 4-bromo- and 4-nitrophenyl-substituents at arylazo (**9** and **25**) showed a toxic effect on the cells.

Conclusion

A new series of novel *N*-(4)-substituted thiosemicarbazone derivatives bearing *N*-(4)-substituted-aryl moieties were synthesized for their expected antiviral activity. The expected anti-viral properties of selected examples from the synthesized derivatives were studied. The results indicated that compound **11** is the active one, while the other tested products were inactive or cytotoxic. Therefore, the present study revealed a new potent anti-viral agent.

Experimental section

Synthesis of the 5-(aryldiazo) salicylaldehyde thiosemicarbazone derivatives

A mixture of salicylaldehyde derivatives **I–V** (0.01 mol) and the thiosemicarbazide derivatives (namely thiosemicarbazide, *N*-(methyl)-thiosemicarbazide, *N*-(ethyl)-

TABLE 1. Antiviral Screening of selected examples of the synthesized thiosemicarbazone derivatives.

Sample	Concentration (10 μg/ml)	Notes
9	Toxic effect	————————————
11	$2 \times 10^{-4.6}$ PFU	(Active compound)
25	Toxic effect	————————————
Positive control	$85^{*}10^{-4.6}$ PFU	

thiosemicarbazide, *N*-(phenyl)-thiosemicarbazide and *N*-(4-methoxyphenyl)-thiosemicarbazide) (0.01 mol) in ethanol (25 mL) was heated under reflux for 1 h and then left to cool. The solid product obtained was filtered off and crystallized from ethanol to give the desired thiosemicarbazone **1–25.**

2-(5-((3-Bromophenyl)diazenyl)-2-hydroxybenzylidene)-N-ethylhydrazinecarbothioamide (8)

Yield 80%; m.p. 224–225 °C; IR: ν/cm^{-1}=3365, 3259 (NH), 1606 (C = N); ^{1}H NMR: δ/ppm: 1.12 (t, 2H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 3.57 (q, 2H, J = 7.0 Hz, $\underline{CH_2}CH_3$), 7.02 (d, 1H, J = 8.8 Hz, Ar–H), 7.53 (t, 1H, J = 9.0 Hz, Ar–H), 7.69 (d, 1H, J = 7.9 Hz, Ar–H), 7.76 (dd, 1H, J = 8.8, 2.2 Hz, Ar–H), 7.86 (d, 1H, J = 7.7 Hz, 1H, Ar–H), 7.93 (s, 1H, Ar–H), 8.40 (s, 1–H, Ar–H), 8.61 (s, 1H, CH = N), 8.66 (br, 1H, NH), 10.97 (br, 1H, OH), 11.48 (br, 1H, NH); ^{13}C NMR: 15.0, 39.8, 117.3, 121.4, 122.9, 123.5, 124.1, 124.6, 131.7, 133.5, 138.9, 145.5, 153.4, 160.1, 176.7; Anal. Calcd. for $C_{16}H_{16}BrN_5OS$ (406.3): C, 47.30; H, 3.97; N, 17.24; Found: C, 47.27; H, 4.01; N, 17.18%.

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