Methyl-2-arylidene hydrazinecarbodithioates: synthesis and biological activity

Manojkumar Mahapatra, Umasankar Kulandaivelu, Philipp Saiko, Geraldine Graser, Thomas Szekeres, Graciela Andrei, Robert Snoeck, Jan Balzarini, Venkatesan Jayaprakash*

Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, Jharkhand 835 215, India

Medicinal Chemistry Research Division, Vaagdevi College of Pharmacy, Hanamkonda, Warangal, Andhra Pradesh 506 001, India

Department of Medical and Chemical Laboratory Diagnostics, General Hospital of Vienna – Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

Rega Institute for Medical Research, KU Leuven, B-3000, Leuven, Belgium

Valens Pharma Services, Regus Citi Centre, Level 6, Chennai Citi Centre, 10/11, Dr.Radakrishnan Salai, Chennai, Tamil Nadu 600 004, India

Received 23 September 2012; Revised 29 November 2012; Accepted 13 December 2012

Methyl-2-arylidene hydrazine-carbodithioate has not been of particular interest to researchers even though its metal complexes are extensively reported on due to their biological activity. This study examined the cytostatic and antiviral activity of twelve methyl-2-arylidene hydrazinecarbodithioates reported by many researchers as intermediates for the synthesis of thiosemicarbazides and the preparation of their metal complexes. Compounds IIc, IIi, and III with tridentate ligand features were found to have the lowest IC50 value (6.5 µM, ≈ 1 µM, and 0.8 µM, respectively) against HL60 human promyelocytic leukemia cells. They were also most inhibitory to human embryonic lung (HEL) fibroblast proliferation (5.3 µM, 17 µM, and 2.6 µM). Compound IIc and IIi show antiviral activity against wild-type herpes simplex virus (HSV), varicella zoster virus (VZV), and acyclovir-resistant HSV; however, these activities were observed at concentrations at which the compounds also markedly inhibit HL60 and HEL cell proliferation.

Keywords: Schiff’s base, methyl hydrazinecarbodithioate, HL60 cell line, anticancer, antiviral, cytotoxicity

Introduction

Many N-substituted thiosemicarbazones were prepared by the condensation of Schiff’s bases of methyl-2-arylidene hydrazinecarbodithioate (MAHCD) with amines (Casero et al., 1980; Collins et al., 1982; Klayman et al., 1979, 1991; Scovill et al., 1982; Shiman et al., 1981). While thiosemicarbazones and their metal complexes were studied for their biological activity (Beraldo & Gambino, 2004; Ettari et al., 2010; Jiang et al., 2006; Katz, 1987; Libert & West, 1992; Matesanz & Souza, 2009; Pandey & Dimmock, 1993; Wnuk & Robins, 2006; Yu et al., 2009), the intermediate MAHCD was rarely studied for its metal complexation behaviour and the complexes for their biological activity (Ali et al., 2002; Kanwar et al.,...
Fig. 1. Similarity of title compounds with Schiff’s base of \( N \)-hydroxy semicarbazides (SNHS) and \( N \)-hydroxy aminoguanidines (SNHAG).

It was proposed that these compounds act by inhibiting ribonucleotide reductase (RR) through metal chelation (Das et al., 1999; Ren et al., 2002; T’ang et al., 1985). With this background, twelve MAHCD derivatives were synthesised and evaluated for anticancer activity against HL60 human promyelocytic leukemia cells and antiviral activity against a panel of viral cell lines.

**Experimental**

**Synthesis of methyl hydrazinecarbodithioate (I) and substituted benzaldehyde hydrazones of methyl hydrazine carbodithioate (II)**

To an ice cooled solution (< 10°C) of 19.8 g (0.300 mol) of potassium hydroxide in 24 mL of water and 20 mL of propan-2-ol, 17.1 mL of 80 % pure hydrazine hydrate were added and constantly stirred. The amount of 18.2 mL (0.300 mol) of ice cooled carbon disulfide was added drop wise to the stirred solution, maintained at < 10°C for over about 1–1.5 h. The bright yellow mixture formed was stirred for an additional 1 h after which ice cooled iodomethane (18.7 mL, 0.300 mol) was added drop wise over a 2 h period. Stirring was continued for an additional 1 h, and the white precipitate obtained was filtered and washed with ice-cold water. The crude product was recrystallised from dichloromethane: yield of 43 %; m.p. = 82°C. (82°C, Audrieth et al. (1954); 81–83°C, Klayman et al. (1979)).

Methyl hydrazinecarbodithioate (20.0 mmol) was dissolved in 20 mL of methanol and then, equimolar amount of aromatic/heteroaromatic aldehyde was added. The mixture was refluxed for 6–12 h and the reaction was monitored by TLC. The hot solution was poured onto crushed ice and the precipitate obtained was filtered (Klayman et al., 1979; Scovill et al., 1982): yield of 60–80 %.

**Anticancer activity assay procedure**

The HL-60 human promyelocytic leukemia cell line was purchased from ATCC (American Type Culture Collection, Manassas, VA, USA). Cells were grown in a RPMI 1640 medium supplemented with a 10 % heat inactivated fetal calf serum (FCS), 1 % L-glutamine and 1 % penicillin–streptomycin in a humidified atmosphere containing 5 % of CO\(_2\). All media and supplements were obtained from Life Technologies (Paisley, Scotland, UK). Cell counts were determined using a micro cell counter CC-108 (SYSMEX, Kobe, Japan).

Cells growing in the logarithmic phase of growth were used in all experiments described below. HL-60 cells (10\(^5\) per mL) were seeded in 25 cm\(^2\) Nunc tissue culture flasks and incubated with increasing concentrations of drugs (IIa–III) at 37°C under cell culture conditions. Cell counts and IC\(_{50}\) values were determined after 24 h, 48 h, and 72 h using the micro cell counter CC-108. Viability of the cells was determined by trypan blue exclusion. Results were calculated as the number of viable cells.

**Antiviral activity assay procedure**

Antiviral assays (except anti-human immunodeficiency virus (HIV) assays) were based on the inhibition of virus-induced cytopathic effect in HEL
(herpes simplex virus type 1 (HSV-1), HSV-2 (G), vaccinia virus, and vesicular stomatitis virus), Vero (parainfluenza-3, reovirus-1, Coxsackie B4, and Punta Toro virus), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus), Madin-Darby canine kidney (MDCK) (influenza A (H1N1; H3N2) and B virus), and CrFK (feline coronavirus (FIPV) and feline herpes virus) cell cultures. Confluent cell cultures in microtiter 96-well plates were inoculated with 100-cell culture inhibitory dose-50 (CCID\textsubscript{50}) of the virus (1 CCID\textsubscript{50} being the virus dose to infect 50\% of the cells) in the presence of varying concentrations (100 nM, 20 mM, 5 mM, 1 mM, 200 nM) of the test compounds. Viral cytopathic effect was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds.

For the HCMV assays, confluent HEL fibroblasts were grown in 96-well microtiter plates and infected with the human cytomegalovirus strains Davis and AD-169 at 100 PFU per well. After a 2 h incubation period, the residual virus was removed and the infected cells were further incubated with a medium containing different concentrations of the test compounds (in duplicate). After incubation for 7-days at 37°C, the virus-induced cytopathic effect was monitored microscopically after ethanol fixation and staining with Giemsa dye. Antiviral activity was expressed as the EC\textsubscript{50} or compound concentration required for the reduction of virus-induced cytopathogenicity by 50\%.

The varicella zoster virus (VZV) drug susceptibility tests were performed on confluent HEL cells in 96-well microtiter plates by the plaque reduction assay. Monolayers were infected with 20 plaque forming units (PFU) of the cell-associated virus per well. For each assay, virus controls (infected-untreated cells) were included. After a 2 h incubation period, the virus inoculum was removed and the media were replaced by different dilutions (in duplicate) of the tested molecules. Serial dilutions of test compounds were incubated with the infected monolayers for five days. After a five day incubation period, the cells were fixed and stained with Giemsa, and the level of the virus-induced cytopathic effect was determined by counting the number of plaques for each dilution. Activity was expressed as EC\textsubscript{50} (effective compound concentration required to reduce virus plaque formation by 50\%) compared to the untreated control.

The anti-HIV activity of the compounds was evaluated against the wild type HIV-1 strain IIIB in MT-4 cell cultures using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Briefly, virus stocks were titrated in MT-4 cells and expressed as the 50\% cell culture infective dose (CCID\textsubscript{50}). MT-4 cells were suspended in culture medium at 10\textsuperscript{5} cells per mL and infected with HIV at the multiplicity of infection of 0.02. Immediately after viral infection, 100 µL of the cell suspension were placed in each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at 50 mM or more as stock solutions. Then, serial dilutions of the test compounds were made. The highest concentration tested was 100 µM of the test compound containing 0.2\% of DMSO, which is by itself not toxic to cell proliferation. After four days of incubation at 37°C, the number of viable cells was determined using the MTT method.

Results and discussion

Compounds IIa–IIl were synthesised following the reaction sequence outlined in Fig. 2. Methyl hydrazinecarbodithioate (I) was prepared by the reaction of hydrazine hydrate (85 mass\%) with carbon disulfide in the presence of potassium hydroxide at a temperature below 10°C; followed by the addition of methyliodide (Audrieth et al., 1954). Condensation of I with aromatic aldehydes/ketones in methanol provided compounds IIa–IIl (Klayman et al., 1991; Scoville et al., 1982). All compounds were characterised by their \textsuperscript{1}H-NMR and FAB-MS data. Physicochemical characterisation data are presented Table 1 and spectral data of compounds IIa–IIl are presented in Table 2.

All compounds were tested for their anticancer activity against the HL-60 human promyelocytic leukemia cell line and the results are presented in Table 3. The compounds were also tested for their antiviral activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 TK\textsuperscript{-} (KOS ACV\textsuperscript{v}), varicella-zoster virus (OKA and 07/1), cytomegalovirus (Davis and AD169), vaccinia virus, vesicular stomatitis virus, feline corona virus, feline herpes virus, human immunodeficiency virus (HIV) type 1 (III\textsubscript{R}) and type 2 (ROD), coxsackie virus B4, respiratory syncytial virus, parainfluenza 3 virus, re-
Table 1. Characterisation data of newly prepared compounds IIa–III

| Compound | R   | R¹  | Formula | M_r | Yield % | M.p. °C |
|----------|-----|-----|---------|-----|---------|---------|
| IIa      | Cl  | H   | C_9H_9ClN_2S_2 | 244 | 67      | 187     |
| IIb      | Cl  | H   | C_9H_9ClN_2S_2 | 244 | 72      | 165     |
| IIc      | OH  | H   | C_9H_10N_2OS_2 | 226 | 61      | 178     |
| IIc      | HOCH_3 | H | C_9H_10N_2OS_2 | 226 | 60      | 139     |
| IIe      | Cl  | H   | C_10H_12N_2OS_2 | 240 | 62      | 143     |
| IIf      | HCO  | H  | C_10H_12N_2OS_2 | 240 | 75      | 141     |
| IIg      | | H   | C_10H_12N_2OS_2 | 224 | 80      | 118     |
| IIh      | CH_3 | H   | C_10H_12N_2OS_2 | 224 | 69      | 153     |
| IIi      | OH  | CH_3 | C_10H_12N_2OS_2 | 240 | 63      | 162     |
| IIj      |    | H   | C_17H_16N_2S_2 | 312 | 169     |
| IIk      |    | H   | C_10H_9N_3OS_2 | 251 | 69      | 181     |
| III      | H   | H   | C_8H_6N_3S_2 | 211 | 63      | 143     |

ovirus, sindbis virus and punta tora virus. Only results for compounds showing activity against any of the viruses are presented in Table 4.

Compound III, IIi, and IIc showed IC_50 values against HL60 cells at the concentration of 0.8 µM, ≈ 1 µM, and 6.5 µM, respectively, after 72 h. It is interesting to note that preferably compounds with tridentate ligand characteristics (III, IIi, and IIc) showed potent anti-proliferative activity against the HL60 cells (Table 3). The activity of compound IIi (2'-hydroxy acetophenone derivative) was higher than that of IIc (2'-hydroxy benzaldehyde derivative) and almost equally potent to III (pyridine 2-carboxaldehyde derivative). All the other compounds (IIa, IIb, IId–IIh, and IIk) were inhibitory at concentrations between 55 µM and 63 µM after 72 h, except for IIj, irrespective of the nature and position of the substitution. Compound IIj did not exert any inhibitory activity on the HL60 cells at the maximum concentration studied (100 µM, after 72 h). All the compounds exhibited a cytotoxic concentration (CC_50) of ≥ 100 µM in the HeLa cell cultures except for III (36 µM), (Table 3). Compounds IIi and III showed the best selectivity towards the HL60 cells and therefore, further investigations are required.

Compounds IIc and IIi resemble the iron chelator 311 (N’-[(2-hydroxynaphthalen-1-yl)-methylidene]-pyridine-4-carbohydrazide) and III resembles triapine (3-aminopyridine-2-carbaldehyde thiourea). Compound IIi having a ketonic methyl group showed activity comparable to that of iron chelator 311 at 48 h. Compound III with a ketonic methyl group has to be considered for further improvement of its activity.

It is interesting to observe that only compounds with tridentate ligand characteristics (IIc, IIi, and III) have shown antiviral activity against a few viruses and
Table 2. Spectral data of newly prepared compounds IIa–III

| Compound | Spectral data |
|----------|---------------|
| IIa      | 1H NMR (DMSO-d6), δ: 2.68 (s, 3H, —SCH3); 7.41–7.87 (m, 4H, ArH); 8.41 (s, 1H, —N—CH—); 12.63 (s, 1H, NH) MS, m/z (I%): 244 (21.60) (M)+, 245 (63.42) (M + 1)+, 246 (16.98) (M + 2)+ |
| IIb      | 1H NMR (DMSO-d6), δ: 2.75 (s, 3H, —SCH3); 7.26–7.68 (m, 4H, ArH); 7.83 (s, 1H, —N—CH—); 10.3 (s, 1H, NH) MS, m/z (I%): 244 (22.04) (M)+, 245 (61.04) (M + 1)+, 246 (16.92) (M + 2)+ |
| IIc      | 1H NMR (DMSO-d6), δ: 2.66 (s, 3H, —SCH3); 6.92–7.42 (m, 4H, ArH); 8.33 (s, 1H, —N—CH—); 10.44 (s, 1H, NH); 13.04 (s, 1H, ArOH) MS, m/z (I%): 226 (20.30) (M)+, 227 (68.61) (M + 1)+, 228 (11.09) (M + 2)+ |
| IIId     | 1H NMR (DMSO-d6), δ: 2.73 (s, 3H, —SCH3); 6.82–7.95 (m, 4H, ArH); 8.14 (s, 1H, —N—CH—); 10.06 (s, 1H, NH); 13.13 (s, 1H, ArOH) MS, m/z (I%): 226 (44.77) (M)+, 227 (42.71) (M + 1)+, 228 (12.52) (M + 2)+ |
| IIe      | 1H NMR (DMSO-d6), δ: 2.67 (s, 3H, —SCH3); 3.88 (s, 3H, —OCH3); 6.90–7.99 (m, 4H, ArH); 8.29 (s, 1H, —N—CH—); 10.17 (s, 1H, NH) MS, m/z (I%): 240 (24.83) (M)+, 241 (58.85) (M + 1)+, 242 (16.32) (M + 2)+ |
| IIf      | 1H NMR (DMSO-d6), δ: 2.67 (s, 3H, —SCH3); 3.86 (s, 3H, —OCH3); 6.72–7.69 (m, 4H, ArH); 7.79 (s, 1H, —N—CH—); 10.06 (s, 1H, NH) MS, m/z (I%): 240 (37.65) (M)+, 241 (43.62) (M + 1)+, 242 (18.73) (M + 2)+ |
| IIg      | 1H NMR (DMSO-d6), δ: 2.53 (s, 3H, CH3); 2.67 (s, 3H, —SCH3); 7.26–7.80 (m, 4H, ArH); 8.12 (s, 1H, —N—CH—); 10.36 (s, 1H, NH) MS, m/z (I%): 224 (23.63) (M)+, 225 (57.06) (M + 1)+, 226 (19.30) (M + 2)+ |
| IIh      | 1H NMR (DMSO-d6), δ: 2.39 (s, 3H, CH3); 2.67 (s, 3H, —SCH3); 7.21–7.63 (m, 4H, ArH); 7.84 (s, 1H, —N—CH—); 10.27 (s, 1H, NH) MS, m/z (I%): 224 (25.05) (M)+, 225 (60.48) (M + 1)+, 226 (14.47) (M + 2)+ |
| IIi      | 1H NMR (DMSO-d6), δ: 2.42 (s, 3H, CH3); 2.73 (s, 3H, —SCH3); 6.94–7.53 (m, 4H, ArH); 9.93 (NH); 11.37 (s, 1H, ArOH) MS, m/z (I%): 240 (22.82) (M)+, 241 (54.35) (M + 1)+, 242 (22.82) (M + 2)+ |
| IIj      | 1H NMR (DMSO-d6), δ: 2.50 (s, 3H, —SCH3); 7.56–8.83 (m, 9H, ArH); 8.66 (s, 1H, —N—CH—); 11.32 (NH) MS, m/z (I%): 95 (26.20), 107 (27.99), 204 (19.91), 221 (25.86) |
| IIk      | 1H NMR (DMSO-d6), δ: 2.67 (s, 3H, —SCH3); 7.2–7.9 (m, 4H, ArH); 8.2 (s, 1H, NH); 8.9 (s, 1H, —CONH—) MS, m/z (I%): 251 (23.29) (M)+, 252 (44.98) (M + 1)+, 253 (31.73) (M + 2)+ |
| IIl      | 1H NMR (DMSO-d6), δ: 2.63 (s, 3H, —SCH3); 6.5–7.4 (m, 4H, ArH); 8.3 (s, 1H, NH) MS, m/z (I%): 211 (20.80) (M)+, 212 (48.32) (M + 1)+, 213 (30.87) (M + 2)+ |

Table 3. Cytotoxic/cytostatic activity of compounds IIa–III against HeLa and HL60 cells

| Code | HeLa cells | HL60 cells |
|------|------------|------------|
|      | CC50 (%)   | IC50 (24 h) | IC50 (48 h) | IC50 (72 h) | IC50 (96 h) |
| IIa  | 100        | ≈ 90       | ≈ 60       | ≈ 60       | –          |
| IIb  | > 100      | > 100      | 70         | 62.5       | –          |
| IIc  | > 100      | > 100      | 6.5        | 6.5        | –          |
| IIId | > 100      | > 100      | 97         | 65         | 63         |
| IIe  | > 100      | > 100      | 59         | 55         | –          |
| IIf  | > 100      | > 100      | 85         | ≈ 60       | ≈ 60       |
| IIg  | > 100      | 96         | 59         | 59         | –          |
| IIh  | 100        | 96         | 69         | 57         | –          |
| IIi  | 100        | ≈ 85       | ≈ 1        | ≈ 1        | –          |
| IIj  | > 100      | > 100      | > 100      | > 100      | –          |
| IIk  | > 100      | 93         | 64         | 57         | –          |
| IIl  | 35.8       | 1          | 0.8        | 0.8        | –          |
| III  | 0.6        | 0.4        | –          | –          | 0.27       |
| TRP  | –          | –          | –          | –          | –          |

a) 50% cytotoxic concentration as determined by measuring the cell viability with the colorimetric formazan-based MTS assay; b) values are taken from Richardson and Milnes (1997), iron chelator 311 = [N1,4-[2-(hydroxynaphthalen-1-yl)-methylidene]-pyridine-4-carbohydrazide]; c) values are taken from Kowal et al. (2009); TRP = triamine (triamine = 3-aminotriphenyl-2-carbonyldihydroxythiosemicarbazone).

are presented in Table 4. Compound III displayed pronounced antiviral activity against HSV-1 (8–42 μM), HSV-2 (9–11 μM), VZV (6.5–42 μM), and vaccinia virus (15–45 μM). It should be noted that III inhibits
We thank Mrs. Leentje Persoons, Mrs. Frieda De Meyer, Mrs. Kristien Erven and Mr. Kris Uyttersprot for excellent technical assistance. Mrs. Anusha Devi Sastry, Mrs. Anita Camps, Lies Van den Heurck, Mrs. Steven Carnans, Mrs. Kristen Erven and Mr. Kris Uyttersprot for excellent technical assistance.

Acknowledgements. The author acknowledges the University Grants Commission (UGC) & All-India Council for Technical Education (AICTE), India, for financial support (JRF) to the first author and the GOA (no. 10/014) of the KU Leuven; Sophisticated Instrumentation Facility (SAIF) of the Central Drug Research Institute (CDRI), Lucknow, for enabling the use of the facility for spectral characterisation of compounds. We thank Mrs. Leentje Persoons, Mrs. Frieda De Meyer, Mrs. Lies Van den Heurck, Mr. Steven Carnans, Mrs. Anita Camps, Mrs. Kristen Erven and Mr. Kris Uyttersprot for excellent technical assistance.

Table 4. Antiviral activity of compounds IIc, IIi, and III in HEL cell cultures

| Code | HSV-1 (KOS) | HSV-2 (G) | Vaccinia virus | Vesicular stomatitis virus | HSV-1 TK- (ACV) | VZV OKA | CMV Davis | MCC | CC50 µM |
|------|-------------|-----------|----------------|----------------------------|-----------------|--------|---------|------|---------|
| IIc  | 10 ± 2      | 11 ± 1    | 12 ± 0         | > 100                      | > 4             | > 100  | 5.3     |      |         |
| IIi  | 45 ± 0      | > 100     | 45 ± 0         | > 100                      | > 4             | > 100  | 17      |      |         |
| III  | 8 ± 1       | 9 ± 0     | 15 ± 6         | > 20                       | > 20            | > 20   | 2.6     |      |         |
| Brivudin | 0.1        | 183       | 29             | > 250                      | 0.01            | –      | > 200   | > 200| 200     |
| Acyclovir | 1          | 0.4      | 250            | > 250                      | 0.8             | 89     | > 200   | > 200| 200     |
| Ganciclovir | 0.03      | 0.03     | > 100          | > 100                      | 20              | –      | 6.3     | 3.1  | > 200   |

a) Compound concentration required to reduce virus-induced cytopathogenicity by 50 %; b) compound concentration required to cause a microscopically detectable alteration of normal cell morphology; c) compound concentration required to inhibit HEL cell proliferation by 50 %.

The wild-type as well as the acyclovir-resistant HSV at comparable compound concentrations (8–20 µM, Table 4). Compound IIc with a 2-hydroxy substitution and compound IIi, an acetonaphone analogue of IIc, show antiviral activity at somewhat higher concentrations than III. Compound IIa that differs from IIc by a hydroxy functional group at the para position did not show any appreciable antiviral activity. Additional analogues of IIc and III are currently under further investigation. It should, however, be noted that IIc, IIi, and III are poorly cytotoxic but they show pronounced cytostatic activity in proliferating HEL and HL60 cell cultures. Therefore, the observed antiviral activity might not be due to direct antiviral activity but rather due to indirect inhibitory action caused by the underlying cytostatic potential of these compounds.

Conclusions

The present investigation revealed that: i) compounds with a metal chelating functional group (IIc, IIi, and III) at their aryl end were found to be active and ii) the methyl dithioate (—CSSCH3) group is not an bioisosteric equivalent of hydroxamate (—CONH2) or amidoxime (—CNHNHOH) (Fig 1.). The compounds investigated are known as intermediates with specific pharmacophoric features for the intended activities that can provide a new scaffold for these activities.

References

Audrieth, L. F., Scott, E. S., & Kippur, P. S. (1954). Hydrazine derivatives of the carbonic and thiocarbonic acids. I. The preparation and properties of thiocarboxyhydrazide. The Journal of Organic Chemistry, 19, 733–741. DOI: 10.1021/jo1370a006.

Ali, M. A., Mirza, A. H., Nazimuddin, M., Dhar, P. K., & Butcher, R. J. (2002). Preparation, characterization and antifungal properties of nickel(II) complexes of tridentate ONS ligands derived from N-methyl-S-methylthiodithiocarbonate and the X-ray crystal structure of the [Ni(ONMeS)CN]·H2O complex. Transition Metal Chemistry, 27, 27–33. DOI: 10.1023/a:1013434113299.

Beraldo, H., & Gambinob, D. (2004). The wide pharmacological versatility of semicarbazones, thiosemicarbazones, and their metal complexes. Mini-Reviews in Medicinal Chemistry, 4, 1915–1927. DOI: 10.1039/b31370a0006.

Caso, S. L., Feng, Y. P., Jiang, Y. Y., Liu, S. Y., Ding, G. Y., & Li, R. T. (2005). Synthesis and in vitro antitumor activity of 4(3H)-quinazolinone derivatives with dithiocarbamate side chains. Bioorganic & Medicinal Chemistry Letters, 15, 1915–1917. DOI: 10.1016/j.bmcl.2005.01.083.

Casero, R. A., Klayman, D. L., Childs, G. E., Scovill, J. P., & Desjardins, R. E. (1980). Activity of 2-acetylpyridine thiosemicarbazones against Trypanosoma rhodesiense in vitro. Antimicrobial Agents and Chemotherapy, 18, 317–322. DOI: 10.1128/aaac.18.6.317.

Collins, F. M., Klayman, D. L., & Morrison, N. E. (1982). Activity of 2-acetylpyridine and 2-acetyquinoline thiosemicarbazones tested in vitro in combination with other antituberculous drugs. The American Review of Respiratory Disease, 125, 58–60.

Das, A., Trousdale, M. D., Ren, S. J., & Lien, E. J. (1999). Inhibition of herpes simplex virus type 1 and adenovirus type 5 by heterocyclic Schiff bases of aminohydroxyguanidine tosy late. Antiviral Research, 44, 201–208. DOI: 10.1016/s0166-3542(99)00070-4.

Ettari, R., Bova, F., Zappalà, M., Grasso, S., & Micałe, N. (2010). Falcipain-2 inhibitors. Medicinal Research Reviews, 30, 136–167. DOI: 10.1002/med.20163.
M. Mahapatra et al./Chemical Papers 67 (6) 650–656 (2013)

Huang, W., Ding, Y., Miao, Y., Liu, M. Z., Li, Y., & Yang, G. F. (2009). Synthesis and antitumor activity of novel dithiocarbamate substituted chromones. European Journal of Medicinal Chemistry, 44, 3687–3696. DOI: 10.1016/j.ejmech.2009.04.004.

Jiang, Z. G., Lebowitz, M. S., & Ghanbari, H. A. (2006). Neuroprotective activity of 3-amino-pyridine-2-carboxaldehyde thiosemicarbazone (PAN-811), a cancer therapeutic agent. CNS Drug Reviews, 12, 77–90. DOI: 10.1111/j.1527-3458.2006.00077.x.

Kaswar, S. S., Lumba, K., Gupta, S. K., Katooch, V. M., SIngh, P., Mishra, A. K., & Kalia, S. B. (2008). Synthesis and mycobactericidal properties of metal complexes of isonicotinylidithiocarbamic acid. Biotechnology Letters, 30, 677–680. DOI: 10.1007/s10529-007-9601-5.

Katz, E. (1987). Thiosemicarbazones: inhibition of the growth of pox viruses and requirement for the growth of an isatin-β-thiosemicarbazone dependent mutant. Journal of Basic and Clinical Physiology and Pharmacology, 6, 119–130. DOI: 10.1515/jbcpp.1987.6.2.119.

Klayman, D. L., Bartosevich, J. F., Scott Griffin, T., Mason, C. J., & Scovill, J. P. (1979). 2-Acetylpyridine thiosemicarbazones. 1. A new class of potential antimalarial agents. Journal of Medicinal Chemistry, 22, 855–862. DOI: 10.1021/jm00193a020.

Klayman, D. L., Lin, A. J., McCall, J. W., Wang, S. Y., Townson, S., Grögl, M., & Kinnamon, K. E. (1991). 2-Acetylpyridine thiosemicarbazones. 13. Derivatives with antifilarial activity. Journal of Medicinal Chemistry, 34, 1422–1425. DOI: 10.1021/jm00108a027.

Kowol, C. R., Trondil, R., Helfer, P., Arion, V. B., Jakupce, M. A., Roller, A., Galanski, M., Berger, W., & Keppler, B. K. (2009). Impact of metal coordination on cytotoxicity of 3-amino-pyridine-2-carboxaldehyde thiosemicarbazone (triapine) and novel insights into terminal dimethylation. Journal of Medicinal Chemistry, 52, 5032-5043. DOI: 10.1021/jm9005284.

Kumar, L., Sarswat, A., Lal, N., Sharma, V. L., Jain, A., Kumar, R., & Verma, V., Maikhuri, J. P., Kumar, A., Shukla, P. K., & Gupta, G. (2010). Imidazole derivatives as possible microbicides with dual protection. European Journal of Medicinal Chemistry, 45, 817–824. DOI: 10.1016/j.ejmech.2009.10.021.

Liberta, A. E., & West, D. X. (1992). Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status. BioMetals, 5, 121–126. DOI: 10.1007/bf01062223.

Matesanz, A. I., & Souza, P. (2009). α-N-heterocyclic thiosemicarbazone derivatives as potential antitumor agents: a structure-activity relationships approach. Mini-Reviews in Medicinal Chemistry, 9, 1389–1396. DOI: 10.2174/13895570978957422.

Neelam, B., Mannar, M., Fehmida, N., Alok, B., Sudha, B., & Amir, A. (2000). Palladium(II) complexes of NS donor ligands derived from S-methyl-dithiocarbazate, S-benzylidithiocarbazate and thiosemicarbazide as antiamoebic agents. European Journal of Medicinal Chemistry, 35, 481–486. DOI: 10.1016/s0223-5234(00)00145-8.

Pandey, S. N., & Dimmock, J. R. (1993). Recent evaluations of thiosemicarbazones and semicarbazones and related compounds for antineoplastic and anticonvulsant activities. Pharmazie, 48, 659–666.

Ren, S., Wang, R., Komatsu, K., Bonaz-Krause, P., Zyrivon, Y., Mckenna, C. E., Cuipke, C., Tokes, Z. A., & Lien, E. J. (2002). Synthesis, biological evaluation, and quantitative structure-activity relationship analysis of new Schiff bases of hydroxysemicarbazide as potential antitumor agents. Journal of Medicinal Chemistry, 45, 410–419. DOI: 10.1021/jm010252q.

Richardson, D. R., & Milnes, K. (1997). The potential of iron chelators of the pyridoxal isonicotinoyl hydrazone class as effective antiproliferative agents II: the mechanism of action of ligands derived from salicylaldehyde benzoyl hydrazone and 2-hydroxy-1-naphthylaldehyde benzoyl hydrazone. Blood, 89, 3025–3038.

Saxena, A., & Tandon, J. P. (1983). Antitumor activity of some diorganotin and tin(IV) complexes of Schiff bases. Cancer Letters, 19, 73–76. DOI: 10.1016/0304-3835(83)90138-6.

Scovill, J. P., Klayman, D. L., & Franchino, C. F. (1982). 2-Acetylpyridine thiosemicarbazones. 4. Complexes with transition metals as antimalarial and antileukemic agents. Journal of Medicinal Chemistry, 25, 1261–1264. DOI: 10.1021/jm00352a036.

Shipman, C., Smith, S. H., Drach, J. C., & Klayman, D. L. (1981). Anti viral activity of 2-acetylpyridine thiosemicarbazones against herpes simplex virus. Antimicrobial Agents and Chemotherapy, 19, 682–685. DOI: 10.1128/aac.19.4.682.

Singh, N. K., Singh, N., Prasad, G. C., Sodhi, A., & Shrivastava, A. (1997). Antitumor activity studies of newly synthesized N-salicyloyl-N′-(p-hydroxybenzathioyl)hydrazine and its copper(II) complex both in vivo and in vitro. Bioorganic & Medicinal Chemistry, 5, 245–251. DOI: 10.1016/s0968-0896(96)00243-x.

T’ang, A., Lien, E. J., & Lai, M. M. C. (1985). Optimization of the Schiff bases of N-hydroxy-N′-aminoguanidine as anticancer and antiviral agents. Journal of Medicinal Chemistry, 28, 1103–1106. DOI: 10.1021/jm001460a202.

Wuuk, S. F., & Robins, M. J. (2006). Ribonucleotide reductase inhibitors as anti-herpes agents. Antiviral Research, 71, 122–126. DOI: 10.1016/j.antiviral.2006.03.002.

Yu, Y., Kalinowski, D. S., Kovaecic, Z., Siafasakis, A. R., Janss, P. J., Stefani, C., Lovejoy, D. B., Sharpe, P. C., Bernhardt, P. V., & Richardson, D. R. (2009). Thiosemicarbazones from the old to new: iron chelators that are more than just ribonucleotide reductase inhibitors. Journal of Medicinal Chemistry, 52, 5271–5294. DOI: 10.1021/jm900552r.