Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2011, 2 (6):107-113

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Semicarbazone analogues: A mini review

Mohamed Jawed Ahsan[a, b,*], Jeyabalan Govinda Samy[a], Habibullah Khalilullah[a] and Md. Shivli Nomani[a]

[a]*New Drug Discovery Research, Department of Medicinal Chemistry, Alwar Pharmacy College, Alwar, Rajasthan, India*
[b]*Department of Pharmaceutical Sciences, National Institute of Medical Sciences University, Jaipur, India*

ABSTRACT

Semicarbazones are compounds which are synthesized by the condensation of semicarbazide and aldehydes/ketones. The literature survey revealed that semicarbazones had been emerged as a compound with broad range of activities including anticonvulsant, antitubercular, anticancer and antimicrobial activity. Dimmock et al., reported an extensive series of semicarbazones and reported 4-(4-fluorophenoxy) benzaldehyde semicarbazone as potential anticonvulsant. Preclinical evaluations have been completed and an IND has been filed for this potential compound. In the present study we have focused on the biological activity of semicarbazone analogues.

Keywords: Semicarbazone; Biological activity.

INTRODUCTION

In organic chemistry, semicarbazone is a derivative of semicarbazide which contains an additional ketone functional group. Its structure is given in the **Fig. 1.**

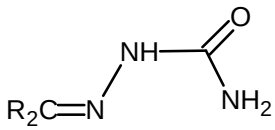
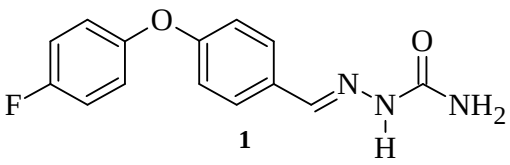


Fig. 1. General Structure of semicarbazone analogues

Dimmock *et al*., reported an extensive series of semicarbazone [1]. The lead compound among the (aryloxyl)aryl semicarbazones was 4-(4-fluorophenoxy) benzaldehyde semicarbazone. Preclinical evaluations have been completed and an (IND) has been filed. The compound is a potent sodium channel blocker (Na^+) and it is planned to be developed for the treatment of neuropathic pain. Phase I Clinical trials are scheduled in the near future (**Fig. 3**)



1

The semicarbazone is formed when ammonia related a compound (nucleophiles) such as semicarbazide is added to the carbonyl group (=CO), they form imine like derivatives (**Fig. 2**).

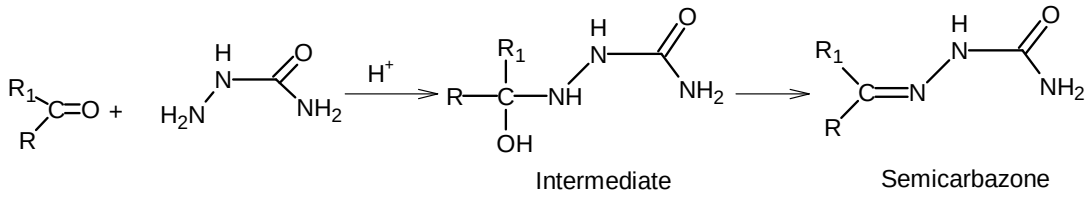
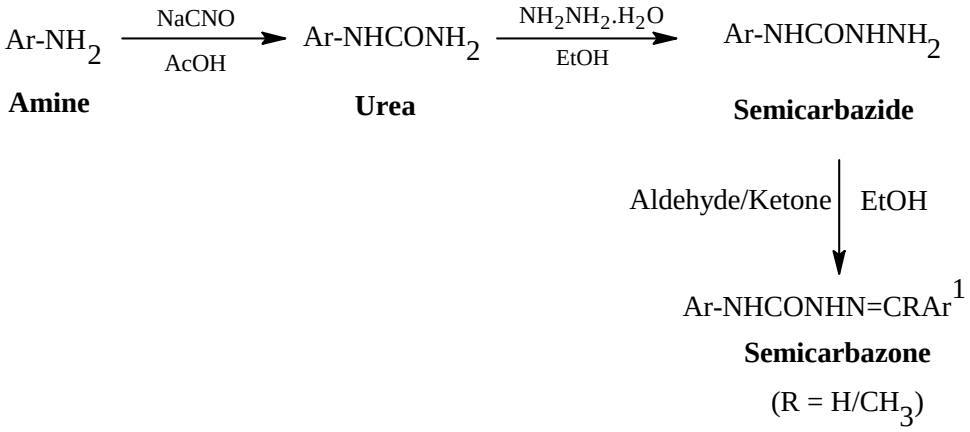


Fig. 2. Synthesis of semicarbazone analogues

The conversion of aldehydes and ketones into imine like derivatives is an exothermic and pH dependent reaction.

General method for the synthesis of semicarbazone analogues

The general method for the synthesis of semicarbazone analogues is presented in Scheme 1.

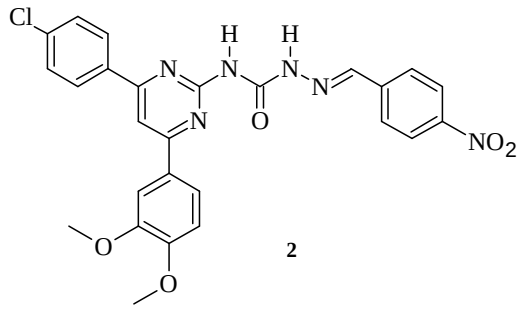


Scheme 1. General method for the synthesis of semicarbazone analogues.

Biological Profile

1. Anticonvulsant activity

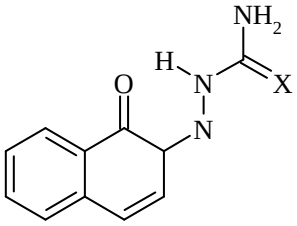
Ozair *et al*., synthesized a series of *N*-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones and tested for their anticonvulsant activity against the two seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity. To assess the unwanted effects of the compounds on liver, estimation of enzymes and proteins was carried out. The most active compound of the series was N^1-[4-(4-Chlorophenyl)-6-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]-N^4-(4-nitrobenzaldehyde) semicarbazone (2) devoid of any neurotoxicity [2].



2

2. Anticancer activity

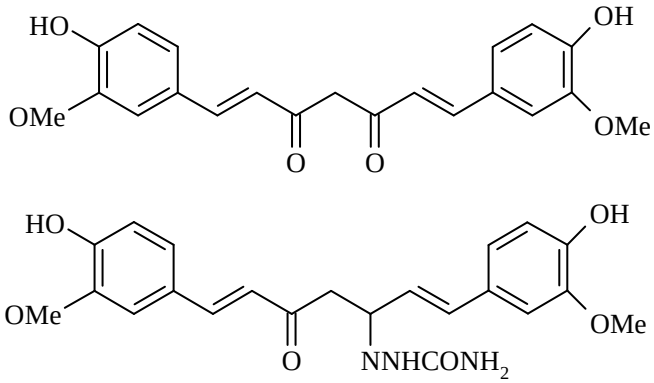
Ni (II) complexes of ortho-napthaquinone thiosemicarbazone and semicarbazone were synthesized and spectroscopically characterized by Afrasiai *et al*. The X-ray crystal structure of both the complexes describe a distorted octahedral coordination with two tridentate mono-deprotonated ligands. *In vitro* anticancer studies on MCF-7 human breast cancer cells reveal that the semicarbazone derivative along with its nickel complex is more active in the inhibition of cell proliferation than the thiosemicarbazone analogue (**3**) [3].



X = O: NQSC
X = S: NQTS

3

A new semicarbazone derivative of curcumin (CRSC) was synthesized and examined by Dutta *et al.* for its antioxidant, antiproliferative, and antiradical activity and compared with those of curcumin (CR) **(4a)**. The antioxidant activity was tested by their ability to inhibit radiation induced lipid peroxidation in rat liver microsomes. The antiproliferative activity was tested by studying the *in vitro* activity of CRSC **(4b)** against estrogen dependent breast cancer cell lines MCF-7. Kinetics of reaction of (2,2′-diphenyl-1-picrylhydrazide) DPPH, a stable hydrogen abstracting free radical was studied to measure the antiradical activity using stopped flow spectrophotometer. Finally one electron oxidized radicals of CRSC were generated and characterized by pulse radiolysis. The results suggest that the probable site of attack for CRSC shows efficient antioxidant and antiproliferative activity although its antiradical activity is less than that of CR [4].



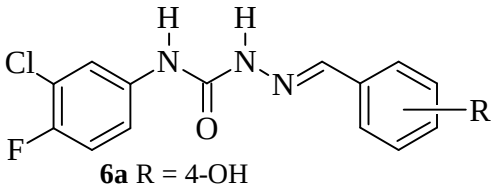
4a-b

As a contribution to the development of novel vanadium complexes with pharmacologically interesting moieties, new dioxovanadium (V) semicarbazone complexes with the formula cis-VO_2L, where L = 5-bromosalicylaldehyde semicarbazone and 2-hydroxy-naphthalen-1-carboxaldehyde semicarbazone have been synthesized by Noblia *et al.* Results were compared with those previously reported for other three analogues complexes of this series. The five

complexes were tested in three different human tumour cell lines for bioactivity as potential antitumor agents, showing selective cytotoxicity on TK-10 cell line. Results showed that structural modifications on the semicarbazone moiety could have a significant effect on the antitumor activity of the vanadium complexes [5].

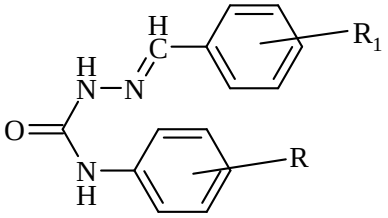
Antimicrobial activity

Ahsan *et al*., reported the antimicrobial activity of a series of sixteen N^1-(3-chloro-4-fluorophenyl)-N^4-substituted semicarbazone derivatives were synthesized and subjected to computational pharmacokinetic studies to predict molecular properties. Among them the compound *2-(4-hydroxybenzylidene)-N-(3-chloro-4-fluorolphenyl)hydrazinecarboxamide* (**5a)** was found to be the most active compound showed good antibacterial inhibition while the compound *2-(4-methoxybenzylidene)-N-(3-chloro-4-fluorolphenyl)hydrazinecarboxamide* (**5b**) was moderately active against fungal strains. They have noticed the compounds bearing OH and NO_2 group at the phenyl ring at position 4 exhibited good antibacterial activity while compound bearing OCH_3 at the phenyl ring at position 4 exhibited moderate antifungal activity [6].



6a R = 4-OH
6b R = 4-OCH_3

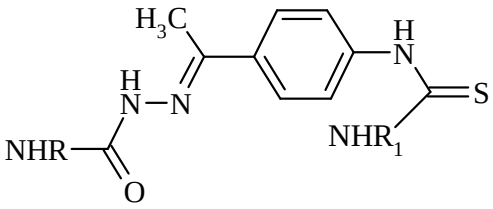
During the course of Sriram *et al.* work on the synthesis and screening of new drugs for tuberculosis, they have identified N_1-(4-acetamido phenyl)-N_4-(2-nitrobenzylidene) semicarbazone (16), which inhibited *in vitro M. tuberculosis* H_{37} Rv; 100% inhibition at 1.56 µ/mL. This paper was first of its kind in which aryl semicarbazones are reported to possess antimycobacterials potency greaterthan *p*-aminosalicylic acid, ethionamide, ethambutol, ciprofloxacin and kanamycin [7].



R = 4-$NHCOCH_3$;
R_1 = 3-NO_2

7

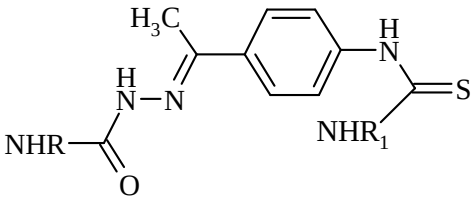
The thioureido derivatives of 4-aminoacetophenone aryl semicarbazone have been prepared by Mishra *et al.* These derivatives have been characterized on the basis of different physicochemical evidences. The anti-HIV-1 (HTLV-III_B) and HIV-2 (ROD) activity and cytotoxicity of the compounds were tested. The compound **(8a)** and **(8b)** showed maximum protection among the series [7].



R = **R_1** = *p*-CH_3
R = *p*-CH_3; **R_1** = OCH_3

8a-b

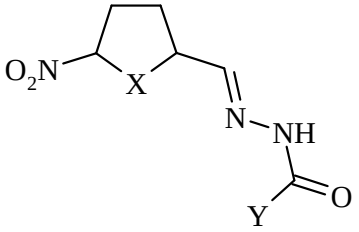
Several novel semicarbazone derivatives were prepared by Cerecetto *et al.* from 5-nitro-2-furaldehyde or 5-nitrothiophene-2-carboxaldehyde, and tested *in vitro* as potential antitrypanosomal agents. The compounds were prepared in good to excellent yields in 2-3 steps from readily available starting materials. Some derivatives **(9)** were found to be active against *T. cruzi* with an activity similar to that of niturtimox [9].



R = **R$_1$** = *p*-CH_3
R = *p*-CH_3; **R$_1$** = OCH_3

9

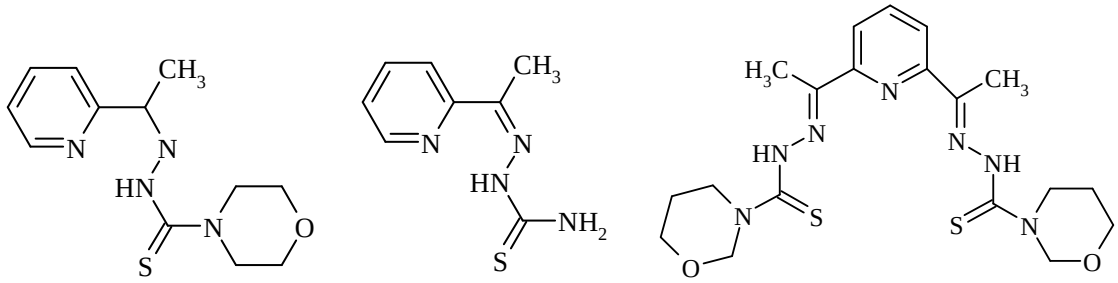
Several novel semicarbazone derivatives were prepared from 5-nitro-2-furaldehyde or 5-nitrothiophene-2-carboxaldehyde and semicarbazides bearing a spermidine mimetic moiety by Cerecetto *et al.* These compounds were tested *in vitro* as potential antitrypanosomal agents and some of them, together with the parent compounds, 5-nitro-2-furaldehyde and 5-nitrothiophene-2-carboxaldehyde semicarbazone derivatives, were also evaluated *in vivo* using infected mice. Two of the compounds **(10a-b)** displayed the highest *in vivo* activity. A correlation was found between lipophilic hydrophilic properties and trypanocidal activity, high R_M values being associated with low *in vivo* effects [10].



Y = butylamino, **X** = O
Y = 2-methoxyethylamino

(10a-b)

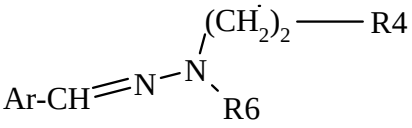
To investigate the relationship between antimicrobial activities and the molecular structures of nickel (II) complexes with thiosemicarbazone and semicarbazone ligands, nickel (II) complexes with ligands Hmtsc **(11a)**, Hatsc **(11b)**, and H_2 dmtsc **(11c)**, were prepared and characterized by Kasuaga *et al*. Their antimicrobial activities were evaluated by the MIC against four bacteria (*B.subtilis, S. aureus, E. coli and P. aeruginosa*), two yeasts (*C. albicans* and *S. cerevisiae*) and two molds (*A. niger* and *P. citrinum*). The 4-coordinate, diamagnetic nickel (II) complexes showed antimicrobial activities which were different from those of free ligands or the starting nickel (II) compounds. [Ni(mtsc)(Oac)] showed selective and effective antimicrobial activites against two gram positive bacteria (*B. subtili s*and *S. aureus*) and modest activities against a yeast (*S. cerevisiae*), [Ni(mtsc)Cl] exhibited moderate activities against a gram positive bacterium (*S. aureus*) and [Ni(atsc)(Oac)] showed modest activities against gram poistive bacteria (*B. subtilis* and *S. aureus*) [11].



11a **11b** **11c**

Miscellaneous activities

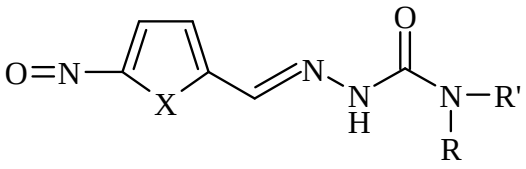
The synthesis and the evaluation of the monoamine oxidase A and B inhibitory activities of 21 new substituted acyl hydrazones **(11)** of various aromatic aldehydes and 4-(benzyloxy) acetophenone, and four substituted semicarbazones of benzaldehyde and 4-(benzyloxy) benzaldehyde, are described by Bernard *et al*. The 4-(benzyloxy) phenyl group contributing to a high lipophilicity led to the most active compounds one of these, compound (IC_{50} = 3 nm, MAO A/MAO B selectivity. 33000), found to act as a reversible and probably tight binding inhibitor. The studied acyclic hydrazones and semicarbazones are structurally related to other reversible and potent inhibitors e.g. heterocyclic compounds such as 1,3,4-oxadiazol-2 (3*H*)-one derivatives in which hydrazono group is intra cyclic. Some of the new inhibitors might find use in the symptomatic treatment of neuode generative processes [12].



Ar = C_6H_5; $\mathbf{R_4}$ = CN, OH
$\mathbf{R_6}$ = COOEt, COMe, CONHMe

12

The physicochemical properties of some 5-nitro-2-furaldehyde semicarbazones **(12)** (nitrofurazones) and thiophene analogues were compared with their *in vitro* and *in vivo* trypanocidal activity against *T. cruzi* (Tulahuen strain) by Merino *et al. T. cruzi* is the etiologic agent of chagas disease [13].



X = O, S; **R** = H
R' = $-CH_2(CH_2)_2CH_3$, $-CH_2CH_2OCH_3$
$-CH_2CH_2Ph$

13

CONCLUSION

Semicarbazone moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological activity. This article mainly focused on the various derivatives of semicarbazones and their biological activity. Thus by studying all the derivatives showing anticonvulsant activity we can say that semicarbazone analogues have been explored in past years and is still be used for future development of new drugs to be used against epilepsy. Also

REFERENCES

[1] J.R. Dimmock, R.N. Puthucode, J. Tuchek, G.B. Baker, C.N. Hinko, C.L. Steinmiller, J. P. Stables, *Drug Dev. Res.* **1999**, 46, 112-125.
[2] O. Alam, P, Mallick, S.P. Verma, S.J. Gilani, S.A. Khan, N. Siddiqui, W. Ahsan, *Eur. J. Med. Chem.* **2010**, 45, 2467-2472.
[3] Z. Afrasiabi, E.K.K. Sinn, W. Lin, Y. Ma, C. Campana, S. Padhye, *J. Inorg. Biochem*. **2005**, 99, 1526-1531.
[4] S. Dutta, S. Padhye, K.I. Priyadarsini, C. Newton, *Bioorg. Med. Chem. Lett*. **2005**, 15, 2738-2744.
[5] P. Noblia, M. Vieites, B.S.P. Costa, E.J. Baran, H. Cerecetto, P. Draper, M. Gonzalez, O.E. Piro, E.E. Castellano, A. Azueta, A.L.D. Cerain, A. Monge-vega, D. Gambino, *J. Inorg. Bio*. **2005**, 99, 443-451.
[6] M.J. Ahsan, M. Amir, M.A. Bakht, M.Z. Hassan, M.S. Nomani, *Arab. J. Chem.* (In press).

[7] D. Sriram, P. Yogeeswari, R. Thirumurugan, *Bioorg. Med. Chem. Lett*. **2004**, 14, 3923-3924.
[8] V. Mishra, S.N. Pandeya, E. Declercq, C. Pannecouque, M. Witvrouw, *Pharmaceut. Acta Helvet*. **1998**, 73, 215-218.
[9] H. Cerecetto, R.D. Maio, M. Gonzalez, M. Risso, G. Sagrera, G. Seoane, A. Denicola, G. Peluffo, C. Quijano, A.O.M. Stoppani, M. Paulino, C. Olea-Azar, M.A. Basombrio, *Eur. J. Med. Chem*. **2000**, 35, 343-350.
[10] H. Cerecetto, R.D. Maio, G. Ibarruri, G. Seoane, A. Denicola, A. Peluffo, C. Quijano, M. Paulino, *Il Farmaco* **1998**, 53, 89-94.
[11] N. Chikar, A. Kasuga, K. Sekino, C. Koumo, N. Shimada, M. Ishikawa, K. Nomiya, *J. Inorg. Biochem*. **2001**, 84, 55-65.
[12] S. Bernard, C. Pillat, T. Oddos, M. Seman, R. Milcent, *Eur. J. Med. Chem*. **1995**, 30, 471-482.
[13] V. Martinez-Merino, H. Cerecetto, *Bioorg. Med. Chem*. **2001**, 9, 1025-1030.