Acta Poloniae Pharmaceutica – Drug Research, Vol. 76 No. 6 pp. 971–986, 2019
DOI: 10.32383/appdr/112124

ISSN 0001-6837
Polish Pharmaceutical Society

ANALYSIS

SYNTHESIS, REACTIONS, AND APPLICATIONS OF 2-THIOHYDANTOIN DERIVATIVES

HEBA A. ELHADY[1,2]*, SOMIA M. MOHAMED[2], HOSSA F. AL-SHAREEF [1] and RASHA E. EL-MEKAWY[1,3]

[1]Department of Chemistry, Faculty of Applied Sciences, Umm Al-Qura University, P. O. Box 13401, Makkah 21955, Saudi Arabia
[2]Department of Chemistry, Faculty of Science, Al-Azhar University (Girls Branch), P.O. Box 11754, Youssef Abbas Str., Cairo, Egypt
[3]Department of Petrochemicals, Egyptian Petroleum Research Institute, Nasr City, Cairo, Egypt

Abstract: On account of the interesting pharmacological properties of 2-thiohydantoin derivatives, and other purposes such as textile printing, catalysts for polymerizations, their uses in the production of resins and plastics, they have been the subject of chemical and biological studies. In this review article, we focused our interest on the most important methods for the synthesis of 2-thiohydantoin derivatives, different reactions and different applications of them. We explored their antitumor, antimicrobial, antidiabetic, anticonvulsant activities, their utilities in treatment of vascular dysfunction and, using them as an inhibitor of fatty acid amide hydrolase.

Keywords: 2-thiohydantoin, antitumor activity, antimicrobial activity, antidiabetic activity, inhibition of fatty

Imidazolidine is 1,3-diazacyclopentane **1**. Its oxo derivative is called imidazolidenone **2** and its thioxo derivative is called imidazolidinthione **3**. The 1,3-imidazolidine-2,4-dione is known as hydantoin**.** It is containing a reactive cyclic urea core. Sulfur analogs of hydantoins are called thiohydantoins (**4**). One or both carbonyl groups are replaced by thiocarbonyl groups (Fig. 1).

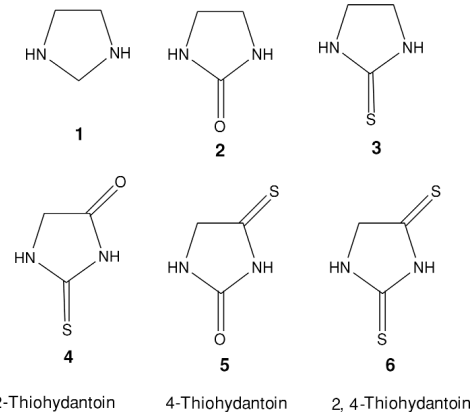


Figure 1.

2-Thiohydantoins (2-thioxoimidazolidin-4-ones) are most notably known due to their wide applications as reagents and intermediates as well as herbicides, therapeutics, and fungicides. They are traditionally considered as useful intermediates in peptide synthesis and structure determination. 2-Thiohydantoins are also used for other purposes, including textile printing, in the production of resins and plastics, and as catalysts for polymerizations (1).

SYNTHESIS OF 2-THIOHYDANTOINS

From a cyanamide and thiophosphate

This method is based on the reaction of methyl *N*-cyano-*N*-alkyl/arylaminoacetate **7** with diethyl thiophosphate **8**. Formation of thiohydantoin (**9**, R= C_6H_5, 4-CH_3-C_6H_4, 4- OCH_3-C_6H_4, R'= H, Me. (Scheme 1.)) takes place at 60 ^oC in good to excellent yields under solvent-free conditions. The by-product **10** can easily be removed from the reaction mixture. The probable mechanism for the formation of **9** is shown, The electrophilic center in the

* Corresponding author: e-mail: hebaa_elhady@yahoo.com, habasuny@uqu.edu.sa

cyanamide group of **7** reacts with diethyl thiophosphate **8** to give an unstable intermediate **11** which further reacts with **8** to give thioureido derivative that isomerizes into stable thiourea derivatives. The intermediate, under the influence of heat, cyclizes into **9** with the loss of MeOH (2).

This method was also extended for the synthesis of bicyclothiohydantoin **13** from N-cyano proline methyl ester **12**. Also, bis-thiohydantoin **15** was successfully synthesized from **14** in good yield under similar reaction conditions as shown below (Scheme 2).

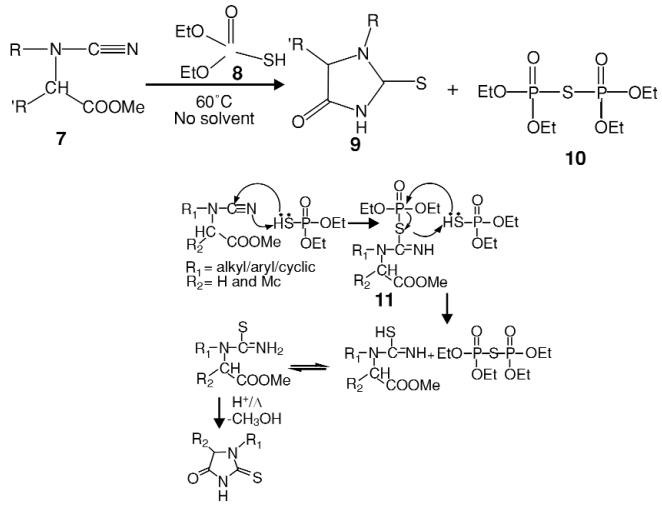
From thiocarbonyl diimidazole and isoquinoline

Boc-protected Tic-OH was coupled with 1-(2-aminoethyl) pipredine using HOBt / EDCI activation and DIEA as a base. After deprotection of the secondary amino group using a TFA/ CH_2Cl_2 mixture, the crude product was dissolved in THF and excess DIEA together with 1,1'-thiocarbonyl diimidazole to yield the fused thiohydantoin derivative **17** (Scheme 3) (3).

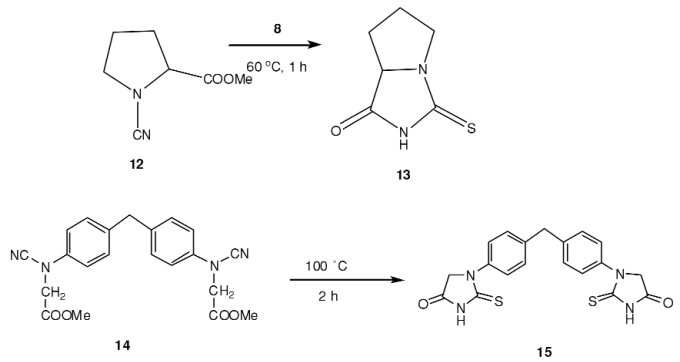
From isocyanates or isothiocyanate

It has been reported that this process is likely to take place through Staudinger reaction which revealed that the nucleophilic attack of the tertiary phosphine on the azide **18** occurred with the formation of phosphazide **19** which reacted with methyl isothiocyanate to yield a betamine **20** that underwent cyclization with the ester functionality with concomitant nitrogen evolution. Finally, hydrolytic cleavage of the resulting cyclized phosphonium salt **21** provided the final product **22** and triphenylphosphine oxide (Scheme 4) (4).

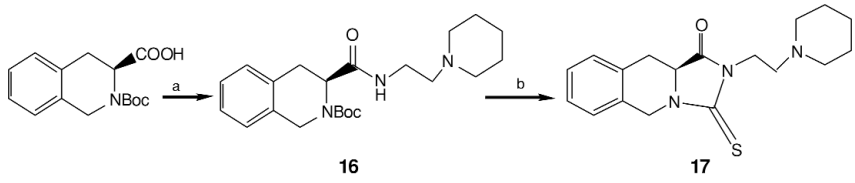
Isothiocyanate derivative **23** was treated with α-aminonitrile **24** to provide amino propanenitrile



Scheme 1. Synthesis of thiohydantoin **9** from methyl *N*-cyano-*N*-alkyl/arylaminoacetate **7** and the probable mechanism.

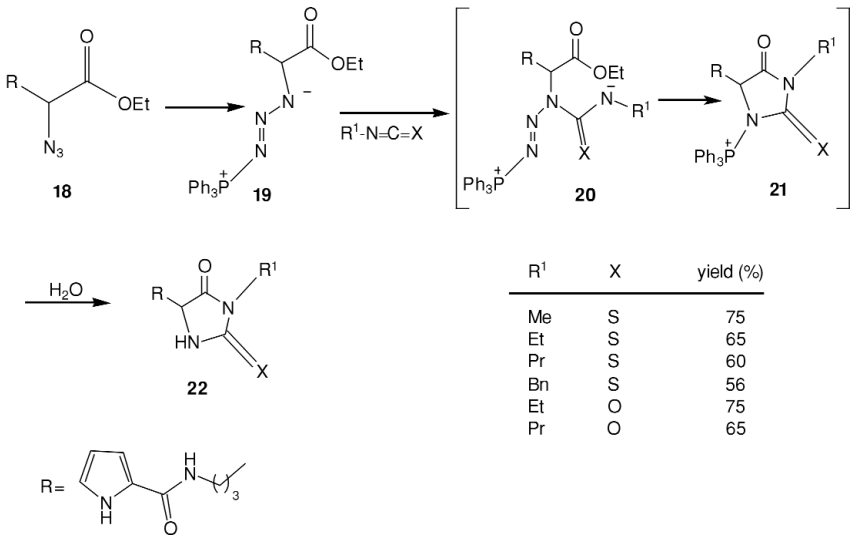


Scheme 2. Synthesis of bicyclothiohydantoin **13** and bis-thiohydantoin **15** from a cyanamide and thiophosphate.



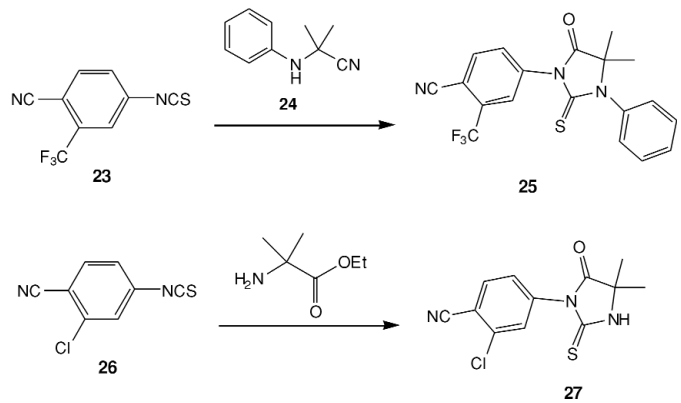
reagents and conditions: (a) aminoethylpiperidine 1 equiv, HOBt 1.1 equiv, EDCI 1.1 equiv, DIEA 2 equiv., CH_2Cl_2, r.t., 2 h., 90%; (b) (i) TFA/CH_2Cl_2 1:1, r.t., 1 h, (ii) 1.1'-thiocarbonyldiimidazole 1.5 equiv, DIEA 4.5 equiv, THF, reflux, overnight, 60%.

Scheme 3. Synthesis of fused thiohydantoin derivative **17**.



R^1	X	yield (%)
Me	S	75
Et	S	65
Pr	S	60
Bn	S	56
Et	O	75
Pr	O	65

Scheme 4. Synthesis of thiohydantoin **22** from the azide **18**.



Scheme 5. Synthesis of the corresponding 3-phenyl-2-thiohydantoin **25** and 3-substituted-2-thiohydantoin **27**.

followed by hydrolysis with mineral acids to afford the corresponding 3-phenyl-2-thiohydantoin **25**. It was also reported that isothiocyanate derivative **26** and aminoisobutyric acid ester were treated with triethylamine to yield 3-substituted-2-thiohydantoin **27** (Scheme 5) (5).

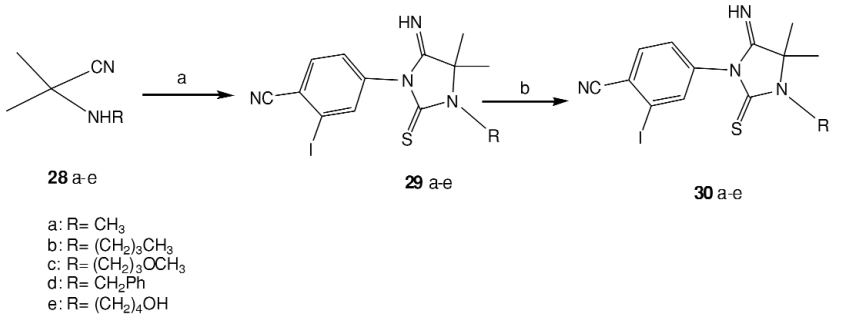
Condensation of 2-iodo-4-isothiocyanatobenzonitrile with 2-amino-2-cyanopropane derivatives

28a-e gave the imino derivatives **29a-e**, which were subsequently converted to the thiohydantoin derivatives **30a-e** by acid hydrolysis (Scheme 6) (6).

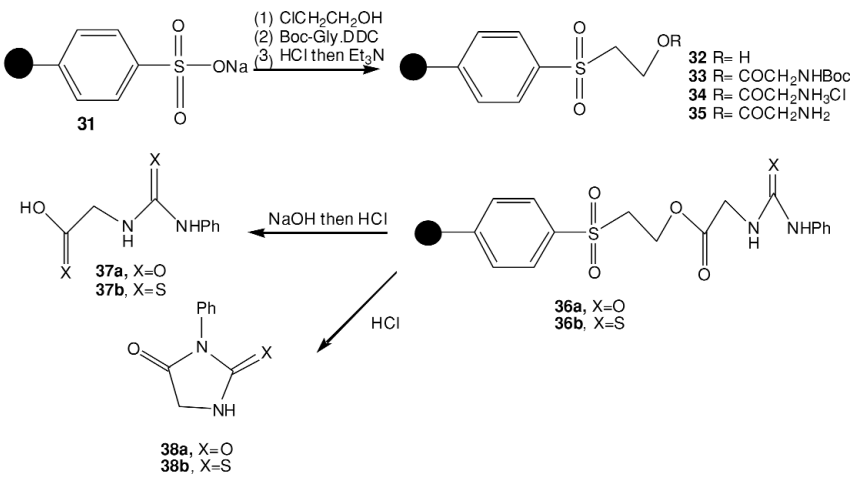
2-Polystyrylsulfonylethanol **32** was prepared by treatment of polystyryl sulfinate resin **31** with 2-chloroethanol. The reaction of **32** with Boc-protected glycine gave resin **33** which was converted to **34** by the treatment with hydrochloric acid in dioxane. Resin **35** was obtained by neutralization of **34** with Et_3N. Polymer-supported urea **36a** was prepared by the treatment of **35** with phenyl isocyanate, while the reaction of **35** with phenyl isothiocyanate gave polymer-supported thiourea **36b**. Direct treatment of compounds **36a** and **b** with aqueous hydrochloric acid released the corresponding hydantoin **37a** and thiohydantoin **37b**, respectively. While base treatment of the same polymer resin **36a** or **b** produced compound **38a** or **b** after acid neutralization (Scheme 7) (7).

Catalytic hydrogenation of α-azidoester **39** using Pd/C as catalyst yielded a separable mixture of two compounds α-aminoester **40** and unexpected spiranic α-lactam (or aziridine) **41**. Treatment of amino ester **40** with phenylisothiocyanate afforded spirothiohydantoin **43** via the corresponding transient thiourea **42** which underwent intermolecular acyl nucleophilic substitution involving NH group (Scheme 8) (8).

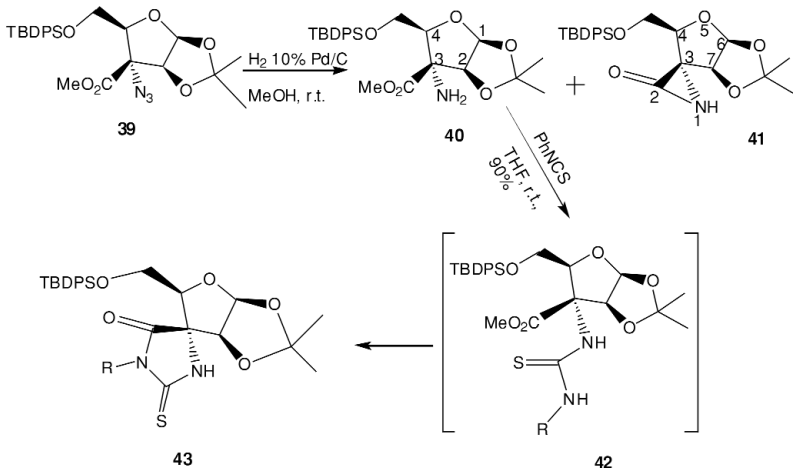
Following the deprotection of compound **44** with 10% piperidine in methylene chloride at room temperature, various isothiocyanates were introduced through 150 W microwave irradiation in methylene chloride to give thiourea intermediate **46**. The cyclization/cleavage step was complete under mild basic conditions with microwave heating. Upon completion of the reaction, polymer support was removed from the homogenous solution to provide the corresponding product **47** (Scheme 9) (9).



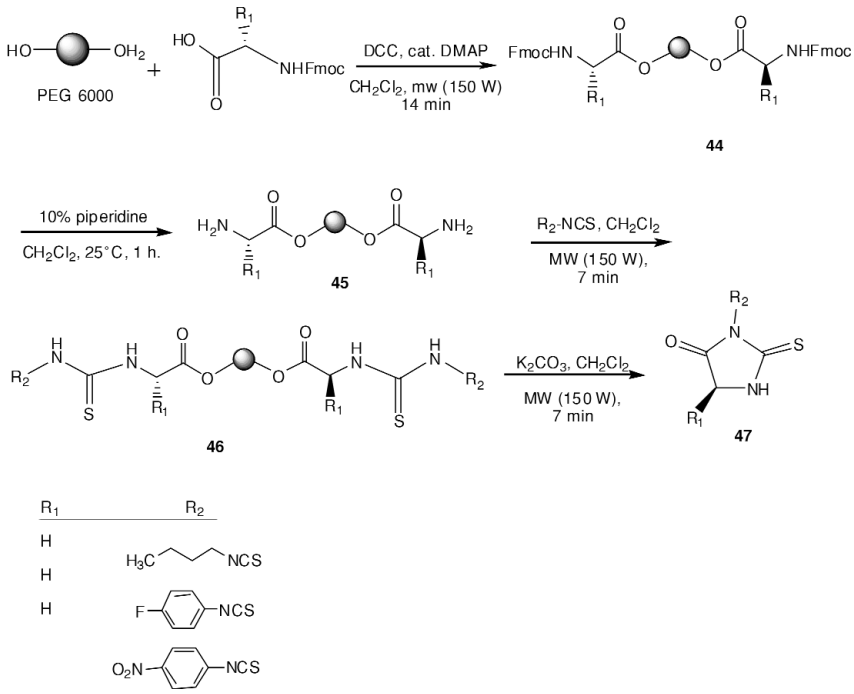
Scheme 6. Synthesis of thiohydantoin derivatives **30a-e**.



Scheme 7. Synthesis of hydantoin **38a** and thiohydantoin **38b** from 2-polystyrylsulfonylethanol **32**.



Scheme 8. Catalytic hydrogenation of α-azidoester **39**.



Scheme 9. Synthesis of thiohydantoin derivatives **47**.

Isothiocyano ester **48** reacted with glycine methylamide **49** to afford the 5-ylidene-2-thioxoimidazolidinones **50** (Scheme 10) (10).

From benzil and urea or thiourea

Diphenylthiohydantoin **52** was obtained from benzil **21** and thiourea in the absence or the presence of microwave activation, this method is known as Biltz's synthesis (**method A**), which is a common way to the synthesis of diphenylthiohydantoin. (**method B**) which is a two-step procedure that can be also used for preparing thiohydantoin **52** by the microwave-assisted condensation of benzil and thiourea followed by H_2O_2 oxidation in DMF/acetic acid at room temperature (Scheme 11) (11, 12).

From thioureido-acetamides and benzil

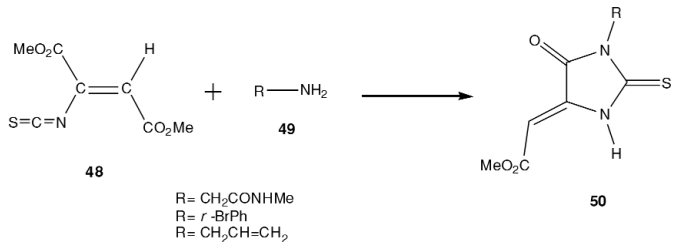
Thioureido-acetamides **54** reacted with benzil derivatives **55** in the presence of sodium hydroxide (NaOH) to produce the functionalized 5,5-diaryl-thiohydantoins **59**. Intermediates of the types **57** and **58** were isolated in related reactions of thiourea and N-methylthiourea (Scheme 12) (10).

From carbonyl compounds

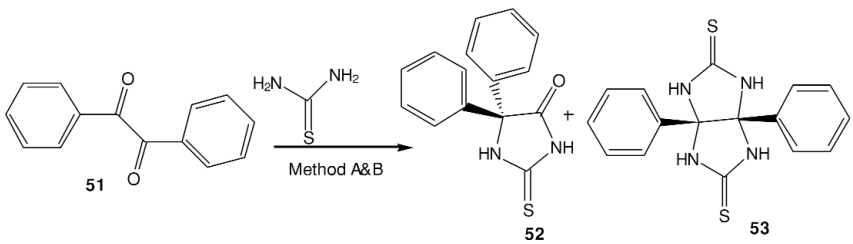
The synthesis of thiohydantoins **64**, **65**, **66**, **67**, **68** is made in aqueous solution in a 'one-pot' manner or by adding separately the three reagents (thiourea **62** or *N*-methythiourea **63**, aldehydes **60**, **61** and P_4O_{10}) at room temperature (Scheme 13) (13).

From 4-imino-imidazolidin-2-one derivatives

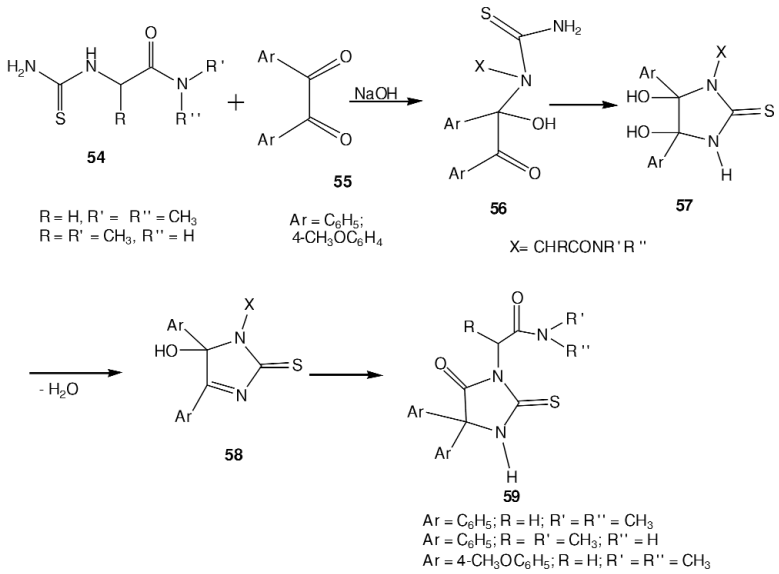
Thionation of 3-amino-4-imidazolidin-2-one derivatives **69** by hydrogen sulfide in dry dichloromethane in the presence of dry pyridine afforded 3-amino-4-thioxo-imidazoldin-2-one **70** while the acidic hydrolysis of the compound furnished the imidazolidine-2,4-dione **71** (Scheme 14) (14, 15).



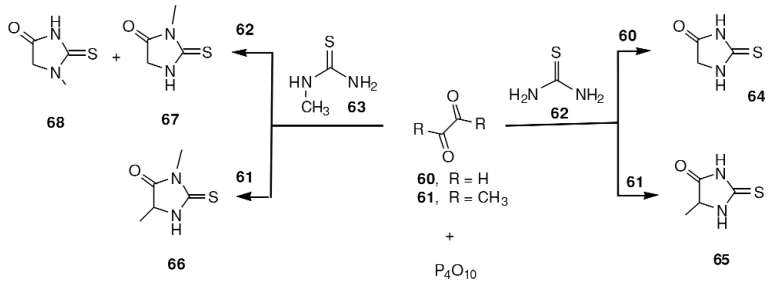
Scheme 10. Synthesis of 5-ylidene-2-thioxoimidazolidinones **50**.



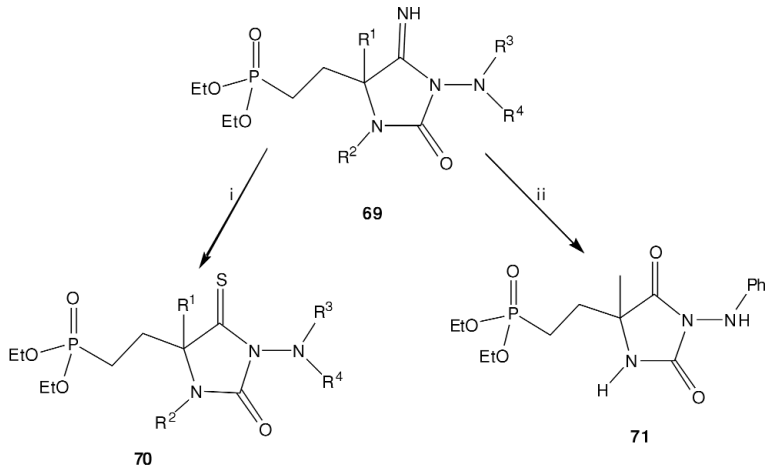
Scheme 11. Synthesis of diphenylthiohydantoin **52**.



Scheme 12. Synthesis of the functionalized 5,5-diaryl-thiohydantoins **59**.



Scheme 13. Synthesis of thiohydantoins **64**, **65**, **66**, **67**, **68**.



R^1	R^2	R^3	R^4
CH_3	H	H	C_6H_5
CH_3	H	H	4-F-C_6H_4
CH_3	H	H	H
CH_3	H	H	*t*-Bu

Scheme 14. Synthesis of 3-amino-4-thioxo-imidazoldin-2-one **70** and imidazolidine-2,4-dione **71**.

From amines

The reaction of 4-amino-2-fluoro-*N*-methylbenzamide **72** with different ketones and trimethylsilyl cyanide gave product **73** which then treated with 4-amino-2-(trifluoromethyl)benzonitrile **74** and thiophosgene and gave 2-thiohydantoins **75** (Scheme 15) (16).

From N-substituted maleimide

Michael addition of 3-ethylhydrazinoacetate to *N*-substituted maleimide **76** led to the formation of 3,4-dihydromaleimides **77** which reacted smoothly with substituted isothiocyanates to give compounds **79** (Scheme 16) (18, 17).

From thiosemicarbazone

Acid-catalyzed condensation of thiosemicarbazide with different ketones **80** such as 4-bromoacetophenone, 5-chloroisatin, benzaldehyde, and acetophenone was carried out to afford substituted hydrazine carbothioamide **81**. The reaction of substituted hydrazine carbothioamides **81** with ethyl chloroacetate in ethanol under reflux gave 2-thiohydantoin derivative **82** (Scheme 17) (19-23).

REACTIONS OF 2-THIOHYDANTOINS

Using the alkyl orthoformate–$ZnCl_2$–Ac_2O reagent system

Kumar and Chauhan have observed that S-methylation and *N*-acetylation of 2-thiohydantoins (**84**, R= H, CH_3) occurred on treatment with trimethyl orthoformate **83** in Ac_2O and $ZnCl_2$ in a one-pot reaction. They been reported that chemoselective alkylation of the thio group occurred whilst

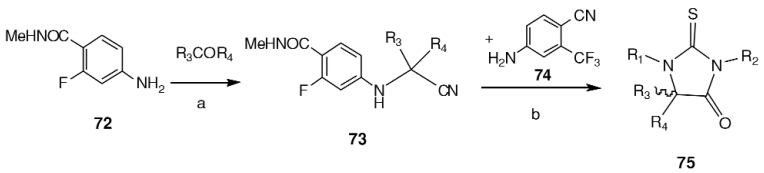
other nucleophilic groups present in the thiohydantoins are acetylated simultaneously in moderate to high yields (Scheme 18) (24).

Reaction with carbonyl compounds

A series of 2-thiohydantoin derivatives **86** were prepared by Knoevenagel condensation of ketones **85** with thiohydantoin **4** in toluene. Cyclization of 2-thiohydantoin derivatives **86** with 1,4-dibromobutane under phase transfer catalysis conditions (potassium carbonate, acetone, benzyl triethylammonium chloride [BTEA] catalyst) gave the corresponding imidazo[2,1-b]thiazepines **87** (Scheme 19) (25).

Condensation of 2-thiohydantoin **4** with suitable aldehydes or ketones (**88**, R^1 = H, CH_3, R^2 = Ph, 4-Cl C_6H_4) occur according to two methods. The reflux in acetic acid with anhydrous sodium acetate (**method A**) or in toluene with ammonium acetate (**method B**) gave 5-arylidene-2-thiohydantoins **89** (Scheme 20) (26, 27).

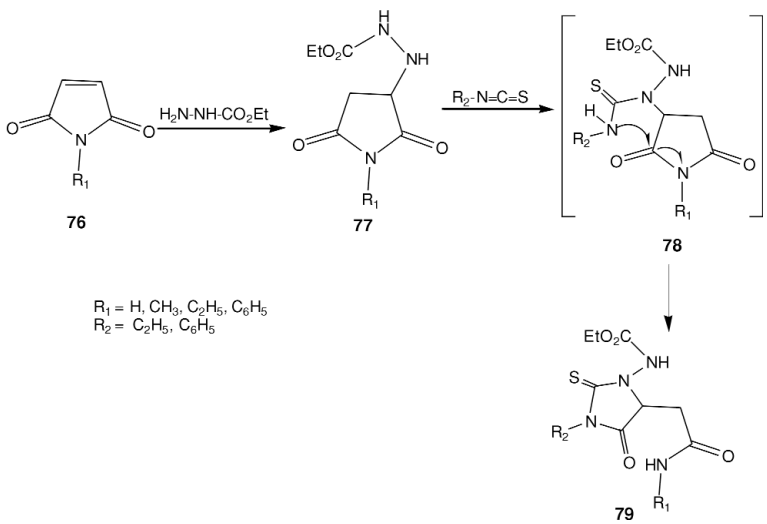
The condensation of aromatic aldehydes with 2-thiohydantoin **4** in the presence of potassium hydroxide, followed by the addition of iodomethane at room temperature leads to the formation of the corresponding 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins **90**. When compounds **90** were heated with hydrazine hydrate in boiling anhydrous ethanol, the corresponding 5-[(*Z*)-arylidene]-2-hydrazono-4-imidazolidinones **91** were obtained. On the other hand, when compounds **90** were heated with hydrazine hydrate in boiling acetic acid the *N*,*N*-bis-(5-(*Z*)-arylidene-4-oxo- 2-imidazolidinylidene)hydrazines **92** were obtained (Scheme 21) (28).



reagents and conditions: (a) AcOH, $MgSO_4$, 25 °C, 24 h; (b) $CSCl_2$, DMF, 80 °C, 12 h

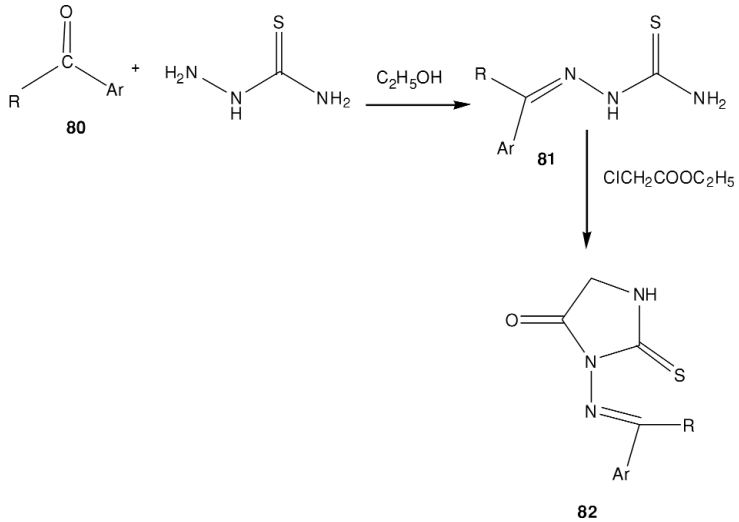
R_1 = 6-Cyano-5-trifluoromethylphenyl.
R_2 = 3-Fluoro-4-(methylcarbamoyl)phenyl, 3-fluoro-4-(methoxycarbonyl)phenyl, 4-carboxy-3-fluorophenyl, 4-carbamoyl-3-fluorophenyl.
R_3 = H, Me, $MeOCH_2$.
R_4 = Me, H, $MeOCH_2$, $PhCH_2OCH_2$, EtO_2CCH_2, $HOCH_2$, $MeOCH_2$.

Scheme 15. Synthesis of 2-thiohydantoins **75**.

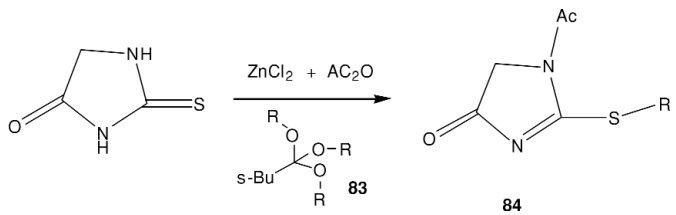


R_1 = H, CH_3, C_2H_5, C_6H_5
R_2 = C_2H_5, C_6H_5

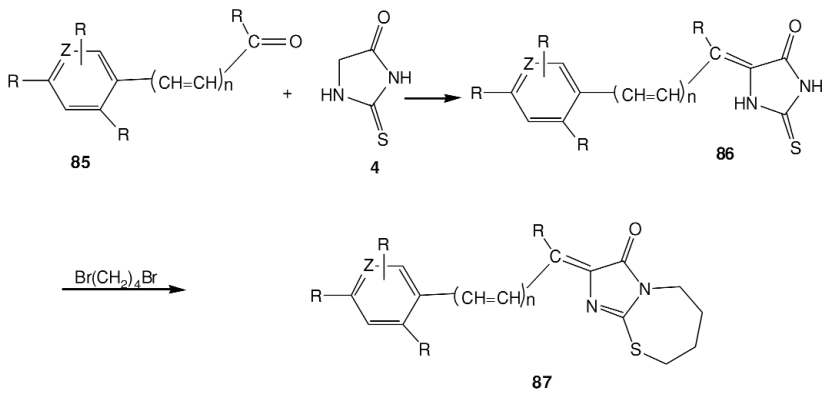
Scheme 16. Synthesis of 2-thioxoimidazolidin-4-one derivatives **79**.



Scheme 17. Synthesis of 2- thiohydantoin **82**.



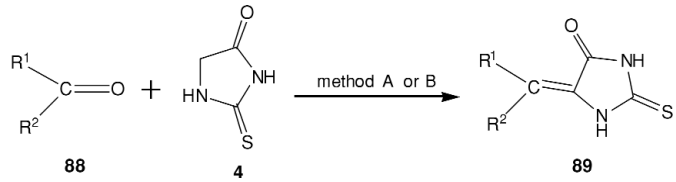
Scheme 18. S-methylation and *N*- acetylation of 2-thiohydantoins.



Z= H, N
n= 0,1

R= H, 2-Cl, 2-CH_3, 4-Cl, 4-Et, 2-F, 2-OCH_3, 4-Ph, 2-Br

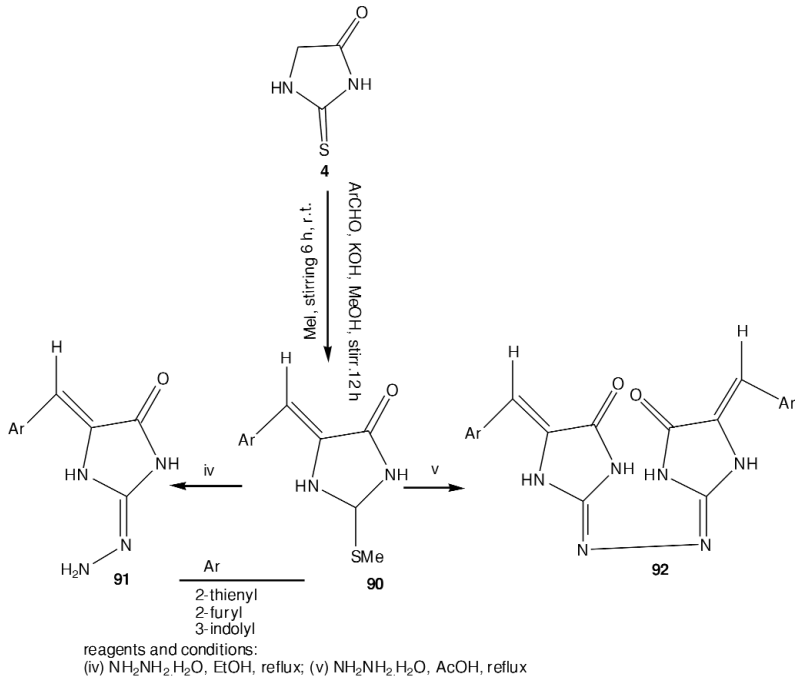
Scheme 19. Knoevenagel condensation of ketones **85** with thiohydantoin **4**.



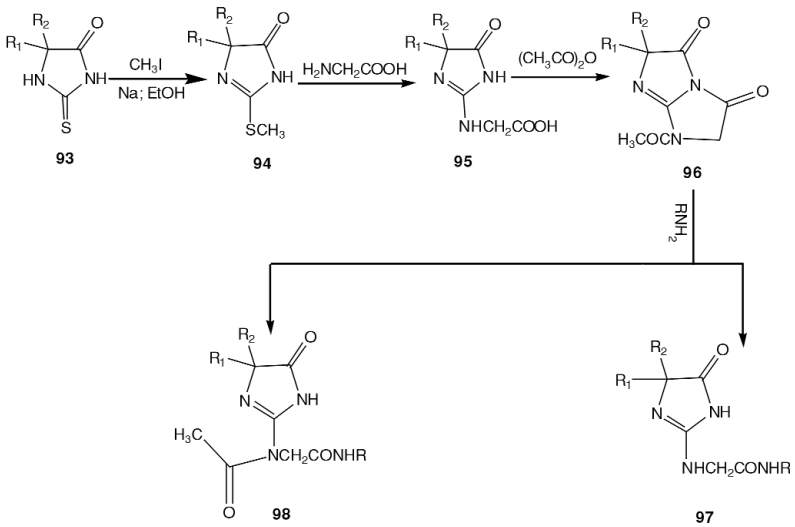
Scheme 20. Condensation of 2-thiohydantoin **4** with aldehydes or ketones.

Reaction with amino acids

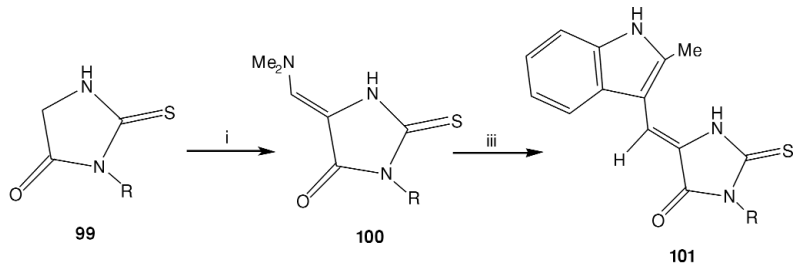
Compound **95** reacted with acetic anhydride to yield the bicyclic acetyl imidazo[2,1*b*]imidazoline-3,5-dione **96** which was cleaved with a twofold excess of ammonia and different amines, substituted or unsubstituted benzylamines, 2-phenylamine and 2-(*N*-morpholine)ethylamine. Upon action of substituted ethylamine, the deacetylated derivatives **97** were obtained. In the reaction with benzylamins, mainly the acetyl derivatives **98** were obtained



Scheme 21. Synthesis of 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins **90**, 5-[(*Z*)-arylidene]-2-hydrazono-4-imidazolidinones **91** and *N*,*N*-bis-(5-(*Z*)-arylidene-4-oxo-2-imidazolidinylidene)hydrazines **92**.

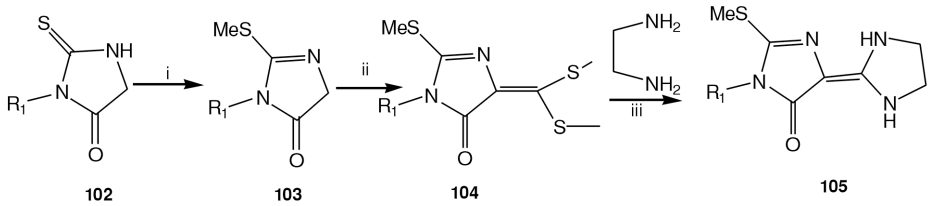


Scheme 22. Reaction of thiohydantoins with amino acids.



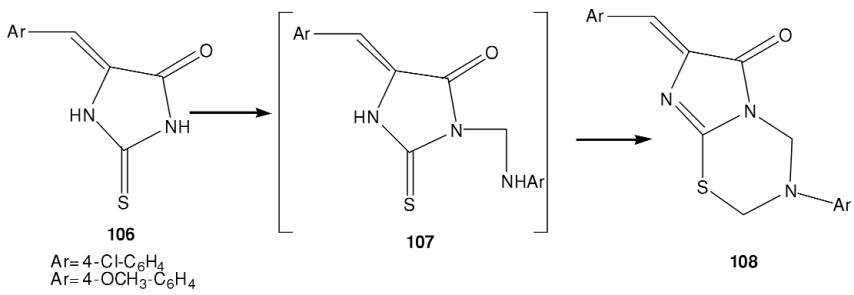
(i) *tert*-BuOCH(NMe_2)$_2$, MeCN or DMF, reflux; (iii) 2-methylindole, AcOH, HBr, r.t.

Scheme 23. Synthesis of 5-[(dimethylamino)methylidine]-2-thioxo-4-imidazolidinones **100** using Bredereck's reagent.



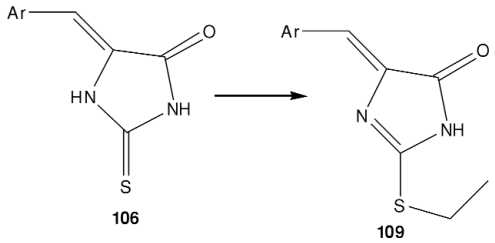
reagents and conditions: (i) MeI 1.5 equiv., K_2co_3 0.5 equiv., MeCN, 40^{0}C, 14 h; (ii) CS_2 1.1 equiv., MeI 2.5 equiv., MeCN, 40^{0}C, 16 h; (iii) (CH_2NH_2) 10 equiv., $CHCl_3$, 70^{0}C, 8 days

Scheme 24. Reaction of 3-substituted-2-thioxo-imidazoldin-4-ones **102** with carbon disulfide.



Ar= 4-Cl-C_6H_4
Ar= 4-OCH_3-C_6H_4

Scheme 25. Reaction of 5-arylidene-2-thiohydantoins **106** with formalin and primary aromatic amine.



Scheme 26. Reaction of 5-arylidene-2-thiohydantoins **106** with monohalogenated compounds.

(Scheme 22). In the case of o-chlorobenzylamine, both of compounds **97** and **98** were isolated (29).

Reaction with Bredereck's reagent

3-Substituted thiohydantoins **99** were converted with tert-butoxy-bis(dimethylamino)methane (Bredereck's reagent) into the corresponding 5-[(dimethylamino)methylidine]-2-thioxo-4-imidazolidinones **100** which were treated with 2-methylindole in acetic acid in the presence of small amount of hydrogen bromide at room temperature to produce the corresponding 5-[(2-methyl-1H-indol-3-yl)methylidine]imidazole derivatives (**101**, R = Et, $CH_2CH = CH_2$, Ph, 4-Me-C_6H_4) (Scheme 23) (30).

Reaction with carbon disulfide

The 3-substituted-2-thioxo-imidazolidin-4-ones **102** were S-alkylated with methyl iodide and potassium carbonate and gave the 2-methylsulfanyl-3,5-dihydroimidazol-4-ones **103**. The ketene dithioacetals **104** are readily prepared by a one-pot reaction of **103** with carbon disulfide, followed by alkylation with methyl iodide. Compound **104** was next reacted with a dry ethylenediamine to afford *N*,*N*-acetals (**105**, R^1 = Me, Bu) (Scheme 24) (31).

Reaction with formalin and primary aromatic amine

The reaction of 5-arylidene-2-thiohydantoins **106** with formalin (32) and primary aromatic amine was accomplished in DMF without any catalyst to yield the imidazo[2,1b][1,3,5]thiadiazine derivatives **108** (Scheme 25).

Reaction with chloro acetonitrile and methyl bromoacetate

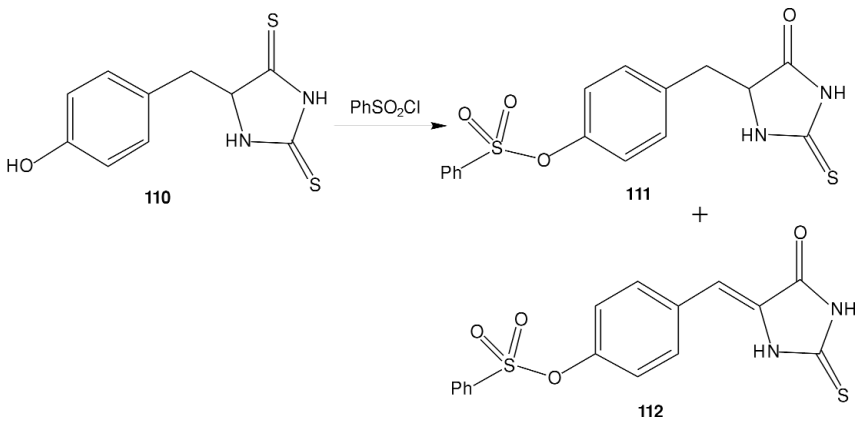
The reaction of 5-arylidene-2-thiohydantoins **106** with monohalogenated compounds such as chloro acetonitrile, ethyl iodide, and methyl bromoacetate was accomplished under the influence of alkali metal alkoxides and gave ethylmercapto derivatives **109** (Scheme 26) (32).

Reaction with phenylsulfonyl chloride

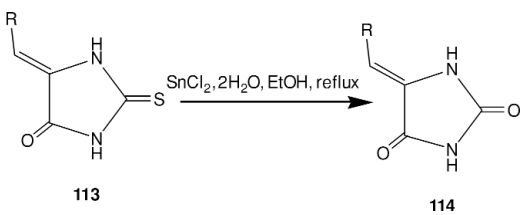
Treatment of 5-(4-hydroxylbenzyl)-thiohydantoin **110** with phenylsulfonyl chloride in acetone in the presence of triethylamine gave **112** and unexpected new product **111** (Scheme 27) (33).

Oxidation reaction

$SnCl_2.2H_2O$ in ethanol has been discovered as an efficient reagent for selective and direct oxidative



Scheme 27. Reaction of 5-(4-hydroxylbenzyl)-thiohydantoin **110** with phenylsulfonyl chloride.



Scheme 28. Oxidation reaction of phenylmethylene-2-thiohydantoins **113** to hydantoin **114**.

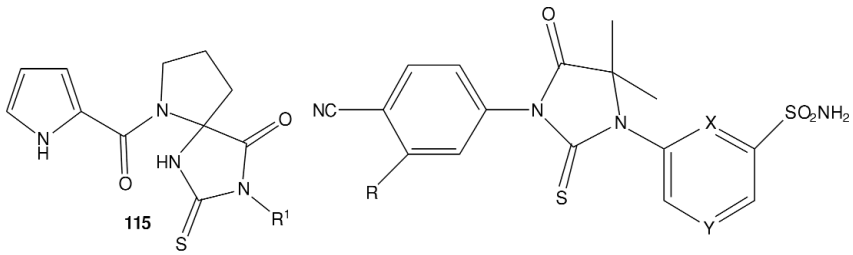
desulfurization of phenylmethylene-2-thiohydantoins **113** to form hydantoin (**114**, R= 2-NO_2-Ph, Ph, 4-Me.Ph, 4-Cl-Ph) (Scheme 28).

APPLICATIONS OF 2-THIOHYDANTOINS

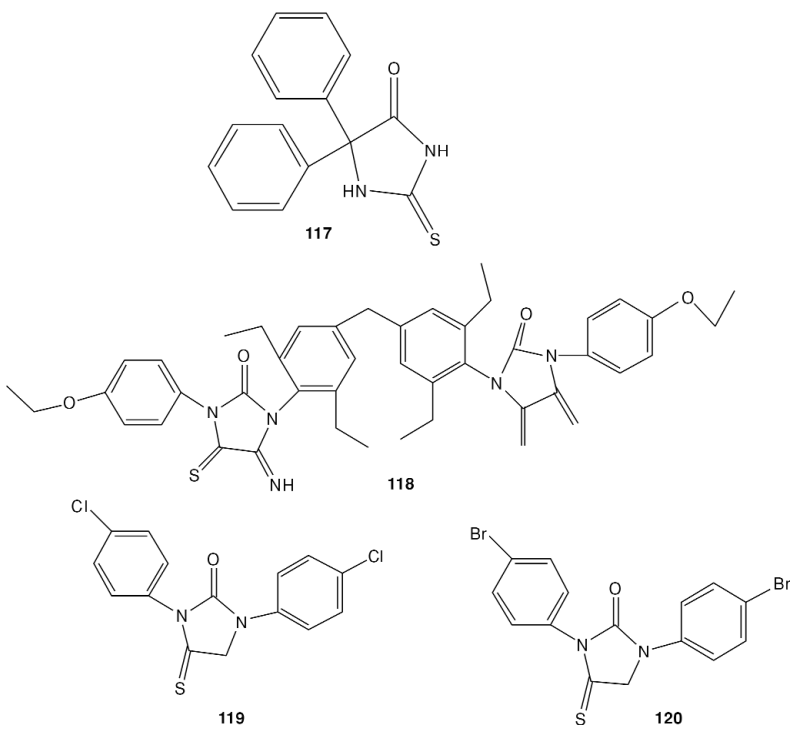
2-Thiohydantoin derivatives have been the subject of chemical and biological studies on account of their interesting pharmacological properties. They are also used for other purposes, including textile printing, as catalysts for polymerizations, in the production of resins and plastics. Some of their utilities are summarized below.

Antitumor activity

Fresneda et al. (34) reported that spirothiohydantoins **115** have cytotoxic activity against 13 human tumor cell lines. They show the most potent activity against prostate carcinoma tumor cells (DU-145), ovarian cells sensitive (IGROV) and (H-MEC-1) endothelium cells. Also, a series of 5,5-dimethylthiohydantoin derivatives were synthesized and evaluated for androgen receptor pure antagonistic activities for the treatment of castration-resistant prostate cancer. Pharmacological assays indicated that compound **116** completely inhibited the *in vivo*



Compound **115, 116**.



Compound **117-120**.

tumor growth of LNCaP-BC2, a castration-resistant prostate cancer model (35).

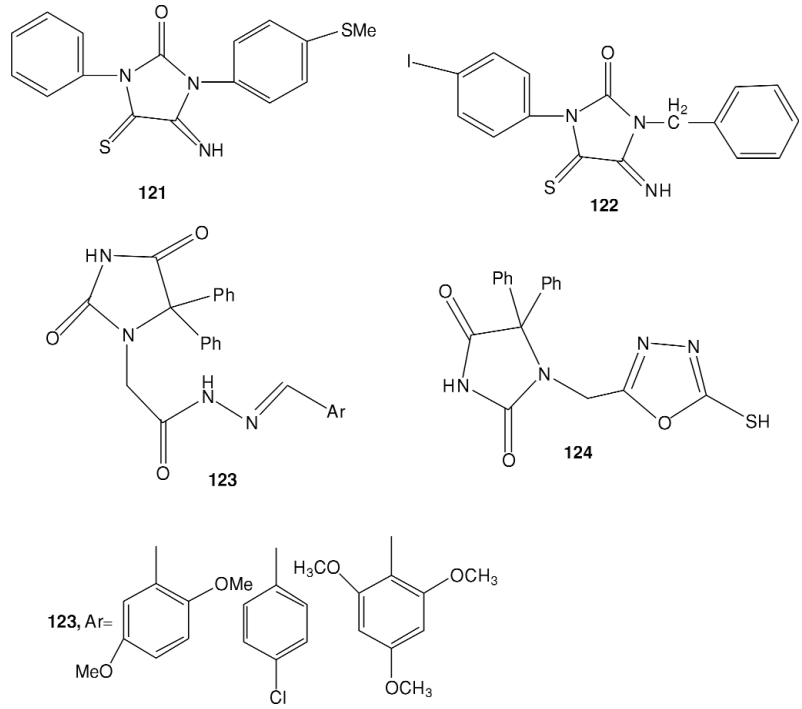
Shih et al. reported that 5,5-diphenyl-2-thiohydantoin **117** has an anti-proliferation effect on human umbilical vein endothelial cells (35). Also, El-Shareif and Moussa have reported that 3,3'-(4,4'-Methylenebis(2,6-diethyl-4,1-phenylene))bis(1-(4-ethoxyphenyl)-4-imino-5-thioxoimidazolidin-2-one) **118**, 1-(4-chlorophenyl)-3-(3,4dichlorophenyl)-4-thioxoimidazolidin-2-one **119**, 1,3-bis(4-bromophenyl)-5-iminoimidazolidine-2,4-dithione **120** produced over 90% inhibition against Ehrlich Ascites carcinoma cells viability. These compounds have also cytotoxic activity against brain tumor cell line U251, human hepatocellular carcinoma cell HEPG2, human breast adenocarcinoma cell line MCF-7, and colon carcinoma cell line HCT116 (36, 37).

Antibacterial and antifungal activity

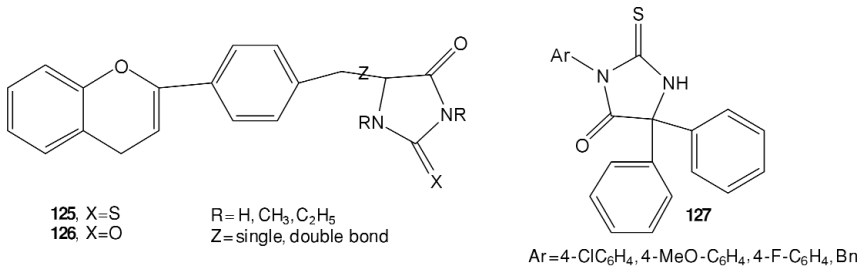
Imidazolidineiminothiones were subjected to in vitro testing of antifungal activity against the following fungal strains: *C. albicans* IMRU-3669 and *A. flavus*. All of the tested compounds were found to possess strong antifungal activity against the two microorganisms. All of the synthesized compounds were tested in vitro for antibacterial activity against the following bacterial strains: Gram-negative bacteria, *Escherichia coli* NCTC-10416, *Sarcina lutea* ATCC-934, and Gram-positive bacteria, *Bacillus subtilis* NCTC-1040, *Staphylococcus aureus*. The results show that compounds **121** (*N*1: phenyl; *N*3: 4-methythiophenyl) and **122** (*N*1: 4-iodophenyl; *N*3: benzyl) exhibited the highest and lowest antibacterial activities in the series, respectively (38 – 41). Also, it was reported that, *N*-Arylidine-2-(phenytoin-1-yl)acetohydrazide **123**, 1-(5-mercapto-[1,3,4]oxadiazol-2-ylmethyl)-5,5-diphenyl-imidazolidine-2,4-dione **124**, have strong antifungal activity against *Candida albicans* (41).

Antidiabetic and anticonvulsant activities

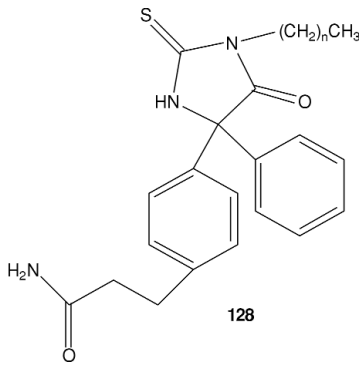
In 2010, Yildiz and Bozdog-Dundur revealed that 4'-flavonyl-2-thiohydantoin **125** and 4'-flavonylhydantoin **126** derivatives were reported as powerful antidiabetic agents (42, 43). While Gangadhar et al. (2013) reported that 3substituted-2-thiohydantoin derivatives **127** have significant anticonvulsant activity. Electron donating groups on the *para* position of 3-phenyl ring show an increase, while halogen group such as fluorine on the *para* position of 3-phenyl ring shows a decrease in anticonvulsant activity (44).



Compound **121-124**.



Compound **125-127**.



Compound **128**.

Use as inhibitor of a fatty acid amide hydrolase

Fatty acid amide hydrolase (*FAAH)* is a membrane-bound enzyme, responsible for the hydrolysis of bioactive lipids. A series of monothiohydantoins were identified by Muccioli et al. as reversible and competitive FAAH inhibitors. Specifically, monothiohydantoin **128** (n = 5) was calculated to bind with the highest affinity within the active site of rat *FAAH* (45).

CONCLUSION

In this review article, we discussed the most important methods for the synthesis of 2-thiohydantoins and their different chemical reactions. They have been the subject of chemical and biological studies on account of their interesting pharmacological properties and their use for other purposes such as textile printing, catalysts for polymerizations, and their use in the production of resins and plastics. Here we explored their antitumor, antimicrobial, antidiabetic, anticonvulsant activities, their utilities in treatment of vascular dysfunction and, using them as an inhibitor of fatty acid amide hydrolase.

Conflict of interest

The authors declare that no conflict of interest exists.

REFERENCES

1. Šmit B., Pavlović R.Z., Radosavljević-Mihailović A., Došen A., Ćurčić M.G. et al.: J. Serb. Chem. Soc. 78, 217 (2013).
2. Kumar V., Rana H., Sankolli R., Kaushik M.P.: Tetrahedron Lett. 53, 2377 (2012).
3. Charton J., Gassiot A.C., Girault-Mizzi S., Debreu-Fontaine M., Melnik P. et al.: Bioorg. Med. Chem. Lett. 15, 4833 (2005).
4. Fresneda P.M., Castańeda M., Sanz M.A., Molina P.: Tetrahedron Lett. 45, 1655 (2004).
5. Yoshino H., Sato H., Shiraishi T., Tachibana K., Emura T. et al.: Bioorg. Med. Chem. 18, 8150 (2010).
6. Van Dort M.E., Jung Y.W.: Bioorg. Med. Chem. Lett. 14, 5285 (2004).
7. Vavsari V.F., Ziarani G.M., Balalaie S., Latifi A., Karimi A. et al.: Tetrahedron 72, 5420 (2016).
8. Merino-Montiel P., López O.,Alvarez E., Fernández-Bolaños J.G.: Tetrahedron 68, 4888 (2012).
9. Lin M., Sun Ch.: Tetrahedron Lett. 44, 8739 (2003).
10. Schmeyers J., Kaupp G.: Tetrahedron 58, 7241 (2002).
11. Muccioli G.G., Poupaert J.H., Wouters J., Norberget B., Poppitz W. et al.: Tetrahedron 59, 1301 (2003).
12. Elarfi M.G., Al-Difar H.A., Elhag Ahmed M.E.: Der Chem. Sin. 3, 299 (2012).
13. Baccolini G., Boga C., Delpivo C., Micheletti G.: Tetrahedron Lett. 52, 1713 (2011).
14. Kurz Th., Geffken D., Widyan Kh.: Tetrahedron 60, 2409 (2004).

15. Kurz Th., Widyan Kh.: Tetrahedron Lett. 45, 7049 (2004).
16. Ivachtchenko A.V., Ivanenkov Y.A., Mitkin O.D., Vorobiev A.A., Kuznetsova I.V. et al.: Eur. J. Med. Chem. 99, 51 (2015).
17. Salhi L., Aichouche S.B., Benmalek Y., Bentarzi Y. et al.: Org. Comm. 6, 87 (2013).
18. Bentarzi Y., Nedjar-Kolli B., Plas A., Chalard P., Troin Y.: ARKIVOC 5, 328 (2010).
19. Mohamed S.M., Unis M., AbdEl Hady H.: Indian J. Chem. B, 105 (2006).
20. Elhady H.A., Al-Nathali H.S., El-Sayed R.: Int. J. Adv. Res. 5, 1716 (2017).
21. Elhady H.A., Aly H.M., Saleh N.M.: Int. J. Adv. Res. 2, 806 (2014).
22. Elhady H.A.: Int. J. Adv. Res. 3, 340 (2015).
23. Elhady H.A., El-Sayed R., Al-Nathali H.S.: Chem. Cent. J. 12, 51 (2018)
24. Kieć-Kononowicz K., Szymańska E.: Farmaco 57, 909 (2002).
25. Kumar R., Chauhan P.M.: Tetrahedron Lett. 49, 5475 (2008).
26. Subtel'na I., Atamanyuk D., Szymańska E., Kieć-Kononowicz K. Zimenkovsky B et al.: Bioorg. Med. Chem. 18, 5090 (2010).
27. Khodair A.I.: Phosphorus, Sulfur Silicon Relat. Elem. 177, 1157 (2002).
28. Karolak-Wojciechowska J., Kieć-Kononowicz K., Mrozek A.: J. Mol. Struct. 597, 73 (2001).
29. Jakse R., Recnik S., Svete J., Golobičet A., Golič L. et al.: Tetrahedron 75, 8395 (2001).
30. Chérouvrier J., Carreaux F., Bazureau M.: Molecules 9, 867 (2004).
31. Hassan A.Y., Said M.M., Sarg M.T., Al-Zahabi H.S., Hussein E.M.: Life Sci. J. 10, 1993 (2013).
32. Han J., Dong H., Xu Z., Lei J., Wang M.: Int. J. Mol. Sci. 14, 12484 (2013).
33. Yavari I., Ghanbari M.M., Shahvelayati A.S., Ghazvini M.: Phosphorus, Sulfur Silicon Relat. Elem. 185, 2551 (2010).
34. Fresneda P.M., Castan eda M., Sanz M. A., Bautista D., Molina P.: Tetrahedron 63, 1849 (2007).
35. El-Sharief A.M., Moussa Z.: Eur. J. Med. Chem. 44, 4315 (2009).
36. Abadi A., Gary B.D., Tinsley H.N., Piazza G.A., Abdel-Halim M.: Eur. J. Med. Chem. 45, 1278 (2010).
37. Moussa Z., El-Sharief M.A, El-Sharief A.M.: Eur. J. Med. Chem. 46, 2280 (2011).
38. Azizmohammadia M., Khoobi M., Ramazani A., Emami S., Zarrin A. et al.: Eur. J. Med. Chem. 59, 15 (2013).
39. Küçükbay H., Durmaz R., Orhan E., Güna S.: Farmaco 58, 431 (2003).
40. Ali O.M., El-Sayed W.A., Eid S.A., Abdel-wahed N.A.M., Abdel-Rahman A.A.H.: Acta Pol. Pharm. 69, 657 (2012).
41. Flosi W.J., DeGoey D.A., Grampovnik D.J., Larry H.Ch., Dekhtyar T. et al.: Bioorg. Med. Chem. 14, 6695 (2006).
42. Yildiz I., Bozdag O.: Med. Chem. Res. 19, 211 (2010).
43. Murasawa Sh., Iuchi K., Sato Sh., Noguchi-Yachide T., Sodeoka M. et al.: Bioorg. Med. Chem. 20, 6384 (2012).
44. Gangadhar Sh.P., Ramesh D.K., Mahajan S.K.: IJRPC 3, 2231 (2013).
45. Estelle G., Giulio G.M., Didier M.L., Michael Sh.: Tetrahedron Lett. 49, 6495 (2008).\

Received: 2.8.2019