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Synthesis, Structure and Biological Activity of Ephedra Heterocycles

Alejandro Cruz, Itzia I. Padilla-Martínez and
María Esther Bautista-Ramírez

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Abstract

Ephedra compounds are well known due to their biological activity. They have been widely used in asymmetric synthesis during the last decades. Recently, we have prepared reviews about the synthesis of acyclic and heterocyclic ephedra derivative compounds reported in the literature. In this chapter, the synthetic methodology to access acyclic and heterocyclic compounds derived from ephedra alkaloids and its structural analysis are discussed, included those due to the substitution of the hydroxy group by chlorine, sulfur, selenium, or nitrogen atoms. Biological activity analysis of some synthesized compounds was done, and some of them have displayed biological activity.

Keywords: ephedrine, chirality, configuration, biological activity, stereospecificity

1. Introduction

Chirality in biological systems is of main significance since in enzymes and drug receptors, the active sites are chiral, and they only interact with molecules of specific configuration. This has synthetic chemists become convinced to accept that all compounds used as pharmaceuticals must be in one of their enantiomeric forms. As a consequence, in the 1980s decade, the Food and Drug Administration (FDA) required pharmaceutical industry to acquire drug candidates in details of the toxic effects of the enantiomers. By this, chemical substances to be used as drugs candidates must be synthesized as optically pure compounds or to be highly enriched.

Biologically active chiral molecules have been extracted from natural products has plants. Extracts from the *Ephedra* sp. genus have been traditionally used in Chinese medicine as nasal

descongestives, cardiac stimulant, and antiasthma agents. The active principle from this plant was first extracted in 1885, isolated, and then purified in 1887 by Nagai [1] who called it ephedrine. The herb, “Ma-Huang” is the best source of ephedrine, up to 1% bulk weight has been obtained from this material. Amounts of *pseudoephedrine*, N-methylephedrine, N-methyl*pseudoephedrine*, *norephedrine*, and *norpseudoephedrine* were found from this herb [2]. Since pharmacological studies done by Chen and Schmidt in 1924 [3], the chemists have been interested in the synthesis of physiologically active analogous of ephedrine derivatives [4]. At the present time, large quantities are used in Western medicine to relieve mucous membrane congestion [5].

Today, ephedrine is a pharmaceutical classified as sympathomimetic agent, weaker but longer acting than adrenaline. It acts as cardiac stimulant, hypertensive agent, hyperglycaemic, and bronchodilator. Ephedrine has been clinically used against hay fever, bronchial asthma, myasthenia gravis, whooping cough, Heart block (Stokes-Adam syndrome), and dysmenorrhea. Because ephedrine crosses the hematoencephalic and placental barriers, have effects on the central nervous system, in consequence, decrease fatigue, sleep (insomnia), and hungry sensations (anorexia) [4].

The non-polar structure of ephedrine makes this substance more liposoluble than catecholamines. It is thermodynamically more stable, in consequence, it is not a substrate for monoamine oxidase (MAO) or the catechol-O-methyltransferase. Thus, it is a diffusible pharmaceutical that has a more prolonged effect as catecholamines [6].

On the other hand, the modern chemistry is interested in the development of new synthetic methods to produce drugs, antibiotics, alimentary additives, etc., with high optical purity. Asymmetric synthesis design requires catalysts, chiral auxiliaries, and reagents able to control the stereochemistry of the reaction products and to be efficiently recycled [7]. Ephedrines, *norephedrines* and its derivatives, have been broadly used as chiral auxiliaries in asymmetric synthesis [8]. Thiols, sulfides, and disulfides obtained from ephedrines have been proven to be very good chiral catalysts [9]. It has been found the use of polymer-supported catalysts applied to organic synthesis with emphasis given to the use of ephedrine chiral catalyst to promote asymmetric reactions [10].

2. Structure of ephedrines

The structure of ephedrine and *pseudoephedrine* was studied by Ladenburg and Oelschägel. They suggested the formula $\text{PhCH(OH)CH(CH}_3\text{)NHCH}_3$ now accepted for the alkaloids [11]. Studies that support this formula were provided by Schmith and Bümmling [12]. The more important fact that ephedrine and *pseudoephedrine* are stereoisomers is easy with which ephedrine can be isomerized to *pseudoephedrine* by acylation or by boiling with HCl (25%) [13], this change has been found to be reversible [14, 15].

Freudenberg and Leithe investigated the configuration about C1 and C2 for ephedrine and *pseudoephedrine* [16–18], and represented the distribution about these centers of asymmetry, for ephedrine by structure **1a** and for *pseudoephedrine* by structure **2a**, **Figure 1**.

Figure 1. Freudenbergl and Leithe representation of ephedrine **1a** and pseudoephedrine **2a**.

Zhu et al. analyzed the relationship of the substituents of the stereogenic center and to the specific optical rotation. The variables used as matrix elements include (1) the substituent masses (**m**), (2) radii (**r**), (3) symmetries (**s**), and (4) electronegativities (**χ**) of the atoms or groups bounded to the stereogenic center. For ephedrine and pseudoephedrine, the calculated values were approximate to the observed rotation values [19]. The preferred conformation of ephedrine **1** and pseudoephedrine **2** was theme of controversy [20–25]. The questions could be answered by the X-ray technique.

Several crystal structures of ephedrine salts were reported: the hydrochloride by Bergin [26] and the hydrogen and the di-hydrogen phosphates by Bugg [27, 28] showed the conformation **1b**. On the other hand, in an X-ray study, Mathew et al. demonstrated the conformation **2b** in structures of (+)-pseudoephedrine and (+)-pseudoephedrine hydrochloride [29]. There was found one strong intermolecular hydrogen bond OH...N in pseudoephedrine which links the molecules into infinite chains around the screw axis. An intramolecular contact N—H...O was observed, but the angle of 108° is not favorable. On the other hand, the C(2)—N bond is nearly parallel to the C(1)—C(*ipso*) bond. This conformation was also found in a bis-(+)-pseudoephedrine complex of Koper II [30], (-)-noradrenaline [31], and dopamine [32]. Similar conformations for norephedrines were found [33] but the difference in energy levels between the various possible conformations in the *nor*-series is less than in the ephedrine series, and interconversion is carried out with ease. This was explained because of the hindering effect of the N-methyl group, **Figure 2** [34].

Finally, ephedrines **1,2** and norephedrines **3,4** have the β-aminoalcohol structure where the phenyl and methyl groups create two chiral centers on each carbon atom and generate four optically active stereoisomers, **Figures 4** and **5**. Freudenbergl et al. [16] and Leithe [17] established

Figure 2. Stable conformations of ephedrine **1b** and pseudoephedrine **2b**.

the relative configuration about the asymmetric centers for (–)-ephedrine and its optical isomers, hence the configurational relationship between ephedrines **1a,b** and *pseudo*-ephedrines **2a,b** series is well known. The stereoisomers with methyl on nitrogen atom are *l*-(1*R*,2*S*)-ephedrine **1a** and *d*-(1*S*,2*R*)-ephedrine **1b**; *d*-(1*S*,2*S*)-*pseudo*ephedrine **2a**, and *l*-(1*R*,2*R*)-*pseudo*ephedrine **2b**, **Figure 3**.

The *l*-ephedrine **1a** is the stereoisomer that produces a more pronounced stimulus on the central nervous system, compared with other drugs [35].

The stereoisomers without methyl on nitrogen atom are called *norephedrines*: *l*-(1*R*,2*S*)-*norephedrine* **3a** and *d*-(1*S*,2*R*)-*norephedrine* **3b**; *d*-(1*S*,2*S*)-*norpseudoephedrine* **4a**, and *l*-(1*R*,2*R*)-*norpseudoephedrines* **4b**, **Figure 4**.

Figure 3. Ephedrine stereoisomers.

Figure 4. *Norephedrine* stereoisomers.

3. Physical properties of ephedrines

Physical properties of some optical isomers of ephedrines as free bases or as acidic salts have been summarized, **Tables 1–4** [36].

Characteristic	mp (°C)	$[\alpha]_D$
Free base (B)	37–39	–41°
Hemihydrate	39–43	–6.3° (EtOH) +11.2° (H ₂ O)
Hydrochloride	216–220	–34° (H ₂ O)
Hydrobromide	205	–
Sulphete	243	–30° (H ₂ O)
Oxalate	249 (dec)	Insol. H ₂ O
Aurichloride	128–131	–
Platinichloride	186	–

Table 1. (1*R*, 2*S*)-(–)-ephedrine forms.

Characteristic	mp (°C)	$[\alpha]_D$
Free base (B)	118–120	–51° (EtOH)
Hemihydrate	–	–
Hydrochloride	185–188	–62. (H ₂ O)
Hydrobromide	–	–
Sulphete	–	–52.5° (H ₂ O)
Oxalate	218 (dec)	Insol. H ₂ O
Aurichloride	126.5–127.5	–
Platinilchloride	–	–

Table 2. (1*R*, 2*R*)-(–)-*pseudo*ephedrine forms.

Characteristic	mp (°C)	$[\alpha]_D$ (°)
Free base (B)	51–54	–14.56(EtOH)
Hemihydrate	–	–
Hydrochloride	172–175	–33° (H ₂ O)
Hydrobromide	–	–
Sulphete	285–286 (dec)	–31.99 (H ₂ O)
Oxalate	245 (dec)	–
Aurichloride	188	–
Platinichloride	221 (dec.)	–

Table 3. (1*R*, 2*S*)-(–)- *norephedrine* forms.

Characteristic	mp (°C)	$[\alpha]_D$
Free base (B)	77–8 (corr.)	–37.9 (MeOH)
Hemihydrate	–	–
Hydrochloride	180–183 (corr.)	–41.7° (H ₂ O)
Hydrobromide	–	–
Sulphete	295 (dec.)	–48.7° (H ₂ O)
Oxalate	235 (dec.)	–
Aurichloride	137–138	–
Platinilchloride	198	–

Table 4. (1*R*, 2*R*)-(-)- *norpseudoephedrine* forms.

4. Biological activity of ephedra heterocycles

A wide approach for the synthesis of new compounds that possess some kind of biological activity is the cyclization of substituted phenethylamines as ephedrine into heterocycles, such as morpholine (phenmetrazine) [37] and 2-amine-oxazolines (4-methylaminorex and 3,4-dimethylaminorex) [38], in such a way that the ephedrine skeleton becomes part of the heterocyclic ring, **Figure 5**.

Some other heterocycles as oxazolidine [39], di- and tetrahydro-1,3,4-oxadiazines [40, 41], 2-thiazoline [42], thiazolidine [43], dihydro-1,3,4-thiadiazine [44], tetrahydro-triazine [45], and imidazolidine [46] derived from ephedrine and *norephedrine* have been reported. Certain of these heterocycles exhibit different biological effects as central nervous system, stimulating, appetite-depressing [37, 38], monoamine oxidase inhibiting antidepressant [40g, 44b], central nervous system depressant [40e, f, 41, 45], analgetic [45], hypocholesterolemic [41], anti-inflammatory [41], antimicrobial [41, 44b], or catechol-amine-potentiating [43] activities. On the other hand, 3,4-dimethyl-5-phenyl-oxazolidine is used as a prodrug [47].

Figure 5. Some heterocyclic compounds with biological activity.

5. Reactions to get chlorodeoxyephedrine derivatives

The bromination reaction of ephedrine hydrochloride **2a** with PBr_5 produce the bromodeoxy-derivative [48]. On the other hand, ephedrine **1a** or *norephedrine* **3a** or its hydrochlorides reacts with SOCl_2 to give chlorodeoxypseudoephedrine **5a** or chlorodeoxynorpseudoephedrine **5b**. The same reaction with *pseudoephedrines* **2a** or **4a** give a 60:40 diastereomeric mixture of *threo:erythro* **5a:6a**, **Scheme 1** [49]. In order to improve the stereoselectivity, chlorination reaction of *pseudoephedrine* stereoisomers **2** at 0°C was carried out. In these conditions, only the corresponding *threo* chlorodeoxystereoisomers **3** were stereoselectively obtained ($\text{S}_{\text{N}}\text{i}$ mechanism), **Scheme 1**, the X-ray diffraction structure of **5a** is depicted in **Figure 6**.

Scheme 1. Chlorodeoxyephedrine hydrochlorides from chlorination reaction of ephedrines **2**.

Figure 6. X-ray diffraction structure of Chlorodeoxyephedrine hydrochloride **5a**.

6. Heterazolidines-2-heterounsaturated from ephedrines

In 1950, Close reported the solvent-free dehydration of ephedrine hydrochloride **1** in the presence of urea at $180\text{--}200^\circ\text{C}$ to afford the imidazolidinone **11a-(t)** and oxazolidinone **15a-(c)**,

Scheme 2 [34]. In that work, it was proposed that urea is converted into ammonium oxocyanate at 180–200°C, which in the presence of hydrogen chloride, ammonium chloride and oxocyanic acid are produced. Finally, ephedrine reacts with oxocyanide acid to produce the nonisolated urea intermediate **7a-(e)**, which cyclization by dehydration affords the *trans*-imidazolidone **11a-(t)**. On the other hand, in a simultaneous manner, cyclization of urea **7a-(e)** by nucleophilic attack of the oxygen atom of ephedrine to the ureidic carbonyl and ammonia elimination produces the oxazolidone heterocycle **15a-(c)**.

The same reaction was revisited with the use of K^+NCO^- instead of urea, and the study was extended with thiocyanates and *pseudoephedrine* **2a-(th)**, *norephedrine* **3b-(e)**, and *norpseudoephedrine* **4b-(th)**, as stereoisomers to produce a series of optically active 1,3-heteroazolidine-2-heterounsaturated compounds **9–15**, **Scheme 3**.

Scheme 2. Dehydration of ephedrine **1a-(e)** with urea according to Close.

Scheme 3. 1,3-heterazolidines-2-heterounsaturated from ephedrine.

6.1. Reaction of ephedrines with oxocyanate

Urea intermediate **7a-(e)**, proposed in the Close's reaction, was isolated when K^+NCO^- is reacted with ephedrine hydrochloride **1** in refluxing ethanol for 72 h (78% yield). The reaction was also performed with *pseudoephedrine* **2**, *norephedrine* **3**, and *norpseudoephedrine* to afford, the urea derivatives **7a-(th)**, **7b-(e)**, and **7b-(th)** in 83, 80, and 86% yield, respectively

(Scheme 4). In the case of the reaction of Na^+NCS^- with ephedrine stereoisomers series **1–4**, only chloride by thiocyanate anion was exchanged to give the corresponding hydrothiocyanates **8a,b** (*e,th*) (Scheme 4). The urea intermediate **7a-e** derived from ephedrine could be crystallized from ethanol and its structure studied by X-ray diffraction (Figure 7).

Scheme 4. Reaction of K^+NCO^- and $\text{NH}_4^+\text{NCS}^-$ with ephedrine **1a,b-(e,th)** in refluxing ethanol.

An intramolecular hydrogen bonding interaction between the hydrogen atom of the hydroxyl group and the ureidic oxygen atom to form a seven membered ring was observed. The $\text{O1H1}\cdots\text{O6}$ distance of 1.820(24) Å [angle of 166.72° (2.25)] represents a strong interaction [50]. The formed hydrogen bond forces the NH_2 group to adopt a syn conformation to the N-Me group [C8N4C5N7 angle of -6.00 (0.26)°]. In addition, both N—CO bond distances are of intermediate value between a single (1.469 Å) and a double (1.279) N—C bond (1.35 Å mean) [51].

When the intermediate **7a-e** was free of solvent heated at 180–200°C for 1 hour, an equimolar mixture of imidazolidone **11a-c** and oxazolidone **15a-c** was formed (Scheme 5). Imidazolidinone **11a-c** was separated by precipitation from a CHCl_3 and purified by recrystallization from ethanol. The structure of *cis* (*c*) isomer instead of the expected *trans* (*t*) isomer [52] was observed on the ^1H and ^{13}C NMR spectra and confirmed by X-ray diffraction analysis. The formation of an aziridinim isocyanate **I** then the isocyanate **II** as intermediates

Figure 7. Molecular structure of ephedrine-urea **7a-(e)**.

Scheme 5. Mechanistic pathway for the cyclization of ephedrine-urea **7a-(e)** to get imidazolidinone **11a-(t)**.

are proposed to explain the retention of C1 configuration in the formation of the *cis*-imidazolidone **11a-(c)** (**Scheme 5**) [53]. On the other hand, the oxazolidone **15a-(c)** is formed in accord to the Close's idea (**Scheme 2**). The *in situ* formation of amides from aminoalcohols involved in oxazolidine formation has been reported in the literature [34, 54].

On the basis of these previous findings, the free of solvent reaction of ephedrines **1,4** with sodium or ammonium thiocyanates were performed.

6.2. Reaction of ephedrines with thiocyanate

In the direct heating of one equimolar of Na^+NCS^- with ephedrine **1** at 180–200°C during 0.5 h, ephedrine hydrothiocyanate **8a-(e)** from the aqueous phase and *trans*-thiazolidine-2-imino hydrothiocyanate **9a-(t)** from the chloroform phase (10% yield) were separated, after $\text{CHCl}_3/\text{H}_2\text{O}$ partition, **Scheme 6**. Deamination of ephedrine hydrothiocyanate **8a-(e)** proceeded to give Ethylphenylketone as lateral product.

The reaction with two molar equivalents of NH_4SCN for 4 hours afforded the thiazolidine-2-imino hydrothiocyanate **9a-(t)** in 50% yield as precipitate from CHCl_3 . The use of NH_4SCN instead of NaSCN salt, avoided deamination, due to its lower melting point (153°C). Compound **9a-(t)** was identified on comparing the structure obtained from chlorodeoxypseudoephedrine [55]. On the other hand, several heterocycles were separated when the remaining chloroform mixture was eluted in a chromatographic column. The mass spectrometry of the separated fractions showed the presence of heterocycles summarized in **Table 5**.

As described above for ephedrine **1**, two molar equivalents of $\text{NH}_4^+\text{NCS}^-$ were heated with *pseudoephedrine* **2**, *norephedrine* **3**, and *norpseudoephedrine* **4**. The identified compounds are listed in **Table 5**.

The reaction mixture of *pseudoephedrine* hydrochloride **2** was treated with a 50:50 of $\text{CHCl}_3/\text{H}_2\text{O}$ mixture. The chloroform phase was eluted in a column chromatography. Using chloroform as eluent, the imidazolidine-2-thione **10a-(c)** was separated in 40% yield as first fraction.

Scheme 6. Heating reaction of ephedrine **1** with NaSCN .

	Heterocycle	9	10	11	12	13	14	15
Ephedrine	X	S	NH	NH	S	S	O	O
	Y	NH ₂ SCN	S	O	S	O	S	O
1a-(e)	<i>Cis</i>		184 (2)	163 (3) [190(27)]	196 (7) [223 (100)]	172 (4)		160 (2) [191 (19)]
	<i>Trans</i>	168(50) [206(98)]	183 (7)	162 (7)	195 (2) [223 (100)]	171(7)		191 (23)
1a-(th)	<i>Cis</i>	169(15) [206(15)]	184 (40) [206 (100)]	163 (5) [190(27)]	196 (6) [223 (100)]	172 [207(64)]		160 (5) [191 (19)]
	<i>Trans</i>			162 (2)	Traces [223 (100)]	171 [207(41)]		159 (20) [191 (23)]
1b-(e)	<i>Cis</i>		Traces [192 (100)]		200 (5) [209 (100)]	176 (5) [193(16)]	189 (2) [193 (35)]	160 (40) [177 (8)]
	<i>Trans</i>		Traces		199 (2) [209 (100)]	175(40) [193(25)]		
1b-(th)	<i>Cis</i>	173(40) [192(62)]	183 (10) [192 (100)]		200 (15) [209 (100)]	175(10) [193(16)]		160 (3)
	<i>Tans</i>	172(10)				174 (5)		159 (3)

Table 5. Carbonyl carbon chemical shift in ppm, proportion (%) and mass spectrometry data [M^+ (%)] of heterocycles 9–15.

Imidazolidones **11a-(c)** and **11a-(t)**, thiazolidinedione **12a-(c)**, and thiazolidinones **13a-(c)** and **13a-(t)** were separated in small quantities in the subsequent three remaining fractions, respectively. On the other hand, after evaporation of the aqueous phase, thiazolidine-2-imino hydrothiocyanate **9a-(c)** and oxazolidinones **15a-(c)** and **15a-(t)** as solid mixtures were identified by mass spectrometry. NMR spectral data of compound **10a-(c)** show a broad signal at 6.32 ppm (^1H) and at 183 ppm (^{13}C) of the N–H and C–S groups, respectively. The molecular ion [$z/e = 206$ (100%), M^+] and X-ray diffraction analysis confirmed the structure, **Figure 8**. The bond distances C2–N1 [1.345(14) Å] and C2–N3 [1.332(13) Å] show an intermediate value between a single and a double bond [51], due to a conjugation through the N1–C2–N3 fragment.

From the reaction mixture of *norephedrine* hydrochloride **3**, compounds **13b-(c)** and **13b-(t)** in a 1:8 proportion were separated by chromatography. Compound **13b-(t)** (40% yield) was separated from **13b-(c)** in a second column using CHCl_3 . The spectra data, molecular ion [$z/e = 193$ (25%), M^+], and the X-ray diffraction structures of compound **13b-(t)** confirm the *trans* configuration (**Figure 9**). A conjugation through the N–C2–S fragment is observed because the bond distances C2–N [1.332(3) Å] and C2–S [1.775(2) Å] are shorter than the corresponding single bonds.

The reaction mixture of *norpseudoephedrine* hydrochloride **4** was separated in a chromatographic column and each fraction analyzed by mass spectrometry, **Table 5**. The fourth fraction contained thiazoline-2-amine hydrothiocyanate **9b-(c)**.

Figure 8. Structure of imidazolidinethione **10a-(c)**.

Figure 9. Structure of *trans*-thiazolidinone **13b-(t)**.

At least four competitive mechanisms are proposed to explain the formation of heterocycles **9-15a,b** in the heating reaction of NH_4SCN with ephedrines **1,2** and *norephedrines* **3,4** (**Scheme 7**). In general, with exception of heating reaction of *norephedrine* **3**, a $\text{S}_{\text{N}}2$ dehydration mechanism by the thiocyanate = isothiocyanate anions as nucleophiles and the subsequent cyclization of the ephedrinethiocyanate (**IV**) and/or ephedrineisothiocyanate (**III**) intermediates formed operate to give the corresponding thiazolidine-2-imino hydrothiocyanates **9a,b** and/ or imidazolidinethiones **10a,b**. The product from thiocyanate predominate in the heating reaction of ephedrine **1**, and for *pseudoephedrine* **2**, the product from isothiocyanate predominate. A stable alkyl ephedrinethiocyanate analogue to **IV** has been isolated, which support the proposed mechanism [56].

In the heating reaction of *norephedrine* **3**, the H_2S obtained by hydrolysis of thiocyanate acts as nucleophile in competitive $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms to form the thiolephedrine thiourea

Scheme 7. Proposed mechanisms to explain the formation of heterocycles 9–15.

VI-(e,th), which cyclization afford thiazolidinethiones **12b(c,t)**. A desulphurization by hydrolysis of thiazolidinethiones **12b(c,t)** explains the formation of thiazolidinones **13b(c,t)**. A mechanism through thioureidic intermediate **V** operates simultaneously, its cyclization affords oxazolidinethione **14b(c)**, which desulphurization gives oxazolidinone **15b(c)**.

Desulphurization of the oxazolidinethione **14a(t)** explains the formation of oxazolidinone **15a(t)** (20%) in the heating reaction of *pseudoephedrine* **2**, **Scheme 6**, this mechanism is favored when one molar equivalent of $\text{NH}_4^+\text{NCS}^-$ is used. In this case, oxazolidinone **15a(t)** (40%) and imidazolidinethione **10a(c)** (20%) were obtained as the major products. Similar results were observed in the heating reaction of *norpseudoephedrine* **4**. If $\text{NH}_4^+\text{NCS}^-$ is changed from two to one molar equivalents, thiazoline-2-amine hydrothiocyanates **9b(c)** decreased from 40 to 15% and oxazolidinone **15b(t)** increased from 3 to 45%.

In general, in the ^1H NMR spectral data of ephedracycles, the $\text{C}-\text{CH}_3$ group of the *cis* isomers appears at low frequency shifts in the range between 0.9 and 0.7 ppm, compared with the same group of the *trans* isomers, appearing between 1.1 and 1.4 ppm, this is due to the shielding effect of the phenyl group.

7. Heterazolidines-2-heteroinsaturated from chloro*pseudo* ephedrine

In continuation with our investigations on the design of new heterocycles derived from ephedrine **1**, in this work, we revisited the cyclization reactions of chloro*deoxypseudo*ephedrine hydrochloride **5a-(th)** (R = Me) with one or two molar equivalents of potassium oxocyanate, sodium thiocyanate, and potassium selenocyanate nucleophiles as cyclizing agents in refluxing ethanol. In addition, the results of the reaction of chloro*deoxynorpseudo*ephedrine hydrochloride **5b-(th)** (R = H) with the above mentioned nucleophiles are reported. An interesting finding of this study was the synthesis of the *trans* isomer of 1,3-oxazolidine-2-iminium chloride **18a-(t)** through the *in situ* chlorinated urea intermediate **7a-(e)**, **Scheme 8**.

Scheme 8. Reactivity of chloro*deoxypseudo*ephedrine hydrochlorides **5** with heterocyanates.

7.1. Reaction of chloro*deoxypseudo*ephedrine hydrochlorides **5** with potassium oxocyanate

Chloro*deoxypseudo*ephedrine hydrochloride **5a-(th)** was reacted with two molar equivalents of KOCN in stirring ethanol at room temperature. The reaction was monitored at 24, 48, and 72 h by ¹H NMR. Two compounds, in 80:20, 60:40, and 40:60 proportions, respectively, were observed. The NMR tube of the 40:60 proportion in DMSO-*d*₆ was heated at 92°C during 1 h, to quantitatively transform the minor proportion compound into the 1,3-oxazolidine-2-iminium oxocyanate **18a-(c)** identified as the only product. The *N*-(1-chloro-1-phenyl-2-methyl-ethyl)-*N*-methyl urea **17a-(th)** in the 80:20 mixture with **18a-(c)** was identified as the intermediate. The use of one molar equivalent of potassium oxocyanate in the same reaction in refluxing 16 h afforded the hydrochloride of the oxazolidine-2-imine **18a-(c)**, which was crystallized from ethanol to be analyzed by X-ray diffraction, the structure is shown in the **Figure 10**.

The reaction is general; the reaction of one molar equivalent of KOCN with chloro*deoxynorpseudo*ephedrine hydrochloride **5b-(th)** (R = H) in refluxing ethanol 8 h afforded the chlorourea derivative **17b-(th)**. The proposed mechanistic pathway represented in **Scheme 9** explains why the reaction is carried out with inversion of the Cl configuration to get the *cis* isomer.

Figure 10. Molecular structure of hydrochloride compound **18a-(c)**.

Scheme 9. Mechanistic pathway involved in the synthesis of compounds **18a-(c)** and **18b-(c)**.

Chlorourea compound **17b-(th)** could be isolated and characterized by NMR. Two signals are observed in the ^1H NMR spectrum 6.04, (d, $^3J = 8.5$ Hz) and 5.55 ppm (s, broad) in a 1:2 proportion, respectively, assigned to NH and NH_2 urea hydrogen atoms, respectively. The NH coupling constant value proposes a hydrogen bonding $\text{NH} \cdots \text{Cl}$ interaction, which makes this hydrogen and H2 to be in an *antiposition*. In addition, the small H^1 , H^2 coupling constant ($^3J = 5.28$ Hz) supports this proposed interaction, **Figure 11**. The ^{13}C NMR spectrum shows the carbonyl carbon signal at 159.6 ppm, according to the proposed structure.

The chlorourea derivative **17b-(th)** was refluxed in ethanol during 24 h. The ^1H NMR spectrum of the solid precipitated showed a 80:20 mixture of two heterocycles. The ^1H NMR chemical shift of the $^+\text{NH}_3$ group appears in 9.65 ppm as a broad signal, H5 and H4 appear at 6.49 (d) and 4.56 ppm (dq), for the major compound. For the minor compound, H5 and H4 appear at 5.26 (d) and 5.41 ppm (dq), respectively. In both compounds, the

Figure 11. Hydrogen bonding interaction proposed in compound **17b-(th)**.

coupling constants are of the same value. In addition, the multiplicity of these signals are interchanged for the minor compound, which are correlated with ^{13}C NMR signals at 65.9 (C4) and 84.6 (C5) ppm, respectively. These results allowed us to assign the *cis*-4-methyl-5-phenyloxazoline-2-ammonium chloride **18b-(c)** as the major compound the *cis*-5-methyl-4-phenyl-oxazoline-2-ammonium hydrochloride **23b-(c)**, as the minor compound, whose formation is explained due to the participation of an aziridine intermediate III, **Scheme 10** [52].

It is known that in chlorination reaction of ephedrine derivatives with thionyl chloride, the C1 configuration is retained through a $\text{S}_{\text{N}}\text{i}$ mechanism, when ephedrine bears a bulky group as oxamide or sulfonamide on the nitrogen atom [57]. In this sense, we obtained the *erythro* isomer of ephedrineurea intermediate **7a-(e)** by the reaction of ephedrine hydrochloride **1a-(e)** with KOCN [58]. This ephedrineurea was chlorinated with thionyl chloride in CHCl_3 to get, *in situ*, 1-(2-chloro-1-methyl-2-phenyl-ethyl)-1-methyl-urea **17a-(e)**. Compound **17a-(e)** was refluxed in ethanol during 8 h. ^1H and ^{13}C NMR spectroscopic data of the solid obtained after solvent removal allowed us to identify the *trans* isomer of 3,4-dimethyl-5-phenyl-oxazolidine-2-iminium chloride **18a-(t)**. This result showed that chlorodeoxyephedrine urea **17a-(e)** was obtained with retention of C1 configuration, which was cyclized with the inversion of C1 configuration to obtain **18a-(t)**. In a similar

Scheme 10. Mechanistic pathway proposed to explain the formation of compound **23b-(c)**.

manner, the same reaction with *norephedrine* hydrochloride **1b-(e)** is stereoselective to get the *cis* isomer of the oxazoline-2-ammonium chloride **18b-(c)**. In contrast, the same procedure for *pseudoephedrine* **1a-(th)** and *norpseudoephedrine* **1b-(th)** hydrochlorides gave a mixture of oxazolidine-2-iminium chlorides **18a** (60:40, *c:t*) and oxazoline-2-ammonium chlorides **18b** (75:25, *c:t*), respectively [59].

7.2. Reaction of chlorodeoxypseudoephedrine hydrochlorides **2** with sodium thiocyanate

It is known that the condensation reaction of chlorodeoxypseudoephedrine hydrochloride **5a-(th)** with two molar equivalents of NaSCN in refluxing ethanol for 8 h stereoselectively affords the *trans*-thiazolidine-2-iminio thiocyanate **9a-(t)** [51].

The reaction of chlorodeoxynorpseudoephedrine hydrochloride **5b-(th)** (*R* = H) with two molar equivalents of KSCN in refluxing ethanol, only chloride is interchanged by thiocyanate anion to give chlorodeoxynorpseudoephedrine hydrothiocyanate **16b-(th)** ($\nu = 2057\text{ cm}^{-1}$, $-\text{SCN}$), even at 24 h of reflux. If hydrothiocyanate **16b-(th)** in DMSO- d_6 is heated (90°C) 1 h in a NMR tube, a 50:50 *cis/trans* mixture of 1,3-thiazoline-2-ammonium thiocyanate **9b** was detected in the ^1H NMR spectrum. However, only the *cis* isomer of **9b-(c)** was stereoselectively produced if the reaction is solvent free heated at 170°C during 3 hours, **Scheme 8**.

7.3. Reaction of chlorodeoxypseudoephedrine hydrochlorides **2** with potassium selenocyanate

As previous result reported for chlorodeoxypseudoephedrine hydrochloride **5a-(th)** [51], the reaction of chlorodeoxynorpseudoephedrine hydrochloride **5b-(th)** with two equivalents of KSeCN in refluxing ethanol for 10 hours affords *trans*-selenazoline-2-ammonium selenocyanate **19b-(t)**. On the other hand, if only one equivalent of KOCN, NaSCN, or KSeCN is used in the reactions, the corresponding hydrochloride salts of the 2-aminoheterocycles are obtained. Both XCN^- (*X* = O, S, Se) and Cl^- salts were liberated with aqueous NaOH to give the corresponding imine **20–22a** or amine **20–22b** compounds. Compound **20b-(c)** and **22b-(t)** were crystallized from ethanol and chloroform, respectively. The structures could be established for X-ray diffraction analysis, **Figures 12** and **13**, respectively.

Figure 12. X-ray diffraction structure of **20b-(c)**.

Figure 13. X-ray diffraction structure of **22b-(t)**.

8. *CIS*-thiazolidinethiones from chloropseudoephedrine

In 1995, we reported the reaction of chlorodeoxypseudoephedrine.hydrochloride **5a-(th)** with 33% aqueous solution of sodium trithiocarbonate (Na_2CS_3) in refluxing ethanol to give *cis*-thiazolidinethione **12a-(c)** (53% yield), **Scheme 11** [60]. However, the same reaction with chlorodeoxynorpseudoephedrine **5b-(th)** failed to give the corresponding *cis*-thiazolidinethione derivative **12b-(c)**.

By this, we encourage us the goal to selectively obtain *cis*- or *trans*-thiazolidinethiones **12a,b** from either chlorodeoxynorpseudoephedrine **5b** or chlorodeoxypseudoephedrine **5a** derived from ephedrine **1,3**.

To get thiazolidinethiones **12a,b**, the chlorhydrates of chlorodeoxypseudoephedrine **5a** or **5b** were reacted with one molar equivalent of sodium dithiocarbonate in ethanol solution at room temperature. In the case of chlorodeoxynorpseudoephedrine·HCl **5b**, a white powder solid was precipitated in stirring ethanol for 6 h. The *cis* and *trans* relationships between the phenyl and the methyl groups in thiazolidinethiones **12b** was deduced from the analysis of their ^1H and ^{13}C NMR spectral data and are in agreement with data reported [49d]. On this bases, the product represented a mixture of *cis:trans*-thiazolidinethiones of **8** in a 9:1 proportion. A $\text{S}_{\text{N}}2$ mechanism to explain the C1 inversion of configuration, then cyclization to get the *cis*-isomer is proposed to be carried out, **Scheme 11**. In addition, a competitive double $\text{S}_{\text{N}}2$ mechanism on C1, then cyclization in which *cis*-aziridine **24b-(c)** as intermediate is involved to explain the presence of the *trans*-isomer **12b-(t)**. Analogous mechanistic observations were proposed

Scheme 11. Mechanistic transformation to get *cis*-thiazolidinethiones from chlorodeoxypseudoephedrine.

to get stereospecifically thiazolidinethiones from the reaction of viciodoalkanecarbamates with potassium ethylxanthate [61]. When the same reaction at 0°C for 6 h was performed, only *cis*-thiazolidinethione **12b-(c)** was precipitated as a white powder in 95% yield. Thiazolidinethione **12b-(c)** is stable as thione tautomer in concentrated solution (δ NH at 8.3 ppm). However, in a diluted solution, the thiol tautomer is present (δ SH at 1.6 ppm).

The reaction of chlorodeoxypseudoephedrine·HCl **5a** at 0°C was performed, and after 3 days off, white orthorhombic crystals of *cis*-thiazolidinethione **12a-(c)** precipitated in 81% yield. The X-ray diffraction structure showed the *cis*-isomer.

To confirm that the *cis*-aziridine is responsible of the *trans*-thiazolidinethione formation, the Kelloggs method was used with the previously obtained *cis*-aziridine **24a-(c)** and **24b-(c)** [62] from chlorodeoxypseudoephedrines **5a** or **5b**. The corresponding *cis*-aziridine was reacted with CS₂ in stirring ethanol by 48 h at 0°C. In the case of the reaction of *cis*-aziridine **24b-(c)**, two compounds in a 70:30 mixture were observed in the ¹H NMR spectra. The CH₃ groups of the two compounds were in 1.35 and 1.44 ppm, respectively. After comparison with reported data, both compounds were identified as *trans* isomers of thiazolidinethiones [63]. The major heterocycle was the *trans*-thiazolidine-thione **12b-(t)** and the minor heterocycle, the *trans*-isothiazolidinethione **25b-(t)**. The ring opening on C3 and C2 of the aziridinium by the aziridinethiocarbamate anion of the intermediate **III** explains the formation of both heterocycles, **Scheme 12**. This aziridinium opening reaction has been observed elsewhere [59, 62].

When *cis*-aziridine **24a-(c)** was reacted with CS₂ in the same reaction conditions, *cis*-thiazolidinethione **12a-(c)** was stereoselectively obtained instead of the expected *trans*-isomer in agreement with the Kellogg's method, **Scheme 13**. In this case, the retention of the C1 configuration is explained by attack of the aziridinium thiocarbamate zwitterion **VI** on the benzylic carbon, followed by the closure of the intermediate **VII** to recover the initial C1 configuration.

Crystals of *Cis*-thiazolidinethione **12a-(c)** were separated from ethanol and its structure studied by X-ray diffraction analysis, **Figure 14**. The N3—C2(S2)—S1 conjugated system is proposed since the distances are of an intermediate value between a single (1.469 Å) and a double (1.279 Å) N—C bond (N3—C2 = 1.35 Å) and a single (1.789 Å) and a double (1.600 Å) C—S bond (S1—C2 = 1.741 Å and S2—C2 = 1.659) [51]. Conjugation makes N3 to be in a sp² hybridization, as the angles C(4)—N(3)—C(12) = 119.9(3), C(2)—N(3)—C(4) = 116.2(3), and C(2)—N(3)—C(12) = 121.6(3) show values close to 120°. On the other hand, the five membered ring is almost planar since

Scheme 12. Mechanistic transformation of *cis*-aziridine **4c** into a mixture of *trans*-thiazolidinethione **8t** and *trans*-isothiazolidinethione **10t**.

Scheme 13. Mechanistic transformation of *cis*-aziridine **24a-(c)** into *cis*-thiazolidinethione **12a-(c)**.

Figure 14. X-ray diffraction structure of *cis*-thiazolidinethione **12a-(c)**.

the torsion angles $\text{N}(3)-\text{C}(2)-\text{S}(1)-\text{C}(5)$ of $5.3(3)^\circ$, $\text{S}(2)-\text{C}(2)-\text{N}(3)-\text{C}(12)$ of $-1.8(5)^\circ$ are very close to 0° , and $\text{S}(2)-\text{C}(2)-\text{S}(1)-\text{C}(5)$ of $-177.4(2)^\circ$, $\text{S}(1)-\text{C}(2)-\text{N}(3)-\text{C}(12)$ of $175.1(3)^\circ$ are close to 180° . An intramolecular contact between a hydrogen atom of the $\text{N}-\text{CH}_3$ group and the sulfur atom of the thiocarbonyl group occurred to form a five member ring. The $\text{C12H12}\cdots\text{S2}$ distance of $2.72(4) \text{ \AA}$ [angle of $111(3)^\circ$] is in the range for a strong interaction [50].

9. Thiazaborolidines from thioephedrine

The synthesis of N-alkyloxazaborolidines **26–28** derived from ephedrine has been reported (**Figure 15**) [64]. In 1995, we reported the analogous compounds made from thioephedrine, and herein, we report several borohydrides derived from thioephedrine (compounds **12a**, **29–37**) following the syntheses depicted in **Scheme 14**.

Hydrolysis of thiosulfate **29** obtained with retention of C1 configuration from the substitution reaction of chloride **5** give the disulfide **30**, **Scheme 14**. The disulfide **30** reacts with $\text{BH}_3\text{-THF}$

Figure 15. Borolidines from ephedrines.

Scheme 14. Thiazaborolidines from ephedrines.

to give a mixture of the stable N-epimers disulfide amine boranes **31** and **32** detected by ^{11}B NMR. This N-epimers are comparable with the N-BH₃ adducts of *pseudo*-ephedrines.

Heating the N-epimers mixture of **31** + **32**, affords the borinic ester **33** as the only product, which in the ^{11}B NMR spectra appears as a triplet [$\delta = -6.4$ ppm, $J(\text{BH}) = 103$ Hz, in CDCl_3 or $\delta = -4.5$ ppm, in $\text{THF}-d_8$]. Two methyl groups in *trans* position was found for borinic ester **33** on the ^1H and ^{13}C NMR data. This allows us to assign the configuration at the nitrogen atom. No borinic esters with a BH₂ group derived from ethanolamines as stable compounds have been observed. Borinic ester **33** was distilled *in vacuo*, and on the ^{11}B NMR spectra of the distilled, a mixture of thiazaborolidine **33**, 10%, and thiazaboroline **34** were observed. Slowly elimination of H₂ transforms borinic ester **33** into thiazaboroline **34**. In the ^{11}B NMR spectrum, compound **34** shows a doublet ($\delta = +40.8$ ppm, $J(\text{BH}) = 154$ Hz). From the distilled, a crystal of compound **33** was separated and its X-ray diffraction structure obtained (Figure 16). The thiazaboroline **34** reacted with BH₃-THF to afford the N-BH₃ adduct **35** (Scheme 1). The structure has been deduced from the ^{11}B NMR data, which indicated a N-BH₃ bond (quadruplet at $\delta = -22.0$ ppm, $J(\text{BH}) = 71$ Hz) and a doublet which is strongly shifted to lower frequencies ($\delta = -7.0$, $J(\text{BH}) = 148$ Hz). A diborane group in which a hydrogen atom from the N-BH₃ adduct is bridging the boron atom of the heterocycle was found. These findings are similar to that found in the *pseudo*ephedrine oxazaborolidine [64a].

Figure 16. X-ray diffraction structure of borolidine **33**.

Thiazolidine-2-thione **12a-(c)** obtained from compound **5a** with sodium trithiocarbonate has been isolated and its reactivity towards BH_3 -THF studied, **Scheme 14**. The reaction was followed by ^{11}B NMR, and a $\text{S}-\text{BH}_3$ adduct **36** ($\delta = -23$ ppm, broad signal) was first detected. The analysis of ^1H NMR spectrum of compound **36** indicates that BH_3 is linked to the thione sulfur atom. Heating the $\text{S}-\text{BH}_3$ adduct **36** afforded the thiazaborolidine **37** which is a triplet at $\delta = -3.8$ ppm ($J(\text{BH}) = 11.5$ Hz) in ^{11}B NMR spectra. This compound **37** is obtained pure when **12a-(c)** is reacted with 3 equivalents of BH_3 -THF. The ^1H and ^{13}C NMR were recorded. The diastereotopic N-methyl groups show that the nitrogen has a stable configuration, the assignment of the ^1H and ^{13}C signals was done by comparison with similar compounds [64b, 65].

Compound **33** has the C-5 atom out of the plane of an envelope conformation of the five member ring. The N—B bond distance is 1.58(1) Å and B—S of 1.922(9) Å. Boron and nitrogen atoms are tetrahedral. The nitrogen atom was found to be of “S” configuration, as deduced from the ^1H and ^{13}C NMR data. The methyl groups are *trans* position. The angles on the nitrogen atom are close to a sp^3 hybridization, C4—N3—C13 112.3(5)°, B2—N3—C13 111.3(5)°, and C4—N3—B2 112.0(5)°.

10. Biological properties of ephedrine and their derivatives

10.1. Ephedrine

Mao (*Ephedra sinica* Stapf), which provides similar effects to ephedrine [66, 67], is used as a component of several herbal medicines. It has been utilized in the treatment of cold and allergy [68, 69]. Clinically, it is utilized to lower fever, relieve pain and headaches, control body weight, relieve inflammatory responses [70, 71], and also rheumatoid arthritis [72].

Ephedrine **1a** and *pseudoephedrine* **2a** are also used to treat cancerous diseases in modern clinical practice, they combined with other preparations relieve arterial spasms, neurotoxic reactions after radiation therapy and chemotherapy [73, 74].

Since 1938, ephedrine was regulated as a drug; however, the herbal source was regulated as a food. However, after the Dietary Supplement Health and Education Act of 1994 (DSHEA) [75] was passed, the herbal products escaped drug regulation. As a consequence, ephedra extracts remains available as a “dietary supplement.” However, after years of battling, stimulant combination products (e.g., ephedra and caffeine) are yet available.

10.2. Chloroephedrine derivatives

Previously was demonstrated that N-β-chloroalkylamine derivatives **5a,b** (Figure 17) possess a different spectrum of anticancer activities [76]. On the other hand, cytotoxic and antitumor activities of ephedrine and N-β-chloroalkylamine derivatives **5a**(1–3), **5b**(1–3) were determined [77].

It was found compounds **5b1**, **5b2**, and **5b3** were active in the cytotoxicity test for ³H-thymidine incorporation. The concentrations causing 50% cytotoxicity were in the range 11.0–45.0 mg/mL. However, derivatives **5a1**, **5a2**, and **5a3** were more active.

Compounds **5a2**, **5b2**, **5a3**, and **5b3** investigated *in vitro* suppressed growth of EAC and S-180 tumor strains to various degrees.

It has been shown that the introduction of phosphorus-and sulfur-containing fragments considerably lowers the toxicity of the alkaloids.

With respect to substances **5a1** and **5b1**, they had similar toxicity to *l*-ephedrine, while the other substances were less toxic. It has been found that the replacement of the oxygen atom in the structure of a thio salt of *l*-ephedrine **5a3** by a second sulfur atom led to a slight rise in toxicity.

10.3. Dithiocarbamate derivatives

N-methyl-*l*-ephedrinedithiocarbamates derived from *l*-ephedrine **1a** and *d*-pseudoephedrine **2a** has been obtained. Dithiocarbamic acid derivatives exhibit a broad-spectrum physiological activity [78]. They were found to act as fungicides, herbicides, insecticides, acaricides, zoocides, nematocides, growth regulators, bactericides, etc. Such dithiocarbamic acid derivatives as Carbathion, Cineb, Vegadex, and Cyram have found practical application in agriculture as pesticides.

10.4. Oxazolidines derivatives

Due to the reversibility of the reaction of ephedrines **1–4** with aldehydes or ketones to get oxazolidine heterocycles (Scheme 15), these compounds could be used as prodrugs [79]. Some

Figure 17. Structures of N-β-chloroalkylamine derivatives **5a,b**.

Scheme 15. Oxazolidines from ephedrine.

of these compounds significantly increased locomotor activity in rats at 50-mg/kg dose. The formaldehyde derivative had similar activity as ephedrine. All other compounds were less active.

Four such compounds were tested in rats for ephedrine-like activity using the hyperthermia and anorexia models. The results showed that all of the compounds decreased food intake significantly, but only the acetone and the salicylaldehyde derivatives caused a significant elevation of body temperature [80].

On this bases, we probed the antioxidant and antimicrobial activity of some heterocyclic compounds derived from ephedrines **1–4** previously synthesized.

11. Determination of biological activity of ephedracycles

Ephedrine is a very good pharmaceutical but it acts as central nervous system stimulant, and ephedrine and their derivatives have been used as drugs of abuse so its prescription has been restricted, we proposed ephedra heterocycles as new derived compounds as pharmaceutical candidates with low central nervous system. We decided to prove the antioxidant and antibiotic activities of several heterocycles synthesized in our laboratory represented in **Tables 6** and **7**, respectively.

Table 6. Antioxidant activity (IC_{50} mol/L) of some synthesized heterocyclic compounds.

Compuesto	<i>Salmonella typhi</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Bacillus subtilis</i>
21b	NA	NA	NA	NA
34	20	8	10	20
9t	NA	NA	NA	NA
21a	NA	6	NA	9
19t	NA	NA	NA	NA
22a	NA	NA	NA	NA
12t	NA	NA	NA	NA
12ac	NA	NA	NA	NA

Inhibition in mm.

No actividad found (NA).

Table 7. Antibiotic activity of some synthesized heterocyclic compounds derived from ephedrine 1–8.

11.1. Antioxidant activity

The DPPH radical scavenging activity of plants was estimated according to the method explained by Cheung, with some modifications. Aliquots of 2 ml of 6×10^{-5} M DPPH methanol were mixed with 50 μ L of the extracts. The mixtures were vigorously shaken and left to stand for 10 min under subdued light. The absorbance at 540 nm was measured against methanol as a blank. The decolorization was spectrophotometrically measured at 517 nm. The radical scavenging activity (RSA) was calculated using the equation:

$$\%RSA = 100 \times (1 - A_E/AD)$$

A_E is the absorbance of the solution containing antioxidant extract, whereas AD is the absorbance of the DPPH* solution.

Compounds **34**, **19t**, and **12t** showed antioxidant activity, **Table 6**.

11.2. Antimicrobial activity

Disk diffusion assay: extracts were tested for antibiotic activity against *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans*. About 50 μ L of extract was solubilized in ETOH and placed on the surface of the inoculated agar and incubated at 30°C, using antibiotic no. 1 medium, and the antibiotic activity was recorded as the diameter of clear zones of inhibited microbial growth around the paper disk.

The antimicrobial activity was determined using strains *S. aureus*, *B. subtilis*, *S. typhi*, and *E. coli* using sensidiscs. The antioxidant activity was measured by the radical 2,2-diphenyl-1-picrihydrazil. Compound **34** presented antimicrobial activity against all microorganisms used and the compound **21a** showed activity only against *S. aureus* and *B. subtilis*, **Table 7**.

Author details

Alejandro Cruz^{1*}, Itzia I. Padilla-Martínez¹ and María Esther Bautista-Ramírez²

*Address all correspondence to: alecruz@ipn.mx

1 Department of Basic Sciences,UPIBI, National Polytechnic Institute, Mexico City, Mexico

2 Department of Pharmaceutical Technology, UPIBI, National Polytechnic Institute, Mexico City, Mexico

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