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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: ephedrines, chirality, configuration, biological activity, stereoespecificity

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 became 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 synthetized 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-methylpseudoephedrine, 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 haematoencephalic and placental barriers, have effects on the central nervous system, in consequence, decrease fatigue, sleep (insomnia), and hungry sensations (anorexia) [4].

The no-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-methyltranspherase. 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, nor Ephedrines 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 PhCH(OH)CH(CH₃)NHCH₃ now accepted for the alkaloids [11]. Studies that support this formula were provided by Schmith and Bümming [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.
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 \((\chi)\) 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 the 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 \(\text{OH}…\text{N}\) in pseudoephedrine which links the molecules into infinite chains around the screw axis. An intramolecular contact \(\text{N—H—O}\) was observed, but the angle of 108° is not favorable. On the other hand, the \(\text{C(2)—N}\) bond is nearly parallel to the \(\text{C(1)—C(ips)}\) 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 nor Ephedrines \(3, 4\) have the \(\beta\)-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 \(5\). Freudenberg et al. \([16]\) and Leithe \([17]\) established
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-(1R,2S)-ephedrine 1a and d-(1S,2R)-pseudoephedrine 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 nor-ephedrines: l-(1R,2S)-nor-ephedrine 3a and d-(1S,2R)-nor-ephedrine 3b; d-(1S,2S)-norpseudoephedrine 4a, and l-(1R,2R)-norpseudoephedrines 4b, Figure 4.

Figure 3. Ephedrine stereoisomers.

Figure 4. Nor-ephedrine 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].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mp (°C)</th>
<th>[α]D (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free base (B)</td>
<td>37–39</td>
<td>–41°</td>
</tr>
<tr>
<td>Hemihydrate</td>
<td>39–43</td>
<td>–6.3° (EtOH) +11.2° (H2O)</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>216–220</td>
<td>–34° (H2O)</td>
</tr>
<tr>
<td>Hydrobromide</td>
<td>205</td>
<td>–</td>
</tr>
<tr>
<td>Sulphite</td>
<td>243</td>
<td>–30° (H2O)</td>
</tr>
<tr>
<td>Oxalate</td>
<td>249 (dec)</td>
<td>Insol. H2O</td>
</tr>
<tr>
<td>Aurichloride</td>
<td>128–131</td>
<td>–</td>
</tr>
<tr>
<td>Platinichloride</td>
<td>186</td>
<td>–</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mp (°C)</th>
<th>[α]D (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free base (B)</td>
<td>118–120</td>
<td>–51° (EtOH)</td>
</tr>
<tr>
<td>Hemihydrate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>185–188</td>
<td>–62° (H2O)</td>
</tr>
<tr>
<td>Hydrobromide</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sulphite</td>
<td>–</td>
<td>–52.5° (H2O)</td>
</tr>
<tr>
<td>Oxalate</td>
<td>218 (dec)</td>
<td>Insol. H2O</td>
</tr>
<tr>
<td>Aurichloride</td>
<td>126.5–127.5</td>
<td>–</td>
</tr>
<tr>
<td>Platinichloride</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2. (1R, 2R)-(−)-pseudoephedrine forms.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mp (°C)</th>
<th>[α]D (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free base (B)</td>
<td>51–54</td>
<td>–14.36° (EtOH)</td>
</tr>
<tr>
<td>Hemihydrate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>172–175</td>
<td>–33° (H2O)</td>
</tr>
<tr>
<td>Hydrobromide</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sulphite</td>
<td>285–286 (dec)</td>
<td>–31.99° (H2O)</td>
</tr>
<tr>
<td>Oxalate</td>
<td>245 (dec)</td>
<td>–</td>
</tr>
<tr>
<td>Aurichloride</td>
<td>188</td>
<td>–</td>
</tr>
<tr>
<td>Platinichloride</td>
<td>221 (dec)</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3. (1R, 2S)-(−)-nor Ephedrine 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 ephedrines 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], tetrahydrotriazine [45], and imidazolidine [46] derived from ephedrines and nor-ephedrines 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].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mp (°C)</th>
<th>$[\alpha]_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free base (B)</td>
<td>77–8 (corr.)</td>
<td>−37.9 (MeOH)</td>
</tr>
<tr>
<td>Hemihydrate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>180–183 (corr.)</td>
<td>−41.7° (H$_2$O)</td>
</tr>
<tr>
<td>Hydrobromide</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sulphate</td>
<td>295 (dec.)</td>
<td>−48.7° (H$_2$O)</td>
</tr>
<tr>
<td>Oxalate</td>
<td>235 (dec.)</td>
<td>–</td>
</tr>
<tr>
<td>Aurichloride</td>
<td>137–138</td>
<td>–</td>
</tr>
<tr>
<td>Platinilchloride</td>
<td>198</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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 nor Ephedrine 3a or its hydrochlorides reacts with SOCl$_2$ to give chlorodeoxypseudoephedrine 5a or chlorodeoxy-norphedrine 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 (S$_{n1}$ mechanism), Scheme 1, the X-ray diffraction structure of 5a is depicted in Figure 6.

![Scheme 1](image1.png)

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

![Figure 6](image2.png)

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 180–200°C to afford the imidazolidinone 11a-(f) 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 ephedrines.

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 \( pseudoephedrine \ 2a \), \( norephedrine \ 3b \), and \( norpseudoephedrine \ 4b \) to afford the urea derivatives \( 7a-(th) \), \( 7b-(e) \), and \( 7b-(th) \) in 83, 80, and 86% yield, respectively.
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).

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 O1H1⋯O6 distance of 1.820(24) Å [angle of 166.72° (2.25)] represents a strong interaction [50]. The formed hydrogen bond forces the NH₂ 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 CHCl₃ and purified by recrystallization from ethanol. The cis (c) isomer instead of the expected trans (t) isomer was observed on the ¹H and ¹³C NMR spectra and confirmed by X-ray diffraction analysis. The formation of an aziridinim isocyanate I then the isocyanate II as intermediates...
are proposed to explain the retention of C1 configuration in the formation of the cis-imidazolidone 11a-(t) (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 CHCl3/H2O partition, Scheme 6. Deamination of ephedrine hydrothiocyanate 8a-(e) proceeded to give Ethylphenylketone as lateral product.

The reaction with two molar equivalents of NH4SCN for 4 hours afforded the thiazolidine-2-imino hydrothiocyanate 9a-(t) in 50% yield as precipitate from CHCl3. The use of NH4SCN 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 NH4’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 CHCl3/H2O 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 5. Mechanistic pathway for the cyclization of ephedrine-urea 7a-(e) to get imidazolidinone 11a-(t).

Scheme 6. Heating reaction of ephedrine 1 with NaSCN.
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 (13C) 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 CHCl3. 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 norpseudoeuphrine hydrochloride 4 was separated in a chromatographic column and each fraction analyzed by mass spectrometry, Table 5. The fourth fraction contained thiazoline-2-amino hydrothiocyanate 9b-(c).

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>X</td>
<td>S</td>
<td>NH</td>
<td>NH</td>
<td>S</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>Y</td>
<td>NH,SCN</td>
<td>S</td>
<td>O</td>
<td>S</td>
<td>O</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>1a-(c)</td>
<td>Cis</td>
<td>184 (2)</td>
<td>163 (3)</td>
<td>196 (7)</td>
<td>172 (4)</td>
<td>160 (2)</td>
<td>191 (19)</td>
</tr>
<tr>
<td></td>
<td>Trans</td>
<td>169(50)</td>
<td>183 (7)</td>
<td>195 (2)</td>
<td>171 (7)</td>
<td>191 (23)</td>
<td></td>
</tr>
<tr>
<td>1a-(th)</td>
<td>Cis</td>
<td>169(15)</td>
<td>184 (40)</td>
<td>196 (6)</td>
<td>172 (207(64))</td>
<td>160 (5)</td>
<td>191 (19)</td>
</tr>
<tr>
<td></td>
<td>Trans</td>
<td>162 (2)</td>
<td>200 (5)</td>
<td>176 (5)</td>
<td>189 (2)</td>
<td>193 (35)</td>
<td>177 (8)</td>
</tr>
<tr>
<td>1b-(c)</td>
<td>Cis</td>
<td>Traces</td>
<td>[192 (100)]</td>
<td>179 (40)</td>
<td>175(10)</td>
<td>159 (20)</td>
<td>191 (23)</td>
</tr>
<tr>
<td></td>
<td>Trans</td>
<td>Traces</td>
<td>[192 (100)]</td>
<td>199 (2)</td>
<td>[209 (100)]</td>
<td>[193(25)]</td>
<td></td>
</tr>
<tr>
<td>1b-(th)</td>
<td>Cis</td>
<td>173(40)</td>
<td>183 (10)</td>
<td>200 (15)</td>
<td>175 (10)</td>
<td>160 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trans</td>
<td>172(10)</td>
<td>174 (5)</td>
<td>159 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Carbonyl carbon chemical shift in ppm, proportion (%) and mass spectrometry data [M+ (%)] of heterocycles 9–15.
At least four competitive mechanisms are proposed to explain the formation of heterocycles 9-15a,b in the heating reaction of NH$_4$SCN with ephedrines 1,2 and norephedrines 3,4 (Scheme 7). In general, with exception of heating reaction of norephedrine 3, a S$_{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 imidazolidinetiones 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 ephedrinethiocynate analogue to IV has been isolated, which support the proposed mechanism [56].

In the heating reaction of norephedrine 3, the H$_2$S obtained by hydrolysis of thiocyanate acts as nucleophyle in competitive S$_{N}$1 and S$_{N}$2 mechanisms to form the thiolephedrine thiourea.
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 NH$_4^+$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 NH$_4^+$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 $^1$H NMR spectral data of ephedracycles, the C—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 chloropseudo ephedrines

In continuation with our investigations on the design of new heterocycles derived from ephedrines 1, in this work, we revisited the cyclization reactions of chlorodeoxypseudoephedrine 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 chlorodeoxynorpseudoephedrine 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.

7.1. Reaction of chlorodeoxypseudoephedrine hydrochlorides 5 with potassium oxocyanate

Chlorodeoxypseudoephedrine 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-d6 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 chlorodeoxynorpseudoephedrine hydrochloride 5b-th (R = H) in refluxing ethanol 8 h afforded the chloroureia 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.
Chlorourea compound 17b-(th) could be isolated and characterized by NMR. Two signals are observed in the $^1$H 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 NH···Cl interaction, which makes this hydrogen and H2 to be in an anti position. In addition, the small H1, H2 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 chloroure derivative 17b-(th) was refluxed in ethanol during 24 h. The $^1$H NMR spectrum of the solid precipitated showed a 80:20 mixture of two heterocycles. The $^1$H NMR chemical shift of the 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
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 S$_{N}$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. $^1$H 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

![Figure 11. Hydrogen bonding interaction proposed in compound 17b-(th).](image)

![Scheme 10. Mechanistic pathway proposed to explain the formation of compound 23b-(c).](image)
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-imino 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) (ν = 2057 cm⁻¹, SCN), even at 24 h of reflux. If hydrothiocyanate 16b-(th) in DMSO-d₆ 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).
8. CIS-thiazolidinethiones from chloropseudoephedrines

In 1995, we reported the reaction of chlorodeoxypseudoephedrine hydrochloride 5a-(th) with 33% aqueous solution of sodium trithiocarbonate (Na$_2$CS$_3$) in refluxing ethanol to give cis-thiazolidinethione 12a-(c) (53% yield), Scheme 11 [60]. However, the same reaction with chlorodeoxypseudoephedrine 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 chlorodeoxypseudoephedrine 5b or chlorodeoxypseudoephedrine 5a derived from ephedrines 1,3.

To get thiazolidinethiones 12a,b, the chlorhydrates of chlorodeoxypseudoephedrines 5a or 5b were reacted with one molar equivalent of sodium dithiocarbonate in ethanol solution at room temperature. In the case of chlorodeoxypseudoephedrine·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 $^1$H 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 $S_N2$ 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 $S_N2$ 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.

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

Scheme 11. Mechanistic transformation to get cis-thiazolidinethiones from chlorodeoxypseudoephedrines.
to get stereospecifically thiazolidinethiones from the reaction of vicidoolkanecarbamates 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. Thiazolidine-thione 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 azirinium by the aziridine-carbamate 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 stereo selectively obtained instead of the expected trans-isomer in agreement with the Kellog’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 = 1.741Å and S2—C2 = 1.659) [51]. Conjugation makes N3 to be in a sp² hybridation, 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 8f and trans-isothiazolidinethione 10f.
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 $0^\circ$, 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 $180^\circ$. An intramolecular contact between a hydrogen atom of the N—CH$_3$ group and the sulfur atom of the thiocarbonyl group occurred to form a five member ring. The C12H12—S2 distance of 2.72(4) Å [angle of 111(3)$^\circ$] is in the range for a strong interaction [50].

9. Thiazaborolidines from thioephedrines

The synthesis of N-alkyloxazaborolidines 26–28 derived from ephedrines has been reported (Figure 15) [64]. In 1995, we reported the analogous compounds made from thioephedrines, 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 BH$_3$-THF...
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-BH$_3$ 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, $\text{J(BH)} = 103$ Hz, in CDCl$_3$ or $\delta = -4.5$ ppm, in THF-$d_8$]. Two methyl groups in trans position was found for borinic ester 33 on the $^1$H and $^{13}$C NMR data. This allows us to assign the configuration at the nitrogen atom. No borinic esters with a BH$_2$ 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 H$_2$ transforms borinic ester 33 into thiazaboroline 34. In the $^{11}$B NMR spectrum, compound 34 shows a doublet ($\delta = +40.8$ ppm, J(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 BH$_3$-THF to afford the N—BH$_3$ adduct 35 (Scheme 1). The structure has been deduced from the $^{11}$B NMR data, which indicated a N—BH$_3$ bond (quadruplet at $\delta = -22.0$ ppm, J(BH) = 71 Hz) and a doublet which is strongly shifted to lower frequencies ($\delta = -7.0$, J(BH) = 148 Hz). A diborane group in which a hydrogen atom from the N—BH$_3$ adduct is bridging the boron atom of the heterocycle was found. These findings are similar to that found in the pseudoephedrine oxazaborolidine [64a].
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 $^1$B NMR, and a S—BH$_3$ adduct 36 ($\delta = -23$ ppm, broad signal) was first detected. The analysis of $^1$H NMR spectrum of compound 36 indicates that BH$_3$ is linked to the thione sulfur atom. Heating the S—BH$_3$ adduct 36 afforded the thiazaborolidine 37 which is a triplet at $\delta = -3.8$ ppm ($J(BH) = 1$ 1.5 Hz) in $^1$B NMR spectra. This compound 37 is obtained pure when 12a-(c) is reacted with 3 equivalents of BH$_3$-THF. The $^1$H and $^{13}$C NMR were recorded. The diasterotopic N-methyl groups show that the nitrogen has a stable configuration, the assignment of the $^1$H 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 $^1$H and $^{13}$C NMR data. The methyl groups are trans position. The angles on the nitrogen atom are close to a $sp^3$ hybridation, C4—N3—C13 112.3(5)$^\circ$, B2—N3—C13 111.3(5)$^\circ$, and C4—N3—B2 112.0(5)$^\circ$.

10. Biological properties of ephedrines and their derivatives

10.1. Ephedrines

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
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 synthetized.

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 synthetized in our laboratory represented in Tables 6 and 7, respectively.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (mol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21b (NA)</td>
<td>34 (3.2x10^-5)</td>
</tr>
<tr>
<td>19 (5.5x10^-3)</td>
<td></td>
</tr>
<tr>
<td>22a (NA)</td>
<td>12t (8.2x10^-3)</td>
</tr>
<tr>
<td>12ac (NA)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Antioxidant activity (IC50, mol/L) of some synthetized heterocyclic compounds.
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 $6 \times 10^{-5}$ M DPPH methanol were mixed with 50 μL 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:

$$\% \text{RSA} = 100 \times \left(1 - \frac{A_{E}}{A_{D}}\right)$$

$A_{E}$ is the absorbance of the solution containing antioxidant extract, whereas $A_{D}$ 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 μL 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. thypi*, and *E. coli* using sensidiscs. The antioxidant activity was measured by the radical 2-2-diphenyl-1-picrylhydrazil. Compound 34 presented antimicrobial activity against all microorganisms used and the compound 21a showed activity only against *S. aureus* and *B. subtilis*, Table 7.

<table>
<thead>
<tr>
<th>Compuesto</th>
<th><em>Salmonella typhi</em></th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Escherichia coli</em></th>
<th><em>Bacillus subtilis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>21b</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>34</td>
<td>20</td>
<td>8</td>
<td>10</td>
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<tr>
<td>9t</td>
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<td>NA</td>
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</tr>
<tr>
<td>12ac</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

Inhibition in mm.

No actividad found (NA).

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