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SYNTHESIS AND INVESTIGATION OF ANTIMICROBIAL ACTIVITY OF SOME POLYFUNCTIONAL [1-(ARYLSELENO)-2-HYDROXYPROPYL] HETEROCYCLIC AMINES

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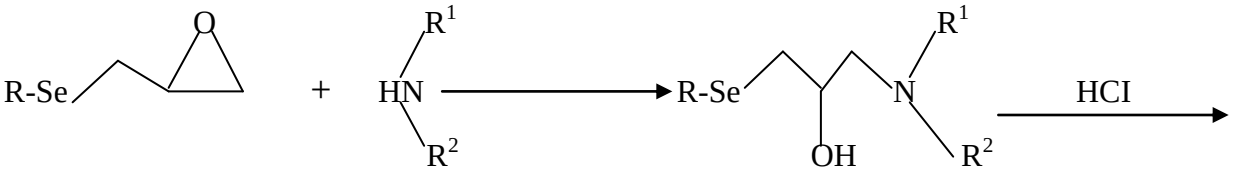
*The polyfunctional [1-(arylseleno)-2-hydroxypropyl] heterocyclic amines such as 1-(phenylseleno)-2-hydroxypropyl]morpholine (PSHM) **;** [1-(phenylseleno)-2 hydroxy-propyl] piperidine (PSHP), 1-(α-naphthylseleno)-2-hydroxypropyl]morpholine (NSHM) and its derivatives were synthesized in this study by using spectroscopic and elemental analysis. They were also evaluated for antimicrobial activity against both Gram-positive and Gram-negative bacteria in vitro comparable to cefalexin. The compounds **1b, 2b and 3b** showed strong activity against Bacillus cereus (ATCC 11778), Sarcina Iutea (ATCC 9341), Salmonelle typhimurium (1,4,5,12;;; 1,2), P.aeruginosa (ATCC, 27853) and Escherichia coli (ATCC 29998).*

Key Words: *arylselenohydroxypropyl heterocyclic amines, antibacterial properties*

Heterocyclic aminoalcohols and their derivatives are important intermediates in organic synthesis. The results of some experiments from different laboratories have suggested that some of the bioactive organic heterocyclic compounds could prevent the animals from harmful effects of malignancies, radioactivity and also showed valuable therapeutic activity in nervous system diseases [1-3]. It has been reported in literature that pyridines and a lot of compounds, including pyridine ring, have acquired a number of pharmacological properties, such as cardiotonic[4], β-adrenergic blocking activity [5], antihypertensive [6], anticonvulsant [7,8] and antibacterial activity [9,10]. Recently, in the studies made by Manna et al. [5] and Abele et al. [11] some amino alcohols derived from oximes were found to exhibit properties of β-adrenergic blocking and antiulcer agents in vitro. In our previous studies, some heterocyclic amino alcohol derivatives including C=N, OH, epoxide groups were synthesized [12- 16] .

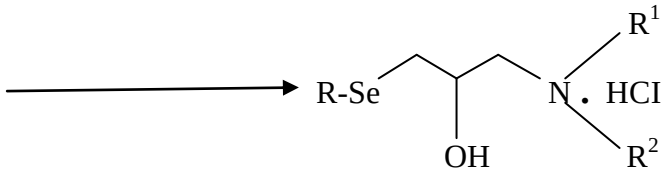
In the present study, arylseleno-epoxypropan, α-naphthylselenoepoxypropan and heterocyclic amines were prepared [12]. The polyfunctional [1-(aryl- seleno)-, 1-(α-naphthylseleno)-2-hydroxy- propyl] and heterocyclic amines: morphoine, piperidine to afford corresponding heterocyclic aminopropanols derivatives. It was determined that the prepared polyfunctional heterocyclic arylselenopro- panols such as 1-(phenylseleno)-2-hydroxypropyl]morpholine (PSHM) **;** [1-(phenylseleno)-2 hydroxypropyl] piperidine (PSHP) and 1-(α-naphthylseleno)-2-hydroxy- propyl]morpholine (NSHM) have antimicrobial characteristics. The arylselenoepoxide and α-naphthylseleno-epoxide derivatives easily reacted with various heterocyclic amines to allow corresponding heterocyclic aminopropanols derivatives. It was determined that the prepared [1-(arylseleno-, α-naphthylseleno)-2-hydroxypropyl] heterocyclic amines have antimicrobial characteristics.

The synthetic routes of [1-(arylseleno-,α-naphthylseleno)-2-hydroxypropyl] heterocyc-lic amines are given in Scheme 1.



1-Phenyl(naphthyl) seleno-2,3-epoxypropan **(1-3)**

1a - 3a



1b - 3b

1a: R= Ph, R^1 R^2 = $(CH_2)_4O$; ; **2a :** R= Ph, R^1 R^2 = $(CH_2)_5$; **3a:** R= N, R^1 R^2 = $(CH_2)_4O$

1b : R= Ph, R^1 R^2 = $(CH_2)_4O$; **2b:** R= Ph, R^1 R^2 = $(CH_2)_5$; **3b:** R= N, R^1 R^2 = $(CH_2)_4O$

Scheme 1. Synthesis of polyfunctional [1-phenyl (naphthyl)seleno)-2-hydroxypropyl] heterocyclic amines and its derivatives: Condensation reactions of 1-(phenyl-seleno)- 2,3-epoxypropane with morpholine (1a,b ;) , piperidine (2a, 2b); of 1-(naphthylseleno)- 2,3-epoxypropane with morpholine (3a,b)

EXPERİMENTAL MATERIALS AND METHODS

All chemicals were purchased from Merck and Aldrich and were used without additional purification. Compounds **1-3** were prepared on the basis of the previously described method [16]. Melting points were determined at Buchi capillary melting point apparatus and proved to be incorrect. The structures of all compounds were characterized by IR spectroscopy. Infrared spectra were recorded on a Pye Unicam SP 1025 spectrometer. The elemental compositions were determined on a Carlo Erba 1106 automatic CHN analyzer.

Synthesis of [1-(arylseleno)-2-hydroxypropyl] heterocyclic amine compounds (General Procedure)

Synthesis of [1-(phenylseleno)-2-hydroxypropyl] morpholine (PSHM) (1a)

A mixture of 1-phenylseleno-2,3-epoxypropan (10.6 g, 0.05 mole) , morpholine (8.7 g, 0.1 mole) and 4-5 drops of water were stirred at 100^0C for 6-7 hours. 14.2 g (95% efficiency) [1-phenylseleno-2 hydroxypropyl] morpholine **(1a),** which has 52^0C melting point, was synthesized.

IR spectrum, υ_{max}, cm^{-1}: 718(C-Se), 1098 (ether, -O-), 3455 (OH), 1580 (N-H) ,
Chemical formula : $C_{13}H_{19}NO_2Se$
Elemental analysis found (calc.)

C: 51.88 H: 6.23 N: 4.54

(52.00) (6.33) (4.66).

Synthesis of 1-(phenylseleno)-2-hydroxypropyl] morpholinechlorohydrat(1b)

Appropriate hydrochloride salts of the synthesized [1-phenylseleno-2hydroxy-propyl] morpholine **(1a)** were prepared by treating them with dry HCI in anhydrous ether in order to dissolve them in water and ethanol as well. Finally, (97 % efficiency) 1-(phenylseleno)-2-hydroxypropyl] morpholinechlorohydrat **(1b)** which has 127-128^{0}C melting point, was synthesized

IR spectrum, υ_{max}, cm^{-1}: 716, 1093, 1574, 2827, 3430
Chemical formula : $C_{13}H_{20}NO_2CI\,Se$
Elemental analysis found (calc.)

C: 45.86 H: 5.72 N: 3.96 CI: 10.43

(46.31) (5.93) (4.15) (10.58).

Synthesis of [1- (phenylseleno)-2-hydroxypropyl] piperidine (PSHP) (2a)

Synthesis of [1- (phenylseleno)-2-hydroxypropyl] piperidine **(2a)** was realized by 8.5g (0.04 mole) 1-phenylseleno-2,3-epoxypropan, 6.8 g (0,8 mole) piperidine and 4-5 drops of water were stirred at 80^{0}C for 5-6 hours. The yello with oily residue was distilled under vacuum, 93% efficiency [1-(phenylseleno)-2-hydroxypropyl] piperidine **(2a)** which has 174-175^{0}C / 3 mm Hg boiling point, was synthesized.
Chemical Formula : $C_{14}H_{21}NOSe$
Elemental analysis found (calc.)

C: 56.21 H: 6.87 N: 4.43

(56.37) (7.04) (4.69)

Synthesis of [1-(phenylseleno)-2-hydroxypropyl] piperidinechlorohydrat(2b)

Using the same method (**1b),** [1-(phenylseleno)-2-hydroxypropyl]piperidine chlorohydrat **(2b)** which has 114-115^{0}C melting point, was synthesized.
Chemical formula : $C_{14}H_{22}NOCISe$

Elemental analysis found (calc.)

C :50.06 H: 6.49 N: 4.06 CI 10.51

(50.22) (6.57) (4.18) (10.61)

Synthesis of 1-(α-naphthylseleno)-2-hydroxypropyl]morpholine (NSHM) (3a)

A mixture of α-naphthylseleno-2,3-epoxypropan (7.9 g, 0.03 mole) , morpholine (4.3 g, 0.05 mole) and 4-5 drops of water were stirred at 60^{0}C for 6-7 hours. 83% efficiency 1-(α-naphthylseleno)-2-hydroxypropyl]morpholine **(3a)** which has 72^{0}C melting point, was synthesized.

IR spectrum, υ_{max}, cm^{-1}: 719(C-Se), 1100 (ether, -O-), 3460 (OH), 1585 (N-H) ,
Chemical formula : $C_{17}H_{21}NO_2Se$
Elemental analysis found (calc.)

C: 58.63 H: 6.13 N: 4.04

(58.28) (6.00) (4.00)

Synthesis of 1-(α-naphthylseleno)-2-hydroxypropyl]morpholinechlorohydrat (3b)

[1-(α-Naphthylselenoseleno)-2hydroxy-propyl] piperidinechlorohydrat **(3b)** which has 124-125^{0}C melting point, was synthesized.

Chemical formula : $C_{17}H_{22}\,NO_2CI\,Se$
Elemental analysis found (calc.)

C :52.56 H: 5.49 N: 3.96 CI 9.51

(52.78) (5.69) (3.62) (9.18)

In vitro Biological assay

Medium : As a solid media, Muller-Hinton Agar (MHA) was prepared as follows: Beef infusion 300 g/l, casein acid hydrolysate 17.5 g /L, starch 1.5 g /L, agar-agar 17 g /L and distilled water (1000 mI, adjusted to pH 7.4) were used for the biological assay of all of the synthesized compounds.

Test microorganisms: Four Gram-positive bacteria B. cereus (ATCC 11778), S.aureus (ATCC 6538),S.Iutea (ATCC 9341) and S.mutans (UCTC 10499) and three Gram-negative bacterian S.typhimurium (1,4,5,12;;; 1,2), P.aeruginosa (ATCC, 27853) and E.coli (ATCC 29998) were used for biological assays.

Antimicrobial activity test :

Diffusion test was carried out to determine the sensitivity of one strain in each bacterial species against four compounds **(1b – 3b).** The solutions of compounds **(1b – 3b)** (0.1 mg/ml) were prepared by dissolving 10 mg of the test compound in pure water (100 mL). Cefalexin (30 μg/ disc) and pure water were used as positive and negative controls, respectively. For this activity test, 20 mL of Mueller-Hinton agar (Difco) was melted at 100^0C and after cooling to 56^0C, it was poured into Petri plates and left on a flat surface, and the surface of the medium was dried at 37^0C. Then, the cultures of each bacterium, having been kept in Mueller – Hinton broth (Difco) at 37^0C for 24 h and diluted with Mueller – Hinton broth to 1 x 10^8 CFU / mL, were pipetted into Mueller – Hinton agar plate prepared as described above. The surface of the medium was allowed to dry. Then, sterile 6 mm diameter fitler paper discs were impregnated with 25 μL of each of the test solutions / disc and placed onto the surface of inoculated labeled Petri plates. The Petri plates were placed in an incubator at 37^0C. After 24 h of incubation, the Petri plates were examined and the diameter of the clear zone of growth inhibition around each disc containing the test compound was measured accurately through the use of a Vernier Caliper and expressed in millimeters as its antimicrobial activity (Table). Each test was run in triplicate.

In vitro antimicrobial activity of the compounds **(1b,2b and 3b)** using disc diffusion assay technique.

Compounds	Diameter of growth inhibition zone (mm)						
	Bc	Sa	SI	Sm	St	Pa	Ec
1b	27	29	40	30	22	31	20
2b	19	15	29	18	20	27	18
3b	9	34	38	32	-	-	14
Cefalexin	20	30	44	30	16	-	12

- = no activity ; Bc = B. cereus (ATCC 11778); Sa = S.aureus (ATCC 6538); SI =S.Iutea (ATCC 9341) ; Sm = S.mutans (UCTC 10499) ; St = S.typhimurium (1,4,5,12;;; 1,2); Pa= P.aeruginosa (ATCC, 27853) and Ec = E.coli (ATCC 29998)

RESULTS AND DISCUSSION

The antimicrobial activity of compounds **(1b-3b)** was evaluated through the use of disc diffusion method [17] against pathogenic four Gram-positive bacteria *Bacillus cereus* (ATCC 11778), Staphylococcus aureus (ATCC 6538), *Sarcina Iutea* (ATCC 9341) and S.mutans (UCTC 10499) and three Gram-negative bacteria *Salmonelle typhimurium* (1,4,5,12;;; 1,2), Pseudomonas aeruginosa (ATCC, 27853) and *Escherichia coli* (ATCC 29998) (Table 1). As can be seen, while compounds **(1b)** and **(2b)** exhibit activity against all bacteria, **(3b)** all of Gram-positive bacteria and mono Gram-negative bacteria *Escherichia coli* (ATCC 29998) become apparent. Among all compounds, which **(1b)** displayed the highest activity against *Escherichia coli* (ATCC 29998) as compared to cefalexin was used in the treatment of a number of infections such as ears, nose or throat, skin or wound, urinary system, organs (i.e., lungs), etc. and there was the least activity against Staphylococcus aureus (ATCC 6538) **(2b).** In addition, when all compounds were compared with each other, **(1b)** was generally found more active than **(2b)** and **(3b)** against all the strains of bacteria under this study due to electron-withdrawing morpholine and piperidine in arylseleno-compounds .

To conclude, polyfonctionel [1-(arylseleno)-2-hydroxypropyl] heterocyclic amines were efficienty prepared through the use of spectroscopic and analytical analysis. They were also evaluated for antimicrobial activity against both Gram-positive and Gram-negative bacteria in vitro comparable to cefalexin. The antimicrobial activity in terms of zone of inhibition was exhibited by all the compounds against all bacteria except for *Salmonelle typhimurium* (1,4,5,12;;; 1,2). The compound **(1b)** showed excellent activity against Gram-positive bacteria *Bacillus cereus* (ATCC 11778), *Sarcina Iutea* (ATCC 9341) and Gram-negative bacteria *Salmonelle typhimurium* (1,4,5,12;;; 1,2), P.aeruginosa (ATCC, 27853) and *Escherichia coli* (ATCC 29998) compared to cefalexin. As is seen from Table, the high activity of the compound **(1b)** reveals that it was suitable for supplemental in vivo and in vitro studies in order to develop new antimicrobial drugs or prodrugs which can be probably used in the treatment of some infection diseases. Moreover, this work may also provide valuable information to the researchers due to the limited coverage of the subject.

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BƏZİ POLİFUNKSİONAL [1-(ARİLSELEN)-2-HİDROKSİLPROPİL] HETEROTSİKLİK AMİNLƏRİN SİNTEZİ VƏ ANTİMİKROB XASSƏLƏRİNİN TƏDQİQİ

K.S.Qurbanlı

Tədqiqat işində polifunksional [1-(arilselen)-2-hidroksilpropil] heterotsiklik aminlər - [1 (fenilselen)-2-hidroksipropil] morfolin (FSHM), [1 (fenilselen)-2-hidroksipropil] piperidin (FSHP), [1-(α-naftilselen-2-hidroksipropil)] morfolin (NSHM) və onların törəmələri sintez edilmiş və spektroskopik, element analizi vasitəsilə tədqiq olunmuşdur. Sefaleksinlə müqayisə etməklə onların eyni zamanda Qram-müsbət və Qram-mənfi bakteriyalara qarşı antimikrob xassələri də tədqiq edilmişdir. 1b, 2b və 3b birləşmələr Bacillus cereus (ATCC 11778), Sarcina Iutea (ATCC 9341), Salmonelle typhimurium (1,4,5,12;:; 1,2), P.aeruginosa (ATCC, 27853) и Escherichia coli (ATCC 29998) qarşı daha güclü antimikrob təsir göstərirlər.

СИНТЕЗ И ИЗУЧЕНИЕ АНТИМИКРОБНЫХ СВОЙСТВ НЕКОТОРЫХ ПОЛИФУНКЦИОНАЛЬНЫХ [1-(АРИЛСЕЛЕН)-2-ГИДРОКСИЛПРОПИЛ] ГЕТЕРОЦИКЛИЧЕСКИХ АМИНОВ

К.С.Курбанлы

Синтезированы полифункциональные [1-(арилселен)-2-гидроксилпропил] гетероциклические амины - [1-(фенилселен)-2-гидроксипропил] морфолин (ФСГМ), [1 (фенилселен)-2-гидроксипропил] пиперидин (ФСГП), [1-(α-нафтилселен-2-гидроксипропил)] морфолин (НСГМ) и их производные и изучены методами спектроскопического и элементного анализа. Изучены их антимикробные свойства к Грам-положительным и Грам-отрицательным бактериям в сравнении с цефалексином. Производные этих соединений проявляют более сильное антимикробное действие против Bacillus cereus (ATCC 11778), Sarcina Iutea (ATCC 9341), Salmonelle typhimurium (1,4,5, 12;:; 1,2), P.aeruginosa (ATCC, 27853) и Escherichia coli (ATCC 29998).