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Der Pharma Chemica, 2011, 3 (4): 210-218
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of some new pyrrole derivatives and their antimicrobial activity

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ABSTRACT

*A new pyrrole derivatives of 5,5'-(3,5-dimethyl-1H-pyrrole-2,4-diyl)bis(1,3,4-oxadiazole-2-thiol)**(3),** 5,5'-(3,5-dimethyl-1H-pyrrole-2,4-diyl)bis(4-amino-4H-1,2,4-triazole-3-thiol)**(4),** 5,5'-(3,5-dimethyl-1H-pyrrole-2,4-diyl)bis(4H-1,2,4-triazole-3-thiol) **(6),** and 5,5'-(3,5-dimethyl-1H-pyrrole-2,4-diyl)bis(1,3,4-thiadiazol-2-amine)**(7)** were prepared from cyclization methods. Synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analysis. The reaction was performed by using ordinary condensation type, which enabled to easy work-up and good yield. Synthesized compounds (**1-7**) were screened for antimicrobial activity.*

Keywords Pyrrole derivatives, Cyclization method, Structural characterization, antimicrobial activity.

INTRODUCTION

Pyrrole derivative are considerable attention of synthetic importance and extensively used in drug discovery[1] and pharmacological activity such as anti-inflammatory [2], cytotoxicity [3, 4], *in vitro* cytotoxic activity against solid tumour models (5, 6), treatment of hyperlipidemias [7], antitumour agents [8]. The pyrrole containing heterocyclic derivatives have been reported in synthetic and effective biological importance [9,10]**.** Pyrrole derivatives have biological activity such as COX-1/COX-2 inhibitors [11] and cytotoxic activity against a variety of marine and human tumor models [12]**.** We are interested in the biological behaviors of these title compounds. The coupling of these heterocyclic derivatives has not been published before but previously reported methods appeared to meet our requirement. Thus, for this study, we are report novel pyrrole derivatives and their antimicrobial activity.

MATERIALS AND METHODS

Experimental

Chemistry

Melting points were recorded in open capillary tubes and are uncorrected. The IR spectra (KBr) were recorded on a Shimadzu 8201pc (4000-400 cm^{-1}). The ^1H NMR and ^{13}C NMR were recorded on Bruker DRX-300 MHz. Mass spectra (EI) were recorded on a Jeol JMS D-300 spectro meter operating at 70eV. The Elemental analysis (C, H, N and S) were recorded using an Elementer analyzer model (Varian EL III). Analytical TLC was performed on Merck silica gel (60 GF_{254}) plates (0.25 mm). Flash column chromatography was carried out on Marck silica gel 60 (particle size 0.040-0.063 mm).

Synthesis of 3,5-dimethyl-1*H*-pyrrole-2,4-dicarbohydrazide(2)

A mixture of 2,4-dimethyl-3, 5-dicarbethoxypyrrole **(1)** (2.39 g, 0.01 mol), hydrazine hydrate (0.80mL, 0.02 mol) in ethanol (20mL), the reaction mixture was heated and refluxed for 6h. The reaction mixture was poured into ice-cooled water. The soiled was obtained and collected by filtration. The resulting solid was recrystallized from absolute ethanol.

Synthesis of 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-oxadi azole-2-thiol)(3)

A mixture of 3,5-dimethyl-1*H*-pyrrole-2,4-dicarbohydrazide **(2)** (2.11g, 0.01mol), added to a solution of KOH (1.12 g, 0.02 mol) in ethanol (30 mL), followed CS_2 (1.2 mL, 0.02 mol) add drop wise, the obtained yellow solution was heated and refluxed till the evolution of H_2S ceased (18–20 h). After cooling, the solution was filtered, and the filtrate was poured into ice-cooled water and acidified with con. HCl to pH 3–4. The solid was filtered, dried and recrystallized from ethanol.

Synthesis of5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4-amino-4H-1,2,4-triazole-3-thiol)(4)

A mixture of 5,5'-(3,5-dimethyl-1H-pyrrole-2,4-diyl)bis(1,3,4-oxadiazole-2-thiol)**(3)** (2.95 g, 0.01 mol) and hydrazine hydrate (0.8 mL, 0.02 mol) in ethanol, the reaction mixture was heated and refluxed for 24 h. Then, the reaction mixture was cooled at room temperature. This crude product was filtered off, washed with ethanol, and recrystallized from ethanol.

IR(KBr) : υ = 3301.15(NH), 2934.75(CH_3), 2667.07(SH), 1576.41(C=N) cm^{-1}; ^1H NMR (300MHz, DMSO-d_6): 11.87(s, 1H, NH), 5.73(s, 4H, 2 x NH_2), 2.23(s, 3H, C5-CH_3), 1.77(s, 3H, C3-CH_3), 13.93(s, 2H, 2 x SH); ^{13}C NMR(300MHz, $CDCl_3$): δ = 167.86(C-SH), 148.77(C4-C), 129.86(C5-CH_3), 118.36(C3-CH_3), 114.80(C2-C), 111.86(C4-C), 14.03(C5-CH_3), 10.9(C3-CH_3)ppm; Elemental analysis **(**$C_{10}H_{13}N_9S_2$): calcd for C 37.14, H 4.05, N 38.98, S 19.83, found C 37.10, H 4.11, N 38.92, S 19.87. EI-Ms, m/z (Relative intensity %): 324.20 (M^+ +1, 5%), 308.38(5%), 293.87(100%), 194.25 (21%), 95.14 (5%), 82.14(22%).

Synthesis of 2,2'-[(3,5-dimethyl-1*H*-pyrrole-2,4-diyl) dicerbonyl] dihydrazinecarbothio - amide (5)

A mixture of 2,4-dimethyl-3,5-dicarbethoxypyrrole**(1)** (2.39 g, 0.01 mol) and thiosemicabarzide(1.85 g, 0.08 mol) in ethanol (20mL), added few drops of con. HCl, the reaction mixture was heated and refluxed for 7h. The excess solvent was removed under reduced

pressure and the reaction mixture was poured into an ice water. The product was collected by filtration and recrystallized from ethanol.

Synthesis of 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4H-1,2,4-tri azole-3-thiol) (6)
A mixture of 2,2'-[(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)dicerbonyl]dihydrazineecarbo thioamide**(5)** (2.20 g, 10 mol) in 2N-NaOH solution, the reaction mixture was heated and refluxed for 5h after cooling, the solution was made acidic with con. HCl and the precipitate was collected from filtration and recrystallized from absolute ethanol.

IR(KBr): υ = 3346.13(NH), 2965.41(CH_3), 1513.05(C=N), 2687.82(SH) cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6): δ = 11.92 (s,1H, NH), 13.88 (s, 2H, SH), 2.82 (s, 3H, 5CH_3), 2.18 (s, 3H, 3CH_3), 1.82(s, 2H, 2 x NH) ppm ; ^{13}C NMR (300MHz, $CDCl_3$): δ = 168.11(C–SH), 157.86 (C_2,C_4 - C), 133.36 (C_5-CH_3), 117.86(C_3-CH_3), 110.86(C_2-C), 108.86 (C_4 -C), 14.03(C_5-CH_3), 10.94(C_3-CH_3) ppm ; Elemental analysis ($C_{10}H_{11}N_7S_2$): Calcd for C 40.94, H 3.78, N 33.42, S 21.86, found C 40.90, H 3.77, N 33.40, S 21.82. EI-Ms, m/z (relative intensity %): 294.72(M^+ +1, 12%), 261.30(13%), 229.24(20%), 95.14(100%), 80.26(5%), 67.56(12%).

Synthesis of 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-thia diazol-2-amine) (7)
The compound 2,2'-[(3,5-dimethyl-1H-pyrrole-2,4-diyl)dicerbonyl]dihydrazinecarbo thioamide **(5)** (3.29 g, 0.1 mol) was dissolved in 4mL con.H_2SO_4, the reaction mixture was stirred at room temperature for a few minutes and left overnight. It was poured on crushed ice. The resulting suspension was kept in NH_3 for 2h. The solid was formed and filtered. The solid was recrystallized form ethanol.

IR(KBr): υ = 3308.15(NH), 3240.67 (NH_2), 1587.32 (C=N) cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6): δ=11.52 (s, 1H, NH), 7.59 (s, 4H, thiadiazol-NH_2), 2.18(s, 3H, C3-CH_3), 2.53(s, 3H, C5-CH_3) ppm; ^{13}C NMR(300MHz, $CDCl_3$): δ = 161.11(C-NH_2), 178.96(C4,C2-C), 133.36(C5-CH_3), 117.86 (C3-CH_3), 116.86(C2- C), 108.96(C4- C), 16.98(C5-CH_3), 10.74 (C3-CH_3) ppm; Elemental analysis($C_{10}H_{11}N_7S_2$): calcd for C 40.94, H 3.78, N 33.42, S 21.86, found C 40.96, H 3.80, N 33.44, S 21.88. EI-Ms, m/z (relative intensity %): 294.54 (M^+ +1, 26%), 263.34(100%), 179.34(36%), 95.43(5%).

***In vitro* Antibacterial screening**
The compounds (**1-7)** were evaluated for their in vitro antibacterial activity against Escherichia coli(MTCC-739), Pseudomonas aeruginosa(MTCC-2435), Streptococcus epidermidis, Klebsiella pneumoniae(recultured), and Staphylococcus aureus(MTCC- 96), by disc diffusion method [13] was performed using Mueller–Hinton agar(Hi-Media) medium. Each compound was tested at a concentration at 100µg/mL in DMSO. The zone of inhibition was measured after 24h incubation at 37ºC.

***In vitro* antifungal screening**
The compounds (**1-7)** were evaluated for their in vitro antifungal activity such as Aspergillus niger, Candia albicans, Microsporum audouinii and Cryptococcus neoformans(recultured) using an disc diffusion method [14] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 100µg/mL in DMSO. The zone of inhibition (mm) was measured incubated at 37°C.

RESULTS AND DISCUSSION

Chemistry

5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol)(**4**), 5,5'- (3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4*H*-1,2,4-triazole-3-thiol)(**6**) and 5,5'-(3,5-di methyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-thiadiazol-2-amine)(**7**) were prepared from cyclization method. The maximum yield of target compound (**4**) is 88%, but other compounds (**6**),(**7**) are lower yield then compound (**4**). The choice of the solvent had a crucial effect on the yield and ethanol was chosen as the best of those used. Physicochemical data of compounds **(2-7)** are summarized in table 1**.** All the reaction sequence is outlined in **scheme 1.**

Diethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate(**1**) is prepared from Fischer and Noller condensation method [15]. The 3,5-dimethyl-1*H*-pyrrole-2,4-dicarbo hydrazide(**2)** is prepared from hydrazinolysis method[16] and 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-oxadiazole-2-thiol)**(3)** is prepared from the compound **(2)** reacted with CS_2 and KOH by cyclization oxiadiazole derivative [17]. The 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol**)(4)** is prepared from hydrazinolysis method[18]. The ^{1}H NMR spectra compound **(4)** shows that a singlet at δ 5.72 corresponding to the NH_2 protons, SH protons resonated as a singlet at δ 13.93 respectively.

^{13}C NMR spectrum of compound (**4**) shows the peak at δ 167.86 corresponding to C-SH group respectively. The mass spectra (EI-MS) of compound **(4)** shows the molecular ion peak at m/z 324.20 (M^+ +1, 5%) corresponding to molecular weight of compound **(4).**

The compound **(5)** is prepared from compound **(1)** reacted with thiosemicarbazide by condensation method[19]. The compound 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4*H*-1,2,4-triazole-3-thiol)**(6)**was prepared from previously reported method [20], the compound **(5)** was reacted with 10% NaOH solution followed by acidification with con. HCl to give compound **(6).** The ^{1}H NMR spectra of compound 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(4*H*-1,2,4-triazole-**3**-thiol)**(6)** shows that signals at δ 11.92 corresponding to NH proton in pyrrole ring and singlet at δ 13.88 corresponding to SH proton respectively**.** The ^{13}C NMR spectra of compound **(6)** shows that peak at δ168.11 corresponding to C-SH and δ 157.86 corresponding to C2-C and C4-C respectively. The mass spectrum (EI-MS) of compound **(6)** shows that molecular ion peak at m/z 294.72 (M^+ + 1, 13%) corresponding to molecular weight of the compound **(6).**

The compound 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-thiadiazol-2-amine)(**7**) is prepared from cyclization method [21], the ^{1}H NMR spectra of compound **(7)** shows that signals at δ 7.59 and δ 11.52 corresponding to NH_2 and NH protons respectively.

The ^{13}C NMR spectra of compound **(7)** shows that peaks at δ 178.96 and δ 161.11 corresponding to C4-C , C2-C and C-NH_2 carbons respectively. The mass spectra (EI-MS) of compound **(7)** shows that molecular ion peak at m/z 294.54 (M^+ +1, 27 %) corresponding to molecular weight of the compound **(7).**

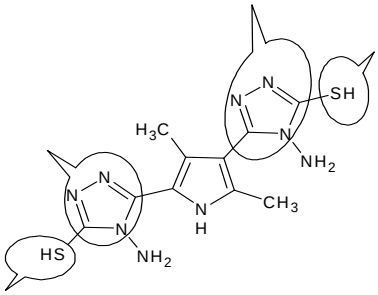
Antibacterial activity

Compound **4** is highly active against *P.aeruginosa* compared with standard. Compound **7** is highly active aganist *S. epridermidis* compared with standard , Compound 4 is highly active against *K.pneumoniae* compared with standard The bacterial zones of inhibition values are summarized in Table 2. Antibacterial activity variations of the compounds (**1**-**7**) are shown in figure 1.

Antifungal activity

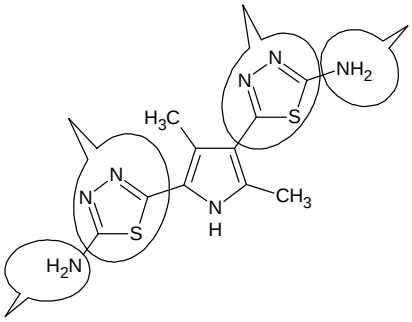
Compound **7** is highly active against *A. naiger* compared with standard. The fungal zones of inhibition values are summarized in Table 3. Antifungal activity variations of the compounds (**1**-**7**) are shown in figure 2.

Structural activity relationship



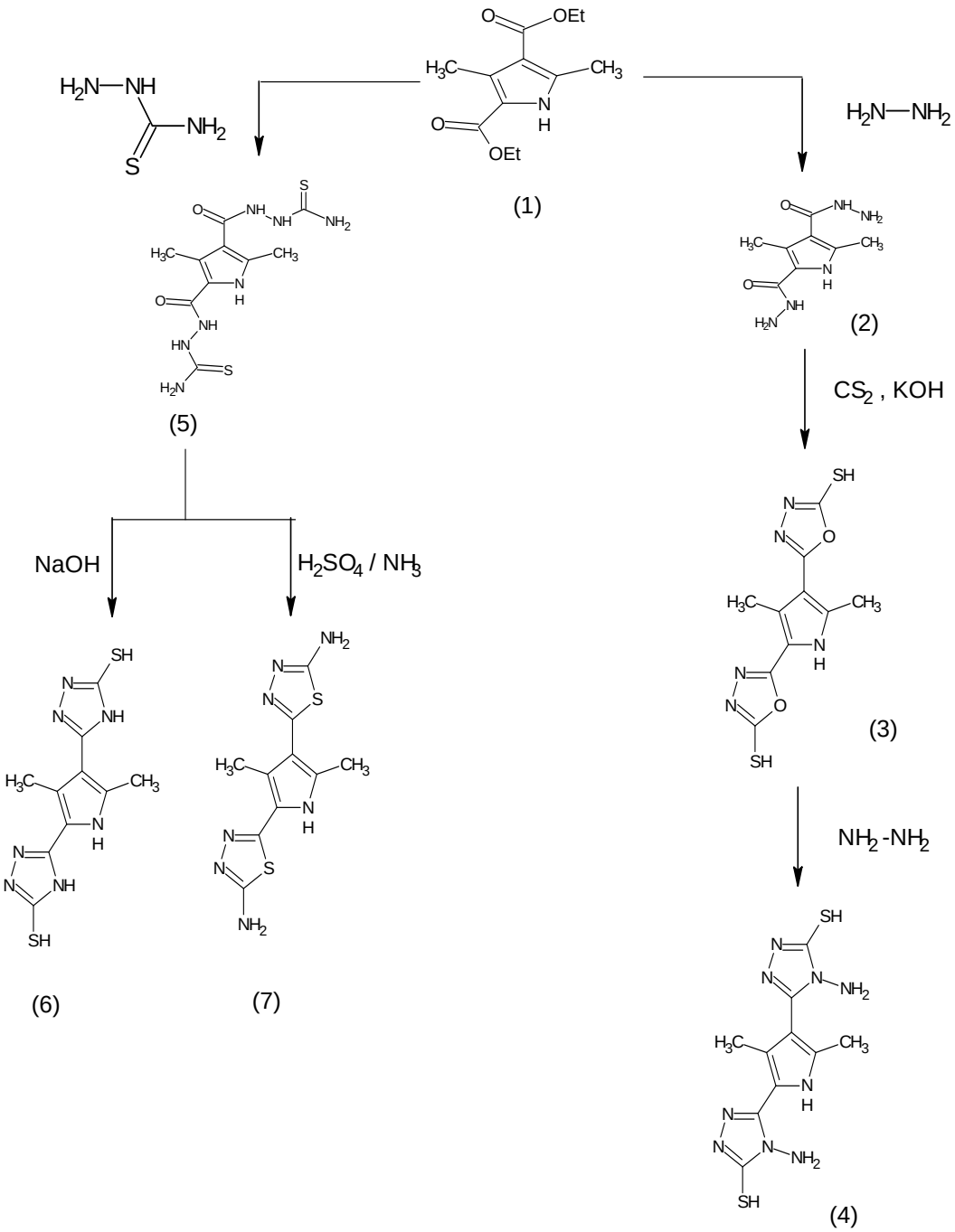
Compound 4

Antibacterial screening of the compound 4 shows that highly active against *P.aeruginosa* compared with standard due to the HS and triazole ring present in pyrrole drivatives where as low activity agnist ather bactrial organisums and very low activty in fungal organisuums.



Compound 7

Antifungal screening of the compound **7** shows that highly active against *A. Niger* due to the presence of NH_2 and thiadiazole ring in pyrrole drivatives where as low activity agnist ather fungal organisums .



Scheme 1. Synthetic route of compounds (1-7)

Table 1. Physicochemical data of compounds (1-7)

Comp. No.	M.W	M.F	Mp°C	Yield %	Colour	Solvent	Reaction Time	Temp. (°C)
2	211.22	$C_8H_{13}N_5O_2$	112	91	Yellow solid	EtOH	6h	Reflux, 80
3	295.34	$C_{10}H_9N_5O_2S_2$	178	90	Yellow solid	EtOH	18h	Reflux, 80
4	323.40	$C_{10}H_{13}N_9S_2$	143	88	Yellow solid	EtOH	24h	Reflux, 80
5	329.40	$C_{10}H_{15}N_7O_2S_2$	122	76	Pale yellow solid	EtOH	7h	Reflux, 100
6	295.37	$C_{10}H_{11}N_7S_2$	168	77	Yellow solid	EtOH	5h	60
7	293.30	$C_{10}H_{11}N_7S_2$	192	79	Yellow solid	EtOH	2h	-

Table 2 Antibacterial activity of compounds (1-7)

Compounds	*E.coli*	*P.aeruginosa*	*S.aureus*	*S. epridermidis*	*K.pneumoniae*
1	6	10	6	-	10
2	10	12	10	-	19
3	-	16	12	-	20
4	15	20	16	10	23
5	-	10	-	19	10
6	-	12	-	21	12
7	-	16	-	20	14
Standard	26	17	22	15	19

The compounds were used at concentration 100µg/mL.
Ciprofloxacin used as a standard.
Zone of inhibition measured at (mm).

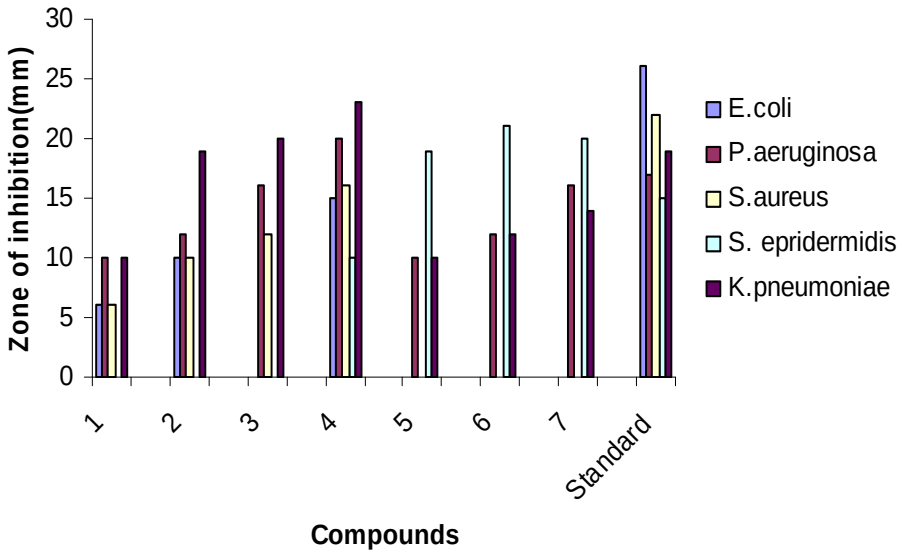


Figure 1. Antibacterial activity of the compounds(1-7)

Table 3 Antifungal activity of compounds (1-7)

Compounds	*A. niger*	*C. albicans*	*C. neoformans*	*M. audouinii*
1	-	-	-	-
2	10	-	-	-
3	12	-	8	10
4	15	-	13	12
5	20	10	10	-
6	22	-	12	-
7	26	-	14	-
Standart	22	24	25	26

The compounds were used at concentration 100µg/mL.
Clotrimazole used as a standard.
Zone of inhibition measured at (mm).

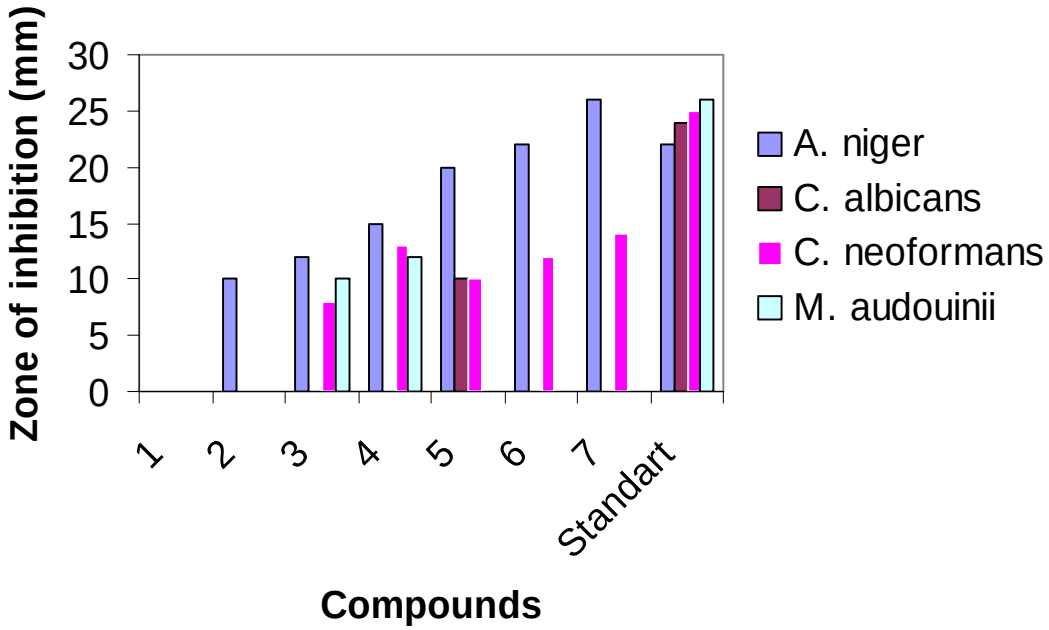


Figure 2. Antifungal activity of the compounds(1-7)

CONCLUSION

This paper describes by pyrrole contain triazole (**4, 6**), thiadazole**(7)** derivatives were prepared by cyclization method with one vial and ordinary reaction type. The methodology was previously reported, but the target molecules are newly synthesized compounds, its use a wide variety of coupled two heterocyclic compounds could be reached in matter of days and its could be used screening for biological activates**.** Synthesized compound were screened for antimicrobial activity. Antibacterial activity of the compound **4** is highly active against *P.aeruginosa* and compound **7** is highly active aganist *S. epridermidis,* Compound **4** is highly active against *K.pneumoniae* compared with standard Ciprofloxacin**,** and antifungal activity of the compound **7** has highly active against *A.niger* compared with Clotrimazole at concentration 100µg/mL, which can be beneficial for further studies. These synthesized compounds could be extended to analysis the various biological activities.

Acknowledgements
We sincerely thank to management of Jamal Mohamed College, for providing laboratory facilities.

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