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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRROLE DERIVATIVES

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ABSTRACT. New pyrrole derivatives were synthesized and structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses data. The reaction was performed by using ordinary condensation type, which enabled to easy work-up and good yield. Synthesized compounds were screened for antimicrobial activity.

KEY WORDS: Pyrrole, 1,3,4-oxadiazol-2-amine, 4H-1,2,4-triazol-3-ol, Cyclization, Antimicrobial activity, Structure activity relationship

INTRODUCTION

Pyrrole derivatives are of considerable synthetic importance due to their extensive used in drug discovery [1] which is linked to their pharmacological activity such as anti-inflammatory [2], cytotoxicity [3-6], treatment of hyperlipidemias [7] and antitumour agents [8]. The pyrrole containing other heterocyclic compounds has been reported previously for biological studies [9]. Oxadiazole linked with pyrrole derivatives are display a broad spectrum of biological activity such as antimicrobial activity [10], antitubercular agents [11]. Triazole linked with pyrrole derivatives have importance of biological and pharmaceutical importance activity such as anti-inflammation [12, 13], antitumor [14] and antimicrobial [15-17]. These references will serve as the main rationales for the synthesis of new pyrrole connecting oxadiazole and triazole derivatives (Scheme 1) and evaluate them for antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

Synthesized compounds are outlined in Scheme 1. Diethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarb-oxylate (**1**) was prepared by using Fischer and Noller condensation method [18]. The compound 2,2'-[(3,5-dimethyl-1*H*-pyrrole-2,-diyl)dicarbonyl]dihydrazinecarbox amide (**2**) was prepared by condensation method [19].

The compound 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(2,4-dihydro-3*H*-1,2,4-triazol-3-ol) (**3**) was synthesized from 10% NaOH solution and acidification with dilute HCl by cyclization method [20, 21]. IR spectrum of the compound **3** showed an absorption band at 1669, 3345 and 3301 cm^{-1} corresponding to C=N, NH and OH, respectively. The ^{1}H NMR spectrum of the compound **3** shows that singlet at δ 11.63 corresponding to NH in pyrrole ring

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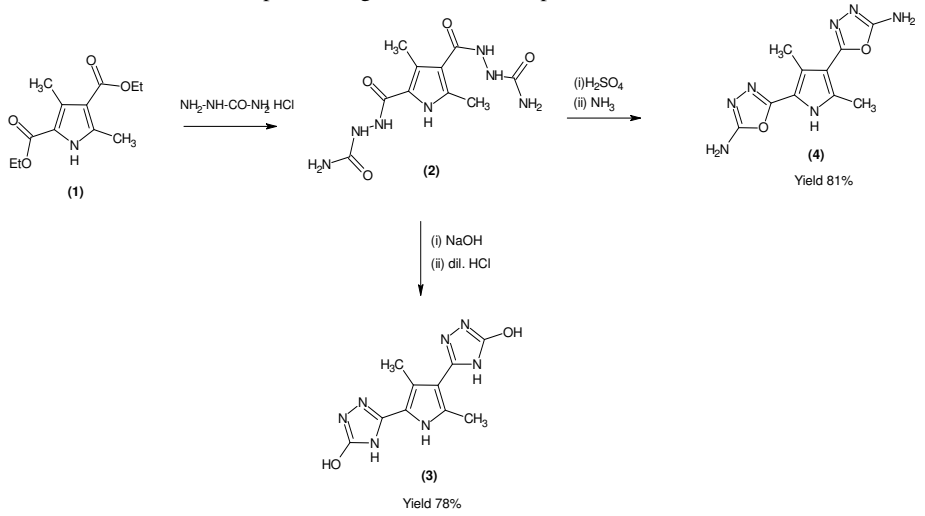
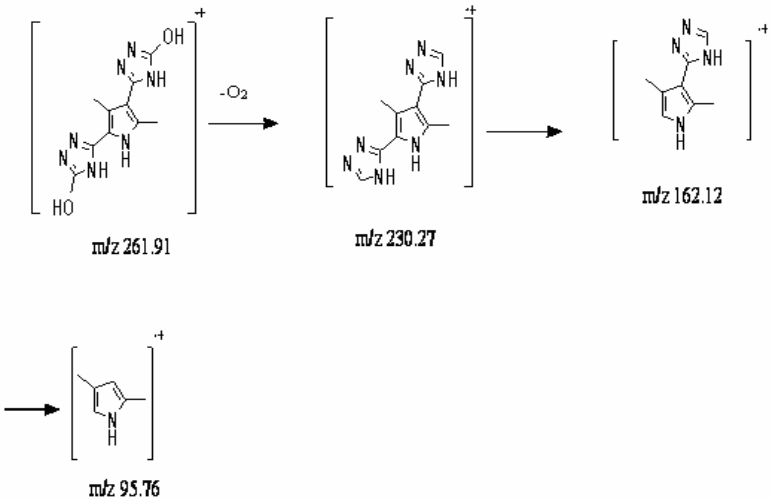
and OH protons resonated as a singlet at δ 11.82, respectively. The ^{13}C NMR spectrum of the compound **3** shows peak at δ 161.11 corresponding to C-OH and 155.86 corresponding to C4-C and C2-C, respectively. The EI-MS spectrum of the compound **3** showed that molecular ion peak at m/z 261.91(M^+, 5%), which is conformed to molecular weight of the compound **3**. Scheme 2 shows the mass spectral fragmentation of compound **2**.



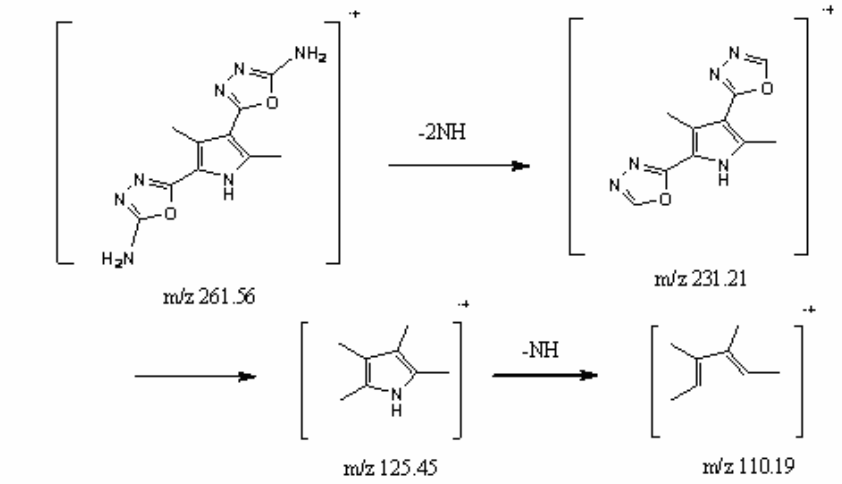
Scheme 1. Synthesis route of compounds **1-4**.



Scheme 2. Mass spectral fragmentation of compound (**3**).

The compound 5,5'-(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)bis(1,3,4-oxadiazol-2-amine)(**4**) was synthesized from compound **2** reacted with H_2SO_4 and neutralized with NH_3 solution by cyclization method [22]. The IR spectra of compound **4** shows that absorption peak at 669, 1644, 3021, 3388 and cm^{-1} attributing to C-O-C, C=N, NH_2 and NH group, respectively. The ^{1}H

NMR spectrum of compound **4** shows that signal at δ 11.34 corresponding to N-H in pyrrole ring and singlet at δ 7.12 for NH_2 protons present in oxadiazole ring and C3-CH_3, C5-CH_3 protons corresponding to singlet at δ 2.69 and 2.93, receptively. The ^{13}C NMR spectrum the compound **4** shows peak at δ 168.11, 110.73 and 114.71 corresponding C-NH_2, C4-C and C2-C respectively. The EI-MS spectrum of the compound **4** showed molecular ion peak at m/z 261.56 (M^+, 10 %), which is conformed to molecular weight of the compound **4**. Scheme 3 shows the mass spectral fragmentation of compound **2**.



Scheme 3. Mass spectral fragmentation of compound (**4**).

Antibacterial activity

The compounds **1-4** were screened for antibacterial activity. Compound **3** is highly active than standard (Ciprofloxacin) against *P. mirabilis* and compound **4** is highly active than standard against *M. luteus* at concentration 100 μg/mL. Figure 1 shows that antibacterial activity of the compound **1-4**. The bacterial zones of inhibition (mm) values are summarized in Table 1.

Table 1. Antibacterial activity of compounds (**1-4**).

Test organisms	Compounds				
	1	**2**	**3**	**4**	Standard
E. coli (MTCC-739)	10	15	8	15	18
P. mirabilis	-	-	21	10	15
Non hemolytic streptococcus	8	-	15	14	16
P. aeruginosa (MTCC-2435)	14	15	-	20	27
M. luteus (MTCC-106)	7	-	10	23	20
E. faecalis	-	-	-	8	29
S. epidermidis	-	24	10	-	27
K. pneumoniae	-	5	-	-	21
Bacillus spp	18	-	-	10	23
S. aureus (MTCC-2940)	-	16	12	6	16

Zone of inhibition was measured at (mm) at concentration of 100 μg/mL, ciprofloxacin is used as the standard.

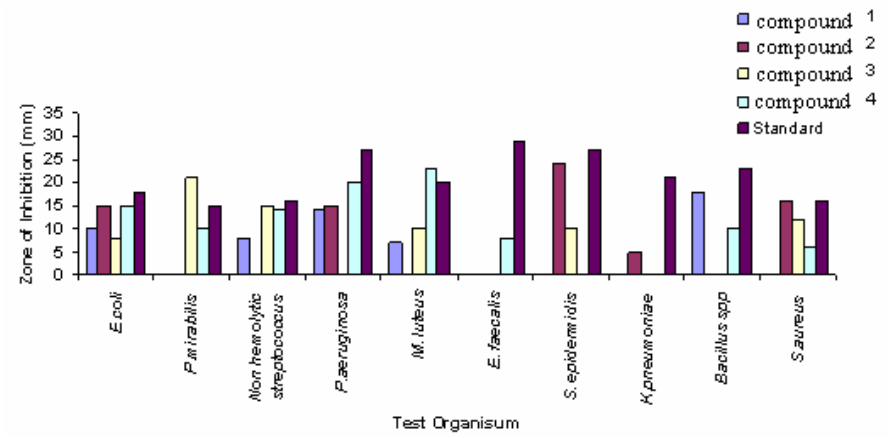


Figure 1. Antibacterial activity of the compound (**1-4**) and standard.

Antifungal activity

The compounds **1-4** were screened for the antifungal activity. Compound **3** is highly active compared with standard (Clotrimazole) against *A. niger*, the compound **4** is highly compared with standard against C. *albicans* at concentration 100 µg/mL. Figure 2 shows that antifungal activity of the compound **1-4**. The fungal zones of inhibition (mm) values are summarized in Table 2.

Table 2. Antifungal activity of compounds (**1-4**).

Test organisms	Compounds				
	1	**2**	**3**	**4**	Standard
A. niger	12	16	26	10	22
C. albicans	8	12	8	20	18
C. neoformans	-	8	10	5	15
M. audouinii	5	16	8	10	16

Zone of inhibition was measured at (mm) at concentration of 100 µg/mL, clotrizaole is used as the standard.

Structure activity relationship

Scheme 4 shows that significance of antibacterial activity in compounds **3** and antifungal activity in compounds **4**. From the results of antimicrobial activity of the pyrrole derivatives, the following structure activity relationships can be derived Antibacterial activity of compound **3** shows that highly active against *P. mirabilis* and antifungal activity of compound **3** shows highly active against *A. niger* at concentration 100 µg/mL due to presence of triazole moiety connected with pyrrole derivative.

Antibacterial activity of compound **4** shows that highly active against *M. luteus* and antifungal activity of compound **4** shows highly active against *C. albicans* at concentration 100 µg/mL due to presence of oxadiazole moiety connected with pyrrole derivative.

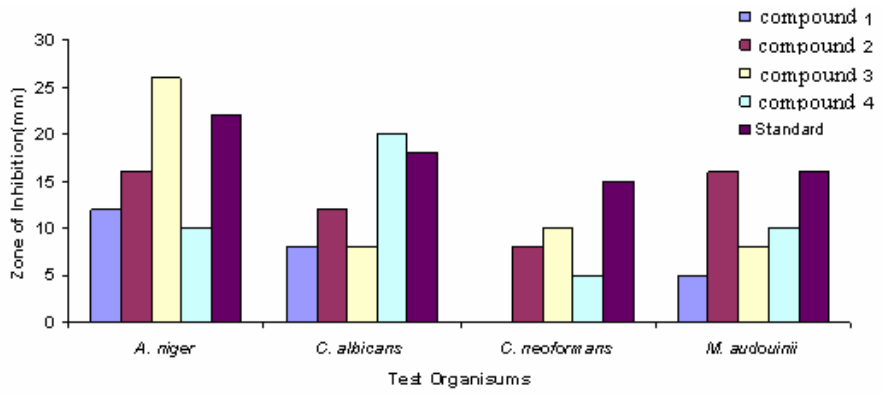
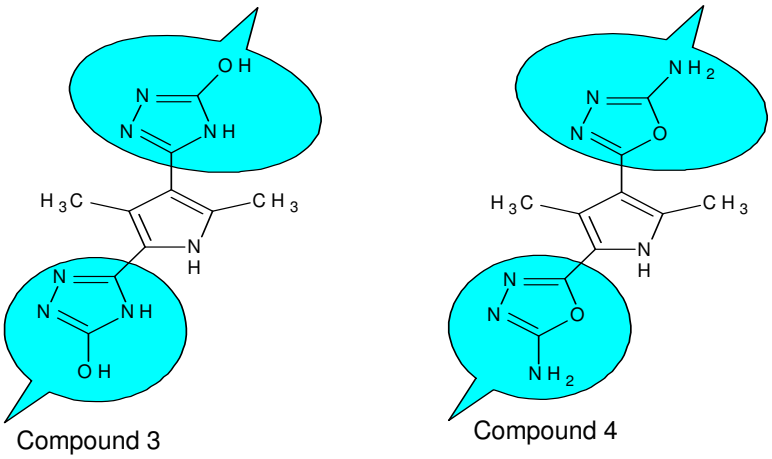


Figure 2. Antifungal activity of the compound (**1-4**) and **s**tandard.



Scheme 4

EXPERIMENTAL

Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra (KBr) were recorded in KBr on a shimadzu 8201pc (4000-400 cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 MHZ. The elemental analysis (C, H, and N,) were recorded using an Elementer analyzer model (Varian EL III). The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

*2,2'-[(3,5-Dimethyl-1H-pyrrole-2,4-diyl)dicarbonyl]dihydrazinecarboxamide (**2**)*

A mixture of 2,4-dimethyl-3,5-dicarbethoxypyrrole (**1**) (2.39 g, 1.0 mol), semicarbazide hydrochloride (1.22 g, 1.0 mol) was added to sodium acetate (0.20 g) in ethanol (8.0 mL), the

reaction mixture was heated and refluxed for 4 h. The reaction mixture was cooled and poured into ice-cooled water. The precipitate was filtered and recrystallized from absolute ethanol.

*5,5'-(3,5-Dimethyl-1H-pyrrole-2,4-diyl)bis(4H-1,2,4-triazol-3-ol) (**3**)*

The mixture of compound **2** (2.97 g, 0.1 mol) in 2N-NaOH solution (20 mL), the reaction mixture was heated and refluxed for 5 h. After cooling, the solution was made acidic with conc. HCl and the precipitate was collected from filtration and recrystallized from absolute ethanol.

Yield 78%; m.p. 147 ºC; MW 261; MF $C_{10}H_{11}N_7O_2$; IR (cm^{-1}): 1669.66 (C=N), 2936.64 (CH_3), 2986.24 (NH-in triazole ring), 3301.53 (OH), 3345.22 (NH-in pyrrole ring); ^{1}H NMR (DMSO-d_6) δ: 11.63 (s, 1H, NH in pyrrole ring), 7.75 (s, 1H, NH in triazole ring), 2.43 (s, 3H, C3-CH_3), 2.14 (s, 3H, C5-CH_3), 11.82 (s, 2H, OH); ^{13}C NMR (DMSO-d_6) δ: 161.11 (C-OH), 155.86 (C2,C4-C), 135.36 (C5-CH_3), 133.36 (C3-CH_3), 116.86 (C2-C), 108.96 (C4-C), 16.98 (C5-CH_3), 10.74 (C3-CH_3); (EI-MS) m/z: 261.91 (M^+, 4%), 230.27 (100%), 162.12, 95.76. Elemental analysis calculated (found): C 49.09 (49.04), H 4.38 (4.40), N 17.89 (17.94).

*5,5'-(3,5-Dimethyl-1H-pyrrole-2,4-diyl)bis(1,3,4-oxadiazol-2-amine) (**4**)*

A mixture of compound **2** (2.97 g, 0.1 mol) was dissolved in 4 mL con. H_2SO_4, the reaction mixture was stirred at room temp for few minutes and left overnight. It was poured on crushed ice. The resulting solid was kept in NH_3 for 2 h. The solid was formed and filtered. The solid was recrystallised form ethanol.

Yield 81%; m.p. 178 ºC; MW 261.24; M.F $C_{10}H_{11}N_7O_2$; IR (cm^{-1}): 669.84 (C-O-C);, 1644.92 (C=N), 3021.96 (NH_2), 3338.85 (NH); ^{1}H NMR (DMSO-d_6) δ: 11.34 (s, 1H, NH), 7.12 (s, 4H, C-NH_2), 2.69 (s, 3H, C3-CH_3), 2.93 (s, 3H, C5-CH_3); ^{13}C NMR (DMSOd_6) δ: 168.11 (C-NH_2), 130.86 (C2,C4-C), 164.90 (C3-C), 118.70 (C5-C), 114.17 (C2-C), 110.73 (C4-C), 14.90 (C5-CH_3), 10.33 (C3-CH_3); (EI-MS) m/z: 261.56 (M^+, 10%), 231.21, 125.45 (100%), 110.19. Elemental analysis calculated (found): C 45.98 (45.97), H 4.24 (4.26), N 37.53 (37.51).

Antimicrobial activity

In vitro antibacterial screening. The compounds **1-4** were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* (MTCC-739), *Proteus mirabilis*, *Non-hemelytic streptococcus*, *Pseudomonas aeruginosa* (MTCC-2435), *Micrococcus luteus* (MTCC-106), *Enterococcus feacalis*, *Streptococcus epidermidis*, *Bacillus spp*, *Klebsiella pneumoniae* (recultured), and *Staphylococcus aureus* (MTCC- 96), by disc diffusion method [23] performed using Mueller–Hinton agar (Hi-Media) medium. Ciprofloxacin was used as a standard. Each compound was tested at concentration 100 μg/mL in DMSO. The zone of inhibition (mm) was measured after 24 h incubation at 37 ºC.

In vitro antifungal screening. The compounds **1-4** were evaluated for their *in vitro* antifungal activity such as *Aspergillus niger*, *Candia albicans*, *Microsporum audouinii* and *Cryptococcus neoformans* (recultured) using disc diffusion method [24] with sabouraud's dextrose agar (Hi-Media). Clotrimazole was used as a standard. Each compound was tested at a concentration of 100 μg/mL in DMSO. The zone of inhibition (mm) was measured incubated at 37 °C.

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