SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME NEW 1,2,4-TRIAZOLE AND FURAN CONTAINING COMPOUNDS

Ihsan A. Shehata

لقد تشييد عدد من المركبات المحتوية على حلقة 1 ,2 ,4- ترايازول المترافقة مع حلقات ذات احلالات مختلفة هي حلقة الفينايل وحلقة البيرول أ والفيوران الخماسية المتغايرة كما تم إجراء المسح الحيوي على هذه المركبات لمعرفة تأثيراتها المضادة للفطريات ، وقد تبين أن لمركبين من هذه المركبات تأثيرات واضحة ضد كل من ك. البيكان وس. سيريفيسيا ، وهذان المركبان هما مركب رقم (11) وأسمه الكيميائي 5 ,6 ثنائي هيدرو -5- أوكسو-5-فينايل-H4-فيورو [c-3,2] بيرول ، ومركب رقم (16) وأسمه الكيميائي 1 ميثايل -2-بيرولايل ميثايل) -4-فينايل -5- (4 كلورو فينايل كاربامويل ميثايل ثيو) 4,2,1 ترايازول. تحتوي هذه المقالة على التفاصيل الخاصة بطرق تشييد هذه المركبات وكذلك التجارب الخاصة بالمسح الحيوي على هذه المركبات لمعرفة تأثيراتها المضادة للفطريات.

Several new 1,2,4-triazole analogs attached to substituted phenyl, pyrrole or furan 5-membered heterocycles were synthesized and screened for their antifungal activity. Compounds 5,6-dihydro-4-oxo-5-phenyl-4*H*-furo[2,3-*c*]pyrrole (**11**) and 3-(1-methyl-2-pyrrolylmethyl)-4-phenyl-5-(4-chlorophenylcarbamoylmethylthio)-1,2,4-triazole (**16**) showed a prominent activity against *C. albicans* and *S.* cerevisiae. The detailed synthesis and the antifungal screening are reported.

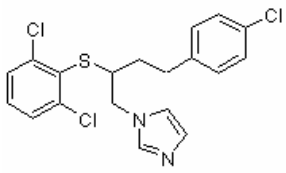
Keywords: Synthesis, 1,2,4-triazole analogs, substituted furans, antifungal activity.

Introduction

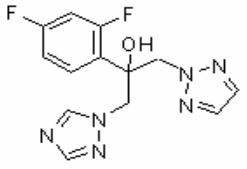
Azole antifungal agents are the largest class of antimycotics available today. The characteristic chemical features of azoles are the presence of a five membered aromatic ring containing nitrogen atoms, attached to a side chain containing at least one aromatic ring (1) examples are in Chart 1, such as Butoconazole (**A**), Fluconazole (**B**) and Chlormidazole (**C**).

Recent studies (2, 3) showed that a combination of terbinafine, amphoteracin B, with fluconazole (**B**) and other azoles may potentiate the antifungal activity due to synergestic effect. Numerous 1,2,4-triazole analogs have been reported to exhibit antifungal activity (4–8). The present study describes the synthesis of some new 1,2,4-triazoles, attached to two aromatic moieties either two phenyl or a phenyl and an isosteric five membered ring equivalent such as 1,3,4-oxadiazole, pyrrole or furan.

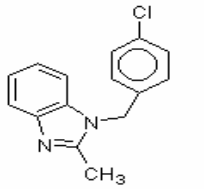
Chart 1.



Butoconazole (**A**)



Fluconazole (**B**)



Chlormidazole (**C**)

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The type of substituents used to prepare these triazoles were selected, keeping in mind the presence of a basic nitrogen, to form a bond with the heme iron of the CYP_{450} prosthetic group. This will prevent the fungal enzymes from oxidizing their normal substrate and the remainder of the drug molecule expected to be able to form bonding interaction with the apoprotein. In addition, certain furan derivatives differently substituted at positions 2- and or 5- were recently reported to possess fungicidal activity (9, 10). In view of these findings and in continuation to our previous studies (11–15), the present study describes the synthesis of certain substituted azole and furan containing derivatives to explore their antifungal activity.

Experimental

Melting points (°C, uncorrected) were recorded on a Fisher-Johns apparatus. IR spectra were recorded on a Pye-Unicam SP 1000 using KBr (cm^{-1}) discs. ^{1}H-NMR spectra were recorded on a Varian EM-360 (90 MHz) instrument using TMS as internal standard (chemical shifts in δ ppm). Microanalytical data (C, H, N) agreed with the proposed structures within ± 0.4% of the theoretical values. All of the chemicals and reagents used were purchased from Aldrich Chemical Co. Solvent evaporations were performed under reduced pressure using a Buchi Rotary Evaporator. Thin layer chromatography was performed on Merck 5 × 10 cm plates precoated with silica gel GF_{254} using short wavelength UV light (254 nm) to detect the UV absorbing compounds. The following organisms were used in the antimicrobial screening: *Escherichia coli* ATCC 10536, *Staphylococcus aureus* ATCC 6538, *Bacillus subitilis* ATCC 6633, *Saccharomyces cerevisiae* ATCC 9763 and *Candida albicans* ATCC 1023, which were obtained from American type culture collection (ATCC), Manassas, Virginia, USA.

2-Methylfuran-3-carboxylic acid hydrazide (2)

To a solution of methyl 2-methylfuran-3-carboxylate (**1**, 1.4 g, 0.01 mol) in methanol (15 ml), hydrazine hydrate (85%, 5 ml) was added and stirred at room temperature. After 3 h. the precipitate was filtered and recrystallized from EtOH to give **2** (85%) yield, mp 145–6° (16).

1-2-Methylfuryl-3-carbonyl)-4-phenyl or benzyl-thiosemicarbazide (3, 4)

The acid hydrazide **2** (1.4 g, 0.01 mol) was treated with the appropriate isothiocyanate derivative (0.01 mol) in ethanol (20 ml) and the reaction mixture was stirred at room temperature for 24 h. The formed precipitate was filtered, dried and recrystallized from EtOH/H_2O to give **3** (70%), m.p. 187–9°. ^{1}H-NMR (DMSO–d_6): δ 9.80 (s, 1H, NH), 9.55 (s, 1H, NH), 9.35 (s, 1H, NH), 7.40–6.75 (m, 7H, Ar), 2.30 (s, 3H, CH_3). **4** (45%) yield (EtOH, H_2O), m.p. 119°C, ^{1}H-NMR (DMSO–d_6): δ 9.88 (s, 1H, NH), 9.35 (s, 1H, NH), 9.16 (s, 1H, NH), 7.65–6.91 (m, 7H, Ar), 4.25–4.45 (d, 2H, CH_2 benzylic) 2.45 (s, 3H, CH_3).

4-Phenyl or benzyl-3-(2-methyl-3-furyl)-2,4-dihydro (3H)-1,2,4-triazole-5-thiole (5, 6)

A stirring mixture of **3** or **4** (0.01 mol) in aqueous sodium hydroxide solution (2N, 10 ml) was refluxed for 4 h. After cooling the solution was acidified with HCl and the formed precipitate was filtered, dried and recrystallized from EtOH to give **5** (66%), m.p. 229–30°C. ^{1}H-NMR (DMSO–d_6): δ 13.35 (s, 1H, SH), 7.90–6.7 (m, 7H, Ar, furan), 2.50 (s, 3H, CH_3). **6** (53%) yield (EtOH/H_2O), m.p. 135–7°C. ^{1}H-NMR (DMSO–d_6): δ 13.30 (s, 1H, SH), 7.85–6.70 (m, 7H, Ar, furan), 4.20–4.40 (s, 2H, CH_2 benzylic), 2.45 (s, 3H, CH_3).

1-Formyl-2-(2-methylfuryl-3-carbonyl)hydrazine (8)

A solution of **2** (1.4 g, 0.01 mol) in formic acid (20 ml) was refluxed for 30 min. The solvent was evaporated and the residue was recrystallized from MeOH to yield **8** (80%), mp 165°C. IR(KBr): 3320-3260 cm^{-1} (NH), 1690–1650 (C=O), ^{1}H-NMR (DMSO–d_6): δ 9.70–9.52 (br. s, 2H, NH), 7.90 (s, 1H, H–C=O), 7.35 (d, 1H, furan), 6.70–6.65 (d, 1H, furan), 2.50 (s, 3H, CH_3).

2-(2-Methyl-3-furyl)-1,3,4-oxadiazole (9)

Method A: To a mixture of **8** (1.7 g, 0.01 mol) in xylene (150 ml), P_2O_5 (2.0 g) was added and the reaction mixture was refluxed for 1 h. The solvent was evaporated, water (10 ml) was added to the residue and extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was recrystallized from MeOH to give **9** (52%), m.p. 120°C.

Method B: A mixture of the hydrazide **2** (1.4 g, 0.01 mol) and triethylorthoformate (5 ml) was heated at reflux for 6 h. The solvent was removed under reduced pressure and the obtained residue was recrystallized from MeOH to give **9** (35%), m.p. 120°C ^{1}H-NMR (DMSO–d_6): δ 7.52 (s, 1H, oxadiazole), 7.50–7.47 (d, 1H, furan), 7.37–7.34 (d, 1H, furan), 2.50 (s, 3H, CH_3).

Methyl 2-bromomethylfuran-3-carboxylate (10)

A mixture of **1** (4.2 g, 0.03 mol), N-bromosuccinimide (5.4 g, 0.033 mol) and benzoyl peroxide (0.25 g) in CCl_4 (150 ml) was refluxed for 6 h. The reaction mixture was cooled, the separated solid was filtered off and the filtrate was evaporated. The brown oily product **10** was used in the next step without further purification.

5,6-Dihydro-4-oxo-5-phenyl-4H-furo[2,3-c] pyrrole (11)

A solution of aniline (2.8 g, 0.03 mol) in CCl_4 (50 ml) was added to the crude **10** (6.6 g, 0.03 mol) and the reaction mixture was stirred for 1 h. at room temperature, then heated under reflux for additional 1 h. After cooling the reaction mixture was successively washed with 4 N HCl (50 ml) then with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was recrystallized from EtOH to give **11** (55%), m.p. 180°. ^{1}H-NMR (DMSO–d_6): δ 8.10–8.0 (m, 5H, Ar), 7.53 (d, 1H, furan), 6.91–6.80 (d, 1H, furan), 3.60 (s, 2H, CH_2), 2.45 (s, 3H, CH_3).

1-Methyl-2-(hydrazinocarbonylmethyl)-pyrrole (13)

To a solution of methyl 1-methylpyrrole-2-acetate **12** (1.5 g, 0.01 mol) in EtOH (10 ml), hydrazine hydrate (85%, 5 ml) was added. The reaction mixture was refluxed for 3 h., then concentrated in vacuum, cooled and diluted with water. The separated solid was filtered, dried and recrystallized from EtOH/H_2O to yield **13** (85%), m.p. 85–86°C (16).

1-(1-Methyl-2-pyrrolylacetyl)-4-phenyl-thiosemicarbazide (14)

To a solution of the hydrazide **13** (1.5 g, 0.01 mol) in EtOH (25 ml) phenylisothiocyanate (1.5 g, 0.01 mol) was added and the reaction mixture was heated under reflux for 1 h. On cooling the precipitated solid was filtered, dried and recrystallized from EtOH to yield **14** (88%), m.p. 169–170°C. IR (KBr): 1690 (C=O), 3100–3550 (NH). ^{1}H-NMR (DMSO–d_6): δ 9.80 (s, 1H, NH), 9.45 (s, 2H, 2NH), 7.50–6.90 (m, 6H, Ar + 1H pyrrole), 6.38–6.50 (t, 1H, pyrrole), 5.80–5.65 (m, 1H, pyrrole), 3.20 (s, 2H, CH_2), 3.25 (s, 2H, CH_3).

3-(1-Methyl-2-pyrrolylmethyl)-4-phenyl-1,2,4-triazole-5-thiole (15)

A mixture of the thiosemicarbazide **14** (2.9 g, 0.01 mol) in aqueous sodium hydroxide solution (2N, 5 ml) was refluxed for 1 h. The reaction mixture was cooled, then adjusted to pH 6 with HCl (10%). The obtained solid was filtered, washed with water and recrystallized from EtOH to give **15** (76%), m.p. 175–77°C. ^{1}H-NMR (DMSO–d_6): δ 13.25 (s, 1H, SH), 7.45–7.10 (m, 5H, Ar), 6.45–6.40 (t, 1H, pyrrole), 5.70–5.59 (q, 1H, pyrrole), 3.35–5.29 (m, 1H, pyrrole), 3.70 (s, 2H, CH_2), 3.20 (s, 3H, CH_3).

3-(1-Methyl-2-pyrroloylmethyl)-4-phenyl-5-(4-chlorophenyl-carbamoylmethylthio)-1,2,4-triazole (16) or 3-(1-methyl-2-pyrrolylmethyl)-4-phenyl-5-(1-pipperidinocarbonylmethylthio)-1,2,4-triazole (17)

To a stirred mixture of the thiol **15** (0.27 g, 0.01 mol) and KOH (0.56 g, 0.01 mol) in absolute ethanol (10 ml), the corresponding N-chloroacetamide (0.01 mol) was added portion wise. The reaction mixture was stirred at room temperature overnight. Ethanol was evaporated and water was added to the residue and the separated solid was recrystallized from EtOH/H_2O to give **16** (62%), m.p. 145–148°. ^{1}H-NMR (DMSO–d_6): δ 10.50 (s, 1H, NH), 6.95–7.80 (m, 9H, Ar), 6.50–6.49 (t, 1H, pyrrole), 5.90–5.80 (t, 1H, pyrrole), 5.45–5.40 (m, 1H, pyrrole), 4.00 (s, 2H, CH_2), 3.80 (s, 2H, CH_2), 3.50 (s, 3H, CH_3). **17** (58%), m.p. 110°C. ^{1}H-NMR (DMSO–d_6): δ 7.40–6.80 (m, 5H, Ar), 6.35–6.15 (t, 1H, pyrrole), 5.59–5.55 (q, 1H, pyrrole), 5.30–5.10 (m, 1H, pyrrole), 4.10 (s, 2H, CH_2), 3.80 (s, 2H, CH_2), 3.30–3.50 (s, 7H, CH_3, & $2CH_2$), 1.90–1.00 (s, 6H, $3CH_2$).

Ethyl 2-(Substituted phenylazo)-3-oxo-butyrate (20, 21)

To a cooled solution of aniline derivative **18** or **19** (0.01 mol) in glacial acetic acid (20 ml) and conc. HCl (30 ml), a cooled solution of sodium nitrite (30%, 20 ml) was dropped with stirring and cooling. After the addition was over, the solution was set

aside for 30 min. and rendered alkaline with saturated solution of sodium acetate. The alkaline diazonium salt solution was dropped at 0°C over a period of 1 h. into a cold stirred solution of ethyl acetoacetate (1.3 g, 0.01 mol), sodium acetate (8 g) in EtOH (20 ml) and water (10 ml). The reaction mixture was stirred further for 1 h. at room temperature. The obtained product was filtered, washed with water, dried and recrystallized from EtOH to give **20** (80%), m.p. 83°C. IR (KBr): 3530–3200 (NH), 1690, 1570 (C=O). ^{1}H-NMR (DMSO–d_6): δ 13.40 (s, 1H, NH, 8.10–6.68 (m, 4H, Ar), 4.29–4.00 (q, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.45–1.30 (t, 3H, CH_3). **21** (73%), (EtOH); m.p. 134–6°. ^{1}H-NMR (DMSO–d_6): δ 13.40 (s, 1H, NH), 8.00–6.60 (m, 3H, Ar), 4.29–4.00 (q, 2H, CH_2), 3.90 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 1.45–1.30 (t, 3H, CH_3).

Ethyl 2-(Substituted phenylhydrazino) -2-iminoacetate (22, 23)

To a stirred solution of **20** or **21** (0.01 mol) and sodium acetate (1.2 g) in glacial acetic acid (10 ml), Br_2 solution (1.6 g, 0.01 mol) in glacial acetic acid (10 ml) was added dropwise. After 10 min. the solution was poured into water (150 ml) then extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and evaporated. The obtained residue was dissolved in acetone (15 ml), then NH_4OH (25%, 4 ml) in acetone (15 ml) was added dropwise with continuous stirring for 30 min. The solvent was evaporated and the residue was dissolved in dilute HCl and extracted with benzene. The aqueous layer was separated and alkalinized to pH 8 (NH_4OH). The obtained residue was filtered, dried and recrystallized from EtOH to give **22** (65%), m.p. 140–2°C. ^{1}H-NMR (DMSO–d_6): δ 9.95 (s, 1H, NH), 7.85–7.70 (m, 4H, Ar), 6.60–6.45 (brs, 2H, 2NH), 4.25–3.50 (q, 2H, CH_2), 1.35–1.25 (t, 3H, CH_3). **23** (70%), m.p. 148°C (EtOH). ^{1}H-NMR (DMSO–d_6): δ 9.95 (s, 1H, NH), 7.83–7.70 (m, 3H, Ar), 6.60–6.45 (brs, 2H, 2NH), 4.23–3.50 (q, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.35–1.25 (t, 3H, CH_3).

Ethyl 1-(substituted phenyl)-5-(4-chlorophenyl) -1,2,4-triazole-3-carboxylate (24, 25)

A mixture of **22** or **23** (0.01 mol), pyridine (10 ml) and 4-chloro benzoyl chloride (0.011 mol) in dioxane (50 ml) was refluxed for 3 h. The reaction mixture was evaporated, dissolved in CH_2Cl_2 and washed with dilute HCl, water, K_2CO_3 solution and finally with water. The organic layer was dried (Na_2SO_4), evaporated and the obtained residue was recrystallized from EtOH to give **24** (65%), m.p. 186°. ^{1}H-NMR (DMSO–d_6): δ 8.30–7.30 (m, 8H, Ar), 4.25–4.10 (q, 2H, CH_2), 1.45–1.30 (t, 3H, CH_3). **25** (63%), m.p. 195°C. ^{1}H-NMR (DMSO–d_6): 8.30–7.40 (m, 8H, Ar), 3.80 (s, 3H, OCH_3), 3.40–3.60 (q, 2H, CH_2), 2.60–2.30 (t, 3H, CH_3).

1-(4-Methoxy-2-nitrophenyl)-5-(4-chlorophenyl)-N-(2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-yl)-1,2,4-triazole-3-carboxamide (26)

A mixture of **25** (0.01 mol) and 4-amino antipyrine (2.0 g, 0.01 mol) in ethanol (30 ml) was refluxed for 6 h. The solvent was evaporated and the residue was recrystallized from EtOH/H_2O to give **26**, (52%), m.p. 214°C. ^{1}H-NMR (DMSO–d_6): δ 8.39–7.21 (m, 12H, ArH), 6.21 (brs, 1H, NH), 3.80 (s, 3H, OCH_3), 3.52 (s, 3H, CH_3), 2.42 (s, 3H, CH_3).

Antimicrobial Testing

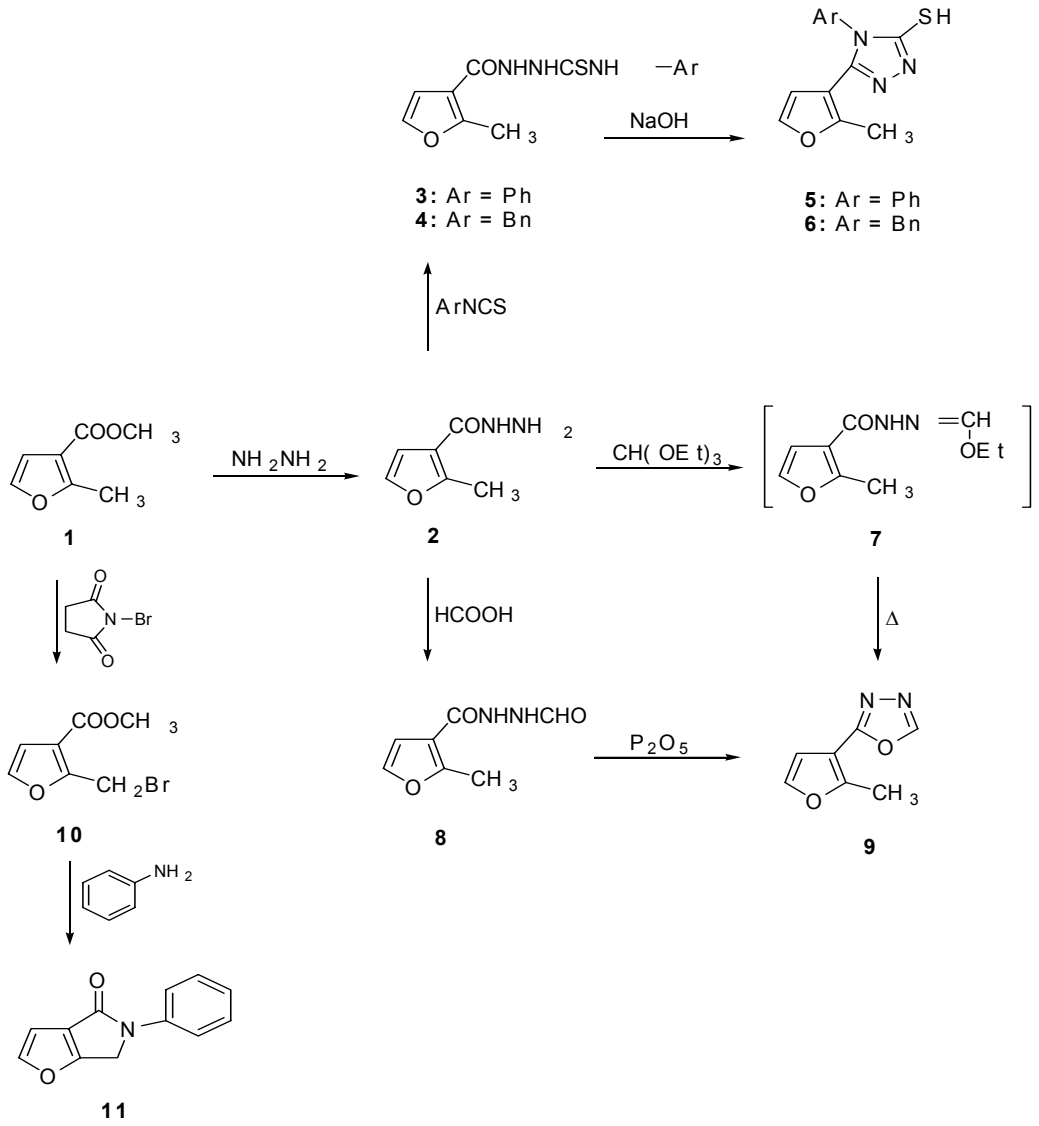
Nutrient agar plates were seeded using 0.1 ml of overnight cultures. Cylindrical plugs were removed from the agar plate using a sterile cork borer and 100 µl of the tested compounds (1 mg/ml DMSO) were added to the well in triplicates. Blank solvent was used as control. Plates inoculated with the microorganisms tested were incubated at 37°C, while those of fungi were incubated at 30°C. Results were taken after 24 h. of incubation and were recorded as average diameter of the inhibition zone in mm (17, 18).

Results and Discussion

A. Chemistry

The general procedures employed for the synthesis of the target compounds are outlined in Scheme 1–3. The starting material 2-methylfuran-3-carboxylic acid hydrazide **2** was prepared from the corresponding methyl ester **1** following reported procedure (16). Treatment of **2** with certain arylisothiocyanate in ethanol at room temperature yielded the corresponding 4-substituted thiosemicarbazide **3**, **4**. Several procedures were reported for the cyclization of substituted thiosemicarbazides to their 1,2,4-triazolethione analogs (19–21). Accordingly, heating of **3, 4** in an aqueous sodium hydroxide solution afforded the

Scheme 1.

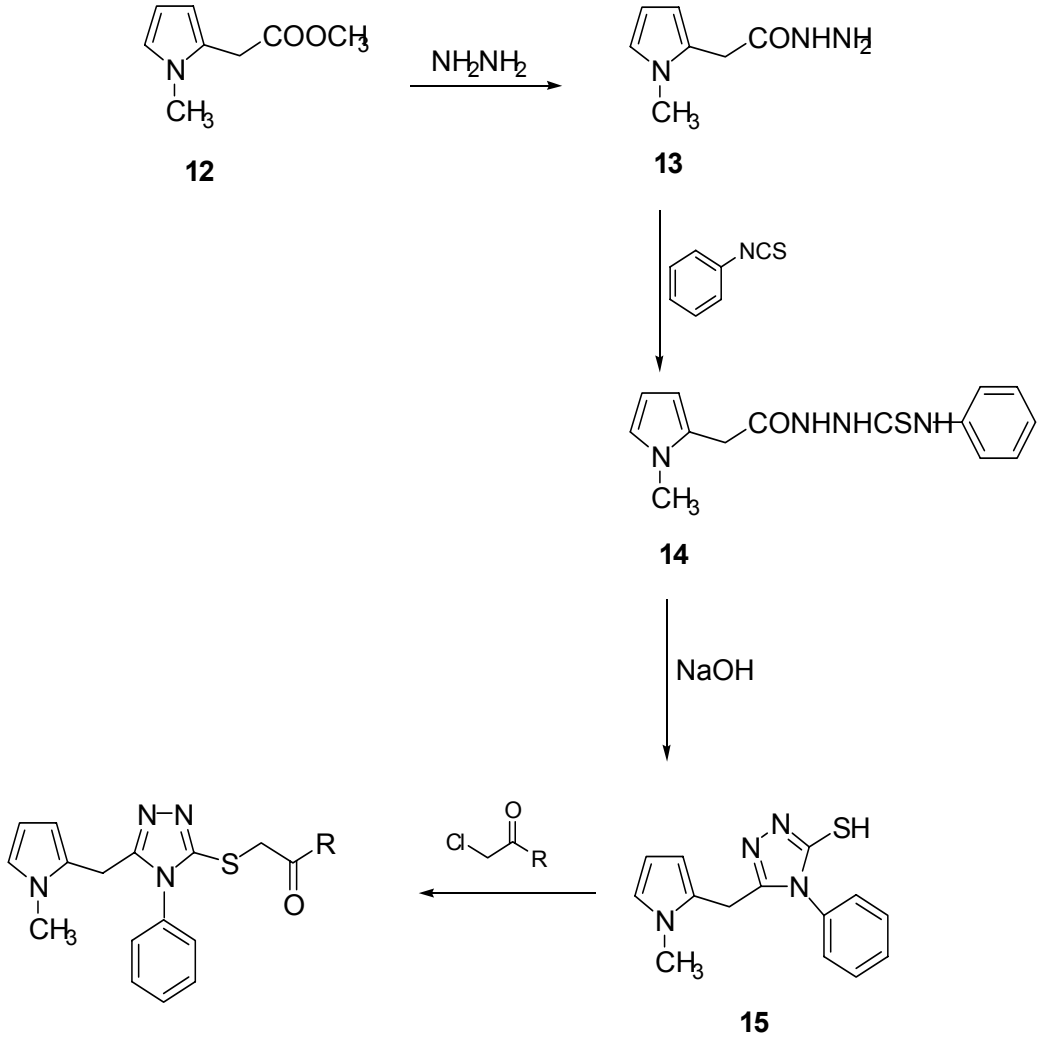


corresponding 3,4-disubstituted - 1,2,4- triazole -5-thiole derivatives **5** and **6** in 66%, 53%, yields respectively (Scheme 1).

The formation of the 1,3,4-oxadiazole derivative **9** was achieved by heating the hydrazide **2** with triethylorthoformate but the yield was relatively low (36%). This may be attributed to the slow cyclization of the intermediate **7**. Compound **9** was prepared in a better yield (52%) using an alternate route by heating the hydrazide **2** with formic acid to afford the N-formyl derivative **8** which was dehydrated by refluxing with phosphorous pentoxide in xylene to afford **9**.

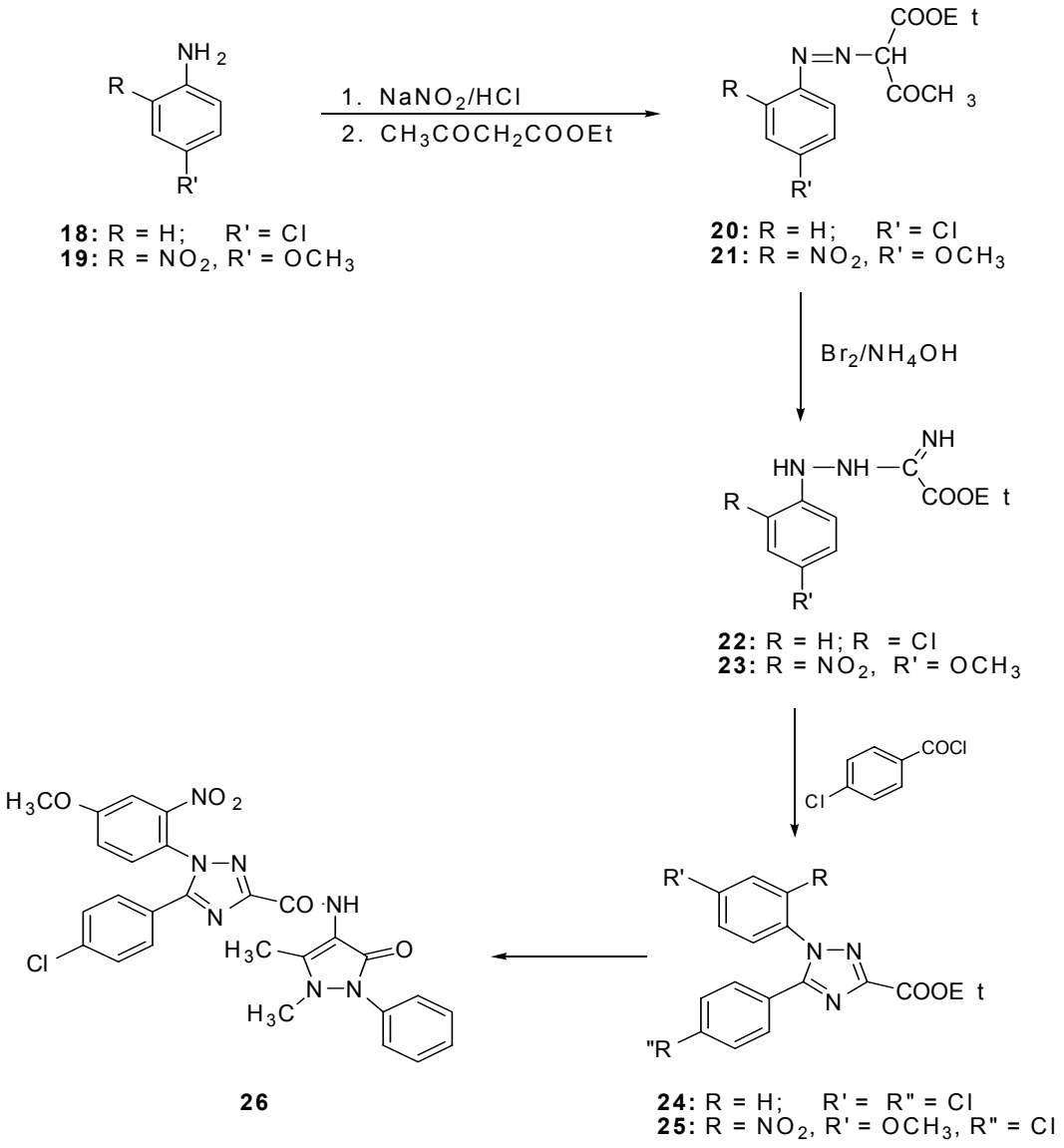
Moreover, bromination of **1** with N-bromosuccinimde in presence of benzoyl peroxide gave **10** as a reddish-brown oily residue. Ring closure of the crude methyl 2-bromomethylfuran-3-carboxylate **10** with aniline afforded the furopyrrolinone derivative **11** in moderate yield (Scheme 1).

Scheme 2.



The synthesis of the target triazole compounds **15, 16, 17** were depicted in Scheme 2. The key intermediate 1-methyl-2-pyrrolylmethyl-4-phenyl-thiosemicarbazide **14** was prepared from the corresponding hydrazide **13** based upon a sequence previously described (16) and outlined in (Scheme 2). Alkaline cyclization gave the triazolethiole **15** in good yield. The amides of triazolothioether derivatives could be prepared via condensation of their corresponding ester with the corresponding amines (22). In the present study, the desired triazolothioether derivatives **16**, **17** were prepared by allowing the mercaptotriazole **15** to react with the appropriate chloroacetamide derivative at room temperature in alkaline medium.

Scheme 3.



The starting materials ethyl 2-(4-methoxy-2-nitrophenylazo)-3-oxo-butyrate **20** and ethyl 2-(4-chlorophenylazo)-3-oxo-butyrate **21** were prepared adopting a method described for similar analogs (23) (Scheme 3). Treatment of **20, 21** with Br_2/HOAC in presence of sodium acetate followed by amination using 25% NH_4OH afforded the arylphenyl-hydrazino iminoacetate esters **22, 23**. Benzoyl chloride has been used for the cyclization of similar hydrazine iminoacetate esters (24) to give their corresponding 1,2,4-triazole analogs. Accordingly, refluxing **22**, **23** with 4-chlorobenzoylchloride in dioxane gave the desired 1,2,4-triazole derivatives **24**, **25** in moderate yield. Fungal infection is usually associated with pain and inflammation. Accordingly, to study the effectiveness of conjugating an anti-inflammatory drug with the tested compounds, hybridization of ethyl 1-(4-methoxy-2-nitrophenyl)-

5-(p-chlorophenyl)-1,2,4-triazole-3-carboxylate **25** with antipyrine moiety was achieved by heating with 4-aminoantipyrine in EtOH for 6 h. to afford **26** in moderate yield (52%).

Structural elucidation of the newly synthesized compounds was achieved based on elementary analysis, ^{1}H-NMR and IR spectra.

B. Antimicrobial Screening

Nine of the newly synthesized compounds were subjected to antimicrobial screening by the *in vitro* cup-plate technique (17, 18) using ampicillin, streptomycin and nystatin as positive controls. The compounds were tested for their activity against the Gram-negative bacteria *E. coli*, and the Gram-positive bacteria *S. aureus* and *B. subtilis*, in addition to pathogenic fungi *C. albicans* and *S. cerevisiae*. The obtained data revealed that none of the tested compounds showed significant activity towards Gram-negative and Gram-positive bacteria. Activity was noticed for compounds **17** and **24** towards the used fungi. While compounds **11**, **16** proved to be the most remarkably active of all the tested compounds towards *C. albicans* and *S. cerevisiae*. Results are shown in (Table 1).

Chart 2.

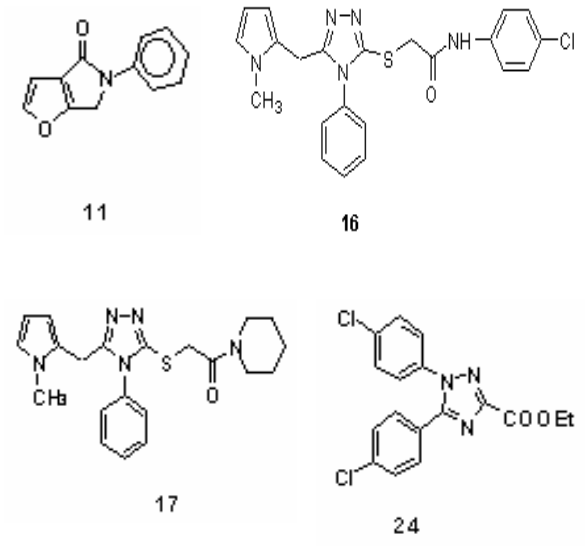


Table 1: Antimicrobial screening results of the tested compounds at 1 mg/ml concentration*.

Compound	*E. coli*	*S. aureus*	*B. subitilis*	*S. cerevisiae*	*C. albicans*
5	–	+	+	–	–
6	–	+	+	–	–
9	–	–	–	–	–
11	+	–	–	++	++
16	–	+	–	++	++
17	–	–	–	+	+
24	+	–	–	+	+
25	–	+	+	–	–
26	+	+	+	–	–
Ampicillin	+++	+++	+++	NT	NT
Streptomycin	+++	+++	+++	NT	NT
Nystatin	NT	NT	NT	+++	+++

-++ – Inactive (inhibition zone < 10 mm; +, moderate activity inhibition zone (10–15 mm); ++ active inhibition zone (15–20 mm); +++ remarkable activity (inhibition zone > 20 mm, NT = not tested.

A close examination of the structures of the active compounds revealed that, in case of 1,2,4-triazole analogs, the best activity were confined with compounds having a thioether moiety at position 3- as in compounds **16**, **17** (structural modified products of butoconazole (**A**, Chart 1). Moreover, halogenated aryl substituents at position 1- or 5- as in compound **24** showed better antifungal activity. Hybridization with the anti-inflammatory drug antipyrine in **26** did not enhance the activity. The structural modification done in chlormidazole (**C**, Chart 1), compound **11**, by replacing the phenyl ring with furan showed prominent antifungal activity.

In conclusion, the present study revealed that 4 of the designed compounds showed selective antifungal activity. The 1,2,4-triazole analogs having a thioether linkage at the position 3- or halogenated aryl substitution at positions 1-, 3- or 5-, in addition to the fused furo[2,3-*c*]pyrrolinone derivatives could be useful for future development through modification or derivatization to design more selective antifungal agents.

Acknowledgements

The author would like to express her special thanks to the Department of Microbiology, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt, for performing the antimicrobial testing of the synthesized compounds.

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