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Synthesis and antimicrobial activity of some new 3,4-disubstituted pyrroles and pyrazoles

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ABSTRACT

*Some new 3,4-disubstituted pyrroles and pyrazoles were prepared from the synthetic intermediate (E)-1-(4-(m-chlorobenzyloxy)-3-methoxyphenyl)-3-(4-aryl)prop-2-en-1-one on treatment with tosylmethyl isocyanide and diazomethane. All the target compounds were evaluated for antimicrobial activity. The chloro substituted pyrroles and pyrazoles (**5c**, **7c**) exhibited pronounced antimicrobial activity particularly against S. aureus and P. chrysogenum.*

Keywords : Activated olefin, pyrrole, pyrazole, cycloaddition, antimicrobial activity

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INTRODUCTION

Heterocycles are ubiquitous in natural products, pharmaceuticals and numerous functional molecules. Pyrroles and their derivatives are known to possess a wide range of biological activities such as antitumor, anti-inflammatory, antibacterial, antioxidant and antifungal [1−7]. There are several pyrrole containing drugs available in the market and some of them are atrovastatin (hyperlipidemic) [8], BM 212 (antifungal and antimycobacterial) [9], tallimustine (anticancer), pyrrolomycin B, pyoluteorin and pyrrolnitrin (antibiotics) [10]. Pyrazoles display a broad spectrum of biological activities *viz.*, cholesterol-lowering, anti-inflammatory, anticancer, antidepressant, antimicrobial [11, 12] and antipsychotic [13−15]. Besides, the pyrazoles are structural motifs in natural products (*S*)-pyrazolylalanine, pyrazomycin and synthetic compounds celecoxib, sildenafil, ionazolac, difenamizole, mepirizole etc. Hence the development of new, versatile and efficient synthetic methodologies to prepare pyrroles and pyrazoles is one of the major challenges in organic synthesis. In fact, the activated olefins are valuable intermediates in a variety of synthetic transformations and useful as building blocks in the development of bioactive heterocycles [16, 17]. Prompted by these observations and our continued interest towards the synthesis of a variety of bioactive heterocycles [18−21], herein we report the synthesis and antimicrobial activity of some new 3,4-disubstituted pyrroles and pyrazoles.

MATERIALS AND METHODS

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT−IR spectrometer as KBr pellets and the wave numbers are given in cm^{-1}. The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker-500 spectrometer operating at 500 MHz. The ^{13}C NMR spectra were

recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Jeol JMS–D 300 and Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer.

General procedure for the synthesis of 1-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-ethanone (3)

To a stirred suspension of potassium carbonate (1 mmol) in *N*,*N*-dimethylformamide (12 mL), a solution of 4-hydroxy-3-methoxyacetophenone (**1**) (2 mmol) in *N*,*N*-dimethylformamide (5 mL) was added dropwise and stirred at room temperature for 4−6 h. Then 1-chloro-3-chloromethylbenzene (**2**) (2.5 mmol) was added and further stirred for 30−40 min. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water followed by saturated sodium chloride solution, dried over anhydrous sodium sulphate and filtered. The resultant solid was purified by recrystallization from 2-propanol.

General procedure for the synthesis of (*E*)-1-(4-(*m*-chlorobenzyloxy)-3-methoxy-phenyl)-3-aryl-prop-2-en-1-ones (4a-d)

To a solution of 10% sodium hydroxide in methanol (30 mL), compound **3** (0.55 mmol) and appropriate araldehyde (0.5 mmol) were added at 0−10 ^{o}C and stirred at room temperature for 2−3 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent under reduced pressure yielded a crude product which was purified by column chromatography (silica gel, 60−120 mesh) using hexane-ethyl acetate (2.5:1) as eluent.

General procedure for the synthesis of (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl-1*H*-pyrrol-3-yl)methanones (5a-d)

An equimolar mixture (1 mmol) of compound **4a-d** and tosylmethyl isocyanide (TosMIC) in dimethyl sulfoxide (8 mL) and dry ether (16 mL) was added dropwise *via* a syringe to a stirred suspension of sodium hydride (50 mg) in dry ether (15 mL). The stirring was continued for 12−16 h. After completion of the reaction the contents were diluted with water. It was extracted with ether and dried (an. Na_2SO_4). Removal of the solvent *in vacuo* yielded a crude product which was purified by passing through a column of silica gel (60−120 mesh) using hexane-ethyl acetate (4:1) as eluent.

General procedure for the synthesis of (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)methanones (6a-d)

To a well cooled solution of compound **4a-d** (5 mmol) in dry ether (20 mL), an ethereal solution of diazomethane (40 mL, 0.4 M) and triethylamine (0.2 mL) were added. The reaction mixture was kept at −20 to −15 °C for 48−50 h. The solvent was removed on a rotary evaporator. The resultant solid was purified by column chromatography (silica gel, 60−120 mesh) using hexane-ethyl acetate, (3:1) as eluent.

General procedure for the synthesis of (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl-1*H*-pyrazol-3-yl)methanones (7a-d)

The compound **6a-d** (1 mmol), chloranil (1.4 mmol) and xylene (10 mL) were refluxed for 21−23 h. Then it was treated with 5% sodium hydroxide solution. The organic layer was separated and repeatedly washed with water and dried. The solvent was removed under vacuum. The solid obtained was purified by recrystallization from 2-propanol.

Spectral Data

1-(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)ethanone (**3**)

Yield 76%. mp: 121−123 ^{o}C. IR (cm^{-1}): 1652 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.53 (s, 3H, CO-CH_3), 3.84 (s, 3H, -OCH_3), 5.22 (s, 2H, -OCH_2), 7.13-7.62 (m, 7H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 27.2, 53.4, 62.9, 125.7, 126.6, 127.4, 129.5, 131.5, 132.7, 133.8, 138.2, 140.5, 141.1, 143.1, 146.2, 185.7. MS: 290.74 [$M^{+\cdot}$]. Anal. Calcd for $C_{16}H_{15}ClO_3$: C, 66.10; H, 5.20. Found C, 66.22; H, 5.24.

(*E*)-1-(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-3-(*p*-methylsulfonylphenyl)prop-2-en-1-one (4a)

Yield 85%. mp: 179−180 ^{o}C. IR (cm^{-1}): 1660 (C=O), 1621 (C=C), 1327, 1151 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 3.31 (s, 3H, SO_2CH_3), 3.92 (s, 3H, -OCH_3), 5.28 (s, 2H, -OCH_2), 7.22 (d, 1H, H_B, J = 18.2 Hz), 7.24-8.17 (m, 12H, Ar-H

& H_A). ^{13}C NMR (DMSO-d_6) δ: 42.5, 525.9, 63.2, 123.1, 134.9, 123.8, 125.1, 125.9, 126.5, 129.0, 129.9, 131.5, 133.4, 134.2, 135.0, 136.8, 138.2, 140.6, 145.8, 148.7, 149.9, 166.5. MS: 456.93 [$M^{+\cdot}$]. Anal. Calcd for $C_{24}H_{21}ClO_5S$: C, 63.08; H, 4.63. Found C, 63.02; H, 4.61.

(*E*)-3-(*p*-Bromophenyl)-1-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)prop-2-en-1-one (4b)
Yield 71%. mp: 182−184 ^{o}C. IR (cm^{-1}): 1658 (C=O), 1619 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.89 (s, 3H, -OCH_3), 5.26 (s, 2H, -OCH_2), 7.20 (d, 1H, H_B, J = 18.0 Hz), 7.42-8.02 (m, 12H, Ar-H & H_A). ^{13}C NMR (DMSO-d_6) δ: 55.4, 62.8, 108.5, 113.3, 118.5, 122.9, 126.1, 126.5, 127.2, 127.7, 128.8, 130.3, 131.1, 134.5, 139.6, 142.6, 147.8, 148.7, 149.0, 152.0, 166.0. MS: 457.74 [$M^{+\cdot}$]. Anal. Calcd for $C_{23}H_{18}BrClO_3$: C, 60.35; H, 3.96. Found C, 60.46; H, 3.99.

(*E*)-1-(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-3-(*p*-trifluoromethylphenyl)-prop-2-en-1-one (4c)
Yield 69%. mp: 170−172 ^{o}C. IR (cm^{-1}): 1664 (C=O), 1625 (C=C); ^{1}H NMR (DMSO-d_6) δ: 3.96 (s, 3H, -OCH_3), 5.30 (s, 2H, -OCH_2), 7.24 (d, 1H, H_B, J = 18.3 Hz), 7.30-8.12 (m, 12H, Ar-H & H_A). ^{13}C NMR (DMSO-d_6) δ: 56.2, 63.5, 123.4, 126.1, 127.2, 127.7, 128.8, 129.2, 129.9, 130.3, 131.1, 133.0, 135.2, 135.9, 139.6, 140.5, 142.6, 147.8, 148.7, 149.0, 150.1, 167.1. MS: 446.84 [$M^{+\cdot}$]. Anal. Calcd for $C_{24}H_{18}ClF_3O_3$: C, 64.51; H, 4.06. Found C, 64.60; H, 4.08.

(*E*)-1-(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-3-(*p*-trifluoromethoxyphenyl)-prop-2-en-1-one (4d)
Yield 73%. mp: 192−194 ^{o}C. IR (cm^{-1}): 1651 (C=O), 1610 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.85 (s, 3H, -OCH_3), 5.24 (s, 2H, -OCH_2), 7.19 (d, 1H, H_B, J = 17.8 Hz), 7.11-7.98 (m, 12H, Ar-H & H_A). ^{13}C NMR (DMSO-d_6) δ: 55.1, 62.4, 122.6, 125.2, 126.5, 127.4, 128.5, 129.2, 130.9, 131.3, 131.8, 132.0, 134.2, 136.4, 140.6, 141.5, 146.5, 148.8, 148.9, 149.8, 154.0, 165.7. MS: 462.84 [$M^{+\cdot}$]. Anal. Calcd for $C_{24}H_{18}ClF_3O_4$: C, 62.28; H, 3.92. Found C, 62.35; H, 3.91.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-methylsulfonylphenyl)-1*H*-pyrrol-3-yl)methanone (5a)
Yield 75%. mp: 196−198 ^{o}C. IR (cm^{-1}): 3272 (NH), 1667 (C=O), 1627 (C=C), 1358, 1168 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 3.20 (s, 3H, SO_2CH_3), 3.81 (s, 3H, -OCH_3), 5.14 (s, 2H, -OCH_2), 6.76 (s, 1H, C_5-H), 7.09-7.92 (m, 12H, C_2-H & Ar-H), 8.80 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 43.5, 55.4, 68.9, 108.5, 113.3, 117.5, 118.6, 120.2, 121.2, 126.1, 126.2, 126.6, 127.2, 127.3, 127.7, 127.9, 129.7, 130.3, 133.0, 135.8, 139.6, 141.7, 147.8, 148.7, 149.0, 171.1. MS: 495.09 [$M^{+\cdot}$]. Anal. Calcd for $C_{26}H_{22}ClNO_5S$: C, 62.96; H, 4.47; N, 2.82. Found C, 63.05; H, 4.50; N, 3.00.

(4-(*p*-Bromophenyl)-1*H*-pyrrol-3-yl)-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-methanone (5b)
Yield 72%. mp: 200−202 ^{o}C. IR (cm^{-1}): 3270 (NH), 1662 (C=O), 1613 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.79 (s, 3H, -OCH_3), 5.11 (s, 2H, -OCH_2), 6.73 (s, 1H, C_5-H), 7.11-7.88 (m, 12H, C_2-H & Ar-H), 8.78 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 55.2, 68.4, 108.1, 113.1, 117.0, 118.4, 122.7, 124.7, 126.8, 128.2, 129.4, 131.5, 133.7, 134.9, 136.5, 139.3, 140.4, 142.8, 144.7, 146.4, 147.6, 149.8, 170.5. MS: 495.02 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{19}BrClNO_3$: C, 60.44; H, 3.85; N, 2.82. Found C, 60.51; H, 3.86; N, 2.94.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethylphenyl)-1*H*-pyrrol-3-yl)methanone (5c)
Yield 78%. mp: 193−195 ^{o}C. IR (cm^{-1}): 3285 (NH), 1675 (C=O), 1629 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.85 (s, 3H, -OCH_3), 5.15 (s, 2H, -OCH_2), 6.79 (s, 1H, C_5-H), 7.09-8.06 (m, 12H, C_2-H & Ar-H), 8.84 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 55.6, 69.3, 108.9, 113.5, 117.8, 119.3, 120.6, 130.4, 131.7, 133.3, 134.4, 136.7, 138.8, 139.4, 140.8, 141.3, 142.8, 144.5, 145.9, 146.6, 148.4, 150.4, 151.9, 171.2. MS: 485.10 [$M^{+\cdot}$]. Anal. Calcd for $C_{26}H_{19}ClF_3NO_3$: C, 64.27; H, 3.94; N, 2.88. Found C, 64.37; H, 3.98; N, 3.05.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethoxyphenyl)-1*H*-pyrrol-3-yl)methanone (5d)
Yield 70%. mp: 210−212 ^{o}C. IR (cm^{-1}): 3268 (NH), 1660 (C=O), 1608 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.76 (s, 3H, -OCH_3), 5.10 (s, 2H, -OCH_2), 6.69 (s, 1H, C_5-H), 7.05-7.72 (m, 12H, C_2-H & Ar-H), 8.76 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 55.0, 67.9, 107.7, 112.6, 116.6, 116.8, 118.3, 125.8, 126.6, 128.4, 130.8, 132.4, 135.4, 136.5, 137.7, 139.5, 141.3, 143.3, 144.8, 146.4, 149.0, 149.5, 151.6, 152.8, 153.8, 169.7. MS: 501.10 [$M^{+\cdot}$]. Anal. Calcd for $C_{26}H_{19}ClF_3NO_4$: C, 62.22; H, 3.82; N, 2.79. Found C, 62.30; H, 3.81; N, 2.93.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-methylsulfonylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl) methanone (6a)
Yield 77%. mp: 206−208 °C. IR (cm^{-1}): 3347 (NH), 1661 (C=O), 1578 (C=N), 1345, 1163 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 3.68 (s, 3H, SO_2CH_3), 3.62 (dd, 1H, H_X, J_{AX} = 5.1 Hz, J_{MX} = 10.4 Hz), 3.78 (s, 3H, -OCH_3), 4.21 (dd, 1H, H_M, J_{AM} = 11.9 Hz), 4.58 (dd, 1H, H_A), 5.20 (s, 2H, -OCH_2), 7.15-7.73 (m, 11H, Ar-H), 10.06 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 43.4, 42.8, 55.2, 56.0, 68.6, 108.2, 118.1, 126.5, 126.8, 127.2, 127.4, 127.5, 131.3, 132.7, 134.5, 135.0, 138.4, 139.2, 144.8, 147.3, 148.7, 149.6, 168.1. MS: 498.10 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{23}ClN_2O_5S$: C, 60.18; H, 4.65; N, 5.61. Found C, 60.31; H, 4.70; N, 5.81.

(4-(*p*-Bromophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)methanone (6b)
Yield 80%. mp: 209−211 °C. IR (cm^{-1}): 3344 (NH), 1658 (C=O), 1574 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.59 (dd, 1H, H_X, J_{AX} = 5.0 Hz, J_{MX} = 10.3 Hz), 3.74 (s, 3H, -OCH_3), 4.18 (dd, 1H, H_M, J_{AM} = 11.7 Hz), 4.55 (dd, 1H, H_A), 5.18 (s, 2H, -OCH_2), 7.10-7.64 (m, 11H, Ar-H), 10.05 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 42.7, 55.0, 55.9, 68.2, 113.5, 118.2, 118.9, 126.5, 127.1, 127.7, 128.9, 130.5, 131.4, 133.5, 135.1, 136.9, 139.6, 143.6, 147.1, 147.8, 149.0, 167.9. MS: 498.03 [$M^{+\cdot}$]. Anal. Calcd for $C_{24}H_{20}BrClN_2O_3$: C, 57.68; H, 4.03; N, 5.61. Found C, 57.78; H, 4.05; N, 5.77.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl) methanone (6c)
Yield 82%. mp: 199−201 °C. IR (cm^{-1}): 3350 (NH), 1664 (C=O), 1585 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.64 (dd, 1H, H_X, J_{AX} = 5.2 Hz, J_{MX} = 10.6 Hz), 3.81 (s, 3H, -OCH_3), 4.24 (dd, 1H, H_M, J_{AM} = 12.0 Hz), 4.62 (dd, 1H, H_A), 5.25 (s, 2H, -OCH_2), 7.21-7.87 (m, 11H, Ar-H), 10.10 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 43.4, 55.4, 56.2, 68.9, 113.3, 118.5, 122.4, 122.8, 126.1, 126.5, 126.7, 126.9, 127.2, 127.7, 130.3, 133.0, 137.1, 137.5, 139.6, 144.0, 147.7, 148.6, 168.2. MS: 488.11 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{20}ClF_3N_2O_3$: C, 61.42; H, 4.12; N, 5.73. Found C, 61.50; H, 4.13; N, 5.87.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl) methanone (6d)
Yield 79%. mp: 215−217 °C. IR (cm^{-1}): 3330 (NH), 1653 (C=O), 1572 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.54 (dd, 1H, H_X, J_{AX} = 4.9 Hz, J_{MX} = 10.1 Hz), 3.71 (s, 3H, -OCH_3), 4.15 (dd, 1H, H_M, J_{AM} = 11.5 Hz), 4.53 (dd, 1H, H_A), 5.11 (s, 2H, -OCH_2), 7.01-7.52 (m, 11H, Ar-H), 10.02 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 42.4, 54.7, 55.5, 68.0, 108.8, 113.5, 118.7, 120.5, 120.9, 125.1, 127.4, 128.4, 130.1, 132.1, 133.0, 135.6, 139.5, 142.4, 146.7, 147.5, 148.7, 149.1, 167.4. MS: 504.11 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{20}ClF_3N_2O_4$: C, 59.47; H, 3.99; N, 5.55. Found C, 59.58; H, 3.97; N, 5.70.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-methylsulfonylphenyl)-1*H*-pyrazol-3-yl)methanone (7a)
Yield 81%. mp: 201−203 °C. IR (cm^{-1}): 3311 (NH), 1679 (C=O), 1626 (C=C), 1582 (C=N), 1349, 1167 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 2.71 (s, 3H, SO_2CH_3), 3.85 (s, 3H, -OCH_3), 5.18 (s, 2H, -OCH_2), 6.65 (bs, 1H, NH), 7.05-7.97 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 44.5, 55.9, 69.4, 114.2, 115.6, 123.8, 125.1, 125.8, 126.5, 127.9, 128.7, 129.2, 129.9, 130.8, 133.5, 134.7, 135.4, 138.5, 141.4, 142.6, 149.2, 153.7, 170.2. MS: 496.96 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{21}ClN_2O_5S$: C, 60.42; H, 4.26; N, 5.64. Found C, 60.55; H, 4.29; N, 5.85.

(4-(*p*-Bromophenyl)-1*H*-pyrazol-3-yl)-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-methanone (7b)
Yield 83%. mp: 207−209 °C. IR (cm^{-1}): 3306 (NH), 1674 (C=O), 1618 (C=C), 1580 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H, -OCH_3), 5.15 (s, 2H, -OCH_2), 6.60 (bs, 1H, NH), 6.98-7.91 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 55.4, 68.9, 110.9, 113.3, 118.7, 120.9, 122.7, 123.9, 125.5, 126.3, 127.3, 127.7, 127.9, 130.3, 133.2, 135.0, 147.9, 149.1, 154.2, 158.3, 163.5, 169.8. MS: 497.77 [$M^{+\cdot}$]. Anal. Calcd for $C_{24}H_{18}BrClN_2O_3$: C, 57.91; H, 3.64; N, 5.99. Found C, 57.62; H, 3.65; N, 5.81.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethylphenyl)-1*H*-pyrazol-3-yl)methanone (7c)
Yield 85%. mp: 198−200 °C. IR (cm^{-1}): 3315 (NH), 1685 (C=O), 1629 (C=C), 1588 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.89 (s, 3H, -OCH_3), 5.21 (s, 2H, -OCH_2), 6.68 (bs, 1H, NH), 7.11-8.05 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 56.2, 69.7, 113.7, 115.2, 123.5, 123.9, 125.4, 126.0, 126.2, 126.9, 127.5, 128.6, 129.1, 130.8, 131.7, 133.8, 134.2, 135.7, 139.7, 142.5, 149.9, 153.4, 170.6. MS: 486.87 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{18}ClF_3N_2O_3$: C, 61.67; H, 3.73; N, 5.75. Found C, 61.79; H, 3.75; N, 5.95.

(4-(*m*-Chlorobenzyloxy)-3-methoxyphenyl)-(4-(*p*-trifluoromethoxyphenyl)-1*H*-pyrazol-3-yl)methanone (7d)
Yield 76%. mp: 215−217 ^{o}C. IR (cm^{-1}): 3301 (NH), 1669 (C=O), 1613 (C=C), 1575 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, 3H, -OCH_3), 5.11 (s, 2H, -OCH_2), 6.57 (bs, 1H, NH), 6.90-7.82 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 55.1, 68.8, 113.2, 114.5, 115.6, 121.7, 123.8, 125.1, 125.4, 126.7, 127.4, 127.9, 128.3, 129.0, 130.5, 132.7, 134.6, 134.9, 142.3, 149.6, 153.8, 160.5, 169.4. MS: 502.87 [$M^{+\cdot}$]. Anal. Calcd for $C_{25}H_{18}ClF_3N_2O_4$: C, 59.71; H, 3.61; N, 5.57. Found C, 59.81; H, 3.60; N, 5.72.

Pharmacology
Antimicrobial activity
The compounds **4(a-d)−7(a-d)** were assayed for antimicrobial activity at three different concentrations (25, 50 and 100 µg/mL). The microorganisms utilized for antimicrobial study are *Staphylococcus aureus*, *Bacillus subtilis*, (Gram-positive) and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (Gram-negative) and for antifungal activity are *Aspergillus niger* and *Penicillium chrysogenum*. Chloramphenicol and Ketoconazole are used as standard drugs for antibacterial and antifungal studies, respectively. The *in vitro* antimicrobial activity was performed by agar well diffusion method against test organisms [22, 23]. Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 µL) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petriplate. Three concentrations of DMSO dissolved compounds (25, 50, 100 µg/mL) were added into the wells by using sterile pipettes. Simultaneously the standard antibiotics, *Chloramphenicol* for antibacterial activity and *Ketoconazole* for antifungal activity (as positive control) were tested against the pathogens. The samples were dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37 ^{o}C for 24 h for bacteria and at 28 ^{o}C for 48 h for fungi. After appropriate incubation the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antimicrobial activity.

Minimum Inhibitory Concentration
Broth dilution test is used to determine Minimum Inhibitory Concentration (MIC) of the test samples [24, 25]. Freshly prepared nutrient broth was used as diluents. The 24 h old culture of the test bacteria and the test fungi were diluted 100 folds in nutrient broth (100 µL bacterial cultures in 10 mL NB). The stock solution of the synthesized compounds was prepared in DMSO by dissolving 5 mg of the compound in 1 mL of DMSO. Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 mL of stock solution contains 6.25, 12.5, 25, 50, 100, 200 mg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 ^{o}C for 24 h for bacteria and at 28 ^{o}C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. Control without test samples and with solvent was assayed simultaneously. The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC. To determine the Minimum Bactericidal Concentration (MBC) [26] and Minimum Fungicidal Concentration (MFC) [27] for each set of test tubes in the MIC determination a loopful of broth was collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi were incubated at 37 ^{o}C for 24 h and at 28 ^{o}C for 48 h respectively. After incubation the lowest concentration that kills the tested organisms was noted as MBC (for bacteria) or MFC (for fungi).

The results pertaining to the antimicrobial study presented in **Tables 1** & **2** and **Figs. 1 & 2** revealed that Gram-positive bacteria were more susceptible towards the tested compounds than Gram-negative bacteria. The 3,4-disubstituted pyrazoles (**7a-d**) exhibited slightly higher antibacterial activity than 3,4-disubstituted pyrroles (**5a-d**). Amongst the tested compounds **5c** and **7c** displayed higher inhibitory activity particularly against *S. aureus* when compared with the standard drug Chloramphenicol. On the other hand, the compounds **5a** and **7a** showed antibacterial activity almost equal to the standard drug particularly against *S. aureus*. All the tested compounds inhibited the spore germination against tested fungi. In fact, all the compounds exhibited slightly higher antifungal activity towards *P. chrysogenum* than *A. niger*. The compounds **5c** and **7c** showed greater antifungal activity particularly against *P. chrysogenum* when compared to the standard drug Ketoconazole.

The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) values of the compounds tested are listed in **Table 3**. MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism (But it is not sure that the microorganisms are completely killed). The MBC/MFC is the lowest concentration of antibiotic required to kill a particular bacterium/fungi. The MBC/MFC involves an additional set of steps performed once the minimum inhibitory concentration (MIC) is determined. The antimicrobials are usually regarded as bactericidal/fungicidal if the

MBC/MFC is not greater than four times the MIC [28]. It was observed in compounds **5c** and **7c**, the MBC value is 2 x MIC in case of *S. aureus* and the MFC value is 2 x MIC in case of *P. chrysogenum.*

The structure-activity relationship of the test compounds indicated that aromatized heterocycles-pyrroles and pyrazoles (**5a-d**, **7a-d**) displayed excellent activity. However, the dihydro derivatives (**6a-d**) exhibited moderate activity whereas activated olefinic compounds showed low activity. The compounds **5c** and **7c** are the potential antimicrobial agents against *S. aureus* and *P. Chrysogenum*. Further, it was observed that compounds having higher electron withdrawing groups displayed greater antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

The synthetic route that leads to the synthesis of the title compounds is depicted in Scheme 1. The starting compound 1-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)ethanone (**3**) was obtained by the treatment of 4-hydroxy-3-methoxyacetophenone (**1**) with 1-chloro-3-chloromethylbenzene (**2**) in the presence of potassium carbonate in dimethylformamide. The ^{1}H NMR spectrum of **3** displayed three singlets at δ 2.53 (CO-CH_3), 3.84 (-OCH_3) and 5.22 ppm (-OCH_2) apart from aromatic signals. The synthetic intermediate (*E*)-1-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-3-(4-aryl)prop-2-en-1-one (**4a-d**) was prepared by Claisen-Schmidt reaction of compound **3** with araldehyde in the presence of sodium hydroxide in methanol. The ^{1}H NMR spectrum of compound **4a** exhibited a doublet at δ 7.22 ppm due to olefin proton H_B. Another doublet due to other olefin proton H_A adjacent to aryl group observed at much downfield region and merged with aromatic protons. The coupling constant J_{AB} = 18.2 Hz indicated that they possess *trans* geometry. Besides, compound **4a** also showed three singlets due to methyl, methoxy and methylene protons, respectively. 1,3-Dipolar cycloaddition of dipolar reagents to dipolarophiles is one of the facile techniques for the synthesis of five membered heterocycles. The olefin moiety present in **4a-d** was exploited to build pyrrole and pyrazole rings. Thus, the treatment of **4a-d** with tosylmethyl isocyanide (TosMIC) in the presence of sodium hydride in a solvent mixture (2:1) of ether and dimethyl sulfoxide gave (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl)-1*H*-pyrrol-3-yl)methanone (**5a-d**). The ^{1}H NMR spectrum of **5a** displayed a singlet at δ 6.76 ppm due to C_5-H of pyrrole ring, whereas the other singlet due to C_2-H appeared at downfield region and merged with aromatic protons. In addition, a broad singlet was present at δ 8.80 ppm due to NH which disappeared on deuteration. Moreover, **5a** exhibited three singlets at δ 3.20 (SO_2CH_3), 3.81 (-OCH_3) and 5.14 ppm (-OCH_2). On the other hand, the cycloaddition of diazomethane to compound **4a-d** in the presence of triethylamine in ether at −20 to −15 ^{o}C for 48−50 h produced (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl)-4,5-dihydro-1*H*-pyrazol-3-yl)methanone (**6a-d**). In the ^{1}H NMR spectrum of **6a**, an AMX splitting pattern was observed due to methylene and methine protons of pyrazoline ring. The three double doublets present at δ 3.62, 4.21 and 4.58 ppm were assigned to H_X, H_M and H_A, respectively. The coupling constant values J_{AX} = 5.1, J_{MX} = 10.4 and J_{AM} = 11.9 Hz indicated that H_A, H_M are *cis*, H_A, H_X are *trans* while H_M, H_X are *geminal*. Apart from this, a broad singlet was observed at δ 10.06 ppm due to NH which disappeared when D_2O was added. Moreover, **6a** displayed three singlets at δ 3.68, 3.78 and 5.20 ppm due to SO_2CH_3, -OCH_3 and -OCH_2, respectively. The oxidation of compound **6a-d** with chloranil in xylene led to (4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-(4-aryl)-1*H*-pyrazol-3-yl)methanone (**7a-d**). The absence of an AMX splitting pattern due to pyrazoline ring protons in **7a-d** confirmed its formation. The structures of all the new compounds were further confirmed by IR, ^{13}C NMR, mass spectra and elemental analyses.

Table 1. The *in vitro* antibacterial activity of compounds 4(a-d)-7(a-d)

Compound	Zone of inhibition (mm)											
	Gram-positive bacteria						Gram-negative bacteria					
	S. aureus			*B. subtilis*			*P. aeruginosa*			*K. pneumoniae*		
	25 µg/ mL	50 µg/ mL	100 µg/ mL	25 µg/ mL	50 µg/ mL	100 µg/ mL	25 µg/ mL	50 µg/ mL	100 µg/ mL	25 µg/ mL	50 µg/ mL	100 µg/ mL
4a	-	11±2	14±1	-	9±3	13±2	-	-	11±2	-	-	10±2
4b	-	10±2	12±2	-	-	11±1	-	-	10±2	-	-	9±3
4c	-	12±1	15±2	-	10±2	14±1	-	-	12±1	-	-	11±2
4d	-	8±1	11±3	-	-	10±3	-	-	9±1	-	-	8±2
5a	29±3	33±1	35±2	24±2	27±1	30±2	17±1	19±2	21±3	12±2	14±2	16±3
5b	27±2	30±2	32±3	23±1	25±2	29±1	15±1	17±3	20±2	11±1	12±1	15±1
5c	32±2	34±3	37±2	28±3	30±2	32±1	19±2	21±1	24±2	13±2	15±1	17±2
5d	24±1	26±2	30±1	22±2	24±3	27±3	13±2	15±2	18±3	9±1	11±2	13±2
6a	20±3	23±3	25±3	17±3	22±2	24±2	12±2	14±2	16±3	-	12±1	14±3
6b	18±1	21±2	23±2	16±2	19±3	22±1	11±1	13±2	15±2	-	11±2	13±1
6c	23±2	25±1	28±3	21±1	23±2	25±1	13±1	15±2	17±3	-	13±2	15±3
6d	16±3	19±2	21±3	14±2	17±1	20±2	10±1	12±2	14±2	-	10±2	12±3
7a	30±2	33±1	35±2	27±1	30±2	32±1	18±2	20±2	22±3	13±2	16±1	19±2
7b	28±1	31±2	33±1	26±2	29±3	31±2	16±2	18±3	20±3	12±1	15±2	17±1
7c	34±1	36±2	38±3	29±2	31±3	34±2	20±1	22±2	25±3	14±2	17±3	20±2
7d	26±2	29±1	32±2	25±1	27±1	29±3	14±2	16±3	19±2	10±1	12±2	14±1
Chloramp-henicol	30±2	33±1	35±2	32±1	34±3	38±1	25±2	27±3	30±2	38±2	40±3	42±3
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-

(-) No activity; (±) Standard deviation.

Table 2. The *in vitro* antifungal activity of compounds 4(a-d)-7(a-d)

Compound	Zone of inhibition (mm)					
	A. niger			*P. chrysogenum*		
	25 µg/ mL	50 µg/ mL	100 µg/ mL	25 µg/ mL	50 µg/ mL	100 µg/ mL
4a	9±3	10±3	11±2	11±3	14±2	17±2
4b	8±2	9±2	10±3	10±2	12±1	15±3
4c	10±2	11±2	12±1	12±3	16±2	19±1
4d	7±3	8±1	9±2	10±1	11±3	14±2
5a	25±2	27±3	29±1	32±1	35±1	38±2
5b	22±1	25±2	27±2	27±2	30±2	33±2
5c	29±1	31±2	34±3	36±1	38±2	40±3
5d	19±2	21±3	24±2	25±3	27±2	31±2
6a	17±1	19±1	21±2	22±2	24±3	28±3
6b	15±1	17±2	20±1	20±1	23±1	26±2
6c	18±2	20±1	22±3	24±1	26±3	29±3
6d	14±3	16±2	19±2	18±1	20±2	23±1
7a	27±1	29±2	31±3	33±2	35±3	38±2
7b	24±2	26±3	28±1	30±3	32±2	34±3
7c	31±1	34±2	36±1	38±2	40±2	42±3
7d	20±3	22±2	25±3	28±1	30±2	32±1
Ketoconazole	31±1	33±3	36±2	34±1	36±2	38±3
Control (DMSO)	-	-	-	-	-	-

(-) No activity; ±Standard deviation

Table 3. MIC, MBC and MFC of compounds 5c and 7c

Compound	Minimum inhibitory concentration					
	MIC (MBC / MFC) µg/ mL					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*P. chrysogenum*
5c	12.5 (25)	50 (>100)	50 (>200)	100 (>200)	50 (>100)	25 (50)
7c	6.25 (12.5)	25 (100)	50 (>100)	100 (>200)	25 (100)	12.5 (25)
Chloramphenicol	6.25	6.25	6.25	12.5	-	-
Ketoconazole	-	-	-	-	6.25	12.5

Fig. 1. The *in vitro* antibacterial activity of compounds 4(a-d)-7(a-d)

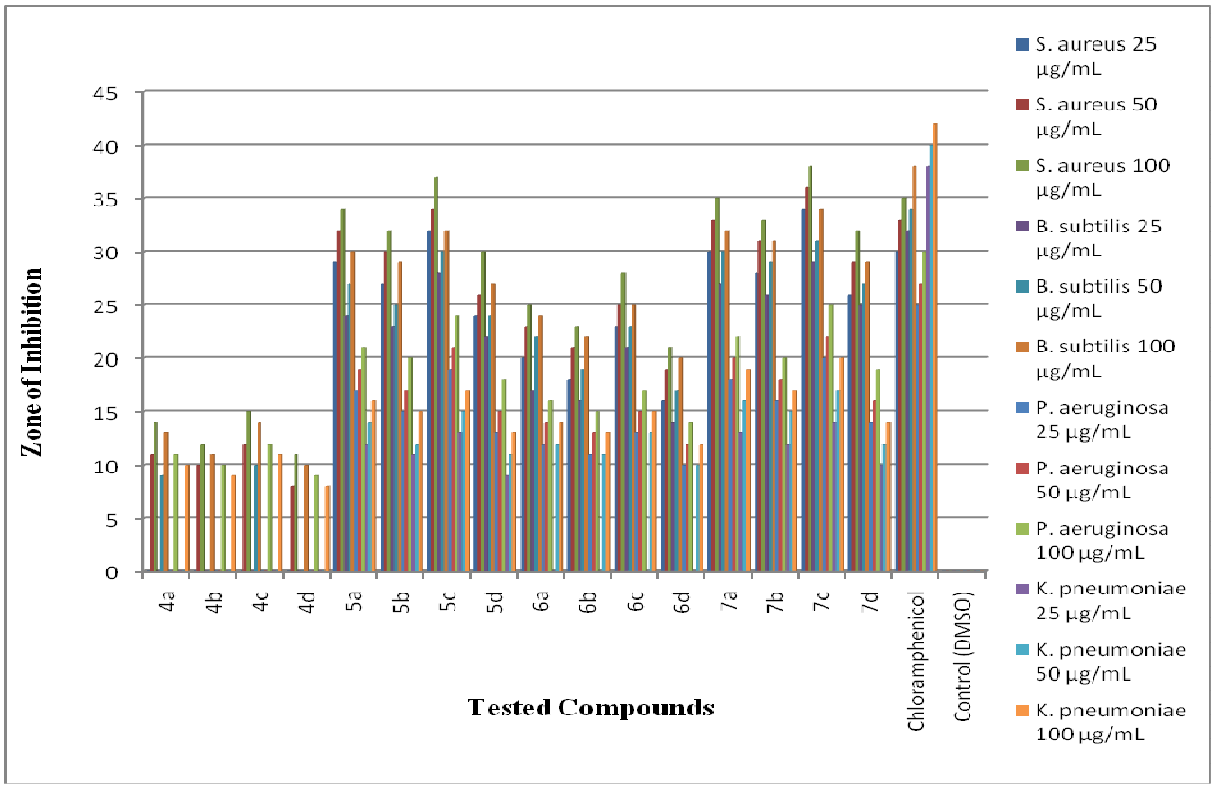
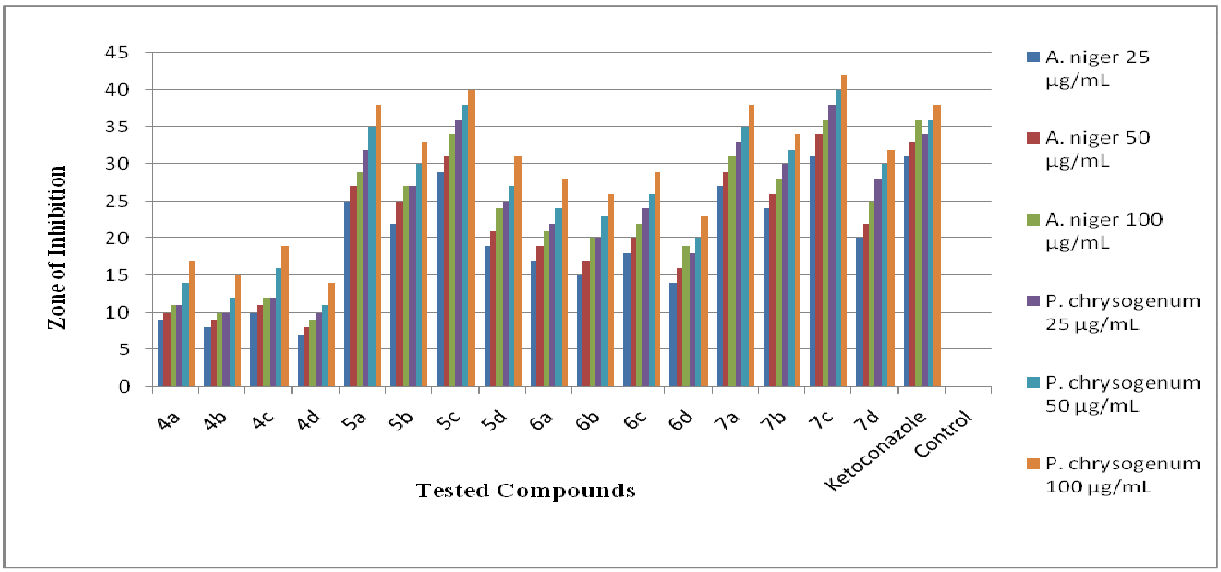


Fig. 2. The *in vitro* antifungal activity of compounds 4(a-d)-7(a-d)



CONCLUSION

In conclusion, some new 3,4-disubstituted pyrroles and pyrazoles were prepared from the synthetic intermediate (*E*)-1-(4-(*m*-chlorobenzyloxy)-3-methoxyphenyl)-3-(4-aryl)prop-2-en-1-one on treatment with tosylmethyl isocyanide and diazomethane. All the target compounds were evaluated for antimicrobial activity. The chloro substituted pyrroles and pyrazoles (**5c**, **7c)** displayed pronounced antimicrobial activity particularly against *S. aureus* and *P.*

chrysogenum. The compounds having pyrrole and pyrazole moieties exhibited significant antimicrobial activity when compared with the other tested compounds. Further, it was observed that compounds having higher electron withdrawing groups showed greater antimicrobial activity.

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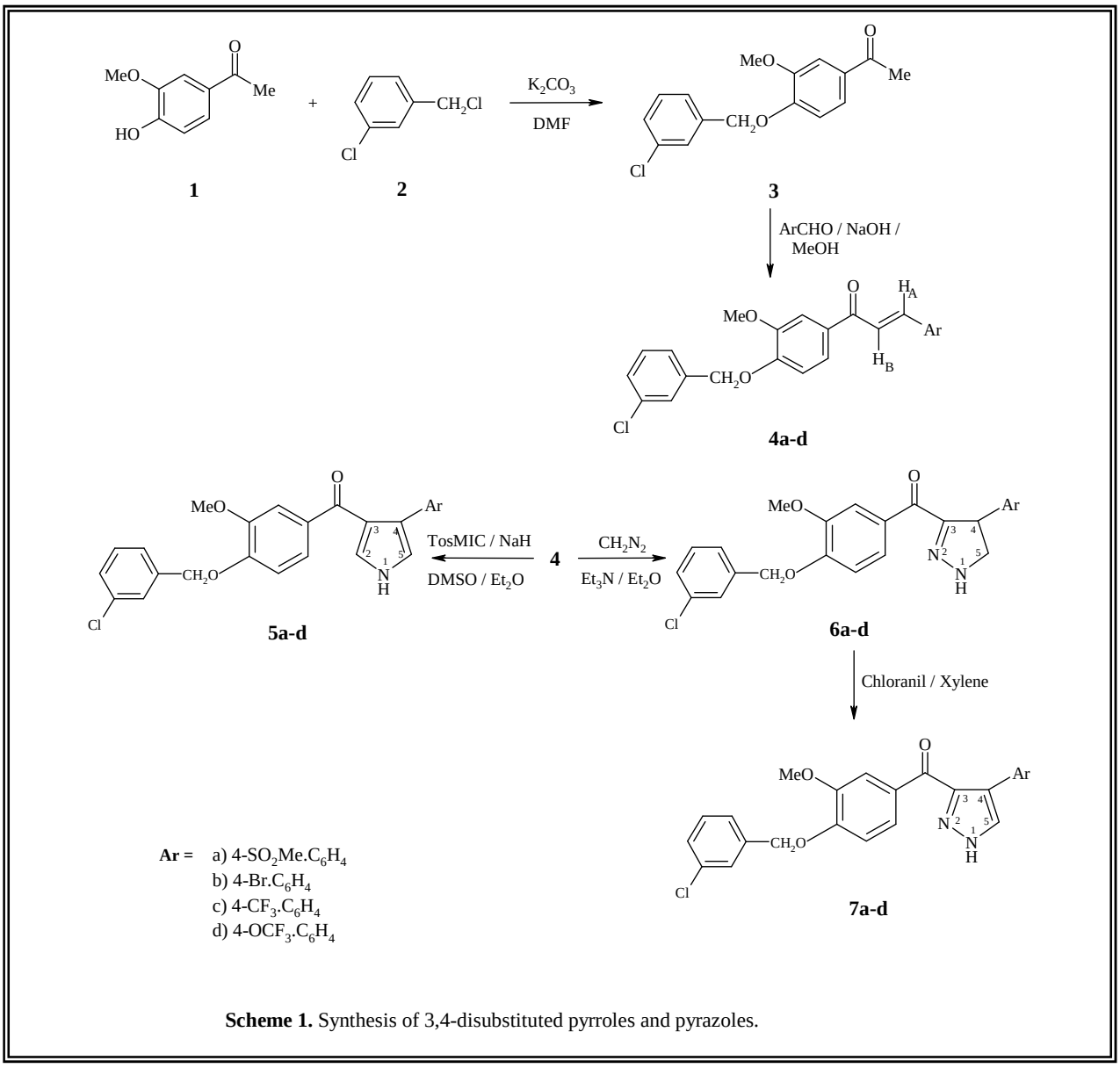

Scheme 1. Synthesis of 3,4-disubstituted pyrroles and pyrazoles.