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Synthesis of Novel 3-Methoxy-4-Phenyl-1-p-Tolyl-1H-Pyrrole-2,5-Dione Derivatives and Study of Their Antimicrobial Activity

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Abstract: A series of 3-methoxy-4-phenyl-1-p-tolyl-1H-pyrrole-2,5-dione **5a-l** were synthesized with almost 80 to 90% yield. All the maleimides were well characterised and screened against panel of four fungal strains and two bacterial strains. The structures of compounds were characterized by their IR, NMR, mass and elemental analysis. The minimum inhibitory concentrations (MICs) of synthesized maleimides were carried out by broth microdilution method. Out of tested maleimides, compounds **5f** and **5j** registered significant activity antibacterial activity. While rest of compounds showed moderate to marginal antimicrobial activity.

Keywords: Maleimide, Maleic anhydride, Antifungal, Antibacterial, MIC

Introduction

The upsurge in the drug resistance for the existing drugs due to appearance of multi resistant strains of bacteria is a matter of concern to the human health [1,2]. There is huge demand for development of newer, safer and more potent antimicrobial drug [3]. The maleimides are well documented in literature for possessing wide range of medicinal applications. It includes antibacterial [4], antifungal [5,6], antiprotozoal [7], anti-inflammatory [8], analgesic [9] and nematicidal activities [10]. Recently, polycyclic maleimide based derivative have been reported for treatment of Alzheimer's disease [11]. Some of the maleimides are well known for anticancer activity [12-15]. Owing to specificity with the biothiols via Micheal type of addition reaction

they are of great interest in bioconjugate chemistry and biotechnology [16].

The main objective of the study was to synthesize the novel maleimide derivatives in view to study their biological activity. Interestingly, N-alkyl derivatives of these maleimides showed the fluorescent properties which is under study. On ground of aforementioned facts and in continuation of our previous investigations on maleimides [17,18] here in we report the synthesis and antimicrobial evaluation of novel 3-aryl-4-methoxy N-aryl maleimide **5a-l**.

Materials and Methods

Melting points are checked on Gallenkamp melting point apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography (TLC). Shimadzu FTIR-408 spectrophotometer was used to record IR spectra in KBr, frequencies were interpreted in cm^{-1}. Varian NMR Mercury-300 was used to record ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra. Chemical shifts were reported in δ values (ppm) relative to internal standard TMS. Shimadzu LC-MS mass spectrometer was used to record mass spectra with an ionization potential of 70 eV. Percentage of C, H and N were checked by Thermo Finnigan Eager 300 EA 1112 series analyser.

General procedure for synthesis of compound 2a-c

A solution of p-substituted phenyl acetonitrile **1a-c** (0.039 mol) in THF (25 mL) was added slowly to slurry of sodium hydride (60% mineral oil, 0.04 mol) in THF (25 mL) followed by dropwise addition of diethyl oxalate (0.045 mol). The reaction mixture was stirred for 2 h at room temperature. On completion of reaction (checked by TLC), reaction mixture was concentrated on rotavapour and poured into cold water (150 mL). On acidification by hydrochloric acid, faint yellow solid was separated, filtered and recrystallized from ethanol.

Ethyl 3-cyano-2-hydroxy-3-phenylacrylate 2a

Yield: 90%; mp: 126-128 °C, (130°C) [19].

Ethyl 3-(4-chlorophenyl)-3-cyano-2-hydroxyacrylate 2b

Yield: 88%; mp: 116-118 °C; IR: 2216, 1733 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 1.34 (t, 3H, CH_3, J = 7.2 Hz), 4.31 (q, 2H, CH_2, J = 7.2 Hz), 7.48 (d, 2H, ArH, J = 8.4 Hz), 7.73 (d, 2H, ArH, J = 8.4 Hz), 7.55 (bs, 1H, OH); MS (70 eV) m/z: 250 $[M-H]^+$; Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57; Found: C, 57.39; H, 4.19; N, 5.66.

Ethyl 3-cyano-2-hydroxy-3-(4-methoxyphenyl)acrylate 2c

Yield: 85%; mp: 94-96 °C, (94°C) [19].

General procedure for synthesis of compound 3a-c

Dimethyl sulphate (2.76 g, 0.021mol) was slowly added to the mixture of **2a-c** (0.021 mol) and anhydrous K_2CO_3 (0.024 mol) in dry acetone (55 mL). It was reflux for 2 h, cooled and filtered. On evaporation of solvent, compound **3a-c** was obtained as faint yellow oil.

ethyl 3-(4-chlorophenyl)-3-cyano-2-methoxyacrylate 3b

Yield: 80%; IR: 2218, 1735 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 1.37 (t, 3H, CH_3), 4.41 (q, 2H, CH_2), 3.90 (s, 3H, OCH_3), 7.55 (d, 2H, ArH, J = 8.4 Hz), 7.77 (d, 2H, ArH, J = 8.4 Hz); MS (70 eV) m/z: 266 $[M+H]^+$; Anal. Calcd for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; N, 5.27;

Found: C, 58.93; H, 4.68; N, 5.46.

General procedure for synthesis of compound 4a-c

A solution of compound **3a-c** (5 g) in glacial acetic acid (60 mL) and water (40 mL) was treated with dropwise addition of con. H_2SO_4 (50 mL). The temperature of exothermic reaction was maintained at 100 °C for 30 min. The reaction mixture was then allowed to cool and diluted with cold water (150 mL) and extracted carefully with ether (3 x 70 mL). The combined ether extracts were washed with 5% KOH, and aqueous extracts were then acidified with dilute H_2SO_4 and extracted with ether. On evaporation of ether, **4a-c** was obtained as solid and it was purified by column chromatography using hexane: ethyl acetate (8:2).

3-methoxy-4-phenylfuran-2,5-dione 4a

Yield: 75%; mp: 112-114 °C, (116°C) [19]; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 4.39 (s, 3H, OCH_3), 7.26-7.97 (m, 5H, ArH).

3-(4-chlorophenyl)-4-methoxyfuran-2,5-dione 4b

Yield: 70%; mp: 88-90 °C; IR: 1838, 1769 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 4.43 (s, 3H, OCH_3), 7.43 (d, 2H, ArH, *J* = 8.4 Hz), 7.95 (d, 2H, ArH, *J*= 8.4 Hz); MS (70 eV) m/z: 239 $[M+H]^+$; HRMS found m/z: 239.0106 $[M+H]^+$; $C_{11}H_8ClO_4$ requires: 239.0111; Anal. Calcd for $C_{11}H_7ClO_4$: C, 55.37; H, 2.96; Found: C, 55.48; H, 2.78.

3-methoxy-4-(4-methoxyphenyl)furan-2,5-dione 4c

Yield: 70%; mp: 96-98 °C, (95 °C) [19]; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 4.26 (s, 3H, OCH_3), 7.07 (d, 2H, ArH), 7.84 (d, 2H, ArH).

General procedure for synthesis of 3-aryl-4-methoxy N-alkyl maleimides 5a-l

3-aryl-4-methoxy maleic anhydrides **4a-c** (4.2 mmol) were refluxed with aromatic amines (4.2 mmol), in ethanol (10 mL) for 20-30 minute. After completion of reaction (checked by TLC), reaction mixture was concentrated under vacuum and dilute with cold water, solid separated was filtered to yield corresponding maleimide **5a-l**. It was purified by column chromatography using hexane: ethyl acetate (7:3).

3-methoxy-4-phenyl-1-p-tolyl-1H-pyrrole-2,5-dione 5a

IR: 1760, 1711, 1634, 1136 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 2.39 (s, 3H), 4.28 (s, 3H), 7.21-7.88 (m, 9H); MS (70 eV) m/z: 294 $[M+H]^+$.

3-(4-chlorophenyl)-4-methoxy-1-p-tolyl-1H-pyrrole-2,5-dione 5b

IR: 1748, 1697, 1636, 1124 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 4.25 (s, 3H), 7. 23 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 8.4 Hz) ; MS (70 eV) m/z: 328 $[M+H]^+$.

3-methoxy-4-(4-methoxyphenyl)-1-p-tolyl-1H-pyrrole-2,5-dione 5c

IR: 1762, 1712, 1611, 1107 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.85 (s, 3H), 4.30 (s, 3H), 6. 90 (d, 2H, *J* = 8.2 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.2 Hz), 7.84 (d, 2H, *J* = 8.8 Hz); MS (70 eV) m/z: 324 $[M+H]^+$.

3-methoxy-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrole-2,5-dione 5d

IR: 1751, 1694, 1632, 1136 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 4.33 (s, 3H), 6.98 (d, 2H, *J* = 9 Hz), 7.27 (d, 2H, *J* = 9 Hz), 7.35-7.88 (m, 5H); ^{13}C NMR: (300 MHz, $CDCl_3$) δ:

55.40, 60.47, 113.02, 114.30, 123.67, 127.73, 127.93, 128.25, 128.72, 129.21, 151.39, 158.94, 165.11, 169.11; MS (70 eV) m/z: 310 $[M+H]^+$.

3-(4-chlorophenyl)-4-methoxy-1-(4-methoxyphenyl)-1H-pyrrole-2,5-dione 5e

IR: 1751, 1704, 1628, 1134 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 3.79 (s, 3H), 4.24 (s, 3H), 7. 05 (d, 2H, *J* = 8.8 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR: (300 MHz, $CDCl_3$) δ: 55.46, 60.62, 111.81, 114.37, 123.47, 126.83, 127.81, 128.53, 130.29, 134.64, 151.43, 159.07, 164.88, 168.89; MS (70 eV) m/z: 344 $[M+H]^+$.

3-methoxy-1,4-bis(4-methoxyphenyl)-1H-pyrrole-2,5-dione 5f

IR: 1752, 1707, 1611, 1098 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 3.84 (s, 3H), 4.30 (s, 3H), 6.94-7.93 (m, 8H); ^{13}C NMR: (300 MHz, $CDCl_3$) δ: 55.22, 55.41, 60.30, 113.32, 113.79, 114.28, 120.85, 123.73, 127.78, 130.61, 149.89, 158.88, 159.81, 165.37, 169.37; MS (70 eV) m/z: 340 $[M+H]^+$.

1-(4-bromophenyl)-3-methoxy-4-phenyl-1H-pyrrole-2,5-dione 5g

IR: 1759, 1703, 1642, 1122 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 4.29 (s, 3H), 7.31-7.87 (m, 9H); MS (70 eV) m/z: 357 $[M+H]^+$.

1-(4-bromophenyl)-3-(4-chlorophenyl)-4-methoxy-1H-pyrrole-2,5-dione 5h

IR: 1761, 1708, 1616, 1109 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 4.37 (s, 3H), 7. 26 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz); MS (70 eV) m/z: 391 $[M+H]^+$.

1-(4-bromophenyl)-3-methoxy-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione 5i

IR: 1759, 1698, 1611, 1113 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 4.31 (s, 3H), 6. 97 (d, 2H, *J* = 7.2 Hz), 7.30 (d, 2H, *J* = 6.6 Hz), 7.55 (d, 2H, *J* = 6.6 Hz), 7.89 (d, 2H, *J* = 7.2 Hz) ; MS (70 eV) m/z: 389 $[M+H]^+$.

1-(4-fluorophenyl)-3-methoxy-4-phenyl-1H-pyrrole-2,5-dione 5j

IR: 1756, 1710, 1636, 1132 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 4.30 (s, 3H), 7.16-7.88 (m, 9H); MS (70 eV) m/z: 298 $[M+H]^+$.

3-(4-chlorophenyl)-1-(4-fluorophenyl)-4-methoxy-1H-pyrrole-2,5-dione 5k

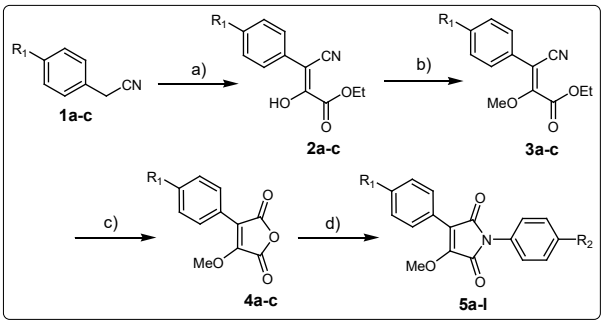
IR: 1761, 1711, 1612, 1110 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 4.37 (s, 3H), 7.13-7.92 (m, 8H); MS (70 eV) m/z: 332 $[M+H]^+$.

1-(4-fluorophenyl)-3-methoxy-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione 5l

IR: 1757, 1706, 1601, 1103 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 4.31 (s, 3H), 6.95-7.93 (m, 8H); MS (70 eV) m/z: 328 $[M+H]^+$.

Antimicrobial Assay

The maleimides **5a-l** were screened against four fungal strains (*Candida albicans* MTCC 227*, Candida tropicalis* MTCC 184*, Aspergillus niger* MTCC 282 *and Aspergillus clavatus* MTCC 1323), one gram positive bacteria (*Staphylococcus aureus* MTCC 96) and one gram negative bacteria (*Escherichia coli* MTCC 443). All the MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against the standard antibacterial (Ampicillin) and antifungal (Griseofulvin) drugs. The MIC values of all compound **5a-l** were carried out by broth microdilution method as described by Rattan [20] using Mueller Hinton broth.



Scheme 1

Reagent and Condition: a) Diethyl oxalate, NaH, THF, rt, 2 h; b) DMS, acetone, K_2CO_3, reflux, 2h; c) AcOH, H_2O, H_2SO_4, 100° C, 30 min; d) p-substituted anilines, EtOH, Reflux, 30 min.

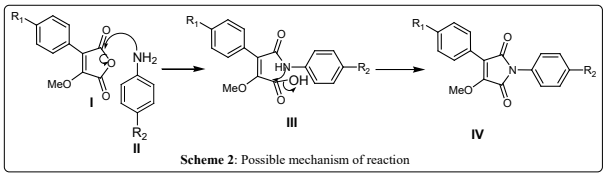
Result and Discussion

Chemistry

Maleimides **5a-l** were prepared in four steps as outlined in scheme 1. Compound **3a**, **3c**, **4a** and **4c** were prepared as per reported method [19]. A modified procedure than literature was employed for synthesise of pyruvate **2a-c** by condensation of p-substituted phenyl acetonitrile **1a-c** with diethyl oxalate in THF using base NaH. The compound **2a-c** were methylated using dimethyl sulphate (DMS) in dry acetone, to furnish compound **3a-c** which on subsequent hydrolysed with con. H_2SO_4 to yield compound **4a-c**. The target compound **5a-l** were synthesized by reacting 3-aryl-4-methoxy maleic anhydrides **4a-c** with corresponding amine, in ethanol at reflux condition with excellent yields. In this step, lone pair of electron of nitrogen aniline (II) attacks on the reactive maleic anhydride (I) to form maleamic acid (III). 3,4 disubstituted maleamic have propensity to get cyclize as shown in scheme 2.

Table 1. Physical and elemental analysis data of maleimides **5a-l**

Compd	R_1	R_2	MP in °C (% Yield)	Mol. Formula (Mol. Wt.)	Calculated % (Found)		
					C	H	N
5a	H	Me	92-94 (78)	$C_{18}H_{15}NO_3$ (293)	73.71 (73.96)	5.15 (5.33)	4.78 (5.11)
5b	Cl	Me	116 (85)	$C_{18}H_{14}ClNO_3$ (327)	65.96 (65.73)	4.37 (4.64)	4.27 (4.57)
5c	OMe	Me	120 (80)	$C_{19}H_{17}NO_4$ (323)	70.58 (70.88)	5.30 (5.56)	4.33 (4.59)
5d	H	OMe	120 (85)	$C_{18}H_{15}NO_4$ (309)	69.89 70.13	4.89 5.13	4.53 4.74
5e	Cl	OMe	118 (80)	$C_{18}H_{14}ClNO_4$ 343	62.89 (62.66)	4.10 (4.32)	4.07 (4.21)
5f	OMe	OMe	116 (83)	$C_{19}H_{17}NO_5$ 339	67.25 (67.67)	5.05 (5.25)	4.13 (4.37)
5g	H	Br	98 (84)	$C_{17}H_{12}BrNO_3$ 356	57.00 (57.19)	3.38 (3.71)	3.91 (3.68)
5h	Cl	Br	166 (83)	$C_{17}H_{11}BrClNO_3$ 390	52.00 (52.25)	2.82 (2.97)	3.57 (3.78)
5i	OMe	Br	154 (85)	$C_{18}H_{14}BrNO_4$ 388	55.69 (55.98)	3.63 (3.91)	3.61 (3.39)
5j	H	F	58 (87)	$C_{17}H_{12}FNO_3$ 297	68.68 (68.82)	4.07 (4.28)	4.71 (4.98)
5k	Cl	F	126 (85)	$C_{17}H_{11}ClFNO_3$ 331	61.55 (61.72)	3.34 (3.11)	4.22 (4.41)
5l	OMe	F	120 (82)	$C_{18}H_{14}FNO_4$ 327	66.05 (66.24)	4.31 (4.54)	4.28 (4.57)



Scheme 2: Possible mechanism of reaction

Spectroscopic analysis

All newly synthesized compounds were characterized by standard spectroscopic methods such as IR, NMR, mass and elemental analysis. As a representative example, spectroscopic data of compound **5f** is as follows.

In the IR spectrum, absorption band at 1752 and 1707 cm^{-1} attributed to imide >C=O stretching frequency. Stretching frequency at 1110 cm^{-1} corresponds to C-O-C bending vibration. ^1H NMR spectrum, three singlets at δ = 3.83, 3.84 and 4.30 attributed to nine protons of three -O-C$\underline{H}_3$ groups and 8 aromatic protons were

appeared as a multiplet in the range of chemical shift at δ = 6.94 to 7.93. In ^{13}C NMR spectrum, three signals appeared at δ = 55.22, 55.41 and 60.30 corresponds to three sp^3 carbons (three -O-$\underline{C}H_3$). In addition, two signal at δ = 169.37 and 165.37 attributed for imide carbonyls (-$\underline{C}$O-N(Ar)-$\underline{C}$O-) and all aromatic carbons appeared at their respective chemical shift. In the mass spectrum, molecular ion peak $(M+H)^+$ was observed at *m/z* value of 340.

Table 2. *In vitro* antimicrobial activity (MIC in μg/mL) of maleimides **5a-l**

Compound	Fungus				Bacteria	
	Candida albicans	*Candida tropicalis*	*Aspergillus niger*	*Aspergillus clavatus*	*Staphylococcus aureus*	*E. coli*
5a	1000	-	-	-	**250**	125
5b	**500**	1000	1000	-	**250**	200
5c	1000	500	-	-	500	125
5d	**500**	1000	-	-	**250**	250
5e	1000	1000	-	-	500	250
5f	**500**	-	500	500	**125**	500
5g	-	-	500	-	**250**	250
5h	-	500	1000	500	**250**	250
5i	-	1000	-	-	**250**	250
5j	1000	1000	500	-	**125**	250
5k	-	500	500	500	**250**	250
5l	-	500	1000	1000	**250**	200
Griseofulvin	500	100	100	100	NA	NA
Ampicillin	NA	NA	NA	NA	250	100

Griseofulvin and Ampicillin were used as reference; (-): Inactive; NA: Not Applicable

In vitro antimicrobial activity

On careful analysis of antimicrobial activities of maleimides (*Table 2*) provides some lead molecules with good antibacterial and antifungal activity. Out of maleimides **5a-l**, compounds with OMe and F substituent registered good to moderate activity. In case of antibacterial activity against Gram positive bacteria, *Staphylococcus aureus*, compound **5f** containing electron donating OMe substituent on both R1and R2 positions registered more potent activity (MIC = 125 μg/mL) Surprisingly, compound **5j** containing electron withdrawing F substituent on R2 position registered more potent activity (MIC = 125 μg/mL). Compounds **5a**, **5b**, **5d**, **5g**, **5h**, **5i**, **5k** and **5l** registered equipotent activity as compared to standard drug ampicillin (MIC = 100 μg/mL). Compound **5a** and **5c** showed moderate activity (MIC = 125 μg/mL) to that of standard ampicillin (MIC = 100 μg/mL) in case of *E. coli*.

In case of antifungal activity against *Candida albicans*, compound **5b**, **5d** and **5f** registered equipotent activity(MIC = 500 μg/mL) as compared to standard drug griseofulvin. Rest of maleimides showed marginal or no significant bioactivity against *Candida tropicalis, Aspergillus niger, and Aspergillus clavatus*.

CONCLUSION

The novel 3-aryl-4-methoxy N-aryl maleimides **5a-l** were prepared in reasonably good yields using simple synthetic protocol. All maleimides were well characterized and evaluated for antimicrobial activity against fungi (*C. albicans*, *C. tropicalis*, *A. niger*, *A. clavatus*) and bacteria (*S. aureus*, *E. coli*). It was concluded that maleimide derivatives with methoxy (**5f**) and fluoro (**5j**) substituents registered good antibacterial activity.

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