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Synthesis and screening of new maleimide derivatives as potential anti-tubercular agents

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ABSTRACT

In the present investigation a series of new maleimide derivatives were synthesized by reacting different anilines with maleic anhydride in presence of acetic anhydride and sodium acetate. The synthesized compounds were identified by using IR, ^{1}H NMR and mass spectral data analysis. The preliminary *in vitro* antimicrobial activity was studied against *S. aureus*, *E. coli* and *A. niger*. Further, the synthesized compounds (**PA1-PA15**) were subjected to *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv using MABA method. The compounds **PA4** (MIC 6.25 µg/ml), **PA8** (MIC 3.125 µg/ml), **PA14** (MIC 3.125 µg/ml) showed significant inhibitory activity against *M. tuberculosis* H37Rv.

INTRODUCTION

As per WHO World TB report 2014, tuberculosis has claimed over 1.5 million lives worldwide during 2013-14, among which 22% are non HIV patients. The incidence of MDR Tb increased significantly from 3,10,000 cases in 2012-13 to an estimated 4,80,000 cases in 2013-14, among which 9% belong to XDR TB. It was also estimated that MDR TB accounts for 14% of total deaths due to TB. Though effective medicines are available for treating drug-susceptible infections, the chances go from bleak to null as we move from MDR to XDR or TDR TB (Seung *et al.*, 2013). Coordinated efforts made by international community resulted in the identification of a few important anti TB agents like BM212, SQ109, AZD5847 and Sutezolid which are in the late phases of clinical trials. Bedaquiline (2013) and Delaminid (2014) are the only two agents approved for treating tuberculosis after Rifampicin (1963).This clearly shows the need for new leads to fight against tuberculosis. In continuation of our efforts in identification of new anti TB agents, we have recently identified potential antitubercular activity in Denigrins A-C, members of diaryl pyrrole alkaloids isolated from the marine sponge *Dendrilla nigra* (Murali *et al.*, 2014).

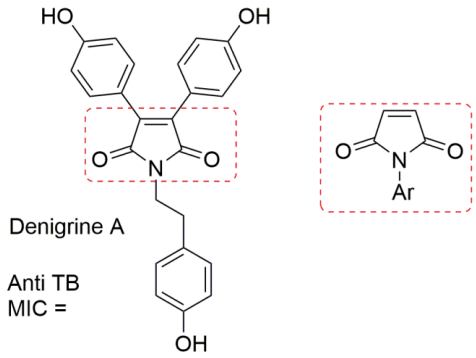

Fig. 1: Chemical structure of Denigrin A from which present work was designed.

Denigrin A (Fig.1) has a relatively simple substituted maleimide structure and showed an MIC 16µg/mL against *M. tuberculosis* H37Rv. We report here the synthesis, screening and SAR studies of maleimide derivatives as antitubercular agents.

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MATERIALS AND METHODS

Reagents and equipment

All the chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by pre-coated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). Iodine vapors and Sulphuric acid spray reagent (10% H_2SO_4/MeOH) were used as visualizing agents. Melting points (m.p.) were determined using an SRS-EZMelt automated melting point instrument, without correction. The IR spectra were recorded on BRUKER FT-IR (software - OPUS 6.4) spectrometer using KBr disc method and the values were expressed in cm^{-1}. The ^{1}H-NMR spectra of the compounds were recorded in DMSO-d_6 or $CDCl_3$ with BRUKER AVANCE 400 MHz NMR spectrometer (software - Topspin) and chemical shifts were expressed in δ (ppm). Shifts reported are relative to the signal of the solvent used in each case and coupling constants are reported in Hz (s: singlet, bs: broad singlet, d: doublet, t: triplet, dd: double doublet, dt: double triplet, m: multiplet). The mass spectra were recorded on AGILENT QQQ LC-MS (ESI-MS) spectrometer (software - Mass Hunter B.03.01).

Chemistry

General procedure for the synthesis of N-aryl maleimides

To a solution of 20mmol of maleic anhydride in diethyl ether (25ml) was taken in three necked flask provided with magnetic stirrer and dropping funnel. A solution of 20mmol of different aromatic amines (Fig. 2) in 5ml of ethyl acetate was run through the dropping funnel.

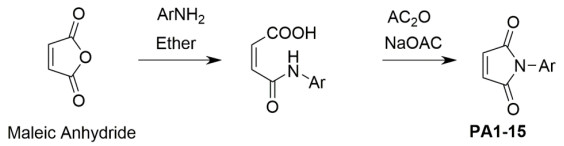

Fig. 2: Schematic diagrams indicating the synthesised compound nos. **PA1 - PA15**.

The resulting thick suspension was stirred at room temperature for about 2hrs.The precipitate obtained was filtered and washed with diethyl ether. This crude product was mixed with 8mmol of anhydrous sodium acetate and 20mmol acetic anhydride and further subjected to heating on a steam bath for 30 minutes. The reaction mixture was cooled to room temperature and poured into ice water. The precipitated product was removed by suction filtration, washed with ice-cold water and then dried. Pure products were obtained either by recrystallization from hexane:ethyl acetate mixtures or column chromatography.

Pharmacology

Antimicrobial studies

The synthesized compounds were subjected to antimicrobial activity. Standard bacterial and fungal strains were procured from the American Type Culture Collection (ATCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The compounds **PA1 - PA15**; were evaluated for *in-vitro* antimicrobial activities by the broth micro-dilution method (Goto *et al.*, 1981) against the following microbial strains: Gram +ve: *S. aureus* (ATCC 11632), Gram-ve: *E. coli* (ATCC 10536) and Fungi: *A. niger* (ATCC 9029). The Minimum Inhibitory Concentration (MIC) of these synthesized compounds was screened *in vitro* by using serial tube dilution method at concentration 150, 100 and 50µg/mL against the above said microorganisms. The bacterial strains were sub-cultured on nutrient agar medium whereas fungal strains were subcultured on malt extract medium. The bacterial and fungal strains were incubated at 37 °C and 28 °C. DMSO was used as a negative control while Amikacin and Fluconazole were used as reference drugs for comparison. The minimum inhibitory concentration (MIC) of all the studied compounds were noted by the appearance of turbidity in test tubes after incubation. The results of the MIC determinations of these compounds have been presented in Table 1

In-vitro Antitubercular Activity Screening – MABA assay

Table 1: Anti-microbial and anti-Tubercular activity of the compounds PA1-PA15.

S. No	Compounds (Code)	Zone of inhibition in mm			MIC value
		BACTERIA		FUNGI	Mycobacteria
		S.aureus (Gram +ve)	*E.coli* (Gram -ve)	*A.niger*	*M. tuberculosis* H37Rv
		Concentration (µg/ml)			
		50 µg	50 µg	50 µg	MIC value (µg/ml)
1.	**PA1**	**21**	**22**	**20**	25
2.	**PA2**	18	17	19	50
3.	**PA3**	6	5	**25**	25
4.	**PA4**	**22**	**20**	**20**	**6.25**
5.	**PA5**	17	17	18	50
6.	**PA6**	16	15	18	50
7.	**PA7**	8	6	6	12.5
8.	**PA8**	12	15	5	**3.125**
9.	**PA9**	7	10	4	50
10.	**PA10**	7	8	4	50
11.	**PA11**	16	18	5	50
12.	**PA12**	**23**	**22**	15	50
13.	**PA13**	**21**	**20**	18	25
14.	**PA14**	16	17	4	**3.125**
15.	**PA15**	18	18	5	50
16.	Amikacin	28	28	-	-
17.	Fluconazole	-	-	26	-
18.	Pyrazinamide	-	-	-	3.125
19	Streptomycin	-	-	-	6.25
20	Ciprofloxacin	-	-	-	3.125

The test compounds (**PA1 - PA15)** were screened for preliminary anti-TB activity against pathogenic strains of *M. tuberculosis* H_{37}Rv (ATCC 27294), using Microplate Alamar Blue

assay (MABA) (Franzblau *et al.*, 1998). The $H_{37}Rv$ culture grown on Lowenstein Jensen (LJ) medium was suspended in sterile Middlebrook 7H9 broth supplemented with 0.2% glycerol and 10% OADC (Oleate-Albumin-Dextrose-Catalase) enrichment and a 1:20 dilution used as the inoculum for MABA. 200µl of sterile de-ionized water was added to all outer perimeter wells of sterile 96 well plates to minimize evaporation of medium in the test wells during incubation. The 96 well plates received 100µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml.

The 96 well Plate was covered and sealed with para film and incubated at 37 ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration, which prevented the color change from blue to pink. The anti-tubercular activity results were presented in Table 1.

RESULTS AND DISCUSSION

Characterization of synthesized compounds

1-phenyl-1H-pyrrole-2,5-dione (PA1)

Yellow needles; Yield 65%; m.p. 90-91^oC; Anal. calc for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09; found: C, 69.34; H, 4.09; N, 18.49;R_f = 0.58 (15% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3094 (C-H aromatic), 1709 (C=O), 1507 (C=C, aromatic); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.336 - 7.492 (m, 5H, Ph C2, C3, C4, C5, C6-H), 6.854 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 174 $[M+1]^+$.

1-(4-nitrophenyl)-1H-pyrrole-2,5-dione (PA2)

Orange crystals; Yield 68%; m.p.162-163^oC; Anal. calc for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84; found: C, 55.08; H, 2.79; N, 12.92; R_f = 0.54 (15% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3105 (C-H aromatic), 1715 (C=O), 1603 (C=C, aromatic), 1522 (NO_2); ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.14 (d, J = 7.1 Hz, 2H, Ph C3, C4-H), 7.61 (d, J = 7.1 Hz, 2H, Ph C2, C6-H), 6.902 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 219$[M+1]^+$.

1-(4-chlorophenyl)-1H-pyrrole-2,5-dione(PA3)

Cream colored crystals; Yield 51%; m.p. 102-103^oC; Anal. calc for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.91; N, 6.75; found: C, 55.90; H, 2.86; N, 6.81; R_f = 0.51 (15% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3084 (C-H aromatic), 1748 (C=O), 1576 (C=C, aromatic), 708 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.41 (m, 4H, Ph C2, C3, C5, C6-H), 6.855 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 208 $[M+1]^+$.

1-(4-bromophenyl)-1H-pyrrole-2,5-dione (PA4)

Pale yellow needles; Yield 45%; m.p.103-104^oC; R_f = 0.58 (35% Ethyl acetate in Hexane); Anal. calc for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56; found: C, 47.70; H, 2.43; N, 5.54; IR (KBr) υ max: cm^{-1}: 3092 (C-H aromatic), 1713 (C=O), 1564 (C=C, aromatic), 584 (C-Br); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.59-7.65 (m, 4H, Ph C2, C3, C5, C6-H), 6.87 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 253$[M+1]^+$.

1-(3,5-dibromophenyl)-1H-pyrrole-2,5-dione (PA5)

Cream colored crystals; Yield 60%; m.p.158-159^oC; Anal. Calc. for $C_{10}H_5Br_2NO_2$: C, 32.69; H, 1.52; N, 4.23; found: C, 32.64; H, 1.49; N, 4.25; R_f = 0.56 (35% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3092 (C-H aromatic), 1719 (C=O), 1585 (C=C, aromatic), 592 (C-Br); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.82 (d, J = 2.3 Hz, 1H, Ph C4-H), 7.65 (d, J = 2.3 Hz, 2H, Ph C2, C-6-H), 6.88 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 331$[M+1]^+$.

1-(2,4-dinitrophenylamino)-1H-pyrrole-2,5-dione (PA6)

Bright orange crystals; Yield 50%; m.p.115-116^oC; Anal. Calc. for $C_{10}H_6N_4O_6$: C, 43.18; H, 2.17; N, 20.14; found: C, 43.16; H, 2.19; N, 20.19; R_f = 0.61 (25% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3371 (N-H), 3112 (C-H aromatic), 1745 (C=O), 1599 (C=C, aromatic), 1537 (NO_2); ^1H NMR (CD_3OD, 400 MHz) δ: 8.49 (s, 1H, Ph C3-H), 8.16 (d, J = 6.8 Hz, 1H, Ph C5-H), 7.42 (d, J = 6.8 Hz, 1H, Ph C6-H),6.79 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 279 $[M+1]^+$.

1-(2-Mercaptophenyl)-1H-pyrrole-2,5-dione (PA7)

Pale brown crystals; Yield 35%; m.p.116-117^oC; Anal. Calc. for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82; found: C,58.52; H, 3.49; N, 6.85; R_f = 0.57 (35% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3258 (S-H), 3096 (C-H aromatic), 1713 (C=O), 1581 (C=C, aromatic) ; ^1H NMR ($CDCl_3$, 400 MHz) δ:7.19-7.45 (m, 3H, Ph C3, C4, C5-H), 7.62 (dd, J = 7.8, 1.9 Hz, 1H, Ph C6-H), 6.82 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 206$[M+1]^+$.

N-(2,5-dioxo-2H-pyrrole-1-(5H)-yl)benzamide(PA8)

Light orange crystals; Yield 55%; m.p.150-151^oC; Anal. Calc. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96; found: C, 61.18; H, 3.75; N, 12.94; R_f = 0.52 (15% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3278 (N-H), 3063 (C-H aromatic), 1740 (C=O), 1628 (C=O), 1523 (C=C, aromatic) ; ^1H NMR ($CDCl_3$, 400 MHz) δ:7.51-7.89 (m, 5H, PhC2, C3, C4, C5, C6-H), 6.88 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 217$[M+1]^+$.

1-(4-nitrophenylamino)-1H-pyrrole-2,5-dione (PA9)

Orange crystals; Yield 65%; m.p.268-269^oC; Anal. Calc. for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02; found: C, 51.50; H, 3.03; N, 27.50; R_f = 0.54 (15% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3448 (N-H), 3066 (C-H aromatic), 1792 (C=O), 1586 (C=C, aromatic), 1543 (NO_2); ^1H NMR (CD_3OD, 400 MHz) δ: 7.96 (d, J=7.1 Hz, 2H, Ph C3, C5-H), 7.12 (d, J = 7.1 Hz, 2H, PhC2, C6-H), 6.81 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 234$[M+1]^+$.

1-(benzylamino)-1H-pyrrole-2,5-dione (PA10)

Brown powder; Yield 25%; m.p.100-102^{o}C; Anal. Calc. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; found: C, 65.31; H, 4.88; N, 13.89; R_f = 0.56 (25% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3449 (N-H), 3068 (C-H aromatic), 1738 (C=O), 1581 (C=C, aromatic); ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.28-7.32 (m, 5H, PhC2, C3, C4, C5, C6-H), 6.83 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 203[M+1]$^+$.

1-(3-bromophenyl)-1H-pyrrole-2,5-dione (PA11)

Cream colored needles; Yield65%; m.p.114-115^{o}C; Anal. Calc. for $C_{11}H_{10}N_2O_2$: C, 47.65; H, 2.40; N, 31.69; found: C, 47.66; H, 2.38; N, 31.69; R_f = 0.51 (25% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3096 (C-H aromatic), 1708 (C=O), 1586 (C=C, aromatic), 594 (C-Br); ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.68 (d, 1.8 Hz, 1H, Ph C2-H), 7.16-7.41 (m, 3H, Ph C4, C5, C6-H), 6.83 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 253 [M+1]$^+$.

1-o-tolyl-1H-pyrrole-2,5-dione (PA12)

Off white powder; Yield 35%; m.p.92-93^{o}C; Anal. Calc. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 17.09; found: C, 70.53; H, 4.86; N, 7.09; R_f = 0.51 (40% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3093 (C-H aromatic), 2928 (aliphatic C-H), 1705 (C=O), 1541 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, 6.5 Hz, 1H, Ph C6-H), 7.11-7.35 (m, 3H, PhC3, C4, C5-H), 6.81 (s, 2H, pyrrole C3 and C4-H), 2.12 (s, 3H, Ar-CH_3); ESI MS m/z: 188[M+1]$^+$.

1-m-tolyl-1H-pyrrole-2,5-dione (PA13)

Pale brown crystals; Yield 42%; m.p.97-98^{o}C; Anal. Calc. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 17.09; found: C, 70.56; H, 4.84; N, 7.08; R_f = 0.54 (50% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3100 (C-H aromatic), 2922 (aliphatic C-H), 1716 (C=O), 1611 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.88-7.29 (m, 4H, Ph C2, C4, C5, C6-H), 6.82 (s, 2H, pyrrole C3 and C4-H), 2.32 (s, 3H, Ar-CH_3); ESI MS m/z: 188 [M+1]$^+$.

1-(2-aminophenyl)-1H-pyrrole-2,5-dione (PA14)

Brown amorphous powder; Yield 28%, m.p.143-145^{o}C; Anal. Calc. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89; found: C, 63.86; H, 4.24; N, 14.87; R_f = 0.53 (45% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3366 (d, -NH_2), 3091 (C-H aromatic), 1718 (C=O), 1557 (-NH bend), 1532 (-C=C- aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.53 (m, 2H, Ph C4, C6-H), 6.89-7.01 (m, 2H, Ph C3, C5-H), 6.81 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 189 [M+1]$^+$.

5.16 3'-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-[1,1'-biphenyl]-4-carboxylic acid (PA15)

Pale yellowcrystals; Yield55%;m.p.244-245^{o}C; Anal. Calc. for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78; found: C, 69.64; H, 3.76; N, 4.70; R_f = 0.52 (30% Ethyl acetate in Hexane); IR (KBr) υ max: cm^{-1}: 3300 (very broad, COOH), 3097 (C-H aromatic), 1716 (C=O), 1697 (C=O), 1555 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.25 (s, 1H, COOH), 7.35-8.04 (m, 8H, biphenyl-C2, C4, C5, C6, C2', C3', C5', C6'-H), 6.82 (s, 2H, pyrrole C3 and C4-H); ESI MS m/z: 294[M+1]$^+$.

CONCLUSION

This research involves the synthesis of N-aryl maleimide derivatives **PA1-PA15.** The novel N-aryl maleimide derivatives were synthesized by the reaction of maleic anhydride with various primary amines and were screened for their antitubercular and antimicrobial activity. Of them **PA1**, **PA4**, **PA12 and PA13 (**at 50µg) showed excellent antibacterial activity and **PA1, PA3** and **PA4 (**at 50µg) showed excellent antifungal activity when compared to standard drugs Amikacin(10 µg) and Fluconazole(5 µg) respectively. The compounds **PA4** (MIC 6.25 µg/ml), **PA8** (MIC 3.125 µg/ml), **PA14** (MIC 3.125 µg/ml) showed significant inhibitory activity against *M. tuberculosis* H37Rv.

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