Research Article

Synthesis and Antibacterial Activity of New Phthalazine Derivatives

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Accepted on: 14-09-2015; **Finalized on:** 31-10-2015.

ABSTRACT

Synthesis of new series of phthalazine derivatives starting from phthalic anhydride and substituted aliphatic aryl/heteroaryl amine and thiol in presence of base were reported. The structures of the synthesized compounds were confirmed by IR, Mass spectra, ^{1}HNMR and ^{13}C NMR spectral data. The synthesized compounds were tested for their *in vitro* antibacterial activity against (Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeuroginosa) and showed a good activity. Investigation of their antimicrobial activity revealed that The activity was increased by substitution with 4i, 4l, 4n, 4e, 4j and 4g respectively. The best compound which exhibited antimicrobial activity against test fungi was p-anisidine.

Keywords: Phthalic anhydride, amines, thiols, phthalazine derivatives, antibacterial activity.

INTRODUCTION

Nitrogen-containing heterocyclic compounds have received much attention as shown by the numerous studies published on their applicability in different areas, especially as drugs[1,2]. Phthalazines are classes of nitrogen heterocycles that are of considerable interest because of their widespread pharmacological and therapeutic properties[3-5]. Phthalazines have been reported to possess antimicrobial[6-8], antitumor[9-12], antihypertensive[13,14], antithrombotic[15], antidiabetic[16,17], anti-T-Cruzi[18], anti-inflammatory[19-25], and vasarelaxant activities[26]. Nevertheless, the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge. In view of the aforementioned facts, it seemed most interesting to study the chemical behavior of 1-chloro-4-*p*-tolylphthalizine (**3c**) towards some nitrogen and sulfur nucleophiles to produce new phthalazine derivatives with the aim to evaluate their antimicrobial activities. The synthesis of new compounds and testing their biological and pharmacological activities are the major goals of drug development projects. Nitrogen-containing heterocyclic compounds have received much attention as shown by the numerous studies published on their applicability in different areas, especially as drugs[1,2]. Phthalazines are examples of nitrogen heterocycles that possess exciting biological properties[3–5]. They form the structural profile for several biologically active compounds and hence they are considered important key elements. Several reports in the literature have focused on the pharmacology of phthalazine derivatives.

MATERIALS AND METHODS

Melting points were determined on Fisher-Johns melting point apparatus and were uncorrected. Microanalyses were performed in the micro Analytical center, university of Cairo. IR spectra (KBr) were recorded on Mattson 5000 FT-IR spectrometer (υ in cm^{-1}), Micro Analytical center, university of Cairo. 1H NMR spectra were recorded on Burker AC 250 FT NMR spectrometer (300MHZ) in DMSO-d6 or CDCl3 using TMS as internal standard, chemical shifts in ppm were expressed in δ units, Micro Analytical center, University of Cairo and 1H-NMR, 13C NMR spectrum were recorded on a BurkerAvance 400(400.13 MHz), a BurkerAvance 400(100.77 MHz), Olum Institute Chemistry, Germany.Mass analyses were performed on JEOL JMS-600H spectrometer. Micro Analytical center, University of Cairo. Reaction times were determined by using TLC on silica gel plates 60 F245 E. Merck, and the spots were visualized by U.V (366-245 nm) lamp.

Synthesis of 1-chloro-4-*p*-tolylphthalazine 3c.

A mixture (5 gm,0.003 mol) of phthalic anhydride, (25 ml, 0.2 mol) of toluene was heated under reflux for 2h, (9 g, 0.6 mol) of $AlCl_3$ anhydrous was added gradually and refluxed for 2h on water bath, acidification of reaction mixture by 100 ml of dil HCl, then evaporate toluene, cool to 0°C, filtered, washed by dis H_2O, finally the residue was dissolved in saturated sol of Na_2CO_3 and precipitated by dil HCl, give **1a**[25,26].

Treatment of 1a with hydrazine hydrate in boiling ethanol, refluxed for 2h on water bath, filtered, dried to give **2b**[27].

Chlorination of 2b by $pocl_3$, DMF and Acetonitrile refluxed overnight then neutralized by Saturated sol Na_2CO_3, filtered, washed by H_2O, dried to give **3c**. Yield: (1.37 gm, 95%), brown crystals, m.p148-150 °C; IR(KBr) cm^{-1} 759(γC-Cl), 1627(γC=N) and devoid any band for (γC=O); ^{1}HNMR (400 MHz, DMSO-d6) ppm: 2.44(s, 3H, Ar-CH3), 7.41 (d,

2H, J = 8.4Hz), 7.6 (d, 2H, J = 8.1Hz), 8.02 (m, 3H), 8.36 (d, 1H, J = 7.8Hz).

General procedure for the synthesis of 4-p-tolyl phthalazine derivatives (4d-g).

A mixture of 1-chloro-4-p-tolylphthalazine (0.1g, 0.3 mol) dissolved in chloroform and an excess of aniline 1.2 eq were heated refluxed at 60-70 °C in presence of 10eq Et_3N for 5-15h.

TLC monitoring was used to ensure the completion of reaction.

The resulting crude product was extracted by chloroform: water (5:10), the solvent was evaporated under vacuum and the separated solid was washed with H_2O, dried and recrystallized to afford the product which purified by using EtOAC/CH_2Cl_2 (1:5) as eluent to yield the pure product.

N-phenyl-4-p-tolyl phthalazin-1- amine 4d.

Yield: (0.1 g, 67%) yellow solid. m.p(209-214°C); IR (KBr) cm^{-1}, 3260 (NH), 1504 (C = N); ^{1}H NMR (400 MHz, DMSO-d6) ppm: 2.41 (s, Ar-CH3), 7.01 (t, 1H, J = 7.2Hz), 7.33 (dd, 4H, J = 6.8, J = 6.8Hz), 7.52 (d, 2H, J = 7.6 Hz), 7.88 (d, 2H, J = 7.6Hz), 7.93 (d, 2H, J = 7.6Hz), 7.98 (t, 1H, J = 6.8Hz), 8.63 (d, 1H, J = 8Hz), 9.24 (s, NH).

N-(4-chlorophenyl)-4-p-tolylphthalazin-1-amine 4e.

Yield: (0.11g, 81%) reddish yellow solid. m.p(180-182°C); ^{1}H NMR (400 MHz, DMSO-d6) ppm: 2.45(s, Ar-CH_3), 7.43 (d, 2H, J = 8Hz), 7.62 (d, 3H, J = 8Hz), 8.06 (m, 6H), 8.38 (d, 1H, J = 8Hz), 10.51 (s, NH); MS: m/z = 345(M^+).

4-p-tolyl-N-(4-(trifluoromethyl) phenyl) phthalazin-1-amine 4f.

Yield: (0.11g, 67%) yellow solid m.p(203-205°C), IR (KBr) cm^{-1}, 3268 (NH), 1617 (C = N); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 2.43 (s, Ar-CH_3), 6.44 (d, 1H, J = 7.8Hz), 6.62 (d, 1H, J = 7.5Hz), 6.97 (d, 1H, J = 6.3Hz), 7.37 (d, 1H, J = 7.2Hz), 7.55 (d, 1H, J = 7.2Hz), 7.69 (d, 1H, J = 7.8Hz), 7.93 (m, 3H), 8.22 (d, 2H, J = 8.4Hz), 8.68 (d, 1H, J = 7.2Hz), 9.65 (s, NH); MS: m/z = 378(M^+).

N-(4-methoxyphenyl)-4-p-tolylphthalazin-1-amine 4g.

Yield: (0.08 g, 60%) green crystals. m.p(60-62°C); IR (KBr) cm^{-1}, 3251 (NH), 1559 (C = N), 1241 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 2.41 (s, Ar-CH_3), 3.76 (s, 1H, O-CH3), 6.94 (d, 2H, J = 7.8Hz), 7.35 (d, 2H, J = 7.8Hz), 7.51 (d, 2H, J = 7.2Hz), 7.79 (d, 1H, J = 8.4Hz), 7.87(d, 2H, J = 6.6Hz), 7.92 (dd, 1H, J = 6.9Hz, J = 10.8Hz), 7.95 (t, 1H, J = 7.8Hz), 8.61 (d, 1H, J = 8.4Hz), 9.12 (s, NH); MS: m/z = 340(M^+).

General procedure for the synthesis of 4-p-tolyl phthalazine derivatives (4h-o).

A mixture of 1-chloro-4-p-tolyl phthalazine (0.1g, 0.3 mol) dissolved in dry DMF and the amine (1 eq.) were heated refluxed at 135-155 °C in presence of 5 eq of Et_3N for 24-72 h. TLC monitoring was used to ensure the completion of reaction.

N1 - (4-p-tolyl phthalazin-1-yl) propane-1,3-diamine 4h

Yield: (0.05g, 44%) grey solid. m.p(250-252°C); ^{1}H NMR (400 MHz, DMSO –d_6) ppm: 1.83 (t, 2H, J = 6.8Hz), 2.40 (s, Ar-CH_3), 3.1 (s, NH_2), 3.46 (S, NH), 3.54 (m, 2H), 3.76 (t, 2H, J = 5.6Hz), 7.34 (dd, 2H, J = 2.8Hz, J = 2.8Hz), 7.50 (t, 2H, J = 9.2Hz), 7.78 (t, 1H, J = 7.2Hz), 7.82 (m, 1H), 8.32 (d, 1H, J = 8Hz), 8.45 (d, 1H, J = 8Hz).

N1- (4- p-tolylphthalazin-1-yl) benzene -1,2-diamine 4i

Yield: (0.1g, 78%) brown solid. m.p(197-200°C); IR (KBr) cm^{-1}, 3120(γNH2), 3220(γNH); ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 2.41(s, Ar-CH_3), 7.35 (d, 2H, J = 8Hz), 7.46 (d, 2H, J = 8Hz), 7.69(m, 2H), 7.88 (m, 4H), 8.33 (s, 2H), 12.83 (s, NH).; ^{13}C NMR (101MHz, DMSO-ds) showed signals at (δ ppm), 166.0, 159.19, 138.39,136.0, 132.0, 131.55 (2C), 130.0, 129.18 carbon for C-N), 129.07, 127.4(2C), 127.0 (2C), 119.6 (2C), 119.2, 117.0 (3C), 20.86

N-methyl-4-p-tolylphthalazin-1-amine 4j

Yield: (0.03g, 31%), yellow solid. mp(185-188°C), IR(KBr) cm^{-1}, 3278 (NH); 1H NMR (400 MHz, DMSO-d_6) ppm: 2.41 (s, Ar-CH_3), 3.14 (s, N-CH3), 7.34 (d, 2H, J = 8Hz), 7.48 (d, 2H, J = 8Hz), 7.63 (s, NH), 7.80 (m, 3H), 8.28 (d, 1H, J = 8Hz). MS: m/z = 249(M^+).

2-(4-p-tolylphthalazin-1-yl amino) benzoic acid 4k

Yield: (0.1g, 72%) brown solid. m.p(175-177°C), IR (KBr) cm^{-1}, 1661 (C = O), 3302 (NH), 3440 (OH acid); ^{1}H NMR (400 MHz, DMSO) PPM: 2.41 (s, Ar-CH_3), 7.35 (d, 2H, J = 8Hz), 7.47 (m, 2H), 7.62 (m, 2H), 7.88 (m, 1H), 8.05 (m, 3H), 8.32 (m, 2H), 12.83 (s, 1H, COOH). MS: m/z = 354 (M^+)

2-(4-p-tolylphthalazin-1-yl amino) propanoic acid 4L

Yield: (0.11g, 92%) brown solid. m.p (172-175°C); IR (KBr) cm^{-1}, 1661 (CO), 3429 (OH); ^{1}H NMR (300MHz, DMSO-d_6) PPM:2.40 (s, Ar-CH_3), 2.50 (q, 1H), 7.34 (d, 1H, J = 6HZ), 7.37 (t, 1H, J = 9.6 HZ), 7.48 (d, 1H, J = 15HZ), 7.61 (d, 1H, J = 6HZ), 7.67 (t, 1H, J = 6HZ), 7.87 (t, 1H, J = 6HZ), 8.03 (m, 1H), 8.31 (m, 1H), 12.8 (s, 1H, COOH).

N - (4-p-tolylphthalazin-1-yl) hydrazinecarboxamide 4m

Yield: (0.06g, 46%) yellow solid. m.p(260-263°C); IR(KBr) cm^{-1}, 1675(γC=O), 2935(γNH), 3620(γNH2); ^{1}H NMR (300MHz, DMSO-d_6) PPM: 2.41 (s, Ar-CH_3), 7.34 (m, 2H), 7.59 (d, 1H, J = 9Hz), 7.66 (d, 1H, J = 6Hz), 7.75 (t, 1H, J = 9Hz), 7.88 (m, 1H), 8.24 (d, 1H, J = 6Hz), 8.33 (d, 1H, J = 6Hz), 12.58(s, NH), 12.78 (s, NH).

1-(4-methylpiperazin-1-yl)-4-p-tolylphthalazine4n.

Yield: (0.06g, 48%) orange solid, m.p (57-60°C); IR(KBr) cm^{-1}, 1564(γC=N); ^{1}H NMR (300 MHz, DMSO-d_6) PPM: 2.32 (s, 3H, N-CH_3), 2.41 (s,Ar-CH_3), 2.65 (s,2H,CH_2). 2.81 (s,2H,CH_2), 3.82 (t,4H, 2CH_2, J = 5.4Hz), 7.35 (d, 2H, J = 6.6), 7.52 (d, 2H, J = 6.9Hz), 7.84 (s, 3H), 8.06 (d, 1H, J = 6Hz); MS: m/z = 317 (M^+).

2-(4-p-tolylphthalazin-1-ylamino)acetic acid 4o.

Yield: (0.09g, 81%), brown solid, m.p (240-243°C); IR (KBr) cm^{-1}, 1662 (CO), 3440 (OH acid); ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 2.41(s, Ar-CH_3), 3.15 (s, CH_2), 7.36 (d, 2H, *J* = 8Hz), 7.47 (m, 2H), 7.68(d, 1H, *J* = 12Hz), 7.88 (m, 2H), 8.33 (m, 1H).

General procedure for the synthesis of S-(4-p-tolyl phthalazine derivatives (4p-s).

A mixture of **3C**(0.1g, 0.3mol) and thiophenols (1eq) in absolute ethanol was heated at 100°C for 4-6 h with excess of 5eq of Et3N. TLC monitoring was used to ensure the completion of reaction. The resulting crude was poured into an ice water and the formed solid was collected by filteration, dried and purified by using EtoAC/CH_2Cl_2 (1:5) as eluent to yield the pure product.

1-(4-chlorophenylthio) -4-p-tolylphthalazine 4p.

Yield: (0.11g, 77%), white solid, m.p(150-152°C); IR (KBr) cm^{-1}, 1450(γC-S), 1628(γC=N); ^{1}H NMR (400 MHz, DMSO-d_6) PPM: 2.43 (s, Ar-CH_3), 7.40 (d, 2H, *J* = 8Hz), 7.57 (m, 4H), 7.77 (d, 2H, *J* = 8Hz), 8.02 (m, 3H), 8.33 (d, 1H, *J* = 8Hz).

1-p-tolyl -4-(p-tolylthio) phthalazine 4Q.

Yield: (0.12g, 89%), white solid, m.p(158-160°C); IR(KBr) cm^{-1}, 1430(γC-S), 1620(γC=N); ^{1}H NMR (400 MHz, DMSO-d_6) PPM: 2.41 (s, Ar-CH_3), 2.43 (s, CH3), 7.36 (d, 2H, *J* = 8Hz), 7.53 (s, 1H), 7.57 (m, 2H), 7.59 (m, 3H), 8.02 (m, 3H), 8.33 (d, 1H, *J* = 8Hz); MS: m/z = 341 (M^+).

1-p-tolyl -4-(2,4,5- trichlorophenylthio) phthalazine 4r.

Yield: (0.12g, 71%) white solid, m.p(171-173°C); IR(KBr) cm^{-1}, 1440(γC-S), 1610(γC=N); ^{1}H NMR (300 MHz, DMSO-d_6) PPM: 2.43 (s, Ar-CH_3), 7.39 (d, 2H, *J* = 7.8Hz), 7.57 (d, 2H, *J* = 7.5Hz), 7.85 (s, 1H), 8.05 (m, 3H), 8.33 (d, 2H, *J* = 7.5Hz); MS: m/z = 431(M^+).

1-(naphthalen-2-yloxy)-4-p-tolylphthalazine 4s.

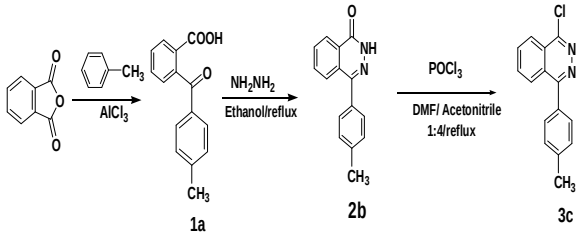
Yield: (0.12g, 84%), white crystals, m.p(185-188 ^{0}C); IR(KBr) cm^{-1}, 1420(γC-O), 1622(γC=N); ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 2.43 (s, Ar-CH_3), 7.39 (d, 1H, *J* = 8Hz), 7.53 (m, 4H), 7.91 (m, 9H), 8.53 (m, 1H); ^{13}C NMR (101 MHz, DMSO-ds), showed signal at (δ ppm), 160. 30, 150.14for carbon (C-O) and (C-N), 130.70, 133.54 , 129.60 ,129.10 ,127.72 , 127.55 , 127.39 , 126.61 , 125.59 , 121.98 , 119.25 , 118.05, 20. 90 for aromatic carbons.; MS: m/z = 362(M^+).

RESULTS AND DISCUSSION

The aim of the work is synthesis of some heterocyclic compound containing phthalazine moiety via aroylation of aromatic system by reaction of phthalic anhydride under Friedel Craft's condition yields the o-aroyl benzoic acid.[27,28]

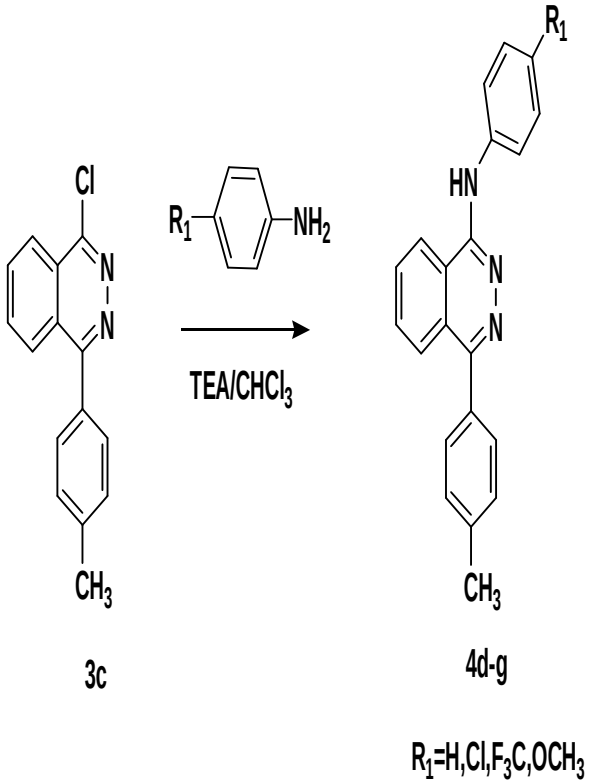
The reaction of toluene with phthalic anhydride in the presence of anhydrousAlCl3 was carried out to give 2-[4-methylbenzoyl] benzoic acid 1a.

According to Merchant[29], compound 1a was further cyclized to 2b using hydrazine hydrate in ethanol moreover, treatment of 2b with phosphorus oxychlorideunder reflux afford the key intermediate 1-chloro-4-p-tolyphthalazin 3caccording to Scheme 1.



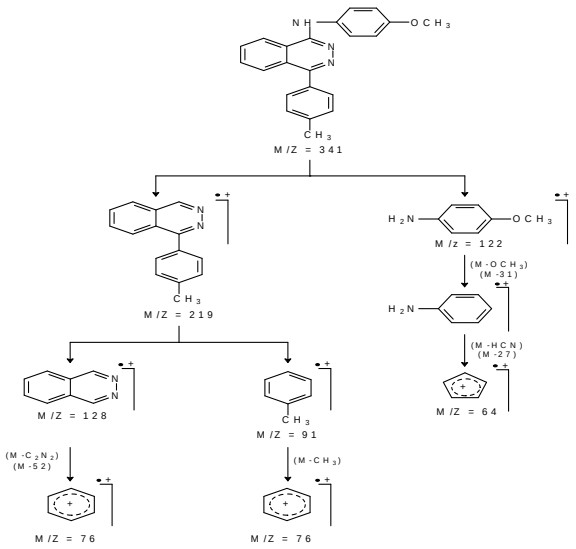
Scheme 1: Synthesis of 1-chloro-4-p-tolyphthalazin 3c.

The reactions of 3c with nitrogen containing nucleophiles such as aniline, p-chloroaniline, Triflouromethyl aniline and p-anisdine in dry chloroform in presence of few drops of triethylamine, and reflux afford the corresponding phthalazine derivatives: 4d-g as depicted in Scheme 2.

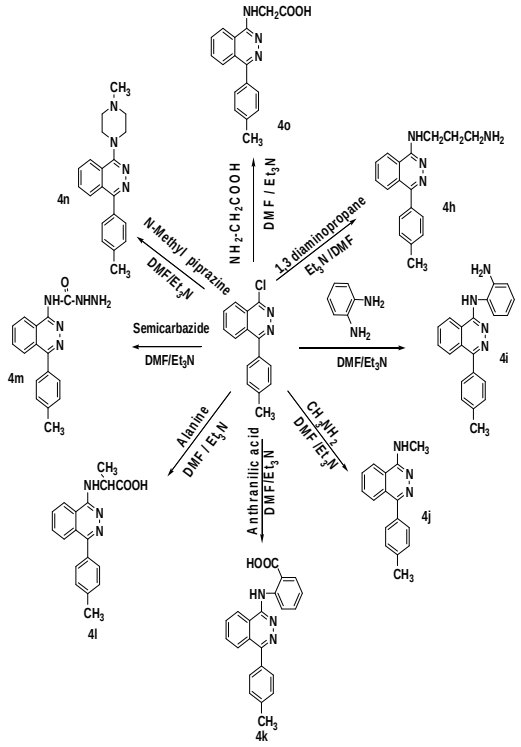


Scheme 2: Synthesis of aminophthalazine derivatives 4d-g.

The structure elucidation of 4d-gshowed a characteristic absorption bands at cm-1: 3251-3268 (NH), 1504-1617(C = N). 1HNMR spectrum (ppm) at 2.41-2.45(s,3H,CH3), 7.01-8.68 (m,aromatic proton) , 9.12-10.83(s,1H,NH), for compound 4g(ppm) 3.76(s,3H,OCH3),.compound 4e,4f mass spectra showed molecular ion peak at m/z = 345, 379. While compound 4g mass spectrum showed the following fragmentation pattern: m/z = 341 (M+, 100), 219(37.5), 122(12.5), 128(7.5), 91(55), 76(7.5) and 64 (10) as shown in Chart 1.

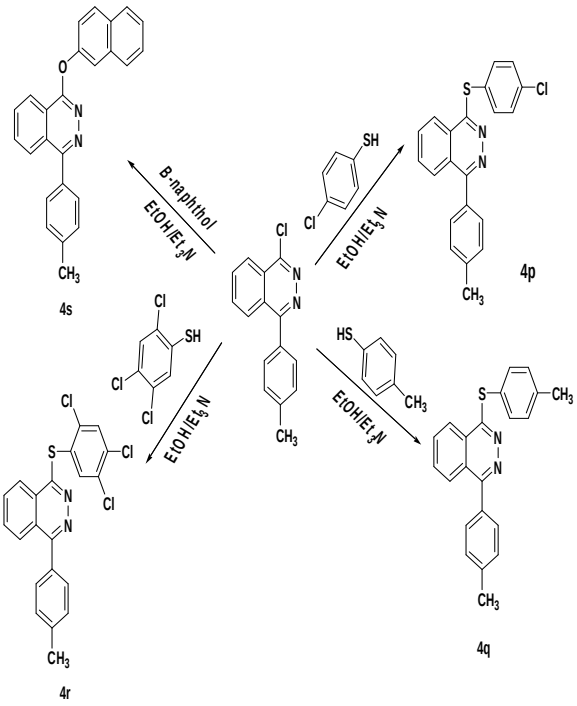


Treatment of 1-chloro-4-p-tolyl phthalazine3c with aromatic or aliphatic amines derivatives in dry DMF with few drops of triethylamineafford thephthalazine derivatives 4h-oas depicted in Scheme 3.



Scheme 3: Synthesis of aminophthalazine derivatives **4h-o**.

On the reaction of 1-chloro-4-p-tolylphthalazine 3c with p-chlorophenylthiol,p-methylphenylthiol,2.4.5-trichlorophenylthiol and β-naphthol in absolute ethanol affordphthalazine derivatives 4p-s according to Scheme 3. The structures of 4p-s were confirmed on the basis of spectral analysis. The IR spectra showed absorption bands at cm-1 1450-1480 (C-S), 1590-1620(C = N), (C-O); while1HNMR spectrum showed signal at (ppm): 2.43(s,3H,CH3)Ar, 7.36-8.33(m, aromatic proton), mass spectrum13CNMR showed signal at (ppm) 160.30, 150.13 for carbon (C-O) and (C = N), 133. 90 ,70, 20.



Scheme 4: Synthesis of thiolophthalazine derivatives **4p-s**

Antibacterial Screening

The antibacterial activities of the synthesized compounds were tested against Escherichia coli NRRL B-210 and Pseudomonas NRRL B-23 (Gram -ve bacteria), Bacillus subtilis NRRL B-543 and Staphylococcus aureus NRRL B-313 (Gram +ve bacteria) using nutrient agar medium. The antifungal activity of these compounds was also tested against Candida albicans NRRL Y-477 using Sabouraud dextrose agar medium. Agar Diffusion. The synthesized compounds were screened *in vitro* for their antimicrobial activity against, by agar diffusion method (Cruickshank 1975). 0.5 ml suspension of each of the aforementioned microorganisms was added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 0.9cm in diameter were made using a cork borer. Amounts of 0.1ml of the synthesized compounds were poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The diameters of the inhibition zone of were measured and compared with that of the standard and the values were tabulated. The same method was carried out using Sabouraud dextrose agar medium on using Candida albicans NRRL Y-477. The plates were then incubated at 30°C for 24 hours and observed for antibacterial activity. The diameters of inhibition zone were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin (50 µg/ml) and Fusidic acid (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively.[29] The observed zone of inhibition is presented in **Table 1.**

Table 1: *In vitro* antimicrobial activity by agar diffusion method of tested Compounds

Compds.	Microorganism inhibition zone diameter (mm)				
	Gram +ve bacteria		Gram –ve bacteria		Fungi
	Bacillus subtilis	Staphylococcus aureus	Escherichia coli	Pseudomonas aeuroginosa	Candida albicans
4d	17	-ve	10	-ve	-ve
4e	16	15	16	15	15
4f	14	15	2	15	12
4g	16	13	20	15	20
4h	12	-ve	**11**	-ve	12
4i	14	**11**	12	**11**	12
4j	12	13	20	18	20
4k	12	10	13	**11**	13
4L	15	13	15	15	12
4m	12	-ve	10	-ve	15
4n	16	13	18	16	12
4O	12	-ve	**11**	**11**	19
4p	12	-ve	12	-ve	12
4Q	12	10	12	10	**11**
4r	**11**	-ve	-ve	-ve	**11**
4s	14	-ve	-ve	**11**	15
Amoxicillin	6.25	6.25	6.25	-	-
Ketoconazole	-	-	-	-	31.25

Highly active (+++)= (inhibition zone > 20 mm); Moderately active (++)=(inhibition zone 15 - 19 mm)

Slightly active (+)= (inhibition zone 10 - 14 mm); Inactive (-ve) = (inhibition zone < 10 mm)

CONCLUSION

Antimicrobial studies of aniline derivatives **4d-g** indicated moderate activity against Bacillus subtilis and slight activity against E coli while have no activity against Staph. Aureus, P. aeuroginosa and Candida albicans. Substitutions with amino groups was proven to improve the antimicrobial activity against test microbes. The activity was increased by substitution with 4i, 4l, 4n, 4e, 4j and 4g respectively. The best compound which exhibited antimicrobial activity against test fungi was p-anisidine. This compound showed high activity against E. coli and C. albicans, Moderate activity against B. subtilis and P. aeurogenosa and slight activity against Staph aureus.

REFERENCES

1. Chorghade, M. S. In Drug Discovery and Development; John Wiley & Sons: Hoboken, New Jersey, Vol. 2, 2007.
2. Lednicer, D.; Mitscher, L. A. In The Organic Chemistry of Drug Synthesis; John Wiley & Sons: New York, Chichester, Brisbane, Toronto, Vol. 1, 1977.
3. M. Napolectane, G. Norcini, F. Pellacini, F. Marchini, G. Morazzoni, P. Ferlenga and L. Pradella. Bioorg. *Med. Chem. Lett*., 10, 2000, 2235.
4. M. Agrawal, P. Kharkar, S. Moghe, T. Mahajan, V. Deka, C. Thakkar, A. Nair, C. Mehta, J. Bose, A. Kulkarni-Almeida, D. Bhedi, R.A. Vishwakarma. Bioorg.Med. Chem. Lett., 23, 2013, 5740.
5. M.R. Ciria, A.M. Sanz, M.J.R. Yunta, F.G. Contreras, P. Navarro, I. Fernansez, M. Pardo, C, Cano, C., *Bioorg. Med. Chem*., 11, 2003, 2143.
6. M.C. Cardia, E. Distinto, E. Maccioni, A. Deloga, 105840b, *J. Heterocyclic. Chem*., 40, 2003, 1011.
7. R. M. Butnariu, M.D. Caprosu, V. Bejan, M. Ungureanu, A. Poiata, C. Tuchilus, M. Florescu, I.I. Mangalagiu, *J. Heterocyclic Chem*., 44, 2007, 1149.
8. C-K. Ryu, R.E. Park, M-Y. Ma, J-H. Nho, Bioog. Med. Chem. Lett., 17, 2007, 2577.
9. Juan, Li, Yan-Fang Zhao, Xiao-Ye Yuan, Jing-XiongXu and Ping Gong, Molecules, 11, 2006, 574.
10. V.M. Loh Jr., X-I, Cockcroft, K.J. Dillon, L. Dixon, J. Drzewiecki, P.J. Eversley, S. Gomez, J. Hoare, F. Kerrigan, I.T.W. Matthews, K.A.Menear, N.M.B. Martin, R.F. Newton, J. Paul, G.C. Smith, J. Vile, A. J. Whittle, Bioorg. Med. Che. Lett., 15, 2005, 2235-2239.
11. S.I. Zhang, Y.J. Liu, Y.F. Zhao, Q.T. Guo, P. Gong, Chin. Chem. Lett., 21, 1071.
12. S. Zhang, Y. Zhao, Y. Liu, D. Chen, W. Lan, O. Zhao, C. Dong, L. Xia, P. Gong, S. Zhang, Eur. *J. Med. Chem.,* 45, 2010, 3504.
13. A. Akashi, T. Chiba, A. Kasahara, Eur. *J. Pharm.,* 29, 1974, 161.

14. E. del Olmo, B. Barboza, M. Ybarra, Jose'LuisLo-Pe'rez, R. Carro'n, M.A. Sevilla, C. Boselli, A.S. Feliciano, Bio. Med. Chem. Lett., 16, 2006, 2786.
15. Johnsen, M.; Rehse, K.; Petz, H.; Stasch, J.; Bischoff, E. Arch. Pharmacol. 336, 2003, 591-597.
16. Madhavan, G.R.; Chakrabarti, R.; Kumar, S. K.; Misra, P.; Mamidi, R.N.; Balraju, V.; Ksiram, K.; Babu, R. K.; Suresh, J.; Lohray, B.B.; Lohray, V.B.; Iqbal, J.; Eur. J. Med.Chem. 36, 2001, 627-637.
17. Lenze, E.M.; Wilson, I.D.; Wright, B.; Partidge, E.A.; Roddgers, C.T.; Haycock, P.R.; Lindon, J.C.; Nicholson, J.K.J. Pharm, Biomed. Anal. 28, 2002, 31-43.
18. M. Sánchez-Moreno, F. Gómez-Conterras, P. Navarro, C. Marin, F. Olmo, M.J.R. Yunta, A. M. Sanz, M.J. Rosales, C. Cano, L. Campayo, *J. Med. Chem.,* 55, 2012, 9900.
19. X-Y. Sun, C. Hu, X-Q. Deng, C-X. Wei, Z-G. Sun, Z-S. Quan. Eur. *J. Med. Chem.,* 45, 2010, 4807.
20. Mosaad, S.M. Abdalla, Mohamed, I. Hegab, Nageh, A. Abo Taleb, Sherifa M. Hasabelnaby, A. Gouda, Eur. *J. Med. Chem.,* 45, 2010, 1267.
21. N. Kaila, A. Huang, A. Moretto, B. Follows, K. Janz, M. Lowe, J. Thomason, T.S. Mansour, C. Hubeau, K. Page, P. Morgan, S. Fish, X. Xu, C. Williams, E. Saiah, *J. Med. Chem.,* 55, 2012, 5088.
22. Van der Mey, M.; Hatzelmann, A.; Van Klink, G.P.; Van der Lann, I.J.; Sterk, G.J.; Thibaut, U.; Timmerman, H., *J. Med. Chem*., 44, 2001, 2511.
23. L.H. Pettus, S. Xu, G-Q. Cao, P.P. Chakrabarti, R.M. Rz\sa, K. Sham, R.P. Wurtz, D. Zhang, S. Middleton, B. Henkle, M.H. Plant, C.J.M. Saris, L. Sherman, L. Wong, D.A. Powers, Y. Tudor, V. Yu, M.R. Lee, R. Syed, F. Hseh, A.S. Tasker, *J. Med.* Chem., 51, 2008, 6280.
24. Nagues, S. habib, Ahmed M. Farghaly, Fawzia A. Ashour, Adnan Bekhit, Heba A. Abd El Razik, TarekAbdElAzeim, *Archiv der Pharmazie*, 344, 2011, 530.
25. Brad, H.; Guo-Qiang, C.; Partha, P.C.; James, R.F.; Liping, P.; Robert, M.R.; Anthony, B.R.; Andreas, R.; Kelvin, S.; Maya, T.; Ryan, P.W.; Shimin, X.; Dawei, Z.; Faye, H.; Matthew, R.L.; Rashed, S.; Vivian, L.; Daved, G.; Matthew, H.P.; Bradley, H.; Lisa, S.; Scot, M.; Lu, M.W.; Andrew, S.T.; *J. Med*. Che., 51, 2008, 6271.
26. F. M.Awadallah, W.I.EL-Kraky, D.O.Saleh, Eur, *J. Med.Chem*., 52, 2012, 14.
27. B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogels Text Book Predical Organic Chemistry, 5 Thed, Longman, England, 1989.
28. J.P. Danial, R.J. Carl, Laboratory Text for Organic Chemistry, 1979.
29. J.R. Merchant, S.D. Kulkarni, M.S. Venkatesh, Indian *J. Chemistry*, 19, 1980, 914.
30. R. Cruickshank, J.P. Duguid, B.P. Marion, R.H.A. Swain, Medicinal Microbiology, twelfth ed., vol. II, Churchill Livingstone, London, 1975, 196-202.

Source of Support: Nil, **Conflict of Interest:** None.