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DESIGN AND FACILE SYNTHESIS OF 6-(THIOPHEN-3-YL)-3-PARA-SUBSTITUTED-[1,2,4] TRIAZOLO[3,4-*a*] PHTHALAZINE DERIVATIVES AS ANTI-MICROBIAL AGENTS

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ABSTRACT
The article is aimed to synthesize, characterize and screening the biological activity of novel a series of 6-(Thiophen-3-Yl)-3-Para-Substituted-[1,2,4] Triazolo[3,4-a] Phthalazine Derivatives (8 a-j)with good yields.The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C NMR and Mass spectral data. The anti-microbial activity of the novel compounds were screened by disc diffusion method. Compounds 8h, 8g, and 8f demonstrated good antimicrobial activity against all the tested microbial strains.FusedPhialazine 1, 2,4 Triazole linked thiophene with 2,5 di fluoro nucleus has shown good antibacterial and antifungal activities.

KEY WORDS :1,4-dichloroPthalazine, Tri azolopthalazines, hydrazine hydrate, Microwave irradiation, Suzuki Coupling, Antimicrobial activity

INTRODUCTION:
Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics[I-II]. Hence, they have attracted considerable attention in the design of biologically active molecules[III-IV] and advanced organic chemistry [V-VI]. Also in the family of Heterocyclic compounds nitrogen containing Heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes[VII].

Phthalazine derivatives, like the other members of the isomeric benzodiazine series, have been widely applied as therapeutic agents due to their anticonvulsant, cardiotonic, vasorelaxant and anti-inflammatory properties[VIII-IX].Majorities of the drugs used in human medicine are hetero cyclic compounds. Common drugs such as Morphine,Lipitor, Penicillin, and non-steroidal anti-inflammatory agents contain at least one heteroatom in their structure [X]. Heterocyclic compounds containing nitrogen group have large area in nature, and their utilization is becoming progressively important as biologically active pharmaceuticals, agrochemicals, and functional materials [XI]. In particular, hydrazine containing hetero cyclic compounds have been considered of great importance on account of pharmacological properties and clinical applications [XII]. Moreover, these of combined phthalazines have biological properties such as inhibition of p38MAPkinase[XIII] for selective binding of GABA receptor [XIV], anti-anxiety drug [XV], antitumor agent[XVI], and high affinity ligand to the a_2d-1 sub unit of calcium-channel[XVII].

Phthalazine derivatives have been greatly used as therapeutic agents owing to their anticonvulsant, cardiotonic, vasorelaxant, anti-inflammatory properties [XVIII–XXIII], and anti-microbial activity [XIV]. Like azelastine, the phthalazine derivatives have antihistaminic effects in the treatment of allergic rhinitis [XXV], and hydralazine is used as antihypertensive agent in the treatment of pulmonary hypertension [XXVI–XXVIII].Some commercially used phthalazine derivatives are shown in **FIG 1**.

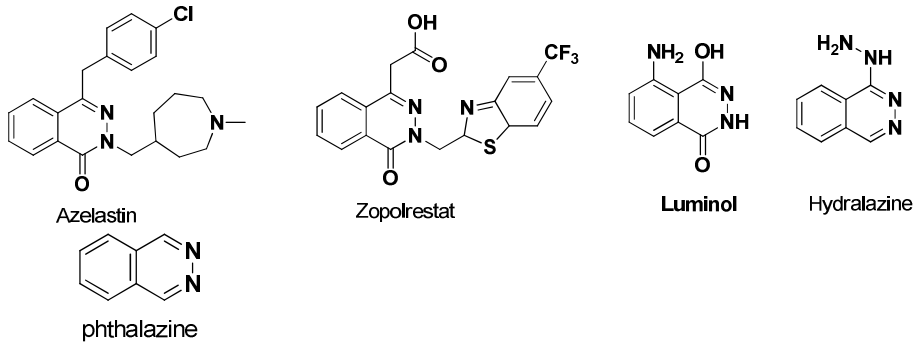
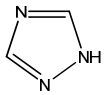


FIG 1: Some commercially used phthalazine derivatives & Structure of Pthalazine.

Pthalazines are synthetically versatile substrates and hence can be used for the synthesis of a large variety of heterocyclic compounds. Pthalazines occupy a distinct and unique place in our life. This Hetero cyclic moiety has great biological and medicinal significance. Various synthetic aspects indicate that Pthalazine derivatives are easy to synthesize which can produce a wide variety of activity.

1, 2, 4-Triazole is one of a pair of Isomeric chemical compounds with molecular formula $C_2H_3N_3$, called Tri azoles **(Fig:2)**, which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1, 2, 4-Triazole is a basic aromatic hetero cycle.



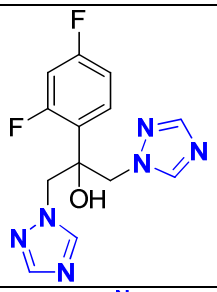
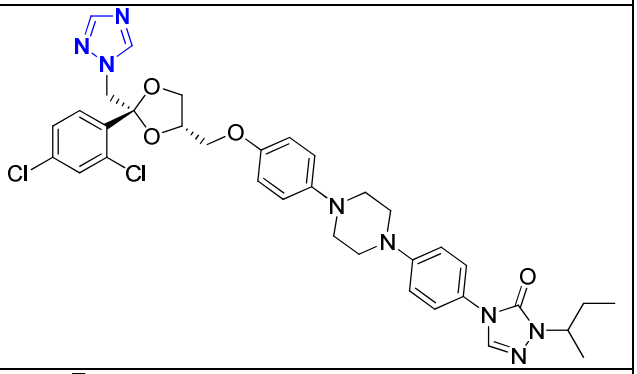
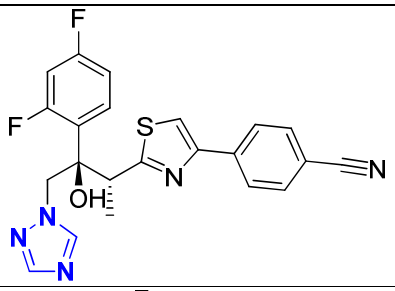
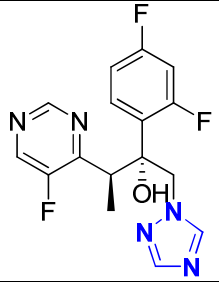
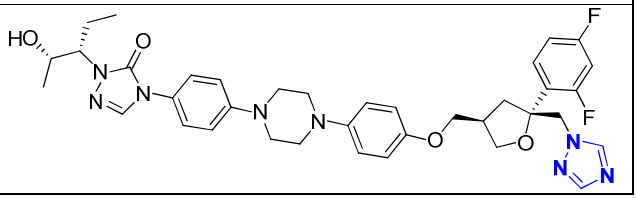
1,2,4 Tri Azole

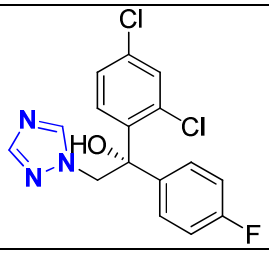
(Fig:2 structure of 1, 2, 4 tri azole)

The 1, 2, 4-triazole compounds are considered interesting heterocycles since they possess Important pharmacological activities such as antifungal and antiviral activities. Examples of antifungal drugs [XXIX, XXX] are fluconazole (1) [XXXI-XXXII], itraconazole (2) [XXXIII], ravuconazole (3) [XXXIV], voriconazole (4) [XXXV-XXXVI], ICI 153066 (5) [XXXVII], and

posaconazole (6) [XXXVIII][**Table 1**]. 1,2,4 tri azole core structure was shown in blue colour in Table 1.

Table 1:Examples of antifungal drugs containing 1, 2, 4 tri azole nucleus:

S.NO	**Anti fungal Drug Name**	**Structure**
1	Flucanazole	
2	Itraconazole	
3	Ravuconazole	
4	Voriconazole	
5	Posaconazole	

6	ICI	

1,2,4-triazoles are very interesting targets for medicinal and pharmaceutical applications. 1,2,4-triazole derivatives investigated due to their wide range of biological activities such as antifungal [XXXIX], antitubercular[XL], anticonvulsants [XLI-XLII], 5- lipoxygenase inhibitors [XLIII]and as anticancer drugs [XLIV], Platinum(II) complexes comprising 1,2,4-triazoles as ligands show antitumor activity similar to cis-platin[XLV-XLVIII]. Literature survey reveals that various 1, 2, 4-triazole derivatives display signify cant biological activities such as Bactericidal [XLIX],Diuretic[L], Fungicidal [LI], Herbicidal [LII], Insecticidal and acaricidal[LIII], Plantgrowthregulator[LIV], Anticancer and Anti-HIV[LV], Antileshmanial[LVI], Antitumor [LVII] activities.

Encouraged by the diverse biological activities of Pthalazine compounds, it was decided to prepare a new series of Pthalazines derivatives. The synthesis of the compounds as per the following Scheme **I** given below.

The synthetic route was depicted in scheme **I**

The structures of all synthesized compounds were assigned on the basis of IR, Mass, ^{1}H NMR spectral data. Further these compounds were subjected for antifungal and anti-bacterial activity.

MATERIALS AND METHODS:

Laboratory chemicals were provided by Rankem India Ltd. and Fisher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene:ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light or P-Anisaldehyde Stain Solution. The IR spectra were received by PerkineElmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H NMR &^{13}C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in $CDCl_3$.

General Information:

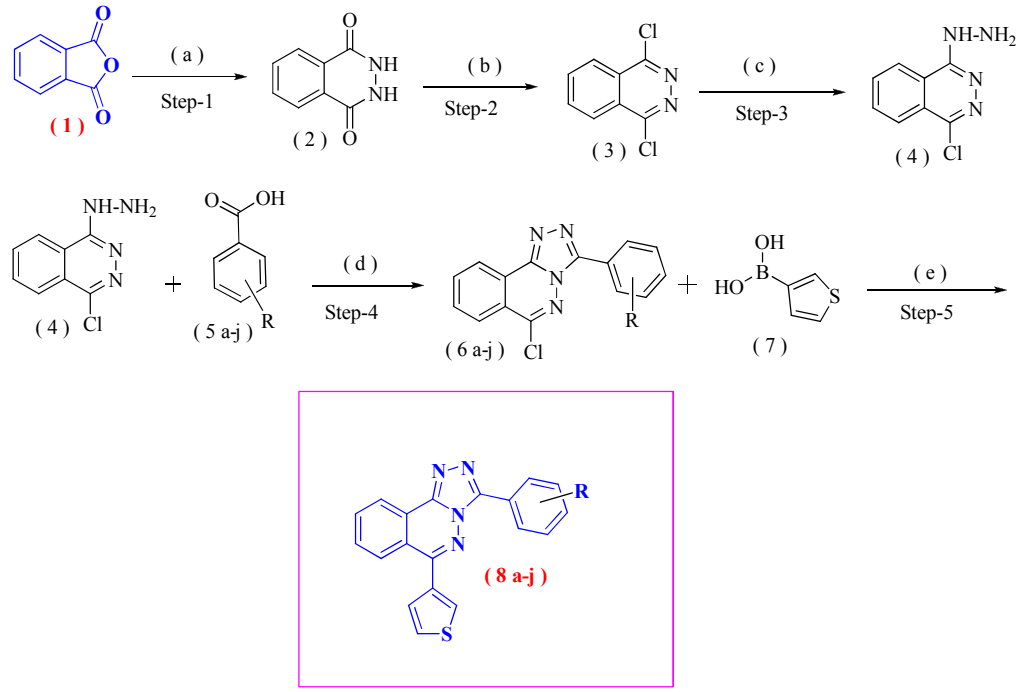
Commercial chemicals were treated as follows: 1,4 di oxane distilled from CaH_2 and degassed (freeze and thaw) three times prior to use; THF, ether, distilled from Na/benzophenone.

The synthesis of the compounds as per the following Scheme **I** given below.

The synthetic route was depicted in scheme **I**

The title compounds 8(a-j) were synthesised in five sequential steps using different reagents and reaction conditions, the 8(a-j) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

SYNTHETIC SCHEME



R = -H, -4 CH_3, -4 OCH_3, -4 NO_2, 3,4 di methoxy, -4 F, 2,5 DI Fluoro, -4 CF_3 , -4 OCF_3, -2,4 di nitro

Reagents and Reaction conditions: ***(a)*** *Acetic acid, Hydrazine hydrate, Reflux, 4 hrs* ***(b)*** *$POCl_3$, Reflux, 6 hrs* ***(c)*** *Ethanol, Hydrazine hydrate, Tri Ethyl amine, RT, 3hrs* ***(d)*** *$POCl_3$, Reflux* ***(e)*** *K_2CO_3, $PdCl_2(Ph_3P)_2$, 1,4-dioxane, H_2O,micro wave irradiation, 120^0C.*

Experimental Section

General Methods: Column chromatography was performed using Silica gel 100-200 mesh size. THF and dioxane were distilled from sodium-benzophenone and dried over MS $5A^0$ and MS $4A^0$, respectively. MeCN and 1,2-dichloroethane (DCE) were distilled from CaH_2. EtOH was distilled from Mg/I_2 and dried over MS $3A^0$. Prior to use, $POCl_3$ was distilled. All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenoneketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–100 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz BrukerAvance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-d_1 or DMSO-d_6 as the internal standard (^1H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

General procedure for the preparation of 2,3-dihydrophthalazine-1,4-dione[LVIII](Compound 2):

The starting material Pthalic anhydride (1) (**1 m.mol**) was dissolved in Acetic acid (10 Volumes). To this mixture hydrazine hydrate (**3 m.mol**) drop wise under ice bath. The

reaction mixture was stirred at room temperature for 20 mints, and then raises temperature at110^{0}C for 4 hrs. The off white solid was precipitated was collected through filtration and washed the chilled water and dried to afford compound 2 (**Yield**80%).
m.p.: 300^0 C above also not melted.
^{1}H NMR (DMSO-d$_6$, 400 MHz): 8.1(d, 2H), 7.9 (d, 2H), 11.2 (bs, 2 H).
^{13}C NMR (DMSO-d$_6$, 100 MHz): 120,134,117,169
IR (KBr, cm^{-1}): O-H (3510, sharp), Ar stretch C-H (3130.34), C-O (1060), C=N (1608.69), C=C (1344.43)
LC-MS Shows 99% purity at RT 1.924 min. Mass 161[M-H]$^+$
General procedure for the preparation of 1, 4-dichlorophthalazine[LIX](Compound 3):
The compound (2) (**10 m.mol**) was added to a stirred solution of phosphoruso xychloride (15 ml). The
mixture was heated to 110°C for 1 h. After the reaction wascomplete (monitored by TLC), T he reaction mixture was cooled to room temperature. The mixture was added dropwise to cru shed ice with stirring for 10 minutes. Then themixture was filtered through a buchner funnel. the filter cake was washed with
H_2O until neutral and dried in a vacuum. Compound (3)(**Yield** 90%) was obtained as a white solid.
m.p.: 160–162^0 C.
^{1}H NMR (DMSO-d$_6$, 400 MHz): 8.1(d, 2H), 7.9 (d, 2H).
^{13}C NMR (DMSO-d$_6$, 100 MHz): 120,134,117,169
IR (KBr, cm^{-1}): O-H (3510, sharp), Ar stretch C-H (3130.34), C-O (1060), C=N (1608.69), C=C (1344.43)
GC-MS (m/z): Shows 99% purity at RT 8.738 min. Mass **198** [M$^+$], 200[M+2], 202[M+4] (9:6:1, it indicates molecule contains two chlorine atoms).
General procedure for the preparation of 1-chloro-4-hydrazinylphthalazine [LX](Compound 4):
1,4-Dichlorophthalazine (20.0 g, 0.1 mol) was added to a solution of hydrazine monohydrate (37.3 ml, 0.3 mol) in ethanol (500 ml), Tri Ethyl amine(0.5 mol) and the mixture Stirred atRT for 3 hrs.
the solid collected by filtration. The material was washed with ether, azeotroped with ethanol and dried in vacuo to afford the compound4.
m.p.: 256–257^0 C.
^{1}H NMR (400 MHz, d$_6$-DMSO) 7.72-8.35 (4H, m, 4 of Ar-H). 4.64 (2H, bs), 7.2 (1H, bs)
^{13}C NMR (DMSO-d$_6$, 100 MHz): 120,134,132, 124, 165, 146, 118,125
IR (KBr, cm^{-1}):3368 & 3272 (-NH_2), 3066 (Ar-H), 1574 (C=C), 1468 (C=N), 660 (C-Cl).

MassShowsMass195[M-H]$^+$, 197[M+2].(3:1, it indicates molecule contains one chlorine atom).
General procedure for the preparation of 6-chloro-3-phenyl-[1,2,4]triazolo[3,4-a]phthalazine (6a),
6-chloro-3-p-tolyl-[1,2,4]triazolo[3,4-*a*]phthalazine (6b), 6-chloro-3-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6c), 6-chloro-3-(4-nitrophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6d), 6-chloro-3-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6e), 6-chloro-3-(4-fluorophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6f), 6-chloro-3-(2,5-difluorophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6g), 6-chloro-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6h), 6-chloro-3-(4-

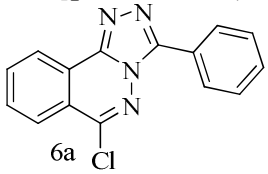
(trifluoromethoxy)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6i), 6-chloro-3-(2,4-dinitrophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine(6j)[LXI]:

Compound (4) (0.1 **m.mol**), and substituted benzoic acids (5 a-j) (0.15**m.mol**) were taken in $POCl_3$ (5 ml) and heated to reflux for 7 hrs. The reaction mass was concentrated under reduced pressure and then quenched in ice . The Solid obtained was filtered off, washed with aqueous $NaHCO_3$ Solution and dried.

Table 2 Yields& Melting Points of Corresponding Compounds (6 a-6j) :

S.NO	Yield (%)	Melting Point (^oC)	Physical appearence
6a	80	102-104	White Solid
6b	82	183-184	Off white Solid
6c	76	126-127	White Solid
6d	76	143-144	Pale Yellow Solid
6e	73	115-116	Pale brown solid
6f	71	124-126	Brown solid
6g	78	190-191	Off white Solid
6h	75	168-169.2^{0}C	White Solid
6i	73	115-116	Pluppy White Solid
6j	72	127-128	Off white Solid.

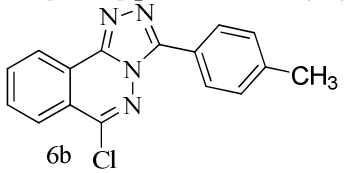
6-chloro-3-phenyl-[1,2,4]triazolo[3,4-*a*]phthalazine (6a) :



6a

^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.9(2H,d), 7.4-8.3 (5H,m).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 120-156 (13 Aromatic carbons).
IR (KBr, cm^{-1}): 3056 (Ar-H), 1544 (C=C), 1428 (C=N), 680 (C-Cl).
EI-MS (m/z): 280 [M^+], 282[M+2], (3:1, it indicates molecule contains one chlorine atom).

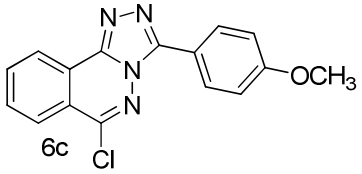
6-chloro-3-p-tolyl- [1,2,4] triazolo [3,4-*a*] phthalazine (6b):



6b

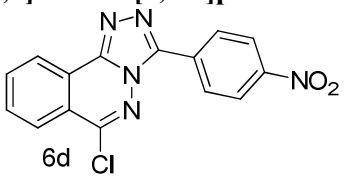
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.9(2H,d), 2.4 (3H,S), 8.6(2H,d), 7.3(2H,d)..
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 123-156 (13 Aromatic carbons), 23(Aromatic methyl carbon).
IR (KBr, cm^{-1}):2957 (SP^3 C-H), 3066 (Ar-H), 1564 (C=C), 1468 (C=N), 670 (C-Cl).
EI-MS (m/z): 295 [M^+], 297[M+2], (3:1, it indicates molecule contains one chlorine atom).

6-chloro-3-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6c) :

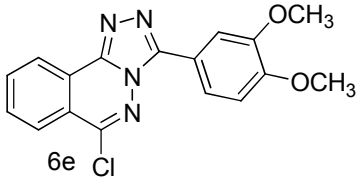


6c

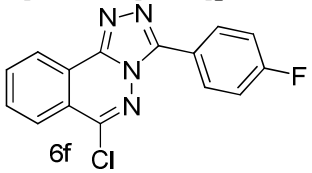
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.85(2H,d), 3.85 (3H,S), 8.1(2H,d), 7.03(2H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 113-2-163(13 Aromatic carbons), 56.5(Aromatic methoxy carbon).
IR (KBr, cm^{-1}): 2968 (SP^3 C-H), 3066 (Ar-H), 1564 (C=C), 1468 (C=N), 656 (C-Cl), C-O-C (1060 & 1230).
EI-MS (m/z): 310 [M^+], 312[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(4-nitrophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6d) :



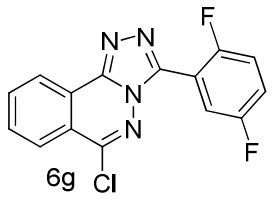
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.83(2H,d), 8.1(2H,d), 8.4 (2H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 124-156(13 Aromatic carbons).
IR (KBr, cm^{-1}):1360& 1520(N-O Symmetric and asymmetric Stretching in nitro group), 3046 (Ar-H), 1574 (C=C), 1468 (C=N), 636 (C-Cl),
EI-MS (m/z): 325 [M^+], 327[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6e) :



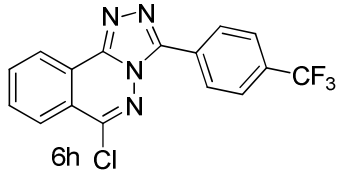
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.83(2H,d), 3.85 (3H,S), 3.88(3H,S),7.3(1H,d, J=2.4 Hz), 7.53(1H,d), 6.9(1H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 110-157(15 Aromatic carbons), 56.5(Aromatic methoxy carbons).
IR (KBr, cm^{-1}): 2988 (SP^3 C-H), 3046 (Ar-H), 1554 (C=C), 1438 (C=N), 676 (C-Cl), C-O-C (1060 & 1230).
EI-MS (m/z): 340 [M^+], 342[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(4-fluorophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6f) :



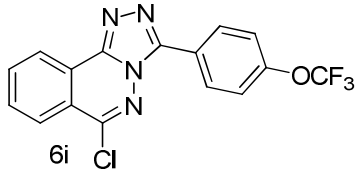
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 7.9(2H,d), 7.85(2H,d), 7.82(2H,d,), 7.4(2H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 125-156 (13 Aromatic carbons).
IR (KBr, cm^{-1}): 3086 (Ar-H), 1584 (C=C), 1668 (C=N), 664 (C-Cl), C-F (1268).
EI-MS (m/z): 299 [M^+], 301[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(2,5-difluorophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6g) :



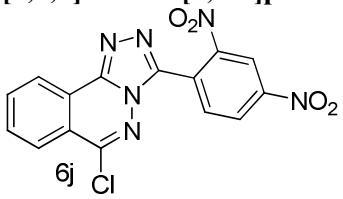
^{1}H NMR (400 MHz, d_1-$CDCl_3$) 7.9(2H,d), 7.83(2H,d), 7.3(1H,d,), 7.2(1H,dd), 7.5(1H,dd, J_{H-F}=, J_{H-H} = 2.4HZ).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 115-158(15 Aromatic carbons).
IR (KBr, cm^{-1}): 3036 (Ar-H), 1582 (C=C), 1438 (C=N), 654 (C-Cl), C-F (1260).
EI-MS (m/z): 316 [M^+], 318[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6h) :



^{1}H NMR (400 MHz, d_1-$CDCl_3$) 7.9(2H,d), 7.85(2H,d), 8.6(2H,d,), 7.7(2H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 125-156(13 Aromatic carbons), 124.3(Trfluoro methyl carbon).
IR (KBr, cm^{-1}): 3066 (Ar-H), 1584 (C=C), 1448 (C=N), 664 (C-Cl), C-F (1278).
EI-MS (m/z): 348 [M^+], 350[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (6i) :



^{1}H NMR (400 MHz, d_1-$CDCl_3$) 7.9(2H,d), 7.85(2H,d), 8.02(2H,d,), 7.06(2H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 123-156 (13 Aromatic carbons), 125.8(Trfluoro methyl carbon).
IR (KBr, cm^{-1}): 3066 (Ar-H), 1584 (C=C), 1448 (C=N), 664 (C-Cl), C-F (1278), 1084(C-O-C).
EI-MS (m/z): 364 [M^+], 366[M+2], (3:1, it indicates molecule contains one chlorine atom).
6-chloro-3-(2,4-dinitrophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine(6j) :



^{1}H NMR (400 MHz, d_1-$CDCl_3$) 8(2H,d), 7.83(2H,d), 8.95(1H,s), 8.74(1H,d),8.34 (1H,d).
^{13}C NMR (d_1-$CDCl_3$, 100 MHz): 123-156(15 Aromatic carbons).
IR (KBr, cm^{-1}): 1350 & 1540(N-O Symmetric and asymmetric Stretching in nitro group), 3046 (Ar-H), 1574 (C=C), 1468 (C=N), 667 (C-Cl),
EI-MS (m/z): 370 [M^+], 372[M+2], (3:1, it indicates molecule contains one chlorine atom).

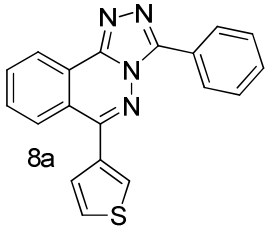
General procedure for the preparation of 3-phenyl-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8a), 6-(thiophen-3-yl)-3-p-tolyl-[1,2,4]triazolo[3,4-*a*]phthalazine (8b), 3-(4-methoxyphenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8c), 3-(4-nitrophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8d), 3-(3,4-dimethoxyphenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8e), 3-(4-fluorophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8f), 3-(2,5-difluorophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8g), 6-(thiophen-3-yl)-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8h), 6-(thiophen-3-yl)-3-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8i) , 3-(2,4-dinitrophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8j) [LXII]:

A mixture of 6a-6j (**0.6 m.mole**), thiophen-3-ylboronic acid (7) (**0.9 m.mol**), K_2CO_3 (**3.3 m.mol**), and $PdCl_2(Ph_3P)_2$ (**0.03 m.mol**), in 5 ml Solvent (Di oxane) was placed in a sealed tube and heated to 120^oC for 30 min using microwave irradiation. The reaction mixture was diluted with water and extracted with EtoAc, Dried with Na_2SO_4 filtered and evaporated to dryness. The Crude product was purified by preparative TLC, affording products (8a-8j). yields are 50-55 %.

Table 3 Yields& Melting Points of Corresponding Compounds (8a-8j) :

S.NO	Yield (%)	Melting Point (^oC)	Physical Appearence
8a	50	235-236	White Solid
8b	52	239-241	Off white Solid
8c	50	105-106	White Solid
8d	51	122-124	white Solid
8e	53	119-121	Off white solid
8f	54.2	125-127	White solid
8g	53	199-201	White solid
8h	52	213-214	White solid
8i	49.6	115-117	White solid
8j	52.3	232-234	White solid

3-phenyl-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8a) :



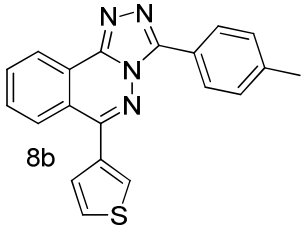
^{1}H NMR (400 MHz, d_6-DMSO) 7.88(2H,d), 7.9(2H,d), 7.4-8.3 (5H,m), 7.95(1H,d, J=3HZ), 7.7(1H,dd, J=7.3HZ, J=3HZ), 7.3(1H,d, J=7.3HZ).

^{13}C NMR (d_6-DMSO, 100 MHz): 120-155(17 Aromatic carbons).

IR (KBr, cm^{-1}): 3066 (Ar-H), 1544 (C=C), 1428 (C=N), 687(C-S-C).

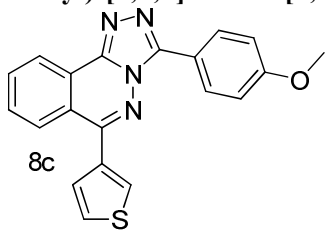
EI-MS (m/z): 329 [M+H].

6-(thiophen-3-yl)-3-p-tolyl-[1,2,4]triazolo[3,4-*a*]phthalazine (8b) :



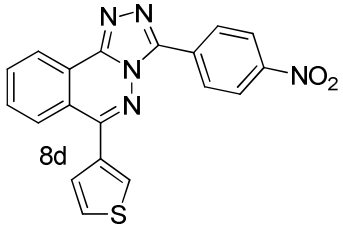
^{1}H NMR (**400 MHz, d_6-DMSO**) 7.8(2H,d), 7.9(2H,d), 2.4 (3H,S), 8.6(2H,d), 7.3(2H,d), 7.95(1H,d, J=3HZ), 7.7(1H,dd, J=7.3HZ, J=3HZ), 7.3(1H,d, J=7.3HZ).
^{13}C NMR (d_6-DMSO, 100 MHz)120-153 (17 Aromatic carbons), 23(Aromatic methyl carbon).
IR (KBr, cm^{-1}): 2959 (SP^3 C-H), 3068 (Ar-H), 1584 (C=C), 1458 (C=N), 677 (C-S-C).
EI-MS (m/z): 343 [M+H].

3-(4-methoxyphenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8c) :



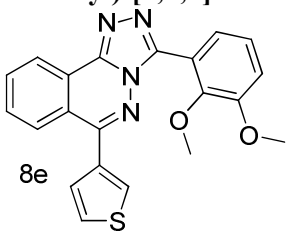
^{1}H NMR (**400 MHz, d_6-DMSO**) 7.8(2H,d), 7.9(2H,d), 3.8 (3H,S), 7.9(2H,d), 7.03(2H,d), 7.95(1H,d, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 7.23(1H,d, J=7.3HZ).
^{13}C NMR (d_6-DMSO, 100 MHz) 120-153 (17 Aromatic carbons), 56(Aromatic methyl carbon).
IR (KBr, cm^{-1}): 2969 (SP^3 C-H), 3066 (Ar-H), 1564 (C=C), 1458 (C=N), C-O-C (1060 & 1230), 667 (C-S-C).
EI-MS (m/z): 359 [M+H]$^+$.

3-(4-nitrophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8d) :



^{1}H NMR (**400 MHz, d_6-DMSO**) 7.85(2H,d), 7.9(2H,d), 8.09(2H,d), 8.33(2H,d), 7.95(1H,d, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 7.23(1H,d, J=7.3HZ).
^{13}C NMR (d_6-DMSO, 100 MHz) 120-152(17 Aromatic carbons), 56(Aromatic methyl carbon).
IR (KBr, cm^{-1}):1350 & 1540(N-O Symmetric and asymmetric Stretching in nitro group), 3046 (Ar-H), 1574 (C=C), 1468 (C=N), 665 (C-S-C).
EI-MS (m/z): 374[M+H].

3-(3,4-dimethoxyphenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8e) :



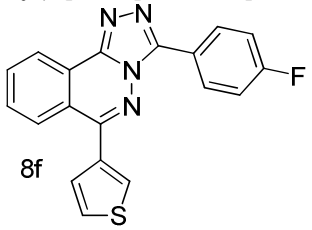
^{1}H NMR (400 MHz, d_6-DMSO) 7.8(2H,d), 7.9(2H,d), 3.8 (3H,S), 3.85(3H,S), 7.6(1H,d), 7.53(1H,dd, J=7HZ, J=3HZ), 7.25(1H,d, J=3HZ), 7.23(1H,d, J=7.3HZ),7.8(1H,dd, J=7.3 HZ, J=3HZ), 8(1H,d, J=3HZ).

^{13}C NMR (d_6-DMSO, 100 MHz) 120-152(19 Aromatic carbons), 56(Aromatic methyl carbon).

IR (KBr, cm^{-1}): 2969 (SP^3 C-H), 3066 (Ar-H), 1564 (C=C), 1458 (C=N), C-O-C (1060 & 1230), 667 (C-S-C).

EI-MS (m/z): 389 [M+H].

3-(4-fluorophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8f) :



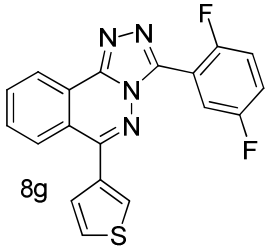
^{1}H NMR (400 MHz, d_6-DMSO) 7.85(2H,d), 7.9(2H,d), 7.8(2H,d), 7.33(2H,d), 7.95(1H,d, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 7.23(1H,d, J=7.3HZ).

^{13}C NMR (d_6-DMSO, 100 MHz) 120-163 (17 Aromatic carbons).

IR (KBr, cm^{-1}): 3054 (Ar-H), 1582 (C=C), 1438 (C=N), C-F (1260),662 (C-S-C).

EI-MS (m/z): 347[M+H].

3-(2,5-difluorophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8g) :



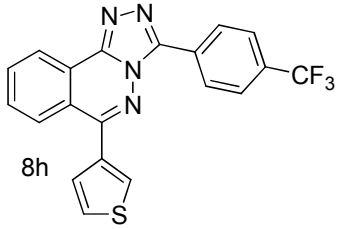
^{1}H NMR (400 MHz, d_6-DMSO) 7.85(2H,d), 7.9(2H,d), 7.5(1H,d, J=3HZ), 7.33(1H,d, J=7.3HZ,), 7.25(1H,dd, J=7.3HZ, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 8(1H,d, J=3HZ), 7.24(1H,d, J=7.3HZ).

^{13}C NMR (d_6-DMSO, 100 MHz) 120-158(19 Aromatic carbons).

IR (KBr, cm^{-1}): 3036 (Ar-H), 1582 (C=C), 1438 (C=N), C-F (1250),662 (C-S-C).

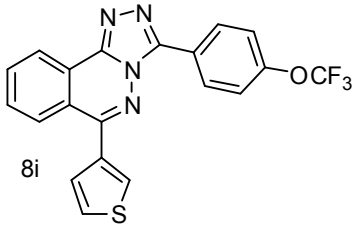
EI-MS (m/z): 365[M+H].

6-(thiophen-3-yl)-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8h) :



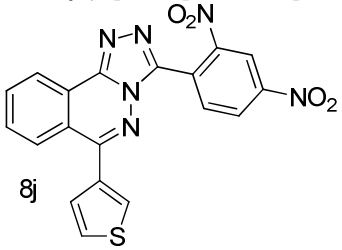
^{1}H NMR (**400 MHz, d_6-DMSO**) 7.85(2H,d), 7.9(2H,d), 8.6(2H,d), 7.7(2H,d), 7.95(1H,d, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 7.23(1H,d, J=7.3HZ).
^{13}C NMR (d_6-DMSO, 100 MHz) 120-153 (17 Aromatic carbons).
IR (KBr, cm^{-1}): 3064 (Ar-H), 1562 (C=C), 1428 (C=N), C-F (1250),662 (C-S-C).
EI-MS (m/z): 397[M+H].

6-(thiophen-3-yl)-3-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8i) :



^{1}H NMR (**400 MHz, d_6-DMSO**) 7.85(2H,d), 7.9(2H,d), 7.9(2H,d), 7.03(2H,d), 7.95(1H,d, J=3HZ), 7.75(1H,dd, J=7.3HZ, J=3HZ), 7.23(1H,d, J=7.3HZ).
^{13}C NMR (d_6-DMSO, 100 MHz) 120-153 (17 Aromatic carbons), 130(Trifluoro methyl carbon).
IR (KBr, cm^{-1}): 3066 (Ar-H), 1582 (C=C), 1438 (C=N), C-F (1250),662 (C-S-C).
EI-MS (m/z): 413[M+H].

3-(2,4-dinitrophenyl)-6-(thiophen-3-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine (8j) :



^{1}H NMR (**400 MHz, d_6-DMSO**) 7.85(2H,d), 7.9(2H,d), 8.99(1H,d, J=3HZ), 8.33(1H,d, J=7.3 HZ), 8.75(1H,dd, J=7.3 HZ, J=3HZ), 7.75(1H,dd, J=6.3HZ, J=2.8HZ), 7.23(1H,d, J=6.3HZ), 8(1H,d, J=2.8HZ).
^{13}C NMR (d_6-DMSO, 100 MHz) 120-152 (19 Aromatic carbons).
IR (KBr, cm^{-1}): 1350 & 1540(N-O Symmetric and asymmetric Stretching in nitro group), 3066 (Ar-H), 1584 (C=C), 1478 (C=N), 660 (C-S-C).
EI-MS (m/z): 419[M+H].

Biological Activity

Antibacterial activity

Antimicrobial screening The samples of synthesized Compounds (8a-8j) for antimicrobial activity were prepared at concentration 40µg/ml in DMSO solvent. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against Gram positive bacteria Staphylococcus aureus (S. aureus) and Bacillus subtilis (B. subtilis), Gram negative bacteria Pseudomonas aeruginosa (P. aeruginosa) and Escherichia coli (E. coli). The antifungal activity was checked against fungi Aspergillusniger (A. niger) and Candida albicans (C. albicans). The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.ThePthalazine-1,2,4 triazolederivates containing Thiophenecore structure with 2,5 di flouro (8g) and $-CF_3$ (8h) showed more activity than other substituent's8g>8h>8i>8j>8f >8 d >8b>8a>8c>8e.

Antibacterial activity of Novel Compounds (8a-8j) :

Table 4 In vitro antibacterial and antifungal activities of the synthesized compounds (8a-8j):

Anti-Bacterial activity (Zone if Inhibition in mm)				**Anti-Fungal Activity (Zone if Inhibition in mm)**		
Compound	**Staphylococcus aureus**	**Bacillus subtilis**	**P. aeruginosa**	**E. coli**	**A. niger**	**C. albicans**
8a	12	11	07	11	23	19
8b	12	16	10	14	09	12
8c	10	28	17	21	14	12
8d	13	17	30	13	11	18
8e	10	19	09	09	12	16
8f	16	12	13	11	10	18
8g	21	13	18	15	18	10
8h	19	10	12	11	17	15
8i	18	16	08	08	17	09
8j	16	12	13	11	10	18
Sparfloxacin	**24**	**25**	**25**	**22**	**---**	**---**
Benzyl penicillin	**18**	**17**	**16**	**16**	**---**	**---**
Fluconazole	**---**	**---**	**---**	**---**	**22**	**20**

RESULTS AND DISCUSSIONS:

The objective of the present work was to synthesize, purify, characterize and evaluate the antimicrobial activity of the newly synthesized Pthalazinetriazole derivatives. The yield of the products ranged from 55-90%. The purity was checked by TLC. The structures of the newly synthesized compounds [8a-8j] are characterized and confirmed by spectral data viz. IR, ^{1}H &^{13}C NMR and Mass spectra and all the synthesized compounds [8a-8j] were screened for antimicrobial activity.

Chemistry:

The Title Compounds Novel 6-(Thiophen-3-yl)-3-Para-Substituted-[1,2,4] Triazolo[3,4-*a*] Phthalazine

Derivativeswere synthesized in good yields (**scheme-I**). All these compounds were tested for Anti-

microbial activity showed considerable activity when compared to the standard drugs .
2,3-dihydrophthalazine-1,4-dione (2) was synthesised from Pthalic anhydride (1), hydrazine hydrate in Acetic acid at reflux for 4 hrs, Compound (2) was converted in to 1,4-dichlorophthalazine compound (3) by using $POCl_3$ at reflux for 6 hrs, Compound (3) was converted into 1-chloro-4-hydrazinylphthalazine compound (4) by using hydrazine hydrate in Ethanol at reflux for 4 hrs, Compound (4) reacts with different substituted benzoic acids (5 a-5j) in $POCl_3$ at reflux to form fused 1,2,4 tri azole Pthalazinederivatives (6a-6j), Compounds (6a-6j) were reacted with thiophen-3-yl-boronic acid (7) under Suzuki reaction conditions in microwave to get target Pthalazine derivatives (8a-8j). Structures of Compounds 8a-8j were confirmed by IR, ^1H &^{13}C NMR, mass Spectroscopic Techniques. All of the Pthalazine tri azoles possess similar basic skeletal structure.

Characterization:

The FT-IR spectra of 8a–8j were recorded using KBr pellets in the range of 4,000–400 cm^{-1}.The IR spectrum of the title Compounds 8(a-j) has given stretching vibration 3420 cm^{-1} due to the stretching vibration corresponding to N-H Stretching vibrations. 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2935 cm^{-1} is due to The stretching vibration corresponding to the SP^3 C-H (methyl gp).The strong Intensity absorption at 1300 & 1500 cm^{-1} is due to The stretching vibration of -N-O Stretching in Nitro group, 1350 cm^{-1} is due to The stretching vibration of C-F bond. 760 cm^{-1} is due to The stretching vibration of C-Cl bond. 660 cm^{-1} is due to The stretching vibration of C-S-C bond. The weak Intensity absorption at 1620 cm^{-1} corresponds to a C=N Stretching vibration.1160cm^{-1} corresponding to C-O-C Stretching.

It has been observed from chemical structure of compound 8(a-j) that different pair of protons. The protons of Methyl group which is attached to benzene ring appeared as a singlet at δ =2.3 ppm, The protons of Methoxy group appeared as a Singlet at δ =3.85 ppm, . The protons attached benzene ring appeared between δ =7.2-8.3 ppm respectively.
The chemical shifts of the final compound carbon vary from δ = 160 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, The carbon chemical shift of the methyl group at δ= 23 ppm. The carbon chemical shift of the Methoxy group at δ= 55 ppm.

From anti-microbial screening data (**Table 4**) of synthesized directives show that the compounds 8h, 8g, and 8i have good antibacterial activity against S. aureus, B. subtilis (Gram positive bacteria) respectively compare to Bacteriomycin. The compounds 2c, 2e, 3b, 3f and 3h have good antibacterial activity against P. aeruginosa (Gram negative bacteria) respectively compare to Benzyl penicillin and Sparfloxacin. The compounds 8h, 8g, and 8i have very good antifungal activity against C. albicans and compounds 8h, 8g, and 8i have good antifungal activity against A. niger compare to Flucanazole. In the present work, a series of pyrazoline and acetylpyrazoline derivatives have been synthesized using new chalcones and hydrazine hydrate with moderate to good yield. The antimicrobial activities of synthesized derivatives show that some derivatives have good results compared to standard drugs data. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products. The analytical data and spectral data support the structure and geometry of the pyrazoline derivatives.
Readily available starting materials and Simple Synthesizing procedures make this method very attractive and convenient for the synthesis of Fused Pthalazinetriazole derivatives. Formation of products was confirmed by recording their ^1H NMR, ^{13}C, FT-IR, mass spectra.

Anti -microbial screening:

The results of Anti -microbialstudies of newly synthesized compounds reveal that the compounds possess significant Anti -microbialactivities. The results of these studies are

given in **Table 4**. From Anti -Microbialscreening results, it has been observed that compounds 8g, 8h&8i possess good activity.

In the present work, a series of Pthalazinetriazole derivatives have been synthesized using new substituted benzoic acids and hydrazine hydrate with moderate to good yield. The antimicrobial activities of synthesized derivatives show that some derivatives have good results compared to standard drugs data. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products. The analytical data and spectral data support the structure and geometry of the Pthalazinetriazole derivatives (8a-8j).

CONCLUSION:

In conclusion, a simple and effective procedure for the preparation of novel 1,2,4-triazoles from a common 1,4-dichlorophthalazine intermediate was developed.The method is very simple, clean and applicable to a variety of reactants. Finally In conclusion, a series of novel Pthalazine1,2,4 tri azole derivatives 8 (a-j) were synthesised in good yield, characterised by different spectral studies and their anti-microbial activity have been evaluated. Among the synthesised compounds 8g, 8h, and 8i showed more anti-microbial activity when compared to other compounds in the series.

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