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Research Article

ONE POT SYNTHESIS OF 2-((4-METHYLPIPERAZIN-1-YL(PHENYL)METHYL)BENZENE-1,3-DIOL DERIVATIVES AND THEIRIN VITROANTIMICROBIAL ACTIVITY

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ABSTRACT

The one pot reaction between 2-naphthol, aryl aldehydes and ammonia or amines yields aminobenzylnaphthols in process known as Betti reaction. This procedure can be interpreted as extension of the mannich condensation with formaldehyde replaced by aromatic aldehydes, secondary amine by ammonia and the C - H acid by an electron-rich aromatic compound such as 2-naphthol.Betti base derivatives of 2-((4-methylpiperazin-1-yl(phenyl)methyl)benzene-1,3-diol were prepared through reactions of resorcinol, aromatic aldehydes and amines in ratio 1:2:1 in presence of fluoriteat room temperature. The structures of the all synthesized compounds were confirmed by IR, H^1-NMR, and Mass spectral studies. All the synthesized compounds were screened for antibacterial and antifungal activity.

INTRODUCTION

At the beginning of the 20th century, Mario Betti discovered the three-component reaction of 2-naphthol, aryl aldehydes and ammonia or amines for the synthesis of aminobenzylnaphthols[1]. Now, this process has been known as the Betti reaction and the aminonaphthol product known as a Bettibase[2]. The phenolic hydroxyl and amino groups in Betti bases can be used in synthetic building blocks. Aminonaphthols have several interesting biological applications, such as antibacterial, hypotensive, and bradycardiac activities[3-5]. Optically active Betti bases can be used as ligands to chelate with organometallic reagents in different reactions to provide highly efficient asymmetric reaction[6-7].In recent years, several more convenient and green procedures for Betti reactions have also been successfully developed[8-15]. The efforts were done to synthesized the Betti's base derivatives in organic solvent such as EtOH and MeOH at room temperature or thermally under solvent less condition[16]. In continuation of our ongoing effort to develop new environmentally benign multicomponent reactions, herein we report the three-component reaction of resorcinol, cyclic amines and aromatic aldehyde[17-18].

MATERIAL AND METHODS

Synthesis of 2-((4-methylpiperazin-1-yl(phenyl)methyl) benzene-1,3-diol: (V_2)

A mixture of n-methyl piperazine (5.08gm,0.05M), Benzaldehyde (5.30gm,0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10mL of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (76%), M.P: 208°C ($C_{18}H_{22}N_2O_2$;Calculated: C,72.46; H,7.43; O,10.72; N,9.39; Found:C,72.40; H,7.41; O.10.70; N,9.35).The compounds 2-((4-methylpiperazin-1-yl(phenyl)methyl) benzene-1,3-diol($\mathbf{V_{1\text{-}10}}$) were obtained by preparation method (Scheme 1)

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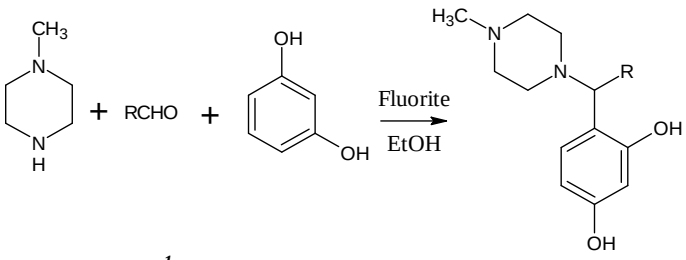
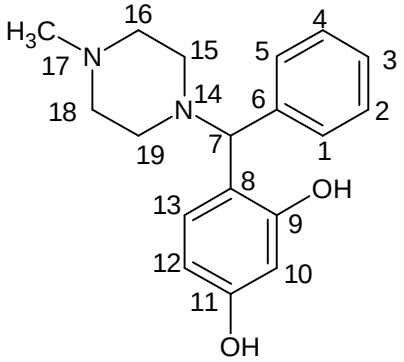
Scheme-1



Spectral Data:[1]HNMR



Sr. No	Ppm	Proton
1	2.09 (3H,S,)	-N-CH_3 [C_{17}]
2	2.31 to 2.50 (8H,m)	methylene [C_{15},C_{16}, C_{18}, C_{19}]
3	4.50(1H,S)	methine-H [C_7]
4	6.13 to 6.90(3H,m)	Ar-H [C_{10}, C_{12} , C_{13}]
5	7.17 to 7.39 (5H,m)	Ar-H [$C_1$to C_5]
6	9.13 and 10.80, (1H,S)	-OH [C_9 and C_{11}]

Spectral Data: IR

Resorcinol ring: 3627.72cm^{-1}(-OH), 3061
Piperazine ring: 2952 cm^{-1}(str,-C-H), 1455 cm^{-1} (bend, -C-H), 1169 cm^{-1}(str,-C-N)
Aromatic ring: 1455,1599,1699 cm^{-1}(C=C), 3027cm^{-1}(str,=C-H), 844,699 cm^{-1}(=C-H)

Spectral Data: MASS

299.13 (M+1), 199.06

Synthesis of 2-(4-methyl-piperazin-1-ylmethyl)benzene-1,3-diol (V_1)

A mixture of n-methyl piperazine (5.08gm,0.05M), Formaldehyde (4.0gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (78%), M.P: 192°C.

Synthesis of 2-[(4-Chloro-phenyl)-(4-methyl-piperazin-1-yl)-methyl]-benzene-1,3-diol(V_3)

A mixture of n-methyl piperazine (5.08gm,0.05M), 4-Chloro benzaldehyde (7.028gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min. The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (80%), M.P: 198°C.

Synthesis of 2-[(3-Chloro-phenyl)-(4-methyl-piperazin-1-yl)-methyl]-benzene-1,3-diol(V_4)

A mixture of n-methyl piperazine (5.08gm,0.05M), 3-Chloro benzaldehyde (7.028gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (77%), M.P: 204°C.

Synthesis of 2-[1-4-methyl-piperazin-1-yl)-3-phenyl-allyl]-benzene-1,3-diol(V_5)

A mixture of n-methyl piperazine (5.08gm,0.05M), Cinnamaldehyde (6.608gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (75%), M.P: 199°C.

Synthesis of 2-[(4-methyl-piperazine-1-yl)-(3-nitro-phenyl)-methyl]-benzene-1,3-diol(V_6)

A mixture of n-methyl piperazine (5.08gm,0.05M), 3-Nitro benzaldehyde (7.556gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (79%), M.P: 219°C.

Synthesis of 2-[(4-Hydroxy-phenyl)-(4-methyl-piperazine-1-yl)-methyl]-benzene-1,3-diol(V_7)

A mixture of n-methyl piperazine (5.08gm,0.05M), 4-Hydroxy benzaldehyde (6.106gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (82%), M.P: 244°C.

Synthesis of 2-[(4-Methoxy-phenyl)-(4-methyl-piperazine-1-yl)-methyl]-benzene-1,3-diol(V_9)

A mixture of n-methyl piperazine (5.08gm,0.05M), 4-Methoxy benzaldehyde (6.80gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min. The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (77%), M.P: 164°C.

Table A Physical data of 2-((4-methylpiperazin-1-yl(phenyl)methyl)benzene-1,3-diol(V1-10)

Compound No.	R	Molecular formula	Solvent For crystallization	M.W	M.P°C	% of C	% of H	% of N
					R_f	Found	Found	Found
						Calculated	Calculated	Calculated
V_1	H	$C_{12}H_{18}N_2O_2$	Ethanol	222.28	192	64.82	8.14	12.58
					0.7	64.84	8.16	12.60
V_2	C_6H_5	$C_{18}H_{22}N_2O_2$	Ethanol	298.38	208	72.40	7.40	9.35
					0.81	72.46	7.43	9.39
V_3	4-Cl-C_6H_4	$C_{18}H_{21}ClN_2O_2$	Ethanol	332.82	198	64.92	6.32	8.40
					0.81	64.96	6.36	8.42
V_4	3-Cl-C_6H_4	$C_{18}H_{21}ClN_2O_2$	Ethanol	332.82	204	64.94	6.33	8.40
					0.86	64.96	6.36	8.42
V_5	CH=CH-C_6H_5	$C_{20}H_{24}N_2O_2$	Ethanol	324.42	199	74.02	7.40	8.60
					0.78	74.04	7.46	8.64
V_6	3-NO_2-C_6H_4	$C_{18}H_{21}N_3O_4$	Ethanol	343.38	219	62.94	6.14	12.20
					0.75	62.96	6.16	12.24
V_7	4-OH-C_6H_4	$C_{18}H_{22}N_2O_3$	Ethanol	314.38	244	68.75	7.04	8.88
					0.81	68.77	7.05	8.91
V_8	3-OH-C_6H_4	$C_{18}H_{22}N_2O_3$	Ethanol	314.38	228	68.73	7.01	8.90
					0.8	68.77	7.05	8.91
V_9	4-OCH_3-C_6H_4	$C_{19}H_{24}N_2O_3$	Ethanol	328.41	164	69.45	7.34	8.50
					0.71	69.49	7.37	8.53
V_{10}	3,4,5-OCH_3-C_6H_3	$C_{21}H_{28}N_2O_5$	Ethanol	388.46	196	64.90	7.24	7.19
					0.78	64.93	7.27	7.21

Synthesis of 2-[(3-Hydroxy-phenyl)-(4-methyl-piperazine-1-yl)-methyl]-benzene-1,3-diol(V_8)

A mixture of n-methyl piperazine (5.08gm,0.05M), 3-Hydroxy benzaldehyde (6.106gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (81%), M.P: 228°C.

The Standard Drugs

Minimal Bactericidal Concentration				
DRUG	E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
-	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
Microgram/ml				
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	--	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Minimal Fungicidal Concentration			
Code no.	C.ALBICANS MTCC 227	A.NIGER MTCC 282	A.CLAVATUS MTCC 1323
Microgram/ml			
Nystatin	100	100	100
Greseofulvin	500	100	100

Synthesis of 2-(4-methyl-piperazin-1-ylmethyl)-(3,4,5-trimethoxy-phenyl)-methyl]-benzene-1,3-diol(V_{10})

A mixture of n-methyl piperazine (5.08gm,0.05M), (9.81gm, 0.05M) and Resorcinol (5.50gm,0.05M) was dissolved in 10ml of 95% ethanol in one pot and was magnetically stirred at room temperature in presence of fluorite (2% weight with respect to all reactants) (Scheme 1). The reaction mixture was stirred for 10-15min.The completion of the reaction was monitored by TLC by using mixture of Acetone and methanol as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst were collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. Yield, (79%), M.P: 208°C.

Biological Activity

All the newly synthesized compounds were tested for their In vitro antibacterial and antifungal activity (MICs, µg/ml) by the

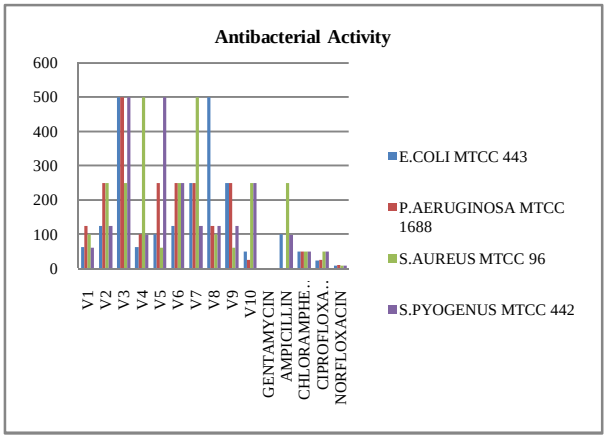
broth dilution method as described by A. Rattan [19] with two Gram-positive bacteria (Staphylococcus aureus MTCC 96 and Streptococcus pyogenus MTCC 442), two Gram-negative bacteria (Escherichia coli MTCC 443 and Pseudomonas aeruginosa MTCC 1688) and three fungi (Candida albicans MTCC 227, Aspergillusniger MTCC 282 and Aspergillusclavatus MTCC 1323) organisms. All MTCC cultures were collected from Chandigarh, (INDIA). The test compounds were dissolved in DMF using Gentamycin, Ampicillin, Chloramphenical, Ciprofloxacin and Norfloxacin as standards drugs for comparison of antibacterial activity. The antifungal activity is compared with the Greseofulvin and Nystatin as standard drugs. The results are given in Table 2 and Table 3.

Table 2

Antibacterial activity table Minimal inhibition concentration				
Code No.	**E.COLI**	**P.Aeruginosa**	**S.Aureus**	**S.Pyogenus**
-	**MTCC 443**	**MTCC 1688**	**MTCC 96**	**MTCC 442**
V_1	62.5	125	100	62.5
V_2	125	250	250	125
V_3	500	500	250	500
V_4	62.5	100	500	100
V_5	100	250	62.5	500
V_6	125	250	250	250
V_7	250	250	500	125
V_8	500	125	100	125
V_9	250	250	62.5	125
V_{10}	50	25	250	250

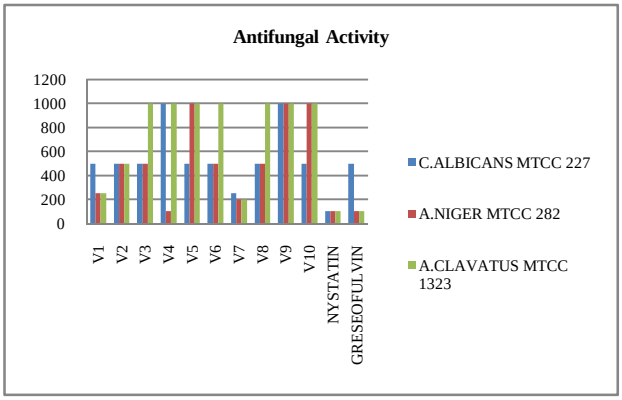
Table 3

Antifungal Activity Table Minimal Inhibition Concentration			
CODE NO.	**C.ALBICANS MTCC 227**	**A.NIGER MTCC 282**	**A.CLAVATUS MTCC 1323**
V_1	500	250	250
V_2	500	500	500
V_3	500	500	1000
V_4	1000	>100	>1000
V_5	500	>1000	>1000
V_6	500	500	>1000
V_7	250	200	200
V_8	500	500	>1000
V_9	>1000	>1000	>1000
V_{10}	500	>1000	>1000



Antibacterial Activity

The antimicrobial activity screening results (Table 2) showed that they possess good antibacterial activity. It can be observed from the result that Compound- V_{10} shows Excellent antibacterial activity against E.Coli and P. Aeruginosa having even better activity compared to standard drugs named Ampicillin and Chloramphenicol. It has similar antibacterial activity to standard drug Ciprofloxacin and Chlromphenicol against P.Aeruginosa and E.Coliorganism respectively. This derivative possess much better activity due to the presence of three -OCH_3 group. Compound- V_1 seems to be more activite than standard drug Ampicillin against E.Coli and S.Pyogenusand and S.Aureus. Compound- V_4 possess more antibacterial activity compared to standard drug Ampicillin against E.Coliand having equal antibacterial activity compared to Ampicillin against S.Pyogenus.



It is due to presence of -Cl group which gives rise to ortho, pera resonance to improve activity. Compound- V_5 shows equal activity compared to Ampicillin against E.Coli . It is also found to be much better activite than Ampicillin against S.Aqureus. Compound- V_8 possesses better activity than Ampicillin against S.Aureus. It is due to presence of -OH group ortho, pera resonance to improve activity. Compound- V_9 shows better activity than Ampicillin against S.Aureus.

Antifungal Activity

The antifungal activity screening result (Table 3) of compounds V_1 to V_{10}. The result indicates that Compound-V_7 shows much better antifungal activity than standard drug Greseofulvin against C.Albicans. Compounds V_1 to V_6 seems to be active as equal as the standard drug greseofulvin against C.Albicans.

CONCLUSION

A series of Betti base derivatives were successfully synthesized. All the compounds were screened for antimicrobial activity. It is evident from the biological screening result that the several Betti base were interestingly found to be more active than their corresponding precursors. The tested compounds were found to be more active against S. aureus, E. coli and C. albicans as compared to standards.

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