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INDIAN NATURAL ZEOLITE CATALYZED SYNTHESIS OF β-AMINOHETERONAPTHOL AND THEIR POTENT ANTIMICROBIAL EFFICACY

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ABSTRACT: A highly resourceful, elegant, simple and green technique with exceptionally facile reaction conditions of one pot three component reaction was applied to synthesized series of novel mannich base having an array of biologically and pharmaceutically active novel heterocycles. The present protocol offered a valuable alternative to known methods and will find applications in the field of green synthesis and antimicrobial study against pathogenic microbes supports the development of bioinformatical database of novel and abandoned heterocycles. These data indicate their potential to become antimicrobial agents against pathogenic and resistant strains of micro-organisms. The novel products were established by Elemental, IR, mass spectroscopic and ^{1}H, ^{13}C NMR analysis. The environmental advantages of the method include short reaction time, excellent yield, easy work-up, elimination of extraction and chromatographic purification process. The synthesized β-amino-heteronapthols were tested for their antimicrobial efficacy against pathogenic bacteria and fungi by comparing their zone of inhibition with standard antibacterial agents (Gentamicin, Amoxicillin) and antifungal agents (Nistatin, Fluconazole).

INTRODUCTION: The incidence of microbial infections in the immune compromised population has significantly increased over the past several years. In particular, *Candida* species, especially *Candida albicans*, are often significant pathogens in patients infected with human immunodeficiency virus (HIV). Another pathogen, *Pneumocysist carinii*, causes a form of pneumonia (PCP) that is believed to be one of the leading causes of death in patients suffering from AIDS [1].

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In addition; the treatment of infectious diseases is more complicated in immunosuppressed patients, such as those infected with the HIV, undergoing anticancer therapy and organ transplants. Consequently, there is a vital need for the development of new antimicrobial agents having potent activity against the resistant micro-organisms.

The rapid development of resistance to existing antibacterial and antifungal drugs possess a major threat to public health and it creates a serious challenge to the scientific community. Pathogenic bacteria are known to acquire resistance via several distinct mechanisms including inactivation of the antibiotic by bacterial enzymes (e.g., β-lactamases hydrolyzing penicillin and cephalosporins); removal of the antibiotic using efflux pumps;

modification of the target of the antibiotic via mutation and genetic recombination (e.g., penicillin-resistance in *Neiserria gonorrhoeae*); and acquisition of a readily transferable gene from an external source to create a resistant target (e.g., Methicillin-resistance in *Staphylococcus aureus* and quinolone-resistant bacteria such as *S. aureus, S. pyogenes, E. coli, P. aeuruginosa,*).

There are certain Gram positive pathogens, such as vancomycin-resistant *Enterococcus faecium*, which are resistant to virtually all commercially available antibiotics. Hence, the usage of the most existing antimicrobials have limited capacity in overcoming the threat of resistance and it is limited not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects [2, 3]. Thus, it would be advantageous to provide a pharmacophore species with useful properties that can be used commercially against pathogenic and resistant microbes.

Mannich bases had abundant commercial applications and it was estimated that at least 35 % of Mannich bases related articles are published in pharmaceutical journals. The first synthesis of racemic Mannich-bases of 2-naphthol was achieved by Betti at the turn of the twentieth century.[4] Thereafter numerous modifications of this reaction surfaced [5-10]. Since these compounds have multiple centers for chelation with metal ions, they are likely to be potent inhibitors of metallo-enzymes [11, 12].

Also, these compounds have the potential to be used as scavengers in cases of heavy metal poisoning [13]. They have a broad range of biological activities including diuretic, anticonvulsant, antipsychotic, antimalarial, antiviral, centrally acting muscle relaxant, and anticancer. Also, Mannich bases of various bioactive compounds have been prepared as prodrugs as means of overcoming some of their limitations [14].

So keeping importance of Mannich base moiety in mind, we had synthesized a series of substituted coumarin derivatives via classical Betti's condensation reaction with their pharmacophores modeling and in vitro microbial activity [15]. Despite the importance of the compounds, the serious downsides of their commercial syntheses includes some or all of the following: refluxing for extensive reaction time, large quantities of mineral or Lewis / Bronsted acids as activators, which on work-up were hydrolyzed with generation of large quantities of corrosive and toxic waste by-products; the use of stoichiometric quantities of reagents that produce metal salts as waste; poor yields; or production of mixtures of regioisomers with low selectivity. The enantioselective transformations and industrial applications were the foremost impediment in the microwave-assisted synthesis of these compounds.

The aforementioned problems of greener synthetic approach of Betti's reaction product were overcome in present work by one pot multi-component zeolite catalyzed condensation of bioactive Betti's reaction products. Inspired by the above facts and in continuation of our ongoing research program in the field of synthesis and antimicrobial activity of medicinally important compounds (J. S. Meshram *et al*., 2011; Kumar *et al*., 2010; Madhukar *et al*., 2009), hereby in this paper we have reported the green synthesis of potent Betti's products exemplified with their antimicrobial efficacy.

Herein, in order to reduce the time period of Betti's reaction product, enantioselective transformations and achieve green chemical synthesis, the reaction was carried out in catalytic medium of zeolites which enhance reaction rate, support reagents, regioselectivity, entrain by-products and enhance product selectivity [16-18]. Furthermore, we have found a novel series of Betti's products that were effective against resistant microbes, and provide significant activity advantage over the art. It had been found that the compounds of this work and composition containing these compounds are effective antimicrobial agents against a broad range of pathogenic microorganisms with advantages in low susceptibility to microbial resistance, reduced toxicity, and improved pharmacology.

MATERIALS & METHODS: The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation where necessary. Melting points were determined in open capillaries and uncorrected. Infrared spectra were recorded on Bruker Alfa-T with direct sampling for analysis.

^{1}H NMR spectra were recorded on a Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard with $CDCl_3$ and DMSO as a solvent. Chemical shifts are given in parts per million (δ scale) and the coupling constants are given in Hz. Mass spectra were recorded on a Waters Micromass Q-T of Micro spectrometer. The reactions were monitored and the purity of products were checked out on Silica gel 60 F254 (Merck) TLC plates with a mixture of petroleum ether (60-80℃) and ethyl acetate as the eluent and the spots were visualized under ultraviolet light and iodine chamber.

Elemental analyses were performed on a Perkin-Elmer 2400 Series II elemental CHNS analyzer. The zeolitic raw mineral was ground and purified via washing with distilled water by means of a fluidized bed process in order to remove the non-zeolitic mineral phases. After vacuum filtration and drying at 200℃, zeolites were reutilized for each reaction.

General procedure for the synthesis of β-amino-quinoline (5): A mixture of 8-hydroxyquinoline (**3**) (1 mmol) and carbonyl compound (**1**) (1 mmol) was stirred at room temperature for 10 min in the presence of zeolite (0.5 g) in ethanol. Then, an equimolar amount of primary or secondary aromatic/aliphatic amine (**2**) was added, and resulting reaction mixture was stirred for 1-1.5 h at 40℃. After completion of the reaction (TLC checked), the coloured solid that separated was filtered, washed with ethanol and purified by recrystallization from ethanol or by filtration through a pad of silica gel using 9:1 petroleum ether–ethyl acetate to afford pure compounds **5** (compounds 5a–5j).

Ethyl4-((2-hydroxy-3-methoxyphenyl)(8-hydroxyquinolin-7-yl)methylamino)benzoate (5a): Light yellow crystalline solid; yield 96% (4.267 g, crystallization) or 99% (4.4 g, filtration), m.p. 173-175℃; refractive index nD^{22}: 1.681. Anal. Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.26; H, 5.44; N 6.30 %. Found: C, 70.35; H, 5.48; N, 6.28 %. IR (cm^{-1}) υ: 3088.4 (OH), 1707.2 ($COOC_2H_5$), 1324.3 (C-N stretching), 3382.6 (NH), 2872.3 (OCH_3). ^{1}H NMR (DMSO, 400 MHz, δ_H ppm, J Hz): 8.64 (s, 1H, quinoline -OH); 7.83-7.89 (m, 5H, quinoline-H); 7.98 (s, 1H, sec. amine -NH); 7.41-7.47 (m, 4H, Ar-H) 1.32 (t, 3H, -CH_3, J= 3.42); 3.91 (q, 2H, -OCH_2-, J= 1.68, 1.72); 7.49 (s, 1H, methine); 7.53-7.57 (m, 3H, vanillin-H); 8.06 (s, 1H, vanillin-OH); 2.55 (s, 3H, vanillin –OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 15.4, 44.2, 59.1, 64.6, 113.2, 113.5, 119.6, 121.2, 121.6, 122.2, 122.3, 123.0, 123.9, 127.5, 128.4, 130.7, 134.5, 137.6, 145.6, 149.2, 150.1, 151.9, 165.9. MS, m/z: 444 (M^+, 100%).

4-((4-hydroxy-3-methoxyphenyl)(8-hydroxy quinolin-7-yl)methyl)amino)acetophenone (5b): Yellow amorphous solid, yield 93% (3.854 g, crystallization) or 96% (3.978 g, filtration), m. p. 192-196℃; refractive index nD^{22}: 1.700. Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76 %. Found: C, 72.51; H, 5.39; N, 6.70 %. IR (cm^{-1}) υ: 3553.8 (OH), 1323.9 (C-N stretching), 3380.8(NH), 2852.2 (OCH_3), 1722.5 (CO). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H: 9.92 (s, 1H, quinoline-OH); 7.64-8.18 (m, 5H, quinoline-H); 7.67 (s, 1H sec. amine HN-); 6.86-7.37 (m, 4H, Ar-H); 2.85 (s, 3H, -CH_3); 5.919 (s, 1H, methine); 6.97-7.38 (m, 3H, vanillin -H); 3.08 (s, 3H, vanillin -OCH_3); 10.28 (s, 1H, vanillin -OH).^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 24.8, 57.1, 57.2, 112.0, 114.1, 116.8, 120.2, 120.8, 121.7, 122.2, 127.6, 128.4, 129.4, 129.7, 135.5,136.3, 137.3, 146.2, 148.2, 148.4, 148.7, 150.3, 152.0, 197.4. MS, m/z: 414 (M^+, 100 %).

Ethyl4-((2-hydroxyphenyl)(8-hydroxyquinolin-7-yl)methylamino)benzoate (5c): Orange needle shape solid, yield 97% (4.02 g, crystallization) or 99% (4.1 g, filtration), m. p. 96-98℃; refractive index nD^{22}: 1.701. Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76 %. Found: C, 72.50; H, 5.38; N, 6.72 %. IR (cm^{-1}) υ: 3582.4 (OH), 1734.9 ($COOC_2H_5$), 1305.5 (C-N stretching), 3431.6 (NH). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 10.13 (s, 1H, quinoline -OH); 7.47-8.13 (m, 5H, quinoline-H); 6.99 (s, 1H sec. amine -NH); 6.79-7.98 (m, 4H, Ar-H) 1.31(t, 3H, -CH_3, J= 7.2); 4.23 (q, 2H, -OCH_2-, J= 1.6, 4.2); 5.62 (s, 1H, methine); 9.63 (s, 1H, -OH); 6.81-7.07 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 15.6, 51.8, 61.3, 112.0, 116.4, 118.5, 119.5, 120.2, 120.9, 121.3, 121.8, 127.6, 128.4, 130.8, 132.3, 135.5, 137.3, 148.5, 151.0, 152.4, 158.6, 166.9. MS, m/z: 414 (M^+, 100 %).

Ethyl4-((2-chloroquinolin-3-yl)(8-hydroxy quinolin-7-yl)methylamino)benzoate (5d): Dark yellow amorphous solid, yield 92% (4.452 g, crystallization) or 95% (4.597 g, filtration), m.p. 225-229℃; refractive index nD^{22}: 1.722. Anal. Calcd. for $C_{28}H_{22}N_3O_3Cl$: C, 69.49; H, 4.58; N, 8.68; Cl, 7.33 %. Found: C, 69.53, H, 4.65; Cl, 7.35; N, 8.57 %. IR (cm^{-1}) υ: 3096.1 (OH), 1716.9 ($COOC_2H_5$), 1323.3 (C-N stretching), 3420.5 (N-H), 1066.8 (C-Cl). ^{1}H NMR (DMSO, 400 MHz, δ ppm, *J* Hz): 9.11 (s, 1H, quinoline -OH); 7.45 -8.69 (m, 5H, quinoline-H); 7.61 (s, 1H sec. amine -NH); 6.79-7.97 (m, 4H, Ar-H) 1.32 (t, 3H, $-CH_3$, *J*= 7.2); 4.24 (q, 2H, $-OCH_2$-, *J*= 7.0, 7.12); 6.43 (s, 1H, methine); 7.70-8.45 (m, 5H, chloroquinolin-H).^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 15.5, 43.8, 60.9, 113.4, 118.6, 121.2, 121.6, 122.3, 126.5, 127.0, 127.4, 127.5, 128.4, 129.9, 130.7, 130.9, 135.6, 136.2, 137.8, 145.6, 148.6, 150.1, 151.9, 152.2, 166.3. MS, m/z : 483 (M^+, 100 %).

4-((furan-2-yl)(8-hydroxyquinolin-7-yl)methyl amino)-1,2-dihydro-2,3-dimethyl-1-phenyl pyrazol-5-one (5e): Dark brown amorphous solid, yield 95% (4.051 g, crystallization) or 97% (4.136 g, filtration), m.p. 166-170℃; refractive index nD^{22}: 1.734. Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14 %. Found: C, 70.29; H, 5.26; N, 13.20 %. IR (cm^{-1}) υ: 3523.6.1 (OH), 1343.2 (C-N stretching), 3423.8 (N-H), 1743.8(CO). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz): 9.71 (s, 1H, quinoline -OH); 7.45-8.68 (m, 5H, quinoline-H); 7.59 (s, 1H sec. amine -NH); 6.79-7.42 (m, 5H, Ar-H); 2.32 (s, 3H, $-CH_3$); 3.21 (s, 3H, N-CH_3); 5.74 (s, 1H, methine); 7.28-7.32 (m, 3H, furan-H).^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 14.2, 34.8, 54.6, 106.7, 110.8, 116.4, 120.1, 120.8, 121.4, 122.8, 123.9, 127.6, 128.4, 129.3, 131.5, 133.9, 135.5, 137.4, 142.1, 148.5, 150.5, 152.5, 160.7. MS, m/z: 426 (M^+, 100 %).

Ethyl4-((furan-2-yl)(8-hydroxyquinolin-7-yl) methylamino)benzoate (5f): Light brown amorphous solid, yield 98% (3.8 g, crystallization) or 99% (3.845 g, filtration), m.p. 148-150℃; refractive index nD^{22}: 1.674. Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21 %. Found: C, 71.23; H, 4.98; N, 7.28 %. IR (cm^{-1}) υ: 3356.4 (OH), 1323.3 (C-N stretching), 3113.5(N-H), 1718.8 ($COOC_2H_5$), 1232.7(COC). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 8.23 (s, 1H, quinoline-OH); 7.36-7.44 (m, 5H, quinoline-H); 7.40 (s, 1H sec. amine HN-); 7.34-7.41 (m, 4H, Ar-H); 1.25 (t, 3H, $-CH_3$, *J*= 5.6); 4.15 (q, 2H, $-OCH_2$, *J*= 3.7, 4.6); 7.25 (s, 1H, methine); 7.32-7.37 (m, 3H, furan-H).^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 15.0, 54.6, 60.9, 106.8, 110.6, 113.7, 118.6, 120.2, 120.9, 121.8, 127.5, 128.7, 130.7, 135.4, 137.6, 142.4, 148.6, 150.3, 151.9, 152.5, 167.1. MS, m/z: 388 (M^+, 100 %).

Ethyl4-(chloro(8-hydroxyquinolin-7-yl)(4-nitrophenyl)methylamino)benzoate (5g): Light orange crystaline solid, yield 97% (4.635 g, crystallization) or 99% (4.732 g, filtration), m.p. 182-186℃; refractive index nD^{22}: 1.697. Anal. Calcd. for $C_{25}H_{20}ClN_3O_5$: C, 62.83; H, 4.22; Cl, 7.42; N, 8.79 %. Found: C, 62.88; H, 4.30; Cl, 7.46; N, 8.72 %. IR (cm^{-1}) υ: 3466.7 (OH), 1346.3 (C-N stretching), 3213.4(N-H), 1720.3 ($COOC_2H_5$), 753.2 (C-Cl), 1465.3 (NO_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz): 9.69 (s, 1H, quinoline -OH); 7.42-7.58 (m, 5H, quinoline-H); 7.61 (s, 1H sec. amine -NH); 6. 19-6.56 (m, 4H, Ar-H); 1.62 (t, 3H, $-CH_3$, *J*= 6.1, 7.2); 4.34 (q, 2H, $-OCH_2$-, *J*= 1.5, 1.6); 7.96-8.12 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 15.3, 61.5, 81.3, 112.2, 118.5, 120.2, 120.9, 121.3, 124.4, 127.6, 128.4, 129.1, 130.7, 135.5, 137.3, 145.4, 148.5, 149.1, 150.9, 152.6, 166.3. MS, m/z: 477 (M^+, 100 %).

Ethyl4-(1-(8-hydroxyquinolin-7-yl)-2-oxo-1,2-diphenylethylamino)benzoate (5h): Yellow amorphous solid, yield 91% (4.573 g, crystallization) or 94% (4.724 g, filtration), m.p. 112-116℃; refractive index nD^{22}: 1.685. Anal. Calcd. for $C_{32}H_{26}N_2O_4$: C, 76.48; H, 5.21; N, 5.57 %. Found: C, 76.55; H, 5.29; N, 5.51 %. IR (cm^{-1}) υ: 3518.4 (OH), 1336.5 (C-N stretching), 3424.3(NH), 1722.3 ($COOC_2H_5$), 1708.6 (CO). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz): 9.87 (s, 1H, quinoline -OH); 7.41-7.58 (m, 5H, quinoline-H); 7. 12 (s, 1H sec. amine -NH); 6.71-7.68 (m, 4H, Ar-H); 1.12 (t, 3H, $-CH_3$, *J*= 7.0); 3.95 (q, 2H, $-OCH_2$-, *J*= 4.0, 8.0); 7.23-7.92 (m, 10H, Ar-H).^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 15.3, 61.4, 74.8, 112.0, 118.5, 120.0, 120.7, 121.3, 126.2, 127.6, 128.2, 128.4, 128.6, 128.8, 129.2, 130.7, 133.1, 136.0, 136.7, 137.3, 139.8, 148.5, 150.2, 152.3, 166.9, 196.5. MS, m/z: 502 (M^+, 100%).

7-(1-(tert-butylamino)-2-hydroxy-1,2-diphenyl ethyl)quinolin-8-ol (5i): Bright yellow crystalline solid, yield 93% (3.836 g, crystallization) or 98% (4.042 g, filtration), m.p. 102-105℃; refractive index nD^{22}: 1.647. Anal. Calcd. for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79 %. Found: C, 78.72; H, 6.88; N, 6.72 %. IR (cm^{-1}) υ: 3518.4 (aliphatic-OH), 3622.3 (aromatic-OH), 1210.6 (C-N stretching), 3321.7(NH), 1361.4 (tert-butyl). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz): 10.02 (s, 1H, quinoline -OH); 7.39-7.61 (m, 5H, quinoline-H); 7.68 (s, 1H sec. amine -NH); 1.32 (s, 9H, -CH_3); 6.43 (s, 1H, methine); 5.27 (s, 1H, -OH); 7.26-7.43 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 30.3, 48.7, 60.8, 90.2, 120.2, 120.9, 121.3, 126.2, 127.1, 127.6, 128.2, 128.4, 128.9, 129.2, 135.5, 137.3, 140.6, 141.2, 148.5, 150.0. MS, m/z: 412 (M^+, 100 %).

7-((6-benzyl-6H-purin-6-ylamino)(4-hydroxy-3-methoxyphenyl)methyl)quinolin-8-ol (5j): Orange amorphous solid, yield 94% (4.742 g, crystallization) or 97% (4.894 g, filtration), m.p. 116-120℃; refractive index nD^{22}: 1.719. Anal. Calcd. for $C_{29}H_{24}N_6O_3$: C, 69.04; H, 4.79; N, 16.66 %. Found: C, 69.12; H, 4.86; N, 16.60 %. IR (cm^{-1}) υ: 3122.3 (OH), 1326.7 (C-N stretching), 2847.9 (OCH_3), (NH), 1845.2 (purine). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz): 9.57 (s, 2H, -OH); 7.43-7.65 (m, 5H, quinoline-H); 6.13 (s, 1H sec. amine -NH); 7.89 (s, 2H, purine-H); 2.67 (s, 2H, CH_2); 7.12-7.24 (m, 5H, Ar-H); 5.39 (s, 1H, methine); 6.74-6.82 (m, 3H, Ar-H); 3.38 (s, 3H, -OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 41.8, 44.21, 56.2, 65.6, 113.7, 117.4, 120.2, 120.9, 121.5, 122.3, 126.0, 127.5, 127.8, 128.5, 128.8, 135.9, 136.4, 137.6, 139.5, 143.2, 148.6, 150.2, 151.9, 154.6, 163.6, 166.8. MS, m/z: 504 (M^+, 95 %).

General procedure for the synthesis of β-amino-chromene (6): A mixture of coumarin **(4)** (1 mmol) and carbonyl compound **(1)** (1 mmol) in ethanol was stirred at 40℃ for 15 min at in the presence of zeolite (0.5 g). Then, an equimolar amount of primary or secondary aromatic/aliphatic amine (2) was added, and resulting reaction mixture was stirred for 1-2 h. After completion of the reaction (TLC checked), the coloured solid that separated was filtered, washed with ethanol and purified by recrystallization from ethanol/methanol or by filtration through a pad of silica gel using 9:1 petroleum ether–ethyl acetate to afford pure compounds 6 (compounds 6a–6g).

4-((4-hydroxy-3,5-dimethoxyphenyl)(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methyl amino)benzoic acid (6a): Orange needle shaped solid, yield 95% (4.535 g, crystallization) or 97% (4.631 g, filtration), m.p. 89-94℃; refractive index nD^{22}: 1.679. Anal. Calcd. for $C_{26}H_{23}NO_8$: C, 65.40; H, 4.86; N, 2.93 %. Found: C, 65.55; H, 5.01; N, 2.82 %. IR (cm^{-1}) υ: 3627.3 (OH), 1595.2 (CO), 1345.8 (C-N stretching), 3413.7(NH), 1396.3 (COOH), 2815.9 (OCH_3). ^1H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 10.62 (s, 1H, coumarin-OH); 2.38 (s, 3H, methyl coumarin); 6.23-7.48 (m, 3H, coumarin-H); 6.81 (s, 1H, sec. amine -NH) 13.74 (s, 1H, COO-H); 6.78-7.84 (m, 4H, Ar-H); 5.16 (s, 1H, methine); 6.40 (s, 2H, Ar-H); 3.83 (s, 6H, -OCH_3); 8.73 (s, 1H, -OH). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 19.4, 51.2, 56.1, 106.0, 112.0, 112.5, 112.7, 113.1, 118.6, 123.0, 123.7, 131.1, 134.9, 137.3, 147.9, 151.0, 152.7, 152.8, 154.9, 161.3, 170.1. MS, m/z: 477 (M^+, 100 %).

8-((2-acetyl-1H-pyrrol-1-yl)(furan-2-yl)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (6b): Light brown amorphous solid, yield 87% (3.161 g, crystallization) or 97% (3.524 g, filtration), m.p. 166-170℃; refractive index nD^{22}: 1.645. Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85 %. Found: C, 69.52; H, 4.78; N, 3.83 %. IR (cm^{-1}) υ: 3410.5 (OH), 1645.2 (cyclic CO), 1352.7 (C-N stretching), 1720.5 (CO).^1H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 9.68 (s, 1H, coumarin-OH); 2.42 (s, 3H, methyl coumarin); 6.23-7.48 (m, 3H, coumarin-H); 2.10 (s, 3H, methyl-H); 6.33-7.81 (m, 3H, pyrrol-H); 6.49 (s, 1H, methine); 6.08-7.58 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 18.9, 28.0, 47.5, 106.7, 110.6, 111.0, 112.0, 112.5, 117.7, 119.6, 123.2, 126.7, 129.9, 142.1, 151.8, 152.5, 152.7, 155.7, 160.8, 188.9. MS, m/z: 363 (M^+, 100 %).

8-((2-acetyl-1H-pyrrol-1-yl)(4-methoxyphenyl) methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (6c): Dull yellow amorphous solid, yield 90% (3.63 g, crystallization) or 97% (3.913 g, filtration), m.p. 130-134℃; refractive index nD^{22}: 1.620. Anal. Calcd. for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47 %. Found: C, 71.58; H, 5.34; N, 3.41 %. IR (cm^{-1}) υ: 3526.9 (OH), 1647.1 (cyclic CO), 1353.6 (C-N

stretching), 2837.4 (OCH_3), 1719.9 (CO). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 10.18 (s, 1H, coumarin-OH); 2.34 (s, 3H, methyl coumarin); 6.21-7.46 (m, 3H, coumarin-H); 1.94 (s, 3H, methyl-H); 6.42-7.68 (m, 3H, pyrrol-H); 7.26 (s, 1H, methine); 3.92 (s, 3H, methoxy-H); 6.69-7.14 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 18.2, 29.2, 54.8, 55.8, 111.1, 112.4, 112.8, 113.3, 115.0, 120.6, 123.2, 123.8, 126.5, 129.1, 129.8, 130.1, 151.2, 152.7, 154.9, 158.1, 161.3, 189.4. MS, m/z : 403 (M^+, 100 %).

Ethyl4-((2-chloroquinolin-3-yl)(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl) methylamino) benzoate (6d): Bright yellow amorphous solid, yield 96% (4.943 g, crystallization) or 97% (5.0 g, filtration), m.p. 98-101℃; refractive index nD^{22}: 1.691. Anal. Calcd. for $C_{29}H_{23}ClN_2O_5$: C, 67.64; H, 4.50; Cl, 6.88; N, 5.44 %. Found: C, 67.72; H, 4.58; Cl, 6.92; N, 5.38 %. IR (cm^{-1}) υ: 3498.3 (OH), 1715.6 (cyclic CO), 3419.9 (NH), 1277.7 (C-N stretching), 1732.4 ($COOC_2H_5$), 1098.6 (Cl). ^{1}H NMR (DMSO, 400 MHz, ppm, *J* Hz) δ_H: 10.53 (s, 1H, coumarin-OH); 2.37 (s, 3H, methyl coumarin); 6.55-7.46 (m, 3H, coumarin-H); 6.80 (s, 1H, sec. amine -NH); 6.71-7.61(m, 4H, Ar-H); 1.33 (t, 3H, $-CH_3$, *J*=8.0); 4.32 (q, 2H, $-CH_2$, *J*=4.0, 8.0); 6.14 (s, 1H, methine); 7.74-9.22 (m, 5H, quinoline-H). ^{13}C NMR ($CDCl_3$,75 MHz, ppm) δ_C: 13.8, 20.1, 45.8, 61.2, 112.0, 112.2, 112.5, 112.7, 118.6, 122.6, 124.4, 126.7, 127.0, 127.5, 130.1, 130.7, 131.0, 136.2, 142.4, 147.4, 150.2, 152.4, 153.6, 155.1, 161.6, 166.7. MS, m/z : 514 (M^+, 100 %).

Ethyl4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)(4-oxo-4H-chromen-2-yl)methyl amino)benzoate (6e): Pale green crystalline solid, yield 90% (4.477 g, crystallization) or 97% (4.825 g, filtration), m.p. 140-142℃; refractive index nD^{22}: 1.679. Anal. Calcd. for $C_{29}H_{23}NO_7$: C, 70.01; H, 4.66; N, 2.82 %. Found: C, 70.11; H, 4.73; N, 2.76 %. IR (cm^{-1}) υ: 3457.7 (OH), 1714.6 (cyclic CO), 3436.3 (NH), 1358.3 (C-N stretching), 1735.7 ($COOC_2H_5$). ^{1}H NMR (DMSO, 400 MHz, ppm, *J* Hz) δ_H: 11.81 (s, 1H, coumarin-OH); 1.33 (s, 3H, methyl coumarin); 7.09-7.95 (m, 3H, coumarin-H); 5.98 (s, 1H, methine); 3.82 (s, 1H sec. amine HN-); 7.56-7.98 (m, 4H, Ar-H); 1.10 (t, 3H, $-CH_3$, *J*= 8.0); 4.33 (q, 2H, $-OCH_2$, *J*=4.0, 8.0); 7.14-8.18 (m, 5H, Chromon-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 14.6, 19.2, 53.6, 61.2, 110.1, 111.9, 112.1, 112.4, 112.6, 116.3, 118.6, 122.5, 123.4, 124.2, 124.6, 125.9, 130.8, 135.2, 149.8, 150.3, 152.6, 153.6, 157.4, 161.6, 166.3, 167.3, 178.2. MS, m/z: 497 (M^+, 100 %).

Ethyl4-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diphenylmethylamino)benzoate (6f): Dark Green amorphous solid, yield 92% (4.651 g, crystallization) or 97% (4.9 g, filtration), m.p. 105-109℃; refractive index nD^{22}: 1.656. Anal. Calcd. for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77 %. Found: C, 76.11; H, 5.46; N, 2.69 %. IR (cm^{-1}) υ: 3467.3 (OH), 1712.9 (cyclic CO), 3438.4 (NH), 1357.9 (C-N stretching), 1736.8 ($COOC_2H_5$). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 10.96 (s, 1H, coumarin-OH); 2.12 (s, 3H, methyl coumarin); 6.23-7.48 (m, 3H, coumarin-H); 5.72 (s, 1H sec. amine HN-); 6.71-7.68 (m, 4H, Ar-H); 1.29 (t, 3H, $-CH_3$, *J*= 5.2); 4.30 (q, 2H, $-OCH_2$, *J*= 3.8, 4.6); 7.23-7.43 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 13.9, 19.6, 59.5, 61.2, 112.1, 112.5, 112.7, 113.2, 118.5, 123.1, 123.8, 126.3, 127.2, 130.1, 130.8, 145.1, 151.2, 152.0, 152.7, 154.8, 161.1, 165.9. MS, m/z: 505 (M^+, 100 %).

8-((furan-2-yl)(morpholino)methyl)-7-hydroxy-4-methyl-2H-chromen-2-one (6g): Light brown amorphous solid, yield 95% (3.242 g, crystallization) or 97% (3.311 g, filtration), m.p. 97-100℃; refractive index nD^{22}: 1.612. Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10 %. Found: C, 66.93; H, 5.56; N, 4.12 %. IR (cm^{-1}) υ: 3105.4 (OH), 1759.1 (cyclic CO), 1343.5 (C-N stretching), 1769.8 (morpholin).^{1}H NMR ($CDCl_3$, 400 MHz, ppm, *J* Hz) δ_H: 10.26 (s, 1H, coumarin-OH); 2. 23(s, 3H, methyl caumain); 6.45-7.47 (m, 3H, coumarin-H); 3.59 (t, 4H, *J*=4.2); 2.67 (t, 4H, *J*=6.0); 6.15 (s, 1H, methine); 6.28-7.65 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C: 20.2, 48.4, 52.9, 67.4, 106.8, 110.6, 111.8, 112.7, 112.9, 116.4, 124.8, 142.4, 151.7, 152.6, 152.7, 155.5, 161.8. MS, m/z: 341 (M^+, 100 %).

RESULTS AND DISCUSSION: In view of emerging importance of green synthesis and our general interest in solid acid catalyzed chemical reactions, we envision expedited Betti's reactions using zeolites as catalysts. Both natural and synthetic zeolites are used as a catalyst to extend the Betti's reaction towards the greener protocol.

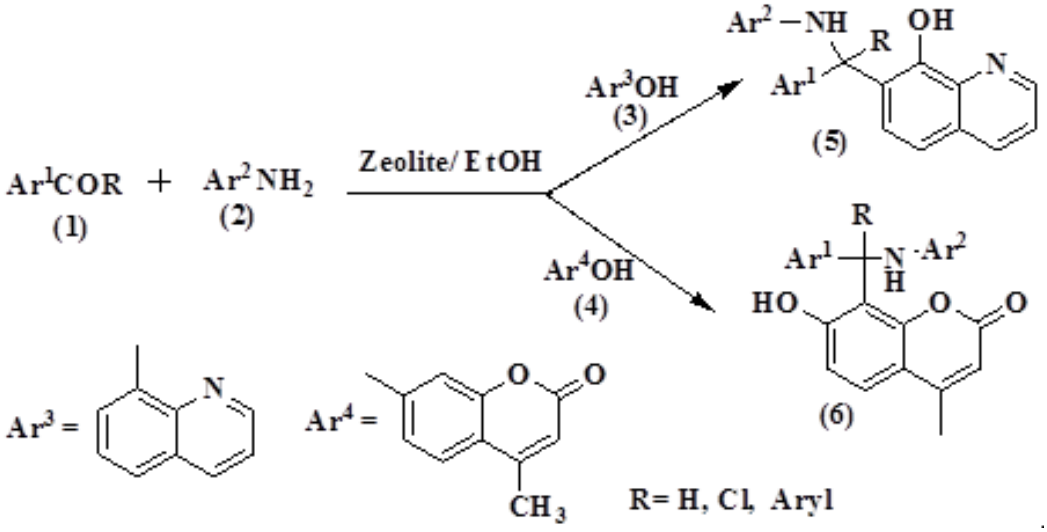
Initially we focused on the synthesis of β-aminoheteronapthol from aromatic carbonyl compound, amine and 8-hydroxy quinoline or coumarin. Most of the earlier proposed procedures for the production of mannich base involve various organic and mineral acid catalyzed reaction conditions.

The synthesis of these compounds was reported by performing the reaction in presence of Lewis acid [19], Bronsted acid catalysts [20], Lewis base [21], transition metal salt [22] catalysts condition and even uncatalyzed one-pot, three-component synthesis of Betti's base in water [23].

However, all of these chemical processes required refluxing for extensive reaction time, large quantities of mineral or Lewis acids as activators which on work-up are hydrolysed with generation of large quantities of corrosive and toxic waste by-products, long reaction time (days) along with purification steps and the uncatalyzed Betti's reaction involves only basic 2-pyridinyl, 2-pyrazinyl and 2-pyrimidinyl amine as amine moiety which act as a catalyst.

Herein, we wish to disclose our results, studying the application of natural and synthetic zeolite as a catalyst in synthesis of some novel and bioactive Betti's reaction products.

Chemistry: The Betti's classical procedure, a Mannich-type aminoalkylation condensation of 2-naphthol and aromatic aldehyde in the presence of ammonia, was modified by condensing carbonyl compound **(1)**, aromatic amine **(2)** and heteronapthol [here, 8-hydroxy quinolone **(3)** or 7-hydroxy-4-methyl-coumarin **(4)**] in presence of zeolite to prepare the β- aminoheteronapthol (**5/6)** (**Scheme 1**).



SCHEME 1: ZEOLITE CATALYZED TAILORED BETTI'S CONDENSATION

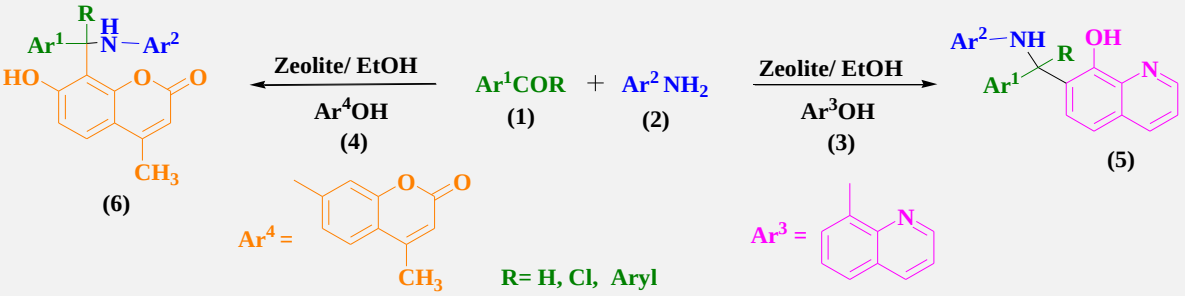
The Indian natural zeolite applied here are Scolecite ($CaAl_2Si_3O_{10}\cdot 3H_2O$), Stilbite ($NaCa_4(Si_{27}Al_9)O_{72}\cdot 28(H_2O)$), Fluorapophyllite ($KCa_4Si_8O_{20}(F,OH)\cdot 8(H_2O)$) and Mesolite ($Na_2Ca_2(Al_2Si_3O_{10})_3\cdot 8H_2O$) and synthetic zeolite are crystalline molecular sieves which can be represented by general formula - $M_{2/n}O[(AI_2O_3).(SiO_2)_X].y\ H_2O$ where, M represents alkali metals with valency-n.

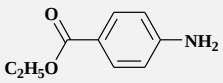
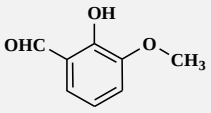
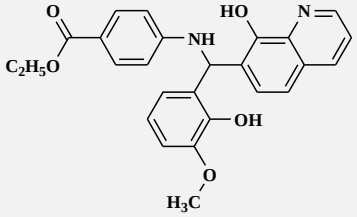
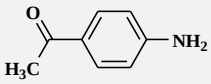
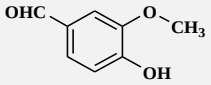
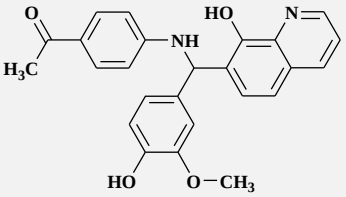
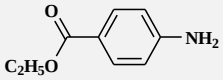
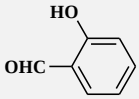
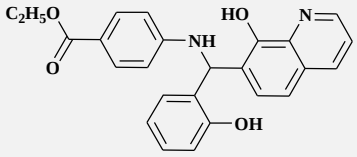
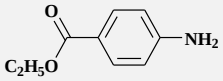
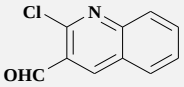
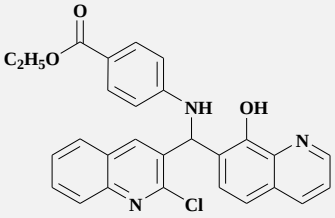
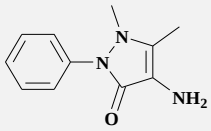
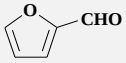
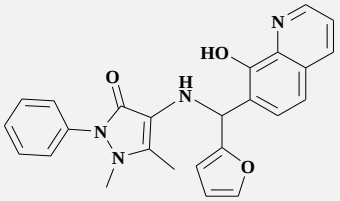
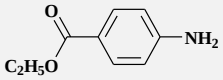
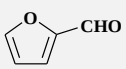
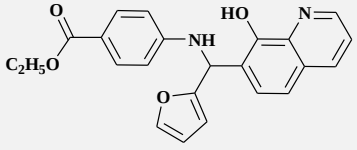
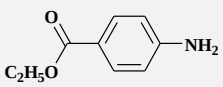
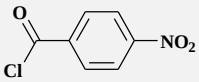
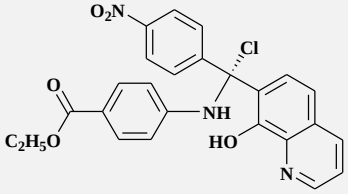
This aluminosilicates are 3A, 4A, 5A and 13X with pore size 3Å, 4Å, 5Å and 10Å respectively. The alkali metal in aluminosilicate 3A and 4A is potassium, 5A is calcium and 13A is sodium.

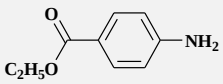
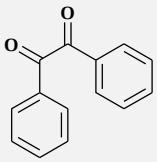
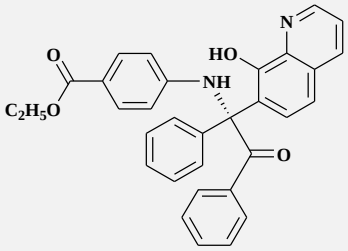
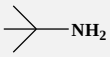
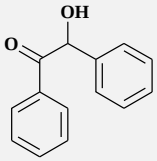
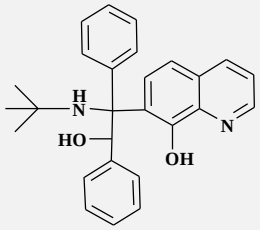
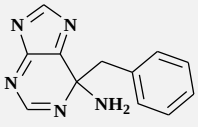
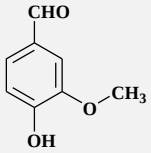
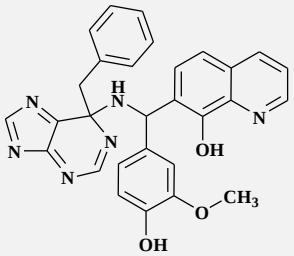
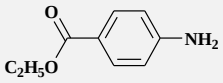
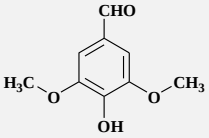
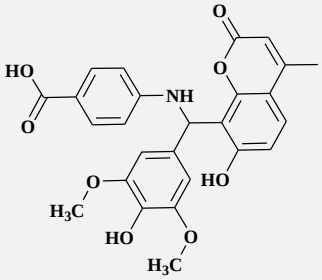
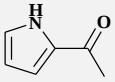
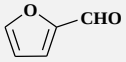
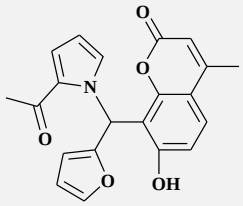
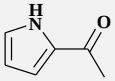
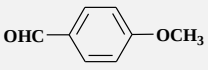
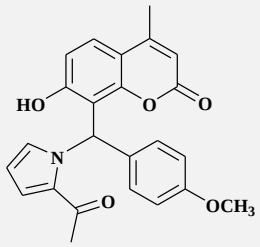
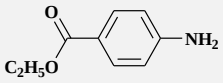
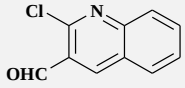
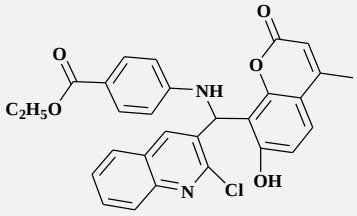
In present work of modified Betti's reaction product synthesis, use of zeolite catalyst reduces the time period of reaction with the yield of 92-98% and the catalyst was recovered completely which was reused in ten consecutive reactions having more than 90% yield.

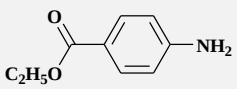
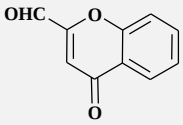
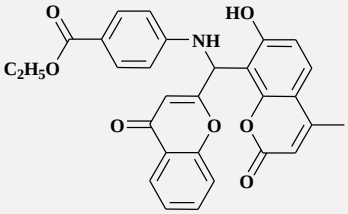
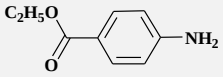
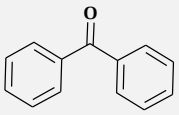
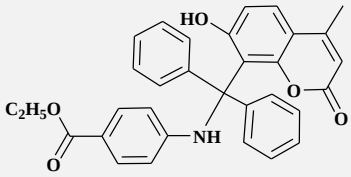
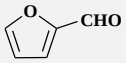
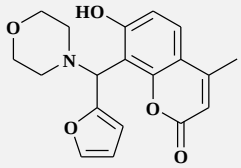
The products of modified Betti's reaction are specified in **Table 1**.

TABLE 1: TAILORED BETTI'S REACTION BETWEEN CARBONYL COMPOUND, AMINE AND HETERONAPTHOL (HERE, QUINOLINE/CHROMENE) [a]



Entry	Ar^2NH_2	Ar^1COR	Reaction time (min)	Yield [b] (%)	Product/ Compound	
1			60	96		5a
2			90	93		5b
3			60	97		5c
4			105	92		5d
5			120	95		5e
6			90	98		5f
7			120	97		5g

8			120	91		5h
9			105	93		5i
10			90	94		5j
11			90	95		6a
12			90	87		6b
13			105	90		6c
14			105	96		6d

15			120	90		6e
16			150	92		6f
17			120	95		6g

The catalyst was cleanly separated after completion of the reaction (monitored by TLC) by simple filtration in hot condition. The obtained solid condensation product was further purified by recrystallization in ethanol. As the granular size of the zeolite is used, 100% recovery of the catalyst is possible even after three consecutive runs. And it was found that the recovered catalyst shows almost same yield with three successive reactions. The recovered catalyst was washed with ethyl acetate, then dried at 70°C prior to use for next run in model reaction and activated at 350℃ after three consecutive runs. The activity of the catalyst decreases after fourth run plausibly due to impediment of pores of the zeolite.

Interestingly, the addition of 0.5 g catalyst was found to be sufficient to provide excellent yield of products (<90%) after moderately short reaction time (typically between 1-3 h). Lower catalyst loading and reaction time (less than 30 min) at room temperature turned out to be inefficient and resulted in significantly reduced yields (85% and below). The protocol was also amenable to a range of substrates, including different aldehydes as well as more challenging substrates, such as ketone and benzoyl chloride (**Table 1**). The products were obtained in excellent yields for all the investigated substrates 85-97%), regardless of the nature and position of the substituents and/or hetero aromatic nature of the carbonyl compound. In any case, reactions take a longer time to reach completion for these more challenging substrates (2-2.5 h) as compared to aldehydes, which provide quantitative conversion to products in 0.5- 2 h of reaction. A series of optimization experiments pointed to a remarkable acceleration of reaction rates and therefore yields, at slightly increased reaction temperatures.

Temperatures as low as 40℃ provided almost quantitative yields of products at reduced reaction time (ranging from 1 to 2 h; **Table 1**) by employing zeolite as catalyst. Yields were somewhat reduced for substrates with larger chains, but in any case the devised protocol was suitable for both aromatic and aliphatic (cyclic and acyclic) substituents. The time period of reaction decreases with further increase in temperature (from 50 to 70℃) but did not have much influence on the yields of products as compared to those at 40℃ (**Figure 1**).

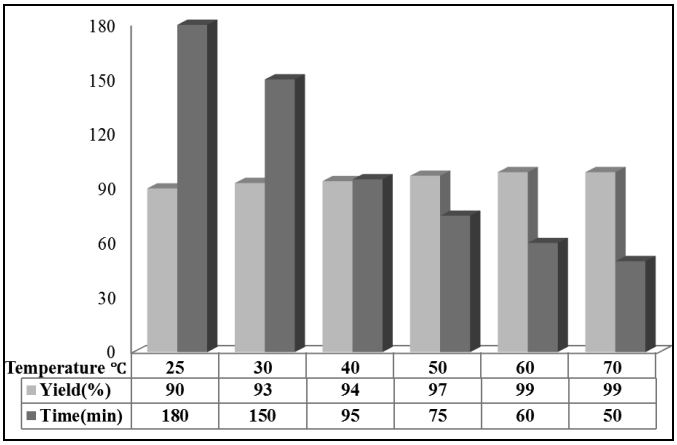
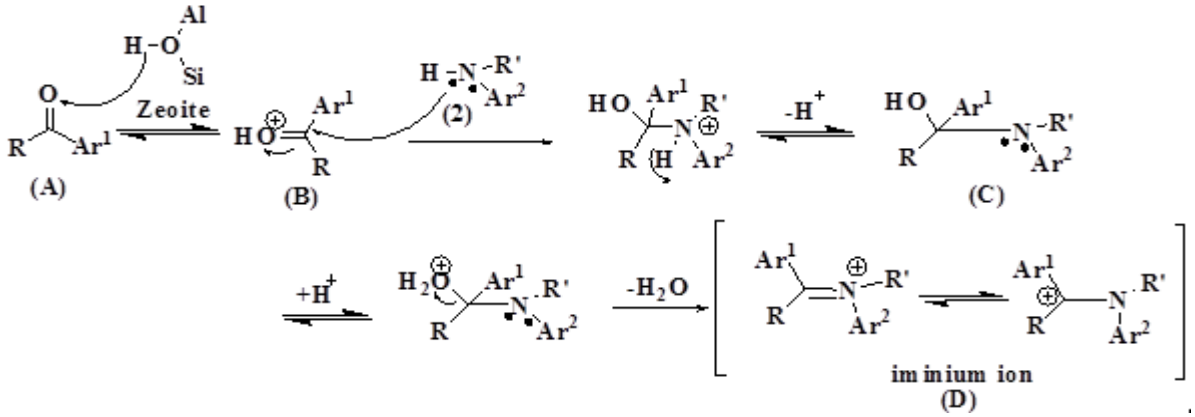


FIGURE 1: THE EFFECT OF REACTION TEMPERATURE ON THE ACTIVITY OF ZEOLITE FOR THE BETTI'S CONDENSATION OF CARBONYL COMPOUND, AMINE AND QUINOLINE/CHROMENE

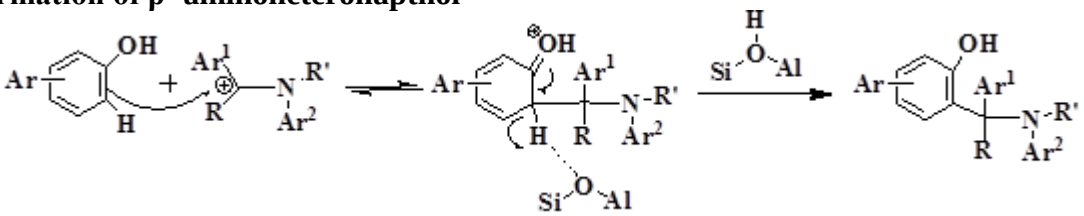
(5/6). Reaction conditions: 1mmol quinoline/chromene, 1 mmol substrate amine and carbonyl compound, 0.5 g zeolite.

But with compared to other catalyst, zeolites affords a much reduced reaction period with promisingly greater yield and a complete green sustainable technique. A plausible mechanism is proposed for the acid catalyzed condensation of carbonyl compound, amine and heterophenol to β-amino-phenol using zeolite (**Scheme 2**). The carbonyl compound A is protonated by transfer of H^+ from zeolite to give B which undergoes ligand exchange reaction through more nucleophilic amine type nitrogen to form C. The facile reductive elimination of water molecule from C concomitantly results in reaction intermediate iminium ion D. Phenol E on electrophilic substitution with iminium ion furnishes β-amino-phenol.

1) Formation of iminium ion:



2) Electrophilic substitution of iminium ion and formation of β- aminoheteronapthol



SCHEME 2: MECHANISM FOR β-AMINOHETERONAPHTHOL FORMATION

***In vitro* antimicrobial screening:** A chemical library of the compounds from the series 5a-5j, 6a-6g and 7a-7p were tested for antimicrobial and antifungal activity. The pharmacophores modeling of these series of compounds was also proposed in terms of prediction of theoretical physico-chemical properties. The fungal and bacterial cultures were kindly provided by Rajiv Gandhi Biotechnology Centre, Nagpur.

Agar well diffusion method was used to determine the antibacterial activity of these compounds, with Amoxicillin and Gentamicin as the standard antimicrobial agent and Nystatin and Flucanazol as the standard antifungal agent. For the diffusion well method, the solvent used was dimethyl sulfoxide (DMSO) and its antimicrobial activity against all the proposed pathogenic microbial cultures was found too negligible to be considered as zero.

The concentrations of the compounds taken were 1, 0.5, 0.25, 0.1, 0.01 and 0.001 mg/ml in DMSO with 20 µl solution in each well (5 mm diameter hole cut in agar gel).

Test-microbes: The antibacterial activity of compound was assessed against pathogenic strains both gram positive and gram negative bacteria, the pathogenic gram positive bacteria for testing were *Staphylococcus aureus, Streptococcus mutants, Bacillus subtilis* and gram negative bacteria were *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Klebsiella pneumonia.* The pathogenic fungi referred for antifungal activity were *Aspergillus niger, Phythophthora sp., Aspergillus flavus, Candida albicans, Rhizopus orazyae* and *Fusarium oxysporium.* All the microbes were subculture in sterilized nutrient broth.

Agar Well Diffusion method: For the antibacterial efficacy, Muller Hinton agar medium (33.9 g) was taken in distilled water (1 lit) which was autoclaved at 15 lbs pressure at 121°C for 15 minutes and poured onto 100 mm petriplates (25-30ml/plate) in molten state. The antimicrobial efficacy of compounds were assessed by the mortification of mycelia growth of fungus observed as a zone of inhibition near the well scratch on Potato Dextrose agar medium. The microbial inoculum (300 µl) was uniformly spread using sterile cotton swab on a sterile Petri dish agar. The 20 µl solution of compounds of concentration 1, 0.5, 0.25, 0.1, 0.01 and 0.001 mg/ml in DMSO was taken in each well cut in agar gel plate.

The systems were incubated under aerobic conditions for 24 h at 36°C ± 1°C for bacterial colony and at 25°C ± 1°C for fungal colonial growth. After incubation, confluent microbial growth was observed. Inhibition of the microbial growth was assayed by measuring the diameter of inhibition zone (mm) formed around the well (NCCLS, 1993). Reference commercial antibacterials used were Amoxicillin and Gentamicin and antifungal used were Nystatin and Fluconazole. Tests were performed in duplicates and results are presented in **Table 2** and **Table 3**.

The compounds 5d, 5f, and 5j provide better antibacterial properties against most of the pathogenic bacterias compared to standard antibacterial, Gentamicin and it has also been found that these Betti's reaction products were active against Methicillin-resistant *Staphylococcus aureus* bacterium and certain quinolone resistant pathogens like *S. pyogenes, E. coli, P. aeuruginosa*. The compounds 5a, 5d, 5f, 5j, 6d and 6g demonstrated very good antifungal results against all the pathogenic fungi under consideration. The pathogenic *Phytophthora* species, which was not successfully medicated, was also found to be overawed by these compounds. These potent products of the invention also have the MIC at very low concentration.

Minimum inhibitory concentration (MIC) determination: Certain compounds of the subject have been found to have MIC values (µg/ml) that are up to about 500 times lower than Amoxicillin and Ciprofloxacin and comparable enough to replace Gentamicin. Moreover invented compound inhibits the antifungal activity against widespread pathogenic fungi having MIC about 10 times reduced amount of known antifungal agents like Fluconazole. The MIC of the compounds is given in **Table 4** and **Table 5**.

TABLE 2: ANTIBACTERIAL EFFICACY OF COMPOUNDS (0.25 mg/ml) AGAINST PATHOGENIC BACTERIA

Compounds	Zone of inhibition						
	Gram positive bacteria			Gram negative bacteria			
	Staphylococcus aureus	*Streptococcus mutants*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella typhi*	*Klebsiella pneumonia*
5a	18	12	12	16	10	42	16
5b	19	14	13	17	12	24	12
5c	29	16	11	20	14	27	23
5d	50	42	40	45	22	68	60
5e	32	28	19	18	14	39	28
5f	68	42	44	60	23	80	65
5g	28	10	32	12	16	18	23
5h	30	24	17	19	16	40	29
5i	16	11	13	-	08	-	14
5j	65	35	37	40	18	24	72
6a	20	18	14	06	12	08	12
6b	22	16	09	14	17	12	18
6c	30	22	18	16	18	37	27
6d	11	06	08	-	07	-	14
6e	-	17	09	-	08	14	18
6f	28	22	15	16	18	33	32
6g	34	24	20	41	21	28	43
A	30	37	41	32	19	38	32
B	11	-	18	10	-	-	12

A= Gentamicin, B= Amoxicillin; [a] = the diameters of zone of inhibition were in cm

TABLE 3: ANTIFUNGAL EFFICACY OF COMPOUNDS (0.25 mg/ml) AGAINST PATHOGENIC FUNGI [a]

Compounds	Zone of inhibition					
	Aspergillus niger	*Phythophthora sp*	*Aspergillus flavus*	*Candida albicans*	*Rhizopus orazyae*	*Fusarium oxysporium*
5a	27	52	38	38	42	36
5b	28	51	-	37	44	34
5c	22	46	33	34	38	-
5d	60	100	54	51	72	60
5e	54	-	48	44	51	40
5f	68	100	56	60	85	100
5g	24	19	22	23	12	21
5h	33	31	26	22	18	20
5i	55	62	23	46	67	54
5j	30	50	45	42	34	48
6a	39	43	38	20	33	39
6b	48	41	33	21	36	34
6c	45	32	31	30	24	31
6d	26	35	36	26	27	29
6e	24	78	34	64	20	28
6f	23	36	34	46	22	33
6g	46	60	38	31	43	41
Nystatin	22	13	24	25	26	18
Fluconazole	-	-	-	20	-	-

[a] = the diameters of zone of inhibition were in cm

TABLE 4: MIC FOR ANTIBACTERIAL EFFICACY [a]

Compounds	Gram positive bacteria			Gram negative bacteria			
	Staphylococcus aureus	*Streptococcus mutants*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella typhi*	*Klebsiella pneumonia*
5d	1	1	1	1	5	1	1
5f	1	1	1	1	5	1	1
5j	5	5	5	1	100	100	1
A	5	0.5	0.5	5	5	5	1
B	250	500	250	250	500	500	250

A= Gentamicin, B= Amoxicillin; [a] = all the values are in µg/ml

TABLE 5: MIC FOR ANTIFUNGAL EFFICACY [a]

Compounds	*Aspergillus niger*	*Phythophthora species*	*Aspergillus flavus*	*Candida albicans*	*Rhizopus orazyae*	*Fusarium oxysporium*
5a	10	10	50	10	10	50
5d	5	1	1	1	1	1
5f	5	1	5	1	5	5
5j	10	10	5	5	5	5
6d	50	100	100	100	50	100
6g	10	50	25	100	25	10
Nistatin	1	1	1	1	1	1
Flucanazol	100	100	100	10	100	100

[a] = all the values are in µg/ml

CONCLUSION: An array of biologically and pharmaceutically active novel heterocycles were engendered by tailored Betti's reaction with green fundamentals. Natural as well as synthetic zeolite was demonstrated in general to be an efficient and versatile catalyst for the three-component Betti's condensation reaction. A range of carbonyl compounds and amines could be efficiently reacted with quinoline/coumarin to give the corresponding substituted β-aminohetero-naphthols. Furthermore, the antibacterial and antifungal properties were characterized by zone of inhibition and compared with standard drugs. The compounds were better antimicrobial agent compared to standards Amoxicillin and Fluconazole. The compounds 5d, 5f and 5j were showing very good antibacterial activity against maximum pathogenic bacteria with lower MIC

than Gentamicin and compounds 5d, 5f, 6d and 6g were having better antifungal activity amongst all and MIC value analogous to Nystatin. Thus these green technologically synthesized compounds could be used as putative more potent antimicrobial compound.

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