Facile green synthesis and potent antimicrobial efficacy of β -aminoheteronaphthol via tailored Betti's protocol and their *bis*-aryl hydrazone click products

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Abstract. A series of novel Mannich base and their hydrazone derivatives were synthesized by highly resourceful, chic, simple and green technique with exceptionally facile reaction conditions of one-pot, three component reaction with an array of biologically and pharmaceutically active novel heterocycles. The protocol offers a valuable alternative to known methods and will find applications in the field of green synthesis and antimicrobial study against pathogenic microbes, supporting the development of bioinformatical database of novel and derelict heterocycles. These data indicate their potential to become antifungal agents. The novel products were established by elemental, IR, mass spectroscopic and NMR analysis. The environmental advantages of the method include short reaction time, excellent yield, easy work-up, absence of extraction and chromatographic purification steps.

Keywords. Green synthesis; zeolite catalyst; click reaction; antimicrobial efficacy.

1. 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, *Pneumocystis carinii*, causes a form of pneumonia (PCP) that is believed to be one of the leading causes of death in patients suffering from AIDS. Furthermore, the treatment of infectious diseases is more complicated in immuno-suppressed patients, such as those infected with the HIV, undergoing anticancer treatment and organ transplants. Therefore, there is a vital need for the development of new antimicrobial agents having potent activity against the resistant microorganisms.¹

The rapid development of resistance to existing antibacterial and antifungal drugs poses a major threat to public health which creates a serious challenge to the

scientific community. Hence the usage of most of the 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 the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects.² 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.³ Thereafter numerous modifications of this reaction surfaced.⁴ Since these compounds have multiple centres for chelation with metal ions, they are likely to be potent inhibitors of metallo-enzymes.⁵ Also, these compounds have the potential to be used as scavengers in cases of heavy metal poisoning.⁶ 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

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prodrugs as means of overcoming some of their limitations.⁷ 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 modelling and *in vitro* microbial activity.⁸ Despite the importance of the compounds, the serious downsides of their commercial syntheses include 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 are hydrolysed 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 are the foremost impediment in the microwave-assisted synthesis of these compounds.

The aforementioned problems of greener synthetic approach of Betti's reaction product are overcome in present work by one-pot multicomponent zeolite catalysed condensation bioactive Betti's reaction products. Inspired by the above facts and in continuation of our ongoing research programme in the field of synthesis and antimicrobial activity of medicinally important compounds,⁹ we report here the click synthesis of novel hydrazide-hydrazone/bisaryl hydrazone derivatives of bioactive Betti's product and evaluated them for antimicrobial activity.

Hydrazones are the most important pharmacophoric cores of several antimicrobial, anticonvulsant, analgesic, antiinflammatory, antinociceptive, antiplatelet, antitubercular, and antitumoural drugs.¹⁰ Hydrazides and hydrazones are present in many of the bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications. This created interest in researchers who have synthesized variety of hydrazide derivatives and screened them for their various biological activities.¹¹ Hydrazones have been explored for the reversible conjugation¹² and labelling¹³ of biomolecules. However, their application has been limited, as most hydrazones are prone to hydrolysis and premature cleavage, whereas hydrazones (and oximes) that are fully stable under biological and mildly acidic conditions undergo slower hydrolysis and are difficult to exchange or cleave.

The formation kinetics of the *bis*-aryl hydrazone bond are 20 to 900 times higher than those of conventional hydrazone/oxime bonds between alkyl aldehydes/ketones and alkyl hydrazide or aminoxy probes.¹⁴ The hydrazide hydrazones have been demonstrated to possess antibacterial,^{15–17} anticonvulsant^{18–20} and antitubercular²¹ activities. Furthermore, the benefits of

click reactions are well-known, and their applications have revolutionized numerous fields including bioconjugate chemistry, material chemistry and polymer sciences.^{22–25} The non-aldol addition reaction between a carbonyl and a nucleophilic nitrogen as a click reaction has key benefits of availability of amines for bioconjugation, rapid incorporation into molecular frameworks, and a simple resultant click product that minimally impacts the nature of the biomolecules.²⁶

Against this background, and also in the context of our interest in the synthesis of biologically significant heterocycles *via* multi-component and click reactions, we report here the green preparation of a library of pharmacologically relevant click fused bisarylhydrazones, containing a Betti's base fabricated by a process that combines the use of zeolite with the synthetic efficiency associated with MCRs, providing a convergence of reaction and environmental economies.²⁷

In this paper, green synthesis of potent Betti's product and hydrazone derivatives are exemplified with their antimicrobial efficacy. Here, in order to reduce the time period of Betti's reaction product, enantioselective transformations and to 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.^{28–30}

Furthermore, we have found a novel series of Betti's products and hydrazone derivatives that are effective against resistant microbes, and provide significant activity advantage over the art. It has been found that the compounds of this innovation 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.

2. Experimental

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. ¹H NMR spectra were recorded on a Cryo-magnet NMR Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard with CDCl₃ 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°C) 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°C, zeolites were reutilized for each reaction.

2.1 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°C. 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**).

2.1a Ethyl 4-[(2-hydroxy-3-methoxyphenyl)(8-hydroxyquinolin-7-yl)methyl]amino}benzoate (5a**):** Light yellow crystalline solid; yield 96% (4.267 g, crystallization) or 99% (4.4 g, filtration), m.p. 173–175°C; refractive index n_D^{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}) ν : 3088.4 (OH), 1707.2 ($COOC_2H_5$), 1324.3 (C–N stretching), 3382.6 (NH), 2872.3 (OCH_3). 1H 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%).

2.1b 1-(4-[(4-Hydroxy-3-methoxyphenyl)(8-hydroxyquinolin-7-yl)methyl]amino}phenyl)ethan-1-one (5b**):** Yellow amorphous solid, yield 93% (3.854 g, crystal-

lization) or 96% (3.978 g, filtration), m. p. 192–196°C; refractive index n_D^{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}) ν : 3553.8 (OH), 1323.9 (C–N stretching), 3380.8 (NH), 2852.2 (OCH_3), 1722.5 (CO). 1H 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%).

2.1c Ethyl 4-[(2-hydroxyphenyl)(8-hydroxyquinolin-7-yl)methyl]amino}benzoate (5c**):** Orange needle shape solid, yield 97% (4.02 g, crystallization) or 99% (4.1 g, filtration), m. p. 96–98°C; refractive index n_D^{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}) ν : 3582.4 (OH), 1734.9 ($COOC_2H_5$), 1305.5 (C–N stretching), 3431.6 (NH). 1H 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%).

2.1d Ethyl 4-[(2-chloroquinolin-3-yl)(8-hydroxyquinolin-7-yl)methyl]amino}benzoate (5d**):** Dark yellow amorphous solid, yield 92% (4.452 g, crystallization) or 95% (4.597 g, filtration), m.p. 225–229°C; refractive index n_D^{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}) ν : 3096.1 (OH), 1716.9 ($COOC_2H_5$), 1323.3 (C–N stretching), 3420.5 (N-H), 1066.8 (C–Cl). 1H 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%).

2.1e 7-[(1,5-Dimethyl-3-methyldene-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino](furan-2-yl)methylquinolin-8-ol (**5e**): Dark brown amorphous solid, yield 95% (4.051 g, crystallization) or 97% (4.136 g, filtration), m.p. 166–170°C; refractive index n_D^{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}) ν : 3523.6.1 (OH), 1343.2 (C-N stretching), 3423.8 (N-H), 1743.8 (CO). ^1H 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, -CH₃); 3.21 (s, 3H, N-CH₃); 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%).

2.1f Ethyl 4-[[furan-2-yl(8-hydroxyquinolin-7-yl)methyl]amino]benzoate (**5f**): Light brown amorphous solid, yield 98% (3.8 g, crystallization) or 99% (3.845 g, filtration), m.p. 148–150°C; refractive index n_D^{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}) ν : 3356.4 (OH), 1323.3 (C-N stretching), 3113.5 (N-H), 1718.8 (COOC_2H_5), 1232.7 (COC). ^1H 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, -CH₃, $J = 5.6$); 4.15 (q, 2H, -OCH₂-, $J = 3.7$, 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%).

2.1g Ethyl 4-[[chloro(8-hydroxyquinolin-7-yl)(4-nitrophenyl)methyl]amino]benzoate (**5g**): Light orange crystalline solid, yield 97% (4.635 g, crystallization) or 99% (4.732 g, filtration), m.p. 182–186°C; refractive index n_D^{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}) ν : 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). ^1H 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, -CH₃, $J = 6.1$, 7.2); 4.34 (q, 2H, -OCH₂-, $J = 1.5$, 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%).

2.1h Ethyl 4-[[1-(8-hydroxyquinolin-7-yl)-2-oxo-1,2-diphenylethyl]amino]benzoate (**5h**): Yellow amorphous solid, yield 91% (4.573 g, crystallization) or 94% (4.724 g, filtration), m.p. 112–116°C; refractive index n_D^{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}) ν : 3518.4 (OH), 1336.5 (C-N stretching), 3424.3 (NH), 1722.3 (COOC_2H_5), 1708.6 (CO). ^1H 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, -CH₃, $J = 7.0$); 3.95 (q, 2H, -OCH₂-, $J = 4.0$, 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%).

2.1i 7-[1-(Tert-butylamino)-2-hydroxy-1,2-diphenylethyl]quinolin-8-ol (**5i**): Bright yellow crystalline solid, yield 93% (3.836 g, crystallization) or 98% (4.042 g, filtration), m.p. 102–105°C; refractive index n_D^{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}) ν : 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, -CH₃); 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%).

2.1j 7-[(6-Benzyl-6H-purin-6-yl)amino](4-hydroxy-3-methoxyphenyl)methylquinolin-8-ol (**5j**): Orange amorphous solid, yield 94% (4.742 g, crystallization) or 97% (4.894 g, filtration), m.p. 116–120°C; refractive index n_D^{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}) ν : 3122.3 (OH), 1326.7 (C-N stretching), 2847.9 (OCH₃), (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, CH₂); 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, -OCH₃). ^{13}C

NMR (CDCl₃, 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%).

2.2 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°C for 15 min 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**).

2.2a 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°C; refractive index n_D^{22} : 1.679. Anal. Calcd. for C₂₆H₂₃NO₈: C, 65.40; H, 4.86; N, 2.93%. Found: C, 65.55; H, 5.01; N, 2.82%. IR (cm⁻¹) ν : 3627.3 (OH), 1595.2 (CO), 1345.8 (C–N stretching), 3413.7 (NH), 1396.3 (COOH), 2815.9 (OCH₃). ¹H NMR (CDCl₃, 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, -OCH₃); 8.73 (s, 1H, -OH). ¹³C NMR (CDCl₃, 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%).

2.2b 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°C; refractive index n_D^{22} : 1.645. Anal. Calcd. for C₂₁H₁₇NO₅: C, 69.41; H, 4.72; N, 3.85%. Found: C, 69.52; H, 4.78; N, 3.83%. IR (cm⁻¹) ν : 3410.5 (OH), 1645.2 (cyclic CO), 1352.7 (C–N stretching), 1720.5 (CO). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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%).

2.2c 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°C; refractive index n_D^{22} : 1.620. Anal. Calcd. for C₂₄H₂₁NO₅: C, 71.45; H, 5.25; N, 3.47%. Found: C, 71.58; H, 5.34; N, 3.41%. IR (cm⁻¹) ν : 3526.9 (OH), 1647.1 (cyclic CO), 1353.6 (C–N stretching), 2837.4 (OCH₃), 1719.9 (CO). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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%).

2.2d Ethyl 4-[(2-chloroquinolin-3-yl)(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methyl]amino]benzoate (**6d**): Bright yellow amorphous solid, yield 96% (4.943 g, crystallization) or 97% (5.0 g, filtration), m.p. 98–101°C; refractive index n_D^{22} : 1.691. Anal. Calcd. for C₂₉H₂₃ClN₂O₅: 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) ν : 3498.3 (OH), 1715.6 (cyclic CO), 3419.9 (NH), 1277.7 (C–N stretching), 1732.4 (COOC₂H₅), 1098.6 (Cl). ¹H 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, -CH₃, J = 8.0); 4.32 (q, 2H, -CH₂, J = 4.0, 8.0); 6.14 (s, 1H, methine); 7.74–9.22 (m, 5H, quinoline-H). ¹³C NMR (CDCl₃, 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%).

2.2e Ethyl 4-[(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°C; refractive index n_D^{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}) ν : 3457.7 (OH), 1714.6 (cyclic CO), 3436.3 (NH), 1358.3 (C–N stretching), 1735.7 ($COOC_2H_5$). 1H 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%).

2.2f Ethyl 4-[(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diphenylmethyl]amino}benzoate (6f): Dark Green amorphous solid, yield 92% (4.651 g, crystallization) or 97% (4.9 g, filtration), m.p. 105–109°C; refractive index n_D^{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}) ν : 3467.3 (OH), 1712.9 (cyclic CO), 3438.4 (NH), 1357.9 (C–N stretching), 1736.8 ($COOC_2H_5$). 1H 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%).

2.2g 8-[Furan-2-yl(morpholin-4-yl)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°C; refractive index n_D^{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}) ν : 3105.4 (OH), 1759.1 (cyclic CO), 1343.5 (C–N stretching), 1769.8 (morpholin). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 10.26 (s, 1H, coumarin-OH); 2.23 (s, 3H, methyl coumain); 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%).

2.3 General procedure for the synthesis of *N'*-substituted arylidenehydrazine derivatives (7)

β -aminoheteronaphthol (**5/6**) (1 mmol) and aldehyde/ketone (1 mmol) were made single phase by dissolving in minimum quantity of ethanol and then added to petri dish containing hydrazine hydrate (80%) (1 mmol). This concoction was then mixed with a glass rod, a dry solid product established within 10 s by exothermic click reaction at room temperature. The solid product was washed with cold ethanol and recrystallized by ethanol **7** (compound **7a–7p**).

2.3a *N'*-[(2-fluorophenyl)methylidene]-4-[(2-hydroxy-3-methoxyphenyl)(8-hydroxyquinolin-7-yl)methyl]amino}benzohydrazide (7a): Light yellow crystalline solid, yield 90% (4.828 g, crystallization) or 95% (5.097 g, filtration), m.p. 104–108°C; refractive index n_D^{22} : 1.649. Anal. Calcd. for $C_{31}H_{25}FN_4O_4$: C, 69.39; H, 4.70; F, 3.54; N, 10.44%. Found: C, 69.45; H, 4.79; F, 3.58; N, 10.38%. IR (cm^{-1}) ν : 3089.1 (OH), 1675.2 (C=N-), 1321.9 (C–N stretching), 3382.8 (NH), 2852.0 (OCH_3), 1096.7 (CF). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 8.68 (s, 2H, -OH); 7.74–7.82 (m, 5H, quinoline-H); 8.12 (s, 1H, sec. amine -NH); 7.36–7.42 (m, 4H, Ar-H); 10.82 (s, 1H, HN-hydrazide); 8.93 (s, 1H, methylene); 7.47–7.63 (m, 4H, Ar-H); 7.55 (s, 1H, methine); 7.31–7.43 (m, 3H, vanillin-H); 1.34 (s, 3H, vanillin $-OCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 50.2, 56.3, 109.5, 112.4, 116.0, 118.3, 120.4, 120.6, 121.0, 121.4, 121.7, 122.9, 123.7, 124.4, 127.7, 128.4, 130.2, 130.8, 132.6, 135.6, 137.3, 143.4, 144.6, 148.5, 150.1, 159.7, 163.3. MS, m/z : 536 (M^+ , 100.0%).

2.3b 7-[(4-Hydroxy-3-methoxyphenyl)(4-[(1-1-2-[(4-methoxyphenyl)methylidene]hydrazin-1-ylidene)ethyl]phenyl]amino)methyl]quinolin-8-ol (7b): Dull orange amorphous solid, yield 93% (5.083 g, crystallization) or 97% (5.3 g, filtration), m.p. 106–110°C; refractive index n_D^{22} : 1.630. Anal. Calcd for $C_{33}H_{30}N_4O_4$: C, 72.51; H, 5.53; N, 10.25%. Found: C, 72.68; H, 5.70; N, 10.21%. IR (cm^{-1}) ν : 3551.9 (OH), 1324.2 (C–N stretching), 3380.8 (NH), 2849.1 (OCH_3), 1726.5 (C=N-). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 9.89 (s, 2H, -OH); 7.62–8.17 (m, 5H, quinoline-H); 6.70 (s, 1H sec. amine HN-); 6.84–7.38 (m, 4H, Ar-H); 3.12 (s, 3H, $-CH_3$); 8.88 (s, 1H, methylene); 7.16–7.74 (m, 4H, Ar-H); 3.03 (s, 3H, Ar- OCH_3); 5.19 (s, 1H, methine); 6.91–7.34 (m, 3H, vanillin-H); 10.23 (s, 3H, vanillin-OH). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 14.6, 55.7, 56.0, 56.3, 112.1, 113.8, 114.6, 116.3, 120.2, 120.9, 121.4, 121.9, 127.0, 127.6, 128.1, 128.5, 130.0, 133.7, 135.5, 136.3, 137.3, 146.2, 148.0, 148.5,

149.4, 149.9, 150.1, 162.8, 197.3. MS, m/z : 546 (M^+ , 100.0%).

2.3c 4-[[2-Hydroxyphenyl](8-hydroxyquinolin-7-yl)methyl]amino}-*N'*-(1-phenylethylidene) benzohydrazide (**7c**): Light orange crystalline solid, yield 87% (4.372 g, crystallization) or 90% (4.523 g, filtration), m.p. 102–106°C; refractive index n_D^{22} : 1.661. Anal. Calcd. for $C_{31}H_{26}N_4O_3$: C, 74.09; H, 5.21; N, 11.15%. Found: C, 74.22; H, 5.32; N, 11.11%. IR (cm^{-1}) ν : 3589.1 (OH), 1704.9 (C=N-), 1325.5 (C-N stretching), 3438.6 (NH). 1H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 10.18 (s, 1H, quinoline -OH); 7.44–8.18 (m, 5H, quinoline-H); 7.05 (s, 1H sec. amine -NH); 6.78–7.96 (m, 4H, Ar-H); 11.58 (s, 1H, -NH hydrazide); 2.32 (s, 3H, -CH₃); 7.52–7.94 (m, 5H, Ar-H); 5.59 (s, 1H, methine); 9.66 (s, 1H, Ar-OH); 6.79–7.09 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 16.8, 50.1, 112.4, 116.6, 119.6, 120.2, 121.0, 121.4, 121.6, 121.8, 127.6, 128.2, 128.4, 128.8, 130.4, 131.2, 131.3, 135.5, 137.3, 137.5, 147.7, 148.5, 150.4, 151.2, 157.9, 163.3. MS, m/z : 502 (M^+ , 100%).

2.3d 4-[[2-chloroquinolin-3-yl](8-hydroxyquinolin-7-yl)methyl]amino}-*N'*-(furan-2-ylmethylidene)benzohydrazide (**7d**): Dark brown amorphous solid, yield 94% (5.151 g, crystallization) or 98% (5.37 g, filtration), m.p. 142–146°C; refractive index n_D^{22} : 1.705. Anal. Calcd. for $C_{31}H_{22}ClN_5O_3$: C, 67.94; H, 4.05; Cl, 6.47; N, 12.78%. Found: C, 67.98; H, 3.96; Cl, 6.49; N, 12.72%. IR (cm^{-1}) ν : 3103.5 (OH), 1625.1 (C=N-), 1333.5 (C-N stretching), 3442.1 (N-H), 1065.3 (Cl). 1H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 9.08 (s, 1H, quinoline -OH); 7.36–8.22 (m, 5H, quinoline-H); 7.28 (s, 1H sec. amine -NH); 7.05–7.88 (m, 4H, Ar-H); 7.95 (s, 1H, HN-hydrazide); 7.25 (s, 1H, methylene); 7.24–7.35 (m, 3H, furan-H); 4.56 (s, 1H, methine); 7.32–7.47 (m, 5H, chloroquinolin-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 50.9, 112.3, 112.7, 118.9, 120.3, 120.9, 121.2, 121.3, 126.6, 127.1, 127.3, 127.5, 127.6, 128.4, 129.9, 130.2, 131.2, 134.6, 135.5, 136.2, 137.3, 144.5, 145.4, 148.6, 149.2, 150.0, 151.2, 152.3, 164.2. MS, m/z : 547 (M^+ , 100%).

2.3e 7-[Furan-2-yl{[(3)-3-[2-[(2-hydroxy-3-methoxyphenyl)methylidene]hydrazin-1-ylidene]-1,5-dimethyl-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]amino}]methyl]quinolin-8-ol (**7e**): Dark brown amorphous solid, yield 86% (4.941 g, crystallization) or 90% (5.171 g, filtration), m.p. 162–164°C; refractive index n_D^{22} : 1.670. Anal. Calcd. for $C_{33}H_{30}N_6O_4$: C, 68.98; H, 5.26; N, 14.63%. Found: C, 69.12; H, 5.32; N, 14.65%. IR

(cm^{-1}) ν : 3525.6 (OH), 1728.7 (C=N-), 1348.1 (C-N stretching), 3430.8 (N-H). 1H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 9.70 (s, 1H, quinoline -OH); 7.42–8.66 (m, 5H, quinoline-H); 7.60 (s, 1H sec. amine -NH); 6.80–7.37 (m, 5H, Ar-H); 2.35 (s, 3H, -CH₃); 3.11 (s, 3H, N-CH₃); 8.54 (s, 1H, methylene); 13.34 (s, 1H, vanillin-OH); 3.43 (s, 3H, vanillin-OCH₃); 6.84–7.22 (m, 3H, vanillin-H); 5.18 (s, 1H, methine); 6.26–7.25 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 9.4, 34.2, 53.8, 56.1, 106.7, 109.2, 110.6, 115.0, 116.6, 119.6, 120.2, 120.9, 121.3, 122.8, 123.9, 124.4, 127.6, 128.4, 129.2, 135.5, 136.2, 126.0, 137.3, 142.1, 148.5, 149.1, 150.3, 150.6, 152.3, 157.3, 164.1. MS, m/z : 574 (M^+ , 100%).

2.3f *N'*-[(1)-(2-chlorophenyl)methylidene]-4-[[furan-2-yl(8-hydroxyquinolin-7-yl)methyl]amino]benzohydrazide (**7f**): Light brown crystalline solid, yield 97% (4.82 g, crystallization) or 99% (4.919 g, filtration), m.p. 96–98°C; refractive index n_D^{22} : 1.674. Anal. Calcd. for $C_{28}H_{21}ClN_4O_3$: C, 67.67; H, 4.26; Cl, 7.13; N, 11.27%. Found: C, 67.74; H, 4.38; N, 11.23%. IR (cm^{-1}) ν : 3536.7 (OH), 1339.4 (C-N stretching), 3125.5 (N-H), 1719.2 (C=N-), 1233.6 (COC), 1098.2 (C-Cl). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 8.23 (s, 1H, quinoline-OH); 7.36–8.21 (m, 5H, quinoline-H); 7.38 (s, 1H sec. amine HN-); 7.34–7.41 (m, 4H, Ar-H); 9.09 (s, 1H, hydrazide-NH); 7.46 (s, 1H, methylene); 7.33–7.45 (m, 4H, Ar-H); 7.25 (s, 1H, methine); 7.32–7.37 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 58.3, 106.8, 110.7, 112.2, 120.2, 120.9, 121.2, 121.3, 126.9, 127.2, 127.6, 128.4, 130.1, 130.2, 132.4, 133.9, 134.7, 135.5, 137.3, 138.8, 142.2, 148.5, 150.2, 151.4, 152.4, 163.5. MS, m/z : 496 (M^+ , 100%).

2.3g *N'*-[(1)-(2-chloroquinolin-3-yl)methylidene]-4-[[furan-2-yl(8-hydroxyquinolin-7-yl)methyl]amino]benzohydrazide (**7g**): Light brown crystalline solid, yield 91% (4.986 g, crystallization) or 93% (5.096 g, filtration), m.p. 221–224°C; refractive index n_D^{22} : 1.705. Anal. Calcd. for $C_{31}H_{22}ClN_5O_3$: C, 67.94; H, 4.05; Cl, 6.47; N, 12.78%. Found: C, 68.18; H, 4.24; Cl, 4.52; N, 12.82%. IR (cm^{-1}) ν : 3350.4 (OH), 1327.2 (C-N stretching), 3413.9 (N-H), 1698.9 (C=N-), 1233.8 (COC), 1068.3 (C-Cl). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 8.82 (s, 1H, quinoline-OH); 7.36–8.19 (m, 5H, quinoline-H); 7.39 (s, 1H sec. amine HN-); 7.34–7.44 (m, 4H, Ar-H); 10.01 (s, 1H, hydrazide-NH); 8.18 (s, 1H, methylene); 7.64–7.97 (m, 5H, chloroquinolin-H); 7.25 (s, 1H, methine); 7.32–7.36 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 58.6, 107.1, 110.8, 112.4, 120.2, 120.9, 121.2,

121.3, 124.2, 126.8, 127.2, 127.6, 127.8, 128.1, 128.4, 130.2, 131.4, 135.7, 137.5, 137.9, 142.1, 143.3, 148.5, 149.7, 150.2, 151.3, 152.5, 152.8, 163.2. MS, m/z : 547 (M^+ , 100%).

2.3h 4-[[Furan-2-yl(8-hydroxyquinolin-7-yl)methyl]amino]-*N'*-[(1)-furan-2-ylmethylidene]benzohydrazide (**7h**): Brown amorphous solid, yield 94% (4.253 g, crystallization) or 97% (4.388 g, filtration), m.p. 130–134°C; refractive index n_D^{22} : 1.679. Anal. Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38%. Found: C, 68.98; H, 4.49; N, 12.34%. IR (cm^{-1}) ν : 3537.4 (OH), 1340.0 (C-N stretching), 3124.9 (N-H), 1719.8 (C=N-), 1235.7 (COC). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 8.72 (s, 1H, quinoline-OH); 7.36–7.47 (m, 5H, quinoline-H); 8.23 (s, 1H sec. amine HN-); 7.34–7.43 (m, 4H, Ar-H); 10.81 (s, 1H, hydrazide-NH); 8.45 (s, 1H, methylene); 6.52–7.75 (m, 3H, furan-H); 7.28 (s, 1H, methine); 6.38–7.37 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 28.6, 106.8, 110.7, 112.2, 112.6, 118.8, 120.2, 120.9, 121.2, 121.3, 127.6, 128.4, 130.2, 134.6, 135.6, 137.4, 142.1, 144.4, 148.6, 149.3, 150.1, 151.2, 152.5, 163.4. MS, m/z : 452 (M^+ , 100%).

2.3i *N'*-[1-(4-Aminophenyl)ethylidene]-4-[[chloro(8-hydroxyquinolin-7-yl)(4-nitrophenyl)methyl]amino]benzohydrazide (**7i**): Dark yellow amorphous solid, yield 89% (5.171 g, crystallization) or 92% (5.345 g, filtration), m.p. 120–124°C; refractive index n_D^{22} : 1.687. Anal. Calcd. for $C_{31}H_{25}ClN_6O_4$: C, 64.08; H, 4.34; Cl, 6.10; N, 14.46%. Found: C, 63.99; H, 4.29; Cl, 6.15; N, 14.51%. IR (cm^{-1}) ν : 3483.4 (OH), 1347.9 (C-N stretching), 3362.3 (N-H), 3489.5 (aromatic -NH₂), 1721.1 (C=N-), 762.1 (C-Cl), 1459.7 (NO₂). 1H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 9.68 (s, 1H, quinoline -OH); 7.42–7.56 (m, 5H, quinoline-H); 7.22 (s, 1H sec. amine -NH); 6.25–6.61 (m, 4H, Ar-H); 10.17 (s, 1H, hydrazide-NH); 2.32 (s, 3H, CH₃); 6.68–7.50 (m, 4H, Ar-H), 5.32 (s, 2H, -NH₂); 7.99–8.28 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 17.1, 81.2, 112.4, 114.2, 120.2, 120.9, 121.2, 121.3, 124.5, 126.7, 127.5, 128.4, 129.1, 130.2, 130.6, 135.5, 137.4, 145.4, 147.7, 148.5, 149.1, 150.1, 150.7, 151.2, 163.2. MS, m/z : 580 (M^+ , 100%).

2.3j 4-[[1-(8-Hydroxyquinolin-7-yl)-2-oxo-1,2-diphenylethyl]amino]-*N'*-[(1)-phenylmethylidene]benzohydrazide (**7j**): Dull yellow crystalline solid, yield 88% (5.074 g, crystallization) or 89% (5.132 g, filtration), m.p. 110–114°C; refractive index n_D^{22} : 1.654. Anal. Calcd. for $C_{37}H_{28}N_4O_3$: C, 77.07; H, 4.89; N, 9.72%. Found: C, 77.21; H, 5.04; N, 9.61%. IR (cm^{-1}) ν : 3518.4 (OH),

1338.2 (C-N stretching), 3429.6 (NH), 1751.2 (C=N-), 1701.8 (CO). 1H NMR ($CDCl_3$, 400 MHz, δ ppm, J Hz): 9.82 (s, 1H, quinoline -OH); 7.42–8.88 (m, 5H, quinoline-H); 7.63 (s, 1H sec. amine -NH); 6.70–7.68 (m, 4H, Ar-H); 12.11 (s, 1H, hydrazide-NH); 8.52 (s, 1H, methylene); 7.52–7.83 (m, 5H, Ar-H); 7.28–8.04 (m, 10 H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 75.3, 112.4, 120.2, 120.9, 121.2, 121.3, 126.4, 127.7, 128.2, 128.4, 128.6, 128.8, 129.2, 130.2, 131.1, 133.1, 133.7, 135.6, 136.7, 137.3, 140.2, 146.8, 148.5, 150.2, 151.4, 163.2, 196.6. MS, m/z : 576 (M^+ , 100%).

2.3k 4-[[{(4-Hydroxy-3,5-dimethoxyphenyl)(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl) methyl]amino]methyl]-*N'*-[(1)-(2-hydroxyphenyl)methylidene]benzohydrazide (**7k**): Orange needle shape solid, yield 91% (5.419 g, crystallization) or 96% (5.717 g, filtration), m.p. 102–106°C; refractive index n_D^{22} : 1.646. Anal. Calcd. for $C_{33}H_{29}N_3O_8$: C, 66.55; H, 4.91; N, 7.06%. Found: C, 66.67; H, 5.08; N, 6.97%. IR (cm^{-1}) ν : 3628.9 (OH), 1605.4 (CO), 1346.7 (C-N stretching), 3443.6 (NH), 1746.7 (C=N-), 2816.3 (OCH₃). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 10.18 (s, 1H, coumarin-OH); 2.39 (s, 3H, methyl coumarin); 6.26–7.38 (m, 3H, coumarin-H); 6.59 (s, 1H, sec. amine -NH); 6.38–7.54 (m, 4H, Ar-H); 13.62 (s, 1H, hydrazide-NH); 8.78 (s, 1H, methylene); 12.06 (s, 1H, Ar-OH); 7.02–7.64 (m, 4H, Ar-H); 6.01 (s, 1H, methine); 6.32 (s, 2H, Ar-H); 3.90 (s, 6H, -OCH₃); 9.22 (s, 1H, Ar-OH). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 18.9, 51.2, 56.4, 106.2, 112.2, 112.5, 112.6, 113.2, 117.8, 118.6, 121.2, 121.4, 123.2, 123.7, 127.5, 130.2, 132.5, 135.0, 137.3, 146.0, 147.9, 151.1, 152.7, 154.9, 157.4, 160.9, 163.3. MS, m/z : 595 (M^+ , 100%).

2.3l 8-[Furan-2-yl{2-[(1)-1-[2-[(2)-3-phenylprop-2-en-1-ylidene]hydrazin-1-ylidene]ethyl]-1H-pyrrol-1-yl}]methyl]-7-hydroxy-4-methyl-2H-chromen-2-one (**7l**): Brown amorphous solid, yield 92% (4.522 g, crystallization) or 95% (4.669 g, filtration), m.p. 136–140°C; refractive index n_D^{22} : 1.632. Anal. Calcd. for $C_{30}H_{25}N_3O_4$: C, 73.30; H, 5.13; N, 8.55%. Found: C, 73.51; H, 5.24; N, 8.46%. IR (cm^{-1}) ν : 3463.7 (OH), 1663.52 (cyclic CO), 1359.1 (C-N stretching), 1715.8 (C=N-), 1623.5 (C=C). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 9.62 (s, 1H, coumarin-OH); 2.14 (s, 3H, methyl coumarin); 6.13–7.98 (m, 3H, coumarin-H); 2.10 (s, 3H, methyl-H); 6.26–7.81 (m, 3H, pyrrol-H); 7.50 (s, 1H, methylene); 6.84–6.90 (m, 1H, ethylene-H); 7.12 (d, 1H, J = 4.4, ethylene -H); 7.28–7.62 (m, 5H, Ar-H); 6.55 (s, 1H, methine); 6.08–7.60 (m, 3H, furan-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 15.6, 20.0, 48.2, 106.8, 108.7, 110.2, 110.6, 112.0,

112.5, 117.7, 119.9, 122.1, 122.8, 123.3, 128.0, 128.5, 128.6, 133.4, 135.2, 142.1, 151.8, 152.5, 152.7, 155.7, 157.3, 160.8, 165.6. MS, m/z : 491 (M^+ , 100%).

2.3m 7-Hydroxy-8-({2-[(1)-1-[2-[(2-hydroxyphenyl)methylidene]hydrazin-1-ylidene]ethyl]-1H-pyrrol-1-yl}(4-methoxyphenyl)methyl)-4-methyl-2H-chromen-2-one (**7m**): Orange crystalline solid, yield 90% (4.694 g, crystallization) or 92% (4.798 g, filtration), m.p. 113–116°C; refractive index n_D^{22} : 1.637. Anal. Calcd. for $C_{31}H_{27}N_3O_5$: C, 71.39; H, 5.22; N, 8.06%. Found: C, 71.48; H, 5.31; N, 8.00%. IR (cm^{-1}) ν : 3536.6 (OH), 1646.8 (cyclic CO), 1356.6 (C-N stretching), 2841.7 (OCH_3), 1723.8 (C=N). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 9.83 (s, 1H, coumarin-OH); 2.39 (s, 3H, methyl coumarin); 6.23–7.42 (m, 3H, coumarin-H); 2.10 (s, 3H, methyl-H); 6.23–7.37 (m, 3H, pyrrol-H); 8.72 (s, 1H, methylene); 11.64 (s, 1H, Ar-OH); 7.22–7.96 (m, 4H, Ar-H); 6.16 (s, 1H, methine); 3.78 (s, 3H, methoxy-H); 6.88–7.10 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 15.4, 19.6, 55.4, 56.1, 108.7, 110.2, 112.4, 112.6, 113.2, 114.8, 117.8, 118.6, 121.4, 122.2, 122.8, 123.0, 123.6, 129.3, 129.8, 132.1, 132.4, 151.0, 152.7, 154.9, 157.3, 158.4, 160.8, 161.1, 164.7. MS, m/z : 521 (M^+ , 100%).

2.3n 8-[(2-Chloroquinolin-3-yl)[(4-{2-[2-[(3-nitrophenyl)methylidene]hydrazin-1-yl]acetyl} phenyl)amino]methyl]-7-hydroxy-4-methyl-2H-chromen-2-one (**7n**): Yellow amorphous solid, yield 86% (5.469 g, crystallization) or 90% (5.724 g, filtration), m.p. 104–108°C; refractive index n_D^{22} : 1.703. Anal. Calcd. for $C_{34}H_{24}ClN_5O_6$: C, 64.41; H, 3.82; Cl, 5.59; N, 11.05%. Found: C, 64.54; H, 3.45; Cl, 5.63; N, 10.89%. IR (cm^{-1}) ν : 3508.2 (OH), 1714.9 (cyclic CO), 3421.9 (NH), 1289.6 (C-N stretching), 1742.3 (C=N-), 1097.9 (C-Cl), 1335.8 (NO_2). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 12.21 (s, 1H, coumarin-OH); 2.38 (d, 3H, methyl coumarin); 6.22–7.48 (m, 3H, coumarin-H); 6.28 (s, 1H, sec. amine -NH); 6.72–7.56 (m, 4H, Ar-H); 9.88 (s, 1H, hydrazide-NH); 9.16 (s, 1H, methylene); 7.78–8.52 (m, 4H, Ar-H); 5.78 (s, 1H, methine); 7.51–8.96 (m, 5H, quinoline-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 19.5, 45.4, 112.2, 112.5, 112.7, 113.3, 121.2, 121.6, 123.0, 123.6, 123.8, 126.2, 126.6, 127.6, 128.4, 129.7, 130.3, 131.8, 132.6, 134.6, 136.1, 138.7, 141.0, 146.3, 148.5, 150.6, 151.0, 152.7, 154.9, 160.9, 163.2. MS, m/z : 633 (M^+ , 100%).

2.3o 7-Hydroxy-4-methyl-8-[(4-oxo-4H-chromen-2-yl)[(4-{2-[2-[(2)-3-phenylprop-2-en-1-ylidene]hydrazin-1-yl]acetyl}phenyl)amino]methyl]-2H-chromen-2-one (**7o**): Light yellow amorphous solid, yield 87%

(5.199 g, crystallization) or 89% (5.318 g, filtration), m.p. 111–114°C; refractive index n_D^{22} : 1.661. Anal. Calcd. for $C_{36}H_{27}N_3O_6$: C, 72.35; H, 4.55; N, 7.03%. Found: C, 72.22; H, 4.49; N, 6.96%. IR (cm^{-1}) ν : 3462.3 (OH), 1715.0 (cyclic CO), 3437.1 (NH), 1349.8 (C-N stretching), 1689.7 (C=N-), 1672.8 (C=C). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 10.38 (s, 1H, coumarin-OH); 1.96 (s, 3H, methyl coumarin); 6.22–7.44 (m, 3H, coumarin-H); 4.96–3.98 (s, 1H sec. amine HN-); 6.74–7.56 (m, 4H, Ar-H); 11.08 (s, 1H, hydrazide-NH); 7.58 (s, 1H, methylene); 6.85 (m, 1H, ethylene); 7.22 (d, 1H, ethylene, $J = 8.2$); 7.30–7.62 (m, 5H, Ar-H); (s, 1H, methine); 6.30–8.10 (m, 5H, chromon-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 19.6, 53.5, 109.9, 111.9, 112.2, 112.4, 112.5, 116.3, 121.2, 122.5, 123.4, 123.8, 124.6, 125.9, 126.4, 127.9, 128.6, 128.6, 130.3, 134.1, 135.4, 137.3, 149.5, 149.9, 152.7, 153.6, 157.2, 160.8, 163.4, 167.3, 178.2. MS, m/z : 597 (M^+ , 100%).

2.3p 4-[[[7-Hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)diphenylmethyl]amino]-N'-[(1)-(4-methoxyphenyl)methylidene]benzohydrazide (**7p**): Bright yellow crystalline solid, yield 83% (5.06 g, crystallization) or 87% (5.3 g, filtration), m.p. 122–126°C; refractive index n_D^{22} : 1.634. Anal. Calcd. for $C_{38}H_{31}N_3O_5$: C, 74.86; H, 5.13; N, 6.89%. Found: C, 74.98; H, 5.30; N, 6.78%. IR (cm^{-1}) ν : 3478.9 (OH), 1714.6 (cyclic CO), 3451.2 (NH), 1347.6 (C-N stretching), 1738.9 (C=N-), 2836.5 (OCH_3). 1H NMR ($CDCl_3$, 400 MHz, ppm, J Hz) δ_H : 10.36 (s, 1H, coumarin-OH); 2.32 (s, 3H, methyl coumarin); 6.28–7.46 (m, 3H, coumarin-H); 6.02 (s, 1H sec. amine HN-); 6.72–7.54 (m, 4H, Ar-H); 12.81 (s, 1H, hydrazide-NH); 8.18 (s, 1H, methylene); 7.06–7.84 (m, 4H, Ar-H); 3.83 (s, 3H, $-OCH_3$); 7.21–7.43 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_C : 19.7, 59.6, 112.2, 112.4, 112.6, 113.2, 114.4, 121.2, 123.1, 123.8, 126.0, 126.2, 127.0, 129.3, 130.3, 145.0, 146.8, 151.1, 152.7, 154.9, 160.8, 162.9, 163.7. MS, m/z : 609 (M^+ , 100%).

3. Results and discussion

In view of emerging importance of green synthesis and our general interest in solid acid catalysed 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 -aminoheteronaphthol from aromatic carbonyl compound, amine and 8-hydroxy quinoline or coumarin.

Scheme 1. Zeolite catalysed tailored Betti's condensation.

Most of the earlier proposed procedures for the production of Mannich-base involve various organic and mineral acid catalysed reaction conditions. The synthesis of these compounds was reported by performing the reaction in the presence of Lewis acid,³¹ Bronsted acid catalysts,³² Lewis base,³³ transition metal salt³⁴ catalysts condition and even uncatalysed one-pot, three-component synthesis of Betti's base in water.³⁵ 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 uncatalysed Betti's reaction involves only basic 2-pyridinyl, 2-pyrazinyl and 2-pyrimidinyl amine as amine moiety which act as a catalyst.

Here, 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 product and their hydrazone (arylidenehydrazine) derivatives by, catalyst-free most placid reaction condition of click synthesis in least amount of solvent.

3.1 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 heteronaphthol [here, 8-hydroxy quinolone (3) or 7-hydroxy-4-methyl-coumarin (4)] in the presence of zeolite to prepare the β -aminoheteronaphthol (5/6) (scheme 1).

The natural zeolite applied here are scolecite ($\text{CaAl}_2\text{Si}_3\text{O}_{10} \cdot 3\text{H}_2\text{O}$), stilbite ($\text{NaCa}_4(\text{Si}_{27}\text{Al}_9)\text{O}_{72} \cdot 28(\text{H}_2\text{O})$), fluorapophyllite ($\text{KCa}_4\text{Si}_8\text{O}_{20}(\text{F},\text{OH}) \cdot 8(\text{H}_2\text{O})$) and mesolite ($\text{Na}_2\text{Ca}_2(\text{Al}_2\text{Si}_3\text{O}_{10})_3 \cdot 8\text{H}_2\text{O}$) and synthetic zeolite are crystalline molecular sieves which can be represented by general formula $-\text{M}_{2/n}\text{O}[(\text{Al}_2\text{O}_3) \cdot (\text{SiO}_2)_x] \cdot y \text{H}_2\text{O}$, where M represents alkali metals with valency- n . These aluminosilicates are 3A, 4A, 5A and 13X with pore size 3 Å, 4 Å, 5 Å and 10 Å, respectively. The alkali metal in aluminosilicate 3A and 4A is potassium, 5A is calcium and 13A is sodium. A detailed study on catalyst standardization is obtained from the chemical oxide-form composition of the zeolitic raw minerals as shown in table 1.

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 three consecutive reactions having more than 90% yield. The products of modified Betti's reaction are specified in table 2.

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

Table 1. Oxide-form chemical composition of the raw mineral, natural zeolites and molecular sieves in weight %.

Catalyst	SiO ₂	Al ₂ O ₃	CaO	Na ₂ O	K ₂ O	H ₂ O	F	Total
Fluorapophyllite	51.98	0.36	25.10	0.61	4.45	16.25	2.20	100.03
Scolecite	45.16	25.90	14.86	0.16	0.06	13.66	–	99.80
Stilbite	52.70	17.71	7.76	2.39	1.09	18.40	–	100.05
Mesolite	46.98	26.43	10.06	4.57	0.05	11.94	–	100.03
Molecular sieves								
3A	41.45	19.68	–	3.58	18.87	18.5	–	100.08
4A	47.50	23.75	–	4.75	–	24.0	–	100.00
5A	40.16	20.58	18.32	6.37	–	14.63	–	100.06
13X	48.59	16.97	–	8.74	–	25.73	–	100.03

Table 2. Tailored Betti's reaction between carbonyl compound, amine and heteronaphthol (here, quinoline/chromene)^a.

<p style="text-align: center;"> $\text{Ar}^4 =$ $\text{R} = \text{H, Cl, Aryl}$ $\text{Ar}^3 =$ </p>					
Entry	Ar ² NH ₂	Ar ¹ COR	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

Table 2. (Continued).

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

Table 2. (Continued).

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

^aAll reactions were performed in EtOH at 40°C in the presence of natural/synthetic zeolite as a catalyst. The solid obtained from the reactions was purified by washing with cold EtOH and by recrystallization in MeOH/EtOH

^bOf pure and isolated product

catalyst shows almost same yield with three successive reactions (table 3). 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°C 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 yields of products (<90%) after moderately short reaction time (typically between 1 and 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 2). 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°C provided almost quantitative yields of products at reduced reaction times (ranging from 1 to 2 h; table 2) 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°C) but did not have much influence on the yields of products as compared to those at 40°C (table 4). But when compared to other catalysts, zeolites afford a much reduced reaction period with promisingly greater yield and a complete green sustainable technique.

Table 3. Recovery and reusability of catalysts.^a

Entry	Cycle	Mannich-base, % yield	Catalyst recovery % weight
1	Fresh	99	100%
2	1st recycle	99	100%
3	2nd recycle	98	100%
4	3rd recycle	97	100%
5	4th recycle	95	100%

^aReaction condition: carbonyl compound: amine: quinoline/chromene, 1:1:1 (mol ratio), natural zeolite = stilbite (0.5 g crystalline), temperature = 40°C

3.1a Bis-aryl hydrazones: Synthesis of these hydrazides, hydrazones and their derivatives involves strong acid catalysed reaction condition of multiple steps of hours or overnights reflux in abundant solvent.³⁶ These harsh reaction conditions and hazardous

Table 4. The effect of reaction temperature on the activity of zeolite for the Betti's condensation of carbonyl compound, amine and quinoline/chromene (**5/6**).

Temperature °C	25	30	40	50	60	70
Yield (%)	90	93	94	97	99	99
Time (min)	180	150	95	75	60	50

Reaction conditions: 1 mmol quinoline/chromene, 1 mmol substrate amine and carbonyl compound, 0.5 g zeolite, with stirring

catalyst, solvent and byproducts were utterly removed here by carrying out the reaction in limited amount of solvent without catalyst using principle of click reaction which is wide scope, high yielding and stereospecific with high atom economy.^{22–25} The hydrazone moiety was selected for its high stability at physiological pH, and liability under strongly acidic and basic conditions as demonstrated by drug delivery agents in tumour targeting.^{37,38} To our knowledge, such catalyst- and solvent-free Betti's bis-arylhydrazone click product has not yet been explored.

In the present work, we mixed equimolar quantities of hydrazine hydrate 80%, β -aminoheteronaphthol (**5/6**) (solubilized in minimum ethanol) and aromatic aldehydes together in a petri dish at room temperature with the help of a glass rod. Surprisingly, the reaction started immediately after mixing and a shiny immense hydrazone product appeared within a few seconds with gentle heat production, scheme 2. The progress of the reaction and by-products was monitored by thin-layer chromatography and then the reaction mixture was allowed to stand for 1–2 min to obtain hydrazone product (**7**) in a complete quantitative yield.

Excited by the above result, a range of β -aminoheteronaphthol hydrazone derivatives were synthesized by the simple mixing of aromatic aldehyde and hydrazine hydrate (80%) with β -aminoheteronaphthol just solubilized in ethanol for homogenous reaction at room temperature; the results are summarized in table 5. All the products were obtained in quantitative yield (>85%) in analytically pure form, recrystallized by ethanol/methanol without any further purification.

A plausible mechanism is proposed for the acid catalysed condensation of carbonyl compound, amine and heteronaphthol to give β -amino-phenol using zeolite (scheme 3). The carbonyl compound (**1**) combines with the amine (**2**) in mild acidic medium provided by zeolite to give (**A**) which on dehydrolysis provides stable electrophile iminium ion (**B**). The heteronaphthol (**C**) functions as a very good carbon nucleophile, giving the intermediate represented by the resonance structures, which subsequently loses a proton to furnish β -amino-phenol. It is easy to identify from this mechanism that acid catalysis aid the reaction and indeed increased rates with greener approach have been observed using zeolite catalysis.

3.2 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 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 agents and nystatin and flucanazol as the standard antifungal agents. For the diffusion well method, the solvent used was dimethylsulphoxide (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 μ l solution in each well (5 mm diameter hole cut in agar gel).

3.2a 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*

Scheme 2. Bis-aryl hydrazone derivative via click reaction.

Table 5. Bis-aryl hydrazones of β -aminoheteronaphthol by click reaction.^a

<div><div><div><div><div>R</div><div>$\text{C}=\text{O}$</div><div>Ar</div></div><div>$(5/6)$</div></div><div>$+$</div><div>$\text{H}_2\text{N}-\text{NH}_2$</div><div>$+$</div><div><div><div>$\text{R}^1$</div><div>$\text{C}=\text{O}$</div><div>$\text{R}^2$</div></div></div><div>$\xrightarrow[\text{ii } \text{R}=\text{CH}_3]{\text{i } \text{R}=\text{OC}_2\text{H}_5}$</div><div><div><div>$\text{R}^1$</div><div>$\text{C}=\text{N}-\text{N}-\text{C}=\text{O}$</div><div>$\text{R}^2$</div><div>$\text{Ar}$</div></div><div>$+$</div><div>$\text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{O}$</div></div><div><div><div>R^1</div><div>$\text{C}=\text{N}-\text{N}=\text{C}$</div><div>$\text{R}^2$</div><div>$\text{Ar}$</div></div><div>$+$</div><div>$2 \text{H}_2\text{O}$</div></div></div></div>						
Entry	Compound	R^1COR^2	Reaction time (s)	Yield ^b (%)	Product	
1	5a		6	90		7a
2	5b		7	93		7b
3	5c		9	87		7c
4	5d		10	94		7d
5	5e		15	86		7e
6	5f		5	97		7f

Table 5. (Continued).

7	5f		8	91		7g
8	5f		9	94		7h
9	5g		12	89		7i
10	5h		10	88		7j
11	6a		6	91		7k
12	6b		5	92		7l
13	6c		7	90		7m

Table 5. (Continued).

14	6d		8	86		7n
15	6e		7	87		7o
16	6f		8	83		7p

^aReaction condition^c Mixing of reactants with a spatula in a petri dish for 10–15 s followed by allowing the mixture to stand for up to 15–30 s if necessary

^bOf pure and isolated product

pneumonia. The pathogenic fungi referred for antifungal activity were *Aspergillus niger*, *Phytophthora* sp., *Aspergillus flavus*, *Candida albicans*, *Rhizopus oryzae* and *Fusarium oxysporium*. All the microbes were sub-culture in sterilized nutrient broth.

3.2b Agar well diffusion method: For the antibacterial efficacy, Muller Hinton agar medium (33.9 g) was taken in distilled water (1 L) which was autoclaved at 15 lbs pressure at 121°C for 15 min and poured onto 100 mm petriplates (25–30 ml/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 μ l) was uniformly spread using sterile cotton swab on a sterile Petri dish agar. The 20 μ l 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 $\pm$ 1°C for bacterial colony and at 25°C $\pm$ 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 flucanazol. Tests were performed in duplicates and results were presented in tables 6 and 7.

The compounds **5d**, **5f**, **5j**, **7a**, **7d** and **7h** provide better antibacterial properties against most of the pathogenic bacteria compared to standard antibacterial, Gentamicin and it has also been found that these Betti's reaction product and bisarylhydrazone are active against Methicillin-resistant *Staphylococcus aureus* bacterium and certain quinolone resistant pathogens like *S. pyogenes*, *E. coli*, *P. aeruginosa*. The compounds **5a**, **5d**, **5f**, **5j**, **6d** and **6g** demonstrated very good antifungal results against all the pathogenic fungi under consideration. The pathogenic *Phytophthora* sp, which was not successfully medicated, was also found to be overawed by these compounds. These potent products also have the MIC at very low concentration.

3.2c Minimum inhibitory concentration (MIC) determination: Certain compounds of the subject have been found to have MIC values (μ g/ml) that are up to about 500 times lower than amoxicillin and ciprofloxacin

Scheme 3. Zeolite catalysed mechanism for β -aminoheteronaphthol formation.

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 flucanazole. The MIC of the compounds is given in tables 8 and 9.

The percentage of mycelial growth inhibition (P) for pathogenic bacteria and fungi was calculated by the formula $P = (C - T) / C \times 100$, where C is the diameter of the control colony and T that of the treated ones (standard drug).³⁸ The growth inhibitions of compounds compared with standard drugs against pathogenic bacteria are shown in figure 1 and against pathogenic fungi are shown in figure 2.

3.2d Structure activity relationship (SAR): In quinoline-based Betti's product (**5a–5j**), the furan (**5d**), 2-chloroquinolin (**5f**) and purine (**5j**) substitution increases antimicrobial activity tremendously as

compared to other substituted benzene and pyrazol ring. Aliphatic amine (**5i**) substitution decreases the antimicrobial activity of Betti's product. 4-oxo-4H-chromene and 2-chloroquinoline ring in coumarin based Betti's product (**6a–6g**) also reduces the antibacterial activity of the Betti's product. Presence of both morpholine and furan ring raise the antibacterial activity in coumarin based Betti's compound (**6g**). The derivatization (**7a–7p**) of Betti's base overall decreases the antibacterial activity.

Antifungal activity of Betti's product and their hydrazone derivatives are comparable with nystatin but the quinoline based Betti's products having 2-chloroquinoline (**5d**) and furan (**5f**) ring substitution has the activity over and much above the nystatin. In coumarin-based Betti's product, 4-oxo-4H-chromene with benzoicaine (**6e**) and furan with morpholine (**6g**) has effective antifungal activity. Syringaldehyde coumarin-based Betti's product has better antifungal activity compared to hydrazone derivative of the Betti's products with

Table 6. Antibacterial efficacy of the compounds (0.25 mg/ml) against pathogenic bacteria.

Compounds	Zone of inhibition						
	Gram-positive bacteria			Gram-negative bacteria			
	<i>Staphylococcus aureus</i>	<i>Streptococcus mutants</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Salmonella typhi</i>	<i>Klebsiella pneumonia</i>
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
7a	31	39	24	35	22	28	27
7b	29	36	23	32	16	14	30
7c	28	26	26	30	25	31	27
7d	–	22	24	26	14	22	25
7e	21	16	18	15	11	17	16
7f	27	38	31	34	17	18	33
7g	26	30	32	31	24	33	29
7h	15	45	20	29	15	27	26
7i	18	28	23	17	14	18	20
7j	23	30	29	28	16	26	25
7k	24	27	22	21	14	23	23
7l	31	32	25	26	14	25	34
7m	30	33	26	28	18	27	29
7n	26	26	21	19	12	19	21
7o	29	30	24	26	15	22	24
7p	14	11	14	16	12	20	19
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 mm

respect to nystatin but its own salicylaldehyde hydrazone derivative (**7k**) has least antifungal activity. The effective antimicrobial activity of the synthesized compounds is mainly due to the presence of vicinal amino hydroxy group in the structure of the compounds.

4. 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 -aminoheteronaphthols. Furthermore, we have developed a general, highly efficient, catalyst-free, least solvent consuming, high yield, step-economic, and eco-friendly method for the synthesis of *bis*-aryl hydrazones derivatives via the one-pot, three component coupling click reaction of β -aminoheteronaphthols, hydrazine hydrate and aldehydes/ketones acetate under lenient conditions. 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

Table 7. Antifungal efficacy of the compounds (0.25 mg/ml) against pathogenic fungi.^a

Compounds	Zone of inhibition					
	<i>Aspergillus niger</i>	<i>Phytophthora</i> sp	<i>Aspergillus flavus</i>	<i>Candida albicans</i>	<i>Rhizopus oryzae</i>	<i>Fusarium oxysporium</i>
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
7a	16	21	23	19	14	18
7b	16	30	24	30	21	24
7c	25	20	19	35	19	–
7d	33	28	25	23	26	26
7e	28	18	19	21	21	22
7f	18	29	23	28	22	25
7g	32	26	21	20	23	24
7h	36	30	20	22	27	07
7i	34	28	16	22	27	24
7j	22	16	14	18	21	20
7k	24	23	08	14	10	11
7l	20	20	19	25	24	18
7m	16	24	21	26	18	21
7n	20	22	23	20	17	19
7o	18	15	16	17	14	12
7p	15	27	13	15	16	17
Nystatin	22	13	24	25	26	18
Flucanazol	–	–	–	20	–	–

^a = the diameters of zone of inhibition were in mm**Table 8.** MIC for antibacterial efficacy.^a

Compounds	Gram-positive bacteria			Gram-negative bacteria			
	<i>Staphylococcus aureus</i>	<i>Streptococcus mutants</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Salmonella typhi</i>	<i>Klebsiella pneumonia</i>
5d	1	1	1	1	5	1	1
5f	1	1	1	1	5	1	1
5j	5	5	5	1	100	100	1
7a	100	50	100	50	250	250	100
7d	500	25	5	5	250	5	5
7h	250	25	5	5	100	5	5
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 9. MIC for antifungal efficacy.^a

Compounds	<i>Aspergillus niger</i>	<i>Phytophthora</i> sp	<i>Aspergillus flavus</i>	<i>Candida albicans</i>	<i>Rhizopus oryzae</i>	<i>Fusarium oxysporium</i>
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
Nystatin	1	1	1	1	1	1
Flucanazol	100	100	100	10	100	100

^a = all the values are in $\mu\text{g/ml}$ **Figure 1.** Growth inhibition of compounds with respect to gentamicin against pathogenic bacteria. **Figure 2.** Growth inhibition of compounds with respect to nystatin against pathogenic fungi.

amoxicillin and flucanazol. 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 compounds.

Supporting information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

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