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SYNTHESIS AND CHARACTERIZATION OF MICROWAVE INDUCED PYRANO[3,2-*c*]CHROMENE, PYRANO[4,3-*b*]PYRAN AND 4*H*-CHROMENE DERIVATIVES OF SUBSTITUTED 2-(4-SUBSTITUTED) PHENYL-*N*-ALLYL-INDOLE, AND THEIR BIOLOGICAL SCREENING

Pratibha Prasad, Pratik. G. Shobhashana, and Manish P. Patel*

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388120, Gujarat, India

E-mail: patelmanish1069@yahoo.com

Abstract:
A new category of indole based pyrano[3, 2-*c*]chromene **8a-d**, pyrano[4,3-*b*]pyran **9a-d** and 4*H* – chromene **10-12a-d** derivatives has been designed and synthesized via microwave-induced one-pot three-component cyclocondensation reaction of 2-(4-substituted) phenyl-*N*-allyl-indole-3-carbaldehyde **1a-d** with active methylene malononitrile **2** and different enolizable michael donars **3-7** in the presence of catalytic amount of triethylamine in ethanol. All the newly synthesized compounds have been characterized by elemental analysis and various spectroscopic methods. All the compounds have been screened against a representative panel of pathogenic strains of bacteria and fungi, preliminary *in vitro* antituberculosis activity against *M. tuberculosis* H37Rv and also for their antimalarial activity against *P. falciparum*.

Key words: *N*-allyl indole,antimicrobial activity, antitubercular activity, pyranopyran

Introduction

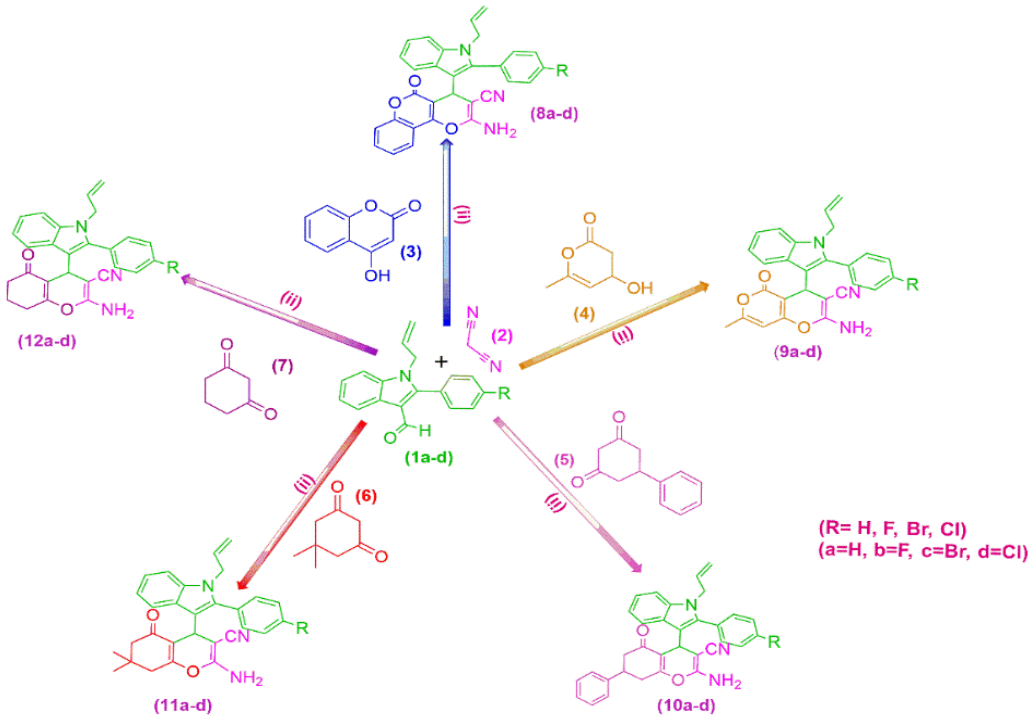
An extensive variety of indole alkaloids have been isolated from marine organisms[I]. Since from several decades synthesis and functionalization of indoles have been the major objectives of research, as it is well known that indole derivatives are an important class of heterocyclic compounds with a wide range of biological activities. Precisely, *N*-1, *C*-2 and *C*-3-substituted indole derivatives have been found to be an significant fragment in many biologically active compounds especially with antimigrane, antidepressant, anti-HIV, analgesic, anti inflammatory, anticancer, antinociceptive and antipsychotic activity etc. [II]. Also, the presence of allyl group at the heterocyclic *N*-atom is found to have influential antimicrobial activity and plays a vital role in the development of new antimicrobial drugs [III]**.** On the other hand, 4*H*-fused pyrans and chromenes are compounds of considerable interest revealing potentially beneficial wide range of chemical properties and biological activities [IV-X], such as antimicrobial and antituberculosis, anticancer and antipsychotics etc.

Thus in addition to the pharmacologically active fused pyrano and chromeno derivatives, other heterocycles in connotation with above mentioned moiety play an vital role in copious biological processes and hold significant chemical and pharmacological importance. Inspired from the aforementioned reports and as a extension of our examination on the synthesis and development of biologically active heterocyclic compounds [XI-XIII]. We were provoked and attempted to involve *N*-allyl-4-phenyl-substituted indole motif with chromene scaffolds and synthesise it into one hybrid heterocyclic molecule which may play a vital role as an important creation part in title compounds. However some inadequacies were observed in executing conventional methods such as, longer reaction time, use of drastic reaction conditions, hazardous organic base and poor yield [XIV]. Hence in comparison to classical approach we adopted an alternative microwave-assisted organic synthetic approach and ecofriendly base NEt_3 which has been demonstrated not only to dramatically accelerate many organic reactions in short time, but also to improve yield and high reaction selectivity [XV].

Results and Discussion

Chemistry

The synthetic approach adopted to obtain the targeted compounds, pyrano[3,2-*c*]chromene **8a–d**, pyrano[4,3-*b*]pyran **9a–d** and 4*H*-chromene **10a–d**, **11a–d** and **12a–d**, derivatives were synthesized by the plausible reaction mechanism depicted in (**Scheme 1)**.



The final aldehyde substituted 2-phenyl-*N*-allyl-indole-3-carbaldehyde **1a–d** was prepared by nucleophilic displacement of bromo group of allyl bromide with 2-phenyl-(4-substituted)-indole-3-carbaldehyde, in refluxing DMF using anhydrous potassium carbonate as base. Thus, the targeted chromeno and pyrano derivatives were synthesized by one-pot three-component cyclocondensation reaction of substituted 2-phenyl-*N*-allyl-indole-3-carbaldehyde **1a–d**, malononitrile **2** and various enolisable ketones **3-7** was performed in a microwave oven

at 340W in the presence of triethylamine as a catalyst to give moderate to good yield (68–84%) substantially through the plausible synthetic route as illustrated in **Fig.1**.

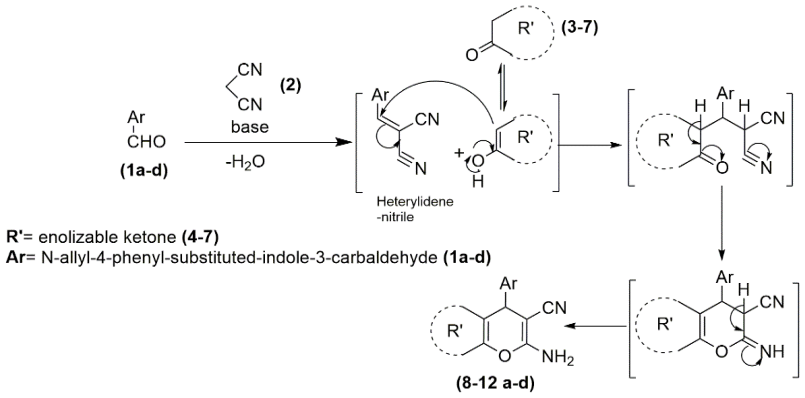


Fig. 1 Plausible mechanistic pathway for the synthesis of chromene, pyrano pyran and pyran derivatives

The reaction may proceed via an in situ initial formation of the hetarylidene nitrile, containing the electron-poor C=C double bond, from the knoevenagel condensation between respective indole-3-carbaldehydes **1a-d** and malononitrile **2** by loss of water molecules. Finally, michael addition of **3-7** to the initially formed unsaturated nitrile, i.e. nucleophilic attack of hydroxyl moiety to the cyano olefins afforded cyclized pyrano and chromeno products.

The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analysis. The molecular weight of compounds was confirmed by mass spectrometry. Physical, analytical and spectroscopic characterization data of all compounds are given in Supplementary material. ^{1}H NMR ($CDCl_3$) spectrum of **11c** exhibited a multiplet peak for enolisable dimedone around 0.08-1.01 ppm stands for two –C$\underline{H}_3$ while four –C$\underline{H}_2$ protons resonates at 2.16-2.47 ppm. Amine, aldehydic and vicinal allylic protons of **11c** resonate as multiplets at around 4.46-4.52 ppm. Whereas trans and cis geminal protons of allylic group resonates as a doublet at around 4.65 and 5.10 ppm respectively, while another single geminal proton also projects multiplet at 5.81-5.88 ppm. Remaining aromatic protons of **11c** resonate as multiplet at 7.07-7.88 ppm. ^{13}C NMR ($CDCl_3$) spectrum shows characteristic peak at 27.08 ppm for cyclized carbon, 28.07 ppm and 28.63 ppm for two methyl dimedone carbons, 63.45 ppm for C–CN, 161.17 ppm for C–NH and 196.37 ppm for C=O, all these peaks thus supports the structure of **11c**. The IR spectrum of compound **11c** exhibited characteristic absorption bands around 3416-3376 cm^{-1}and 2187 cm^{-1} for (asym. and sym. stretching) –NH and C=N stretching respectively. The characteristic absorption band of C=O stretching and C–O–C ether stretching are observed around 1671 cm^{-1} and 1263 cm^{-1}.

Biological results

Antibacterial activity- Upon reviewing the antimicrobial screening data (**Table 1**), it has been observed that majority of the compounds showed outstanding activity against gram positive bacteria *S. pneumonia*, *B. subtilis* and *C. tetani* as compared to ampicillin, ciprofloxacin and norfloxacin standard drugs. Against gram positive bacteria *C. tetani* compound **8a** (R' = 4-hydroxy-coumarin, R = H), **8d** (R' = 4-hydroxy-coumarin, R = Br) (MIC 62.5 µg/mL) was found to have outstanding activity; compounds **9a** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = H), **10c** (R' = 5-phenylcyclohexane-1,3-dione, R = Cl), **11d** (R' = dimedone, R = Br), **12a** (R' = 1,3cyclohexanedione, R = H) (MIC 100 µg/mL) showed significant activity as compared to ampicillin (MIC 250 µg/mL) and showed equivalent

results to ciprofloxacin (MIC 100 µg/mL). Further against *B. subtilis* compound **9c** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Cl), **12c** (R' = 1,3cyclohexanedione, R = Cl) (MIC 62.5 µg/mL) and against *S. pneumoniae* compounds **8c** (R' = 4-hydroxy-coumarin, R = Cl), **10a** (R' = 5-phenylcyclohexane-1,3-dione, R = H) (MIC 62.5 µg/mL) was found to have outstanding activity in comparison to the standard drug ampicillin; while compounds **8b** (R' = 4-hydroxy-coumarin, R = F), **8d** (R' = 4-hydroxy-coumarin, R = Br) **9d** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Br), **10a** (R' = 5-phenylcyclohexane-1,3-dione, R = H), **10c** (R' = 5-phenylcyclohexane-1,3-dione, R = Cl), **12b** (R' = 1,3cyclohexanedione, R = F), **12d**(R' = 1,3cyclohexanedione, R = Br) (MIC 100 µg/mL) showed significant activity as compared to ampicillin (MIC 250 µg/mL) and were equipotent to norfloxacin (MIC 100 µg/mL).

Table 1 *In vitro* antimicrobial activities (MIC, µg/mL) of the synthesized compounds.

Entry	Gram-negative bacteria			Gram-positive bacteria			Fungi	
	E. C. MTCC 443	S.T. MTCC 98	V.C. MTCC 3906	S. P. MTCC 1936	B. S. MTCC 441	C. T. MTCC 449	C. A. MTCC 227	T. R. MTCC 297
8a	**100**	200	200	200	**200**	**62.5**	>1000	>1000
8b	250	**12.5**	250	**100**	**100**	**200**	>1000	1000
8c	**100**	**62.5**	**100**	**62.5**	**100**	**200**	**500**	1000
8d	250	**100**	125	**100**	**100**	**62.5**	**100**	**500**
9a	200	200	200	200	**125**	**100**	**250**	1000
9b	**62.5**	250	**62.5**	200	**250**	**250**	**250**	**500**
9c	**100**	**100**	250	200	**62.5**	**200**	>1000	>1000
9d	200	125	**100**	**100**	**100**	**200**	1000	>1000
10a	250	250	250	**62.5**	**100**	**200**	>1000	1000
10b	**100**	**100**	125	**100**	**250**	**250**	**500**	**500**
10c	200	250	**100**	200	**100**	**100**	1000	>1000
10d	**100**	**100**	250	200	**250**	**250**	**100**	>1000
11a	**100**	**100**	200	200	**200**	**250**	1000	1000
11b	**100**	**62.5**	**100**	**100**	**200**	**200**	**500**	>1000
11c	200	250	500	125	**200**	**125**	**500**	1000
11d	250	**100**	200	200	**125**	**100**	**250**	**500**
12a	**62.5**	**100**	500	500	**125**	**100**	1000	>1000
12b	**100**	250	**100**	200	**100**	**200**	**500**	1000
12c	**62.5**	**100**	125	**100**	**62.5**	**125**	**>**1000	1000
12d	**100**	250	**100**	200	**100**	**200**	**500**	1000
Ampicillin	**100**	**100**	**100**	**100**	**250**	**250**	-	-
Ciprofloxacin	**25**	**25**	**25**	**50**	**50**	**100**	-	-
Norfloxacin	**10**	**10**	**10**	**10**	**100**	**50**	-	-
Nystatin	-	-	-	-	-	-	**100**	**500**
Greseofulvin	-	-	-	-	-	-	**500**	**500**

Bold values indicate the active compounds; E.C., Escherichia coli; S.T., Salmonella typhi; V.C., Vibrio cholerae; S.P., Streptococcus pneumoniae; B.S., Bacillus subtilis; C.T., Clostridium tetani; C.A., Candida albicans; T.R., Trichophyton rubrum. MTCC: Microbial Type Culture Collection; '-' indicates that not tested

Whereas in inhibiting gram negative bacteria in comparison to the standard drug ampicillin and ciprofloxacin compound **8b** (R' = 4-hydroxy-coumarin, R = F) (MIC 12.5 µg/mL) showed outstanding against *S. typhi.* Compounds**9b** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = F), **12a** (R' = 1,3cyclohexanedione, R = H), **12c** (R' = 1,3cyclohexanedione, R = Cl)(MIC 62.5 µg/mL) against *E. coli*; compounds **8c**(R' = 4-hydroxy-coumarin, R = Cl), **11b**

(R' = dimedone, R = F) (MIC 62.5 µg/mL) against *S. typhi* and compound **9b** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = F) (MIC 62.5 µg/mL) against *V. cholerae* showed excellent activity as compared to ampicillin. Whereas compounds **8a** (R' = 4-hydroxy-coumarin, R = H), **8c** (R' = 4-hydroxy-coumarin, R = Cl) **9c** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Cl), **10b** (R' = 5-phenylcyclohexane-1,3-dione, R = F), **10d** (R' = 5-phenylcyclohexane-1,3-dione, R = Br), **11a** (R' = dimedone, R = H), **12b** (R' = 1,3cyclohexanedione, R = F), **12d** (R' = 1,3cyclohexanedione, R = Br) (MIC 100 µg/mL) against *E. coli* compound **8d** (R' = 4-hydroxy-coumarin, R = Br), **9c** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Cl), **10b** (R' = 5-phenylcyclohexane-1,3-dione, R = F), **10d** (R' = 5-phenylcyclohexane-1,3-dione, R = Br), **11a** (R' = dimedone, R = H), **11d** (R' = dimedone, R = Br), **12a** (R' = 1,3cyclohexanedione, R = H), **12c** (R' = 1,3cyclohexanedione, R = H) (MIC 100 µg/mL) against *S. typhi* and compounds **8c** (R' = 4-hydroxy-coumarin, R = Cl), **9d** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Br), **10c** (R' = 5-phenylcyclohexane-1,3-dione, R = Cl), **11b** (R' = dimedone, R = F), **12b** (R' = 1,3cyclohexanedione, R = F), **12d** (R' = 1,3cyclohexanedione, R = Br) (MIC 100 µg/mL) against *V. cholerae* were equipotent as compared to standard drug ampicillin. **Antituberculosis activity**- Some excellent results from the antimicrobial studies encouraged us to go for the preliminary screening of the title compounds for their *in vitro* antituberculosis activity against *M. tuberculosis* H37Rv bacteria. Antituberculosis activity screening of the synthesized compounds was conducted at 250 $mgmL^{-1}$ concentrations. Compounds **8b** (R' = 4-hydroxy-coumarin, R = F), **9a** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = H) and **10c** (R' = 5-phenylcyclohexane-1, 3-dione, R = Cl) found to possess excellent highest potency with 94, 92 and 90 % inhibition respectively. While two compounds **8c** (R' = 4-hydroxy-coumarin, R = Cl) and **11c** (R' = dimedone, R = Cl) are moderately active against *M. tuberculosis* H37Rv. All other compounds showed poor inhibition of *M. tuberculosis* growth. From the above results, it can be concluded that compounds **8b** and **9a** may become a new class of antitubercular agents in future.

Table 2 *In vitro* antituberculosis activity (% inhibition) of compounds against M. tuberculosis H37Rv (at concentration 250 µg/mL).

Entry	% Inhibition	Entry	% Inhibition
8a	62	10d	82
8b	**94**	11a	76
8c	**89**	11b	64
8d	56	**11c**	**86**
9a	**91**	11d	62
9b	83	12a	74
9c	81	12b	73
9d	62	12c	53
10a	53	12d	65
10b	75	**Rifampicin**	98
10c	**90**	**Isoniazid**	99

Antimalarial activity- All synthesized compounds were screened for their *in vitro* antimalarial activity against *P. falciparum* strain. All experiments were performed in duplicate and the IC_{50} mean value is shown in (**Table 3)**. The compounds **8b** (R' = 4-hydroxy-coumarin, R = F), **8c** (R' = 4-hydroxy-coumarin, R = Cl), **9b** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = F), **9d** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Br), **10b** (R' = 5-phenylcyclohexane-1,3-dione, R = F), **10c** (R' = 5-phenylcyclohexane-1, 3-dione, R =

Cl), **11a** (R' = dimedone, R = H), **11b** (R' = dimedone, R = F), **12c** (R' = 1,3 cyclohexanedione, R = Cl) showed principal activity *against P. falciparum* strain in comparison to quinine IC_{50} 0.268 as there IC_{50} were in the range of 0.032 - 0.096. Whereas compound **9d** (R' = 4-hydroxy-6-methyl-2*H*-pyran-2-one, R = Br) was found to possess moderate activity i.e. IC_{50} 0.032 aligned with chloroquine. Rest of the remaining other compounds showed less antimalarial activity against *P. falciparum* strain in comparison to chloroquine and quinine drugs.

Table 3 *In vitro* antimalarial activity of compounds

Entry	IC_{50}(µg/mL)	Entry	IC_{50}(µg/mL)
8a	1.063	10d	1.49
8b	**0.071**	**11a**	**0.037**
8c	**0.052**	**11b**	**0.051**
8d	1.48	11c	0.89
9a	1.84	11d	0.64
9b	**0.096**	12a	1.45
9c	1.054	12b	0.68
9d	**0.032**	12c	0.71
10a	1.81	**12d**	**0.081**
10b	**0.053**	**Chloroquine**	0.020
10c	**0.046**	**Quinine**	0.268

The bold characters indicate the higher or equal activity compared to standard drugs.

Structure–activity relationship (SAR) - The structural activity relationship (SAR) analysis (**Fig. 2**) demonstrated that a change in the peripheral substituent and various different nature of the heterocyclic motifs fused at positions 5 and 6 in pyran were liable for a broad range of antimicrobial, antituberculosis and antimalarial activities. The investigation revealed that the compounds with 4-fluoro and chloro phenyl ring at the 2-position of the indole nucleus. Also, the lipophilicity of allylic substitution at indole nitrogen, plays an important role to stimulate the potency of the compounds. Compounds **8a-d** bearing 4-hydroxy-coumarin showed maximum antibmicrobial activity against *S. typhi*, *C. tetani*, *C. albicans* as well as increased antimalarial and antitubercular activitry against *P. falciparum* strain and *M. tuberculosis* H37Rv respectively, where compound **8b** was inclusively active of all with fluoro phenyl ring substitution. Compounds **9b** containing 4-hydroxy-6-methyl-2*H*-pyran-2-one motif showed highest inhibition against bacterial strain *E. coli*, *V. cholerae* and also showed highest inhibition against both fungal pathogens *C. albicans* and *T. rubrum*,also antimalarial activity against malarial pathogen.

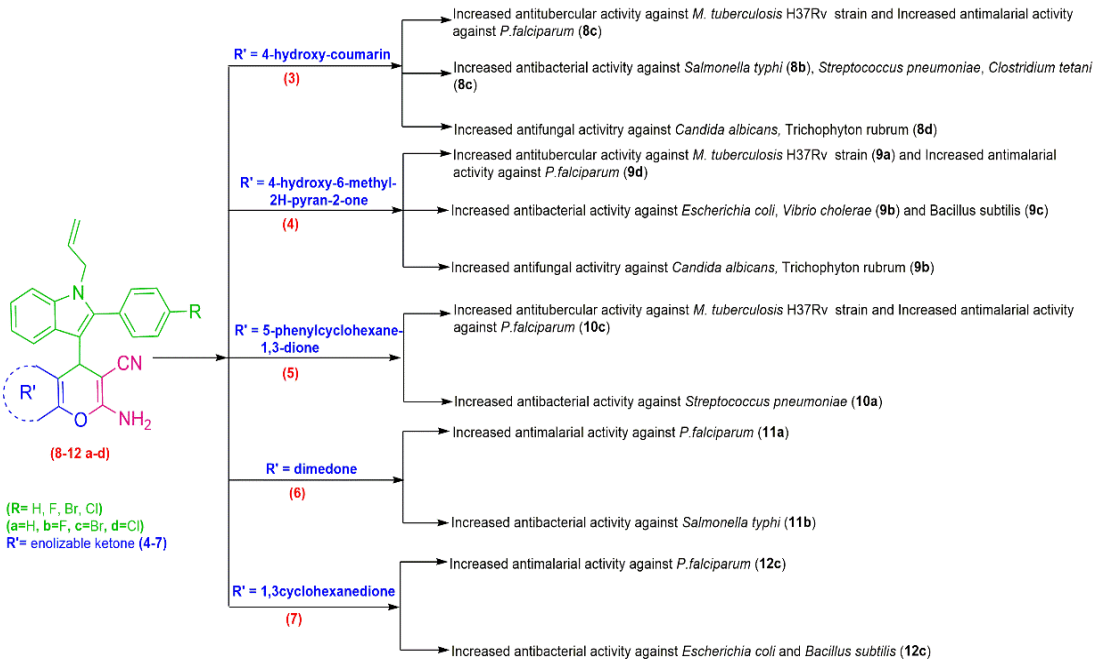


Fig. 2 Structure–activity relationship for antimicrobial, antituberculosis and antimalarial activity of the synthesized compounds

Whereas compound **9c** against *B. subtilis* and *M. tuberculosis* H37Rv showed increased antibacterial and antitubercular activity respectively. Compound **10c** containing 5-phenylcyclohexane-1, 3-dione showed good antifungal activity as well maximum activity against tubercular and malarial pathogen. Whereas compound bearing dimedone illustrated maximum activity against *P. falciparum* strain.Compounds **12c** with fused 1, 3 cyclohexanedione moiety were found to be active against bacterial pathogens *E. coli, B. subtilis* and an*timalarial pathogen.* Antimalarial and antitubercular evaluation showed that 4-fluoro and chloro phenyl ring containing compounds are the most potent of all synthesized compounds. Thus, probing and evaluating the activity data, it is noteworthy to mention that the overall activity of the target compounds depends not only on the nature of the peripheral substituents appended through phenyl ring , positional changes, their spatial relationship, but also upon pharmacologically active heteroaromatic intermediates which are fused to form various derivatives also as well.

Experimental

Chemistry

Required acetophenone, phenyl hydrazine, polyphosphoric acid, triethylamine and phosphorous oxychloride were obtained commercially. Moreover, malononitrile and enolizable ketones were obtained from Sigma-Aldrich and were used without further purification. Solvents were purified and dried before being used. The required substituted 2-phenyl-*N*-allyl-indole-3-carbaldehyde **1a–d** was prepared by Vilsmeier-Haack reaction according to literature procedure [XVI].All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel, $60F_{254}$, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds; eluent-hexane:ethyl acetate: (5:5). UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin Elmer, USA) and all compounds are within ±0.4% of theory specified. The

IR spectra were recorded in KBr on a PerkinElmer Spectrum GX FT-IR Spectrophotometer (PerkinElmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in $CHCl_3$ on a Bruker Advance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

General procedure for the synthesis of targeted compounds

Substituted 2-phenyl-*N*-allyl-indole-3-carbaldehyde **1a–d** (1 mmol), malononitrile **2** (1 mmol), 4-hydroxy-coumarin **3**/4-hydroxy-6-methyl-2*H*-pyran-2-one **4**/ 5-phenylcyclohexane-1,3-dione **5**/ dimedone **6**/1,3cyclohexanedione**7** (1 mmol) were mixed thoroughly in ethanol with catalytic NEt_3 (20 mol%) and were charged in 100 mL round bottom flask equipped with condenser. The reaction mixture was subjected to microwave irradiation at 340 W (50% of output power) for 4–6 min. The reaction mixture attained 75ºC temperature at this power level. The progress of reaction was monitored by TLC (hexane:ethyl acetate = 4:6). After the completion of reaction, the reaction mixture was cooled to room temperature. The separated solid was filtered, washed with ethanol, dried and recrystallized from chloroform:methanol (9:1) to obtain crude product. The physicochemical and spectroscopic characterization data of the prepared compounds are given below.

4-(1-allyl-2-phenyl-1*H*-indol-3-yl)-2-amino-3-methyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (8a)

White solid; m. p. 280°C; IR (KBr, ν,cm^{-1}): 3420 and 3371 (asym and sym. Stretching of -NH_2), 2185 (-C≡N stretching), 1671 (C=O Stretching) 1209 (C-O-C ether stretching)^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.55-4.66 (m, 4H, N-C$\underline{H}_2$CH=C$\underline{H}_2$trans, C$\underline{H}$O), 5.10 (d,1H, N-CH_2CH=C$\underline{H}_2$cis), 5.74 -5.81 (m,1H, NCH_2C$\underline{H}$), 6.98-7.87 (m,15H, Ar-$\underline{H}$+N$\underline{H}_2$); ^{13}CNMR (100 MHZ, DMSO-d_6) δ ppm: 28.78,45.89, 63.37, 104.13, 109.60, 111.17, 112.60, 112.86, 116.91, 118.15, 118.27,119.39, 121.92, 122.33, 123.89, 124.48, 125.90, 129.06, 131.56, 132.39, 133.04, 136.12, 138.92,152.63, 153.64, 156.18, 159.91, 161.61(C=O); MS (m/z) Cald.:471.18, found:471.45, Anal. Calc. for: **$C_{30}H_{21}N_2O_3$:** C, 76.42; H, 4.49; N, 8.91 Found: C, 76.24; H, 4.53; N, 9.01 %

4-(1-allyl-2-(4-fluorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (8b)

White solid; m. p. 275°C; IR (KBr, ν,cm^{-1}): 3451 and 3369 (asym and sym. stretching of -NH_2), 2196 (-C=N stretching), 1668 (C=O Stretching), 1221(C-O-C ether stretching); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.52-4.84 (m, 6H, N-C$\underline{H}_2$CH=C$\underline{H}_2$trans, C$\underline{H}$O, N$\underline{H}_2$), 5.11 (d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.81 -5.85 (m, 1H, NCH_2C$\underline{H}$), 7.03-7.84 (m, 12H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) δ ppm: 28.35, 46.15, 63.37, 104.13, 110.60, 112.60, 112.86, 116.91, 118.15, 118.28, 119.93,121.88, 122.21, 123.41, 124.43, 125.91, 129.97, 131.46, 132.51, 133.23, 136.72, 138.34, 152.56, 153.02, 156.49, 159.87, 162.83, 161.91(C=O); MS (m/z) Cald.: 489.51, found: 489.85, Anal. Calc. for: **$C_{30}H_{20}FN_3O_3$:** C, 73.61; H, 4.12; N, 8.58 Found: C, 73.76; H, 5.07 N, 7.94 %

4-(1-allyl-2-(4-bromophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (8c)

White solid; m. p. 278°C; IR (KBr, ν,cm^{-1}): 3445 and 3365 (asym and sym. Stretching of -NH_2), 2187 (-C≡N stretching), 1667 (C=O Stretching), 1225 (C-O-C ether stretching); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.50-4.83 (m, 6H, N-C$\underline{H}_2$CH=C$\underline{H}_2$trans, C$\underline{H}$O, N$\underline{H}_2$), 5.10

(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.79-5.83 (m, 1H, NCH_2C$\underline{H}$), 7.03-7.82 (m, 12H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) *ð* ppm: 28.32, 46.13, 63.34, 104.15, 110.58, 112.57, 112.83, 116.87, 118.13, 118.23, 119.89,121.79, 122.18, 123.35, 124.46, 125.87, 129.94, 131.48, 132.53, 133.27, 135.65, 136.78, 138.31, 152.58, 153.08,156.52, 159.83, 161.85(C=O); MS (m/z) Cald.: 550.41, found: 550.63, Anal. Calc. for: **$C_{30}H_{20}BrN_3O_3$:** C, 65.47; H, 3.66; N, 7.63 Found: C, 65.53; H, 3.72; N, 7.75 %

4-(1-allyl-2-(4-chlorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (8d)

White solid; m. p. 301^{o}C; IR (KBr, ν,cm^{-1}): 3457 and 3373 (asym and sym. stretching of -NH_2), 2185 (-C=N stretching), 1672 (C=O Stretching), 1230 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 4.52-4.85 (m, 6H, N-C$\underline{H}_2$CH=C$\underline{H}_2$trans, C$\underline{H}$O, N$\underline{H}_2$), 5.21 (d, 1H, N-CH_2CH =C$\underline{H}_2$ cis), 5.78-5.84 (m, 1H, NCH_2C$\underline{H}$), 7.05-7.84 (m, 12H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) *ð* ppm:28.30, 46.15, 63.32, 104.18, 110.65, 112.56, 112.97, 116.72, 118.15, 118.21, 119.83,121.83, 122.20, 123.31, 124.51, 125.85, 129.91, 131.51, 132.52, 133.28, 135.65, 136.72, 138.28, 152.53, 153.13,156.57, 159.81, 161.84(C=O); MS (m/z) Cald.: 505.96, found: 505.84, Anal. Calc. for: **$C_{30}H_{20}ClN_3O_3$:** C, 71.22; H, 3.98; N, 8.31 Found: C, 71.36; H, 4.08; N, 8.28 %

4-(1-allyl-2-phenyl-1*H*-indol-3-yl)-2-amino-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (9a)

White solid; m. p. 251^{o}C; IR (KBr, ν,cm^{-1}): 3408 and 3375 (asym and sym. Stretching of -NH_2), 2209 (-C≡N stretching), 1673 (C=O Stretching), 1261(C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 2.23 (s, 3H, CH_3), 4.55-4.70 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.81(d,1H, N-CH_2CH=C$\underline{H}_2$trans), 5.11(d,1H, N-CH_2CH=C$\underline{H}_2$cis), 5.79 -5.85 (m,1H, NCH_2C$\underline{H}$), 6.91-8.04 (m,11H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) *ð* ppm: 20.15, 27.83, 45.89, 63.16, 101.07, 108.29, 109.12, 111.17,112.36, 115.34, 116.22, 118.08, 119.24, 121.27,123.39, 130.92, 131.33, 133.89, 136.48, 138.90, 155.06, 156.56, 157.39, 161.04, 162.12(C=O); MS (m/z) Cald.:435.16, found:435.45, Anal. Calc. for: **$C_{27}H_{21}N_3O_3$:** C, 74.47; H, 4.86; N, 9.97 Found: C, 74.04; H, 4.69; N, 10.06 %

4-(1-allyl-2-(4-fluorophenyl)-1*H*-indol-3-yl)-2-amino-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (9b)

White solid; m.p 281^{o}C; IR (KBr, ν,cm^{-1}): 3485 and 3325 (asym and sym. stretching of -NH_2), 2189 (-C≡N stretching), 1675 (C=O Stretching), 1247 (C-O-C ether stretching); ^{1}H NMR (400 MHz $CDCl_3$) *ð* ppm: 2.21 (s, 3H, CH_3), 4.54-4.83 (m, 6H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N-CH_2CH=C$\underline{H}_2$trans, N$\underline{H}_2$), 5.11(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.80 -5.88 (m, 1H, NCH_2C$\underline{H}$), 7.06-7.64 (m, 9H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) *ð* ppm: 20.14, 27.86, 46.12, 63.40, 101.07, 108.52, 109.76, 110.60, 116.59, 118.16, 118.35, 119.70, 121.84, 123.42, 130.00, 131.45, 133.24, 136.89, 138.34, 156.51, 157.14, 157.42, 161.64, 162.30, 163.43(C=O); MS (m/z) Cald.: 453.15, found: 453.52, Anal. Calc. for: **$C_{27}H_{20}FN_3O_3$:**71.51; H, 4.45; F, 4.19; N, 9.27; Found: C, 71.35; H, 4.05; N, 9.43 %

4-(1-allyl-2-(4-bromophenyl)-1*H*-indol-3-yl)-2-amino-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (9c)

White solid; m. p. 264^{o}C; IR(KBr, ν,cm^{-1}): 3414 and 3382 (asym and sym. Stretching of -NH_2), 2210 (-C≡N stretching), 1681 (C=O Stretching), 1256(C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 2.14 (s, 3H, C$\underline{H}_3$), 4.52-4.64 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.81(d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.10(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.80 -5.88 (m, 1H,

$NCH_2C\underline{H}$), 7.06-7.85 (m, 9H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) δ ppm: 20.16, 27.74, 46.09, 64.91, 97.59, 101.15, 104.43, 108.56, 110.57, 116.49, 118.14, 119.65, 121.63, 125.85, 128.42, 130.51, 133.32, 136.73, 138.57, 142.42, 145.56, 148.02, 156.46, 157.46, 162.27(C=O); MS (m/z) Cald.: 513.07, found: 513.23, Anal. Calc. for: **$C_{27}H_{20}BrN_3O_3$:** C, 63.05; H, 3.63; N, 8.40 Found: C, 63.14; H, 3.62; N, 8.39 %

4-(1-allyl-2-(4-chlorophenyl)-1*H*-indol-3-yl)-2-amino-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (9d)

White solid; m. p. 271^{o}C; IR (KBr, ν,cm^{-1}): 3485 and 3334 (asym and sym. stretching of -NH_2), 2198 (-C≡N stretching), 1659 (C=O Stretching), 1261 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.12 (s, 3H, $C\underline{H}_3$), 4.51-4.63 (m, 5H, N-$C\underline{H}_2CH$, $C\underline{H}O$, $N\underline{H}_2$), 4.79(d, 1H, N-CH_2CH=$C\underline{H}_2$trans), 5.12(d, 1H, N-CH_2CH=$C\underline{H}_2$cis), 5.79 -5.81 (m, 1H, $NCH_2C\underline{H}$), 7.04-7.83 (m, 9H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ, $CDCl_3$) δ ppm: 20.14, 27.62, 46.13, 64.83, 97.62, 101.18, 104.41, 108.54, 110.53, 116.51, 118.17, 119.63, 121.71 125.78, 128.38, 130.49, 133.30, 136.71, 138.54, 142.44, 145.54, 148.07, 156.51, 157.43, 162.25(C=O); MS (m/z) Cald.: 469.12, found: 469.24, Anal. Calc. for: **$C_{27}H_{20}ClN_3O_3$:** C, 69.01; H, 4.29; N, 9.22 Found: C, 68.97; H, 4.08; N, 9.15 %

4-(1-allyl-2-phenyl-1*H*-indol-3-yl)-2-amino-5-oxo-7-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (10a)

White solid; m. p. 271^{o}C; IR (KBr, ν,cm^{-1}): 3421 and 3373 (asym and sym. Stretching of -NH_2), 2208 (-C≡N stretching), 1678 (C=O Stretching), 1263 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.52-2.79 (m, 4H, 2x$C\underline{H}_2$), 3.27- 3.43 (m, 1H, $C\underline{H}$), 4.51-4.68 (m,5H,N-$C\underline{H}_2CH$, $C\underline{H}O$, $N\underline{H}_2$), 4.84(d, 1H, N-CH_2CH=$C\underline{H}_2$trans), 5.15(d,1H, N-CH_2CH=$C\underline{H}_2$cis), 5.75-5.87 (m, 1H, $NCH_2C\underline{H}$), 6.98-7.97 (m, 14H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 27.16, 34.41, 38.12, 43.81, 45.98, 63.47, 110.30, 110.61, 113.92, 116.12, 118.45, 119.56, 121.42, 123.86, 126.93, 127.28, 128.98, 129.56, 130.48, 131.94, 132.92, 133.82, 135.01, 136.72, 137.18, 138.05, 156.56, 158.78, 195.24(C=O); MS (m/z) Cald.: 497.60, found: 497.16, Anal. Calc. for: **$C_{33}H_{27}N_3O_2$:** C, 79.66; H, 5.47; N, 8.44 Found: C, 79.18; H, 5.28; N, 8.68 %

4-(1-allyl-2-(4-fluorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-7-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (10b)

White solid; m. p. 291^{o}C; IR (KBr, ν,cm^{-1}): 3414 and 3374 (asym. and sym. Stretching of -NH_2), 2164 (-C≡N stretching), 1673 (C=O Stretching), 1251 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.51-2.78 (m, 4H, 2xCH_2), 3.28-3.45 (m, 1H, CH), 4.52-4.65 (m, 5H, N-CH_2CH, CHO, NH_2), 4.85 (d, 1H, N-CH_2CH=CH_2trans), 5.13(d, 1H, N-CH_2CH=CH_2cis), 5.73-5.88 (m, 1H, NCH_2CH), 6.99-7.98 (m, 13H, Ar-H); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 27.14, 34.42, 38.14, 43.83, 45.97, 63.45, 110.28, 110.64, 113.87, 116.10, 118.47, 119.62, 121.47, 123.85, 126.91, 127.30, 128.94, 129.53, 130.51, 131.92, 133.02, 133.86, 135.03, 136.75, 137.25, 138.12, 156.49, 158.81, 195.18(C=O); MS (m/z) Cald.: 515.59, found:515.40, Anal. Calc. for: **$C_{33}H_{26}FN_3O_2$:** C, 76.88; H, 5.08; N, 8.15 Found: C, 77.05; H, 5.15; N, 8.02 %

4-(1-allyl-2-(4-bromophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-7-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (10c)

White solid; m. p. 256^{o}C; IR (KBr, ν,cm^{-1}): 3432 and 3365 (asym and sym. Stretching of -NH_2), 2176 (-C=N stretching), 1668 (C=O Stretching), 1252 (C-O-C ether stretching);^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.53-2.85 (m, 4H, 2xCH_2), 3.30-3.47 (m, 1H, CH), 4.50-

4.67 (m, 5H, N-CH_2CH,CHO, NH_2), 4.87 (d, 1H, N-CH_2CH=CH_2trans), 5.12(d, 1H, N-CH_2CH=CH_2cis), 5.72-5.86 (m, 1H, NCH_2CH), 6.97-7.99 (m, 13H, Ar-H); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 27.12, 34.34, 38.16, 43.80, 45.95, 63.46, 110.30, 110.63, 113.85, 116.14, 118.45, 119.64, 121.51, 123.87, 126.88, 127.28, 128.92, 129.51, 130.54, 131.87, 133.07, 133.84, 135.08, 136.78, 137.31, 138.18, 156.53, 158.79, 195.15(C=O); MS (m/z) Cald.: 576.49, found: 575.68, Anal. Calc. for: **$C_{33}H_{26}BrN_3O_2$:** C, 68.75; H, 4.55; N, 7.29 Found: C, 69.01; H, 4.64; N, 7.18 %

4-(1-allyl-2-(4-chlorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-7-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (10d)

White solid; m. p. 287^{o}C; IR(KBr, ν,cm^{-1}): 3443 and 3359 (asym and sym. Stretching of –NH_2), 2183 (-C≡N stretching), 1672 (C=O Stretching), 1256 (C-O-C ether stretching);^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.55-2.84 (m, 4H, 2xCH_2), 3.27-3.41 (m, 1H, CH), 4.51-4.87 (m, 6H, N-C$\underline{H}_2$CH=C$\underline{H}_2$trans, C$\underline{H}$O, N$\underline{H}_2$), 5.12(d, 1H, N-CH_2CH=CH_2cis), 5.72-5.85 (m, 1H, NCH_2CH), 7.22-7.82 (m, 13H, Ar-H); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 27.14, 34.38, 38.19, 43.97, 46.20, 63.53, 110.51, 110.64, 113.97, 116.60, 118.30, 119.81, 121.65, 126.04, 126.57, 126.63, 127.35, 128.48, 128.94, 129.73, 132.79, 133.36, 134.92, 136.82, 137.74, 141.75, 156.85, 158.56, 195.23(C=O); MS (m/z) Cald.: 532.04, found: 532.15, Anal. Calc. for: **$C_{33}H_{26}ClN_3O_2$:** C, 74.50; H, 4.93; N, 7.90 Found: C, 74.64; H, 5.01; N, 8.01 %

4-(1-allyl-2-phenyl-1*H*-indol-3-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (11a)

White solid; m. p. 278^{o}C; IR (KBr, ν,cm^{-1}): 3416 and 3335 (asym. and sym. Stretching of -NH_2), 2189 (-C≡N stretching), 1672 (C=O Stretching) 1251 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.84-1.01 (m, 6H, 2XC$\underline{H}_3$), 2.16-2.50 (m, 4H, 2XC$\underline{H}_2$), 4.45-4.63 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.82(d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.10(d,1H,N-CH_2CH=C$\underline{H}_2$cis), 5.80-5.87 (m, 1H, $NCH_2C\underline{H}$), 6.91 -8.02 (m, 9H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 26.92, 28.11, 28.71, 32.04, 40.69, 45.92, 50.78, 63.51, 110.86, 113.07, 113.92, 115.18, 115.94, 116.87,118.21, 118.62, 119.29, 121.89, 125.36, 127.01, 132.86, 133.39, 136.40, 137.14, 156.98, 161.02, 196.30 (C=O); MS (m/z) Cald.: 449.55, found: 449.61, Anal. Calc. for: **$C_{29}H_{27}N_3O_2$:** C, 77.48; H, 6.05; N, 9.35 Found: C, 77.59; H, 5.59; N, 9.95 %

4-(1-allyl-2-(4-fluorophenyl)-1*H*-indol-3-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile(11b)

White solid; m. p. 285^{o}C; IR (KBr, ν,cm^{-1}): 3423 and 3361 (asym. and sym. Stretching of -NH_2), 2176 (-C≡N stretching), 1668 (C=O Stretching), 1247 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.85-1.00 (m, 6H, 2XC$\underline{H}_3$), 2.14-2.52 (m, 4H, 2XC$\underline{H}_2$), 4.43-4.62 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.80(d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.13(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.81-5.88 (m, 1H, $NCH_2C\underline{H}$), 6.92 -8.08 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) δ ppm: 26.10, 28.87, 28.73, 32.06, 40.71, 45.89, 50.74, 63.53, 110.91, 113.14, 113.97, 115.13, 115.96, 116.82,118.24, 118.67, 119.30, 121.91, 125.41, 127.06, 132.92, 133.41, 136.48, 137.11, 156.85, 161.13, 196.28 (C=O); MS (m/z) Cald.: 467.54, found: 467.64, Anal. Calc. for: **$C_{29}H_{26}FN_3O_2$:** C, 74.50; H, 5.61; N, 8.99 Found: C, 74.45; H, 5.49; N, 9.09 %

4-(1-allyl-2-(4-bromophenyl)-1*H*-indol-3-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (11c)

White solid; m. p. 261°C; IR (KBr, ν,cm^{-1}): 3416 and 3376 (asym and sym. Stretching of -NH_2), 2187 (-C=N stretching), 1671 (C=O Stretching), 1263 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 0.88-1.01 (m, 6H, 2XC$\underline{H}_3$), 2.16-2.47 (m, 4H, 2XC$\underline{H}_2$), 4.46-4.52 (m, 5H, N-C$\underline{H}_2$CH,C$\underline{H}$O, N$\underline{H}_2$), 4.65(d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.10(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.81-5.88 (m, 1H, NCH_2C$\underline{H}$), 7.07 -7.88 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm: 27.08, 28.07, 28.63, 32.05, 40.71, 46.15, 50.88, 63.45, 110.47, 113.10, 113.74, 115.07, 115.30, 116.48,118.40, 118.90, 119.52, 121.46, 125.88, 127.16, 133.42, 133.48, 136.76, 137.85, 156.93, 161.17, 196.37(C=O); MS (m/z) Cald.: 528.45, found: 527.61, Anal. Calc. for: **$C_{29}H_{26}BrN_3O_2$:** C, 65.91; H, 4.96; N, 7.95 Found: C, 66.03; H, 5.03; N, 8.05 %

4-(1-allyl-2-(4-chlorophenyl)-1*H*-indol-3-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (11d)

White solid, m. p. 284°C; IR (KBr, ν,cm^{-1}): 3451 and 3364 (asym and sym. Stretching of -NH_2), 2175 (-C≡N stretching), 1668 (C=O Stretching), 1262 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 0.97-1.03 (m, 6H, 2XC$\underline{H}_3$), 2.14-2.43 (m, 4H, 2XC$\underline{H}_2$), 4.45-4.53 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.63(d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.07(d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.82-5.87 (m, 1H, NCH_2C$\underline{H}$), 7.06 -7.85 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm: 27.10, 28.13, 28.65, 32.14, 40.73, 46.18, 50.79, 63.51, 110.45, 113.17, 113.81, 115.04, 115.41, 116.52, 118.39, 118.87, 119.51, 121.52, 125.88, 127.20, 133.41, 133.51, 136.81, 137.83, 156.91, 161.20, 196.35(C=O); MS (m/z) Cald.: 484.00, found: 483.87, Anal. Calc. for: **$C_{29}H_{26}ClN_3O_2$:** C, 71.97; H, 5.41; N, 8.68 Found: C, 72.04; H, 5.56; N, 8.71 %

4-(1-allyl-2-phenyl-1*H*-indol-3-yl)-2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12a)

White solid; m. p. 249°C; IR (KBr, ν,cm^{-1}): 3432 and 3365 (asym and sym. Stretching of -NH_2), 2168 (-C≡N stretching), 1667 (C=O Stretching) 1242 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 2.00-2.68 (m, 6H, CH_2), 4.45-4.59 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.81 (d,1H, N-CH_2CH=C$\underline{H}_2$trans), 5.11 (d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.84-5.89 (m, 1H, NCH_2C$\underline{H}$), 6.78-8.03 (m,9H,Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm: 20.16, 27.83, 30.19, 37.10, 46.16, 63.48, 101.16, 110.15, 113.10, 114.19, 116.37,118.40, 119.97, 121.42, 126.43, 128.09, 129.59, 132.03, 133.06, 134.46, 136.41, 138.04, 156.42, 159.92,196.12(C=O); MS (m/z) Cald.: 421.50, found: 421.67, Anal. Calc. for: **$C_{27}H_{23}N_3O_2$:** C, 76.94; H, 5.50; N, 9.97 Found: C, 77.15; H, 5.49; N, 9.86 %

4-(1-allyl-2-(4-fluorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12b)

White solid; m. p. 285°C; IR(KBr, ν,cm^{-1}): 3418 and 3357 (asym and sym. Stretching of –NH_2), 2179 (-C≡N stretching), 1681 (C=O Stretching), 1253 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 2.01-2.69 (m, 6H, CH_2), 4.43-4.57 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.83 (d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.09 (d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.83-5.88 (m, 1H, NCH_2C$\underline{H}$), 6.76-8.02 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm: 20.15, 27.85, 30.17, 37.09, 46.14, 63.43, 101.14, 110.13, 113.08, 114.15, 116.32,118.38, 119.85, 121.51, 126.02, 127.87, 129.56, 132.05, 133.03, 134.45, 136.39, 138.04, 156.23, 159.90,196.10(C=O); MS (m/z) Cald.: 439.49, found: 439.64, Anal. Calc. for: **$C_{27}H_{22}FN_3O_2$:** C, 73.79; H, 5.05; N, 9.56 Found: C, 73.83; H, 4.89; N, 9.76 %

4-(1-allyl-2-(4-bromophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12c)

White solid; m. p. 294^{o}C; IR(KBr, ν,cm^{-1}): 3435 and 3384 (asym and sym. Stretching of -NH_2), 2181 (-C≡N stretching), 1665 (C=O Stretching) 1251 (C-O-C ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$) *ð* ppm: 2.00-2.58 (m, 6H, CH_2), 4.45-4.61 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.82 (d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.12 (d,1H, N-CH_2CH=C$\underline{H}_2$cis), 5.81-5.87 (m, 1H, NCH_2C$\underline{H}$), 6.78-8.01 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm:20.13, 27.83, 30.14, 37.11, 46.12, 63.41, 101.16, 110.12, 113.06, 114.16, 116.30,118.41, 119.81, 121.54, 126.05, 127.85, 129.59, 132.07, 133.13, 134.51, 136.42, 138.08, 156.20, 159.86,196.07(C=O); MS (m/z) Cald.: 500.40 , found: 500.55, Anal. Calc. for: **$C_{27}H_{22}BrN_3O_2$:** C, 64.81; H, 4.43; N, 8.40 Found: C, 64.93; H, 4.59; N, 8.52 %

4-(1-allyl-2-(4-chlorophenyl)-1*H*-indol-3-yl)-2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12d)

White solid; m. p. 279^{o}C; IR(KBr, ν,cm^{-1}): 3420 and 3387 (asym and sym. Stretching of –NH_2), 2185 (-C≡N stretching), 1676 (C=O Stretching), 1261 (C-O-C ether stretching);^{1}H NMR(400 MHz, $CDCl_3$) *ð* ppm: 2.00-2.68 (m, 6H, CH_2), 4.44-4.50 (m, 5H, N-C$\underline{H}_2$CH, C$\underline{H}$O, N$\underline{H}_2$), 4.83 (d, 1H, N-CH_2CH=C$\underline{H}_2$trans), 5.10 (d, 1H, N-CH_2CH=C$\underline{H}_2$cis), 5.83-5.88 (m, 1H, NCH_2C$\underline{H}$), 7.10-7.83 (m, 8H, Ar-$\underline{H}$); ^{13}CNMR (100 MHZ $CDCl_3$) *ð* ppm:20.39, 27.28, 30.05, 37.04, 46.23, 63.46, 101.16, 110.53, 113.86, 114.13, 116.53, 118.31, 119.66, 121.56, 126.01, 128.43, 129.75, 132.84, 133.38, 134.85, 136.79, 138.62, 156.74, 159.26, 196.26(C=O); MS (m/z) Cald.: 455.94, found: 456.08, Anal. Calc. for: **$C_{27}H_{22}ClN_3O_2$:** C, 71.13; H, 4.86; N, 9.22 Found: C, 71.24; H, 5.07; N, 9.31 %

Pharmacology

Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity was carried out by broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [XVII]. Antibacterial activity was screened against antibacterial *E.coli* MTCC 443, *S. typhi* MTCC 98, *V. cholerae* MTCC 3906 as Gram-negative bacteria and *S. pneumonia* MTCC 1936, *B. subtilis* MTCC 441 and *C. tetani* MTCC 449 as Gram-positive bacteria by using ampicillin, ciprofloxacin and norfloxacin as standard antibacterial drugs. Antifungal activity was screened against two fungal species *C. albicans* MTCC 227 and *T.rubrum* MTCC 97.Where, griseofulvin and nystatin were used as standard antifungal drugs. The antimicrobial screening data are shown in (**Table 1)**. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test.

Evaluation of antituberculosis activity

All the synthesized compounds were evaluated for their *in vitro* antituberculosis activity against the *M. tuberculosis* H37Rv strain. Primary screening of all the newly synthesized compounds was conducted at 250 mgmL by using Lowensteine–Jensen medium as described by Rattan[XVIII]. The observed screening results are showed in (**Table 2)** in the form of % inhibition, relative to that of standard antitubercular drug Rifampicin and Isoniazid which were used as the standard drugs.

Evaluation of antimalarial activity

All synthesized chromene and pyran derivatives were evaluated for their *in vitro* antimalarial activity against *P. falciparum* strain. Chloroquine and quinine were used as the reference

drugs. The pharmacological screening results are expressed as the drug concentration resulting in 50% inhibition (IC_{50}) of parasite growth. The obtained antimalarial screening data are presented in **Table 3**.

Conclusion

In conclusion, we have demonstrated a convenient method for the synthesis of pyrano[3,2-*c*]chromene, pyrano[4,3-*b*]pyran and 4*H*-chromene derivatives bearing N-allyl indole moiety have been synthesized by environmentally benign, microwave-assisted, one-pot multicomponent reaction in presence of non-hazardous triethylamine as a catalyst. This synthetic strategy allows the consolidation of two promising biopotent nucleus into a single scaffold through a straightforward method. All the compounds were screened for their antimicrobial, antimalarial and antituberculosis activities with the hope of discovering much potent antimicrobial, antimalarial and antituberculosis agents. It can be concluded from pharmacological screening that many of the synthesized compounds exhibited better antimicrobial activity against gram positive bacteria, but showed less effectiveness towards gram negative bacteria. In antifungal screening compounds **8d**, **10d** were found to be much potent to standard drug nystatin and equipotent to gresofulvin. Compounds **8b**, **9a**, **10c** exhibited most efficient antitubercular activity. While for antimalarial activity, compound **8c**, **9d**, **10b**, **10c**, **11a** and **11b** showed excellent activity against *P. falciparum* strains as compared to quinine. Therefore, on the basis of SAR analysis, it can be resolved that the lipophilicity of allylic group, change of the peripheral substituents and various different nature of the heterocyclic motifs fused at positions 5 and 6 in pyran were profoundly responsible to influence antimicrobial, antituberculosis and antimalarial potency.

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