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Microwave assisted synthesis of new indophenazine 1,3,5-trisubstruted pyrazoline derivatives of benzofuran and their antimicrobial activity

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ABSTRACT

2-[1-(5,8-Dihydro quinoxalino[2,3-*b*]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl] phenyl derivatives were synthesized from 2-(5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl) acetohydrazide and (2*E*)-1-(1-benzofuran-2-yl)-4-phenylbut-2-en-1-ones derivatives using microwave-assisted route. The structures of all the compounds have been established on the basis of analytical and spectral data. Among the 14 compounds IPB-1, IPB-5, IPB-10, IPB-11 and IPB-12 were found good antibacterial activity and MICs were found bellow 10 μg/mL against *Escherichia coli, Pseudomonas aeruginosa* and *Streptococcus aureus,* which can compared with sparfloxacin and norfloxacin.

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Pyrazoline and benzofuran heterocyclic systems are known to exhibit a wide range of biological properties such as antihyperglycemic[1], analgesic[2], antiinflammatory[3], antibacterial[4], antifungal[4], and antitumor[5] activities. The incorporation of heterocyclic ring into the benzofuran and pyrazoline ring would be more potent against multidrug resistant bacteria[6,7] than benzofuran and pyrazoline ring alone. An in-depth study has been directed toward the design and synthesis of fused-pyrazole derivatives.[8–10] Pyrazolo-oxazinones ring systems[11] have not been studied yet regarding its activity against multidrug resistant bacteria. The present study has been described the microwave-assisted synthesis[12–14] of 2-[1-(5,8-dihydro quinoxalino[2,3-*b*]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl] phenyl derivatives[19] **7** from 2-(5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl) acetohydrazide[18] **5** with (2*E*)-1-(1-benzofuran-2-yl)-4-phenylbut-2-en-1-ones[20–23] **6** (benzofuran chalcones) and their antibacterial activity against multidrug resistant bacteria. Microwave-assisted synthetic route has also been developed for the synthesis of 5,8-dihydro quinoxalino[2,3-*b*]indole (indophenazine)[15] **3**, ethyl 5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl acetate (6-carbethoxymethyl indophenazine)[17] **4** and 2-(5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl) acetohydrazide (Indophenazine-6-acetic acid hydrazide) **5** using a domestic convection microwave oven (Model No: Samsung, CE1072L-TS).

The antibacterial activity was screened against multidrug resistant *Escherichia coli, Pseudomonas aeruginosa, Streptococcus pneumoniae, Streptococcus agalactiae, Salmonella typhi, Streptococcus aureus,* and *Streptococcus pyogenes* bacteria and carried out by cylinder and well method.[24,25] The MICs were determined using Mueller–Hinton Broth (MHB) culture media. Agar media (2% in water) was supplemented in 5% sheep blood and then incubated in 10% CO_2 atmosphere for overnight. After incubation inoculates were diluted with ringer (oxoid) solution. The final concentration of inoculums was made approximately 10 CFU/mL. The multidrug resistant strains of *E. coli, P. aeruginosa, S. pneumoniae, S. agalactiae, S. typhi, S. aureus,* and *S. pyogenes* were treated in Todd–Hewitt medium (Oxoid).[6,7] 2 μL of the diluted strains were inoculated onto the individual agar plates. The drug spots were then applied on the agar culture plate and final size of spots were around 5 × 103 CFU/spot. The inoculated plates were then incubated at 37 °C for 20 h in an incubator. After 20 h of incubation, the zone of inhibitions[2] were measured in mm and compared with standard drugs and vehicle (Table 1).

The antifungal activity was screened against *Candida albicans* using agar couture medium.[7,24] All the compounds were prepared with different concentration in DMF and were injected into the 6 mm wells. The plates were incubated at 30 °C for 30–72 h and then measured zone of inhibitions in mm and compared with standard drugs.

The microwave-assisted reactions[26,27] are more economical, environmentally friendly (green synthesis), good yield and more time saving method, which was adopted for the synthesis of all the compounds in Scheme 1. The microwave-assisted synthetic

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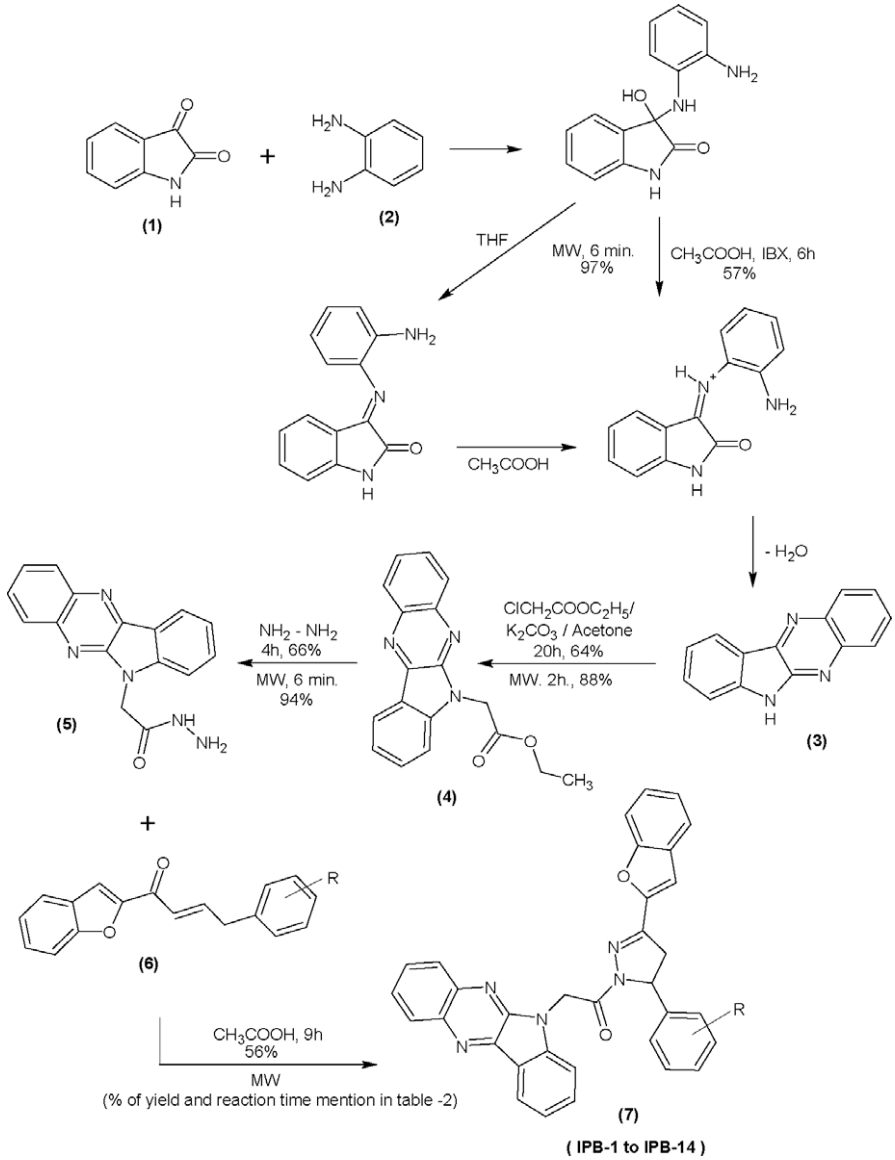
Table 1
Antibacterial activities measure by zone of inhibition in mm and MICs were measure by μg/mL of all final compounds

Name of compd	–R	Gram-negative bacteria								Gram-positive bacteria					
		E. coli		*P. aeruginosa*		*S. typhi*		*S. agalactiae*		*S. pneumoniae*		*S. aureus*		*S. pyogenes*	
		mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC
IPB-1	–OH (*o*)	18	1.00	15	3.5	12	9.5	11	22.0	13	8.5	13	6.0	10	26.0
IPB-2	$–OCH_3$ (*o*)	9	16.5	12	14.5	10	11.5	9	25.0	7	15.5	11	7.5	15	22.5
IPB-3	$–N(CH_3)_2$ (*p*)	10	13.5	11	14.0	13	9	7	36.5	10	9.5	14	7.0	9	25.5
IPB-4	–COOH (*o*)	11	13.0	14	6.5	12	10.5	10	24.0	8	15.0	12	8.5	10	30.5
IPB-5	$–NO_2$ (*m*)	13	10.5	16	5.5	14	8	12	26.0	10	13.0	9	12.5	12	28.0
IPB-6	–OH (*o*), OCH_3 (*p*)	11	13.5	10	18.5	16	5	11	28.0	11	14.5	13	9.0	14	26.0
IPB-7	–OH (*p*)	10	14.0	8	26.0	12	8.5	8	32.5	8	19.5	14	6.5	15	20.5
IPB-8	–Cl (*p*)	7	22.5	10	16.5	15	5.5	10	28.0	10	16.0	8	16.5	14	22.0
IPB-9	–Cl (*o*)	8	21.5	9	17.5	14	7	10	30.0	9	15.0	11	10.0	12	25.0
IPB-10	$–NO_2$ (*o*)	16	5.5	12	10.5	13	8.5	12	22.0	10	14.5	12	9.5	10	24.0
IPB-11	$–OCH_3$ (*p*)	17	5.0	13	12.5	16	4.5	14	19.0	11	12.0	12	8.0	14	23.5
IPB-12	–H	14	8.0	11	15.5	20	2	8	28.5	8	17.0	16	2.5	12	28.5
IPB-13	Furan ring	10	15.0	8	21.0	14	5.6	10	26.5	9	16.5	10	10.5	8	30.0
IPB-14	–CH=CH–Ar	8	20.5	10	18.5	12	10	9	22.5	10	14.5	14	4.5	10	26.5
Sparfloxacin		30	0.26	33	4.6	34	0.04	38	12.0	34	0.50	36	0.25	38	15.0
Norfloxacin		20	1.3	28	1.8	22	0.12	32	22.0	24	20.2	28	1.5	30	2.6

Escherichia coli, Pseudomonas aeruginosa, Streptococcus pneumoniae, Streptococcus agalactiae, Salmonella typhi, Streptococcus aureus, and *Streptococcus pyogenes*.
mm = zone of inhibitions. MIC = minimum inhibitory concentration.



Scheme 1.

Table 2
Microwave assisted synthesis compare with ordinary synthesis of all the final compounds in Scheme 1

Compound names	–R	Ordinary synthesis		Microwave assisted synthesis	
		Time of synthesis[a] (h)	Yield[b] (%)	Irradiation[c] time (min)	Yield[b] (%)
IPB-1	–OH (*o*)	8	28	25	88
IPB-2	$–OCH_3$ (*o*)	9.5	37	20	90
IPB-3	$–N(CH_3)_2$ (*p*)	9	56	25	92
IPB-4	–COOH (*o*)	8	62	25	96
IPB-5	$–NO_2$ (*m*)	9	72	25	98
IPB-6	–OH (o), OCH_3 (*p*)	9.5	60	30	90
IPB-7	–OH (*p*)	9	36	30	86
IPB-8	–Cl (*p*)	8	57	28	91
IPB-9	–Cl (*o*)	8	62	28	92
IPB-10	$–NO_2$ (*o*)	8.5	68	25	94
IPB-11	$–OCH_3$ (*p*)	9	62	28	95
IPB-12	–H	9.5	58	30	88
IPB-13	Furan ring	8	47	26	84
IPB-14	–CH=CH–Ar	8	52	25	92

[a] Reflux in heating equipments.
[b] Percentages of yield calculated from practical and theoretical yields.
[c] 40% irradiation energy used (320 W).

procedure was compared with ordinary synthetic route in Table 2. The synthesized compounds were established by IR, ^{1}H NMR, mass and elemental analysis data using Shimadzu-IR 8300, Joel-GSX 400 m, Parkin-Elmer 2400 Series II analyzer and MSN-9629 instruments, respectively.

The N–H, one proton in indophenazine ring was established by sharp ^{1}H NMR peak at 9.834 ppm (s, 1H) and 3402, 3169, 3130 cm^{-1} in IR. Oxazolidine ring was established by ^{1}H NMR peak at 8.42–7.65 ppm, by IR (cm^{-1}): 3402, 3169 *v*(NH), 1686 *v*(CH), 1617 *v*(C=N). 6-carbethoxymethyl indophenazine structure was characterized by sharp ^{1}H NMR peak at 5.064–1.25 ppm (s, N–CH_2), where N–H peak was absent and additional 4.18 ppm (d, 2H, *J = 7.12*) O–CH_2–CH_3, 1.25 ppm (d, 3H, *J = 9.32*) O–CH_2–CH_3 peaks were obtained. The IR peaks 1738 and 1748 cm^{-1} (C=O), 1678 (CH), 1614 (C=C) and (C=N) were supported for the establishment of the structure. Indophenazine-6-acetic acid hydrazide structure was characterized by sharp ^{1}H NMR peak at 8.92 (s, 1H) N*H*NH_2 and 5.78 (s, 2H) NHNH_2. The IR peaks 1614 cm^{-1} (C=C) and (C=N), 1546 cm^{-1} (NH), 1488, 1467 cm^{-1} (C=N) and (C=C) were reconfirmed the structure. First final compound IPB-1 was elucidated by ^{1}H NMR, IR, Mass and elemental analysis data, where ^{1}H NMR and IR peaks of $NHNH_2$ were not found, but sharp ^{1}H NMR peak at 3.6 (s, 1H) for one proton in position 5 and 2.3 (s, 2H) for two protons at position 4 in pyrazoline ring, were established the structure of pyrazoline. In Mass spectra, *m*/*z*: 537.75 (molecular ion peak) was found same with actual molecular weight of the compound and 100% base peak of the important fragment was also recorded at *m*/*z*: 145.20. The IR data, 3373 (O–H str.), 1345, 1169 (C–O str.) and the data of elemental analysis were reestablished the structure of first final compound by 0.84% different in calculated C, H, N, O values with founded values. Similar way we interpreted and characterized all the final compounds.[19] Antibacterial activity of the compounds was endowed with higher activity against 7 different multidrug resistant organisms in various concentrations (Table 1). The MICs of the compounds were found satisfactory and compared with standard fluoroquinolones drugs. By comparing the compounds IPB-1, IPB-5, IPB-10, IPB-11 and IPB-12 were found better active against *E. coli, P. aeruginosa, S. typhi* and *S. aureus* but rests of other pathogens were not found signified activity. IPB-1, IPB-5, IPB-10, IPB-11 and IPB-12 were having inhibited capacity than others against *E. coli.* The MICs of the compounds were found as 1.0, 10.5, 5.5, 5.0 and 8.0 μg/mL, respectively. None of the above has been significant activity against*S. pneumoniae* and *S. agalactiae*. IPB-5, IPB-6, IPB-10, IPB-11 and IPB-12 were good enough, MICs of the compounds were found at 12.5, 9.0, 9.5, 8.0 and 2.5 μg/mL, respectively, against *S. aureus.* All the compounds were found to possess good activity against *S. pyogenes* except, IPB-4 and IPB-13. Not a single compound was exhibited significant antifungal activity against *C. albicans.*

Structure–activity relationships suggested that substituted phenyl ring (IPB-1 to IBP-11) at 5-position in 4,5-dihydro pyrazole produced various antibacterial activity against gram positive and gram negative bacteria listed in Table 1. The *ortho* substitution in phenyl ring with –OH (IPB-1), $–NO_2$ (IPB-10) and *para* substitution in phenyl ring by $–OCH_3$ (IPB-11) at 5-position pyrazole produced the best antibacterial activity against gram negative bacteria. Unsubstituted phenyl ring (IPB-12) at 5-position pyrazole produced moderate antibacterial activity. When phenyl ring was replaced by five member ring (IPB-13) at 5-position of pyrazole ring caused reduction in antibacterial activity. The single C–C bond between pyrazole ring and 5-phenyl ring can be replaced by ethenyl bridge (IPB-14) resulted in moderate antibacterial activity. *Ortho* substitution in phenyl ring with $–OCH_3$ (IPB-2), –Cl (IPB-9) and *para* substitution in phenyl ring by –OH (IPB-7), –Cl (IPB-8) at 5-position pyrazole produced less or inactive antibacterial activity against gram negative bacteria. The common structure of compounds did not support any antifungal activity against *C. albicans*.

It can be concluded that, the microwave-assisted synthesis in having higher regioselective, and more time saving than ordinary synthesis of pyrazoline containing benzofuran with indophenazine ring. The potency and selective compounds make them valid leads for synthesizing new compounds with better activity and exhibiting lower MICs values.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.161.

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15. Indophenazine (5,8-dihydro quinoxalino[2,3-*b*]indole) **3** was prepared by stirring 0.05 mol of isatin **1** with equivalent amount of *ortho*-phenylene diamines **2** at room temperature in presence of 2-Iodoxybenzoic acid (IBX) according to previously published procedures.[16] Yield 70% and mp 262 °C.
The microwave assisted synthesis of indophenazine was established; using equivalent amount of isatin (0.05 mol) and *ortho*-phenylene diamine in 8 mL of glacial acetic acid into a 50 mL conical flask (borosilicate), which covered with small funnel. The flask was placed in a microwave oven for 6 min at 20% (160 W) energy level. The progress of the reaction was monitored by TLC (Benzene:Methanol, 3:1). The solution was poured in 100 mL ice-cold water and neutralized with 5% $NaHCO_3$ solution. The organic layer was extracted with diethyl ether (2 × 5 mL) and washed with brine (2 × 5 mL), and dried over $MgSO_4$. The solvent was evaporated by rotary evaporator and pure compound was obtained by recrystallization with hot ethyl acetate. Yield 97% and mp: 264 °C; IR (KBr) ν_{max} (cm^{-1}): 3402, 3169, 3130 ν(NH), 1686 ν(CH), 1617 ν(C=C), ν(C=N), 1555 d(NH), 1490, 1465 ν(C=N), ν(C=C), 1300 d(CH), 1242, 888 ν(C=C), 1166, 789, 747 d(CH), 689 π(CH), 663 d(CH), 626 π(NH), 549 π(C=C).; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.40 (s, 1H) NH, 7.45–7.58 (d, 1H, *J* = 7.2 Hz) CH, 7.22–7.42 (m, 4H, *J* = 8.4 Hz) CH, 6.92–7.22 (m, 3H, *J* = 8.1 Hz) isatin ring.
Indophenazine (5,8-dihydro quinoxalino[2,3-*b*]indole) **3** was prepared by stirring 0.05 mol of isatin **1** with equivalent amount of *ortho*-phenylene diamines **2** at room temperature in presence of 2-Iodoxybenzoic acid (IBX) according to previously published procedures.[16] Yield 70% and mp 262 °C.
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17. 6-Carbethoxymethyl indophenazine (ethyl 5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl acetate) **4** was prepared by microwave irradiation (160 W) from indophenazine (0.01 mol) **3** and ethyl chloro acetate (0.015 mol) into a 50 mL conical flask (borosilicate). To that added 2 mL of dry acetone and 0.2 mol of anhydrous potassium carbonate portion wise. Then covered the flask with small funnel and irradiated for 2 h. The solvent was evaporated under reduced pressure and poured in to 100 mL ice-cold water with stirring. Solid was separated by filtration and recrystallized from hot 95% ethanol. Yield 88% and mp: 188 °C; IR (KBr) ν_{max} (cm^{-1}): 1738 and 1748 (C=O), 1678 (CH), 1614 (C=C) and (C=N), 1488 and 1467 (C=N), (C=C), 1320 (CH), 1225 (C–O), 1240, 880 (C=C), 1158, 781, 750 (CH), 692 (CH), 671 (CH), 551 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36–7.48 (d, 1H, *J* = 6.9 Hz) CH, 7.26–7.40 (m, 4H, *J* = 8.0 Hz) CH, 7.10–7.25 (m, 3H, *J* = 8.3 Hz) isatin ring, 5.12 (s, 2H) CH_2, 4.18 (d, 2H, *J* = 7.11 Hz) CH_2CH_3.
18. Indophenazine-6-acetic acid hydrazide (2-(5,8-dihydro quinoxalino[2,3-*b*]indol-5-yl) acetohydrazide) **5** was synthesized from 6-carbethoxymethyl indophenazine (0.1 mol) **4** and hydrazine hydrate (99%, 0.4 mol) into 30 mL of absolute ethanol in a 50 mL conical flask (borosilicate). The flask was covered by small funnel and placed in a microwave oven for 140 s at 40% (320 W) energy level. Excess of ethanol was removed under reduced pressure, and then resulting solution was poured in ice-cold water. Solid was obtained by filtration and recrystallized from hot dioxan. Yield 94% and mp: 216 °C; IR (KBr) ν_{max} (cm^{-1}): 1738, 1748 (C=O), 1678 (CH), 1614 (C=C) and (C=N), 1546 (NH), 1488, 1467 (C=N) and (C=C), 1320 (CH), 1225 (C–O), 1240 and 880 (C=C), 1158, 781 and 750 (CH), 692 (CH), 671 (CH), 632 (NH), 551 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.92 (s, 1H) N*H*NH_2, 7.36–7.48 (d, 1H, *J* = 6.9 Hz) CH, 7.26–7.40 (m, 4H, *J* = 8.0 Hz) CH, 7.10–7.25 (m, 3H, *J* = 8.3 Hz) isatin ring, 5.78 (s, 2H) NHNH_2, 4.95 (d, 2H, *J* = 7.23) NCH_2.
19. 1. General procedure for the synthesis of 2-[1-(5,8-dihydro quinoxalino[2,3-*b*]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl] phenyl derivatives **7** from benzofuran chalcones (0.01 mol) **6** and indophenazine-6-acetic acid hydrazide (0.02 mol) **5** were dissolved in 20 mL of glacial acetic acid in a 50 mL conical flask made up of borosil. The flask was then covered with small funnel (borosilicate) and irradiated by a microwave oven at 40% (320 W) energy level; the reaction times are mention in Table 2. Reaction was monitored by TLC using silica gel-G. The excess of solvent was evaporated under reduced pressure and resulting solution was poured in ice-cold water with stirring. The solid was separated by filtration and recrystallized from suitable solvent. IPB-1: White solid was recrystallized from 95% of ethanol; yield: 88%, mp: 155–157 °C, R_f = 0.88 (benzene:ethyl acetate, 3:1); λ_{max}: 236.2 nm; IR (KBr) ν_{max} (cm^{-1}): 3373 (O–H str.), 1454 (aromatic), 1345, 1169 (C–O str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.86 (s, 1H) OH, 7.79 (dd, 2H, *J* = 3.41, 6.2 Hz) CH, 7.55 (s, 4H), 7.39 (s, 6H), 3.6 (s, 1H), 2.3 (s, 2H); MS (FAB) *m*/*z*: 537.75 (m^+), 145.20 (100%); $C_{33}H_{23}N_5O_3$ (537.57): Calcd: C, 73.73; H, 4.31; N, 13.03; O, 8.93. Found: C, 73.90; H, 4.18; N, 13.56. IPB-2: Yellowish white solid was recrystallized from methanol; yield: 90%, mp: 71–73 °C, R_f = 0.79 (benzene:ethyl acetate, 2:1); λ_{max}: 306.6 nm; IR (KBr) ν_{max} (cm^{-1}): 1169–1026 (C-O-C str.), 2839 (CH_3 str.), 1456 (CH_3 def.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.15 (dd, 2H, *J* = 3.44, 6.32 Hz), 7.7 (dd, 2H *J* = 3.44, 6.32 Hz), 7.55 (d, 4H, *J* = 8.7 Hz), 7.39 (s, 6H), 6.89 (d, 4H, *J* = 8.73 Hz), 4.97 (s, 2H) NCH_2, 4.01(s, 3H) OCH_3, 3.61 (s, 6H), 2.4 (s, 2H); MS (FAB) *m*/*z*: 551.90 (m^+), 145.13 (100%); $C_{34}H_{25}N_5O_3$ (551.60): Calcd: C, 74.034; H, 4.57; N, 12.71; O, 8.70. Found: C, 73.97; H, 4.18; N, 12.16. IPB-3: White solid was recrystallized from methanol; yield: 92%, mp: 103–105 °C, R_f = 0.94 (benzene:ethyl acetate, 2:1); λ_{max}: 296.4 nm; IR (KBr) ν_{max} (cm^{-1}): 2925, 2804 (Ar–N–CH_3 str.), 1446 (CH_3 ban.), 1365, 1317 (C–N str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.05 (d, 1H, *J* = 8.52 Hz), 7.92 (s, 1H), 7.58 (d, 1H, *J* = 1.55, 8.5 Hz), 7.48 (d, 6H, *J* = 7.64 Hz), 6.9 (d, 4H, *J* = 8.74 Hz), 5.85 (d, 1H, *J* = 8.36)CH, 3.9 (s, 6H), 2.4 (s, 3H); MS (FAB) *m*/*z*: 565.12 (m^+), 145.20 (100%); $C_{34}H_{28}N_6O_2$ (564.64): Calcd: C, 74.45; H, 5.01; N, 14.88; O, 5.68. Found: C, 74.96; H, 5.18; N, 14.51. IPB-4: White solid was recrystallized from 95% of ethanol; yield: 96%, mp: 198–200 °C, R_f = 0.54 (benzene:ethyl acetate, 3:1); λ_{max}: 298.2 nm; IR (KBr) ν_{max} (cm^{-1}): 3402 (O–H str.), 1711, 1697 (C=O str.), 1173–1074 (C–O str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.13 (s, 1H) COOH, 8.21 (dd, 2H, *J* = 3.6, 6.32 Hz), 8.10 (d, 1H, *J* = 8.51 Hz), 7.80 (dd, 2H, *J* = 3.41, 6.22 Hz), 7.57 (s, 4H), 7.29 (s, 6H), 3.55 (s, 6H), 2.13 (s, 2H); MS (FAB) *m*/*z*: 565.87 (m^+), 145.20 (100%); $C_{34}H_{23}N_5O_4$ (565.58): Calcd: C, 72.21; H, 4.01; N, 12.38; O, 11.32. Found: C, 72.90; H, 4.28; N, 12.56. IPB-5: White solid was recrystallized from methanol; yield: 98%, mp: 97–99 °C, R_f = 0.63 (benzene:ethyl acetate, 3:1); λ_{max}: 265.4 nm; IR (KBr) ν_{max} (cm^{-1}): 1527 (asy) (NO_2 str.), 1346 (sym) (NO_2 str.), 883 (C–N str.). 877; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.2 (d, 1H, *J* = 2.38 Hz), 8.53 (dd, 1H, *J* = 2.38, 9.10 Hz), 8.39 (d, 1H, *J* = 9.10 Hz), 7.6 (s, 4H), 7.42 (s, 6H).; MS (FAB) *m*/*z*: 566.35(m^+), 145.14 (100%); $C_{33}H_{22}N_6O_4$ (566.57): Calcd: C, 69.96; H, 3.91; N, 14.83; O, 11.30. Found: C, 70.10; H, 3.78; N, 14.36. IPB-6: Light yellow solid was recrystallized from methanol; yield: 90%, mp: 223–225 °C, R_f = 0.54 (benzene:ethyl acetate, 3:1); λ_{max}: 267.6 nm; IR (KBr) ν_{max} (cm^{-1}): 3240 (O–H str.), 1383 (O–H ben.), 1170–1080 (C–O str.), 1020 (C–O–C str.), 2927 (CH_3 str.), 1450 (CH_3 def.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.25 (dd, 2H, *J* = 3.34, 6.34 Hz), 7.81 (dd, 2H, *J* = 3.47, 6.36 Hz), 7.35 (d, 4H, *J* = 8.41 Hz), 7.42 (s, 6H), 7.31 (d, 1H, *J* = 4.23) Ph–OH, 6.82 (d, 4H, *J* = 8.73 Hz), 3.20 (s, 3H) Ph-OCH_3, 2.4 (s, 2H); MS (FAB) *m*/*z*: 567.62 (m^+), 145.22 (100%); $C_{34}H_{25}N_5O_4$ (566.57): Calcd: C, 71.95; H, 4.44; N, 12.34; O, 11.28. Found: C, 71.23; H, 4.18; N, 12.56. IPB-7: White solid was recrystallized from methanol; yield: 86%, mp: 154–156 °C, R_f = 0.78 (benzene:ethyl acetate, 3:1); λ_{max}: 220.3 nm; IR (KBr) ν_{max} (cm^{-1}): 3367 (O-H str.), 1367–1252 (O–H ben.), 1172–1012 (C–O str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.32 (dd, 2H, *J* = 3.45, 6.32 Hz), 7.81 (dd, 2H, *J* = 3.54, 6.41 Hz), 7.24 (s, 4H), 7.42 (s, 6H), 6.27 (s, 1H) OH, 3.56 (s, 6H), 2.3 (s, 2H); MS (FAB) *m*/*z*: 537.55 (m^+), 145.30 (100%); $C_{33}H_{23}N_5O_3$ (537.57): Calcd: C, 73.73; H, 4.31; N, 13.03; O, 8.93. Found: C, 73.14; H, 4.48; N, 13.36. IPB-8: White solid was recrystallized from 95% of ethanol; yield: 91%, mp: 213–215 °C, R_f = 0.95 (benzene:ethyl acetate, 3:1); λ_{max}: 197.6 nm; IR (KBr) ν_{max} (cm^{-1}): 3240 (C–Cl str.), 1035 (C–O–C str.), 2930 (CH_3 str.), 1447 (CH_3 def.), 1599, 786, 746 (C–Cl str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.5 (dd, 2H, *J* = 3.42, 7.23 Hz), 7.82 (dd, 2H, *J* = 3.40, 8.40 Hz), 7.52 (dd, 4H, *J* = 1.42, 8.64 Hz), 7.15 (dd, 4H, *J* = 2.63, 8.64 Hz), 5.75 (s, H), 4.96 (s, 2H), 3.56 (s, 2H); MS (FAB) *m*/*z*: 556.84 (m^+), 144.97 (100%); $C_{33}H_{22}N_5O_2Cl$ (556.04): Calcd: C, 71.29; H, 3.99; N, 12.60; O, 5.71; Cl, 6.38. Found: C, 71.72; H, 4.14; N, 12.36. IPB-9: White solid was recrystallized from 95% of ethanol; yield: 92%, mp: 195–197 °C, R_f = 0.87 (benzene:ethyl acetate, 3:1); λ_{max}: 216.4 nm; IR (KBr) ν_{max} (cm^{-1}): 3255 (C–Cl str.), 1042 (C–O–C str.), 2912 (CH_3 str.), 1433 (CH_3 def.), 1601, 790, 748 (C–Cl str.);; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.31 (dd, 2H, *J* = 3.44, 6.22 Hz), 7.82 (dd, 2H, *J* = 3.44, 6.40 Hz), 7.22 (s, 4H), 7.40 (s, 6H), 3.55 (s, 6H), 2.3 (s, 2H); MS (FAB) *m*/*z*: 556.34 (m^+), 145.40 (100%); $C_{33}H_{22}N_5O_2Cl$ (556.04): Calcd: C, 71.29; H, 3.99; N, 12.60; O, 5.71; Cl, 6.38. Found: C, 71.12; H, 3.62; N, 12.16. IPB-10: Light yellow solid was recrystallized from methanol; yield: 94%, mp: 105–107 °C, R_f = 0.82 (benzene:ethyl acetate, 3:1); λ_{max}: 280.6 nm; IR (KBr) ν_{max} (cm^{-1}): 3089, 1599, 1552 (asy) (NO_2 str.), 1344 (sym) (NO_2 str.), 815 (C–N str.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.1 (d, 1H, *J* = 2.41 Hz), 8.56 (dd, 1H, *J* = 2.32, 9.20 Hz), 8.30 (d, 1H, *J* = 9.17 Hz), 7.6 (s, 4H), 7.22 (s, 6H); MS (FAB) *m*/*z*: 566.95(m^+), 145.14 (100%); $C_{33}H_{22}N_6O_4$ (566.57): Calcd: C, 69.96; H, 3.91; N, 14.83; O, 11.30. Found: C, 70.13; H, 3.48; N, 14.86. IPB-11: Light brown solid was recrystallized from methanol; yield: 95%, mp: 164–166 °C, R_f = 0.64 (benzene:ethyl acetate, 3:1); λ_{max}: 240.2 nm; IR (KBr) ν_{max} (cm^{-1}): 3010, 1602, 1170–1026 (C–O–C str.), 2837 (CH_3 str.), 1446 (CH_3 def.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (dd, 2H, *J* = 3.42, 6.30 Hz), 7.69 (dd, 2H, *J* = 3.39, 6.30 Hz), 7.57 (d, 4H, *J* = 8.72 Hz), 7.41 (s, 6H), 6.90 (d, 4H, *J* = 8.63 Hz), 3.60 (s, 6H), 2.35 (s, 2H); MS (FAB) *m*/*z*: 552.00 (m^+), 145.20 (100%); $C_{34}H_{25}N_5O_3$ (551.60): Calcd: C, 74.03; H, 4.57; N, 12.71; O, 8.70. Found: C, 74.17; H, 4.78; N, 12.96. IPB-12: Light yellowish solid was recrystallized from methanol; yield: 88%, mp: 215–217 °C, R_f = 0.86 (benzene:ethyl acetate, 3:1); λ_{max}: 203.2 nm; IR (KBr) ν_{max} (cm^{-1}): 3063, 1660, 1592; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.10 (d, 1H, *J* = 8.52 Hz), 7.91 (s, 1H), 7.63 (dd, 1H, *J* = 1.72, 8.52 Hz), 7.22 (s, 4H), 7.40 (s, 6H), 3.55 (s, 6H); MS (FAB) *m*/*z*: 519.00 (m^+), 145.00 (100%); $C_{33}H_{23}N_5O_2$ (537.57): Calcd: C, 75.99; H, 4.44; N, 13.43; O, 6.13. Found: C, 76.12; H, 4.68; N, 13.59. IPB-13: Yellowish white solid was recrystallized from methanol; yield: 84%, mp: 185–187 °C, R_f = 0.95 (benzene:ethyl acetate, 3:1); λ_{max}: 358.0 nm; IR (KBr) ν_{max} (cm^{-1}): 3134 (C-H str.), 1550 (furan), 742 (C–H ban.); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (d, 1H, *J* = 8.53 Hz), 7.89 (s, 1H), 7.62 (dd, 1H, *J* = 1.70, 8.56 Hz), 7.24 (s, 4H), 7.42 (s, 6H), 5.73 (s, 1H), 5.82 (d, 2H, *J* = 5.23), 3.58 (s, 4H); MS (FAB) *m*/*z*: 509.81(m^+), 145.00 (100%); $C_{32}H_{23}N_5O_2$ (509.57): Calcd: C, 75.43; H, 4.55; N, 13.75; O, 6.28. Found: C, 75.40; H, 4.18; N, 13.86. IPB-14: Light brown solid was recrystallized from methanol; yield: 92%, mp: 173–175 °C, R_f = 0.89 (benzene:ethyl acetate, 4:1); λ_{max}: 348.7 nm; IR (KBr) ν_{max} (cm^{-1}): 2933, 1610, 978 (R–CH = CHR); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.44 (d, 1H, *J* = 8.60 Hz), 7.78 (s, 1H), 7.55 (dd, 1H, *J* = 2.70, 8.20 Hz), 7.32 (s, 4H), 7.60 (s, 6H), 3.52 (s, 4H); MS (FAB) *m*/*z*: 549.17(m^+), 145.10 (100%); $C_{35}H_{27}N_5O_2$ (549.63): Calcd: C, 76.49; H, 4.95; N, 12.74; O, 5.82. Found: C, 76.90; H, 4.13; N, 12.56.
20. General procedure for the synthesis of (2*E*)-1-(1-benzofuran-2-yl)-4-phenylbut-2-en-1-ones (benzofuran chalcones)[21–23] **6** from 2-acetyl benzofuran (0.05 mol) and different aromatic aldehydes (0.05 mol) were taken in 20 mL of ethanol (98%) in 50 mL conical flask made up of borosil. To

that added 20% KOH/NaOH solution (8 mL), and covered the flask with small funnel (borosilicate). The flask was placed in a microwave oven at 30% (240 W) energy level for 8 min. The resulted solution was poured in 100 mL ice-cold water, and acidified with concd HCl. Excess of solvent was removed under reduced pressure and solid was obtained by filtration.

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