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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of some (3-phenyl-5-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanones: new derivatives of 1,3,5-trisubstituted pyrazolines

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Abstract A series of (3-phenyl-5-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl) methanones was synthesized by condensing suitably substituted chalcones, i.e., 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-ones, and isoniazid in acetic acid. The structure of newly synthesized compounds has been established on the basis of analytical and spectral data. The new compounds were screened for antimicrobial activity and most of them showed good activity comparable with that of standard drugs ciprofloxacin and fluconazole. Compounds containing methoxy group showed high antimicrobial activity.

Keywords Pyrazole · Isoniazid · Chalcones · Pyrazoline · Antimicrobial activity

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Introduction

Nitrogen containing heterocyclic compounds are core structure of numerous biological active compounds and exhibit wide varieties of application in pharmacological and agrochemical industries. Pyrazole motif and its derivatives are well established in literature as important biologically active heterocyclic compounds due to their widespread potential pharmacological activities such as anti-inflammatory (Tewari and Mishra, 2001), antipyretic (Wiley and Wiley, 1964), antimicrobial (Sridhar *et al.*, 2004), antiviral (Janus *et al.*, 1999), antitumour (Xia *et al.*, 2007), anticonvulsant (Michon *et al.*, 1995), and antidepressant (Bailey *et al.*, 1985) activities. The widely prescribed anti-inflammatory pyrazole derivatives, celecoxib (Cheng *et al.*, 2006) and deracoxib (Chowdhury *et al.*, 2008; Abdel-Hafez *et al.*, 2009) are selective COX-2 inhibitors with reduced ulcerogenic side effects.

Isoniazid, a first line drug used in the treatment of tuberculosis, is a prodrug, which is transformed to isonicotinic acid (Marrakchi *et al.*, 2000), isonicotinamide, and isonicotinaldehyde on the surface of *M. tuberculosis* by KatG enzyme (Nguyen *et al.*, 2002; Argyrou *et al.*, 2006). Literature survey shows that none of the stable derivatives of isonicotinic acid, isonicotinamide, and isonicotinaldehyde has demonstrated bactericidal effect (Johnsson *et al.*, 1995). Thus, it is presumed that the activity of isoniazid is due to the reaction of a reactive intermediate species with the β-nicotinamide adenine dinucleotide (NAD^+/NADH), which is a cofactor of the long-chain 2-*trans*-enoyl-acyl carrier protein reductase InhA (Delaine *et al.*, 2007; Quémard *et al.*, 1996), a key enzyme involved in the biosynthesis of mycolic acids, specific components of the mycobacterial cell wall (Daffé and Draper, 1998). Isoniazid may be bacteriostatic or bactericidal in action, depending on

the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division (Sriram and Yogeeshwari, 2008).

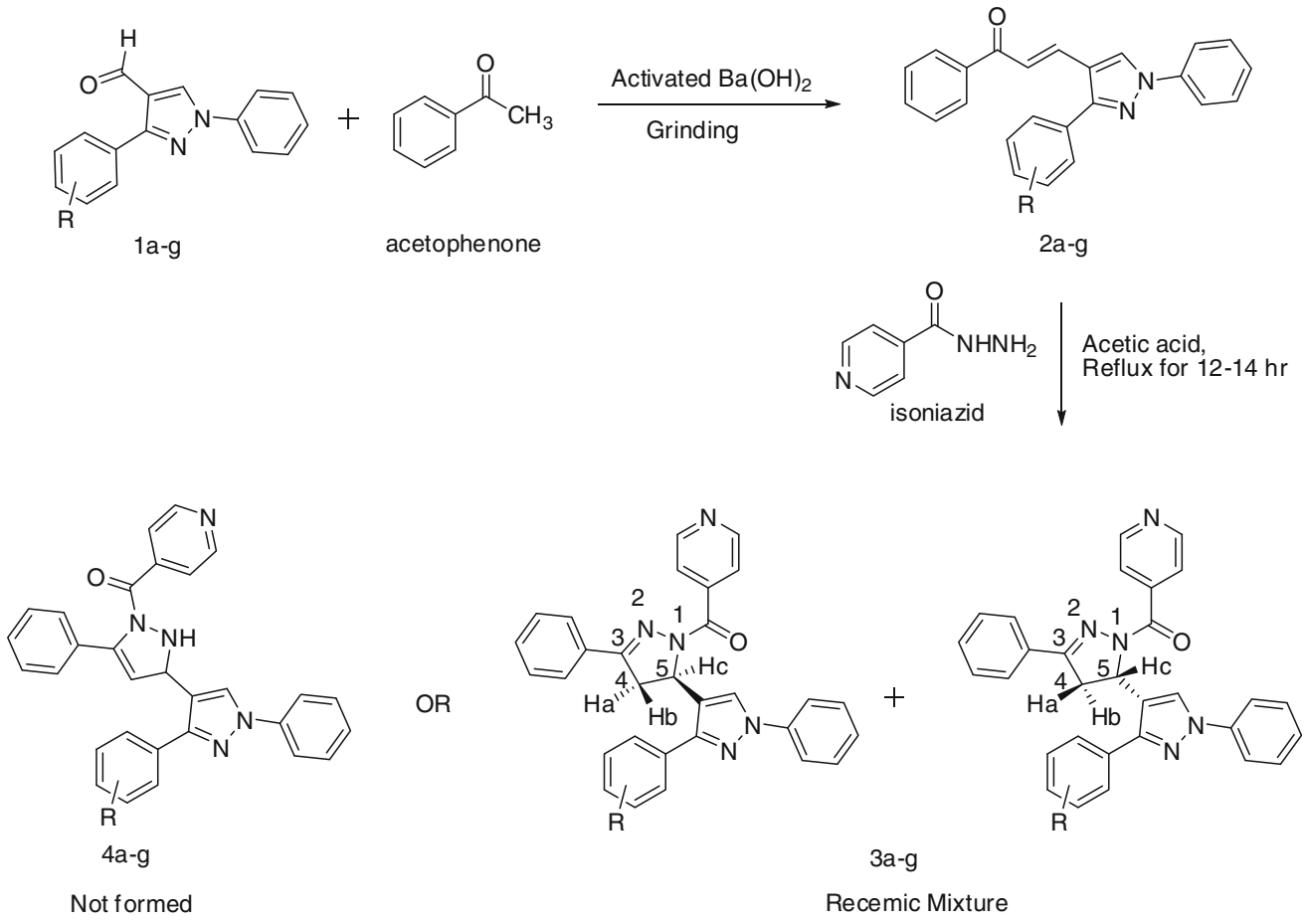
Diverse pharmacological activities such as anti-inflammatory (Sharma *et al.* 2010), anti-hypertensive (Turan-Zitouni *et al*. 2000), antimicrobial (Manna and Agrawal, 2009), anticancer (Shaharyar *et al.*, 2010), antimalarial (Acharya *et al*., 2010), antidepressant (Prasad *et al.*, 2005), anticonvulsant (Ozdemir *et al.*, 2007), antioxidant (Jeong *et al.*, 2004) and MAO inhibitors (Jagrat *et al.*, 2011) have been reported for pyrazoline derivatives. Recently Ali et al. (2007) and Acharya *et al*., (2010) have reported that 1,3,5-trisubstituted pyrazolines having isonicotinyl or nicotinyl group at 1-position exhibit anti-HIV and antimalarial activity, respectively.

Keeping the above observation in our mind and in continuation of our program on the synthesis of biological active heterocyclic compounds (Kumar, 2009; Kumar and Kumar, 2010; Kumar *et al*. 2011a, b), we planned to synthesize (3-phenyl-5-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanones: new derivatives of 1,3,5-trisubstituted pyrazoline.

Result and discussion

Chemistry

The synthetic scheme used for the synthesis of (3-phenyl-5-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanones (**3a**–**g**) is outlined in Scheme 1. First, 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-ones (**2a**–**g**) were synthesized by grinding the pyrazole aldehydes and acetophenone with activated barium hydroxide in a mortar and pestle without solvent (Kumar *et al*., 2011a, b). Then these propenone derivatives were condensed with isoniazid by refluxing in glacial acetic acid for 12–14 h. After



R= (a) 4-OCH_3; (b) 2-OCH_3;(c) 4-CH_3; (d) 4-F; (e) 4-Cl; (f) 4-Br; (g) H

Scheme 1 Synthesis of 1,3,5-trisubstituted pyrazolines

completion of reaction (TLC), the reaction mixture was poured on to crushed ice and recrystallized the filtered product with ethanol, afforded the final products **3a–g** in 70–80 % yields. No electronic effects of substituent were observed. The purity of compounds was checked by TLC. Spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and mass) of newly synthesized compounds **3a–g** were in full agreement with their proposed structure. The IR spectra of compounds **3a–g** exhibited characteristic peak at 1628–1643 cm^{-1} due to the presence of isonicotinyl group. In ^{1}H-NMR, the signals of the respective protons of the prepared titled compounds **3a–g** were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra of **3a** showed three doublet of doublets (dd) at δ for C_5-Hc = 5.925, Hb = 3.361, C_4-Ha = 3.608 ppm with coupling constants $J_{a,b}$ = 17.7 Hz (*geminal*), $J_{a,c}$ = 11.7 Hz (*cis*), $J_{b,c}$ = 4.5 Hz (*trans*) corresponding to methyne proton and methylene protons. In case of chalcones of formyl pyrazole **2a–g**, the pyrazolyl proton which resonated as a singlet at 8.3–8.5 ppm, showed a significant downfield shift in **3a–g** and it appeared as a singlet at 7.9–8.0 ppm. Hence, three dd with different *J* values indicate the formation of only pyrazoline **3a–g** and not the other isomer **4** (Scheme 1). ^{1}H-NMR spectra also clearly indicates that Ha and Hb are diastereotropic hydrogens.

Biological result and discussion

All the newly synthesized compounds **3a–g** have been evaluated for their antibacterial and antifungal activity against five standard bacterial species including gram-positive (*Staphylococcus aureus*, *Bacillus pumilis*, and *Bacillus subtilis*) and gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria and four standard fungi (*Candida albicans*, *Candida tropicalis*, *Aspergillus niger*, and *Aspergillus flavus*). Antimicrobial activity tests were performed by using a broth micro dilution method (NCCLS, 2000; Lorian, 1986) and results are summarized in Table 1.

All the newly synthesized compounds (**3a–g**) showed the promising antimicrobial activity against different strains of bacterium and fungus. Compounds bearing methoxy group (**3a**, **3b**) showed highest activity against different strains of bacterium and fungus. Only compound **3b** displayed broad spectrum antimicrobial activity. The higher antifungal activity of *ortho*-methoxy substituent may be due to position of oxygen of methoxy group in relation to the heterocyclic ring. As can be seen in Fig. 1, the heterocyclic ring and methoxy group in the synthesized compound are almost overlapping triazole and hydroxyl group in fluconazole. In many antifungal agents like Econazole, Miconazole, Ticonazole, and Fenticonazole, oxygen atom is placed at ortho like position to heterocyclic ring. The better activity of fluoro and chloro derivatives than bromo is a general trend in antimicrobials, e.g., fluoroquinolones and griseofulvin (Foye *et al*., 1995).

Conclusion

Outcome of the condensation reactions of isoniazid with pyrazole chalcones may result the formation of recemic mixture (**3a–g**), where C_4-atom indicates the chiral center and protons on adjacent carbon atom C_5 are diastereotropic in nature. It is shown by coupling constant of Ha and Hb with Hc [$J_{a,c}$ = 11.7 Hz (*cis*), $J_{b,c}$ = 4.5 Hz (*trans*)].

By comparing the antibacterial and antifungal potential of compounds with different substituent, the following conclusions were drawn: (a) the presence of methoxy group increases the antimicrobial activity of compounds, (b) at *ortho* position methoxy group increases antifungal activity also, (c) out of halogen substituted pyrazolines, fluorine substituted pyrazoline have maximum antimicrobial activity, (d) all compounds are more active against bacterium in comparison to fungus strain.

Table 1 MIC of synthesized compounds

S. no.	Compounds	Microorganisms and MIC (mg/L)								
		S. aureus	*B. pumilis*	*B. subtillus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. tropicalis*	*A. niger*	*A. flavus*
1	**3a**	6.25	6.25	6.25	6.25	12.5	12.5	12.5	50	50
2	**3b**	6.25	6.25	6.25	6.25	6.25	6.25	6.25	50	50
3	**3c**	6.25	12.5	12.5	12.5	25	25	50	100	100
4	**3d**	6.25	25	12.5	12.5	12.5	50	50	200	200
5	**3e**	12.5	25	25	25	25	100	100	>200	200
6	**3f**	12.5	25	25	50	50	50	100	>200	200
7	**3g**	25	50	50	50	50	200	200	100	>200
8	Ciprofloxacin	3.125	3.125	3.125	3.125	3.125				
9	Fluconazole						3.125	6.25	12.5	12.5

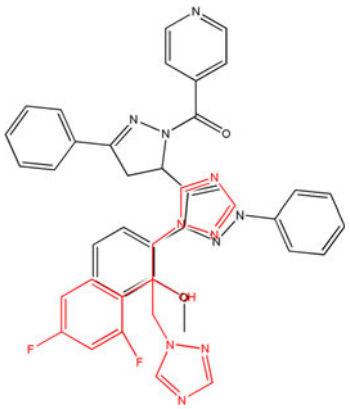


Fig. 1 Overlapping of compound **3b** with fluconazole

Antimicrobial activity

Microdilution assays

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, **3a**–**g**, defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards. The inocula of microorganisms (10^6 cfu/mL) were prepared from 24 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity (McFarland, 1907). The test compound dissolved in dimethyl sulfoxide (DMSO) was first diluted to the highest concentration (800 μg/mL) to be tested. Then serial twofold dilutions were made in concentration ranges from 1.562 to 800 μg/mL in 10 mL sterile tubes. A prepared suspension of the standard microorganisms was added to each dilution in a 1:1 ratio. Growth (or its lack) of microorganisms was determined visually after incubation for 24 h at 37 °C. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. The MIC values were studied for five reference bacterial (*Staphylococcus aureus*, *Bacillus pumilis*, *Bacillus subtillus*, *Escherichia coli*, and *Pseudomonas aeruginosa*) and three fungal (*Candida albicans, Aspergillus niger*, and *Aspergillus flavus*) strains. In this case, ciprofloxacin and fluconazole were used as standard drugs for comparison in the antimicrobial study. Control experiments using DMSO were done for antimicrobial activity studies.

Experimental

All chemicals (Qualigens) used in this study were of the highest purity available and purchased from local vendors. Melting points were determined on a buchi oil heated melting apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker (400, 300, and 200 MHz) spectrometer using TMS as internal standard (chemical shift in δ, ppm). IR spectra were taken on a Perkin Elmer 1600, FTIR spectrophotometer using KBr pellets. The elemental analyses were performed on a Carlo Erba 1106 elemental analysis. TLC was run on silica gel G plates using acetone–benzene (1:3) as irrigant.

All the starting pyrazole aldehydes and their chalcones with acetophenone were prepared according to literature procedures (Kumar *et al*., 2011a, b).

General procedure for the synthesis of pyrazole substituted chalcones (**2a**–**g**) with activated barium hydroxide

A mixture of acetophenone (4 mmol), pyrazole aldehyde (4 mmol) and activated barium hydroxide (C-200) (1.515 g, 8 mmol) was blended thoroughly in mortar and pestle and resulting homogeneous mixture was ground at room temperature for 5–10 min. The completion of reaction was indicated by wetting with formation of yellow colored reaction mixture. The progress of reaction was monitored by TLC. 30 g crushed ice was added to the reaction mixture and acidified with conc HCl. Filtered the yellow colored product on suction pump and recrystallized the product from isopropyl alcohol. Spectra of some representative chalcones:

*1-Phenyl-3-[3-(4-methoxyphenyl)-1-phenyl-4-pyrazolyl]prop-2-en-1-one (**2a**)*

M.p.: 164–166 °C. IR (ν_{max}, in KBr): 3033, 3011, 1653, 1601, 1427, 1322, 1300, 1242, 966, 847, 754. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.74 (s, 3H, OCH_3); 7.31–8.00 (m, 16H, ArH, C_2-H, C_3-H); 8.35 (s, 1H, pyrazolyl-H). Anal. Calcd. for $C_{25}H_{20}N_2O_2$; C, 78.93; H, 5.30; N, 7.36. Found C 79.08, H 5.42, N 7.45.

*1-Phenyl-3-[3-(2-methoxyphenyl)-1-phenyl-4-pyrazolyl]prop-2-en-1-one (**2b**)*

M.p.: 156–158 °C. IR (ν_{max}, in KBr): 1654 cm^{-1} (CO stretch) 3062, 3019, 1654, 1589, 1511, 1422, 1237, 1101, 1057, 966, 832, 787. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.786 (s, 3H, OCH_3); 7.017(d, 1H, $J = 8.04$ Hz); 7.073 (t, 1H, $J = 7.36$ Hz); 7.126 (1H, d, $J = 16.12$ Hz); 7.304 (t, 1H, $J = 7.29$ Hz); 7.409–7.518 (m, 7H); 7.675 (1H, d, $J = 16.12$ Hz); 7.759 (2H, d, $J = 8.08$); 7.853 (2H, m); 8.318 (s, 1H, pyrazolyl-H). Anal. Calcd. for $C_{25}H_{20}N_2O_2$; C, 78.93; H, 5.30; N, 7.36. Found C 78.98, H 5.18, N 7.41.

*1-Phenyl-3-[3-(4-bromophenyl)-1-phenyl-4-pyrazolyl]prop-2-en-1-one (**2f**)*

M.p.: 162–164 °C. IR (ν_{max}, in KBr): 3077, 3012, 1653, 1588, 1522, 1431, 1220, 1166, 827, 765, 689, 638. ^{1}H

NMR ($CDCl_3$, 400 MHz, δ): 7.344 (d, 1H, $J = 8.04$ Hz); 7.359 (d, 1H, $J = 14.40$ Hz); 7.456–7.619 (m, 9H); 7.767 (d, 2H, $J = 7.32$ Hz); 7.823 (d, 1H, $J = 14.40$ Hz); 7.948 (d, 2H, $J = 7.32$ Hz) 8.336 (s, 1H, pyrazolyl-H). Anal. Calcd. for $C_{24}H_{17}BrN_2O$; C 67.14; H 3.99; N 6.53. Found C 67.34, H 4.11, N 6.48.

General procedure for the synthesis of (3-phenyl-5-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanones

To the solution of the appropriate pyrazole chalcone (5 mol) (**2a–g**) in 20 mL of acetic acid, isoniazid (5 mol) was added and the reaction mixture was refluxed for 8–10 h. Progress of reaction was monitored on TLC. After completion of reaction, the reaction mass was poured on to crushed ice. The products thus separated were filtered and recrystallized from ethanol to give final products. Purity of the products was checked by TLC.

[5-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl)methanone (**3a**)

Yield: 76 %, m.p.: 270–272 °C. IR (KBr, cm^{-1}): 3056, 3020, 2988, 1643, 1597, 1504, 1435, 1335, 1296, 1250, 1173, 1065, 1034, 964, 833, 756, 687, 609. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 3.207 (Hb, dd, $J_{b,c} = 4.7$ Hz, and $J_{b,a} = 17.7$ Hz), 3.699 (Ha, dd, $J_{a,c} = 11.7$ Hz and $J_{a,b} = 17.7$ Hz), 3.810 (3H, s, CH_3), 6.072 (Hc, dd, $J_{c,a} = 11.7$ Hz and $J_{c,b} = 4.7$ Hz), 6.955 (2H, d, $J = 8.8$ Hz), 7.267–7.453 (6H, m), 7.601–7.715 (6H, m), 7.845 (2H, d, $J = 5.9$ Hz), 7.887 (1H, s, pyrazolyl-H), 8.737 (2H, d, $J = 5.9$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.48, 158.20, 156.28, 150.45, 149.87, 141.66, 139.88, 133.19, 130.81, 130.37, 129.34, 129.31, 128.77, 128.66, 128.39, 128.25, 126.88, 126.57, 126.22, 125.85, 119.10, 114.79, 114.73, 55.65, 53.84, 41.35. Mass: *m/z*: 500.32 (M + 1). Anal. Calcd. for $C_{31}H_{25}N_5O_2$: C, 74.53; H, 5.04; N, 14.02. Found: C, 74.71; H, 5.09 N, 14.18.

[5-(3-(2-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl)methanone (**3b**)

Yield: 80 %, m.p.: 128–130 °C. IR (KBr, cm^{-1}): 3055, 3022, 2987, 1636, 1597, 1551, 1504, 1435, 1335, 1242, 1119, 1057, 1026, 964, 833, 756, 687, 617. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ): 3.361 (Hb, dd, $J_{b,c} = 4.8$ Hz, and $J_{b,a} = 17.7$ Hz), 3.608 (Ha, dd, $J_{a,c} = 11.7$ Hz and $J_{a,b} = 17.7$ Hz), 3.698 (3H, s, CH_3), 5.925 (Hc, dd, $J_{c,a} = 11.7$ Hz and $J_{c,b} = 4.5$ Hz), 6.840 (1H, d, $J = 8.4$ Hz), 6.994 (1H, t, $J = 7.2$ Hz), 7.328 (1H, d, $J = 7.5$ Hz), 7.339–7.481 (6H, m, $J = 8.4$ Hz, $J = 8.7$ Hz and $J = 7.5$ Hz), 7.617 (2H, d, $J = 7.5$ Hz), 7.703–7.745 (4H, m, $J = 4.8$ Hz and $J = 7.8$ Hz), 7.980 (1H, s, pyrazolyl-H), 8.736 (2H, d, $J = 5.1$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.48, 157.99, 156.30, 150.41, 149.91, 141.62, 139.75, 133.23, 130.78, 130.33, 129.39, 129.33, 128.66, 128.41, 128.22, 126.58, 126.23, 125.78, 119.78, 118.98, 111.26, 56.10, 53.66, 41.42. Mass, *m/z*: 500.30 (M + 1). Anal. Calcd. for $C_{31}H_{25}N_5O_2$: C, 74.53; H, 5.04; N, 14.02. Found: C, 74.66; H, 5.15; N, 14.22.

(3-Phenyl-5-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone (**3c**)

Yield: 75 %, m.p.: 232–234 °C. IR (KBr, cm^{-1}): 3051, 2987, 1643, 1597, 1551, 1504, 1435, 1335, 1234, 1065, 964, 825, 756, 687, 625. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 2.371 (3H, s, CH_3), 3.204 (Hb, dd, $J_{b,c} = 4.7$ Hz, and $J_{b,a} = 17.6$ Hz), 3.703 (Ha, dd, $J_{a,c} = 11.6$ Hz and $J_{a,b} = 17.6$ Hz), 6.090 (Hc, dd, $J_{c,a} = 11.6$ Hz and $J_{c,b} = 4.7$ Hz), 7.216–7.453 (8H, m), 7.609–7.765 (6H, m), 7.846 (2H, d, $J = 5.9$ Hz), 7.885 (1H, s, pyrazolyl-H), 8.736 (2H, d, $J = 5.9$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.42, 156.35, 150.48, 149.78, 141.71, 139.78, 133.11, 130.81, 130.33, 129.35, 129.33, 128.75, 128.65, 128.36, 128.24, 126.83, 126.53, 126.35, 125.76, 119.10, 53.66, 41.33, 21.28. Mass: *m/z*: 484.2093 (M + 1). Anal. Calcd. for $C_{31}H_{25}N_5O$: C, 77.00; H, 5.21; N, 14.48. Found: C, 77.12; H, 5.32; N, 14.61.

(5-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone (**3d**)

Yield: 70 %, m.p.: 242–244 °C. IR (KBr, cm^{-1}): 3066, 2991, 1640, 1592, 1555, 1499, 1431, 1336, 1228, 1071, 959, 821, 759, 682. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 3.205 (Hb, dd, $J_{b,c} = 4.7$ Hz, and $J_{b,a} = 17.6$ Hz), 3.729 (Ha, dd, $J_{a,c} = 11.6$ Hz and $J_{a,b} = 17.6$ Hz), 6.042 (Hc, dd, $J_{c,a} = 11.6$ Hz and $J_{c,b} = 4.7$ Hz), 7.133–7.462 (8H, m), 7.462–7.786 (6H, m), 7.838 (2H, d, $J = 5.7$ Hz), 7.883 (1H, s, pyrazolyl-H), 8.738 (2H, d, $J = 5.7$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.49, 161.98, 156.32, 150.39, 149.91, 141.64, 139.79, 133.23, 130.79, 130.39, 129.36, 129.29, 128.76, 128.59, 128.40, 128.29, 126.86, 126.58, 126.25, 125.91, 119.15, 116.79, 116.70, 53.85, 41.39. Mass: *m/z*: 488.1842 (M + 1). Anal. Calcd. for $C_{30}H_{22}FN_5O$: C, 73.91; H, 4.55; N, 14.37. Found: C, 74.05; H, 4.66; N, 14.48.

(5-(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone (**3e**)

Yield: 76 %, m.p.: 254–256 °C. IR (KBr, cm^{-1}): 3077, 3042, 2966, 1645, 1596, 1545, 1500, 1423, 1340, 1219, 1157, 1066, 827, 764, 688, 638. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 3.202 (Hb, dd, $J_{b,c} = 4.7$ Hz, and $J_{b,a} = 17.5$ Hz), 3.734 (Ha, dd, $J_{a,c} = 11.6$ Hz and $J_{a,b} = 17.5$ Hz), 6.052 (Hc, dd, $J_{c,a} = 11.6$ Hz and $J_{c,b} = 4.7$ Hz), 7.315–7.502 (8H, m), 7.621–7.786 (6H, m), 7.840 (2H, d, $J = 5.7$ Hz), 7.887 (1H, s, pyrazolyl-H), 8.783 (2H, d, $J = 5.7$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.40, 156.32, 149.82, 139.68, 134.77, 132.81, 131.96, 131.82, 130.99, 130.51, 130.28, 130.06, 129.58, 129.45, 128.86, 128.62, 127.40, 126.80, 125.87, 121.95, 121.87, 119.41, 119.21, 53.47, 41.49. Mass: *m/z*: 504.1546, 506.1517 (M + 1), Anal. Calcd. for $C_{30}H_{22}ClN_5O$: C, 71.49; H, 4.40; N, 13.90. Found: C, 71.61; H, 4.46; N, 14.02.

(5-(3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone (**3f**)

Yield: 73 %, m.p.: 236–238 °C. IR (KBr, cm^{-1}): 3033, 2991, 1640, 1600, 1535, 1504, 1435, 1328, 1288, 1219, 1173, 1142, 1072, 1011, 963, 826, 760, 687, 625. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 3.197 (Hb, dd, $J_{b,c} = 4.7$ Hz, and $J_{b,a} = 17.6$ Hz), 3.736 (Ha, dd, $J_{a,c} = 11.5$ Hz and $J_{a,b} = 17.6$ Hz), 6.049 (Hc, dd, $J_{c,a} = 11.5$ Hz and $J_{c,b} = 4.7$ Hz), 7.386–7.452 (7H, m), 7.549–7.705 (7H, m), 7.835 (2H, d, $J = 5.8$ Hz), 7.886 (1H, s, pyrazolyl-H), 8.782 (2H, d, $J = 5.8$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.38, 156.30, 149.84, 139.63, 134.84, 132.79, 131.98, 131.86, 131.00, 130.65, 130.30, 130.12, 129.63, 129.42, 128.88, 128.64, 127.45, 126.83, 125.93, 123.67, 122.60, 121.97, 121.89, 119.42, 119.19, 53.49, 41.50. Mass: *m/z*: 548.15 (100.0 %), 550.22 (97.3 %). Anal. Calcd. for $C_{30}H_{22}BrN_5O$: C, 65.70; H, 4.04; N, 12.77. Found: C, 65.84; H, 4.11; N, 12.93.

(5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone (**3g**)

Yield: 75 %, m.p.: 246–248 °C. IR (KBr, cm^{-1}): 3078, 3066, 1628, 1597, 1551, 1504, 1435, 1373, 1353, 1242, 1157, 1103, 1034, 918, 825, 756, 694, 617. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 3.217 (Hb, dd, $J_{b,c} = 4.8$ Hz, and $J_{b,a} = 17.6$ Hz), 3.718 (Ha, dd, $J_{a,c} = 11.5$ Hz and $J_{a,b} = 17.6$ Hz), 6.093 (Hc, dd, $J_{c,a} = 11.5$ Hz and $J_{c,b} = 4.8$ Hz), 7.383–7.477 (8H, m), 7.676–7.807 (7H, m), 7.835 (2H, d, $J = 5.9$ Hz), 7.897 (1H, s, pyrazolyl-H), 8.788 (2H, d, $J = 5.9$ Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.44, 156.39, 150.70, 149.86, 141.66, 139.81, 133.15, 130.93, 130.83, 129.42, 129.36, 128.86, 128.74, 128.57, 128.45, 128.34, 126.90, 126.69, 126.64, 125.87, 123.76, 121.88, 119.19, 53.69, 41.53. Mass: 469.1903 *m/z*: 470.25 (M + 1). Anal. Calcd. for $C_{30}H_{23}N_5O$: C, 76.74; H, 4.94; N, 14.92. Found: C, 76.91; H, 5.07; N, 15.11.

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