ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 10, pp. 1795–1800. © Pleiades Publishing, Ltd., 2020.

Synthesis, Characterization, and Comparative Study of Some Heterocyclic Compounds Containing Isoniazid and Nicotinic Acid Hydrazide Moieties

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Received May 25, 2020; revised June 10, 2020; accepted June 16, 2020

Abstract—Some new derivatives of six-membered heterocyclic compounds containing isoniazid and nicotinic acid hydrazide fragments have been synthesized according to green procedures with excellent yields. The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, IR, and mass spectra and elemental analyses. The compounds were screened for their in vitro antibacterial and antifungal activities. The results showed that the isoniazid derivatives are more active than their analogs containng a nicotinic hydrazide moiety.

Keywords: isoniazid, nicotinic hydrazide, antimicrobial activity

DOI: 10.1134/S1070428020100218

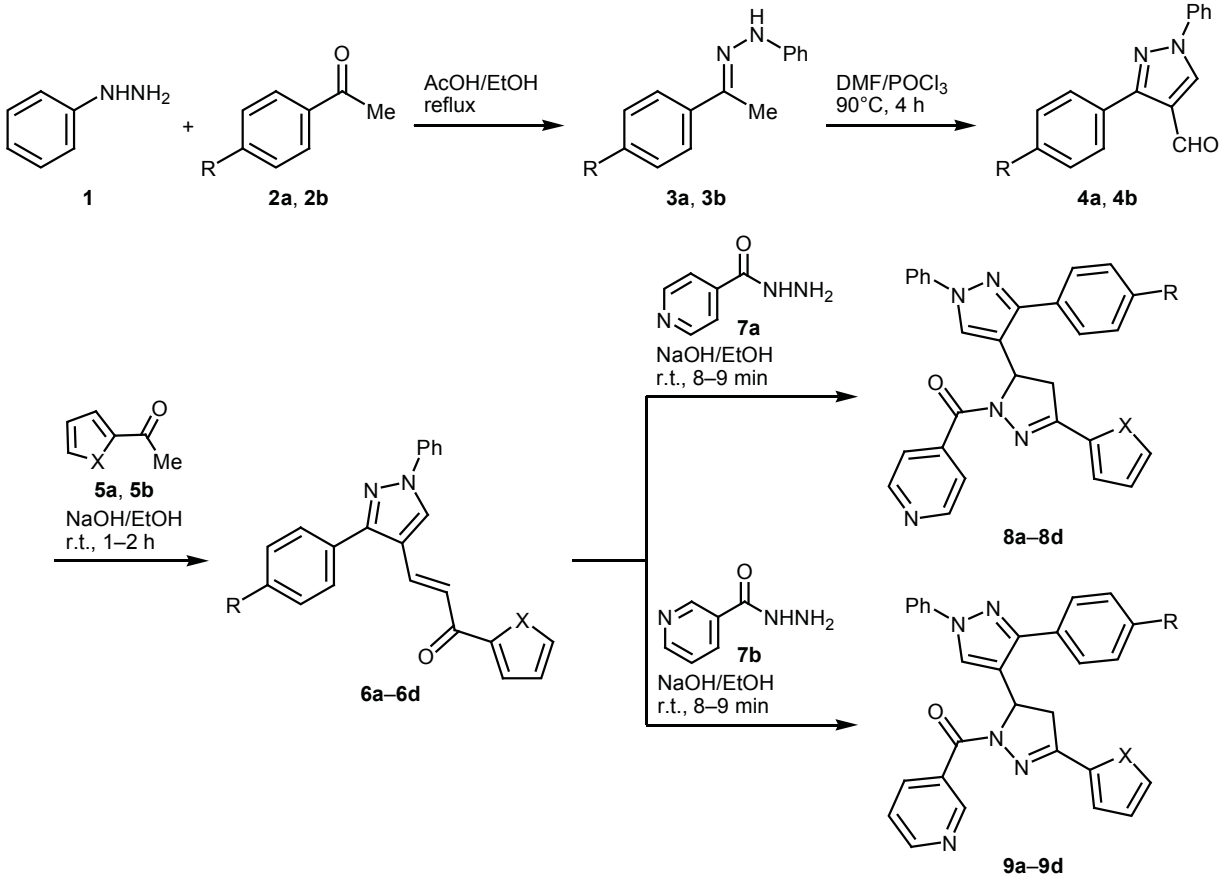
INTRODUCTION

Investigation of heterocyclic compounds is an interesting topic from both theoretical and practical points of view. There are a huge number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Nitrogen heterocycles are most copious in nature than those containing oxygen or sulfur. Heterocyclic compounds are crucial to life in different ways. Most of sugars and their derivatives, including vitamins and some members of vitamin B group, have heterorings with a nitrogen atom. Analysis of the US FDA-approved drugs database shows that 59% of small-molecule drugs contain nitrogen heteroatom in a heterocycle [1]. Nitrogen-containing six-membered heterocyclic compounds have acquired enormous significance in the field of drug discovery. In this work we report the synthesis and comparative study of antimicrobial activities of two types of six-membered heterocyclic compounds derived from isoniazid and nicotinic acid hydrazide. Isoniazid is isonicotinic acid hydrazide which plays a vital role in the manufacture of various drugs such as anticancer, antitubercular, antifungal, antibacterial, and antiviral agents [2–5]. Nicotinic acid hydrazide which is isomeric to isoniazid has multiple applications and has long been known as biologically active compound. Pyridine derivatives have remarkable pharmaceutical importance because of their biological activity as anti-HIV [6], antitubercular, antimicrobial [7], antidiabetic [8], anti-inflammatory [9], antiplasmodial [10], and anticancer [11] activities. Our goal was to synthesize and evaluate biological activity of some isoniazid and nicotinic acid hydrazide derivatives.

RESULTS AND DISCUSSION

In this study, new series of bipyrazole derivatives bearing isoniazid and nicotinic acid hydrazide moieties were synthesized as shown in Scheme 1. The starting compounds, 1*H*-pyrazole-4-carbaldehydes **4a** and **4b** were prepared by the Vilsmeier–Haack reaction according to literature procedure [12]. The key intermediates, chalcones **6a**–**6d** were synthesized in good to excellent yields by base-catalyzed Claisen–Schmidt condensation of aldehydes **4a** and **4b** with 2-acetylthiophene (**5a**) and 2-acetylfuran (**5b**) in the presence of NaOH (5 mol %) in aqueous ethanol at room temperature. Finally, cyclization of **6a**–**6d** with isoniazid and nicotinic acid hydrazide using NaOH as catalyst in ethanol

Scheme 1.



R = H (**a**, **b**), MeO (**c**, **d**); X = S (**a**, **c**), O (**b**, **d**).

at room temperature afforded target compounds **8a**–**8d** and **9a**–**9d**, respectively (Scheme 1).

The structure of **8a**–**8d** and **9a**–**9d** was confirmed by elemental analyses and FT-IR, ^{1}H and ^{13}C NMR, and mass spectra. In the IR spectra of **8a**–**8d** and **9a**–**9d**, the C–H stretching band was observed at 2925–3025 cm^{-1}, and the C=N and C=O stretchings were observed at 1587–1610 and 1685–1710 cm^{-1}, respectively. In the ^{1}H NMR spectra of these compounds, the 4-H protons of the dihydropyrazole ring resonated as multiplets at δ 3.29–3.45 and 4.05-4.17 ppm. The 5-H proton of the same ring appeared as a multiplet at δ 5.82–5.99 ppm due to vicinal coupling with the two magnetically nonequivalent protons on C^4. The mass spectra of all compounds **8** and **9** showed the molecular ion peak in conformity with the assigned structure.

All compounds **8a**–**8d** and **9a**–**9d** were screened for their antibacterial and antifungal activities using the broth dilution method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [13, 14]. Mueller–Hinton broth was used as the nutrient medium for the test bacteria, and Sabouraud dextrose broth was used for fungi. The inoculum size for the test strains was adjusted to 10^8 CFU per milliliter according to the McFarland turbidity standards. Each compound was dissolved in DMSO to a stock concentration of 2000 μg/mL. Primary and secondary screenings were performed. All compounds were screened for their antibacterial activity against *Bacillus subtilis* (MTCC 441), *Clostridium tetani* (MTCC 449), *Staphylococcus aureus* (MTCC 96), *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 98), *Candida albicans* (MTCC 227), and *Trichophyton rubrum* (MTCC 296) at concentrations of 1000, 500, and 250 μg/mL for primary screening. Stock solutions were diluted with DMSO to get the desired concentration. The compounds that showed antimicrobial activity in the primary screening were further screened at concentrations of 200, 100, 62.5, 50, and 25 μg/mL. A 10-μL portion of each solution was inoculated in a 96-well plate, and microbial growth was noted after 24 and 48 h. The lowest concentration at which no visible growth (turbidity) was observed was considered as the mini-

Table 1. In vitro antimicrobial activity of compounds **8a**–**8d** and **9a**–**9d** (MIC, μg/mL)

Compd. no.	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	B. subtilis	*C. tetani*	*S. aureus*	*E. coli*	*S. typhi*	*V. cholerae*	*C. albicans*	*T. rubrum*
8a	250	250	500	200	200	250	>1000	>1000
8b	**100**	**50**	500	500	500	**100**	500	500
8c	250	**100**	125	200	250	**200**	1000	500
8d	200	250	**62.5**	250	250	**200**	1000	1000
9a	500	250	250	250	250	500	1000	1000
9b	500	**200**	200	200	200	500	500	500
9c	250	**200**	250	200	250	250	1000	>1000
9d	125	500	500	125	**100**	**100**	**250**	**100**
Ampicillin	100	250	100	100	100	250	–	–
Chloramphenicol	50	50	50	50	50	50	–	–
Ciprofloxacin	50	100	25	25	25	50	–	–
Norfloxacin	10	50	10	10	10	100	–	–
Nystatin	–	–	–	–	–	–	100	100
Griseofulfin	–	–	–	–	–	–	500	100

mum inhibitory concentration (MIC). Ampicillin, chloramphenicol, ciprofloxacin, and norfloxacin were used as standard antibacterial drugs, and nystatin and griseofulvin were used as standard antifungal drugs. The results are summarized in Table 1.

Isoniazid derivatives **8a**–**8d** showed a good antibacterial activity compared to nicotinic acid hydrazide derivatives **9a**–**9d**. Compound **8b** was found to be equipotent to ampicillin against gram-positive *B. subtilis* (MIC 100 μg/mL), and its activity against *C. tetani* (MIC 50 μg/mL) was higher than those of ampicillin (MIC 250 μg/mL) and ciprofloxacin (MIC 100 μg/mL) and was comparable to that of norfloxacin. The activity of **8c** against *C. tetani* (MIC 100 μg/mL) was similar to that of ciprofloxacin. Compound **8d** was more active than ampicillin against *S. aureus* (MIC 62.5 and 100 μg/mL, respectively), whereas its activity against gram-negative *E. coli* was comparable to the activity of ampicillin (MIC 100 μg/mL). The synthesized isoniazid derivatives showed moderate to good antifungal activity, whereas the nicotinic acid hydrazide derivatives showed moderate to low antifungal activity. Thus, isoniazid derivatives **8a**–**8d** proved to be more effective against all microorganisms than nicotinic hydrazide derivatives **9a**–**9d**.

EXPERIMENTAL

All reagents (analytical grade) were purchased from Sigma–Aldrich and were used without further purification. The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel 60 F_{254} (Merck); layer thickness 0.25 mm. The components were visualized by exposure to UV light or iodine vapor. The melting points were measured in open capillary tubes on an Electrothermal melting point apparatus. The IR spectra were recorded with a FTIR MB 3000 spectrophotometer using ZnSe optics (490–8500 cm^{-1}). The mass spectra were recorded on a Shimadzu LCMS 2010 spectrometer (Japan). The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively, using the residual proton and carbon signals of the solvent as internal standard. The elemental analysis was done with a Perkin Elmer 2400 Series II elemental analyzer (USA).

General procedure for the synthesis of 1-phenyl-2-[1-(4-R-phenyl)ethylidene]hydrazines 3a and 3b. Phenylhydrazine (0.1 mol) and 3-4 drops of acetic acid were added to a solution of acetophenone or *p*-methoxyacetophenone (0.1 mol) in anhydrous ethanol (20 mL), and the mixture was stirred at 70–80°C for 1 h. The mixture was then left to stand at room temperature, and the solid product was filtered off, washed with ethanol, and dried. Compounds **3a** and **3b** were sufficiently pure and were used without further purification.

General procedure for the synthesis of 3-(4-R-phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes 4a and 4b. Cold DMF (0.4 mol) was added dropwise with stirring over a period of 30 min to

phosphoryl chloride (0.4 mol), and the mixture was stirred for further 45 min at 0°C. Compound **3a** or **3b** (0.08 mol) was then added, and the mixture was allowed to warm up to room temperature, heated at 90°C for 4 h, cooled, and poured into a mixture of crushed ice and water. The solid product was filtered off, dried, and recrystallized from chloroform–methanol (1:1).

General procedure for the synthesis of (*E*)-3-[1-phenyl-3-(4-R-phenyl)-1*H*-pyrazol-4-yl]-1-[thiophen(or furan)-2-yl]prop-2-en-1-ones 6a–6d. Equimolar amounts of compound **4a** or **4b** and 2-acetylthiophene (**5a**) or 2-acetylfuran (**5b**) were added to a solution of sodium hydroxide (5 mol %) in a water–ethanol mixture (1:2, 30 mL). The mixture was stirred at room temperature for 1–2 h, and the solid product was filtered off, and recrystallized from methanol.

(*E*)-3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one (6a). Yield 92%, mp 139–141°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1694 (C=O), 1567 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.10–8.18 m (15H, H_{arom}, CH=CH), 9.35 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 118.5, 119.4, 121.5, 122.2, 122.6, 126.1, 126.6, 127.3, 128.4, 128.6, 128.9, 129.5, 130.4, 131.5, 132.2, 133.5, 134.3, 139.5, 150.1, 150.4, 162.9, 186.4.

(*E*)-3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-(furan-2-yl)prop-2-en-1-one (6b). Yield 90%, mp 142–144°C. IR spectrum, ν, cm^{-1}: 3022 (C–H_{arom}), 1690 (C=O), 1560 (C=C). ^{1}H NMR spectrum, δ, ppm: 7.09–8.17 m (15H, H_{arom}, CH=CH), 9.35 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 118.2, 120.2, 121.9, 122.8, 123.3, 126.6, 126.8, 127.2, 128.3, 128.5, 128.8, 129.6, 130.4, 131.6, 132.4, 133.3, 134.6, 139.2, 150.4, 151.8, 163.2, 186.6.

(*E*)-3-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(thiophen-2-yl)prop-2-en-1-one (6c). Yield 92%, mp 137–139°C. IR spectrum, ν, cm^{-1}: 3015 (C–H_{arom}), 1694 (C=O), 1549 (C=C). ^{1}H NMR spectrum: 3.85 s (3H, OCH_3), 7.12–8.13 m (14H, H_{arom}, CH=CH), 9.36 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 56.6, 118.6, 119.7, 121.7, 122.3, 122.8, 126.2, 126.8, 127.5, 128.2, 128.5, 128.6, 129.9, 130.6, 131.7, 132.5, 133.6, 134.4, 139.7, 150.3, 150.6, 163.1, 186.5.

(*E*)-1-(Furan-2-yl)-3-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6d). Yield 92%, mp 141–143°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1688 (C=O), 1550 (C=C). ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, OCH_3), 7.12–8.14 m (14H, H_{arom}, CH=CH), 9.35 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 56.5, 119.2, 119.8, 121.6, 122.5, 123.1, 126.4, 126.7, 127.4, 128.2, 128.6, 129.1, 129.8, 130.4, 131.5, 132.2, 133.8, 134.6, 139.4, 150.0, 150.8, 163.3, 186.4

General procedure for the synthesis of compounds 8a–8d and 9a–9d [15, 16]**.** A mixture of compound **6a**–**6d**, isoniazid (**7a**) or nicotinic acid hydrazide (**7b**), aqueous sodium hydroxide, and ethanol (10 mL) was stirred at room temperature for 8–9 min. After completion of the reaction, the solid product was filtered off and recrystallized from methanol.

{1′,3′-Diphenyl-5-(thiophen-2-yl)-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-4-yl)methanone (8a). Yield 86%, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1695 (C=N), 1560 (C=C). ^{1}H NMR spectrum, δ, ppm: 3.36 d.d (1H, 4-H), 4.07 d.d (1H, 4-H), 5.82 d.d (1H, 5-H), 7.10–8.76 m (18H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 40.6, 61.5, 117.2, 119.9, 121.7, 123.1, 124.4, 125.8, 126.2, 127.2, 129.2, 129.3, 140.8, 149.7, 155.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 475.15 (100.0), 476.15 (30.3), 477.14 (4.5), 477.15 (2.7), 476.14 (1.8), 477.15 (1.7), 478.15 (1.4). Calculated for $C_{28}H_{21}N_5OS$: *M* 475.57.

{5-(Furan-2-yl)-1′,3′-diphenyl-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-4-yl)methanone (8b). Yield 88%, mp 235–238°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1696 (C=N), 1563 (C=C). ^{1}H NMR spectrum, δ, ppm: 3.44 d.d (1H, 4-H), 4.16 d.d (1H, 4-H), 5.92 d.d (1H, 5-H), 7.04–8.77 m (18H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.1, 55.8, 59.1, 109.4, 109.9, 114.2, 117.2, 119.9, 121.7, 123.2, 126.2, 128.5, 129.3, 139.7, 140.8, 141.7, 142.1, 149.7, 149.9, 155.6, 160.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 459.17 (100.0), 460.17 (30.3), 461.18 (2.7), 460.17 (1.8), 461.18 (1.7). Calculated for $C_{28}H_{21}N_5O_2$: *M* 459.51.

{3′-(4-Methoxyphenyl)-1′-phenyl-5-(thiophen-2-yl)-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-4-yl)methanone (8c). Yield 85%, mp 237–239°C. IR spectrum, ν, cm^{-1}: 3015 (C–H_{arom}), 1601 (C=N), 1567 (C=C). ^{1}H NMR spectrum, δ, ppm: 3.35 d.d (1H, 4-H), 3.84 s (3H, OCH3), 4.12 d.d (1H, 4-H), 5.89 d.d (1H, 5-H), 7.03–8.77 m (17H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 40.6, 55.8, 61.5, 114.8, 117.2, 119.9, 121.7, 123.2, 124.4, 125.3, 125.8, 126.2, 127.4, 128.5, 129.3, 139.7, 149.7, 155.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 505.16 (100.0), 506.16 (31.4), 507.15 (4.5), 507.16 (2.7), 507.16 (2.0), 506.15 (1.8), 508.16 (1.4). Calculated for $C_{29}H_{23}N_5O_2S$: *M* 505.60.

{5-(Furan-2-yl)-3′-(4-methoxyphenyl)-1′-phenyl-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-4-yl)methanone (8d). Yield 82%, mp 226–228°C. IR

spectrum, ν, cm^{-1}: 3012 (C–H_{arom}), 1605 (C=N), 1561 (C=C). ^1H NMR spectrum, δ, ppm: 3.37 d.d (1H, 4-H), 3.82 s (3H, OCH_3), 4.12 d.d (1H, 4-H), 5.84 d.d (1H, 5-H), 7.03–8.76 m (17H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.1, 56.5, 109.4, 109.9, 117.2, 119.9, 121.7, 123.2, 126.2, 127.5, 128.7, 129.2, 133.2, 139.7, 140.8, 141.7, 142.1, 149.7, 149.9, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 459.17 (100.0), 460.17 (30.3), 461.18 (2.7), 460.17 (1.8), 461.18 (1.7). Calculated for $C_{29}H_{23}N_5O_3$: *M* 459.54.

{1,3′-Diphenyl-5-(thiophen-2-yl)-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-3-yl)methanone (9a). Yield 87%, mp 233–235°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1695 (C=N), 1550 (C=C). ^1H NMR spectrum, δ, ppm: 3.36 d.d (1H, 4-H), 4.07 d.d (1H, 4-H), 5.82 d.d (1H, 5-H), 6.93–9.02 m (18H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 40.6, 61.1, 117.2, 119.9, 123.2, 124.4, 125.1, 125.8, 126.2, 127.2, 127.4, 127.5, 128.7, 129.2, 129.3, 129.9, 130.7, 133.2, 135.7, 139.7, 148.1, 148.7, 149.9, 155.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 475.15 (100.0), 476.15 (30.3), 477.14 (4.5), 477.15 (2.7), 476.14 (1.8), 477.15 (1.7), 478.15 (1.4). Calculated for $C_{28}H_{21}N_5OS$: *M* 475.57.

{5-(Furan-2-yl)-1′,3′-diphenyl-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-3-yl)methanone (9b). Yield 84%, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1695 (C=N), 1550 (C=C). ^1H NMR spectrum, δ, ppm: 3.44 d.d (1H, 4-H), 4.16 d.d (1H, 4-H), 5.92 d.d (1H, 5-H), 7.10–9.02 m (18H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.1, 55.8, 58.7, 109.4, 109.4, 109.9, 114.8, 117.2, 119.9, 121.7, 123.2, 125.3, 126.2, 128.5, 129.3, 130.7, 135.3, 139.7, 140.8, 141.7, 142.1, 148.1, 148.7, 155.6, 160.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 459.17 (100.0), 460.17 (30.3), 461.18 (2.7), 460.17 (1.8), 461.18 (1.7). Calculated for $C_{28}H_{21}N_5O_2$: *M* 459.51,

{3′-(4-Methoxyphenyl)-1′-phenyl-5-(thiophen-2-yl)-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-3-yl)methanone (9c). Yield 86%, mp 237–239°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1695 (C=N), 1550 (C=C). ^1H NMR spectrum, δ, ppm: 3.36 d.d (1H, 4-H), 3.84 s (3H, OCH_3), 4.13 d.d (1H, 4-H), 5.84 d.d (1H, 5-H), 7.03–8.76 m (18H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.1, 55.8, 58.7, 109.4, 109.4, 109.9, 114.8, 117.2, 119.9, 121.7, 123.2, 125.3, 126.2, 128.5, 129.3, 130.7, 135.3, 139.7, 140.8, 141.7, 142.1, 148.1, 148.7, 155.6, 160.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 505.16 (100.0), 506.16 (31.4), 507.15 (4.5), 507.16 (2.7), 507.16 (2.0), 506.15 (1.8), 508.16 (1.4). Calculated for $C_{29}H_{23}N_5O_2S$: *M* 505.60.

{5-(Furan-2-yl)-3′-(4-methoxyphenyl)-1′-phenyl-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl}(pyridin-3-yl)methanone (9d). Yield 82%, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3017 (C–H_{arom}), 1696 (C=N), 1552 (C=C). ^1H NMR spectrum, δ, ppm: 3.44 d.d (1H, 4-H), 3.84 s (3H, OCH_3), 4.16 d.d (1H, 4-H), 5.92 d.d (1H, 5-H), 7.04–8.76 m (17H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.1, 55.8, 58.7, 109.4, 109.4, 109.9, 114.8, 117.2, 119.9, 121.7, 123.2, 125.3, 126.2, 128.5, 129.3, 130.7, 135.3, 139.7, 140.8, 141.7, 142.1, 148.1, 148.7, 155.6, 160.6, 167.2. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 489.18 (100.0), 490.18 (31.4), 491.19 (4.7), 490.18 (1.8). Calculated for $C_{29}H_{23}N_5O_3$: *M* 489.18.

ACKNOWLEDGMENTS

The authors are thankful to the Head, Department of Chemistry, M.G. Science Institute, Gujarat University, Ahmedabad, for providing research facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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