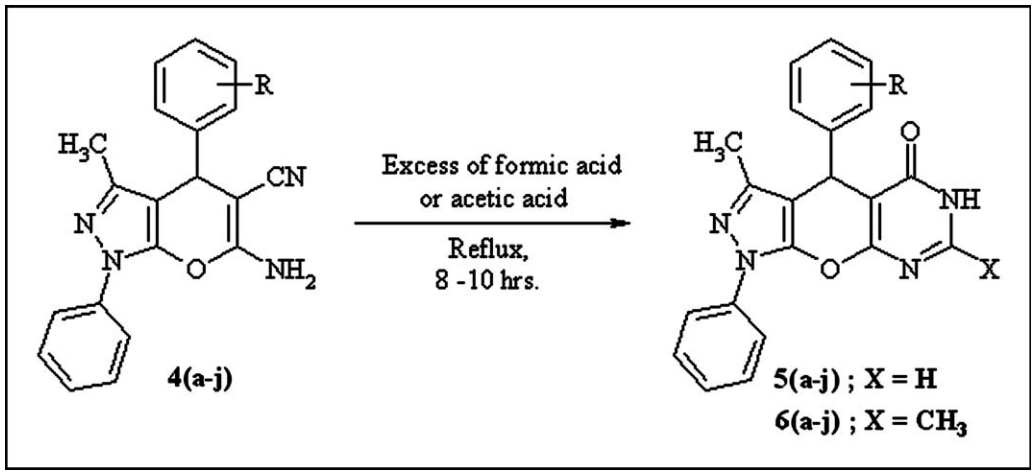
Synthesis, Characterization, and *In Vitro* Biological Studies of Some Novel Pyran Fused Pyrimidone Derivatives

Prashant T. Mistry, Nimesh R. Kamdar, Dhaval D. Haveliwala, and Saurabh K. Patel*

Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, Gujarat, India
*E-mail: saurabh@vnsgu.ac.in

Received May 20, 2010
DOI 10.1002/jhet.700
Published online 31 December 2011 in Wiley Online Library (wileyonlinelibrary.com).



A variety of pyrano[2,3-*d*]pyrimidine-5-one derivatives **5,6(a-j)** have been synthesized from 6-amino-4-(substituted phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives **4(a-j)** via cyclization using formic acid and acetic acid. All the newly synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. All the synthesized compounds have been screened for antibacterial, antifungal and antitubercular activity.

J. Heterocyclic Chem., **49**, 349 (2012).

INTRODUCTION

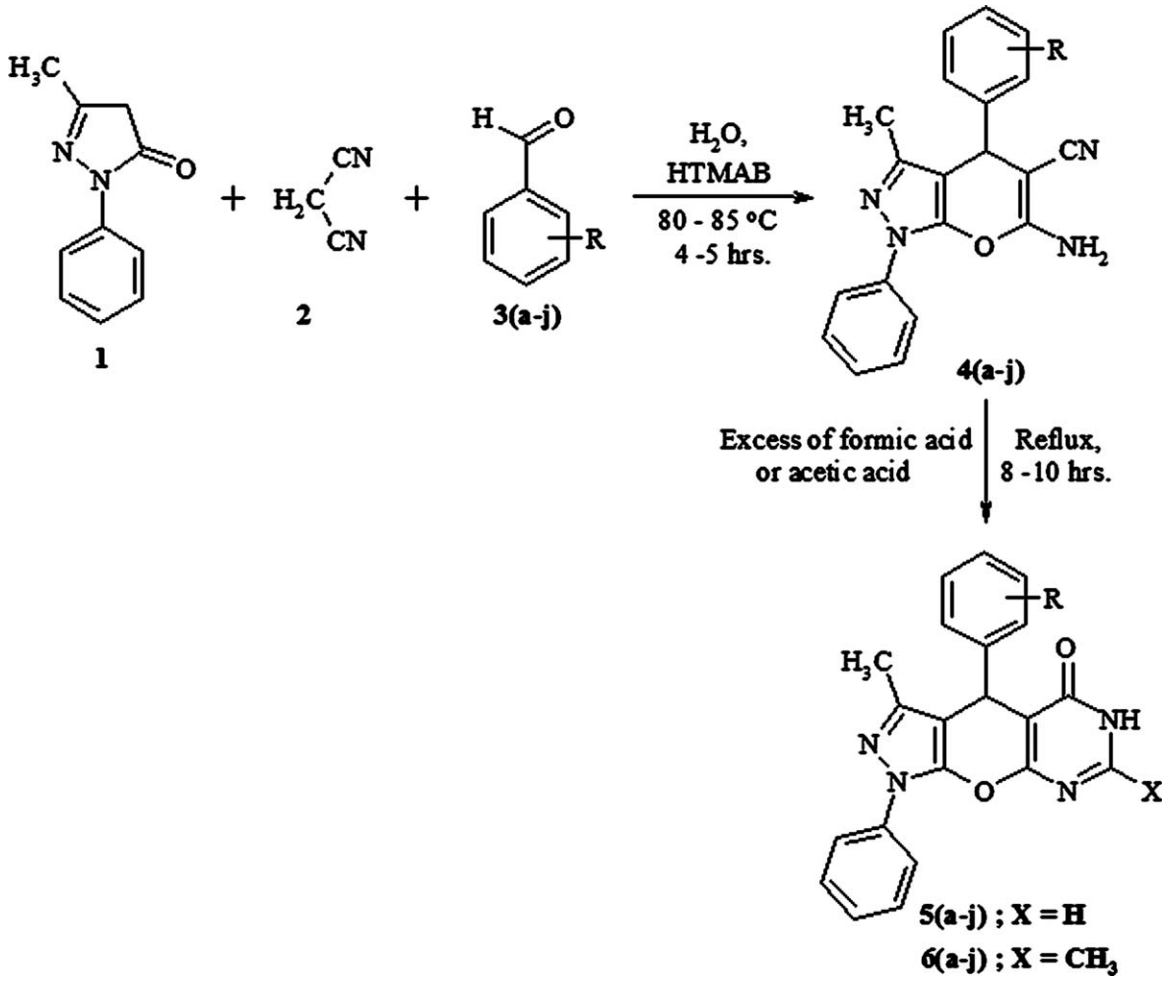
Pyran and fused 4*H*-pyran derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their biological and pharmacological properties such as antimicrobial [1–7], antitubercular [8,9], antiviral [10], antileishmanial [11], antibacterial [12], antihypertensive [13], antifungal [14], vasorelaxant [15], antirheumatic [16], and anticonvulsant [17] activities. Pyran derivatives are well known as HIV protease inhibitors [18] and sialidase inhibitors related to zanamivir [19,20]. Morever, pyran derivatives are also possess growth inhibitory activity in breast cancer cells [21]. In addition, synthetic studies of pyrimidine and its derivatives have been documented extensively because of their structural diversity and association with a wide spectrum of biological activity. Pyrimidone derivatives have attracted a great deal of interest owing to their antimicrobial [22–24], analgesic [25], anticancer [26], antioxidant [27], antibacterial [28], antiviral [29], antiinflammatory [30], antiplatelet [31], antiproliferative [32], and antitumor [33] activities.

Ortho amino cyano derivatives have been employed as convenient starting materials for the preparation of wide variety of fused pyrimidone using formic acid and acetic acid, such as thino[2,3-*d*]pyrimidine [34], pyrano[2,3-*d*]pyrimidine [35], pyrazolo[3,4-*d*]pyrimidine [36], furo[2,3-*d*]pyrimidine [37–38], thiazolo[2,3-*b*]pyrimidine [39], pyrido[2,3-*d*]pyrimidine [40,41], and pyrimido[4,5-*b*]quinoline [42]. Above encouraging literature reviews prompted us to synthesize a fertile source of biologically important prototypes by combining pyrimidone and pyran moiety. In continuous of our previous work on ortho amino cyano functionality [43,44], a new tricyclic series of pyranopyrimidone derivatives by incorporating the pyrazole moiety have been synthesized and evaluated for their antimicrobial and antitubercular activity.

RESULTS AND DISCUSSION

Chemistry. The starting molecules 6-amino-4-(substituted phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **4(a-j)** were prepared according to

Scheme 1. Synthetic route of compounds **5(a–j)** and **6(a–j)**.



the method reported by Jin *et al*. in presence of hexadecyltrimethyl ammonium bromide (HTMAB) in aquous media [45]. Treatment of **4(a-j)** with excess of formic acid and acetic acid afforded 3-methyl-4-(substituted phenyl)-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano [2,3-*d*]pyrimidine-5(1*H*)-one **5(a-j)** and 4-(substituted phenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′: 5,6]pyrano[2,3-*d*]pyrimidine-5(1*H*)-one **6(a-j)** respectively (Scheme 1). The structures of all the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

The IR spectra of **5(a-j)** showed absorption bands in the region of 3168–3145, 1740–1726 and 1636–1625 cm^{-1} revealed to —NH, >C=O and —C=N groups, respectively, with agreement of singlet at 11.50–11.43 and 8.16–8.10 δ ppm accounted for —NH and —CH (pyrimidone ring) in ^{1}H NMR spectra. This was further substantiated by the ^{13}C NMR spectra, exhibited signals at 138.16–138.88 and 165.08–165.45 δ ppm due to —CH and >C=O of pyrimidone ring. Compounds **6(a-j)** showed IR absorption bands around 3158–3140, 1742–1725, and 1640–1626 cm^{-1} attributed to —NH, >C=O and —C=N groups, respectively. ^{1}H NMR spectra revealed that the disappearance of $-NH_2$ peak and the appearance of a singlet at 11.18–11.10 and 2.48–2.41 δ ppm corresponds to —NH and $-CH_3$ protons (pyrimidone ring), confirm the formation of title compounds. This was further confirmed by ^{13}C NMR spectra, which showed $-CH_3$ (pyrimidone ring) and >C=O signals at 19.75–20.12 and 165.17–165.78 δ ppm, respectively.

Biological activity. All of the newly synthesized compounds were tested for their *in vitro* antibacterial and antifungal activity (minimal inhibitory concentrations (MICs), μg/mL) by broth dilution method as described by Rattan [46] with two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442), two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688), and three fungi (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323) organisms. Ampicillin,

Table 1

Antimicrobial activity of the synthesized compounds (MICs, μg/mL).

		Gram-positive bacteria		Gram-negative bacteria		Fungal species		
Compounds	-R	*S. aureus*	*S. pyogenus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
4a	-H	250	250	100	200	500	500	500
4b	4-OCH_3	500	1000	250	250	200	1000	1000
4c	4-OH	100	200	150	200	150	>1000	1000
4d	4-F	250	250	500	500	200	500	500
4e	2-Cl	500	500	100	250	500	>1000	>1000
4f	3-Cl	250	250	500	500	1000	>1000	>1000
4g	4-Cl	500	250	500	1000	1000	>1000	>1000
4h	3-NO_2	200	200	100	100	500	500	1000
4i	3-Br	100	100	150	200	100	250	250
4j	4-CH_3	150	150	62.5	100	500	1000	1000
5a	-H	500	500	250	500	200	1000	1000
5b	4-OCH_3	500	500	250	250	500	1000	1000
5c	4-OH	500	500	500	500	1000	1000	1000
5d	4-F	500	1000	250	250	1000	1000	1000
5e	2-Cl	250	250	100	500	1000	1000	1000
5f	3-Cl	500	500	500	500	500	>1000	>1000
5g	4-Cl	100	150	100	100	500	500	500
5h	3-NO_2	100	100	250	250	250	200	200
5i	3-Br	100	100	62.5	150	500	>1000	>1000
5j	4-CH_3	500	200	200	250	1000	>1000	1000
6a	-H	500	500	250	500	1000	>1000	>1000
6b	4-OCH_3	500	500	500	500	200	250	250
6c	4-OH	500	500	100	100	500	1000	1000
6d	4-F	1000	1000	250	250	500	250	250
6e	2-Cl	200	200	200	250	1000	500	1000
6f	3-Cl	500	500	250	500	>1000	1000	1000
6g	4-Cl	250	250	500	500	500	1000	1000
6h	3-NO_2	1000	1000	1000	1000	>1000	>1000	>1000
6i	3-Br	1000	1000	500	500	>1000	>1000	>1000
6j	4-CH_3	250	250	500	500	1000	>1000	>1000
Ampicillin		250	100	100	100	-	-	-
Nystatin		-	-	-	-	100	100	100
Greseofulvin		-	-	-	-	500	100	100

Nystatin, and Griseofulvin were used as standard drugs for antimicrobial activity. For *in vitro* antitubercular activity, primary screening of the compounds has been conducted at 62.5 μg/mL against *Mycobacterium tuberculosis* $H_{37}Rv$ strain using Lowenstein-Jensen medium (conventional method) as described by Rattan [46]. The antitubercular activity data were compared with that of standard drug Rifampicin at 40 μg/mL concentration, which showed 99% inhibition. Antimicrobial and antitubercular activity data of all the newly synthesized compounds were compared with standard drugs as well as with corresponding precursors.

Antibacterial activity. It is evident from the screening results that the ortho amino cyano derivatives showed good antibacterial activity but on conversion to pyrimidone derivatives, a significant variation was observed. From the screening results, **4h (3-NO_2)** and **4j (4-CH_3)** demonstrated excellent activity against *S. aureus, E. coli*, and *P. aeruginosa*, whereas against *S. aureus* and *E. coli*, compound **4a (-H)** exhibited good activity compared with ampicillin. Compound **4i (3-Br)** possesses elevated activity against only on Gram-positive species (*S. aureus* and *S. pyogenes*) as compared with reference drug ampicillin. Compounds **4c (4-OH)** and **4d (4-F)** possess excellent to good potency against *S. aureus* compared with ampicillin. Ortho and meta chloro substituted compounds, **4e (2-Cl)** and **4f (3-Cl)**, demonstrated significant and interesting activity against *S. aureus* and *E. coli* compared with ampicillin. In contrast, para chloro substituted compound, **4g (2-Cl),** was found poor active. Para chloro substituted compound, **5g (4-Cl)**, possesses elevated potency against *S. aureus, E. coli*, and *P. aeruginosa* as compared with ampicillin drug, which was more potent than the corresponding precursor **4g (4-Cl)**. Although meta chloro substituted compound, **5f (3-Cl)**, comparatively reduced the activity. Bromo derivative, **5i (3-Br)**, gave significant potency against *E. coli, S. aureus*, and *S. pyogenes* as compared with ampicillin,

Table 2

Antitubercular activity of the synthesized compounds against *Mycobacterium tuberculosis $H_{37}Rv$* (% inhibition).

Compounds	-R	% Inhibition	Compounds	-R	% Inhibition
4a	-H	21	**5f**	3-Cl	62
4b	4-OCH_3	5	**5g**	4-Cl	14
4c	4-OH	11	**5h**	3-NO_2	98
4d	4-F	42	**5i**	3-Br	21
4e	2-Cl	69	**5j**	4-CH_3	45
4f	3-Cl	13	**6a**	-H	28
4g	4-Cl	29	**6b**	4-OCH_3	97
4h	3-NO_2	41	**6c**	4-OH	32
4i	3-Br	6	**6d**	4-F	54
4j	4-CH_3	97	**6e**	2-Cl	12
5a	-H	24	**6f**	3-Cl	9
5b	4-OCH_3	8	**6g**	4-Cl	54
5c	4-OH	17	**6h**	3-NO_2	19
5d	4-F	19	**6i**	3-Br	26
5e	2-Cl	35	**6j**	4-CH_3	32

Rifampicin = 99% inhibition (40 μg/mL)
All the synthesized compounds were tested at concentration of 62.5 μg/mL.

which was equipotent to the corresponding precursor **4i (3-Br)** in case of Gram-positive species (*S. aureus* and *S. pyogenes*) but interestingly, it was more potent in case of *E. Coli*. Ortho chloro substituted compound, **5e (2-Cl)**, possess significant potency against *S. aureus* and *E. coli* as compared with ampicillin drug, which was equipotent in case of *E. coli* and more potent in case of *S. aureus* as compared with corresponding precursor **4e (2-Cl)**. Nitro derivative, **5h (3-NO_2)**, gave good activity against only on Gram-positive species (*S. aureus* and *S. pyogenes*) compared with standard drug ampicillin, which was more potent than the corresponding precursor **4h (3-NO_2)** in case of both Gram-positive species (*S. aureus* and *S. pyogenes*) but it was not as potent as corresponding precursor in case of both Gram-negative species *(E. coli and P. aeruginosa*). Hydroxy substituted compound, **6c (4-OH)**, revealed significant potency in case of both Gram-negative species *(E. coli and P. aeruginosa*), whereas it failed to gave activity on both Gram-positive species compared with standard drug ampicillin, which was not as potent as starting precursors in case of *S. aureus*, but more potent than the corresponding precursor **4c (4-OH)** in case of *E. coli* and *P. aeruginosa*. Ortho and para chloro substituted compounds, **6e (2-Cl)** and **6g (4-Cl)**, exhibited significant potency against *S. aureus* compared with standard drug ampicillin, which was more potent than the corresponding precursors, whereas meta chloro substituted compound **6f (3-Cl)** displayed poor activity. The remaining compounds showed moderate to poor activities (Table 1).

Antifungal activity. Pyrano[2,3-*d*]pyrimidine-5-one derivatives **5,6(a-j)** exhibited good to moderate activity as compared with standard drugs as well as corresponding precursors. From the screening results, starting molecules **4b (4-OCH_3)**, **4c (4-OH)**, **4d (4-F)**, **4e (2-Cl)**, **4h (3-NO_2)** and **4j (4-CH_3)** exhibited excellent to good potency against *C. albicans* as compared with greseofulvin. Interestingly, bromo substituted compound, **4i (3-Br)**, was found very active in case of *C. albicans* compared with both of standard drug nystatin and greseofulvin. Compounds **5a (-H)**, **5f (3-Cl)**, **5g (4-Cl)**, and **5h (3-NO_2)** showed significant potency against *C. albicans* compared with greseofulvin, which were found to be more potent than the corresponding precursors. Methoxy substituted compound, **5b (4-OCH_3)**, demonstrated significant activity than its precursor **4b (4-OCH_3)** against *C. albicans* as compared with greseofulvin. Compounds **6b (4-OCH_3)**, **6c (4-OH)**, **6d (4-F)**, and **6g (4-Cl)** possess excellent to good potency against *C. albicans* as compared with greseofulvin, which were equipotent or less potent than their corresponding precursor. The remaining compounds showed moderate to poor activities (Table 1).

Antitubercular activity. The antitubercular activity of newly synthesized compounds was tested against *Mycobacterium tuberculosis $H_{37}Rv$* at concentration of 62.5 μg/mL. Among the synthesized compounds, **4j (4-CH_3)**, **5h (3-NO_2)**, and **6b (4-OCH_3)** exhibited >95% inhibition against *Mycobacterium tuberculosis $H_{37}Rv$*. All the other synthesized compounds showed moderate to poor activities (Table 2).

CONCLUSION

A variety of pyrano[2,3-*d*]pyrimidine-5-one derivatives **5,6(a-j)** were successfully synthesized from ortho amino cyano derivatives and screened for antibacterial,

antifungal, and antitubercular activity. From the biological screening result, most of the compounds of pyrano[2,3-*d*]pyrimidine-5-one derivatives **5,6(a-j)** demonstrated more significant antibacterial and antifungal activity than the corresponding precursors. For bacterial species, most of the compounds were found to be active compared with ampicillin drug. But for other standard drugs they were found to be moderate active. Several newly synthesized compounds were found to be active against *C. albicans* but for other fungal species, were found to be poor. Antitubercular activity of several compounds were markedly good against *Mycobacterium tuberculosis $H_{37}Rv$* compared with that of rifampicin.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel as adsorbent [Mobile phase: toluene/ethyl acetate (7.5:2.5)] and visualization was accomplished by UV light or iodine vapour. IR spectra were recorded on Shimadzu and Thermo Scientific Nicolec is 10 Fourier transform infrared (FTIR) spectrophotometer, using KBr pallets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer using tetramethylsilane as the internal standard in $CDCl_3$ or DMSO as solvent. Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer. Analytical data of C, H and N were within ±0.4% of the theoretical values. Compounds **4(a-j)** were prepared according to the method reported by Jin *et al* [45] and were characterized accordingly.

General procedure for the synthesis of 3-methyl-4-(substituted phenyl)-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5(1*H*)-one 5(a-j) and 4-(substituted phenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5(1*H*)-one 6(a-j). A mixture of **4(a-j)** (2.0 mmol) and excess of formic acid or acetic acid (10 mL) was refluxed for 8–10 h (monitored by TLC). After completion of reaction, the reaction mixture was left to cool to room temperature, and then poured into ice cold water (50 mL). The product was separated by filtration and washed with cold water. The crude product was purified by recrystallization from ethanol to give corresponding cyclized product **5(a-j)** and **6(a-j)**, respectively.

3-Methyl-1,4-diphenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5a). Light brown solid; 57%; mp: 186–189°C; IR (KBr) υ (cm^{-1}): 3422 (—NH), 3067, 2923 (Ar C—H), 1716 (>C=O), 1601 (—C=N), 1160, 1028 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.46 (s, 1H, —NH), 8.14 (s, 1H, —CH of pyrimidone ring), 7.92–6.78 (m, 10H, Ar-H), 4.88 (s, 1H, —CH), 1.80 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.32 (CH_3), 38.22 (CH), 94.12 (C), 99.61 (C), 122.21 (CH), 124.89 (CH), 126.79 (CH), 128.53 (CH), 129.42 (CH), 138.16 (CH of pyrimidone ring), 143.02 (C), 144.57 (C), 145.43 (C), 162.68 (C), 165.08 (>C=O); Anal. Calcd for $C_{21}H_{16}N_4O_2$: C 70.77, H 4.53, N 15.72; Found: C 70.75, H 4.52, N 15.73.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5b). Dark brown solid; 53%; mp: 256–258°C; IR (KBr) υ (cm^{-1}): 3158 (—NH), 3055 (Ar C-H), 1736 (>C=O), 1628 (—C=N), 1220, 1035 (—OCH_3), 1138, 1067 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.49 (s, 1H, —NH), 8.15 (s, 1H, —CH of pyrimidone ring), 7.97–6.75 (m, 9H, Ar-H), 4.85 (s, 1H, —CH), 3.72 (s, 3H, —OCH_3), 1.78 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.25 (CH_3), 38.06 (CH), 54.41 (OCH_3), 94.44 (C), 99.53 (C), 112.12 (CH), 122.29 (CH), 126.98 (CH), 128.62 (CH), 129.33 (CH), 138.20 (CH of pyrimidone ring), 140.11 (C), 144.21 (C), 159.32 (C—OCH_3), 162.68 (C), 165.08 (>C=O); Anal. Calcd for $C_{22}H_{18}N_4O_3$: C 68.38, H 4.70, N 14.50; Found: C 68.40, H 4.69, N 14.48.

4-(4-Hydroxyphenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5c). Dark brown solid; 59%; mp: 232–235°C; IR (KBr) υ (cm^{-1}): 3266 (—OH), 3152 (—NH), 3059 (Ar C—H), 1727 (>C=O), 1634 (—C=N), 1142, 1073 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.47 (s, 1H, —NH), 8.13 (s, 1H, —CH of pyrimidone ring), 7.88–6.81 (m, 9H, Ar-H), 5.31 (s, 1H, —OH), 4.89 (s, 1H, — CH), 1.81 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.29 (CH_3), 38.21 (CH), 94.39 (C), 100.10 (C), 117.13 (CH), 122.27 (CH), 127.05 (CH), 128.23 (CH), 129.28 (CH), 137.88 (C), 138.29 (CH of pyrimidone ring), 140.23 (C), 144.15 (C), 154.05 (C—OH), 163.11 (C), 165.26 (>C=O); Anal. Calcd for $C_{21}H_{16}N_4O_3$: C 67.73, H 4.33, N 15.05; Found: C 67.74, H 4.31, N 15.07.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5d). Light yellow solid; 51%; mp: 209–212°C; IR (KBr) υ (cm^{-1}): 3148 (—NH), 3066 (Ar C-H), 1736 (>C=O), 1628 (—C=N), 1133, 1080 (C—O—C), 744 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.84 (s, 1H, —NH), 7.93–6.93 (m, 10H, Ar—H), 4.93 (s, 1H, —CH), 2.22 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.31 (CH_3), 38.29 (CH), 94.31 (C), 99.60 (C), 117.04 (CH), 117.69 (CH), 122.23 (CH), 128.21 (CH), 129.53 (CH), 137.98 (C), 138.61 (CH of pyrimidone ring), 142.11 (C), 144.08 (C), 159.07 (C-F), 162.79 (C), 165.13 (>C=O); Anal. Calcd for $C_{21}H_{15}N_4O_2F$: C 67.37, H 4.04, N 14.97; Found: C 67.39, H 4.01, N 14.95.

4-(2-Chlorophenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5e). Cream solid; 60%; mp: 261–263°C; IR (KBr) υ (cm^{-1}): 3162 (—NH), 3055 (Ar C-H), 1732 (>C=O), 1636 (—C=N), 1127, 1074 (C—O—C), 762 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.43 (s, 1H, —NH), 8.10 (s, 1H, —CH of pyrimidone ring), 7.96–6.78 (m, 9H, Ar-H), 4.88 (s, 1H, —CH), 1.82 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.42 (CH_3), 32.19 (CH), 95.08 (C), 99.53 (C), 122.57 (CH), 126.49 (CH), 128.15 (CH), 129.29 (CH), 130.23 (CH), 134.13 (C—Cl), 138.53 (CH of pyrimidone ring), 142.28 (C), 143.98 (C), 159.29 (C), 165.33 (>C=O); Anal. Calcd for $C_{21}H_{15}N_4O_2Cl$: C 64.54, H 3.87, N 14.34; Found: C 64.51, H 3.89, N 14.36.

4-(3-Chlorophenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5f). Yellow solid; 56%; mp: 210–212°C; IR (KBr) υ (cm^{-1}): 3156 (—NH), 3059 (Ar C—H), 1725 (>C=O), 1641 (—C=N), 1130, 1070 (C—O—C), 755 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.47 (s, 1H, —NH), 8.13 (s, 1H, —CH of pyrimidone ring), 7.87–6.72 (m, 9H, Ar-H), 4.89 (s, 1H, —CH), 1.80 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.39

(CH_3), 37.06 (CH), 94.52 (C), 99.43 (C), 122.50 (CH), 125.37 (CH), 126.82 (CH), 127.97 (CH), 129.33 (CH), 131.13 (CH), 135.53 (C—Cl), 138.34 (CH of pyrimidone ring), 143.13 (C), 144.02 (C), 145.79 (C), 162.19 (C), 165.45 (>C=O); Anal. Calcd for $C_{21}H_{15}N_4O_2Cl$: C 64.54, H 3.87, N 14.34; Found: C 64.56, H 3.85, N 14.33.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo [4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5g). Yellow solid; 71%; mp: 252–254°C; IR (KBr) υ (cm^{-1}): 3153 (—NH), 3066 (Ar C-H), 1732 (>C=O), 1634 (—C=N), 1138, 1066 (C—O—C), 758 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.48 (s, 1H, —NH), 8.16 (s, 1H, —CH of pyrimidone ring), 7.94–6.76 (m, 9H, Ar-H), 4.86 (s, 1H, —CH), 1.82 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.31 (CH_3), 37.96 (CH), 94.43 (C), 99.68 (C), 122.66 (CH), 128.21 (CH), 129.09 (CH), 130.27 (CH), 131.10 (C—Cl), 138.87 (CH of pyrimidone ring), 142.94 (C), 144.13 (C), 163.13 (C), 165.30 (>C=O); Anal. Calcd for $C_{21}H_{15}N_4O_2Cl$: C 64.54, H 3.87, N 14.34; Found: C 64.55, H 3.90, N 14.36.

3-Methyl-4-(3-nitrophenyl)-1-phenyl-4,6-dihydropyrazolo[4′, 3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5h). Light brown solid; 67%; mp: >280°C; IR (KBr) υ (cm^{-1}): 3146 (—NH), 3057 (Ar C-H), 1722 (>C=O), 1626 (—C=N), 1536, 1359 (—NO_2 asym, sym), 1133, 1070 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.49 (s, 1H, —NH), 8.14 (s, 1H, —CH of pyrimidone ring), 7.97–6.75 (m, 9H, Ar-H), 4.87 (s, 1H, —CH), 1.81 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.31 (CH_3), 36.19 (CH), 94.61 (C), 99.83 (C), 122.57 (CH), 124.65 (CH), 128.32 (CH), 129.27 (CH), 133.13 (CH), 138.59 (CH of pyrimidone ring), 143.41 (C), 145.09 (C), 148.89 (C—NO_2), 162.12 (C), 165.37 (>C=O); Anal. Calcd for $C_{21}H_{15}N_5O_4$: C 62.84, H 3.77, N 17.45; Found: C 62.83, H 3.79, N 17.43.

4-(3-Bromophenyl)-3-methyl-1-phenyl-4,6-dihydropyrazolo[4′, 3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5i). Light brown solid; 62%; mp: >280°C; IR (KBr) υ (cm^{-1}): 3150 (—NH), 3065 (Ar C-H), 1732 (>C=O), 1642 (—C=N), 1138, 1076 (C—O—C), 862 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.44 (s, 1H, —NH), 8.12 (s, 1H, —CH of pyrimidone ring), 7.92–6.75 (m, 9H, Ar-H), 4.85 (s, 1H, —CH), 1.79 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.47 (CH_3), 38.35 (CH), 94.53 (C), 99.71 (C), 122.39 (CH), 124.94 (C-Br), 127.11 (CH), 128.29 (CH), 129.54 (CH), 131.19 (CH), 138.44 (CH of pyrimidone ring), 143.35 (C), 145.21 (C), 160.23 (C), 165.71 (>C=O); Anal. Calcd for $C_{21}H_{15}N_4O_2Br$: C 57.95, H 3.47, N 12.87; Found: C 57.97, H 3.44, N 12.86.

3-Methyl-4-(4-methylphenyl)-1-phenyl-4,6-dihydropyrazolo [4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (5j). Cream solid; 61%; mp: 273–275°C; IR (KBr) υ (cm^{-1}): 3148 (—NH), 3060 (Ar C-H), 2854 (—CH_3), 1740 (>C=O), 1635 (—C=N), 1131, 1071 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.46 (s, 1H, —NH), 8.14 (s, 1H, —CH of pyrimidone ring), 7.89–6.72 (m, 9H, Ar-H), 4.87 (s, 1H, —CH), 2.33 (s, 3H, —CH_3), 1.81 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.61 (CH_3), 22.41 (C—CH_3 of phenyl ring), 38.29 (CH), 94.66 (C), 99.59 (C), 122.51 (CH), 127.23 (CH), 128.03 (CH), 129.44 (CH), 130.26 (CH), 134.88 (C—CH_3 of phenyl ring), 138.30 (CH of pyrimidone ring), 142.85 (C), 144.12 (C), 163.10 (C), 165.52 (>C=O); Anal. Calcd for $C_{22}H_{18}N_4O_2$: C 71.34, H 4.90, N 15.13; Found: C 71.37, H 4.88, N 15.11.

3,7-Dimethyl-1,4-diphenyl-4,6-dihydropyrazolo[4′,3′:5,6] pyrano[2,3-d]pyrimidine-5(1H)-one (6a). Dark brown solid; 72%; mp: 187–190°C; IR (KBr) υ (cm^{-1}): 3432 (—NH), 3070, 2924 (Ar C—H), 1712 (>C=O), 1603 (—C=N), 1159, 1098 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.12 (s, 1H, —NH), 8.01–7.12 (m, 10H, Ar—H), 4.94 (s, 1H, —CH), 2.15 (s, 3H, —CH_3) 1.73 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.31 (CH_3), 20.05 (C—CH_3 of pyrimidone ring), 38.25 (CH), 94.39 (C), 99.46 (C), 122.33 (CH), 124.97 (CH), 126.82 (CH), 128.68 (CH), 129.27 (CH), 137.90 (C), 143.81 (C), 145.07 (C—CH_3 of pyrimidone ring), 162.40 (C), 165.17 (>C=O); Anal. Calcd for $C_{22}H_{18}N_4O_2$: C 71.34, H 4.90, N 15.13; Found: C 71.36, H 4.89, N 15.15.

4-(4-Methoxyphenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6b). Reddish brown solid; 69%; mp; 242–245°C; IR (KBr) υ (cm^{-1}): 3156 (—NH), 3074 (Ar C-H), 1731 (>C=O), 1627 (—C=N), 1222, 1038 (—OCH_3), 1132, 1058 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.14 (s, 1H, —NH), 7.98–6.75 (m, 9H, Ar-H), 4.87 (s, 1H, —CH), 3.71 (s, 3H, -OCH_3), 2.45 (s, 3H, —CH_3), 1.79 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.23 (CH_3), 19.96 (C—CH_3 of pyrimidone ring), 38.32 (CH), 54.82 (C—OCH_3), 94.53 (C), 100.10 (C), 112.38 (CH), 122.51 (CH), 127.17 (CH), 128.22 (CH), 129.35 (CH), 138.02 (C), 140.20 (C), 144.11 (C), 145.23 (C—CH_3 of pyrimidone ring), 159.69 (C—OCH_3), 162.51 (C), 165.23 (>C=O); Anal. Calcd for $C_{23}H_{20}N_4O_3$: C 68.99, H 5.03, N 13.99; Found: C 69.01, H 5.05, N 14.00.

4-(4-Hydroxyphenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6c). Brown solid; 58%; mp: 259–262°C; IR (KBr) υ (cm^{-1}): 3262 (—OH), 3151 (—NH), 3065 (Ar C—H), 1738 (>C=O), 1625 (—C=N), 1139, 1052 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.12 (s, 1H, —NH), 7.94–6.72 (m, 9H, Ar-H), 5.34 (s, 1H, —OH), 4.83 (s, 1H, —CH), 2.42 (s, 3H, —CH_3), 1.81 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.63 (CH_3), 19.89 (C—CH_3) of pyrimidone ring), 38.13 (CH), 94.74 (C), 99.59 (C), 117.10 (CH), 122.35 (CH), 127.03 (CH), 128.27 (CH), 129.41 (CH), 138.15 (C), 139.85 (C), 144.82 (C), 145.04 (C—CH_3 of pyrimidone ring), 153.78 (C—OH), 162.62 (C), 165.57 (>C=O); Anal. Calcd for $C_{22}H_{18}N_4O_3$: C 68.38, H 4.70, N 14.50; Found: C 68.37, H 4.69, N 14.52.

4-(4-Fluorophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6d). Brown solid; 55%; mp: >280°C; IR (KBr) υ (cm^{-1}): 3146 (—NH), 3072 (Ar C-H), 1727 (>C=O), 1633 (—C=N), 1135, 1060 (C—O—C), 747 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.15 (s, 1H, —NH), 7.90–6.69 (m, 9H, Ar-H), 4.86 (s, 1H, —CH), 2.46 (s, 3H, —CH_3), 1.80 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.81 (CH_3), 19.79 (C—CH_3 of pyrimidone ring), 38.52 (CH), 94.66 (C), 99.80 (C), 116.91 (CH), 122.36 (CH), 128.14 (CH), 129.33 (CH), 138.30 (C), 141.80 (C), 144.92 (C), 145.13 (C—CH_3 of pyrimidone ring), 159.78 (C-F), 162.81 (C), 165.55 (>C=O); Anal. Calcd for $C_{22}H_{17}N_4O_2F$: C 68.03, H 4.41, N 14.43; Found: C 68.01, H 4.42, N 14.41.

4-(2-Chlorophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6e). Dark brown solid; 52%; mp: 202–205°C; IR (KBr) υ (cm^{-1}): 3142 (—NH), 3070 (Ar C-H), 1733 (>C=O), 1629 (—C=N), 1142, 1058 (C—O—C), 755 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ

(ppm): 11.17 (s, 1H, —NH), 8.01–6.75 (m, 9H, Ar-H), 4.85 (s, 1H, —CH), 2.43 (s, 3H, —CH_3), 1.82 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.78 (CH_3), 19.77 (C—CH_3 of pyrimidone ring), 32.42 (CH), 94.71 (C), 99.89 (C), 122.30 (CH), 126.37 (CH), 127.92 (CH), 129.21 (CH), 130.32 (CH), 134.11 (C—Cl), 138.18 (C), 142.60 (C), 143.82 (C), 145.34 (C—CH_3 of pyrimidone ring), 159.42 (C), 165.22 (>C=O); Anal. Calcd for $C_{22}H_{17}N_4O_2Cl$: C 65.27, H 4.23, N 13.84; Found: C 65.24, H 4.21, N 13.85.

4-(3-Chlorophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6f). Yellow solid; 54%; mp: 231–233°C; IR (KBr) υ (cm^{-1}): 3150 (—NH), 3076 (Ar C—H), 1737 (>C=O), 1638 (—C=N), 1147, 1054 (C—O—C), 748 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.13 (s, 1H, —NH), 8.06–6.81 (m, 9H, Ar-H), 4.87 (s, 1H, —CH), 2.42 (s, 3H, —CH_3), 1.80 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.36 (CH_3), 20.12 (C—CH_3 of pyrimidone ring), 36.44 (CH), 94.69 (C), 99.85 (C), 122.15 (CH), 125.49 (CH), 126.28 (CH), 128.20 (CH), 129.05 (CH), 131.17 (CH), 135.22 (C—Cl), 138.25 (C), 142.90 (C), 144.09 (C), 145.29 (C—CH_3 of pyrimidone ring), 162.35 (C), 165.59 (>C=O); Anal. Calcd for $C_{22}H_{17}N_4O_2Cl$: C 65.27, H 4.23, N 13.84; Found: C 65.29, H 4.22, N 13.82.

4-(4-Chlorophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6g). Dark brown solid; 66%; mp: 226–228°C; IR (KBr) υ (cm^{-1}): 3155 (—NH), 3067 (Ar C-H), 1730 (>C=O), 1631 (—C=N), 1136, 1062 (C—O—C), 752 (C—Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.16 (s, 1H, —NH), 7.90–6.66 (m, 9H, Ar-H), 4.84 (s, 1H, —CH), 2.44 (s, 3H, —CH_3), 1.79 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.51 (CH_3), 19.76 (C—CH_3 of pyrimidone ring), 38.42 (CH), 94.80 (C), 99.98 (C), 122.26 (CH), 128.43 (CH), 129.09 (CH), 130.16 (CH), 131.31 (C—Cl), 138.29 (C), 143.57 (C), 144.13 (C), 145.41 (C—CH_3 of pyrimidone ring), 162.53 (C), 165.76 (>C=O); Anal. Calcd for $C_{22}H_{17}N_4O_2Cl$: C 65.27, H 4.23, N 13.84; Found: C 65.26, H 4.25, N 13.82.

3,7-Dimethyl-4-(3-nitrophenyl)-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6h). Light brown solid; 61%; mp: 250–253°C; IR (KBr) υ (cm^{-1}): 3148 (—NH), 3065 (Ar C-H), 1728 (>C=O), 1636 (—C=N), 1542, 1360 (—NO_2 asym, sym), 1140, 1064 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.14 (s, 1H, —NH), 7.94–6.72 (m, 9H, Ar-H), 4.86 (s, 1H, —CH), 2.45 (s, 3H, —CH_3 of pyrimidone ring), 1.81 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.26 (CH_3), 19.91 (C—CH_3), 36.05 (CH), 94.75 (C), 99.90 (C), 122.71 (CH), 124.37 (CH), 128.19 (CH), 129.02 (CH), 132.79 (CH), 133.66 (CH), 138.35 (C), 143.89 (C), 144.95 (C), 145.23 (C—CH_3), 148.56 (C—NO_2), 161.92 (C), 165.28 (>C=O); Anal. Calcd for $C_{22}H_{17}N_5O_4$: C 63.61, H 4.12, N 16.86; Found: C 63.59, H 4.10, N 16.85.

4-(3-Bromophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6i). Yellowish brown solid; 68%; mp: 268–271°C; IR (KBr) υ (cm^{-1}): 3150 (—NH), 3070 (Ar C-H), 1725 (>C=O), 1628 (—C=N), 1135, 1058 (C—O—C), 855 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.15 (s, 1H, —NH), 7.98–6.76 (m, 9H, Ar-H), 4.86 (s, 1H, —CH), 2.41 (s, 3H, —CH_3), 1.82 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.40 (CH_3), 19.94 (C—CH_3 of pyrimidone ring), 38.16 (CH), 94.69 (C), 100.11 (C), 122.50 (CH), 125.22 (C-Br), 127.14 (CH), 128.21 (CH), 129.42 (CH), 131.03 (CH), 138.34 (C), 143.91 (C), 144.89 (C), 145.35 (C—CH_3), 160.39 (C), 165.75 (>C=O); Anal. Calcd for $C_{22}H_{17}N_4O_2Br$: C 58.81, H 3.81, N 12.47; Found: C 58.83, H 3.82, N 12.49.

3,7-Dimethyl-4-(4-methylphenyl)-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5(1H)-one (6j). Dark brown solid; 63%; mp: 218–221°C; IR (KBr) υ (cm^{-1}): 3153 (—NH), 3062 (Ar C-H), 2857 (—CH_3), 1734 (>C=O), 1633 (—C=N), 1133, 1063 (C—O—C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.13 (s, 1H, —NH), 7.87–6.69 (m, 9H, Ar-H), 4.83 (s, 1H, —CH), 2.34 (s, 3H, —CH_3), 2.43 (s, 3H, —CH_3), 1.80 (s, 3H, —CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.48 (CH_3), 20.19 (C—CH_3 of pyrimidone ring), 22.34 (C—CH_3 of phenyl ring), 38.33 (CH), 94.56 (C), 99.42 (C), 122.26 (CH), 127.44 (CH), 128.35 (CH), 129.29 (CH), 130.75 (CH), 134.93 (C—CH_3 of phenyl ring), 137.84 (C), 143.87 (C), 144.95 (C), 145.64 (C—CH_3 of pyrimidone ring), 162.28 (C), 165.61 (>C=O); Anal. Calcd for $C_{23}H_{20}N_4O_2$: C 71.86, H 5.24, N 14.57; Found: C 71.85, H 5.22, N 14.59.

IN VITRO ANTIMICROBIAL SCREENING

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs ampicillin, nystatin, and greseofulvin. Mueller–Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 colony forming unit per milliliter by comparing the turbidity. Dimethyl sulfoxide (DMSO) was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compound concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test included a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted obtaining 2000 μg/mL concentration, as a stock solution. In primary screening 1000, 500, and 250 μg/mL concentrations of the synthesized

compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 200, 150, 125, 100, 62.5, 50, 25, 12.5, 6.250, 3.125, and 1.562 μg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

IN VITRO ANTITUBERCULAR SCREENING

Drug susceptibility and % inhibition of the test compounds against *M. tuberculosis H37Rv* were performed by L. J. medium (conventional method) where primary 62.5 μg/mL dilutions of each test compound were added liquid L. J. Medium and then media were sterilized by inspissations method. A culture of *M. tuberculosis H37Rv* growing on L. J. medium was harvested in 85% saline in bijou bottles. All the test compounds were dissolved in DMSO. These tubes were then incubated at 37°C for 24 h followed by streaking of *M. tuberculosis H37Rv* (5 × 104 bacilli per tube). These tubes were then incubated at 37°C. Growth of bacilli was seen after 12 days, 22 days, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis H37Rv*. The standard strain *M. tuberculosis H37Rv* was tested with known drug rifampicin (40 μg/mL; 99%).

Acknowledgment. The authors are thankful to the Department of Chemistry, V. N. S. G. University, Surat, for providing the laboratory facilities, Atul Ltd., Valsad, for library and chemical facilities, and D. Rajani, Microcare Laboratory, Surat, for antitubercular and antimicrobial activity. The authors also thank RTML, Vapi, SAIF, Chandigarh, and CDRI, Lucknow, for analytical facilities.

REFERENCES AND NOTES

[1] Bedair, A. H.; El-Hady, N. A.; El-Latif, M. S. A; Fakery, A. H.; El-Agrody, A. M. Farmaco 2000, 55, 708.

[2] Fakery, A. H.; El-Sayed, E. M.; El-Ghareab, K. A. Acta Pharm 2000, 50, 111.

[3] El-Agrody, A. M.; El-Latif, M. S. A.; El-Hady, N. A.; Fakery, A. H.; Bedair, A. H. Molecules 2001, 6, 519.

[4] Ramiz, M. M. M.; El-Sayed, W. A.; El-Tantawy, A. I.; Abdel-Rahman, A. A. H. Arch Pharm Res 2010, 33, 647.

[5] Thumar, N. J.; Patel, M. P. Arkivoc 2009, 13, 363.

[6] Mishriky, N.; Girgis, A. S.; Asaad, F. M.; Ibrahim, Y. A.; Sobieh, U. I.; Fawzy, N. G. Boll Chim Farm 2001, 140, 129.

[7] Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K. A. R.; El-Agrody, A. M. Farmaco 2001, 56, 965.

[8] Ferreira, S. B.; da Silva, F. C.; Bezerra, F. A. F. M.; Lourenco, M. C. S.; Kaiser, C. R.; Pinto, A. C.; Ferreira, V. F. Archiv der Pharmazie 2010, 343, 81.

[9] Vyas, D. H.; Tala, S. D.; Akbari, J. D.; Dhaduk, M. F.; Joshi, K. A.; Joshi, H. S. Ind J Chem 2009, 48B, 833.

[10] Angeles, M. G.; Marco, J. Bioorg Med Chem Lett 1997, 24, 3165.

[11] Xuesen, F. D. F.; Yingying, Q.; Xinying, Z.; Wang, J.; Loiseau, P. M.; Andrei, G.; Snoeck, R.; Clercq, E. D. Bioorg Med Chem Lett 2010, 20, 809.

[12] Kumar, D, Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. Eur J Med Chem 2009, 44, 3805.

[13] Sanfilippo, P. J.; McNally, J. J.; Press, J. B.; Falotico, R.; Giardino, E.; Katz, L. B. Bioorg Med Chem Lett 1993, 3, 1385.

[14] Ram, V. J.; Goel, A.; Shukla, P. K.; Kapil, A. Bioorg Med Chem Lett 1997, 7, 3101.

[15] Chiou, W. F.; Li, S. Y.; Ho, L. K.; Hsien, M. L.; Don, M. J. Eur J Med Chem 2002, 37, 69.

[16] Smith, C. W.; Bailey, J. M.; Billingham, M. E. J.; Chandrasekhar, S.; Dell, C. P.; Harvey, A. K.; Hicks, C. A.; Kingston, A. E.; Wishart, G. N. Bioorg Med Chem Lett 1995, 5, 2783.

[17] Aytemir, M. D.; Cali, U.; Ozalp, M. Arch Pharm 2004, 337, 281.

[18] Hamilton, H. W.; Tait, B. D.; Gajda, C.; Hagen, S. E.; Ferguson, D.; Lunney, E. A.; Pavlovsky, A.; Tummino, P. J. Bioorg Med Chem Lett 1996, 6, 719.

[19] Smith, P. W.; Robinson, J. E.; Evans, D. N.; Sollis, S. L.; Howes, P. D.; Trivediand, N.; Bethell, R. C. Bioorg Med Chem Lett 1999, 9, 601.

[20] Kerrigan, S. A.; Pritchard, R. G.; Smith, P. W.; Stoodley, R. J. Tetrahedron Lett 2001, 42, 8889.

[21] Kolokythas, G.; Kostakis, I. K.; Pouli, N.; Marakos, P.; Kousidou, O. C.; Tzanakakis, G. N.; Karamanos, N. K. Eur J Med Chem 2007, 42, 307.

[22] Ali, T. E. Eur J Med Chem 2009, 44, 4385.

[23] Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Akberali, P. M.; Shetty, N. S. Bioorg Med Chem Lett 2006, 14, 2040.

[24] Kumar, N.; Singh, G.; Yadav, A. K. Heteroat Chem 2001, 12, 52.

[25] Sondhi, S. M.; Singh, N.; Johar, M.; Kumar, A. Bioorg Med Chem 2005, 13, 6158.

[26] Amr, A. G. E.; Mohamed, A. M.; Mohamed, S. F.; Abdel-Hafez, N. A.; Hammam, F.G.; Bioorg Med Chem 2006, 14, 5481.

[27] Padmaja, A.; Payani, T.; Reddy, G. D.; Padmavathi, V. Eur J Med Chem 2009, 44, 4557.

[28] Sharma, P.; Kumar, A.; Sharma, M.; Eur J Med Chem 2006, 41, 833.

[29] Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, M. E. Bioorg Med Chem 2008, 16, 7102.

[30] Hafez, H. N.; El-Gazzar, A. B. A.; Nawwar, G. A. M. Eur J Med Chem 2010, 45, 1485.

[31] Roma, G.; Cinone, N.; Braccio, M. D.; Grossi, G.; Bioorg Med Chem 2000, 8, 751.

[32] Ranise, A.; Spallarossa, A.; Schenone, S.; Bruno, O.; Bondavalli, F.; Pani, A.; Marongiu, M. E.; Mascia, V.; Colla, P. L.; Loddo, R. Bioorg Med Chem 2003, 11, 2575.

[33] Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Noaman, E.; Ghorab, M. M. Eur J Med Chem 2010, 45, 738.

[34] Abdel-Rahman, B.; Hussein, H. A. R.; Hafez, H. N. Acta Pharm 2007, 57, 395.

[35] Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K. A. R.; El-Agrody, A. M. Farmaco 2001, 56, 965.

[36] Shamroukh, A. H.; Rashad, A. E.; Sayed, H. H.; Phosphorus Sulfur Silicon Relat Elem 2005, 180, 2347.

[37] Krayushkin, M. M.; Ivanov, S. N.; Martynkin, A. Y.; Lichitsky, B. V.; Dudinov, A. A.; Uzhinov, B. M. Russ Chem Bull 2001, 50, 2424.

[38] Nalbandyan, G. K.; Mkrtchyan, A. P.; Noravyan, A. S.; Dzhagatspanyan, I. A.; Melikyan, G. G.; Sukasyan, R. S. Pharma Chem J 1999, 33, 74.

[39] Abdel-Razik, H. H. Chem Pap 2006, 60, 268.

[40] Dandia, A.; Arya, K.; Khaturia, S.; Yadav, P. Arkivoc 2005, 13, 80.

[41] Fadda, A. A.; El-Latif, E. A.; Bondock, S.; Samir, A. Synth Commun 2008, 38, 4352.

[42] Elkholy, Y. M.; Morsy, M. A. Molecules 2006, 11, 890.

[43] Kamdar, N. R.; Haveliwala, D. D.; Mistry, P. T.; Patel, S. K. Med Chem Res 2011, 20, 854.

[44] Kamdar, N. R.; Haveliwala, D. D.; Mistry, P. T.; Patel, S. K. Eur J Med Chem 2010, 45, 5056.

[45] Jin, T. S.; Wang, A. Q.; Cheng, Z. L.; Zhang, J. S.; Li., T. S. Synth Commun 2005, 35, 137.

[46] Rattan, A. Antimicrobials in Laboratory Medicine, Churchill, B. I., Livingstone: New Delhi, 2000, pp. 85–108.