ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 11, pp. 2712–2718. © Pleiades Publishing, Ltd., 2017.

The New Green Procedure for Pyrazolopyrimidinone Based Dihydropyrimidinones and Their Antibacterial Screening[1]

Muralidhar Allam, A. K. D. Bhavani*, and Sumathi Vodnala

Department of Chemistry, University College of Science, Osmania University, Hyderabad, Telangana, 500007 India
**e-mail: durgabhavani237@gmail.com*

Received October 7, 2017

Abstract—A series of novel hybrid aza heterocycles containing pyrazolopyrimidinone and dihydropyrimidinone scaffolds was developed using Cu(II) catalyzed Biginelli condensation as an efficient, new green synthetic method under mild and solvent free conditions. Pyrazolopyrimidinone based aldehydes, alkyl acetoacetates and urea/thiourea were used as the components in the reaction to afford hybrid aza heterocycles in high to excellent yields. The products were screened for in vitro antibacterial activity and all of those demonstrated high to excellent activity.

Keywords: pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one, 3,4-dihydropyrimidin-2(1*H*)-one, Biginelli reaction, $CuCl_2 \cdot 2H_2O$, antibacterial activity

DOI: 10.1134/S1070363217110299

Pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one ring system, structurally analogous to nucleotide base, is an important structural template in medicinal research and in drug discovery. The derivatives of pyrazolopyrimidinones have potential biological properties by exhibiting anti-viral, antitumor activity [1] in addition to analgesic, antifungal, antimicrobial, anti-proliferative, anticoagulant and anti-inflammatory activities [2].

On the other hand, 3,4-dihydropyrimidin-2(1*H*)-one (DHPM), either from natural or synthetic origin are having wide range of biological applications. The marine alkaloids Crambescidins and Crambescins containing a DHPM core were significantly known to possess antiviral and cytotoxic properties [3]. Batzelladines A and B with DHPM core were recognized as anti HIV agents [4]. The synthesized DHPM derivatives are also well known for potent vasodilative, antiviral, anti-tubercular and anticancer activities [5, 6]. Generally, the dihydropyrimidinones are synthesized by Biginelli condensation method as an oldest well known multicomponent acid or Lewis acid catalyzed reaction [7–12]. Low price, readily available cupric chloride dihydrate was also used as a green catalyst in the preparation of DHPM either in the presence of aqueous surfactant [13] or concentrated HCl [14] or under microwave conditions [15]. Here we are reporting an efficient green synthesis of novel dihydropyrimidinones from pyrazolopyrimidinone based aldehydes utilizing $CuCl_2 \cdot 2H_2O$ catalyzed Biginelli method as an environmentally benign synthesis under mild and solvent free conditions at 100°C.

RESULTS AND DISCUSSION

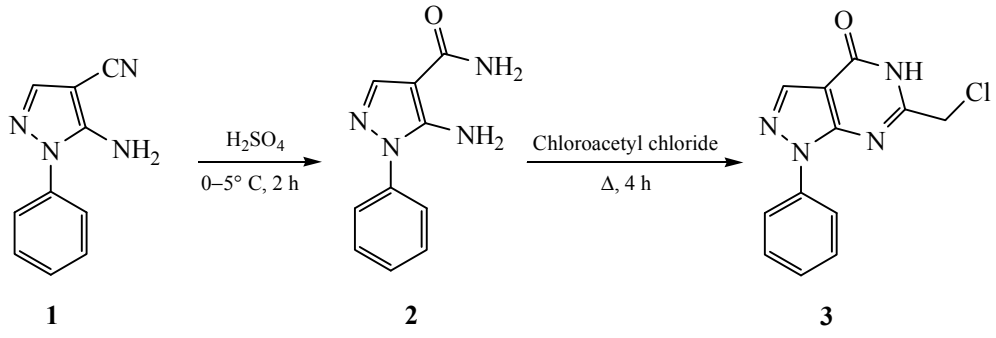
6-(Chloromethyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**3**) was chosen as the starting compound for preparation of target pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one based dihydropyrimidinones. The former was synthesized in two steps from 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile (**1**) via the amide compound **2** (Scheme 1) [16].

The amide nitrogen in compound **3** was methylated using dimethyl sulfide in dry acetone to afford methylated derivative **4**. The structure of compound **4** was confirmed by spectral data. The presence of N-CH_3 and CH_2Cl groups in **4** were evidenced by the appearance of singlet signals at 3.76 and 4.66 ppm respec-tively in its ^{1}H NMR spectrum and at 30.4 and 44.4 ppm in ^{13}C NMR spectrum.

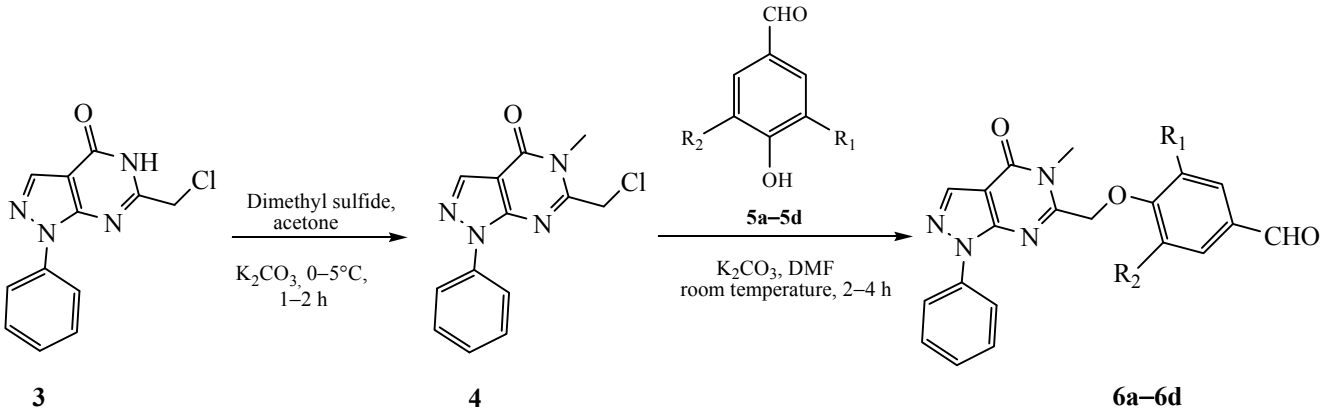
The key precursors of the target compounds, pyrazolopyrimidinone based aldehydes, were obtained by using the chloromethyl compound **4** and various *p*-hydroxy araldehydes. Dehydrohalogenation reaction of compound **4** with *p*-hydroxy araldehydes **5a–5d** in the presence of potassium carbonate in DMF at room temperature lasted for 2–4 h and gave the corres-

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 6-(chloromethyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**3**).



Scheme 2. Synthesis of 4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}araldehydes (**6a–6d**).



6: $R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = OMe$ (**b**); $R^1 = H$, $R^2 = OEt$ (**c**); $R^1 = R^2 = OMe$ (**d**).

ponding 4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}araldehydes (**6a–6d**) in high yields (Scheme 2). In the aldehyde derivatives **6a–6d** presence of the singlet signal in the range of 9.86–9.92 ppm and at 190.7 ppm in the corresponding ^{1}H NMR and ^{13}C NMR spectra, respectively, indicated the aldehyde group in the products. Presence of the OCH_2 group was confirmed by appearance of a singlet in the region of ^{1}H NMR 5.22–5.33 ppm and a singlet signal at 69.2–73.6 ppm of ^{13}C NMR spectra.

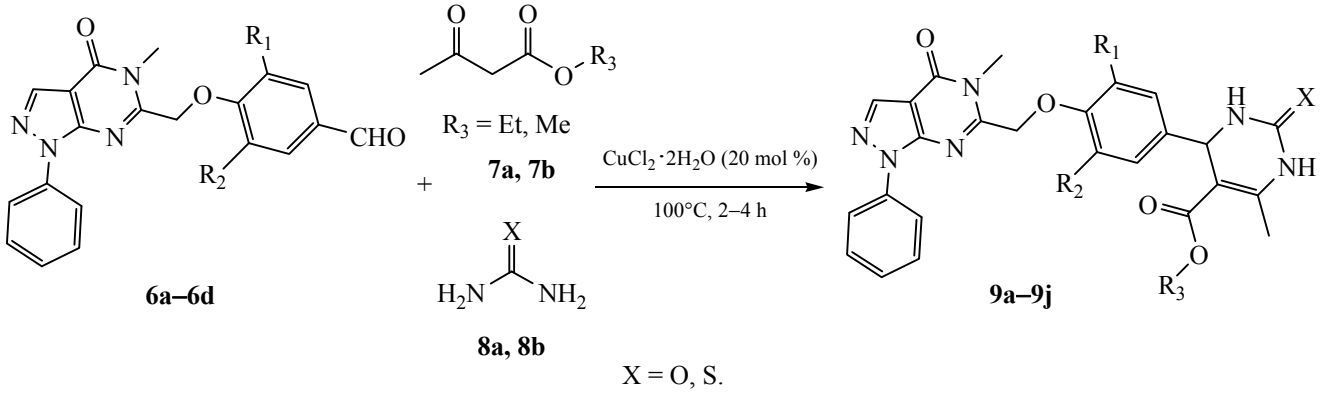
Initially, the Biginelli condensation of pyrazolopyrimidinone based aldehyde **6a** with ethyl acetoacetate **7a**, and urea **8a** was carried out in approximately equimolar ratio using 20 mol % of copper chloride as a catalyst at 100°C under solvent free conditions giving the product **9a** (Scheme 3). The reaction did not proceed without a catalyst or gave traces of the product.

The method was further extended to the synthesis of various pyrazolopyrimidinone based dihydropyrimidinones. The Biginelli condensation reaction of pyrazolopyrimidinone based aldehydes **6a–6d** was carried out individually with ethyl acetoacetate **7a** or methyl acetoacetate **7b** and urea **8a** or thiourea **8b** under the optimized conditions (Table 1).

Structures of dihydropyrimidinone derivatives **9a–9j** were confirmed based on their spectral data. For example, the compound **9a** exhibited signals for dihydropyrimidinone ring protons at 5.29 ppm as a singlet (C<u>H</u>). The ethoxy and methyl groups of DHPM were indicated by signals at 1.11 as a triplet ($CH_2C\underline{H}_3$), 3.99 as quartet ($C\underline{H}_2CH_3$) and at 2.54 ppm as a singlet (DHPM–$C\underline{H}_3$) in the ^{1}H NMR spectrum. Structure for the compound **9a** was confirmed by HRMS that demonstrated the $[M + H]^+$ peak *m/z* at 515.2013, correlated with the molecular formula $C_{27}H_{27}N_6O_5$.

Biological evaluation. *Antibacterial activity.* The newly synthesized compounds **9a–9j** were screened for their antibacterial activity against *Escherichia coli*, *Klebsyella pneumonia, Staphylococcus aureus,* and *Bacillus subtilis* strains by the disk diffusion method [17]. Ampicillin was used as a control and its solution as well as the test compounds solutions were made

Scheme 3. Synthesis of pyrazolopyrimidinone based dihydropyrimidinones **9a–9j**.



with concentrations of 10, 20, and 30 μg/mL in DMSO. Antibacterial activity was measured as zone of inhibition in mm (Table 2). According to the accumulated data all compounds demonstrated high to excellent activity. Though the compounds **9e** and **9f** did not show any activity against *E. coli,* and **9d** was inactive against *K. pneumonia*.

EXPERIMENTAL

Melting points were measured in open capillary tubes. ^{1}H and ^{13}C NMR spectra were measured on a Bruker-Avance (400 MHz) Spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. High Resolution Mass Spectra were measured on a Q-TOF mass spectrometer. Purity of the compounds was tested by TLC on silica gel plates.

Table 1. Physical data of the compounds **9a–9j**[a,b]

Comp. no.	Substituents	Yield, %
9a	R_1 = H, R_2 = H, R_3 = Et, X = O	80
9b	R_1 = H, R_2 = H, R_3 = Me, X = O	81
9c	R_1 = H, R_2 = OMe, R_3 = Et, X = O	89
9d	R_1 = H, R_2 = OMe, R_3 = Me, X = O	78
9e	R_1 = H, R_2 = OEt, R_3 = Me, X = O	76
9f	R_1 = R_2 = OMe, R_3 = Me, X = O	96
9g	R_1 = H, R_2 = OEt, R_3 = Et, X = S	80
9h	R_1 = H, R_2 = OEt, R_3 = Me, X = S	80
9i	R_1 = R_2 = OMe, R_3 = Et, X = S	81
9j	R_1 = R_2 = OMe, R_3 = Me, X = S	88

[a] Isolated yields. [b] All reactions were carried out using 0.2 mmol of **6**, **8** with 0.22 mmol of **7** in the presence of 20 mol % of $CuCl_2 \cdot 2H_2O$ at 100°C for 2–4 h.

Synthesis of 6-(chloromethyl)-5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (4). To a solution of compound **3** (5 g, 19.23 mmol) in dry acetone 3 equiv. of K_2CO_3 (7.96 g, 57.69 mmol) were added. The mixture was stirred at 0–5°C for 10 min, then 1.2 equiv. of dimethyl sulfide (1.41 g, 22.8 mmol) was added drop wise and stirred for 2 h. After completion of the reaction, the solvent was distilled off and the remaining mixture poured into ice cold water. The separated crude product was filtered off and purified by silica gel column chromatography using petroleum ether–ethyl acetate mixture (8 : 2) as an eluent to afford the compound **4.** Yield 90%, mp 168–170°C. ^{1}H NMR spectrum, δ, ppm: 3.76 s (3H, NCH_3), 4.66 s (2H, CH_2Cl), 7.34–7.40 m (1H, Ar-H), 7.48–7.56 m (2H, Ar-H), 8.03–8.09 m (2H, Ar-H), 8.26 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 30.4, 44.4, 106.3, 122.0, 127.2, 129.1, 136.2, 138.3, 149.7, 154.6, 158.0.

Synthesis of 4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}-araldehydes (6a–6d). To a solution of compound **4** (1 g, 3.63 mmol) in DMF, 3 equiv. of K_2CO_3 (1.5 g, 10.9 mmol) were added and stirred for 10 min. Then 4.3 mmol of *p*-hydroxy aromatic aldehyde **5** (4.3 mmol) were added and the reaction mixture was stirred for 2–4 h. After completion of the process, the resultant mixture was poured into the ice cold water, the solid residue was filtered off and dried. The crude product was purified by column chromatography using petroleum ether–ethyl acetate mixture (8 : 2) as an eluent to afford the corresponding compounds **6a–6d**.

4-{(5-Methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}benzaldehyde

Table 2. Anti-bacterial activity of synthesized compounds **9a–9j**

Comp. no.	Bacterial growth inhibition zone, mm											
	B. Subtilis			*E. Coli*			*K. Pneumonia*			*S. Aureus*		
	concentration, μg/mL											
	10	20	30	10	20	30	10	20	30	10	20	30
9a	14	16	20	15	16	20	12	14	17	13	15	18
9b	15	16	19	–	–	–	12	15	17	14	16	19
9c	14	17	19	16	18	20	13	16	18	12	16	18
9d	15	15	17	14	18	20	–	–	–	11	13	17
9e	12	16	17	–	–	–	12	18	18	14	17	19
9f	13	16	19	–	–	–	14	16	20	15	17	19
9g	14	16	18	14	16	18	15	17	19	14	17	21
9h	16	19	22	19	21	23	16	18	21	19	21	24
9i	14	16	18	15	17	19	14	15	17	16	17	19
9j	17	20	22	18	19	23	16	18	21	19	21	23
Ampicillin	16	18	21	17	18	22	15	17	20	18	20	22

(6a). Yield 93%, mp 164–166°C. ^{1}H NMR spectrum, δ, ppm: 3.74 s (3H, NCH_3), 5.30 s (2H, OCH_2), 7.13–7.19 m (2H, Ar-H), 7.32–7.39 m (1H, ArH), 7.43–7.50 m (2H, Ar-H), 7.85–7.92 m (2H, Ar-H), 7.96–8.01 m (2H, Ar-H), 8.26 s (1H, pyrazole-H), 9.92 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 30.3, 69.3, 106.3, 115.1, 121.8, 127.3, 129.1, 131.1, 132.0, 136.2, 138.3, 149.7, 153.8, 158.0, 162.1, 190.5.

3-Methoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}benzaldehyde (6b). Yield 93%, mp 189–191°C. ^{1}H NMR spectrum, δ, ppm: 3.76 s (3H, NCH_3), 3.92 s (3H, OCH_3), 5.33 s (2H, OCH_2), 7.16 d (1H, J = 8.1 Hz, Ar-H), 7.30–7.39 m (1H, Ar-H), 7.49–7.43 m (4H, Ar-H), 7.94–8.00 m (2H, Ar-H), 8.25 s (1H, pyrazole-H), 9.87 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 30.2, 56.06, 69.2, 106.3, 115.1, 121.8, 127.3, 129.1, 131.1, 132.0, 136.2, 138.3, 149.7, 153.8, 158.0, 162.1, 190.5.

3-Ethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}benzaldehyde (6c). Yield 95%, mp 128–130°C. ^{1}H NMR spectrum, δ, ppm: 1.45 t (3H, J = 7.0 Hz, CH_2–C<u>H</u>$_3$), 3.79 s (3H, NCH_3), 4.15 q (2H, J = 7.0 Hz, C<u>H</u>$_2$–CH_3), 5.32 s (2H, OCH_2), 7.18 d (1H, J = 8.0 Hz, Ar-H), 7.35 t (1H, J = 7.4 Hz, Ar-H), 7.39–7.51 m (4H, Ar-H), 7.99 d (2H, J = 7.7 Hz, Ar-H), 8.26 s (H, pyrazole-H), 9.86 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 30.2, 64.5, 70.4, 106.4, 111.0, 113.9, 121.8, 125.7, 127.1, 129.0, 131.6, 136.1, 138.4, 149.7, 149.8, 152.0, 154.0, 158.1, 190.7.

3,5-Dimethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}benzaldehyde (6d). Yield 90%, mp 174–176°C. ^{1}H NMR spectrum, δ, ppm: 3.84 s (6H, OCH_3), 3.93 s (3H, NCH_3), 5.22 s (2H, OCH_2), 7.10 s (2H, Ar-H), 7.28–7.35 m (1H, Ar-H), 7.7–7.48 m (2H, Ar-H), 7.81–7.92 m (2H, Ar-H), 8.25 s (1H, pyrazole-H), 9.86 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 30.5, 56.1, 73.6, 106.2, 121.1, 126.9, 128.9, 132.7, 136.0, 138.3, 140.3, 149.8, 153.7, 154.9, 158.3, 190.8.

Synthesis of pyrazolopyrimidinone based dihydropyrimidinone derivatives (9a–9j). $CuCl_2 \cdot 2H_2O$ (20 mol %) was added to a mixture of an aldehyde **6** (0.2 mmol) with 1.1 equiv. of alkyl acetoacetate **7** (0.22 mmol) and 1 equivalent of urea/thiourea **8** (0.2 mmol). The reaction mixture was heated at 100°C for 2–4 h. Upon completion of the process (according to TLC), the reaction mixture was poured into an ice-cold water and stirred for 5–10 min. The precipitated crude product was filtered off and purified by column chromatography using petroleum ether–ethyl acetate mixture (6 : 4) as an eluent to afford the compounds **9a–9j.**

Ethyl 6-methyl-4-(4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9a). Yield 80%, mp 260–262°C. ^{1}H NMR spectrum, δ, ppm: 1.11 t (3H, *J* = 7.0 Hz, CH_2-C<u>H</u>$_3$), 2.54 s (3H, DHPM-CH_3), 3.67 s (3H, NCH_3), 3.99 q (2H, *J* = 7.2 Hz, C<u>H</u>$_2$–CH_3), 5.14 s (2H, OCH_2), 5.29 s (1H, CH), 5.75 br.s (1H, NH), 6.91 d (2H, *J* = 8.4 Hz, Ar-H), 7.22–7.25 m (2H, Ar-H), 7.29 d (1H, *J* = 7.6 Hz, Ar-H), 7.43 s (2H, Ar-H), 7.71 br.s (1H, NH), 7.97 d (2H, *J* = 7.3 Hz, Ar-H), 8.19 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 18.2, 53.6, 59.5, 66.7, 70.2, 100.0, 105.7, 115.1, 121.3, 127.2, 127.6, 129.5, 136.5, 138.1, 138.4, 148.6, 150.3, 152.6, 157.0, 157.3, 157.7, 165.8. HRMS [ESI], *m/z*: 515.2013 (515.2043) $[M + H]^+$. $C_{27}H_{27}N_6O_5$.

Methyl 6-methyl-4-(4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9b). Yield 81%, mp 256–258°C. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, DHPM-CH_3), 3.56 s (3H, NCH_3), 3.68 s (3H, OCH_3), 5.15 s (2H, OCH_2), 5.30 s (1H, CH), 5.72 br.s (1H, NH), 6.59 br.s (1H, NH), 6.92 d (2H, *J* = 8.7 Hz, Ar-H), 7.23 s (1H, Ar-H), 7.26 – 7.34 m (1H, Ar-H), 7.44 t (2H, *J* = 7.9 Hz, Ar-H), 7.73 s (1H, Ar-H), 7.99 d (2H, *J* = 7.6 Hz, Ar-H), 8.20 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 17.4, 28.3, 49.7, 68.1, 76.2, 113.4, 120.5, 124.0, 125.8, 126.7, 127.8, 134.7, 136.9, 142.4, 146.5, 147.4, 148.5, 151.4, 155.6, 157.8, 161.4, 165.9. HRMS [ESI], *m/z*: 501.1880 (501.1808) $[M + H]^+$. $C_{26}H_{25}N_6O_5$.

Ethyl 4-(3-methoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9c). Yield 89%, mp 212–214°C. ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, *J* = 7.1 Hz, CH_2–C<u>H</u>$_3$), 2.35 s (3H, DHPM-CH_3), 3.77 s (3H, NCH_3), 3.83 s (3H, OCH_3), 4.07 q (2H, *J* = 7.1 Hz, C<u>H</u>$_2$-CH_3), 5.21 s (2H, OCH_2), 5.38 s (1H, CH), 5.49 br.s (1H, NH), 6.85 d (1H, *J* = 8.1 Hz, Ar-H), 6.89 d (1H, *J* = 1.8 Hz, Ar-H) 6.97 d, (1H, *J* = 8.2 Hz, Ar-H), 7.22 br.s (1H, NH), 7.34 t (1H, *J* = 7.4 Hz, Ar-H), 7.48 t (2H, *J* = 7.9 Hz, Ar-H), 8.02 d (2H, *J* = 7.7 Hz, Ar-H), 8.25 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 14.2. 18.9, 30.3, 55.4, 55.9, 60.1, 70.9, 101.4, 110.4, 113.5, 114.8, 116.7, 117.7, 118.6, 121.9, 127.0, 129.1, 136.0, 138.5, 145.9, 146.4, 150.0, 152.8, 154.8, 165.5. HRMS [ESI], *m/z*: 545.2137 (545.2149) $[M + H]^+$. $C_{28}H_{29}N_6O_6$.

Methyl 4-(3-methoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9d). Yield 78%, mp 238–240°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, DHPM-CH_3), 3.62 s (3H, NCH_3), 3.77 s (3H, OCH_3), 3.84 s (3H, OCH_3), 5.21 s (2H, OCH_2), 5.31 br.s (1H, NH), 5.36 s (1H, CH), 6.63 br.s (1H, NH), 6.84 d.d, (1H, *J* = 8.2, 2.1 Hz, Ar-H), 6.89 d (1H, *J* = 2.0 Hz, Ar-H), 6.98 d (1H, *J* = 8.3 Hz, Ar-H), 7.35 t (1H, *J* = 7.4 Hz, Ar-H), 7.48 t (2H, *J* = 7.9 Hz, Ar-H), 8.02–8.03 m (2H, Ar-H), 8.25 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 18.4. 30.3, 51.1, 54.4, 56.0, 70.5, 100.2, 106.2, 110.7, 114.8, 118.3, 121.6, 127.0, 128.9, 135.8, 138.3, 139.1, 146.0, 147.6, 149.6, 149.9, 158.0, 166.2. HRMS [ESI], *m/z*: 531.1969 (531.1992) $[M + H]^+$. $C_{27}H_{27}N_6O_6$.

Methyl 4-(3-ethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9e). Yield 76%, mp 240–242°C. ^{1}H NMR spectrum, δ, ppm: 1.39 s (3H, OCH_2–C<u>H</u>$_3$), 2.33 s (3H, DHPM-CH_3), 3.63 s (3H, NCH_3), 3.81 s (3H, OCH_3), 4.04 d (2H, *J* = 6.3 Hz, OCH_2–CH_3), 4.95 br.s (1H, NH), 5.21 s (2H, OCH_2), 5.62 br.s (1H, NH), 6.74 s (1H, CH), 6.89–6.95 m (2H, Ar-H), 7.29–7.36 m (2H, Ar-H), 7.45–7.54 m (2H, Ar-H), 8.03 d (2H, *J* = 7.0 Hz, Ar-H), 8.25 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 14.7, 18.8, 30.4, 55.4, 60.1, 64.4, 71.4, 101.7, 106.4, 111.8, 116.2, 118.6, 121.8, 127.0, 129.0, 136.1, 138.4, 138.91, 145.7, 146.5, 149.6, 149.9154.8, 158.3, 165.6. HRMS [ESI], *m/z*: 545.2137 (545.2149) $[M + H]^+$. $C_{27}H_{27}N_6O_5$.

Methyl 4-(3,5-dimethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9f). Yield 96%, mp 249–251°C. ^{1}H NMR spectrum, δ, ppm: 1.19 s (3H, DHPM-CH_3), 3.52 s (3H, OCH_3), 3.69 s (6H, 2OCH_3), 3.87 s (3H, NCH_3), 5.03 s (2H, OCH_2), 5.25 s (1H, CH), 6.00 br.s (1H, NH), 6.47 s (1H, Ar-H), 7.27 s (2H, Ar-H), 7.40 s (2H, Ar-H), 7.90 d (2H, *J* = 7.0 Hz, Ar-H), 7.98 br.s (1H, NH), 8.18 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 18.6, 30.6, 51.0, 55.4, 55.9, 73.8, 100.5, 103.2, 106.2, 121.7, 126.9, 128.9, 134.7, 135.9, 138.5, 140.8, 147.0, 150.1, 153.1, 153.3, 155.5, 158.5, 166.1.

Ethyl 4-(3-ethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)meth-

oxy}phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9g). Yield 80%, mp 225–227°C. ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, *J* = 7.1 Hz, CH_2–C<u>H</u>$_3$), 1.41 t (3H, *J* = 7.0 Hz, CH_2–C<u>H</u>$_3$), 2.34 s (3H, DHPM-CH_3), 3.81 s (3H, NCH_3), 4.05 d.q (4H, *J* = 10.2, 7.0 Hz, 2C<u>H</u>$_2$–CH_3), 5.21 s (2H, OCH_2), 5.36 s (1H, CH), 5.44 br.s (1H, NH), 6.84 d.d (1H, *J* = 8.2 Hz, ArH), 6.87 s (1H, Ar-H), 6.97 d (1H, *J* = 8.3 Hz, Ar-H), 6.99 br.s (1H, NH), 7.35 t (1H, *J* = 7.4 Hz, Ar-H), 7.48 t (2H, *J* = 7.9 Hz, Ar-H), 8.02 d (2H, *J* = 7.6 Hz, Ar-H), 8.25 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 13.8, 14.5, 18.6, 30.2, 55.2, 59.9, 64.2, 71.2, 101.5, 106.2, 111.6, 116.0, 118.4, 121.6, 126.8, 128.8, 135.9, 138.2, 138.7, 145.5, 146.3, 149.4, 149.7, 154.6, 158.1, 165.3, 174.1.

Methyl 4-(3-ethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9h). Yield 80%, mp 238–240°C. ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, *J* = 7.0 Hz, OCH_2–C<u>H</u>$_3$), 2.34 s (3H, DHPM-CH_3), 3.62 s (3H, NCH_3), 3.81 s (3H, OCH_3), 4.04 q (2H, *J* = 6.9 Hz, OC<u>H</u>$_2$–CH_3), 5.21 s (2H, OCH_2), 5.35 s (1H, CH), 5.44 br.s (1H, NH), 6.88–6.84 m (2H, Ar-H), 6.99 d (1H, *J* = 8.2 Hz, Ar-H),7.09 br.s (1H, NH), 7.35 t (1H, *J* = 7.4 Hz, Ar-H), 7.48 t (2H, *J* = 7.9 Hz, Ar-H), 8.03 d (2H, *J* = 7.8 Hz, Ar-H), 8.25 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 18.5, 30.3, 50.8, 54.7, 64.2, 71.3, 100.3, 106.2, 111.8, 115.9, 118.5, 121.7, 126.9, 129.0, 135.8, 138.3, 139.5, 146.2, 147.5, 149.3, 150.0, 154.4, 155.0, 158.1, 166.2, 176.3.

Ethyl 4-(3,5-dimethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9i). Yield 81%, mp 265–267°C. ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, *J* = 7.1 Hz, OCH_2–C<u>H</u>$_3$), 2.33 s (3H, DHPM-CH_3), 3.74 s (6H, 2OCH_3), 3.93 s (3H, NCH_3), 4.03 q (2H, *J* = 7.1 Hz, OCH_2–CH_3), 5.09 s (2H, OCH_2), 5.34 s (1H, *J* = 2.7 Hz, CH), 5.40 br.s (1H, NH), 6.51 br.s (1H, NH), 7.01 d (1H, *J* = 7.8 Hz, Ar-H), 7.32 t (2H, *J* = 7.4 Hz, Ar-H), 7.43–7.47 m (2H, Ar-H), 7.91–7.99 m (2H, Ar-H), δ 8.24 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 14.1, 18.9, 30.7, 56.0, 60.1, 70.5, 73.9, 101.3, 103.2, 106.3, 121.7, 126.9, 128.9, 134.8, 136.0, 138.5, 140.6, 145.9, 146.2, 150.1, 152.6,153.3, 155.5, 158.4, 165.5, 176.1.

Methyl 4-(3,5-dimethoxy-4-{(5-methyl-4-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methoxy}phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9j). Yield 88%, mp 261–263°C. ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H, DHPM-CH_3), 3.48 s (3H, NCH_3), 3.65 s (6H, 2OCH_3), 3.84 s (3H, OCH_3), 5.01 s (2H, OCH_2), 5.23 s (1H, CH), 6.06 br.s (1H, NH), 6.45 d (2H, *J* = 7.7 Hz, Ar-H), 7.24 d (1H, *J* = 2.2 Hz, Ar-H), 7.37 d (2H, *J* = 7.6 Hz, Ar-H), 7.87 s (2H, Ar-H), 8.06 br.s (1H, NH), 8.14 s (1H, pyrazole-H). ^{13}C NMR spectrum, δ_C, ppm: 18.6, 30.6, 51.0, 55.3, 55.9, 73.7, 100.5, 103.2, 106.2, 121.7, 126.9, 129.0, 134.7, 135.9, 138.5, 140.8, 147.2, 150.1, 153.2, 155.6, 158.5, 166.1, 173.1.

Antibacterial activity. The final compounds **9a–9j** were screened for anti-bacterial activity by the disk diffusion method in nutrient agar. The medium was prepared by adding agar powder to the nutrient broth (NB), pH was adjusted to 7.2–7.4 and sterilized in autoclave at 121°C for 15 min. The sterile nutrient agar was placed in Petri dishes and cooled to 50–45°C. Actively growing agar slant culture suspension of bacteria was inoculated separately on the agar plates. Sterile filter paper discs (6 mm diameter) prepared from standard Whatman filter paper were dipped in the test compound solutions as well as ampicillin solution of different concentrations and after drying, they were introduced on test organism seeded plates. The plates with test compound discs were incubated for 24 h at 37°C. After 24 h, and the diameters of the inhibition zones were measured in mm.

CONCLUSIONS

A number of new hybrid aza heterocycles containing pyrazolopyrimidinone and dihydropyrimidinone scaffolds was synthesized by an efficient, simple, green method using inexpensive copper chloride catalyzed Biginelli reaction under mild and solvent free conditions. All final compounds **9a–9j** demonstrated high to excellent antibacterial activity. Activity of **9h** and **9j** is comparable with that of ampicillin drug.

ACKNOWLEDGMENTS

Authors are grateful to the Director, Central Facilities for Research and Development (CFRD), Osmania University, Hyderabad for providing laboratory facilities. This work was also financially supported by the project under UGC-UPE FAR program. One of the authors, Muralidhar Allam, is grateful to UGC, New Delhi for award of SRF.

REFERENCES

1. EI-Bendary, E.R. and Badria, F.A., *Arch. Pharm.,* 2000, vol. 333, no. 4, p. 99. doi 10.1002/(SICI)15214184 (20004)333
2. Yewale, S.B., Ganorkar, S.B., Baheti, K.G., and Shelke, R.U., *Bioorg. Med. Chem. Lett.,* 2012, vol. 22, no. 21, p. 6616. doi org/10.1016/j.bmcl.2012.08.119
3. Blunt, J.W. and Munro, M.H.G., *Dictionary of Marine Natural Products with CDROM,* USA: Chapman and Hall/CRC, Taylor and Francis Group, 2008.
4. Patil, A.D., Kumar, N.V., Wilhelmus, C.K., Mark, F.B., Alan, J.F., Charles, D.B., Shing, M., Truneh, A., and Brad C., *J. Org. Chem.,* 1995, vol. 60, no. 5, p. 1182. doi 10.1021/jo00110a021
5. Hidetsura, C., Masaru, U., Keiyuu, S., Akira, M., Mariko, H., Yoshiko, O., Yumi, T., Mikiko, H., and Kazuo, A., *J. Med. Chem.,* 1989, vol. 32, no. 10, p. 2399. doi 10.1021/jm00130a029
6. Yadlapalli, R.K., Chourasia, O.P., Kiranmayi, V., Manjula, S., and Ramu, S.P., *Bioorg. Med. Chem. Lett.,* 2012, vol. 22, no. 8, p. 2708. doi 10.1016/ j.bmcl.2012.02.101
7. Sun, Q., Wang, Y.Q., Ge, Z.M., Cheng, T.M., and Li, R.T.A., *Synthesis,* 2004, p. 1047. doi 10.1055/s-2004-822331
8. De, S.K. and Gibbs, R.A., *Synthesis,* 2005, p. 1748. doi 10.1055/s-2005-869899
9. Liu, C.J., Wang, J.D., and Li, Y.P., *J. Mol. Catal. A: Chem*., 2006, vol. 258, p. 367. doi org/10.1016/ j.molcata.2006.07.037
10. Kalita, H.R. and Phukan, P., *Catal. Commun*. 2007, vol. 8, no. 2, p. 179. doi org/10.1016/ j.catcom.2006.06.004
11. Zhang, X., Li, Y., Liu, C., and Wang, J., *J. Mol. Catal A: Chem.* 2006, vol. 253, p. 207. doi org/10.1016/ j.molcata.2006.03.018
12. Ichiro, S., Yuko, S., and Takeda, K., *Tetrahedron Lett.* 2006, vol. 47, p. 7861 doi 10.1016/j.tetlet.2006.09.019
13. Feng, X., Jian-Jun, W., and You-Ping, T., *Synth. Commun.,* 2008, vol. 38, no. 8, p. 1299. doi 10.1080/00397910701873524
14. Vijai, N.P., Ragini, G., and Bindu, V., *Indian J. Chem. B*, 2008, vol. 47, p. 434.
15. Gohain, M., Prajapati, D., and Sandhu, J.S., *Synlett*., 2004, no. 2, p. 235. doi 10.1055/s-2003-43374
16. Mervat, M., El-Enany., Mona, M. K., Omneya, M. K., Hala, B.E., *Eur. J. Med. Chem.,* 2010, vol. 45, no. 11, p. 5286. doi org/10.1016/j.ejmech.2010.08.048
17. Cruickshank, R., Duguid, J.P., Marion, B.P., and Swain, R.H.A., *Medicinal Microbiology*, London: Churchil Livingstone, 1975, vol. 2, p. 196.