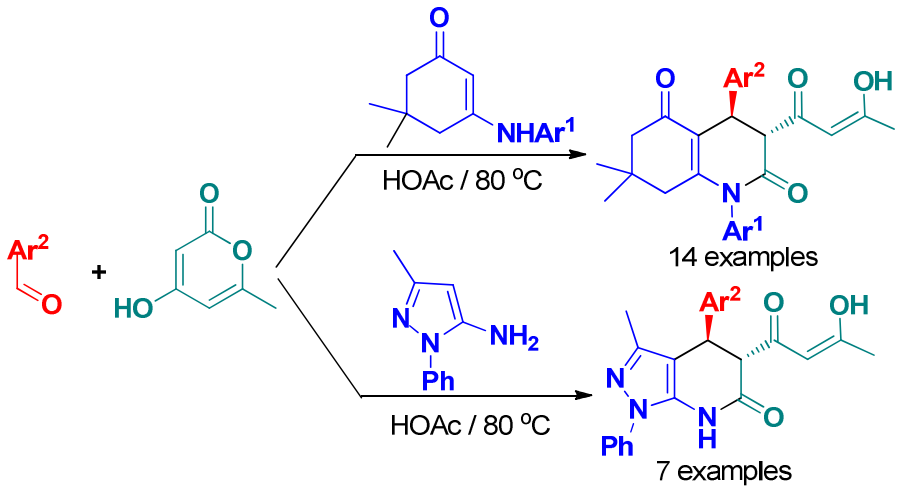
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Highly diastereoselective synthesis of quinoline-2,5-diones and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones under microwave irradiation

Bo Jiang, Yan-Bo Liang, Li-Fang Kong, Xing-Jun Tu, Wen-Juan Hao, Qin Ye and Shu-Jiang Tu



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Highly diastereoselective synthesis of quinoline-2,5-diones and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones under microwave irradiation

Bo Jiang,*[a] Yan-Bo Liang,[a] Li-Fang Kong,[b] Xing-Jun Tu,[a] Wen-Juan Hao,[a] Qin Ye,[a] and Shu-Jiang Tu*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

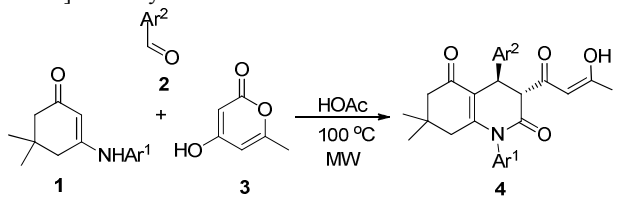
A new and flexible three-component reaction has been established for highly diastereoselective synthesis of bicyclic hexahydroquinoline-2,5-diones and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones using low-cost and readily accessible 4-hydroxypyran-2-ones, aromatic aldehydes, *N*-aryl enaminones and pyrazole-5-amines. This reaction process involves a Knoevenagel condensation/Michael addition cyclization /ring-opening of 4-hydroxypyran-2-one sequence.

Introduction

The development of efficient synthesis of azaheterocyclic scaffolds, particularly, those of quinolone ring-containing ones, is of chemical and biomedical importance and has been actively pursued in organic and medicinal research for several decades.[1-3] The structurally diverse and intriguing 2-quinolone family has been found to exhibit significant biological activities such as anticancers[4], herbicide safeners[5], and antitumor agents.[6] As a result, a great number of 2-quinolones, such as 4-arylquinoline-2(1*H*)-ones,[7] 3,4-disubstitutedquinoline-2(1*H*)-ones,[8] and *N*-substituted 2-quinolones[9] have been synthesized. Recently, Yao and co-workers reported the NHC-catalyzed synthesis of 4-aryl-tetrahydroquinoline-2,5-diones.[10] Pasha and co-workers developed a four-component approach for constructing quinoline-3-carboxylates using ZnO catalyst.[11] Kumar et al. also described a domino protocol for the synthesis of quinoline-2,5-dione analogues.[12] Most of these strategies involve either metal catalysts,[7,8,11] or lengthy reaction times,[7,9,10,11] and laborious workup.[7,8,12] Therefore, an exploration of a facile protocol for the direct formation of 2-quinolone derivatives, especially their diastereoselective synthesis, would be highly desirable and has practical benefits.

On the other hand, multicomponent domino reactions (MDRs) have emerged as an important tool for the creation of structural diversity and combinatorial libraries. These reactions combine three or more reagents in a one-pot process, affording a final product containing portions derived from each of the reacting molecules under mild conditions.[13] In recent years, enormous efforts have been made by conducting multicomponent domino reactions toward the formation of many biologically active substances and natural products.[14] However, to the best of our knowledge, the utilization of multicomponent reactions for the highly diastereoselective construction of quinoline-2,5-diones through ring-opening of 4-hydroxypyran-2-one has not been documented so far.

In the past several years, we have developed various MDRs for the construction of biologically active heterocyclic compounds[15] As a continue of our works on this project, we now developed a new three-component domino reaction of *N*-aryl enaminones **1** with aromatic aldehydes **2** and 4-hydroxypyran-2-ones **3** leading to the formation of polyfunctionalized quinoline-2,5(1*H*,6*H*)-dione derivatives in good yields (Scheme 1). The present work represents the special example for diastereoselective construction of these types of quinoline-2,5(1*H*,6*H*)-diones through domino [3+2+1] heterocyclization.



Scheme 1 Diastereoselective synthesis of quinoline-2,5-diones **4**

Results and discussion

To begin this study, we chose 5,5-dimethyl-3-(phenylamino) cyclohex-2-enone (**1a**), 2,3-dimethoxybenzaldehyde (**2a**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) as the standard substrates to search for suitable reaction conditions under microwave (MW) irradiation. The above reactions were performed at 80 °C in various solvents including CH_3CN, H_2O, EtOH, and HOAc. As shown in Table 1, HOAc was proven to be the best solvent (Table 1, entry 4). Subsequently, the reaction was performed in HOAc and repeated many times in different temperatures in a sealed vessel under microwave irradiation for 20 min. The best yield of product **4a** (78%) was obtained as the reaction temperature was increased to 100 °C (Table 1, entry 6). A further increase in reaction temperature did not deliver higher yield of **4a** (Table 1, entry 7). Subsequently, the same reaction was carried out under conventional heating conditions at 100 °C for 180 min, affording the product **4a** in 74% yield (Table 1, entry 8).

With these results in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aromatic aldehydes and enaminones were

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Table 1. Optimization for the synthesis of **4a** under MW

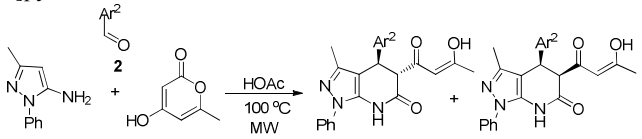
Entry	Solvent	T / °C	Time / min	Yield[a] (%)
1	CH_3CN	80	20	31
2	H_2O	80	20	27
3	EtOH	80	20	45
4	HOAc	80	20	63
5	HOAc	90	20	73
6	HOAc	100	20	78
7	HOAc	110	20	75
8	HOAc	100	180[b]	74

[a] Total yield of two isomers, [b]Conventional heating

investigated, and a series of new multi-functionalized tetrahydroquinoline-2,5(1*H*,6*H*)-dione were afforded in good yields and diastereoselectivity. As shown in Table 2, at the beginning, we made a search for the aldehyde substrate scope, enaminone (**1a)** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) were used as model substrates (Table 2), and the results indicated that aromatic aldehydes bearing chloro, or methoxy group were suitable for the synthesis of compound **4**. The bulky *o*-substituted aldehydes **2a** and **2d** were converted into the corresponding quinoline-2,5-diones **4a** and **4d** in 78% and 87% yield, respectively. Subsequently, the enaminone scope of this interesting transformation was investigated (Table 2). Several different *N*-substituents were compared and substituents bearing electron-donating (4-methoxyphenyl, **1c**) or electron-withdrawing (4-bromophenyl, **1e**) groups were found to be suitable for this domino reaction. The results exhibit the scope and generality of the new multicomponent domino reaction with respect to a range of enaminone and aldehyde substrates. Impressively, the ^{1}H NMR analysis of the products **4a-m** indicates the presence of a mixture of two diastereoisomers resulting from generation of two new asymmetric carbons. The ratio of the isomers was up to 97:3 as demonstrated by ^{1}H NMR integration of the crude mixture.

To explore this three-component reaction scope, we used pyrazole-5-amines to replace *N*-aryl enaminones to investigate the possibility of this transformation. The substituents on the aromatic ring of the aryl aldehydes **2** did not hamper the reaction process. Reactions of chloro- (**2b** and **2i**), or methoxy-substituted (**2a**, **2d**, **2j**, and **2k**) aryl aldehydes **2** with 4-hydroxy-6-methyl-2H-pyran-2-one **3** and pyrazole-5-amines **5** all worked well to provide the desired pyrazolo[3,4-*b*]pyridinones **6** in 69-82% yields with short reaction times. It is worthy of mention that the resulting pyrazolo[3,4-*b*]pyridinones are attractive heterocyclic compounds and are being extensively investigated because of their wide range of biological and pharmaceutical activities such as hypotensives,[16] antitumor,[17] antibacterial,[18] inhibitors of protein kinase,[19] and glycogen synthase kinase-3 (GSK-3).[20]

Table 3. Diastereoselective synthesis of pyrazolo[3,4-*b*]pyridinones **6** under MW[a]

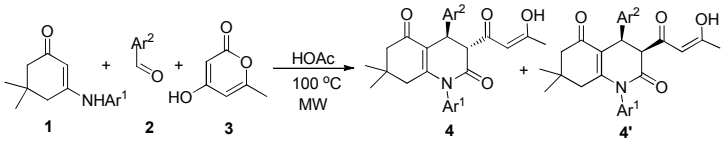


Entry	6	Ar^2	Time/min	Yield/%[b]	*anti:syn* (**6**:**6'**)
1	**6a**	2,3-$(MeO)_2C_6H_3$ (**2a**)	15	73	90:10
2	**6b**	4-ClC_6H_4 (**2b**)	10	79	93:7
3	**6c**	3,4,5-$(MeO)_3C_6H_2$ (**2d**)	16	82	92:8
4	**6d**	C_6H_5 (**2e**)	12	74	92:8
5	**6e**	2,4-$Cl_2C_6H_3$ (**2i**)	18	69	92:8
6	**6f**	4-$MeOC_6H_4$ (**2j**)	16	73	93:7
7	**6g**	3,4-$(MeO)_2C_6H_3$ (**2k**)	12	78	90:10

[a] Reagents and conditions:100 °C, HOAc (1.5 mL) microwave heating. [b] Total yield of two isomers

In all cases, the reaction proceeded at a very fast speed and can be finished within 30 minutes. The reaction process is environmentally friendly because water is nearly the sole by-product. In most cases, the products precipitated out after the reaction mixture was poured into cold water. The structures of these products were confirmed by their IR, ^{1}H NMR, ^{13}C NMR,

Table 2 Diastereoselective synthesis of quinoline-2,5-diones **4** under MW[a]



Entry	4	Ar^1	Ar^2	Time/min	Yield/%[b]	*anti:syn* (**4**:**4'**)
1	**4a**	C_6H_5 (**1a**)	2,3-$(MeO)_2C_6H_3$ (**2a**)	20	78	90:10
2	**4b**	C_6H_5 (**1a**)	4-ClC_6H_4 (**2b**)	18	72	90:10
3	**4c**	C_6H_5 (**1a**)	2,3-$Cl_2C_6H_3$ (**2c**)	25	75	93:7
4	**4d**	C_6H_5 (**1a**)	3,4,5-$(MeO)_3C_6H_2$ (**2d**)	24	87	92:8
5	**4e**	4-MeC_6H_4 (**1b**)	C_6H_5 (**2e**)	22	79	91:9
6	**4f**	4-MeC_6H_4 (**1b**)	4-BrC_6H_4 (**2f**)	18	78	92:8
7	**4g**	4-$MeOC_6H_4$ (**1c**)	4-ClC_6H_4 (**2b**)	26	86	92:8
8	**4h**	4-$MeOC_6H_4$ (**1c**)	2,3-$Cl_2C_6H_3$ (**2c**)	25	72	93:7
9	**4i**	4-ClC_6H_4 (**1d**)	C_6H_5 (**2e**)	24	70	92:8
10	**4k**	4-ClC_6H_4 (**1d**)	4-ClC_6H_4(**2b**)	28	75	92:8
11	**4j**	4-ClC_6H_4 (**1d**)	4-MeC_6H_4 (**2g**)	26	71	97:3
12	**4l**	4-BrC_6H_4 (**1e**)	4-ClC_6H_4 (**2b**)	20	77	96:4
13	**4n**	4-BrC_6H_4 (**1e**)	2,3-$Cl_2C_6H_3$ (**2c**)	30	65	90:10
14	**4m**	4-BrC_6H_4 (**1e**)	4-$O_2NC_6H_4$ (**2h**)	17	69	92:8

[a] Reagents and conditions: 100 °C, HOAc (1.5 mL) microwave heating. [b] Total yield of two isomers.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

and HRMS spectra. The crystal structure of compound **4a** was unequivocally determined by X-ray analysis (Fig. 1). During these processes, up to three sigma bonds were formed accompanied by the ring-opening of 4-hydroxy-6-methyl-2H-pyran-2-one.

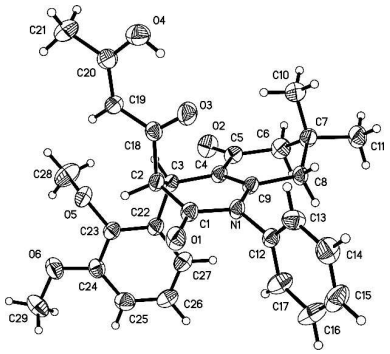
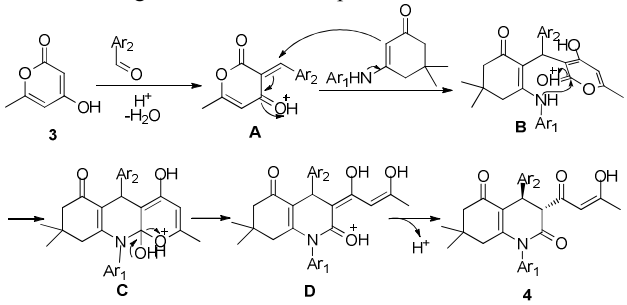


Figure 1 ORTEP drawing of **4a**

On the basis of experimental results, a reasonable mechanism for this domino reaction is represented in Scheme 2. Firstly, the Knoevenagel condensation between 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** and aryl aldehydes **2** in HOAc occurs, leading to intermediate **A**, followed by Michael addition with enaminones to yield intermediate **B**. Intermediate **B** then undergoes intramolecular cyclization (**B** to **C**) and subsequent ring-opening,[21] which converts into the final hexahydroquinoline-2,5-diones **4** through a tautomerization process.



Scheme 2 the reasonable mechanism for forming products **4**

Conclusions

In summary, we have developed new and flexible three-component reactions of 4-hydroxypyran-2-one, that led to the efficient synthesis of hexahydroquinoline-2,5-diones and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones with high diastereoselectivity (up to 97:3). This reaction process involves a Knoevenagel condensation/Michael addition cyclization /ring-opening of 4-hydroxypyran-2-one sequence. Undoubtedly, this multicomponent strategy provides a straightforward pathway to construct the target molecules in an atom-economic manner. Other features of this tactic include mild conditions, flexibility of structural modification, reliable scalability, and high bond-forming efficiency.

Experimental Section

General

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by infrared detector during microwave heating.

Typical Procedure for the Preparation of **4-(2,3-Dimethoxyphenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-1-phenyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4a)**

Typically, 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone (**1a**, 1.0 mmol, 0.22g) was introduced in a 10 mL Initiator^{TM} reaction vial. Then, 2,3-dimethoxybenzaldehyde (**2a**, 1.0 mmol, 0.17g), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**, 1.0 mmol, 0.13g), and acetic acid (1.5 ml) were successively added. Subsequently, the reaction vial was capped and then pre-stirred for 20 seconds. The mixture was irradiated (Time: 20 min, Temperature: 100 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: acetone 3:1) revealed that conversion of the starting material **1a** was complete. The system was diluted with cold water (40 mL). The solid product was collected by Büchner filtration and recrystallization by EtOH.

White solid, mp 177-178 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.59-7.42 (m, 3H, ArH), 7.34 (d, J = 7.6 Hz, 1H, ArH), 7.16 (d, J = 7.0 Hz, 1H, ArH), 6.99 (t, J = 8.0 Hz, 1H, ArH), 6.84 (d, J = 8.4 Hz, 1H, ArH), 6.67 (d, J = 7.6 Hz, 1H, ArH), 5.87 (s, 1H, CH), 4.99 (s, 1H, CH), 4.06 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.79 (d, J = 5.2 Hz, 1H, CH), 2.27 (d, J = 5.6 Hz, 2H, CH_2), 2.25-1.91 (m, 5H, CH_2 and CH_3), 1.02 (s, CH_3), 1.00 (s, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.8, 195.1, 185.5, 167.4, 154.4, 153.3, 146.5, 137.2, 133.4, 129.8, 129.6, 128.9, 128.1, 124.2, 118.1, 114.1, 112.0, 98.6, 60.7, 58.4, 55.9, 50.1, 41.8, 33.3, 32.9, 29.4, 27.2, 23.0;

IR (KBr, ν, cm^{-1}) 1714, 1644, 1620, 1596, 1379, 1271, 1186, 744;

HRMS (ESI) m/z: calcd for $C_{30}H_{34}NO_7$, 520.2335 $[M+H]^+$, found: 520.2355.

4-(4-Chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-1-phenyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4b)

White solid, mp 113-114 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.50-7.47 (m, 3H, ArH), 7.34-7.24 (m, 5H, ArH), 6.99 (s, 1H, ArH), 5.76 (s, 1H, CH), 4.77 (s, 1H, CH), 3.86 (s, 1H, CH), 2.27 (s, 2H, CH_2), 2.13-2.03 (m, 4H, CH_2 and CH_3), 1.96 (d, J = 16.0 Hz, 1H, CH_2), 0.97 (s, 3H, CH_3), 0.95 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 197.3, 169.9, 169.7, 167.5, 161.0, 138.1, 137.3, 131.4, 130.0, 129.4, 128.4, 128.3, 127.9, 126.5, 125.2, 112.4, 103.8, 101.9, 36.3, 35.6, 27.7, 21.4, 19.7;

IR (KBr, ν, cm^{-1}) 1703, 1647, 1619, 1491, 1376, 1262, 1145, 969;

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

HRMS (ESI) m/z: calcd for $C_{27}H_{27}ClNO_4$, 464.1628 $[M+H]^+$, found: 464.1633.

4-(2,3-Dichlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-1-phenyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4c)

White solid, mp 226-227 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.40-7.34 (m, 3H, ArH), 7.27-7.17 (m, 2H, ArH), 7.15-7.11 (m, 2H, ArH), 7.04 (d, J = 8.0 Hz, 1H, ArH), 5.92 (s, 1H, CH), 5.11 (s, 1H, CH), 3.88 (s, 1H, CH), 2.34-2.26 (m, 2H, CH_2), 2.19 (d, J = 16.0 Hz, 1H, CH_2), 2.10 (s, 3H, CH_3), 2.4 (d, J = 7.2 Hz, 1H, CH_2), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.3, 193.8, 186.2, 166.9, 155.2, 138.4, 136.8, 134.4, 132.2, 129.9, 129.8, 129.8, 129.5, 129.2, 128.0, 127.6, 125.2, 113.7, 98.4, 56.8, 49.9, 41.8, 36.2, 33.4, 29.5, 26.9, 23.1;

IR (KBr, ν, cm^{-1}) 1716, 1648, 1619, 1595, 1519, 1375, 1145, 969;

HRMS (ESI) m/z: calcd for $C_{27}H_{26}Cl_2NO_4$, 498.1239 $[M+H]^+$, found: 498.1245.

3-((*Z*)-3-Hydroxybut-2-enoyl)-7,7-dimethyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4d)

White solid, mp 207-209 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.60-7.42 (m, 3H, ArH), 7.34 (d, J = 6.4 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 6.56 (s, 2H, ArH), 5.78 (s, 1H, CH), 4.73 (s, 1H, CH),3.91 (s, 1H, CH), 3.83 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 2.35-2.22 (m, 2H, CH_2), 2.13-2.04 (m, 4H, CH_2 and CH_3), 1.98 (d, J = 17.6 Hz, 1H, CH_2), 0.98 (s, 6H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.9, 193.5, 186.3, 167.7, 153.5, 152.8, 137.1, 136.91, 136.0, 129.8 (129.8), 129.5, 129.1, 116.1, 103.9, 98.4, 60.8, 58.4, 56.1, 50.0, 41.7, 37.3, 33.3, 28.8, 27.3, 23.1;

IR (KBr, ν, cm^{-1}) 1699, 1651, 1628, 1595, 1492, 1296, 1187, 975;

HRMS (ESI) m/z: calcd for $C_{30}H_{33}NO_7$, 520.2335 $[M+H]^+$, found: 520.2355.

3-((*Z*)-3-Hydroxybut-2-enoyl)-7,7-dimethyl-4-phenyl-1-(*p*-tolyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4e)

White solid mp 169-170 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.36-7.26 (m, 6H, ArH), 7.24-7.19 (m, 2H, ArH), 6.93 (s, 1H, ArH), 5.77 (s, 1H, CH), 4.77 (s, 1H, CH), 3.89 (s, 1H, CH), 2.42 (s, 3H, CH_3), 2.28-2.26 (m, 2H, CH_2), 2.16-2.08 (m, 4H, CH_3 and CH_2), 1.98 (d, J = 16 Hz, 2H, CH_2), 0.97 (s, 6H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.9, 193.6, 186.3, 167.6, 153.2, 140.2, 139.1, 134.2, 130.4 (130.4), 129.1, 129.0, 127.6, 127.3, 126.9, 126.8, 115.8, 98.5, 58.5, 50.1, 41.7, 37.2, 33.3, 29.2, 27.1, 23.2, 21.3;

IR (KBr, ν, cm^{-1}) 1697, 1647, 1622, 1592, 1421, 1379, 1129, 1011;

HRMS (ESI) m/z: calcd for $C_{28}H_{30}NO_4$, 444.2175 $[M+H]^+$, found: 444.2177.

4-(4-Bromophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-1-(*p*-tolyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4f)

White solid, mp 169-170 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.43 (d, J = 7.6 Hz, 2H, ArH), 7.31 (d, J = 7.6 Hz, 1H, ArH), 7.27 (d, J = 4.8 Hz, 1H, ArH), 7.19 (d, J = 7.6 Hz, 3H, ArH), 6.87 (d, J = 7.6 Hz, 1H, ArH), 5.76 (s, 1H, CH), 4.74 (s, 1H, CH), 3.85 (s, 1H, CH), 2.42 (s, 3H, CH_3), 2.26 (d, J = 6.8 Hz, 2H, CH_2), 2.19-2.09 (m, 1H, CH_2), 2.07 (s, 3H, CH_3), 1.97 (d, J = 17.6 Hz, 1H, CH_2), 0.96 (s, 3H, CH_3), 0.95 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.8, 193.2, 186.3, 167.4, 153.4, 139.3, 139.2, 134.0, 132.1, 130.5, 130.4, 129.0, 128.6, 127.6, 121.2, 115.5, 98.4, 58.1, 50.0, 41.7, 36.5, 33.4, 29.2, 27.1, 23.1, 21.3;

IR (KBr, ν, cm^{-1}) 1707, 1650, 1619, 1489, 1451, 1379, 1262, 1016;

HRMS (ESI) m/z: calcd for $C_{28}H_{28}BrNO_4$, 522.1280$[M+H]^+$, found: 522.1287.

4-(4-Chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-1-(4-methoxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4g)

White solid, mp 168-170 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.26-7.19 (m, 3H, ArH), 7.02 (d, J = 8.4 Hz, 1H, ArH), 6.97 (d, J = 8.8 Hz, 1H, ArH), 6.90 (d, J = 8.4 Hz, 1H, ArH), 5.75 (s, 1H, CH), 4.75 (s, 1H, CH), 3.86 (s, 4H, CH and OCH_3), 2.26 (d, J = 6.0 Hz, 2H, CH_2), 2.20-2.08 (m, 1H, CH_2), 2.07 (s, 3H, CH_3), 1.98 (d, J = 17.6 Hz, 1H, CH_2), 0.97 (s, 3H, CH_3), 0.96 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.3, 193.9, 186.2, 167.2, 159.8, 155.6, 138.5, 134.4, 132.2, 130.4, 129.8, 129.2, 128.9, 127.6, 125.1, 115.1, 115.0, 113.6, 98.4, 56.8, 55.6, 49.8, 41.8, 36.2, 33.3, 29.5, 27.0, 23.1;

IR (KBr, ν, cm^{-1}) 1708, 1652, 1623, 1489, 1376, 1260, 1144, 1093;

HRMS (ESI) m/z: calcd for $C_{28}H_{29}ClNO_5$, 494.1734$[M+H]^+$, found: 494.1754.

4-(2,3-Dichlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-1-(4-methoxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4h)

White solid, mp 189-190 °C;

^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.38 (d, J = 7.6 Hz, 1H, ArH), 7.25 (d, J = 12.0 Hz, 1H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 7.00 (s, 4H, ArH), 5.91 (s, 1H, CH), 5.09 (s, 1H, CH), 3.86 (s, 4H, CH and OCH_3), 2.28 (s, 2H, CH_2), 2.22 (s, 1H, CH_2), 2.10 (s, 3H, CH_3), 2.05 (s, 1H, CH_2), 1.04 (s, 3H, CH_3), 1.00 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 196.1, 190.2, 168.7, 162.6, 154.3, 140.2, 137.1, 136.3, 132.9, 132.4, 132.1, 128.6, 126.6, 123.0, 121.0, 119.7, 116.7, 95.2, 59.6, 37.3, 36.5, 28.2, 21.7, 20.1;

IR (KBr, ν, cm^{-1}) 1700, 1626, 1575, 1513, 1248, 1182, 1132, 804;

HRMS (ESI) m/z: calcd for $C_{28}H_{28}Cl_2NO_5$, 528.1344$[M+H]^+$, found: 528.1345.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

1-(4-chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4i)

white solid mp 165-166 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.50-7.44 (m, 2H, ArH), 7.33-7.24 (m, 6H, ArH), 6.97 (d, J = 8.0 Hz, 1H, ArH), 5.76 (s, 1H, CH), 4.77 (s, 1H, CH), 3.90 (s, 1H, CH), 2.28-2.57 (m, 2H, CH_2), 2.15-2.08 (m, 4H, CH_2, CH_3), 1.96-1.92 (m, 2H, CH_2), 1.00 (s, 3H, CH_3), 0.98 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.8, 193.9, 186.2, 167.6, 152.5, 139.9, 135.4, 135.0, 131.0, 130.0, 129.3, 129.1, 127.4, 126.8, 126.7, 116.1, 98.5, 58.4, 50.0, 41.8, 37.3, 33.5, 29.3, 27.1, 23.1;
IR (KBr, ν, cm^{-1}) 1695, 1655, 1634, 1419, 1375, 1296, 1191, 826;
HRMS (ESI) m/z: calcd for $C_{27}H_{27}ClNO_4$, 464.1638[M+H]$^+$, found: 464.1642.

1,4-Bis(4-chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*, 6*H*)-dione (4j)
White solid, mp 159-160 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.49 (t, J = 8.0 Hz, 2H, ArH), 7.40 (d, J = 8.0 Hz, 1H, ArH), 7.36-7.25 (m, 2H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 7.05 (d, J = 8.0 Hz, 1H, ArH), 6.98 (d, J = 7.6 Hz, 1H, ArH), 5.90 (s, 1H, CH), 5.08 (s, 1H, CH), 3.88 (s, 1H, CH), 2.34-2.28 (m, 2H, CH_2), 2.23 (d, J = 18.0 Hz, 1H, CH_2), 2.10 (s, 3H, CH_3), 2.03 (d, J = 18.0 Hz, 1H, CH_2)., 1.05 (s, 3H, CH_3), 1.00 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.9, 193.3, 185.1, 167.5, 153.4, 139.2, 138.7, 134.0, 133.1, 130.5, 130.4, 129.2, 129.0, 128.3, 127.6, 115.6, 98.3, 58.4, 50.0, 41.7, 36.4, 33.4, 29.2, 27.1, 22.9, 21.3;
IR (KBr, ν, cm^{-1}) 1693, 1657, 1634, 1488, 1375, 1153, 1015, 797;
HRMS (ESI) m/z: calcd for $C_{27}H_{26}Cl_2NO_4$, 498.1239[M+H]$^+$, found: 498.1236.

1-(4-Chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-4-(*p*-tolyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*, 6*H*)-dione (4k)
White solid, mp 163-164 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.33-7.18 (m, 6H, ArH), 7.19 (d, J = 8.0 Hz, 1H, ArH), 6.87 (d, J = 7.6 Hz, 1H, ArH), 5.75 (s, 1H, CH), 4.76 (s, 1H, CH), 3.86 (s, 1H, CH), 2.42 (s, 3H, CH_3), 2.27 (s, 2H, CH_2), 2.18-1.91 (m, 5H, CH_2 and CH_3), 0.97 (s, 3H, CH_3), 0.96(s, 3H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 196.1, 190.3, 168.7, 162.6, 154.4, 139.6, 137.2, 136.3, 132.9, 132.4, 129.2, 129.1, 128.2, 126.5, 123.0, 119.7, 116.8, 95.2, 59.7, 37.3, 36.5, 28.2, 21.7, 20.1;
IR (KBr, ν, cm^{-1}) 1703, 1653, 1624, 1512, 1375, 1261, 1146, 816;
HRMS (ESI) m/z: calcd for $C_{28}H_{29}ClNO_4$, 478.1785 [M+H]$^+$, found: 478.1783.

1-(4-Bromophenyl)-4-(4-chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4l)
White solid, mp 182-183 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.66-7.60 (m, 2H, ArH), 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.22 (d, J = 8.0 Hz, 3H, ArH), 6.87 (d, J = 7.6 Hz, 1H, ArH), 5.73 (s, 1H, CH), 4.75 (s, 1H, CH), 3.87 (s, 1H, CH), 2.33-2.24 (m, 2H, CH_2), 2.11 (d, J = 18.0 Hz, 1H, CH_2), 2.07 (s, 3H, CH_3), 1.93 (d, J = 17.6 Hz, 1H, CH_2), 0.97 (s, 6H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 195.8, 193.6, 185.0, 167.4, 152.6, 138.5, 135.8, 133.2, 133.0, 131.2, 129.2, 129.6, 128.1, 123.2, 115.9, 98.3, 58.3, 50.0, 41.7, 36.5, 33.5, 29.2, 27.1, 22.8;
IR (KBr, ν, cm^{-1}) 1712, 1640, 1593, 1475, 1367, 1223, 1069, 999;
HRMS (ESI) m/z: calcd for $C_{27}H_{25}BrClNO_4$, 542.0733[M+H]$^+$, found: 542.0739.

1-(4-Chlorophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4m)
White solid, mp 179-180 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 7.64 (t, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 8.0 Hz, 1H, ArH), 7.26 (d, J = 8.8 Hz, 1H, ArH), 7.16 (s, 1H, ArH), 6.99 (t, J = 6.8 Hz, 2H, ArH), 5.90 (s, 1H, CH), 5.08 (s, 1H, CH), 3.87 (s, 1H, CH), 2.38-2.27 (m, 2H,), 2.24 (d, J = 16.4 Hz, 1H, CH_2), 2.10 (s, 3H, CH_3), 2.02 (d, J = 17.8 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 1.00 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.2, 194.1, 185.0, 167.0, 154.7, 138.2, 135.8, 134.5, 133.3, 133.0, 132.2, 131.3, 129.9, 129.7, 127.6, 125.0, 123.3, 113.8, 98.3, 56.9, 49.8, 41.8, 36.3, 33.4, 29.6, 26.9, 22.9;
IR (KBr, ν, cm^{-1}) 1695, 1655, 1634, 1491, 1419, 1375, 1191, 826;
HRMS (ESI) m/z: calcd for $C_{27}H_{27}ClNO_4$, 464.1638[M+H]$^+$, found: 464.1642.

1-(4-Bromophenyl)-3-((*Z*)-3-hydroxybut-2-enoyl)-7,7-dimethyl-4-(4-nitrophenyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (4n)
White solid, mp 190-191 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.18-8.16 (d, J = 8.0 Hz, 2H, ArH), 7.65-7.61 (m, 2H, ArH), 7.46-7.44 (d, J = 8.0 Hz, H, ArH), 7.21-7.19 (m, 1H, ArH), 7.90-7.88 (d, J = 8.0 Hz, 1H, ArH), 5.77 (s, 1H, CH), 4.89 (s, 1H, CH), 3.90 (s, 1H, CH), 2.27 (s, 2H, CH_2), 2.16-2.12 (m, 1H, CH_2), 2.10 (s, 3H, CH_3),1.964 (d, J = 16.0 Hz, 1H, CH_2), 0.98 (s, 6H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 195.6, 192.9, 186.4, 167.0, 153.1, 147.5, 147.1, 135.5, 133.1, 131.1, 129.5, 127.9, 127.9, 124.3, 123.3, 115.2, 98.2, 57.6, 49.9, 41.8, 36.9, 33.5, 29.2, 27.0, 23.0;
IR (KBr, ν, cm^{-1}) 1718, 1643, 1613, 1490, 1374, 1308, 1182, 850;
HRMS (ESI) m/z: calcd for $C_{27}H_{26}BrN2O_6$, 553.0974[M+H]$^+$, found: 553.0981.

Typically, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**5**, 1.0 mmol, 0.17g) was introduced in a 10 mL Initiator^{TM} reaction vial. Then, 2,3-dimethoxybenzaldehyde (**2a**, 1.0 mmol, 0.17g), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**, 1.0 mmol, 0.13g), and acetic acid (1.5

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

ml) were successively added. Subsequently, the reaction vial was capped and then pre-stirred for 20 seconds. The mixture was irradiated (Time: 15 min, Temperature: 100 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: acetone 3:1) revealed that conversion of the starting material **5** was complete. The system was diluted with cold water (40 mL). The solid product was collected by Büchner filtration and recrystallization by EtOH.

4-(2,3-Dimethoxyphenyl)-5-((*Z*)-3-hydroxybut-2-enoyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6a)

White solid, mp 158-160 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.13 (s, 1H, NH)7.55-7.44 (m, 4H, ArH), 7.44-7.33 (m, 1H, ArH), 6.80 (d, J = 8.8 Hz, 1H, ArH), 6.76-6.70 (m, 2H, ArH), 5.54 (s, 1H, CH), 4.59 (d, J = 6.8 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 190.3, 188.7, 167.4, 158.9, 147.2, 137.1, 136.2, 132.7, 129.9, 128.5, 127.9, 123.0, 114.3, 102.0, 100.3, 60.5, 55.3, 38.0, 23.9, 12.4;
IR (KBr, v, cm^{-1}) 3430, 3150, 1679, 1609, 1540, 1457, 1353, 752;
HRMS (ESI): m/z calcd for: $C_{25}H_{25}N_3O_5$, 446.1716 [M-H]$^-$, found: 446.17137.

4-(4-Chlorophenyl)-5-((*Z*)-3-hydroxybut-2-enoyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6b)

White solid, mp 181-182 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.12 (s, 1H, NH), 7.49 (q, J = 7.8 Hz, 4H,A rH), 7.39 (t, J = 6.8 Hz, 1H, ArH), 7.31 (d, J = 8.0 Hz, 2H, ArH), 7.16 (d, J = 8.0 Hz, 2H, ArH),5.56 (s, 1H, CH) 4.65 (d, J = 6.0 Hz, 1H, CH), 3.64 (d, J = 6.0 Hz, 1H, CH), 2.03 (s, 3H, CH_3), 1.93 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 190.0, 188.7, 167.1, 146.7, 140.0, 138.1, 136.3, 134.6, 132.2, 132.0, 130.4, 129.2, 129.1, 123.4, 123.1, 123.0, 121.4, 100.9, 100.2, 60.2, 38.1, 23.9, 12.5;
IR (KBr, v, cm^{-1}) 3154, 3051, 1768, 1601, 1491, 826;
HRMS (ESI): m/z calcd for: $C_{23}H_{20}ClN_3O_3$, 420.1115[M-H]$^-$, found: 420.1134.

5-((*Z*)-3-Hydroxybut-2-enoyl)-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6c)

White solid, mp 156-158 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.30 (s, 1H, NH), 7.52-7.44 (m, 4H, ArH), 7.41-7.34 (m, 1H, ArH), 6.58-6.29 (m, 2H, ArH), 5.55 (s, 1H, CH), 4.58 (d, J = 6.4 Hz, 1H, CH), 3.84 (s, 3H, , OCH_3), 3.81 (s, 6H, OCH_3), 2.03 (s, 3H, CH_3), 1.99 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 190.0, 188.7, 167.1, 146.7, 140.0, 138.2, 136.3, 134.6, 132.2, 132.0, 130.4, 129.2, 129.1, 123.4, 123.1, 123.0, 121.4, 100.9, 100.2, 60.2, 38.1, 23.9, 12.5;
IR (KBr, v, cm^{-1}) 3447, 3056, 1651, 1612, 1597, 1335, 982, 754;
HRMS (ESI): m/z calcd for: $C_{26}H_{27}N_3O_6$, 476.1822 [M-H]$^-$, found: 476.1830.

5-((*Z*)-3-Hydroxybut-2-enoyl)-3-methyl-1,4-diphenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6d)

White solid, mp 220-222 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.02 (s, 1H, NH), 7.55-7.43 (m, 4H, ArH), 7.40-7.29 (m, 4H, ArH), 7.21 (d, J = 7.2 Hz, 2H, ArH), 5.59 (s, 1H, CH), 4.63 (s, 1H, CH), 3.70 (s, 1H, CH), 2.03 (s, 3H, CH_3), 1.93 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 190.4, 188.5, 167.3, 147.2, 140.9, 137.2, 136.3, 129.9, 129.1, 127.9, 127.5, 127.4, 123.0, 101.7, 100.1, 60.3, 38.6, 23.8, 12.4;
IR (KBr, v, cm^{-1}) 3719, 3090, 1671, 1602, 1498, 1276, 758, 689;
HRMS (ESI): m/z calcd for: $C_{23}H_{21}N_3O_3$, 386.1505[M-H]$^-$, found: 386.156.

4-(2,4-Dichlorophenyl)-5-((*Z*)-3-hydroxybut-2-enoyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6e)

White solid, mp 158-159 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.30 (s, 1H, NH), 7.48 (t, J = 5.2 Hz, 5H, ArH), 7.40-7.36 (m, 1H, ArH), 7.16 (d, J = 8.4 Hz, 1H, ArH), 6.88 (d, J = 8.4 Hz, 1H, ArH), 5.77 (s, 1H, CH), 5.02 (d, J = 2.4 Hz, 1H, CH), 3.74 (d, J = 2.8 Hz, 1H, CH), 2.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 191.3, 187.1, 166.9, 146.9, 137.4, 137.2, 136.4, 134.1, 133.9, 130.1, 129.9, 129.8, 127.9, 127.8, 123.0, 100.0, 98.8, 58.8, 34.5, 23.4, 12.1;
IR (KBr, v, cm^{-1}): 3484, 3058, 1621, 1594, 1510, 1319, 1131, 756;
HRMS (ESI): m/z calcd for: $C_{23}H_{19}Cl_2N_3O_3$, 454.0725 [M-H]$^-$, found: 454.0723.

5-((*Z*)-3-Hydroxybut-2-enoyl)-4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6f)

White solid, mp 186-187 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.20 (s, 1H, NH), 7.51-7.47 (m, 4H, ArH), 7.40-7.37 (m, 1H, ArH), 7.12 (d, J = 8.4 Hz, 2H, ArH), 6.85 (d, J = 8.6 Hz, 2H, ArH), 5.56 (s, 1H, CH), 4.58 (d, J = 6.0 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 2.02 (s, 3H, CH_3), 1.93 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 192.4, 187.2, 167.7, 152.9, 147.1, 146.5, 137.2 136.9, 134.6, 129.8, 127.8, 124.1, 123.1, 120.1, 111.9, 100.8, 99.2, 60.4, 55.8, 33.6, 23.5, 12.1;
IR (KBr, v, cm^{-1}) 3152, 3050, 2930, 1678, 1602, 1511, 1246, 759;
HRMS (ESI): m/z calcd for: $C_{24}H_{23}N_3O_4$, 416.1611[M-H]$^-$, found: 416.1626.

4-(3,4-Dimethoxyphenyl)-5-((*Z*)-3-hydroxybut-2-enoyl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (6g)

White solid, mp 181-183 °C;
^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.13 (s, 1H, NH), 7.55 - 7.44 (m, 4H, ArH), 7.44-7.33 (m, 1H, ArH), 6.80 (d, J = 8.8 Hz, 1H, ArH), 6.76-6.70 (m, 2H, ArH), 5.54 (s, 1H, CH), 4.59 (d, J = 6.8 Hz, 1H, CH)3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm) 190.2, 188.8, 167.4, 149.3, 148.3, 147.2, 137.1, 136.2, 133.0, 129.9, 128.0, 123.0, 119.7, 111.3, 110.4, 101.9, 100.6, 60.3, 56.0, 55.9, 38.5, 24.0, 12.5;
IR (KBr, v, cm^{-1}) 3435, 3173, 1685, 1598, 1517, 1259, 1238, 1026, 749, 695;

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

HRMS (ESI) m/z calcd for: $C_{25}H_{25}N_3O_5$, 446.1716 $[M-H]^-$, found: 446.1713.

Acknowledgements

We are grateful for financial support from the NSFC (No. 21232004, 21272095 and 21102124), PAPD of Jiangsu Higher Education Institutions, and the Qing Lan Project (12QLG006).

Notes and references

[a] *School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu, P. R. China. Fax: +8651683500065; Tel: +8651683500065; E-mail: jiangchem@jsnu.edu.cn (B. Jiang); laotu@jsnu.edu.cn (S.-J. Tu)*

[b] *Department of Basic Teaching, Air Force Logistic Academy, Xuzhou, Jiangsu, P. R. China.*

*Electronic supplementary information (ESI) available. CCDC 1023380 (**4a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/*

1 (a) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. J. Zamboni, *J. Org. Chem*., 1996, **61**, 3398. (b) Y. L. Chen, K. C. Fang, J.-Y. Sheu, S. L. Hsu and C. C. Tzeng, *J. Med. Chem*., 2001, **44**, 2374.

2 (a) B. Kalluraya and S. Sreenivasa, *Farmaco,* 1998, **53**, 399. (b) D. Doube, M. Blouin, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J. P. Fagueyret, R. W. Friesen, M. Girard, Y. Girard, J. Guay, P. Tagari and R. N. Young, *Bioorg. Med. Chem. Lett.,* 1998, **8**, 1255.

3 T.-C. Ko, M.-J. Hour, J.-C. Lien, C.-M. Teng, K.-H. Lee, S.-C. Kuo and L.-J. Huang, *Bioorg. Med. Chem. Lett.,* 2001, **11**, 279.

4 (a) P. Ferrer, C. Avendaño and M. Söllhuber, *Liebigs Ann.,* **1995**, 1895; (b) E. van Cutsem, H. van de Velde, P. Karasek, H. Oettle, W. L. Vervenne, A. Szawlowski, P. Schoffski, S. Post, C. Verslype, H. Neumann, H. Safran, Y. Humblet, J. P. Ruixo, Y. Ma and D. von Hoff, *J. Clin. Oncol.,* 2004, **22**, 1430.

5 G. Wolfgang, B. Hermann, R. Christopher and K. Thomas, DE Patent 19727410, 1999.

6 (a) P. R. Angibaud, M. G. Venet, W. Filliers, R. Broeckx, Y. A. Ligny, P. Muller, V. S. Poncelet and D. W. End, *Eur. J. Org. Chem*., **2004**, 479. (b) B. M. Andresen, M. Couturier, B. Cronin, M. D'Occhio, M. D. Ewing, M. Guinn, J. M. Hawkins, V. J. Jasys, S. D. LaGreca, J. P. Lyssikatos, G. Moraski, K. Ng, J. W. Raggon, A. M. Stewart, D. L. Tickner, J. L. Tucker, F. J. Urban, E. Vazquez and L. L. Wei, *Org.Process Res. Dev*., 2004, **8**, 643.

7 (a) S. Y. Sit and N. A. Meanwell, U.S. Patent 5892045, 1999. (b) P. Hewawasam, J. E. Jr. Starrett and S. G. Swartz, U.S. Patent 5972961, 1999. (c) P. Hewawasam and J. E., Jr. Starrett, U.S. Patent 6184231, 2001.

8 (a) M. Sharma and V. B. Gupta, *Pharmaceuticals,* 2010, **3**, 3167. (b) T. N. Glasnov, W. Stadlbauer and C. O. Kappe, *J. Org. Chem*., 2005, **70**, 3864. (c) R. W. Carling, P. D. Leeson, K. W. Moore, C. R. Moyes, M. Duncton, M. L. Hudson, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, M. D. Tricklebank and K. L. Saywell, *J. Med. Chem.,* 1997, **40**, 754.

9 (a) M. Hammouda, M. M. Mashaly, E. M. Afsah, *Pharmazie.,* 1994, **49**, 365. (b) M. G. Assy and F. M. Abd-El Motti, *Egypt. J. Chem*., 1996, **39**, 581. (c) M. G. Assy and M. F. M. Abd-Ell, *Indian J. Chem., Sect.,* 1996, **35**, 608. (d) M. G. Assy, R. M. Fikry and N. H. Aouf, *J. Indian Chem. Soc*., 1997, **74**, 152. (e) E. Dahlén, M. Andersson, K. Dawe, A. C. Tellander, C. Brunmark, A. Bjork and G. Hedlund, *Autoimmunity,* 2000, **32**, 199.

10 C.-S. Yao, W.-H. Jiao and Z.-X. Xiao, *Tetrahedron,* 2013, **69**, 1133.

11 M. A. Pasha and A. Siddekha, *Tetrahedron Lett.,* 2012, **53**, 6306.

12 M. Kumar, A. K. Arya and K. Gupta, *Tetrahedron Lett.,* 2012, **53**, 6035.

13 (a) J. Alemán and S. Cabrera, *Chem. Soc. Rev.,* 2013 **42**, 774. (b) M. B. Gawande, V. D. B. Bonifácio, R. V. Luque, P. S. Brancoa and R. S. Varma, *Chem. Soc. Rev.,* 2013, **42**, 5522. (c) V. Nair, R. S. Menon, A. T. Bijub and K. G. Abhilashc, *Chem. Soc. Rev*., 2012, **41**, 1050. (d) N. Isambert, M. del M. S. Duque, J. C. Plaquevent, Y. Genisson, J. Rodriguez and T. Constantieux, *Chem. Soc. Rev*., 2011, **40**, 1347. (e) G. Li, H. X. Wei, S. H. Kim and M. D. Carducci, *Angew. Chem., Int. Ed.,* 2001, **40**, 4277.

14 For reviews, sees: (a) B. Groenendaal, E. Ruijter and R. V. A. Orru, *Chem. Commun.,* **2008**, 5474. (b) A. Padwa, *Chem. Soc. Rev.,* 2009, **38**, 3072. (c) L. F. Tietze, T. Kinzel and C. C.Brazel, *Acc. Chem. Res.,* 2009, **42**, 367. (d) A. Domling, W. Wang and K. Wang, *Chem. Rev.,* 2012, **112**, 3083. (e) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.,* 2011, **50**, 6234. (f) B. Jiang, T. Rajale, W. Wever, S.-J. Tu and G. Li, *Chem.-Asian J.,* 2010, **5**, 2318.

15 (a) W. Fan, Q. Ye, H.-W. Xu, B. Jiang, S.-L. Wang and S.-J. Tu, *Org. Lett.,* 2013, **15**, 2258. (b) B. Jiang, X. Wang, H.-W. Xu, M.-S. Tu, S.-J. Tu and G. Li, *Org. Lett.,* 2013, **15**, 1540. (c) Y. Li, H. Xu, L. Fu, Q. Shi, B. Jiang and S.-J. Tu, *Chin. J. Chem.,* 2013, **31**, 737. (d) G. Tong, H. Xu, W. Fan, B. Jiang, S.-L. Wang and S.-J. Tu, *Chin. J. Chem.,* 2013, **31**, 1039.

16 N. Aatika and M. A. Pasha, *J. Saudi Chem. Soc.,* 2011, **15**, 55.

17 A. S. Straub and J. P. C. Alonso-Alija, *Bioorg. Med. Chem. Lett*., 2001, **11**, 781.

18 (a) R. Lin, P. J. Connolly, Y. Lu, G. Chiu, S. Li, Y. Yu, S. Huang, X. Li, S. L. Emanuel, S. A. Middleton, R. H. Gruninger, M. Adams, A. R. Fuentes-Pesquera and L. M. Greenberger, *Bioorg. Med. Chem. Lett*., 2007, **17**, 4297. (b) Q. Ye, J. Cao, X. Zhou, D. Lv, Q. He, B. Yang and Y. Hu, *Bioorg. Med. Chem*., 2009, **17**, 4763.

19 L. R. S. Dias, M. B. Santos, S. de Albuquerque, H. C. Castro, A. M. T. de Souza, A. C. C. Freitas, M. A. V. DiVaio, L. M. Cabral and C. R. Rodrigues, *Bioorg. Med. Chem.,* 2007, **15**, 211.

20 J. Witherington, V. Bordas, A. Gaiba, N. S. Garton, A. Naylor, A. D. Rawlings, B. P. Slingsby, D. G. Smith, A. K. Takle amd R. W. Ward, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 3055.

21 (a) J. Svetlik, N. Pronayova and V. Hanus, *J. Heterocyclic Chem*., 2000, **37**, 395-399. (b) P. De March, M. Moreno-Manas and J. L. Roca, *J. Heterocyclic Chem.*, 1984, **21**, 1371. (c) B. Jiang, B.-M. Feng, S.-L. Wang, S.-J. Tu and G. Li, *Chem. Eur. J.*, 2012, **18**, 9823.