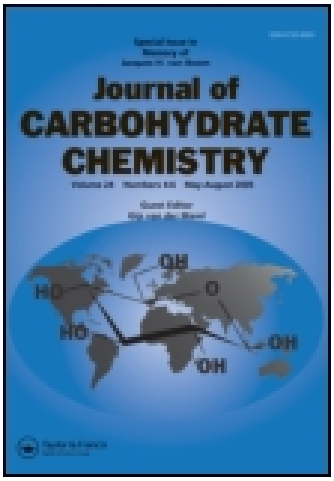

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Synthesis, Structure Characterization, and X-ray Crystallography of Novel 1-Benzyl-3-phenyl-1H-pyrazole-5-carboxylate Derivatives with a Carbohydrate Moiety

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Published online: 27 Jun 2011.

To cite this article: Song Lian , Jin-Ting Liu , Liang-Wen Zheng , Wei-Yong Liu & Bao-Xiang Zhao (2011) Synthesis, Structure Characterization, and X-ray Crystallography of Novel 1-Benzyl-3-phenyl-1H-pyrazole-5-carboxylate Derivatives with a Carbohydrate Moiety, Journal of Carbohydrate Chemistry, 30:1, 1-15, DOI: 10.1080/07328303.2011.583371

To link to this article: http://dx.doi.org/10.1080/07328303.2011.583371

Journal of Carbohydrate Chemistry, 30:1–15, 2011

ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328303.2011.583371

Synthesis, Structure Characterization, and X-ray Crystallography of Novel 1-Benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate Derivatives with a Carbohydrate Moiety

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A series of novel (2*S*,3*R*,4*S*,5*R*)-3,4,5-triacetoxy-tetrahydro-2*H*-pyran-2-yl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate derivatives (**3**) were synthesized by the reaction of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**2**) and 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylic acid (**1**) in the presence of sodium bicarbonate and tetrabutylammonium bromide in dichloromethane at reflux temperature. The structures of new compounds were determined by IR and ^{1}H NMR spectroscopy and HR mass spectrometry (HRMS), and the configuration of the newly generated chiral carbon (C-1) in the xylose ring was tentatively assigned based on the X-ray crystallographic structure of **3d** and **3g**.

Keywords Synthesis; Structure; Pyrazole; Xylose; X-ray

INTRODUCTION

Many pyrazole derivatives are known to exhibit a wide range of biological properties such as cannabinoid hCB1 and hCB2 receptors, anti-inflammatory

Received June 14, 2010; accepted April 19, 2011.
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activity, inhibitors of p38 kinase, CB1 receptor antagonists, and antimicrobial activity.[1–5] Extensive studies have been devoted to arylpyrazole derivatives such as celecoxib, a well-known cyclooxygenase-2 inhibitor.[6–8] In our previous papers, we synthesized a series of novel multisubstituted pyrazole derivatives such as ethyl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate derivatives,[9] ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate derivatives,[10] ethyl 3-(*o*-chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate,[11] 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide,[12] 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives,[13] and 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide hydrazone derivatives,[14,15] as well as fused-pyrazole derivatives including 6-(aroxymethyl)-2-aryl-6,7-dihydropyrazolo[5,1-*c*][1,4]oxazin-4-one derivatives,[16] pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one,[17] and 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one.[18,19] The evaluation of biological activity showed that these compounds can inhibit A549 lung cancer cell growth.

It is accepted that incorporation of potential biologically active moieties into body-friendly-type compounds should reduce toxic or other disadvantageous side effects and, thus, obtain molecules with better chances for pharmacological applications. The incorporation of sugar into prospective pharmaceutical candidates is a major strategy to obtain activity and safety advantages. Recently, some *O*-glucoside-containing compounds have been isolated from natural plants[20,21] and the synthesis of *O*-glycosides has received considerable attention due to their occurrence in a variety of natural products endowed with numerous biological activities.[22,23] A search of the literature revealed very few reports concerning pyrazole-glycoside[24,25]; however, there were no reports about pyrazole-xyloside.

In our ongoing interest in the preparation of novel pyrazole derivatives with sugar moiety,[26] herein, we would like to report the synthesis and structure characterization of a series of novel (2*S*,3*R*,4*S*,5*R*)-3,4,5-triacetoxy-tetrahydro-2*H*-pyran-2-yl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate derivatives.

RESULTS AND DISCUSSION

Synthesis of the Compounds

(2*S*,3*R*,4*S*,5*R*)-3,4,5-Triacetoxy-tetrahydro-2*H*-pyran-2-yl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate derivatives (**3**) were synthesized by the reaction of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**2**)[27,28] and 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylic acid (**1**), which can be easily obtained by the alkali hydrolysis of corresponding ethyl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate[29] in the presence of sodium bicarbonate and tetrabutylammonium bromide in dichloromethane at reflux for 2 to 4 h as outlined in Figure 1.

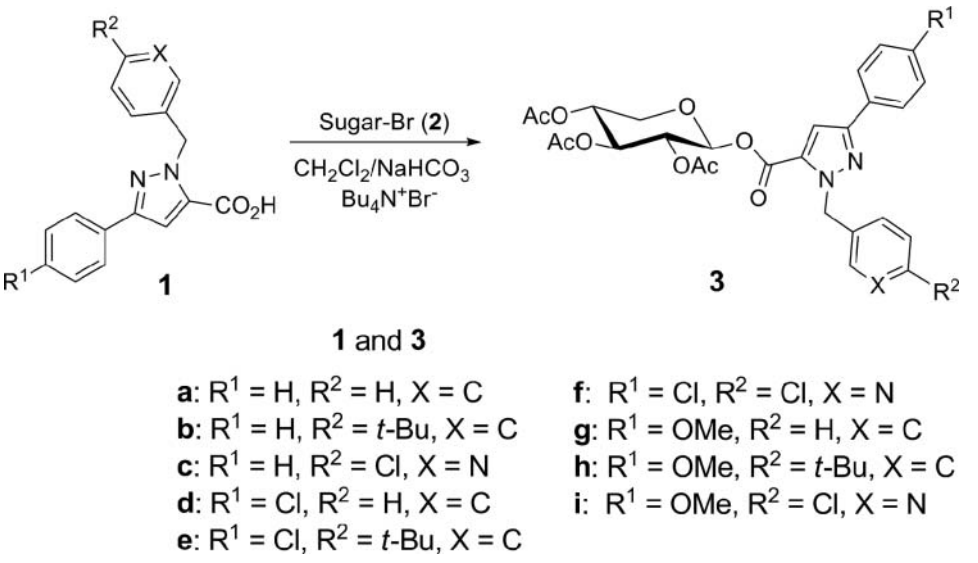

Figure 1: Synthesis of compounds **3**.

Structure Characterization of the Compounds

The structures of the compounds **3** were determined by the analyses of their spectral data including ^{1}H NMR, IR, and HRESIMS. Compound **3d**, for example, obtained as white crystals, gave a [M+H]-ion peak at m/z 517.1470 in the HRESIMS, in accord with the molecular formula $C_{28}H_{28}ClN_2O_9$. In the IR spectra, the carbonyl group absorptions were observed in the 1732–1757 cm^{-1} region. Two *ortho*-aromatic proton signals in 4-chlorophenyl moiety appear at the range of $\delta = 7.76$ and 7.39 ppm as doublet peaks ($J = 8.5$ Hz). The multiplet peaks from 7.26 to 7.31 ppm are benzene proton signals. The singlet signal appeared at $\delta = 7.15$ ppm and is consistent with pyrazole moiety. The doublet peaks at $\delta = 5.88$ ($J = 6.6$ Hz) are consistent with the proton in the 1-position of sugar moiety. Two doublet peaks at $\delta = 5.80$ and 5.74 ($J = 14.7$ Hz) are consistent with the protons of methylene in benzyl moiety. Two triplet peaks at $\delta = 5.29$ ($J = 8.0$ Hz) and 5.16 ($J = 7.5$ Hz) are consistent with the proton of the 2- and 3-position in the sugar moiety, respectively. A multiplet peak at $\delta = 4.98$–5.03 (m, 1H, $C_{4\text{-H}}$) is consistent with the proton in the 4-position of sugar moiety. Finally, two double doublet peaks at $\delta = 4.18$ ($J = 4.8$, 12.1 Hz) and 3.59 ($J = 8.0$, 12.1 Hz) are consistent with the methylene protons in sugar moiety. All other signals are consistent with the structure of **3d**.

Single-Crystal Structure

The single crystals were grown from ethyl acetate at rt. The molecular view of **3d** and **3g** is shown in Figures 2 and 3, respectively. A summary of crystallographic data collection parameters and refinement parameters for **3d**

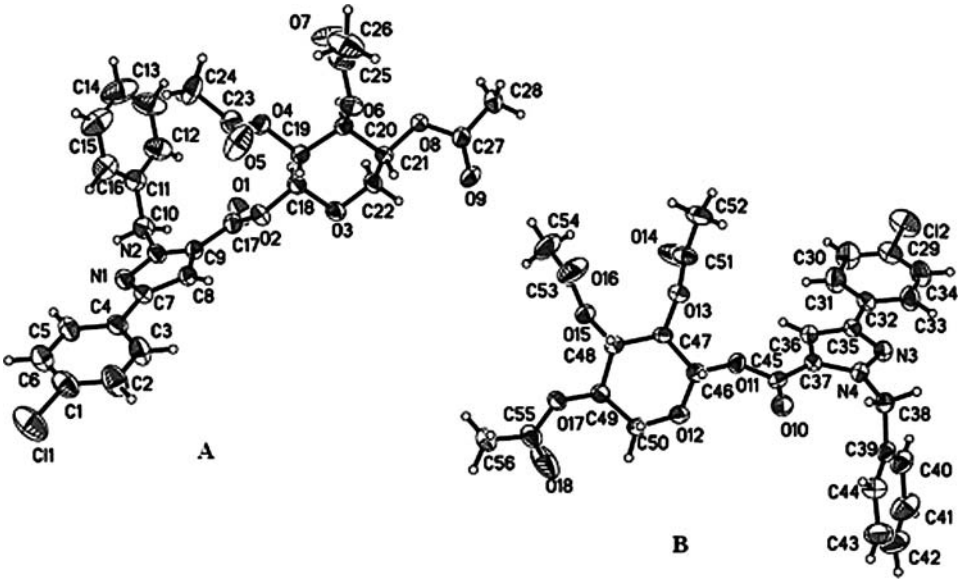

Figure 2: The molecular structure of **3d**, showing displacement ellipsoids drawn at the 50% probability level for non-H atoms.

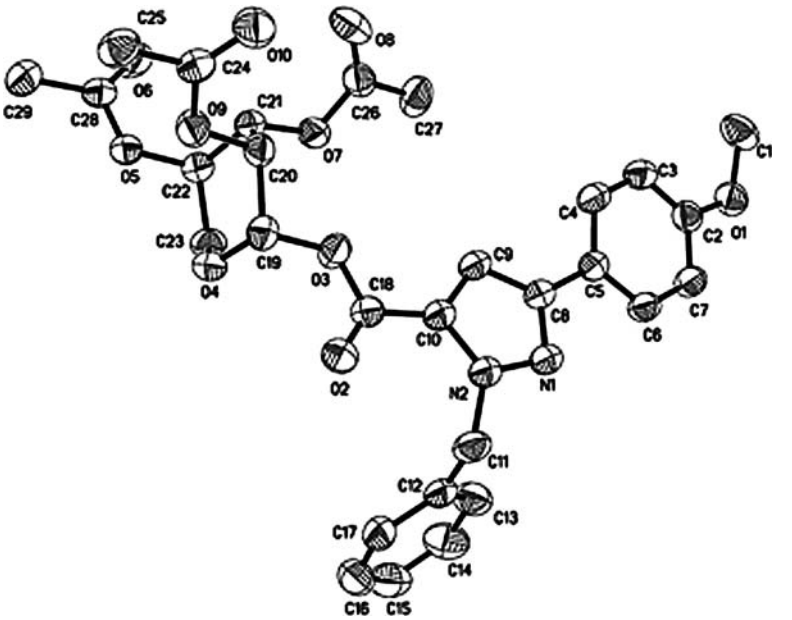

Figure 3: The molecular structure of 3g, showing displacement ellipsoids drawn at the 50% probability level. H atoms are omitted for clarity.

Table 1: Crystal data and structure refinement for **3d** and **3g**

	3d	3g
Empirical formula	C28 H27 Cl N2 O9	C29 H30 N2 O10
Formula weight	570.97	566.55
Temperature	273(2) K	273(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic
Space group	P1	$P2_1$
Unit cell dimensions	a = 8.1078(10) Å, α = 79.748(2)°	a = 11.3169(13) Å
	b = 8.6406(10)Å, β = 82.991(2)°	b = 7.7734(9) Å, β = 94.034(2)°
	c = 23.281(3)Å, γ = 63.334(2)°	c = 16.317(2) Å
Volume	1432.6(3) A^3	1431.9(3) $Å^3$
Z	2	2
Calculated density	1.324 mg/m^3	1.314 mg/m^3
Absorption coefficient	0.188 mm^{-1}	0.100 mm^{-1}
F(000)	596	596
Crystal size	0.16 × 0.13 × 0.10 mm	0.15 × 0.12 × 0.10 mm
θ range for data collection	0.89 to 25.05°	1.80 to 25.05°
Limiting indices	$-9 \le h \le 9$, $-6 \le k \le 10$, $-24 \le l \le 27$	$-13 \le h \le 8$, $-9 \le k \le 9$, $-19 \le l \le 19$
Reflections collected/unique	7675/6059 (R(int) = 0.0217)	7610/4854 (R(int) = 0.016)
Completeness to θ = 25.05°	99.4%	99.7%
Absorption correction	Multiscan	Multiscan
Max. and min. transmission	0.9814 and 0.9705	0.9901 and 0.9851
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	6059/3/722	4854/1/371
Goodness-of-fit on F^2	1.051	1.14
Final *R* indices ($I > 2\sigma(I)$)	R_1 = 0.0462, wR_2 = 0.1122	R1 = 0.0368, wR2 = 0.0860
R indices (all data)	R_1 = 0.0673, wR_2 = 0.1341	R1 = 0.0508, wR2 = 0.0946
Largest diff. peak and hole extinction parameter	0.23 and −0.25 e. $Å^{-3}$ 0.018 (2)	0.21 and −0.10 e. $Å^{-3}$ 0.0083 (15)

and **3g** are compiled in Table 1, whereas important bond lengths and angles are depicted in Tables 2 and 3.

In the crystal asymmetric unit of **3d** there are two independent molecules (**A** and **B**, Fig. 2), whereas in **3g** there is one molecule (Fig. 3). The most distinct structural differences between both molecules of **3d** are found in the angles between the planes of the phenyl and the pyrazole ring. The *p*-chlorophenyl [C(29)–C(34)] and pyrazole ring [N(3), N(4), C(35)–C(37)] are almost coplanar in **B** with a dihedral angle of 1.5(4)°, while the dihedral angles are 19.5(4)° for

Table 2: Selected bond lengths (Å) and angles (°) for **3d**

Cl(1)-C(1)	1.737(6)	N(4)-C(37)	1.377(6)
Cl(2)-C(29)	1.729(6)	N(4)-C(38)	1.453(5)
O(1)-C(17)	1.183(6)	C(4)-C(7)	1.473(6)
O(2)-C(17)	1.344(6)	C(7)-C(8)	1.390(6)
O(2)-C(18)	1.430(5)	C(8)-C(9)	1.378(6)
O(3)-C(18)	1.406(6)	C(9)-C(17)	1.464(6)
O(3)-C(22)	1.435(5)	C(32)-C(35)	1.475(7)
O(10)-C(45)	1.194(5)	C(35)-C(36)	1.383(7)
O(11)-C(45)	1.352(5)	C(36)-C(37)	1.372(6)
O(11)-C(46)	1.419(5)	C(37)-C(45)	1.454(6)
O(12)-C(46)	1.405(5)	C(17)-O(2)-C(18)	117.5(4)
O(12)-C(50)	1.426(5)	O(3)-C(18)-O(2)	106.2(3)
N(1)-C(7)	1.341(6)	C(18)-O(3)-C(22)	109.4(3
N(1)-N(2)	1.345(5)	O(4)-C(19)-C(18)	106.8(4)
N(2)-C(9)	1.347(6)	O(6)-C(20)-C(21)	108.8(4)
N(2)-C(10)	1.469(6)	O(8)-C(21)-C(20)	104.6(3)
N(3)-C(35)	1.341(6)	O(12)-C(46)-O(11)	107.1(3)
N(3)-N(4)	1.342(5)	O(11)-C(45)-C(37)	108.0(4)
O(4)-C(19)	1.431(5)	C(46)-O(12)-C(50)	110.7(3)

the *p*-chlorophenyl [C(1)–C(6)] and pyrazole ring [N(1), N(2), C(7)–C(9)] in **A** and 13.8(2)° for the *p*-methoxyphenyl [C(2)–C(7)] and pyrazole ring [N(1), N(2), C(8)–C(10)] in **3g**. The bond lengths between the phenyl and pyrazole ring are 1.473(6) Å [C(4)–C(7)], 1.475(7) Å [C(32)–C(35)], and 1.464(3) Å [C(5)–C(8)] for **A**, **B,** and **3g**, respectively.

It is interesting to find that the pyranose moiety of **A** and **B** adopts normal $^4C_1$ conformation,[30] with puckering parameters $Q = 0.569(5)$ Å, $\theta = 10.4(5)°$,

Table 3: Selected bond lengths (Å) and angles (°) for **3g**

O(1)-C(1)	1.145(3)	N(2)-C(10)	1.359(3)
O(1)-C(2)	1.377(3)	N(2)-C(11)	1.471(3)
O(2)-C(18)	1.200(3)	C(5)-C(8)	1.464(3)
O(3)-C(18)	1.347(2)	C(8)-C(9)	1.388(3)
O(3)-C(19)	1.445(2)	C(9)-C(10)	1.360(3)
O(4)-C(19)	1.378(3)	C(10)-C(18)	1.454(3)
O(4)-C(23)	1.430(3)	C(11)-C(12)	1.495(4)
O(5)-C(22)	1.445(3)		
O(5)-C(28)	1.348(3)	C(2)-O(1)-C(1)	117.66(19)
O(6)-C(28)	1.195(3)	C(18)-O(3)-C(19)	117.37(16)
O(7)-C(21)	1.436(3)	C(19)-O(4)-C(23)	114.18(17)
O(7)-C(26)	1.342(3)	C(22)-O(5)-C(28)	116.35(17)
O(8)-C(26)	1.188(3)	C(21)-O(7)-C(26)	117.45(18)
O(9)-C(20)	1.435(3)	C(20)-O(9)-C(24)	117.93(18)
O(9)-C(24)	1.329(3)	C(8)-N(1)-N(2)	105.70(16)
O(10)-C(24)	1.201(3)	N(1)-N(2)-C(10)	111.77(15)
N(1)-C(8)	1.335(3)	N(1)-N(2)-C(11)	118.40(16)
N(1)-N(2)	1.341(2)	C(10)-N(2)-C(11)	129.23(17)

and $\phi = 341(3)^\circ$ for **A** and Q = 0.566(5) Å, $\theta = 11.6(5)^\circ$, and $\phi = 330(3)^\circ$ for **B**, in which all substituents are equatorial. By contrast, that of **3g** adopts $^1C_4$ conformation with puckering parameters Q = 0.484(2) Å, $\theta = 172.9(2)^\circ$, and $\phi = 147(2)^\circ$ and axial disposition for all substituents.[31,32]

Based on data of the crystalline state, it is easily observed that the compounds **3d** and **3g** are β-anomers, which is consistent with the mechanism of SN_2 reaction of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide and nucleophilic reagents.

In the unit cell of **3d,** two symmetry-independent molecules **A** and **B** are held together by one weak hydrogen bond between H(54C) and O(9) [C(54)-H(54C)—O(9), 2.41 Å, 3.118(14) Å, 131°]. Ladder-like one-dimensional aggregates result from an intermolecular C-Cl—π of the pyrazole ring and Cl(2) [Cl—Cg1: 3.914(4) Å, 109.9(3)°, symmetry code: $-1 + x$, y, $-1 + z$; Cg1 is the centroid of the N(1)/N(2)/C(7)/C(8)/C(9) ring] and π-π interactions between the four *p*-chlorophenyl rings of the neighboring units [Cg3—Cg7: 3.900(5) Å, $\beta = 14.10^\circ$, symmetry code: $1 + x, y, 1 + z$; Cg(7)—Cg(3): 3.900(5) Å, $\beta = 13.73^\circ$, symmetry code, $-1 + x, y, -1 + z$; Cg3 is the centroid of the C(1)–C(6) ring and Cg7 is the centroid of the C(29)–C(34) ring] (Fig. 4). These ladders are further assembled into a two-dimensional layer via weak hydrogen bonding of C(26)-H(26C)—O(18). The adjacent layers are further interconnected though weak hydrogen bonds of C(10)-H(10B)—O(5) and C(44)-H(44)—O(14) (Table 4).

There are two types of super-molecular interactions in the crystal of **3g**, namely, C-H—O hydrogen bonding and C-H—π interactions (Fig. 5, Table 4).

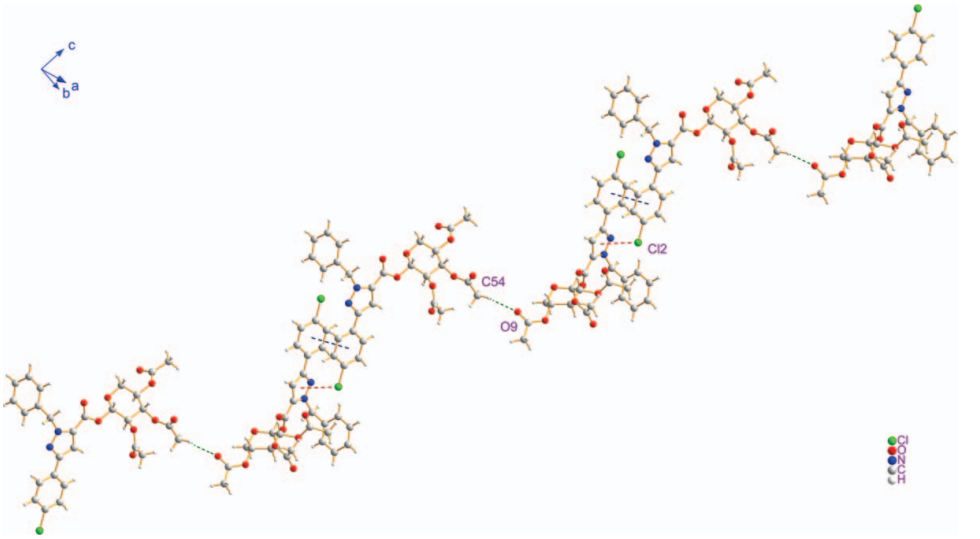

Figure 4: Crystal packing of **3d.** C-Cl—π interaction, π–π stacking interaction, C-H—O hydrogen bonding (color figure available online).

Table 4: Intermolecular "weak" hydrogen bond data for compounds **3d** and **3g**

Compound	D-H—A	D–H (Å)	H—A (Å)	D—A (Å)	∠DHA (°)	Symmetry codes
3d	C(10)-H(10B)—O(5)	0.97	2.56	3.502(7)	165	−1 + x, 1 + y, z
	C(26)-H(26C)—O(18)	0.96	2.51	3.265(10)	136	2 + x, y, z
	C(44)-H(44)—O(14)	0.93	2.51	3.366(8)	153	x, −1 + y, z
	C(54)-H(54C)—O(9)	0.96	2.41	3.118(14)	131	
3g	C(15)-H(15)—O(8)	0.93	2.59	3.497(4)	166	−1 + x, 1 + y, z
	C(22)-H(22)—O(10)	0.98	2.49	3.193(3)	129	x, 1 + y, z
	C(23)-H(23B)—O(1)	0.97	2.59	3.241(3)	125	−x, 1/2 + y, -z
	C(25)-H(25)—O(2)	0.96	2.53	3.168(3)	124	−x, −1/2 + y, 1-z
	C(25)-H(25)—O(4)	0.96	2.59	3.465(3)	152	−x, −1/2 + y, 1-z

The molecules of **3g** form a one-dimensional columnar structure via the C-H—O hydrogen bond of C(23)-H(23B)—O(1) and C(22)-H(22)—O(10) along the *b*-axis. In the one-dimensional columnar structure, the molecules of **3g** are antiparallel each other. These one-dimensional columnar structures are connected via C(27)-H(27A)—π interaction [H(27A)—Cg4 = 2.84 Å, C(27)—Cg4 = 3.697(4) Å, ∠C(27)H(27A) Cg4 = 149°, Cg4 is the centroid of the C(11)–C(16) ring] and C-H—O hydrogen bonding [C(15)-H(15)—O(8)] cross-links to form a two-dimensional layer. The two-dimensional layer is extended into a three-dimensional structure by C(25)-H(25B)—O(2) and C(25)-H(25B)—O(4) weak hydrogen bond.

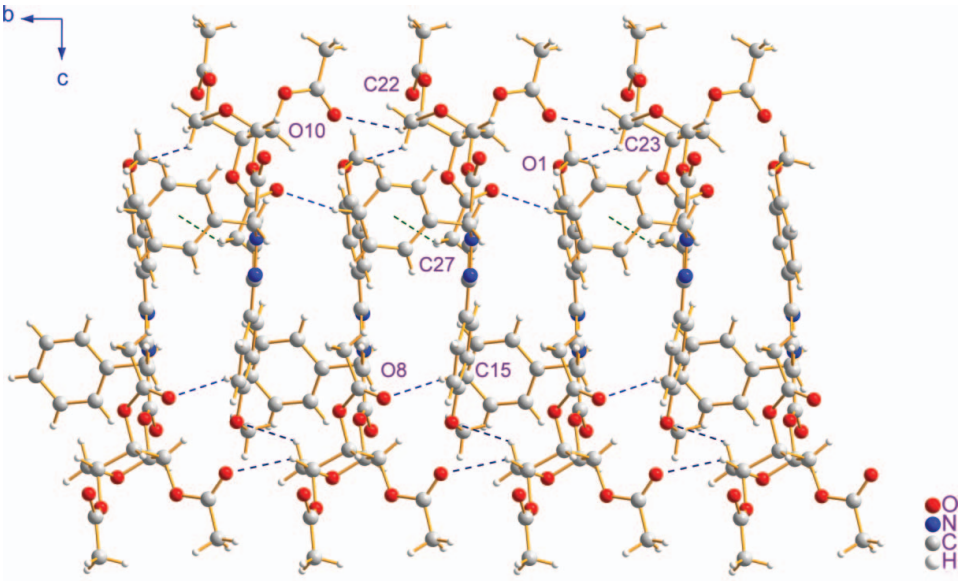

Figure 5: Crystal packing of **3g.** C-H—π interaction, C-H—O hydrogen bonding (color figure available online).

CONCLUSION

A series of novel (2S,3R,4S,5R)-3,4,5-triacetoxy-tetrahydro-2*H*-pyran-2-yl 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylate derivatives (**3**) were synthesized by the reaction of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**2**) and 1-benzyl-3-phenyl-1*H*-pyrazole-5-carboxylic acid (**1**) in the presence of sodium bicarbonate and tetrabutylammonium bromide in dichloromethane at reflux temperature. The structures of new compounds were determined by IR and ^{1}H NMR spectroscopy and HR mass spectrometry (HRMS). Representatively, the spatial structures of compounds **3d** and **3g** were determined by using X-ray diffraction analysis. Currently, investigations are under way to elucidate the bioactivity of these pyrazole derivatives with xylose moiety, and the results will be reported in due course.

EXPERIMENTAL

Reagents and Apparatus

All solvents were predried and distilled prior to use. All reactions were carried out under nitrogen and monitored by TLC on silica gel 60 F_{254} plates (Merck KGaA). ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using $CDCl_3$ as solvents and tetramethylsilane (TMS) as internal standard. Melting points were determined on an XD-4 digital micro melting point apparatus. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). HRMS spectra were recorded on an LTQ Orbitrap Hybrid mass spectrograph. Crystals of **3d** and **3g** mounted on glass fiber were studied with a Bruker SMART CCD Detector single-crystal X-ray diffractometer with a graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) source at 0°C. All structures were solved by the direct method using the SHELXS program of the SHELXTL package and refined by the full-matrix least-squares methods with SHELXL.[33] The nonhydrogen atoms were located in successive difference Fourier syntheses and refined with anisotropic thermal parameters on F^2. The organic hydrogen atoms were generated geometrically (C-H 0.93–0.98 Å). The absolute configuration for both **3d** and **3g** was established by the structure determination of a compound containing a chiral moiety of known absolute configuration. Friedel opposites for **3g** were merged, but for **3d** (containing Cl atoms), the absolute configuration was confirmed by anomalous dispersion effects in diffraction measurements on the crystal with a Flack parameter of 0.09(10).[34] A summary of crystallographic data collection parameters and refinement parameters for **3d** and **3g** are compiled in Table 1.

General Procedure for the Synthesis of Compound 3

To a flask compound **1a–i** (1 mmol) and saturated aqueous $NaHCO_3$ (5 mL) were added. Then 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide **2** (1 mmol), TBAB (1 mmol), and CH_2Cl_2 (5 mL) were added and the mixture was stirred at reflux for 2 to 4 h. The progress of the reaction was monitored by TLC. The aqueous layer was separated and extracted with CH_2Cl_2 (10 mL $\times$ 3). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was further purified by column chromatography (petroleum ether/ethyl acetate = 2:1) on silica gel to afford compound **3a–i**.

*(2S,3R,4S,5R)-2-((1-benzyl-3-phenyl-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3a**)*

Yield: 60.9%, white solid, mp: 155–158°C; IR (KBr) ν: 1745 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 1.88 (s, 3H, CH_3), 2.09 (s, 6H, 2 $\times$ CH_3), 3.60 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 7.9$ Hz, $C_{5a\text{-}H}$), 4.19 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 4.7$ Hz, $C_{5b\text{-}H}$), 4.98–5.02 (m, 1H, $C_{4\text{-}H}$), 5.15 (t, 1H, $J = 7.2$ Hz, $C_{2\text{-}H}$), 5.25 (t, 1H, $J = 7.9$ Hz, $C_{3\text{-}H}$), 5.76 (d, 1H, $J = 16.5$ Hz, NCH_2Ar), 5.81 (d, 1H, $J = 16.5$ Hz, NCH_2Ar), 5.89 (d, 1H, $J = 6.4$ Hz, $C_{1\text{-}H}$), 7.18 (s, 1H, 4-H), 7.26–7.31 (m, 6H, ArH), 7.35 (d, 1H, $J = 7.3$ Hz, ArH), 7.43 (t, 2H, $J = 7.3$ Hz, ArH), 7.83 (d, 2H, $J = 7.2$ Hz, ArH); HRMS m/z calcd for $[M+H]^+$ $C_{28}H_{29}N_2O_9$: 537.1873; Found: 537.1876.

*(2S,3R,4S,5R)-2-((1-(4-(tert-butyl)benzyl)-3-phenyl-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3b**)*

Yield: 45.4%, white solid, mp: 172–173°C; IR (KBr) ν: 1757, 1737 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 9H, $C(CH_3)_3$), 1.87 (s, 3H, CH_3), 2.09 (s, 6H, 2 $\times$ CH_3), 3.61 (dd, 1H, $J_1 = 12.2$ Hz, $J_2 = 7.8$ Hz, $C_{5a\text{-}H}$), 4.20 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 4.7$ Hz, $C_{5b\text{-}H}$), 4.98–5.03 (m, 1H, $C_{4\text{-}H}$), 5.16 (t, 1H, $J =$ 7.2 Hz, $C_{2\text{-}H}$), 5.26 (t, 1H, $J = 7.8$ Hz, $C_{3\text{-}H}$), 5.72 (d, 1H, $J = 14.6$ Hz, NCH_2Ar), 5.79 (d, 1H, $J = 14.6$ Hz, NCH_2Ar), 5.91 (d, 1H, $J = 6.4$ Hz, $C_{1\text{-}H}$), 7.17 (s, 1H, 4-H), 7.27 (d, 2H, $J = 7.4$ Hz, p-tertbutylbenzyl), 7.34 (t, 3H, $J = 7.3$ Hz, p-tertbutylbenzyl ArH + ArH), 7.42 (t, 2H, $J = 7.5$ Hz, ArH), 7.82 (d, 2H, $J = 7.8$ Hz, ArH); HRMS m/z calcd for $[M+H]^+$ $C_{32}H_{37}N_2O_9$: 593.2499; Found: 593.2490.

*(2S,3R,4S,5R)-2-((1-((6-chloropyridin-3-yl)methyl)-3-phenyl-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3c**)*

Yield: 66.5%, white solid, mp: 75–80°C; IR (KBr) ν: 1741 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.03 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.62 (dd, 1H, $J_1 = 12.2$ Hz, $J_2 = 7.8$ Hz, $C_{5a\text{-}H}$), 4.22 (dd, 1H, $J_1 =$ 12.2 Hz, $J_2 = 4.8$ Hz, $C_{5b\text{-}H}$), 4.99–5.04 (m, 1H, $C_{4\text{-}H}$), 5.16 (t, 1H, $J =$

7.2 Hz, $C_{2\text{-H}}$), 5.27 (t, 1H, J = 7.9 Hz, $C_{3\text{-H}}$), 5.76 (s, 2H, NCH_2Ar), 5.89 (d, 1H, J = 6.4 Hz, $C_{1\text{-H}}$), 7.17 (s, 1H, 4-H), 7.27 (d, 1H, J = 9.2 Hz, PyH), 7.36 (t, 1H, J = 7.1 Hz, ArH), 7.43 (t, 2H, J = 7.4 Hz, ArH), 7.66 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz, PyH), 7.80 (d, 2H, J = 7.2 Hz, ArH), 8.46 (d, 1H, J = 2.2 Hz, PyH); HRMS m/z calcd for $[M+H]^+$ $C_{27}H_{27}ClN_3O_9$: 572.1436; Found: 572.1423.

*(2S,3R,4S,5R)-2-((1-benzyl-3-(4-chlorophenyl)-1H-pyrazole-5-carbonyl)oxy) tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3d**)*

Yield: 50.3%, white solid, mp: 160–163°C; IR (KBr) ν: 1746 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 1.99 (s, 3H, CH_3), 2.08 (s, 6H, 2 × CH_3), 3.59 (dd, 1H, J_1 = 12.1 Hz, J_2 = 8.0 Hz, $C_{5a\text{-H}}$), 4.18 (dd, 1H, J_1 = 12.1 Hz, J_2 = 4.8 Hz, $C_{5b\text{-H}}$), 4.98–5.03 (m, 1H, $C_{4\text{-H}}$), 5.16 (t, 1H, J = 7.4 Hz, $C_{2\text{-H}}$), 5.29 (q, 1H, J = 8.0 Hz, $C_{3\text{-H}}$), 5.74 (d, 1H, J = 14.7 Hz, NCH_2Ar), 5.80 (d, 1H, J = 14.7 Hz, NCH_2Ar), 5.88 (d, 1H, J = 6.6 Hz, $C_{1\text{-H}}$), 7.15 (s, 1H, 4-H), 7.26–7.31 (m, 5H, ArH), 7.39 (d, 2H, J = 8.5 Hz, p-chlorophenyl ArH), 7.76 (d, 2H, J = 8.5 Hz, p-chlorophenyl ArH); HRMS m/z calcd for $[M+H]^+$ $C_{28}H_{28}ClN_2O_9$: 571.1483; Found: 571.1470.

*(2S,3R,4S,5R)-2-((1-(4-(tert-butyl)benzyl)-3-(4-chlorophenyl)-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3e**)*

Yield: 57.8%, white solid, mp: 179–182°C; IR (KBr) ν: 1756 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 1.28 (s, 9H, $C(CH_3)_3$), 1.98 (s, 3H, CH_3), 2.08 (s, 6H, 2 × CH_3), 3.60 (dd, 1H, J_1 = 12.1 Hz, J_2 = 8.0 Hz, $C_{5a\text{-H}}$), 4.19 (dd, 1H, J_1 = 12.1 Hz, J_2 = 4.8 Hz, $C_{5b\text{-H}}$), 4.99–5.04 (m, 1H, $C_{4\text{-H}}$), 5.16 (t, 1H, J = 7.4 Hz, $C_{2\text{-H}}$), 5.26 (t, 1H, J = 8.0 Hz, $C_{3\text{-H}}$), 5.71 (d, 1H, J = 14.6 Hz, NCH_2Ar), 5.78 (d, 1H, J = 14.6 Hz, NCH_2Ar), 5.90 (d, 1H, J = 6.2 Hz, $C_{1\text{-H}}$), 7.14 (s, 1H, 4-H), 7.27 (d, 2H, J = 7.2 Hz, ArH), 7.33 (d, 2H, J = 8.4 Hz, p-tertbutylbenzyl ArH), 7.38 (d, 2H, J = 8.5 Hz, p-tertbutylbenzyl ArH), 7.75 (d, 2H, J = 8.5 Hz, ArH); HRMS m/z calcd for $[M+H]^+$ $C_{32}H_{36}ClN_2O_9$: 627.2109; Found: 627.2166.

*(2S,3R,4S,5R)-2-((3-(4-chlorophenyl)-1-((6-chloropyridin-3-yl)methyl)-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3f**)*

Yield: 46.5%, white solid, mp: 76–80°C; IR (KBr) ν: 1756 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 2.03 (s, 3H, CH_3), 2.09 (s, 6H, 2 × CH_3), 3.61 (dd, 1H, J_1 = 11.7 Hz, J_2 = 8.0 Hz, $C_{5a\text{-H}}$), 4.21 (dd, 1H, J_1 = 11.9 Hz, J_2 = 4.5 Hz, $C_{5b\text{-H}}$), 4.97–5.07 (m, 1H, $C_{4\text{-H}}$), 5.16 (t, 1H, J = 7.3 Hz, $C_{2\text{-H}}$), 5.27 (t, 1H, J = 8.0 Hz, $C_{3\text{-H}}$), 5.75 (s, 2H, NCH_2Ar), 5.88 (d, 1H, J = 6.4 Hz, $C_{1\text{-H}}$), 7.14 (s, 1H, 4-H), 7.28 (d, 1H, J = 10.3 Hz, PyH), 7.40 (d, 2H, J = 8.2 Hz, ArH), 7.66 (d, 1H, J = 8.1 Hz, PyH), 7.73 (d, 2H, J = 8.3 Hz, ArH), 8.46 (s, 1H, PyH); HRMS m/z calcd for $[M+H]^+$ $C_{27}H_{26}Cl_2N_3O_9$: 606.1046; Found: 606.1037.

*(2S,3R,4S,5R)-2-((1-benzyl-3-(4-methoxyphenyl)-1H-pyrazole-5-carbonyl)oxy) tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3g**)*

Yield: 64.2%, white solid, mp: 145–146°C; IR (KBr) ν: 1757, 1732 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 1.99 (s, 3H, CH_3), 2.08 (s, 6H, 2 × CH_3), 3.59 (dd, $J_1 = 12.2$ Hz, $J_2 = 7.9$ Hz, $C_{5a\text{-}H}$), 3.85 (s, 3H, CH), 4.18 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 4.7$ Hz, $C_{5b\text{-}H}$), 4398–5.03 (m, 1H, $C_{4\text{-}H}$), 5.15 (t, 1H, $J = 7.3$ Hz, $C_{2\text{-}H}$), 5.25 (t, 1H, $J = 7.9$ Hz, $C_{3\text{-}H}$), 5.74 (d, 1H, $J = 14.8$ Hz, NCH_2Ar), 5.80 (d, 1H, $J = 14.8$ Hz, NCH_2Ar), 5.88 (d, 1H, $J = 6.4$ Hz, $C_{1\text{-}H}$), 6.95 (d, 2H, $J = 8.7$ Hz, p-methoxyphenyl ArH), 7.10 (s, 1H, 4-H, ArH), 7.26–7.31 (m, 5H, ArH), 7.75 (d, 2H, $J = 8.7$ Hz, p-methoxyphenyl ArH); HRMS m/z calcd for $[M+H]^+$ $C_{29}H_{31}N_2O_{10}$: 567.1979; Found: 567.1967.

*(2S,3R,4S,5R)-2-((1-(4-(tert-butyl)benzyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3h**)*

Yield: 52.3%, white solid, mp: 83–87°C; IR (KBr) ν: 1756 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 1.28 (s, 9H, $C(CH_3)_3$), 1.99 (s, 3H, CH_3), 2.08 (s, 6H, 2 × CH_3), 3.66 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 7.9$ Hz, $C_{5a\text{-}H}$), 4.19 (dd, 1H, $J_1 = 12.2$ Hz, $J_2 = 4.8$ Hz, $C_{5b\text{-}H}$), 4.98–5.03 (m, 1H, $C_{4\text{-}H}$), 5.15 (t, 1H, $J = 7.3$ Hz, $C_{2\text{-}H}$), 5.25 (t, 1H, $J = 7.9$ Hz, $C_{3\text{-}H}$), 5.70 (d, 1H, $J = 14.7$ Hz, NCH_2Ar), 5.77 (d, 1H, $J = 14.7$ Hz, NCH_2Ar), 5.90 (d, 1H, $J = 6.4$ Hz, $C_{1\text{-}H}$), 6.95 (d, 2H, $J = 8.8$ Hz, ArH), 7.09 (s, 1H, 4-H), 7.26 (d, 2H, $J = 8.3$ Hz, p-tertbutylbenzyl ArH), 7.32 (d, 2H, $J = 8.4$ Hz, p-tertbutylbenzyl ArH), 7.75 (d, 2H, $J = 8.7$ Hz, ArH); HRMS m/z calcd for $[M+H]^+$ $C_{33}H_{39}ClN_2O_{10}$: 623.2605; Found: 623.2602.

*(2S,3R,4S,5R)-2-((1-((6-chloropyridin-3-yl)methyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carbonyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**3i**)*

Yield: 60.3%, white solid, mp: 119–121°C; IR (KBr) ν: 1745 (C=O) cm^{-1}; ^1H NMR (400M Hz, $CDCl_3$) δ: 2.03 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.62 (dd, 1H, $J_1 = 12.0$ Hz, $J_2 = 7.9$ Hz, $C_{5a\text{-}H}$), 3.85 (s, 3H, CH), 4.22 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 4.6$ Hz, $C_{5b\text{-}H}$), 5.02 (dd, 1H, $J_1 = 12.4$ Hz, $J_2 = 7.5$ Hz, $C_{4\text{-}H}$), 5.16 (t, 1H, $J = 7.2$ Hz, $C_{2\text{-}H}$), 5.27 (t, 1H, $J = 7.8$ Hz, $C_{3\text{-}H}$), 5.74 (s, 2H, NCH_2Ar), 5.88 (d, 1H, $J = 6.4$ Hz, $C_{1\text{-}H}$), 6.96 (d, 2H, $J = 8.4$ Hz, ArH), 7.01 (s, 1H, 4-H), 7.27 (d, 1H, $J = 6.8$ Hz, PyH), 7.65 (d, 1H, $J = 7.4$ Hz, PyH), 7.72 (d, 2H, $J = 8.4$ Hz, ArH), 8.45 (s, 1H, PyH); HRMS m/z calcd for $[M+H]^+$ $C_{28}H_{29}ClN_3O_{10}$: 602.1541; Found: 602.1536.

SUPPLEMENTARY MATERIALS

CCDC 773566 and 773567 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.

uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033.

ACKNOWLEDGMENTS

This study was supported by the Science and Technology Developmental Project of Shandong Province (2008GG10002034) and 973 Program (2009CB526507).

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