Solvent-free microwave-assisted synthesis of tetrahydrooxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones

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Abstract

A series of novel oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones were synthesized by the reaction of ethyl 3-aryl-1-(2-oxo-2-arylethyl)-1*H*-pyrazole-5-carboxylate derivatives and aminoethanol under microwave-assisted one-step and solvent-free conditions.

Keywords: Fused oxazoles, pyrazines, pyrazoles, microwave assisted synthesis, X-ray analysis

Introduction

Heterocyclic compounds are of significance since they play prominent roles in many fields of science including organic, bioorganic, agricultural, pharmaceutical, medicinal chemistry and materials science.[1,2] Searching for new small molecules which can interact with biological systems as chemical-genetic probes or drug leads has created an ever-increasing demand for efficient synthetic sequences leading to diverse "drug-like" structures.[3] Among the heterocycles, the piperazine ring is a structural motif found in numerous pharmaceutically active natural products, such as tetrazomine and quinocarcin (Figure 1), and in many polycyclic compounds of biological and industrial significance.[4-7]

On the other hand, pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents and still continue to attract considerable attention due to their broad range of biological activities. Among them, pyrazole fused heterocycles are an interesting class of compounds with wide range of biological activities such as analgesic, anticancer, antibacterial, antifungal, radioprotective, antiproliferative and antimalarial.[8-14]

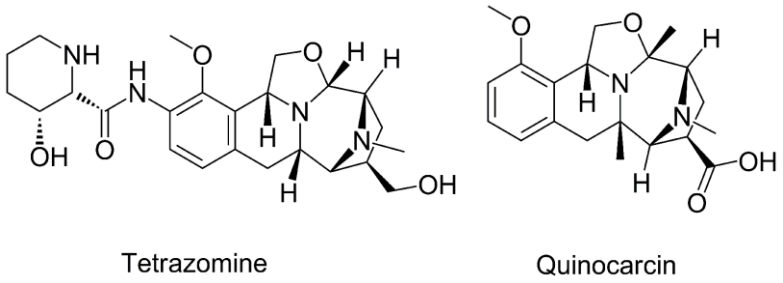


Figure 1. Structures of tetrazomine and quinocarcin.

Microwave-assisted organic synthesis (MAOS) has aroused a growing interest in chemists, since it was first reported in 1986.[15,16] The use of this "non-conventional" synthetic method brings several advantages over conventional reactions, such as drastically reduced reaction times, higher yields and higher selectivity, lower quantities of byproducts and, consequently, easier work-up and purification of the products.[17,18] MAOS is recommended as a "green" technology, since, using efficient and less hazardous energy sources, it can be applied in solvent-free conditions, and increasing "atom economy" by improving product selectivity and chemical yield.[19,20]

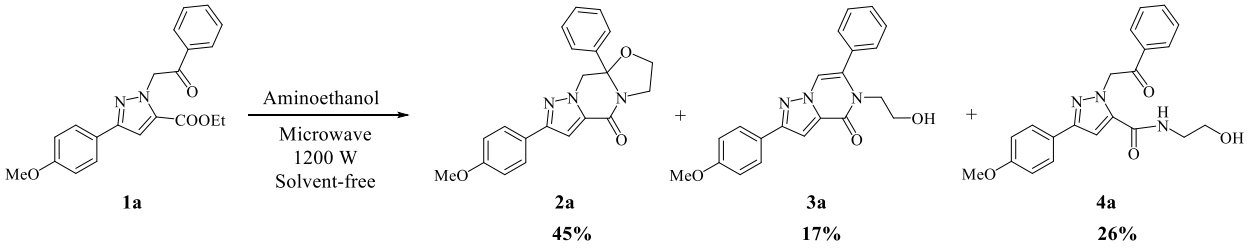
In the light of the above-mentioned facts and as an ongoing investigation on the development of new routes for the preparation of biologically active heterocyclic compounds, we herein describe the reaction of ethyl 3-aryl-1-(2-aryl-2-oxoethyl)-1*H*-pyrazole-5-carboxylate derivatives with aminoethanol under microwave (MW) irradiation and the formation of some novel 5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones. To the best of our knowledge, the oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one heterocyclic system has not been reported previously. This method affords an easy and efficient way to prepare oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones and permits us to introduce great molecular diversity, including substituent and skeleton diversity of oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones.

Results and Discussion

Chemistry

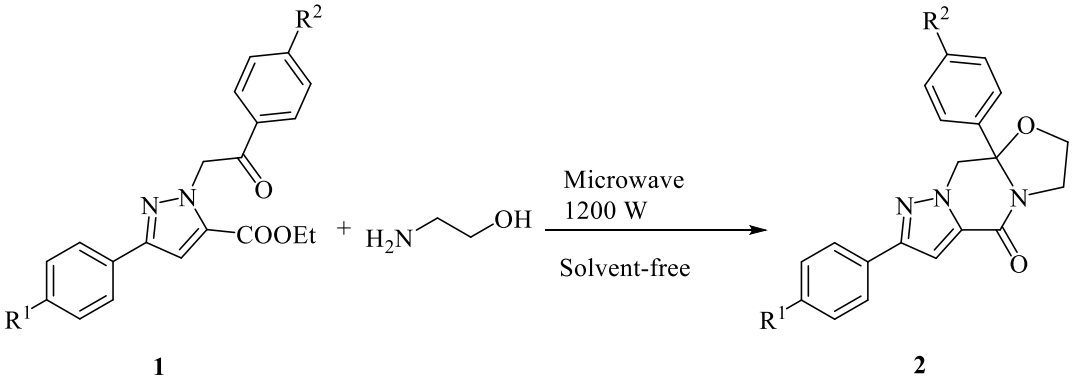
In recent reports from our team, we have described an efficient approach to the synthesis of novel pyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones by microwave-irradiating a mixture of ethyl 3-aryl-1-(2-aryl-2-oxoethyl)-1*H*-pyrazole-5-carboxylate derivatives and 2-(2-aminoethoxy)ethanol or 2-morpholinoethanamine without using toxic solvents and catalysts. Contrasting with the conventional approach, the application of microwave irradiation reduces the reaction time and the experimental procedure is operationally simple and leads to high yields.[21] Encouraged by this result, we wondered whether a similar reaction could be carried out between the same pyrazole-5-carboxylate derivatives and aminoethanol. To our surprise, treatment of ethyl 3-(4-

methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-5-carboxylate **1a** with aminoethanol under microwave and solvent-free conditions afforded 7-(4-methoxyphenyl)-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one **2a** in 45% yield as the major product, rather than 5-(2-hydroxyethyl)-2-(4-methoxyphenyl)-6-phenylpyrazolo[1,5-*a*]-pyrazin-4(5*H*)-one **3a**, which was also formed, but only in minor quantities (Scheme 1).



Scheme 1. The microwave-assisted reaction of pyrazole ester **1a** with 2-aminoethanol.

Following the same procedure, a series of reactions of **1a-i** with aminoethanol were performed under microwave irradiation and the most satisfactory results for the synthesis of compounds **2a-i** were obtained as shown in Scheme 2 and Table 1. The substituent groups have an effect on the reactions. When R^2 is chlorine, which is recognized to be an electron-withdrawing group, the nucleophilic addition on the carbonyl carbon more easily undergo because the positive charge is stronger, and the products are formed in higher yields. The mechanism is under investigation.



Scheme 2. Synthesis of 7,10a-diaryltetrahydrooxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones **2**.

The structure of compounds **2** were determined by IR, NMR and HRMS. Thus, for example **2i**, obtained as white solid, gave a [M+H]-ion peak at *m/z* 392.1622 in the HRMS, in accord with the molecular formula $C_{22}H_{22}N_3O_4$. In the IR spectra, the lactam carbonyl group absorption bands and the ether group vibrations were observed at 1666 cm^{-1} and 1248 cm^{-1}, respectively. In the ^1H NMR spectrum of compound **2i** in $CDCl_3$, the methylene protons of the pyrazinone moiety

resonated as a pair of doublets (*J* 12.1 Hz) in the ranges δ = 4.55 and 4.82 ppm. A singlet signal appearing at δ = 7.11 ppm is consistent with the proton at position 6, on the pyrazole ring.

Table 1. Yields and reaction time for **2a-i** under solvent-free microwave conditions

Entry	Products	R^1	R^2	Time (min)[a]	Yield (%)[b]
1	**2a**	OMe	H	4	45
2	**2b**	Cl	H	3	48
3	**2c**	H	H	4	45
4	**2d**	H	Cl	3	60
5	**2e**	Cl	Cl	3	62
6	**2f**	OMe	Cl	4	56
7	**2g**	H	OMe	4	48
8	**2h**	Cl	OMe	4	40
9	**2i**	OMe	OMe	6	40

[a] The end of reaction determined by TLC. [b] Isolated yield.

Crystallography

Compound **2i** crystallizes in the centrosymmetric space group *C*2/*c*. Two enantiomeric forms are present and the structure of the *S* form is shown in Figure 2. The structure of compound **2i** consists of two methoxy-substituted benzene rings and an oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazine frame in which a pyrazine ring fused with one pyrazole and an oxazole ring. All of the bond lengths and bond angles in the aromatic rings are in the normal range (Table 2).

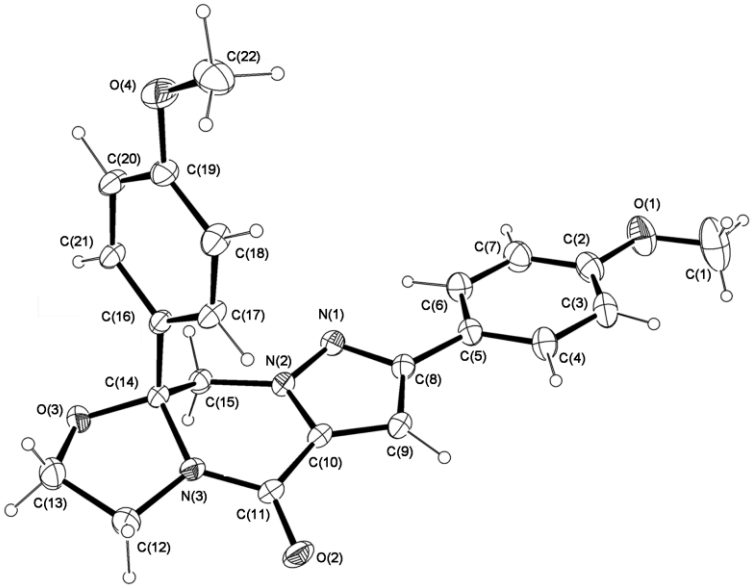


Figure 2. ORTEP view of compound **2i.** Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level and hydrogen atoms are shown as cycles.

Table 2. Selected bond lengths (Å) and angles (˚) of compound **2i**

N1–C8	1.345(2)	N3–C14	1.470(2)
N1–N2	1.341(2)	N3–C11	1.345(2)
N2–C10	1.355(2)	C10–C11	1.467(3)
C9–C10	1.372(3)	O3–C14	1.416(2)
C8–C9	1.402(3)	O3–C13	1.412(3)
N2–C15	1.443(2)	C12–C13	1.490(3)
C14–C15	1.520(3)	C12–N3	1.453(3)
C10–N2–C15	123.99(15)	N3–C14–O3	102.93(14)
N2–C15–C14	107.03(14)	C14–O3–C13	106.28(16)
C15–C14–N3	109.19(14)	O3–C13–C12	107.49(18)
C14–N3–C11	125.49(15)	C13–C12–N3	101.83(17)
N3–C11–C10	113.78(15)	C12–N3–C14	109.96(15)
C11–C10–N2	119.24(16)	O3–C14–C16	111.25(14)
N3–C14–C16	112.23(14)	C16–C14–C15	112.49(15)
N3–C11–O2	122.97(18)	C10–C11–O2	123.24(17)

The C2–O1 and C19–O4 bond lengths suggest some double-bond character due to resonance delocalization of the O-atom lone pairs with the benzene ring. Two of the methoxy groups lie essentially in the plane of the attached benzene rings, with the C22-O4-C19-C20 and C1-O1-C2-C7 torsion angles being 179.87(23)° and –179.47(30)°, respectively.

In the molecular structure, the non-aromatic pyrazinone ring adopts a twist-boat conformation.[22] The total puckering amplitude Q is at 0.4656(19)Å and the ring-puckering parameters in compound **2i** are, for the atom sequence N2-C10-C11-N3-C14-C15, θ = 65.7(2)° and φ = 272.1(2)°.[23] Regardless of these ring puckerings, the pyrazine ring is approximately coplanar with the adjacent pyrazole ring, with a dihedral angle between these rings of 11.10(5)°. The oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazine moiety is nearly coplanar with the benzene ring (C2-C3-C4-C5-C6-C7), although with a dihedral angle of 13.59(5)°. The oxazolo[3,2-*a*]pyrazolo-[1,5-*d*]pyrazine moiety and the other benzene ring (C16-C17-C18-C19-C20-C21) are almost perpendicular with a dihedral angle of 83.33(5)°.

The crystal packing of **2i** is complex, despite the lack of any functional groups for classical hydrogen bonding. In the crystal lattice, the N1 atom of the pyrazole ring interacts with the H18 of benzene moiety through a pair of linear C18–H18···N1 hydrogen bonds to form two kinds of $R_2^2(16)$ dimers (Figure. 3) [$R_2^2(16)_R$: refers to the motif generated by pairs *R* form of the **2i** molecules. $R_2^2(16)_S$: refers to the motif generated by pairs *S* molecules.]. Furthermore, inversion-related $R_2^2(16)_R$ ring motifs and the adjacent $R_2^2(16)_S$ ring motifs lie on either side of a $R_4^2(14)$ motif formed by C22–H22$_C$···N1 intramolecular hydrogen bonds. $R_2^2(16)_R$, $R_4^2(14)$ and $R_2^2(16)_S$ ring motifs occur alternately, aggregating into a supramolecular ladder-like

arrangement. On the other hand, adjacent ladders are crosslinked by pairs of C20–H20···O2 hydrogen bonds and C15–H15$_B$···π interactions (Figure 4 and Table 3).

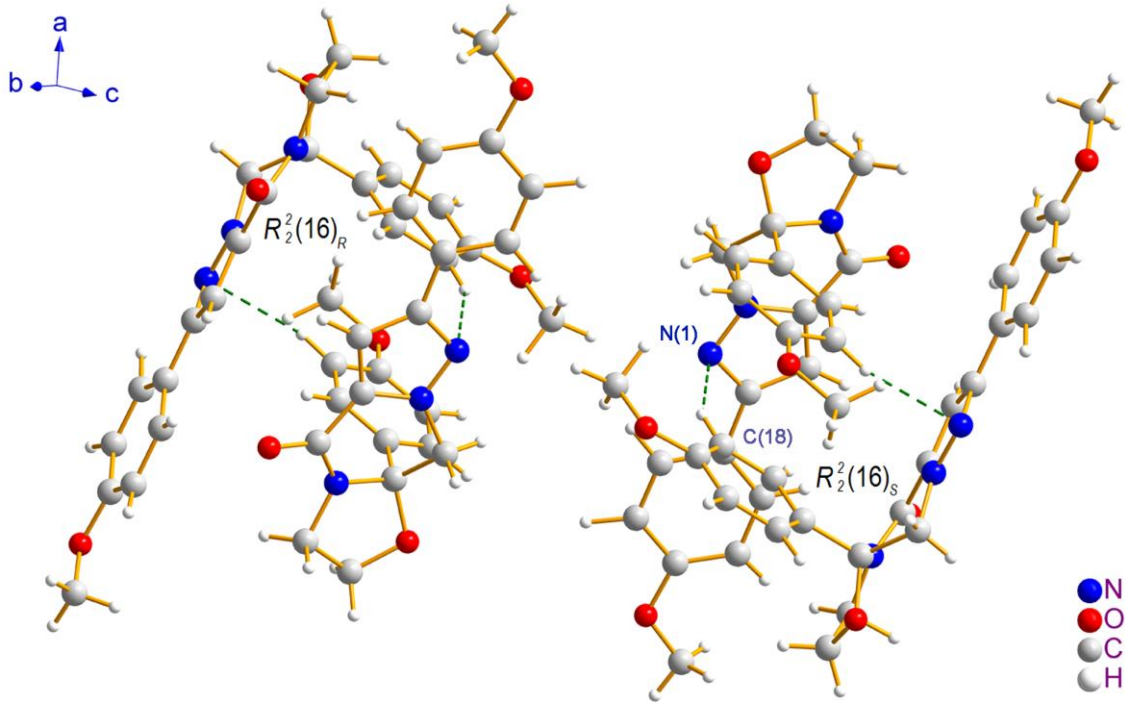


Figure 3. Dimers formed by C18–H18···N1 intermolecular hydrogen bond of compound **2i**.

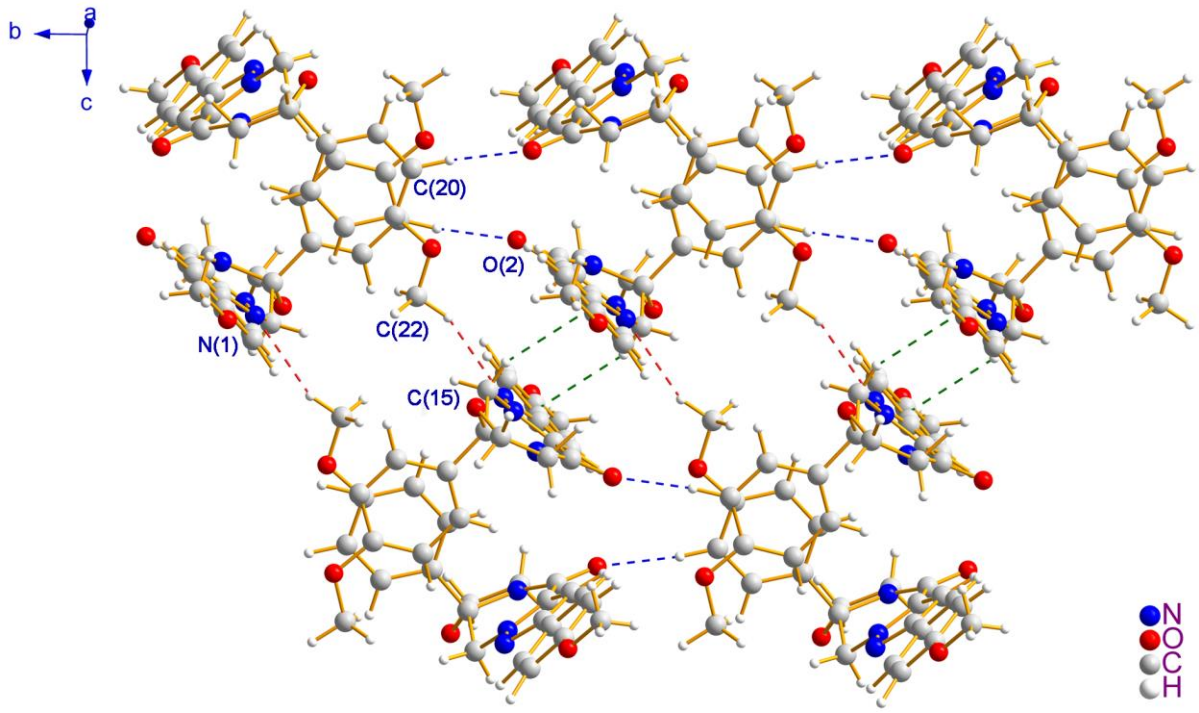


Figure 4. Packing diagram of compound **2i**. Short contacts are showed as dashed lines.

Table 3. Hydrogen bonding geometry for structure **2i** (*Cg*1 refers to the centroid of ring C2-C3-C4-C5-C6-C7)

D–H···A/π	D–H [Å]	H···A/π [Å]	D···A/π [Å]	D–H···A/π [°]
C18–H18···N1^{i}	0.97(2)	2.62(2)	3.457(3)	144.5(16)
C20–H20···O2^{ii}	1.03(2)	2.22(2)	3.239(2)	168.2(17)
C22–H22$_C$···N1^{iii}	1.04(4)	2.61(4)	3.551(4)	150(3)
C15–H15$_B$···*Cg*1^{iv}	0.93(2)	2.76(2)	3.589(2)	149.5

Symmetry codes: (i) –x, y, ½ – z; (ii) x, y – 1, z; (iii) x, –y, z + ½; (iv) –x, 1 – y, –z.

File CCDC 779359 contains the supplementary crystallographic data for compound **2i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033; or by e-mail: deposit@ccdc.cam.ac.uk).

Conclusions

In summary, we have developed an efficient method for the preparation of tetrahydro-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-ones in solvent-free microwave-assisted conditions.

Experimental Section

General. Thin-layer chromatography was carried out with Merck silica gel (60 F_{254}). Melting points were determined with an XD-4 digital micro melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra were obtained on a Bruker Avance 400 (100 MHz) spectrometer with TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts (δ) were measured in ppm with respect to the solvent ($CDCl_3$: ^{1}H: δ = 7.26 ppm, DMSO-d_6: ^{1}H: δ = 2.50 ppm). Coupling constants (*J*) are given in Hz. IR spectra were measured as KBr plates with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded with a LTQ Orbitrap Hybrid mass spectrograph. Microwave-assisted reactions were carried out in a Start Synth Microwave Synthesis Lab station.

General procedure for the synthesis of compounds 2, 3a, 4a

To an open glass vessel, ethyl 3-aryl-1-(2-aryl-2-oxoethyl)-1*H*-pyrazole-5-carboxylate **1** (1.0 mmol), obtained according to our previous reported method,[24] and aminoethanol (183 mg, 3.0

mmol) were added and were then irradiated constantly at 1200 W in the microwave cavity for the time given in Table 1. The reaction end was monitored by TLC. The reaction mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:2) to afford the products **2**. Byproducts **3a** and **4a** have been also isolated.

7-(4-Methoxyphenyl)-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]-pyrazin-5-one (**2a**). White solid (163 mg,45%), mp 236–238 ºC. IR (KBr, cm^{-1}). 1671 (C=O), 1249 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 3.60–3.66 (m, 1H, NCH_2), 3.82 (s, 3H, OCH_3), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.10 (m, 1H, OCH_2), 4.32–4.37 (m, 1H, OCH_2), 4.58 (d, *J* 12.3 Hz, 1H, CH_2), 4.86 (d, *J* 12.3 Hz, 1H, CH_2), 6.90 (d, *J* 8.7 Hz, 2H, Ar-H), 7.13 (s, 1H, pyrazole-H), 7.33 (s, 5H, Ar-H), 7.66 (d, *J* 8.7 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ = 159.8, 154.8, 152.5, 138.5, 135.1, 129.4, 129.0 (2C), 126.8 (2C), 125.5 (2C), 124.9, 114.1 (2C), 103.9, 93.3, 65.1, 57.8, 55.3, 42.2; HRMS ($C_{21}H_{19}N_3O_3$). calcd for $[M + H]^+$ 362.1505, found 362.1495.

7-(4-Chlorophenyl)-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]-pyrazin-5-one (**2b**). **w**hite solid (176 mg 48%), mp 250–251 ºC. IR (KBr, cm^{-1}). 1668 (C=O), 1255 (C-O-C); ^{1}H NMR (400-MHz, $CDCl_3$, ppm). δ 3.61–3.66 (m, 1H, NCH_2), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.10 (m, 1H, OCH_2), 4.33–4.38 (m, 1H, OCH_2), 4.59 (d, *J* 12.3 Hz, 1H, CH_2), 4.87 (d, *J* 12.3 Hz, 1H, CH_2), 7.17 (s, 1H, pyrazole-H), 7.33 (s, 5H, Ar-H), 7.34 (d, *J* 7.8 Hz, 2H, Ar-H), 7.66 (d, *J* 7.8 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ = 154.6, 151.5, 138.4, 135.3, 134.1, 130.7, 129.5, 129.0 (2C), 128.9 (2C), 126.8 (2C), 125.4 (2C), 104.4, 93.3, 65.1, 58.0, 42.3; HRMS ($C_{20}H_{16}ClN_3O_2$). calcd for $[M + H]^+$ 366.1009, found 366.1012.

7,10a-Diphenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one (**2c**). White solid (150 mg, 45%), mp 245 ºC. IR (KBr, cm^{-1}). 1676 (C=O), 1251 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm). δ 3.60–3.66 (m, 1H, NCH_2), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.11 (m, 1H, OCH_2), 4.32–4.37 (m, 1H, OCH_2), 4.59 (d, *J* 12.3 Hz, 1H, CH_2), 4.87 (d, *J* 12.3 Hz, 1H, CH_2), 7.21 (s, 1H, pyrazole-H), 7.30 (t, *J* 7.5 Hz, 1H, Ar-H), 7.33 (s, 5H, Ar-H), 7.37 (t, *J* 7.5 Hz, 2H, Ar-H), 7.73 (d, *J* 7.5 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ 154.8, 152.6, 138.4, 135.2, 132.2, 129.4, 129.0 (2C), 128.7 (2C), 128.3, 125.5 (2C), 125.4 (2C), 104.4, 93.3, 65.1, 57.9, 42.2. HRMS ($C_{20}H_{17}N_3O_2$). calcd for $[M + H]^+$ 332.1399, found 332.1394.

10a-(4-Chlorophenyl)-7-phenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]-pyrazin-5-one (**2d**). Yellow solid (221 mg, 60%), mp 226–228 ºC. IR (KBr, cm^{-1}). 1665 (C=O), 1258 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm). δ:3.59–3.64 (m, 1H, NCH_2), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.11 (m, 1H, OCH_2), 4.33–4.38 (m, 1H, OCH_2), 4.58 (d, *J* 12.4 Hz, 1H, CH_2), 4.82 (d, *J* 12.4 Hz, 1H, CH_2), 7.21 (s, 1H, pyrazole-H), 7.27 (d, *J* 8.7 Hz, 2H, Ar-H), 7.30 (d, *J* 8.7 Hz, 2H, Ar-H), 7.32 (t, *J* 7.6 Hz, 1H, Ar-H), 7.38 (t, *J* 7.6 Hz, 2H, Ar-H), 7.74 (d, *J* 7.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ 154.7, 152.8, 137.1, 135.6, 135.0, 132.0, 129.2 (2C), 128.8 (2C), 128.4, 127.0 (2C), 125.5 (2C), 104.6, 92.9, 65.2, 57.8, 42.3; HRMS ($C_{20}H_{16}ClN_3O_2$). calcd for $[M + H]^+$ 366.1009, found 366.1015.

7,10a-Bis(4-chlorophenyl)-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one (**2e**). Yellow solid (248 mg 62%), mp 300–301 ºC. IR (KBr, cm^{-1}). 1661 (C=O), 1249 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 3.59–3.64 (m, 1H, NCH_2), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.10 (m, 1H, OCH_2), 4.33–4.38 (m, 1H, OCH_2), 4.58 (d, *J* 12.3 Hz, 1H, CH_2), 4.80 (d, *J* 12.3 Hz, 1H, CH_2), 7.17 (s, 1H, pyrazole-H), 7.26 (d, *J* 8.7 Hz, 2H, Ar-H), 7.31 (d, *J* 8.7 Hz, 2H, Ar-H), 7.35 (d, *J* 8.6 Hz, 2H, Ar-H), 7.67 (d, *J* 8.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). *δ* = 154.6, 151.7, 137.0, 135.7, 135.2, 134.2, 130.6, 129.3 (2C), 128.9 (2C), 127.0 (2C), 126.8 (2C), 104.5, 92.9, 65.2, 57.8, 42.3; HRMS ($C_{20}H_{15}Cl_2N_3O_2$). calcd for $[M + H]^+$ 400.0620, found 400.0619.

10a-(4-Chlorophenyl)-7-(4-methoxyphenyl)-2,3,10,10a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one (**2f**). Yellow solid (223 mg, 56%), mp 248–251 ºC. IR (KBr, cm^{-1}). 1663 (C=O), 1251 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 3.58–3.64 (m, 1H, NCH_2), 3.82 (s, 3H, OCH_3), 3.86–3.92 (m, 1H, NCH_2), 4.04–4.10 (m, 1H, OCH_2), 4.33–4.38 (m, 1H, OCH_2), 4.56 (d, *J* 12.4 Hz, 1H, CH_2), 4.80 (d, *J* 12.4 Hz, 1H, CH_2), 6.91 (d, *J* 8.8 Hz, 2H, Ar-H), 7.13 (s, 1H, pyrazole-H), 7.27 (d, *J* 8.7 Hz, 2H, Ar-H), 7.31 (d, *J* 8.7 Hz, 2H, Ar-H), 7.67 (d, *J* 8.8 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). *δ* = 159.8, 154.8, 152.7, 137.2, 135.5, 135.0, 129.2 (2C), 127.0 (2C), 126.8 (2C), 124.8, 114.1 (2C), 104.1, 92.9, 65.2, 57.7, 55.3, 42.2; HRMS ($C_{21}H_{18}ClN_3O_3$). calcd for $[M + H]^+$ 396.1115, found 396.1113.

10a-(4-Methoxyphenyl)-7-phenyl-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]-pyrazin-5-one (**2g**). **W**hite solid (175 mg, 48%), mp 182–183 ºC. IR (KBr, cm^{-1}). 1668 (C=O), 1248 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 3.61–3.67 (m, 1H, NCH_2), 3.76 (s, 3H, OCH_3), 3.84–3.92 (m, 1H, NCH_2), 4.01–4.08 (m, 1H, OCH_2), 4.31–4.36 (m, 1H, OCH_2), 4.58 (d, *J* 12.3 Hz, 1H, CH_2), 4.86 (d, *J* 12.3 Hz, 1H, CH_2), 6.83 (d, *J* 8.8 Hz, 2H, Ar-H), 7.20 (s, 1H, pyrazole-H), 7.24 (d, *J* 8.8 Hz, 2H, Ar-H), 7.30 (t, *J* 7.6 Hz, 1H, Ar-H), 7.38 (t, *J* 7.6 Hz, 2H, Ar-H), 7.74 (d, *J* 7.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). *δ* = 160.3, 154.8, 152.5, 135.2, 132.2, 130.2, 128.7 (2C), 128.3, 126.9 (2C), 125.5 (2C), 114.2 (2C), 104.3, 93.2, 65.0, 58.0, 55.3, 42.3; HRMS ($C_{21}H_{19}N_3O_3$). calcd for $[M + H]^+$ 362.1505, found 362.1498.

7-(4-Chlorophenyl)-10a-(4-methoxyphenyl)-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one (**2h**). White solid (160 mg, 40%), mp 273–276 ºC. IR (KBr, cm^{-1}). 1665 (C=O), 1246 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 3.61–3.66 (m, 1H, NCH_2), 3.76 (s, 3H, OCH_3), 3.84–3.92 (m, 1H, NCH_2), 4.01–4.07 (m, 1H, OCH_2), 4.30–4.36 (m, 1H, OCH_2), 4.56 (d, *J* 12.3 Hz, 1H, CH_2), 4.84 (d, *J* 12.2 Hz, 1H, CH_2), 6.83 (d, *J* 8.7 Hz, 2H, Ar-H), 7.16 (s, 1H, pyrazole-H), 7.24 (d, *J* 8.7 Hz, 2H, Ar-H), 7.34 (d, *J* 8.7 Hz, 2H, Ar-H), 7.67 (d, *J* 8.7 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). *δ* = 160.4, 154.6, 151.5, 135.4, 134.1, 130.8, 130.2, 128.9 (2C), 126.9 (2C), 126.8 (2C), 114.3 (2C), 104.3, 93.2, 65.0, 58.1, 55.3, 42.3; HRMS ($C_{21}H_{18}ClN_3O_3$). calcd for $[M + H]^+$ 396.1115, found 396.1117.

7,10a-Bis(4-methoxyphenyl)-2,3,10,10a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyrazolo[1,5-*d*]pyrazin-5-one (**2i**). White solid (159 mg, 40%), mp 230 ºC; IR (KBr, cm^{-1}). 1666 (C=O), 1248 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 3.60–3.65 (m, 1H, NCH_2), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84–3.92 (m, 1H, NCH_2), 4.01–4.07 (m, 1H, OCH_2), 4.30–4.35 (m, 1H, OCH_2),

4.55 (d, *J* 12.1 Hz, 1H, CH_2), 4.82 (d, *J* 12.1 Hz, 1H, CH_2), 6.83 (d, *J* 8.8 Hz, 2H, Ar-H), 6.90 (d, *J* 8.8 Hz, 2H, Ar-H), 7.11 (s, 1H, pyrazole-H), 7.24 (d, *J* 8.8 Hz, 2H, Ar-H), 7.67 (d, *J* 8.8 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ = 160.3, 159.7, 154.8, 152.4, 135.1, 130.3, 126.9 (2C), 126.8 (2C), 125.0, 114.2 (2C), 114.1 (2C), 103.8, 93.2, 64.9, 57.9, 55.3 (2C), 42.3; HRMS ($C_{22}H_{21}N_3O_4$). calcd for $[M + H]^+$ 392.1610, found 392.1622.

A crystal of **2i** suitable for X-ray analysis was grown by slow evaporation from ethyl acetate solution. The diffraction measurement was carried out by graphite monochromated Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer. The structure was solved with direct methods using the SHELXS-97 program, and refined on F^2 by full-matrix least-squares with the SHELXL-97 package.[25] All data were corrected by multi-scan method using SADABS program. Molecular graphics were designed by using ORTEP-3 and DIAMOND 3.2.[26] PLATON program was also used for structure analysis.[27] The crystal data and details concerning data collection and structural refinement are given in Table 4.

Table 4. Summary of crystal data and structure refinement for compound **2i**

Compound	**2i**
Empirical formula	$C_{22}H_{21}N_3O_4$
Formula weight	391.42
Crystal system	Monoclinic
Space group	*C*2/*c*
a /Å	22.404(3)
b/Å	9.8671(14)
c/Å	17.712(2)
α/°	90.00
β/°	96.043(2)
γ/°	90.00
Z	8
D_x /g cm^{-3}	1.335
V/Å^{-3}	3893.7(9)
T/K	273(2)
μ /mm^{-1}	0.093
F (000)	1648
Reflection collected	11240
Data/restraints/ parameters	4420/0/326
θ Range for data collection/°	1.83 – 27.56
R(int)	0.0227
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0543, ωR_2 = 0.1639
R indices (all data)	R_1 = 0.0756, ωR_2 = 0.1841
Goodness of fit on F^2	1.032
Max./min., $\Delta\rho$ /e Å^{-3}	0.420; –0.214

5-(2-Hydroxyethyl)-2-(4-methoxyphenyl)-6-phenylpyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (**3a**). White solid: (62 mg, 17%), mp 129–130 ºC. IR (KBr, cm^{-1}). 3407 (OH), 1658 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 3.77 (t, *J* 5.3 Hz, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 4.08 (t, *J* 5.3 Hz, 2H, OCH_2), 6.97 (d, *J* 8.7 Hz, 2H, Ar-H), 7.30 (s, 1H, pyrazole-H), 7.40 (s, 1H, CH), 7.44–7.45 (m, 2H, Ar-H), 7.49–7.52 (m, 3H, Ar-H), 7.86 (d, *J* 8.7 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ = 160.2, 157.4, 153.2, 133.5, 131.9, 131.0, 130.1 (2C), 129.8, 129.0 (2C), 127.5 (2C), 124.7, 114.3 (2C), 111.0, 101.5, 62.0, 55.4, 47.5; HRMS ($C_{21}H_{19}N_3O_3$). calcd for $[M + H]^+$ 362.1505, found 362.1501.

***N*-(2-Hydroxyethyl)-3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-5-carboxamide** (**4a**). White solid (100 mg, 26%), mp 167–169 ºC. IR (KBr, cm^{-1}). 3352 (OH), 3288 (NH), 1704(C=O), 1645 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm). δ 3.48 (dd, *J* 10.0, 5.1 Hz, 2H, NCH_2), 3.72 (t, *J* 5.1 Hz, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 6.09 (s, 2H, CH_2), 6.68 (s, 1H, CONH), 6.86 (s, 1H, pyrazole-H), 6.90 (d, *J* 8.7 Hz, 2H, Ar-H), 7.50 (t, *J* 7.6 Hz, 2H, Ar-H), 7.62 (t, *J* 7.6 Hz, 1H, Ar-H), 7.68 (d, *J* 8.7 Hz, 2H, Ar-H), 8.00 (d, *J* 7.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6). δ 193.7, 159.6, 159.6, 149.2, 137.3, 135.1, 134.3, 129.4(2C), 128.4 (2C), 126.7 (2C), 125.7, 114.8 (2C), 104.2, 60.0, 58.8, 55.6, 42.0; HRMS ($C_{21}H_{21}N_3O_4$). calcd for $[M + H]^+$ 380.1610, found 380.1608.

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