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DOMINO [3+2+1] HETEROANNULATION FOR STEREOSELECTIVE SYNTHESIS OF *ANTI*-PYRAZOLO[3,4-*d*][1,3]OXAZINES

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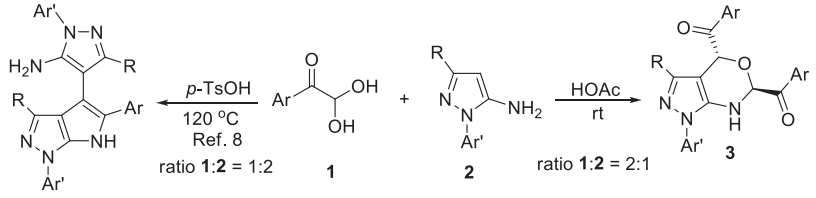
Abstract – A novel three-component domino reaction of arylglyoxals with pyrazol-5-amines in HOAc has been developed, providing an efficient and stereoselective access to polysubstituted *anti*-pyrazolo[3,4-*d*][1,3]oxazines in a intermolecular manner. Features of this strategy include mild conditions, convenient one-pot operation, and excellent stereoselectivity, which make highly attractive.

Heterocyclic compounds embedded with 1,3-oxazine are prevalent in numerous natural products and pharmaceutical leads, possessing a wide range of biological activities such as *anti*-tumor,[1] *anti*-bacterial,[2] *anti*-HIV[3] and antimalarial agents.[4] So the interest on 1,3-oxazine molecules has recently increased. Recently, Abonia and co-workers reported the three-step synthesis of *N*,*N*-protected pyrazolo[3,4-*d*][1,3]oxazine derivatives by treatment of pyrazolamines with aqueous formaldehyde without involving stereochemistry.[5] To the best of our knowledge, stereoselective synthesis of *anti*-pyrazolo[3,4-*d*][1,3]oxazines *via* multicomponent domino reactions (MDRs), has not been well documented yet.

Multicomponent domino reactions, defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.[6-8] In our previous report, we established multicomponent domino reactions of arylglyoxals **1** and pyrazol-5-amines **2** in 1:2 molar ratio in DMF using *p*-TsOH as a promoter at 120 °C, providing

pyrrolo[2,3-*c*]pyrazole derivatives[9] (Scheme 1). During our continued study of this project, we found when the ratio of **1** and **2** was changed to 2:1 and reaction temperature dropped to room temperature, polysubstituted pyrazolo[3,4-*d*][1,3]oxazine derivatives were unexpectedly obtained through metal-free [3+2+1] cyclizations (Scheme 1). Herein, we would like to report this interesting reaction.



Scheme 1. Synthesis of polysubstituted pyrazolo[3,4-*d*][1,3]oxazine **3**

We started this study by subjecting 1-(4-chlorophenyl)-2,2-dihydroxyethanone **1a** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2a** in DMF using *p*-TsOH as a promoter at room temperature. Instead of pyrrolo[2,3-*c*]pyrazoles, this reaction proceeded smoothly to generate unprecedented *anti*-pyrazolo[3,4-*d*][1,3]oxazine derivatives **3a** as a single isomer in 60% yield without observation of *syn*-pyrazolo[3,4-*d*][1,3]oxazine **3a'**. Therefore, we reasoned the temperatures play an important effect on reaction direction. Furthermore, various solvents, such as toluene, MeCN, and EtOH, were employed as reaction media. As shown in Table 1, we found that all of them give lower chemical yields than that in DMF. Next, we continued to screen different Brønsted acid promoters for this domino reaction. When a stronger Brønsted acid, CF_3CO_2H, was used, the reaction did not work whereas acetic acid (HOAc) gave a 75% chemical yield. Other $EtCO_2H$, *i*-$PrCO_2H$ and *n*-$PrCO_2H$ did not work efficiently. It turned out that acetic acid can serve not only as a suitable solvent but also as an adequate Brønsted acid promoter for the present reaction. The structural elucidation and the attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis. Furthermore, the structure of compound **3a** was confirmed by X-ray crystallographic analysis (Figure 1).

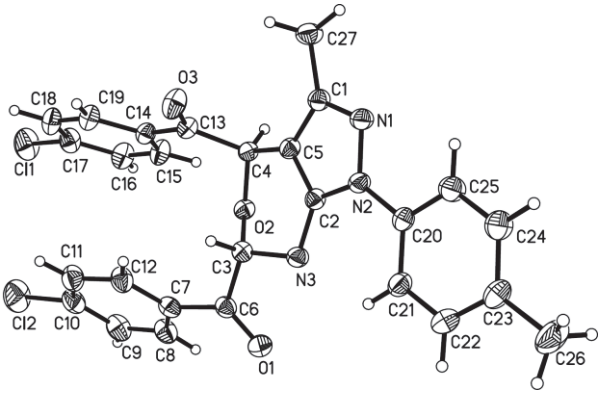
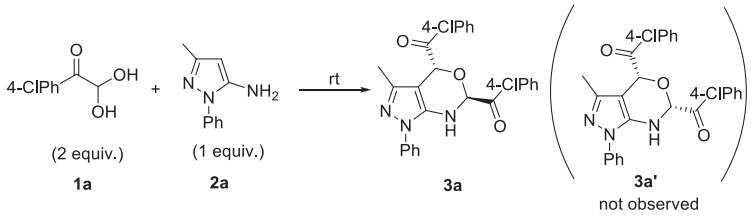


Figure 1. X-Ray structure of **3a**[10]

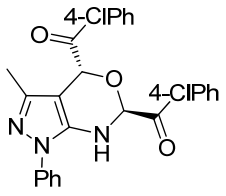
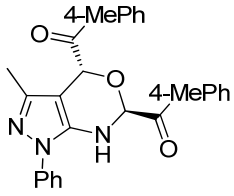
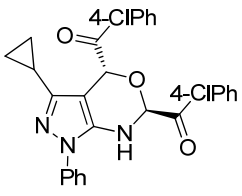
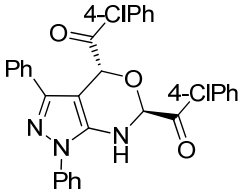
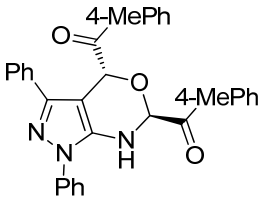
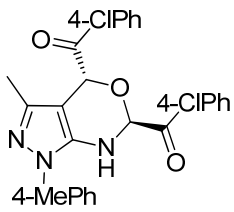
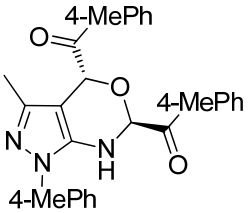
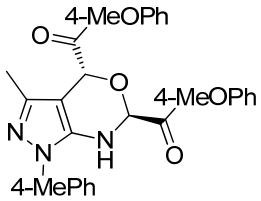
Table 1. Optimization for the synthesis of **3a**



Entry	Promoter	Solvent	Yield / %
1	*p*-TsOH	DMF	60
2	*p*-TsOH	toluene	32
3	*p*-TsOH	MeCN	43
4	*p*-TsOH	EtOH	57
5	CF_3CO_2H	-	trace
6	HOAc	-	75
7	$EtCO_2H$	-	38
8	*i*-$PrCO_2H$	-	45
9	*n*-$PrCO_2H$	-	53

With these acceptable reaction conditions in hands, we next examined the scope of this new domino process by using various easily available starting materials. A variety of functional groups in arylglyoxals were well tolerated to give moderate to good yields of *anti*-pyrazolo[3,4-*d*][1,3]oxazine **3**. The variation of substituents at pyrazole C3 positions, including methyl, cyclopropyl and phenyl groups, afforded good yields of *anti*-pyrazolo[3,4-*d*][1,3]oxazine **3** within short times. Furthermore, we were eager to see the outcome of the reaction when pyrazol-5-amines **2** with a *p*-tolyl group residing at the N1 position were employed as a multicomponent partners with arylglyoxals, they all give corresponding *anti*-pyrazolo[3,4-*d*][1,3]oxazine **3** with good yields. As revealed in Table 2, a library of new multi-functionalized *anti*-pyrazolo[3,4-*d*][1,3]oxazine **3** was synthesized in good to excellent yields in order to evaluate the scope of the protocol. The structure of product **3b** was also determined by X-ray crystallographic analysis (Figure 2). In general, these MDRs give new examples for synthesizing heterocycles in an efficient and atom-economic strategy to discover new bioactive compounds.

Table 2. Synthesis of pyrazolo[3,4-*d*][1,3]oxazine derivatives **3**

			
3a (75%)	**3b** (80%)	**3c** (83%)	**3d** (81%)
			
3e (77%)	**3f** (75%)	**3g** (83%)	**3h** (76%)

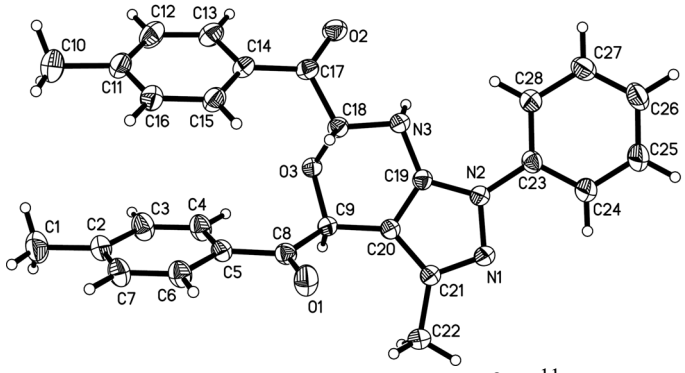
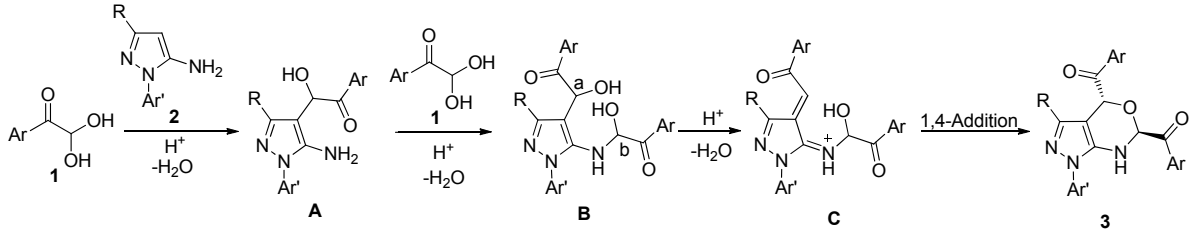


Figure 2. X-Ray structure of **3b**[11]

On the basis of experimental results, a tentative reaction mechanism for this domino reaction is postulated in Scheme 2. Arylglyoxals **1** protonated by HOAc underwent dehydration and subsequent addition with pyrazol-5-amines **2** to intermediate **A**, followed by second dehydration with arylglyoxals **1** to intermediate **B**. Considering the stronger nucleophilicity at the 4-position of pyrazole ring than the amino group, the hydroxyl group at a-position of **B** was more reactive for the elimination than ones at b-site, thereby forming the intermediate **C**. The intermediate **C** was transformed into the final pyrazolo[3,4-*d*][1,3]oxazines **3** through 1,4-addition process.



Scheme 2. Possible mechanism for the formation of **3**

In conclusion, we have developed new multicomponent domino reactions (arylglyoxals and 1-arylpyrazol-5-amines) for highly stereoselective synthesis of *anti*-pyrazolo[3,4-*d*][1,3]oxazine derivatives. This domino strategy formed up to three σ-bonds in a one-pot operation from common starting materials, providing a new insight into multicomponent reactions. The mild reaction condition and selective modification of pyrazolooxazines skeleton as well as high bond-forming efficiency (BFE) make it highly viable for future applications. Further investigations are in progress in our laboratory to test their biological activity.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q Ⅱ HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer

Synthesis of pyrazolo[3,4-*d*][1,3]oxazine derivatives 3a

In a 25-mL reaction vial, 1-(4-chlorophenyl)-2,2-dihydroxyethanone (**1a**, 2.2 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2a**, 1.0 mmol) and HOAc (1.5 mL) were then successively added. Subsequently, the mixture was stirred at room temperature until TLC revealed that conversion of the starting material **2a** was complete. Then the solid was obtained through filtration and washed with 2 mL 95% EtOH to give the almost pure product **3a**, which were further purified by recrystallization from 95% EtOH to afford the desired **3a**.

(3-Methyl-1-phenyl-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis((4-chlorophenyl)-methanone) (3a)

A white solid; Mp 199-200 ºC;

IR (KBr, ν, cm^{-1}): 3263, 1704, 1686, 1598, 1509, 1455, 1399, 1335;

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.07-8.02 (m, 2H, Ar-H), 7.77 (t, J = 9.2 Hz, 4H, Ar-H), 7.60 (d, J = 8.4 Hz, 2H, Ar-H), 7.47 (t, J = 7.6 Hz, 2H, Ar-H), 7.36 (d, J = 8.4 Hz, 2H, Ar-H), 7.28 (t, J = 7.6 Hz, 1H, Ar-H), 6.55 (d, J = 8.8 Hz, 1H, CH), 6.39 (s, 1H, CH), 5.92 (d, J = 9.2 Hz, 1H, NH), 2.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 196.9, 191.8, 145.7, 140.6, 139.4, 139.2, 134.1, 133.0, 131.8, 131.7, 131.2, 129.4, 129.2, 128.9, 126.2, 121.4, 100.7, 80.2, 73.5, 13.6;

HRMS (ESI): *m/z* calcd for: $C_{26}H_{18}Cl_2N_3O_3$, 490.0723 $[M-H]^-$; found: 490.0703.

(3-Methyl-1-phenyl-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis(*p*-tolylmethanone) (3b)

A pale pink solid; Mp 189-190 ºC;

IR (KBr, ν, cm^{-1}): 3263, 1696, 1676, 1599, 1509, 1453, 1393, 1335;

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.99 (d, J = 8.0 Hz, 2H, Ar-H), 7.80 (d, J = 7.6 Hz, 2H, Ar-H), 7.72 (d, J = 8.0 Hz, 2H, Ar-H), 7.46 (t, J = 7.6 Hz, 2H, Ar-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 7.28 (t, J = 7.6 Hz, 1H, Ar-H), 7.12 (d, J = 8.4 Hz, 2H, Ar-H), 6.46 (d, J = 9.2 Hz, 1H, CH), 6.40 (s, 1H, CH), 5.95 (d, J = 9.2 Hz, 1H, NH), 2.42 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 197.5, 191.9, 145.4, 145.0, 144.8, 140.8, 139.4, 133.1, 131.7, 130.0, 129.8, 129.6, 129.5, 129.4, 126.1, 121.4, 100.9, 79.8, 72.7, 21.7, 21.7, 13.6;

HRMS (ESI): *m/z* calcd for: $C_{28}H_{24}N_3O_3$, 450.1816 $[M-H]^-$; found: 450.1810.

(3-Cyclopropyl-1-phenyl-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis((4-chlorophenyl)methanone) (3c)

A white solid; Mp 230-232 ºC;

IR (KBr, ν, cm^{-1}): 3256, 1691, 1677, 1592, 1518, 1453, 1390, 1334;

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.10 (d, J = 8.4 Hz, 2H, Ar-H), 7.77 (d, J = 8.4 Hz, 4H, Ar-H), 7.61 (d, J = 8.4 Hz, 2H, Ar-H), 7.46 (t, J = 7.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.4 Hz, 2H, Ar-H), 7.27 (t, J = 7.6 Hz, 1H, Ar-H), 6.56 (d, J = 9.2 Hz, 1H, CH), 6.50 (s, 1H, CH), 5.96 (d, J = 8.8 Hz, 1H, NH), 1.59-1.53 (m, 1H, CH), 0.77-0.70 (m, 3H, CH_2), 0.65-0.61 (m, 1H, CH_2);

HRMS (ESI): *m/z* calcd for: $C_{28}H_{20}Cl_2N_3O_3$, 516.0880 $[M-H]^-$; found: 516.0871.

(1,3-Diphenyl-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis((4-chlorophenyl)methanone) (3d)

A white solid; Mp >300 ºC;

IR (KBr, ν, cm^{-1}): 3261, 1702, 1687, 1597, 1508, 1453, 1398, 1331;

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.11-8.09 (m, 2H, Ar-H), 7.94-7.92 (m, 2H, Ar-H), 7.66-7.59 (m, 6H, Ar-H), 7.54 (t, J = 7.6 Hz, 2H, Ar-H), 7.38-7.28 (m, 6H, Ar-H), 6.95 (s, 1H, CH), 6.69 (d, J = 9.2 Hz, 1H, CH), 5.82 (d, J = 9.2 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.5, 190.9, 147.2, 141.3, 138.9, 138.7, 133.3, 133.1, 132.3, 131.3, 130.5, 129.0, 128.8, 128.4, 128.3, 127.7, 126.3, 126.1, 124.3, 121.5, 99.3, 79.2, 72.8;

HRMS (ESI): *m/z* calcd for: $C_{31}H_{20}Cl_2N_3O_3$, 552.0880 $[M-H]^-$; found: 552.0864.

(1,3-Diphenyl-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis(p-tolylmethanone) (3e)

A white solid; Mp >300 ºC;

IR (KBr, ν, cm^{-1}): 3258, 1700, 1687, 1597, 1518, 1458, 1398, 1333;

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.07 (d, J = 8.0 Hz, 2H, Ar-H), 7.97-7.94 (m, 2H, Ar-H), 7.63-7.60 (m, 2H, Ar-H), 7.57-7.53 (m, 4H, Ar-H), 7.38-7.27 (m, 6H, Ar-H), 7.03 (d, J = 8.0 Hz, 2H, Ar-H), 6.93 (s, 1H, CH), 6.60 (d, J = 9.2 Hz, 1H, CH), 5.76 (d, J = 9.2 Hz, 1H, NH), 2.43 (s, 3H, CH_3),

2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 195.4, 191.4, 147.5, 145.1, 145.0, 142.1, 139.3, 133.7, 132.8, 131.5, 130.1, 129.9, 129.6, 129.5, 129.4, 129.0, 128.3, 126.8, 126.6, 122.0, 100.2, 79.3, 72.7, 21.7, 21.7;

HRMS (ESI): *m/z* calcd for: $C_{33}H_{26}N_3O_3$, 512.1972 $[M-H]^-$; found: 512.1958.

(3-Methyl-1-(*p*-tolyl)-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis((4-chlorophenyl)-methanone) (3f)

A white solid; Mp 210-211 °C;

IR (KBr, ν, cm^{-1}): 3250, 1694, 1672, 1590, 1513, 1450, 1390, 1331;

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.03 (d, J = 8.8 Hz, 2H, Ar-H), 7.76 (d, J = 8.8 Hz, 2H, Ar-H), 7.64 (d, J = 11.2 Hz, 2H, Ar-H), 7.60 (d, J = 8.4 Hz, 2H, Ar-H), 7.37 (d, J = 8.4 Hz, 2H, Ar-H), 7.27 (d, J = 8.0 Hz, 2H, Ar-H), 6.48 (d, J = 9.2 Hz, 1H, CH), 6.38 (s, 1H, CH), 5.92 (d, J = 8.8 Hz, 1H, NH), 2.33 (s, 3H, CH_3), 1.98 (s, 3H, CH_3);

HRMS (ESI): *m/z* calcd for: $C_{27}H_{20}Cl_2N_3O_3$, 504.0882 $[M-H]^-$; found: 504.0863.

(3-Methyl-1-(*p*-tolyl)-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis(*p*-tolylmethanone) (3g)

A pale pink solid; Mp 193-194 °C;

IR (KBr, ν, cm^{-1}): 3270, 1700, 1678, 1607, 1519, 1453, 1394, 1324;

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.99 (d, J = 8.4 Hz, 2H, Ar-H), 7.73 (d, J = 8.4 Hz, 2H, Ar-H), 7.66 (d, J = 8.4 Hz, 2H, Ar-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 6.39 (s, 1H, CH), 6.38 (d, J = 8.8 Hz, 1H, CH), 5.95 (d, J = 8.8 Hz, 1H, NH), 2.42 (s, 3H, CH_3), 2.34 (s, 6H, CH_3), 1.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 197.6, 191.9, 145.0, 144.9(5), 144.8, 140.6, 137.0, 135.4, 133.1, 131.7, 130.0, 129.8, 129.8, 129.6, 129.5, 121.4, 100.6, 79.8, 72.8, 21.7, 21.6(8), 20.9, 13.6;

HRMS (ESI): *m/z* calcd for: $C_{29}H_{26}N_3O_3$, 464.1972 $[M-H]^-$; found: 464.1961.

(3-Methyl-1-(*p*-tolyl)-1,4,6,7-tetrahydropyrazolo[3,4-*d*][1,3]oxazine-4,6-diyl)bis((4-methoxyphenyl)-methanone) (3h)

A white solid; Mp 190-192 °C;

IR (KBr, ν, cm^{-1}): 3266, 1693, 1673, 1599, 1518, 1453, 1391, 1325;

^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.10 (d, J = 8.8 Hz, 2H, Ar-H), 7.82 (d, J = 8.8 Hz, 2H, Ar-H), 7.67 (d, J = 8.4 Hz, 2H, Ar-H), 7.26 (d, J = 8.0 Hz, 2H, Ar-H), 7.08 (d, J = 8.8 Hz, 2H, Ar-H), 6.83 (d, J = 8.8 Hz, 2H, Ar-H), 6.39 (s, 1H, CH), 6.31 (d, J = 9.2 Hz, 1H, CH), 5.94 (d, J = 9.2 Hz, 1H, NH), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 196.5, 190.5, 164.2, 164.1, 145.0, 140.7, 137.1, 135.4, 132.3, 132.0, 129.8, 128.3, 126.9, 121.4, 114.5, 114.2, 100.8, 79.5, 72.5, 56.1, 56.0, 20.9, 13.6;

HRMS (ESI): *m/z* calcd for: $C_{29}H_{26}N_3O_5$, 496.1871 $[M-H]^-$; found: 496.1859.

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10. Crystal data for **3a**: $C_{27}H_{20}Cl_2N_3O_3$, Triclinic, space group P-1(2), a = 9.7673(4) Å, b = 11.6173(5)

Å, c = 11.7744(5) Å, α = 89.676(2) º, β = 74.062(2) º, γ = 71.862(2) º, V = 1216.18(9) Å^3, Mr = 505.36, Z = 2, Dc = 1.380 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 0.30 mm^{-1}, F(000) = 522, R = 0.0541, wR_2 = 0.1684, largest diff. Peak and hole: 0.567 and -0.333 e/Å^3.

11. Crystal data for **3b**: $C_{28}H_{25}N_3O_3$, Triclinic, space group P-1, a = 10.0531(4) Å, b = 10.0649(4) Å, c = 12.5856(5) Å, α = 67.638(2) º, β = 86.453(2) º, γ = 87.748(2) º, V = 1175.26(8) Å^3, Mr = 451.51, Z = 2, Dc = 1.276 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 0.084 mm^{-1}, F(000) = 476, R = 0.0445, wR_2 = 0.1249, largest diff. Peak and hole: 0.242 and -0.157 e/Å^3.