Facile Synthesis and Bioactivity of Novel *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines

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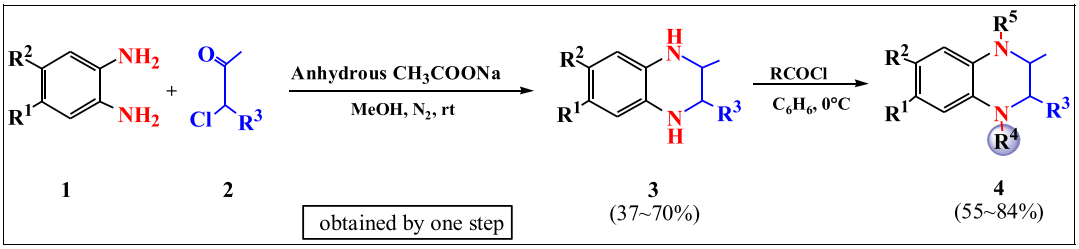

A series of novel *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines were designed and synthesized by cyclization and acylation. The structures of all the novel compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry. The configuration of **4d** was determined by X-ray diffraction. The preliminary biological tests showed that all the products could protect maize against the injury caused by acetochlor to some extent.

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INTRODUCTION

Some quinoxaline derivatives are used as organic semiconductors, chemical switches [1], supramolecular receptors [2], and others. Among all of the derivatives of quinoxalines, *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines have received great concern because of their excellent pharmacological activity and biological activity, such as antitumor drugs, cell adhesion agents, organic synthesis intermediates, and agricultural chemicals [3–6].

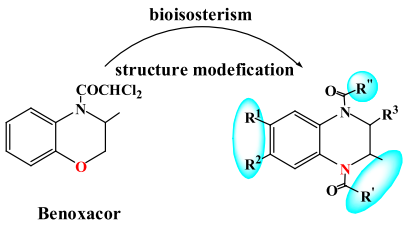
Several synthetic routes to substituted 1,2,3,4-tetrahydroquinoxalines have been reported. The common synthetic method was substituted *o*-phenylenediamines, which reacted with various ketones, followed by reduction [7–10]. Catalytic hydrogenation of quinoxaline was also a good choice of preparation for substituted 1,2,3,4-tetrahydroquinoxaline derivatives [11–14]; for example, Qin and Tang achieved asymmetric hydrogenation of quinoxalines [15,16]. Mirjalili reported the cyclization of substituted 2-nitroaniline with butanedione, followed by catalytic hydrogenation in the presence of $InCl_3$ to prepare substituted 1,2,3,4-tetrahydroquinoxalines [17]. Substituted 1,2,3,4-tetrahydroquinoxalines were also obtained with substituted *o*-phenylenediamines and dihydroxy compounds, followed by oxidation–cyclization in the presence of Au [18]. Merisor introduced the synthesis of substituted-1,2,3,4-tetrahydroquinoxalines with substituted 2-nitroaniline in $(EtO)_3P$-toluene, followed by microwave-assistant cyclization reaction [19]. However, most of these reported methods suffered with unsatisfactory yields, complicated experimental procedures, strict reaction conditions, and especially expensive catalysts. The reduction was necessary in the aforementioned reports. In view of these facts and continuous with our previous work [20,21], the novel target compounds with potential herbicide safener activity, *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines (**4**), were designed with benoxacor as the template compound, using the principle of bioisosterism [22], replacing *O* atom with *N* atom, and a combination of the pharmacophore to probe the relationship between structure and activity (Scheme 1).

The title compounds were synthesized with substituted *o*-phenylenediamines and chloroacetone or 1-chloroethyl methyl ketone as the starting material via only cyclization and acylation reactions (Scheme 2). What is novel about this synthetic route is that expensive catalysts are unnecessary and mild reaction conditions are applied. It does not have to go through a reduction of a quinoxaline ring system.

RESULTS AND DISCUSSION

Substituted-1,2,3,4-tetrahydroquinoxalines **3** were prepared by cyclization with various substituted *o*-phenylenediamine **1** and halogenated ketone **2** under N_2 for 2–3 h at room temperature, with 37–70% yields. 1,2-Dihydroquinoxaline, the by-product, was also obtained at the same time, which made the yields were low. The results showed that the modified methods were only suitable for some simple aliphatic α-chloroketones. The aliphatic α-bromoketones, α-halogenated cyclohexanone, aromatic α-chloroketones, and aromatic α-bromoketones

Scheme 1. Design of *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines. [Color figure can be viewed at wileyonlinelibrary.com]



will lead to substituted quinoxalines or substituted 1,2-dihydroquinoxalines [16,23,24]. It was confirmed that 3-phenyl-1,2-dihydroquinoxaline **5** was prepared with *o*-phenylenediamine and α-bromoacetophenone at the same condition. Subsequently, *N*-dichloroacetyl-3-phenyl-1,2-dihydroquinoxaline **6** was obtained via acylation (Scheme 3). The substitution affected the yields greatly (Table 1). Compound **3d** gave the better yield than others with electron-donating group on the piperazine ring. There was no reaction occurred in the benzene with halogen or nitro, for the electron-drawing group on the benzene reducing the reactivity. Compound **3** was unstable with two amino, and they were converted to quinoxaline or dihydroquinoxaline easily.

The target compound **4** was synthesized by acylation reaction in the presence of anhydrous K_2CO_3 at 0°C with 55–84% yields (Table 2). The reaction temperature should be improved to 35°C when phenoxy acetyl chloride was employed. Compounds **4d**–**4m** were with good yields, up to 75–84%, for the electron-donating group (CH_3) on the piperazine increasing the reactivity. Furthermore, the yields of compounds **4a**, **4d**, **4k**, and **4p** with two dichloroacetyl substitution on the piperazine were better than others. Thus, compound **4d** had the best yield, up to 84%, for the electron-donating group on the piperazine and the two dichloroacetyl substitution.

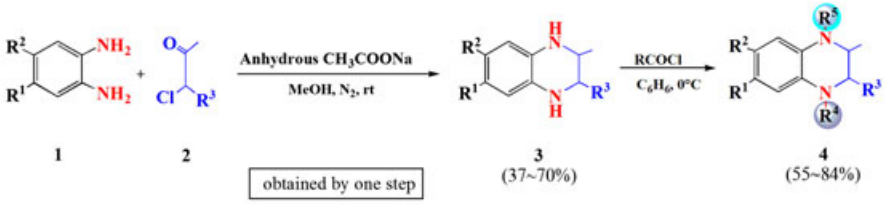
Finally, the block-shaped colorless single crystal of **4d** was cultured by dissolving it in ethyl acetate, followed by slow evaporation at room temperature. The X-ray data were collected on a Bruker AXSII charged coupling device area-detector diffractometer (Rigaku Corporation, Japan) using graphite-monochromated Mo *K*a radiation (λ = 0.71073 Å) at 293(2) K [25]. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least squares on F^2, SHELXL-97 [25].The

Table 1

Structure and yields of compound **3**

Compound	R^1	R^2	R^3	mp (°C)	Yield (%)
3a	H	H	H	63–64	54
3d	H	H	CH_3	112–113	70
3j	CH_3	H	CH_3	93–94	37

Scheme 2. Synthetic route of *N*,*N*′-disubstituted-1,2,3,4-tetrahydroquinoxalines. [Color figure can be viewed at wileyonlinelibrary.com]



a: $R^1 = R^2 = R^3$=H, R^4=R^5=$COCHCl_2$; b: $R^1 = R^2 = R^3$=R^5=H, R^4=$COCHCl_2$; c: $R^1 = R^2 = R^3$=R^4=H, R^5=$COCHCl_2$; d: $R^1 = R^2$ =H, R^3= CH_3, R^4= R^5=$COCHCl_2$;
e: $R^1 = R^2$ =R^5=H, R^3= CH_3, R^4=$COCCl_3$; f: $R^1 = R^2$=H, R^3= CH_3, R^4=R^5=$COCHCl_3$; g: $R^1 = R^2$ =R^5=H, R^3= CH_3, R^4=$COCH_2OCOCH_3$;
h: $R^1 = R^2$ =H, R^3= CH_3, R^4=R^5=$COCH_2OCOCH_3$; i: $R^1 = R^2$ =H, R^3= CH_3, R^4=R^5=$COCH_2OC_6H_5$; j: $R^1 = R^3$=CH_3, R^2= R^5 =H, R^4=$COCH_2Cl$;
k:$R^1 = R^3$=CH_3, R^2= H, R^4=R^5 =$COCHCl_2$; l: $R^1 = R^3$=CH_3, R^2= R^5 =H, R^4=$COCCl_3$; m: R^1= R^5 =H, R^2 = R^3=CH_3, R^4=$COCCl_3$;
n: $R^1 = R^3$ =CH_3, R^2= H, R^4=R^5=$COCH_2OCOCH_3$; o: $R^1 = R^3$ =CH_3, R^2= H, R^4=R^5=$COCH_2OC_6H_5$; p: R^1 =OCH_3, R^2= H, R^3 =CH_3, R^4=R^5=$COCHCl_2$.

Scheme 3. Synthetic route of *N*-dichloroacetyl-3-phenyl-1,2-dihydroquinoxaline. [Color figure can be viewed at wileyonlinelibrary.com]

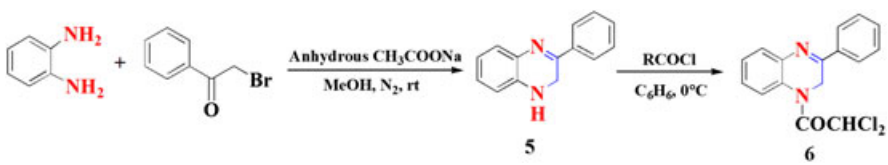


Table 2

Structure and yields of compound **4**

Compound	R^1	R^2	R^3	R^4	R^5	mp (°C)	Yield (%)
4a	H	H	H	Cl_2CHCO	Cl_2CHCO	124–125	80
4b	H	H	H	Cl_2CHCO	H	–	62
4c	H	H	H	H	Cl_2CHCO	–	55
4d	H	H	CH_3	Cl_2CHCO	Cl_2CHCO	141–142	84
4e	H	H	CH_3	H	Cl_3CCO	114–115	69
4f	H	H	CH_3	Cl_3CCO	Cl_3CCO	136–137	56
4g	H	H	CH_3	H	CH_3COOCH_2CO	117–118	64
4h	H	H	CH_3	CH_3COOCH_2CO	CH_3COOCH_2CO	137–138	68
4i	H	H	CH_3	$C_6H_5OCH_2CO$	$C_6H_5OCH_2CO$	161–162	75
4j	CH_3	H	CH_3	$ClCH_2CO$	H	–	70
4k	CH_3	H	CH_3	Cl_2CHCO	Cl_2CHCO	127–128	69
4l	CH_3	H	CH_3	Cl_3CCO	H	138–139	72
4m	CH_3	H	CH_3	H	Cl_3CCO	160–161	80
4n	CH_3	H	CH_3	CH_3COOCH_2CO	CH_3COOCH_2CO	–	59
4o	CH_3	H	CH_3	$C_6H_5OCH_2CO$	$C_6H_5OCH_2CO$	136–137	63
4p	OCH_3	H	CH_3	Cl_2CHCO	Cl_2CHCO	131–132	70

molecular structure and the packing diagram of compound **4d** were shown in Figures 1 and 2.

Compound **4d** was crystallized in the monoclinic space group $P\ 2_1/c$, a = 13.326(3) Å, b = 13.668(3) Å, c = 18.615(4) Å, β = 96.89(3) °, V = 3366.0(13) Å^3, and Z = 8. It was noteworthy that compound **4d** was consisted of two rings benzene plane and piperazine plane, just as shown in Figure 1. The bond lengths and bond angles of **4d** indicated that there was π-p-π-p-π large conjunctive effect between O(1), C(11), N(1), benzene, N(2), C(13), and O(2), which results in shorter bond length of N(1)–C(1) [1.4310(48)], N(1)–C(10) [1.3596(2)], N(2)–C(6) [1.4349(49)], and N(2)–C(12) [1.361(5)] than the typical C–N bond length [1.472 (2) Å]. The C(7) and C(8) were chiral carbon atoms with the *R*-configuration and *S*-configuration, respectively. Compound **4d** contained an original benzene ring and a new six-member ring. The later, plane II, was made up of C6/N2/C7/C8/N1/C1 atoms. Plane I [C1, C2, C3, C4, C5, and C6] made a dihedral angle of 27.798(119) °, with plane II [C1, C6, C7, C8, N1, and N2]. The presence of the intermolecular hydrogen bond C(10)–H (10B) … Cl(6) led to the stability of the compound (Fig. 2). No significant π-π and C–H … π interactions were found in the crystal structure.

All compounds could protect maize from the injury by acetochlor (5 mg/kg) (Table 3). Among them, compound **4n** showed the best result. The protection of compounds **4a**–**d** and **4p** was better than benoxacor, and compounds **4m**, **4f**, and **4g** were very poor in antidotal effect. Dichloroacetyl or acetoxyacetyl at piperazine of 1,2,3,4-tetrahydroquinoxaline would improve the detoxifying characteristics; in contrast, the trichloroacetyl has the opposite effect.

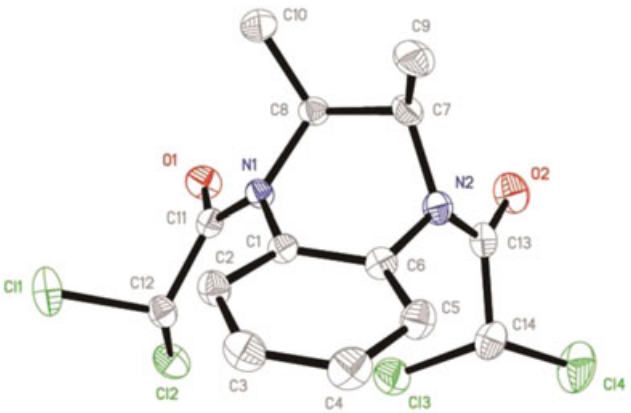


Figure 1. The molecular structure of **4d**. [Color figure can be viewed at wileyonlinelibrary.com]

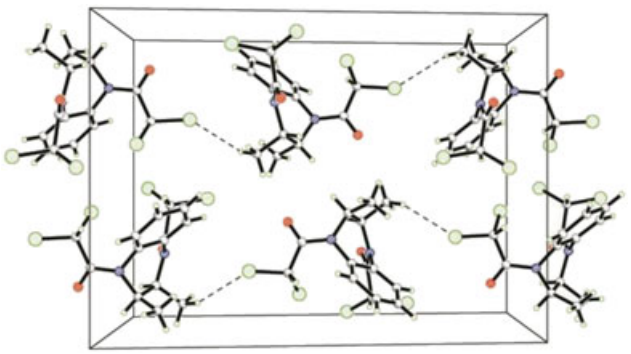


Figure 2. Packing diagram of compound **4d** in a unit cell. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3

Safener activity of compounds **4a**–**p** to growth index of maize[a,b,c,d]

Compound	Recovery of plant height (%)	Recovery of plant weight (%)	Recovery of root length (%)	Recovery of root weight (%)
Benoxacor	109[a]	111[a,b]	70[a,b]	81[a]
4a	113[a]	118[a]	73[a,b]	46[a]
4b	95[a]	100[b,c,d]	108[a,b]	41[a]
4c	91[a]	96[b,c,d]	108[a,b]	43[b]
4d	87[a]	91[b,c,d]	88[a,b]	42[a]
4e	6[b,c]	4[d]	21[a]	31[a]
4f	5[b,c]	4[d]	72[a,b]	36[a]
4g	3[c]	3[d]	6[a,b]	38[a]
4h	8[b,c]	5[d]	9[a,b]	46[a]
4i	103[a]	101[a,b,c]	15[a,b]	58[a]
4j	83[a,b]	91[b,c,d]	52[a,b]	40[a]
4k	125[a]	114[b,c,d]	5[a,b]	23[a]
4l	10[b,c]	8[b,c,d]	21[a,b]	43[a]
4m	9[b,c]	19[b,c,d]	32[a,b]	57[a]
4n	135[a]	127[b,c,d]	68[a,b]	51[a]
4o	6[b,c]	26[c,d]	9[a,b]	43[a]
4p	107[a]	104[b,c,d]	64[a,b]	82[a]

[a]Data are means of three replicates.
[b]Recovery Rate(%) $= \frac{\text{Treated with compounds} - \text{Treated with acetochlor}}{\text{Contrast} - \text{Treated with acetochlor}}$.
[c]The treated water was used as contrast.
[d]Small letter is significant at the 0.05 level.

CONCLUSIONS

In conclusion, we reported an efficient, convenient, and inexpensive method to synthesized a series of novel *N,N′*-disubstituted-1,2,3,4-tetrahydroquinoxalines. There are some notable advantages in the present method, such as the mild reaction conditions, simple experimental procedure cheap, easily obtained raw materials, and high product yields. The preliminary bioassay indicated that *N, N′*-disubstituted-1,2,3,4-tetrahydroquinoxalines could be good safeners to acetochlor.

EXPERIMENTAL

All the reagents were analytical grade and used without further purification. The melting point was measured on a Beijing Taike point apparatus (X-4) and was uncorrected. The IR spectra were recorded on a Bruker ALPHA-T spectrometer (KBr). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-300 or AV-600 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectrum was recorded on a high-resolution mass spectrometer of Bruker Apex-Ultra in which ionization was used for mass spectra recording (electrospray ionization). Crystallographic data of the compound were mounted on a Rigaku RAXIS-RAPID charged coupling device area-detector diffractometer.

General procedure for the preparation of 3a, **3d**, **3j**, and **5**. A mixture of substituted *o*-phenylenediamines **1** (37 mmol) and anhydrous CH_3COONa (50 mmol) in anhydrous MeOH (40 mL) was stirred for 10 min, and halogenated ketone **2** (44.4 mmol) was added dropwise. The mixture was reacted under a strictly inert atmosphere, within 2–3 h at room temperature (25°C). The mixture was filtered to remove the NaCl and diluted with ethyl acetate after the solvent was removed and then washed with saturated sodium chloride aqueous solution (30 mL × 3), dried over anhydrous Na_2SO_4, and evaporated in vacuum; the residues were purified over silica gel with petroleum ether and ethyl acetate (4:1 ratio) as eluent until compound **3** was collected. All data of compounds **3a**, **3d**, and **3j** are summarized in the Supporting Information.

2-Methyl-1,2,3,4-tetrahydroquinoxaline (3a) *[26].* Yellow solid. Yield 54%. mp 63–64°C. IR (KBr, cm^{-1}) *v*: 3357–3312 (N–H), 2974–2862 (C–H), 1604–1423 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.49–6.62 (m, 4H, Ar-H), 3.50–3.60 (m, 3H, N-CH_2, N-CH), 3.03–3.36 (m, 2H, 2 × N–H), 1.17–1.22 (m, 3H, −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 133.58, 133.20, 118.73, 118.73, 113.46, 113.46, 48.28, 45.75, 19.93.

2,3-Dimethyl-1,2,3,4-tetrahydroquinoxaline (3d) *[27].* Yellow solid. Yield 70%. mp 112–113°C. IR (KBr, cm^{-1}) *v*: 3336–3287 (N–H), 2967–2863 (C–H), 1598–1450 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.51–6.60 (m, 4H, Ar-H), 3.49–3.51 (d, J = 5.7 Hz, 4H, 2 × (NH−)), 1.12–1.15 (d, J = 6.3 Hz, 6H, 2 × −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 132.64, 132.64, 118.63, 118.63, 114.49, 114.49, 49.09, 49.09, 17.27, 17.27.

2,3,6-Trimethyl-1,2,3,4-tetrahydroquinoxaline (3j). Yellow solid. Yield 37%. mp 93–94°C. IR (KBr, cm^{-1}) *v*: 3380–3351 (N–H), 2973–2862 (C–H), 1614–1450 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.36–6.44 (d, J = 24.6 Hz, 3H, Ar-H), 3.45 (s, 2H, 2 × N–H), 3.03–3.10 (q, J = 7.5 Hz, 2 × N-CH), 2.21 (s, 3H, Ar-CH_3), 1.17–1.19 (d, J = 5.4 Hz, 6H, 2 × −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 133.62, 131.03, 128.16, 118.94, 114.70, 114.24, 52.26, 52.26, 20.77, 19.10, 19.10.

2-Phenyl-3,4-dihydro-2H-quinoxaline (5) *[28].* Yellow solid. Yield 82%. mp 136–138°C. IR (KBr, cm^{-1}) *v*: 3404–3378 (N–H), 2965–2854 (C–H), 1607–1445 (C═C), 1559 (C═N). 1H NMR (300 MHz, $CDCl_3$, ppm): δ: 9.35 (s, 1H, Ar-H), 8.13–8.23 (m, 2H, Ar-H), 7.76–7.81 (m, 1H, Ar-H), 7.54–7.62 (m, 1H, Ar-H), 7.35–7.40 (m, 2H, Ar-H), 6.60–6.67 (m, 2H, Ar-H), 4.48–4.52 (dd, J_1 = 3.0 Hz, J_2 = 8.4 Hz, 1H, N–H), 3.31–3.50 (m, 2H, N-CH2). 13C NMR (75 MHz, $CDCl_3$, ppm): δ: 193.33, 153.31, 146.94, 142.75, 139.59, 137.47, 132.64, 130.79, 129.74, 129.62, 129.54, 128.99, 128.69, 46.96.

General procedure for the preparation of 4a–**p** and **6**. A mixture of substituted 1,2,3,4-tetrahydroquinoxalines **3a–c** (18.4 mmol) and anhydrous Na_2CO_3 (3.14 g, 22.1 mmol)

in benzene (30 mL) was stirred at 0°C. Dichloroacetyl chloride (36 mmol) was dropwise to the mixture with stirring continued for 1 h. When the reaction finished, the solution was washed with saturated NaCl aq. (30 mL × 3). The organic phase was dried over anhydrous Na_2SO_4, and the benzene was removed under vacuum; the crude products were purified by silica gel chromatography, eluting with petroleum ether-ethyl acetate mixture (3:1) until compound **4** was collected. The physical and spectra data of the compounds **4a–p** were as follows.

N,N′-bis(dichloroacetyl)-2-methyl-1,2,3,4-tetrahydroquinoxaline (4a) [29]. White solid. Yield 80%. mp 124–125°C. IR (KBr, cm^{-1}) *v*: 3034–2931 (C–H), 1692 (C═O), 1545–1394 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.49 (s, 4H, Ar-H), 6.34–6.40 (d, J = 20.1 Hz, 2H, 2 × $CHCl_2$), 4.99–5.08 (m, 2H, N-CH_2), 2.86 (s, 1H, N-CH), 1.24–1.26 (d, J = 4.8, 3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 163.28, 162.36, 135.44, 132.71, 129.10, 128.90, 125.85, 124.56, 64.01, 63.64, 53.96, 51.77, 18.47; high-resolution mass spectrometry (HRMS) *m/z*. Calcd. for $C_{13}H_{12}Cl_4N_2O_2$: 367.9653. Found: 368.9730 $[M + H]^+$.

N-dichloroacetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (4b). Yellow liquid. Yield 62%. IR (KBr, cm^{-1}) *v*: 3375 (N–H), 2968–2870 (C–H), 1668 (C═O), 1606–1454 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.64–7.07 (m, 5H, Ar-H, CO-$CHCl_2$), 4.25–4.26 (dd, J_1 = 3.0 Hz, J_2 = 12.3 Hz, 1H, N–H), 4.10–4.13 (q, J = 7.2 Hz, 1H, N-CH), 3.69 (s, 1H, N-CH), 3.19–3.21 (m, 1H, N-CH), 1.23–1.26 (d, J = 6.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 163.60, 138.61, 127.96, 122.65, 121.90, 116.65, 114.88, 63.64, 47.95, 46.20, 19.90; HRMS *m/z*. Calcd. for $C_{11}H_{13}Cl_2N_2O$: 258.0326. Found: 259.0404 $[M + H]^+$.

N-*dichloroacetyl-3-methyl-1,2,3,4-tetrahydroquinoxaline (4c).* Yellow liquid. Yield 55%. IR (KBr, cm^{-1}) *v*: 3385 (N–H), 2966–2855 (C–H), 1681 (C═O), 1600–1462 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.63–7.06 (m, 5H, Ar-H, CO-$CHCl_2$), 4.22–4.27 (dd, J_1 = 3.0 Hz, J_2 = 12.3 Hz, 1H, N–H), 4.07–4.14 (q, J = 7.2 Hz, 1H, N-CH), 3.68 (s, 1H, N-CH), 3.15–3.22 (m, 1H, N-CH), 1.22–1.24 (d, J = 6.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 163.64, 138.66, 128.05, 122.69, 121.80, 116.63, 114.90, 63.69, 47.99, 46.19, 19.97; HRMS *m/z*. Calcd. for $C_{11}H_{12}Cl_2N_2O$: 258.0326. Found: 259.0404 $[M + H]^+$.

N,N′-bis(dichloroacetyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4d). White solid. Yield 84%. mp 141–142°C. IR(KBr, cm^{-1}) *v*: 3018–2941 (C–H), 1693 (C═O), 1596–1462 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.45–7.47 (m, 4H, Ar-H), 6.33 (s, 2H, 2 × $CHCl_2$), 5.20–5.21 (m, 2H, 2 × N-CH), 1.04–1.06 (d, J = 6.3 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 162.48, 162.48, 133.31, 133.31, 129.08, 129.08, 126.03, 126.03, 63.97, 63.97, 55.08, 55.08, 15.05, 15.05; HRMS *m/z*. Calcd. for $C_{14}H_{14}Cl_4N_2O_2$: 381.9809. Found: 382.9879 $[M + H]^+$.

Crystal data for compound 4d. $C_{14}H_{14}Cl_4N_2O_2$, monoclinic, space group $P2_1/c$, a = 13.326(3) Å, b = 13.668(3) Å, c = 18.615(4) Å, V = 3366.0(13) $Å^3$, β = 96.89(3) °, Z = 8, D_c = 1.516 cm^{-3}, μ = 0.710 mm^{-1}, F(000) = 1568. Independent reflections were obtained in the range of $3.08 < \theta < 25.00$ °, 5917. The final least-square cycle gave R_1 = 0.0497 and ωR_2 = 0.0833 for 3160 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.311 and −0.252 e/$Å^{-3}$, respectively. Crystallographic data have been deposited at The Cambridge Crystallographic Data Centre as supplementary publication number CCDC1442229. These data can be obtained free of charge from The Cambridge Crystallographic Data via www.ccdc.cam.ac.uk/data_request/cif

N-trichloroacetyl-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4e). Yellow solid. Yield 69%. mp 114–115°C. IR (KBr, cm^{-1}) *v*: 3394 (N–H), 2980–2872 (C–H), 1681 (C═O), 1606–1500 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.54–7.58 (dd, J_1 = 1.2 Hz, J_2 = 9.6 Hz, 1H, Ar-H), 6.98–7.04 (m, 1H, Ar-H), 6.69–6.75 (m, 1H, Ar-H), 6.59–6.63 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H, Ar-H), 4.72–4.79 (m, 1H, N-CH), 4.03 (s, 1H, N-H), 3.77–3.85 (m, 1H, N-CH) 1.11–1.23 (dd, J_1 = 6.3 Hz, J_2 = 31.2 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 157.67, 137.21, 126.85, 126.78, 120.73, 117.38, 114.63, 94.16, 52.59, 49.44, 18.16, 10.91; HRMS *m/z*. Calcd. for $C_{12}H_{13}Cl_3N_2O$: 306.0093. Found: 307.0166 $[M + H]^+$.

N,N′-bis(trichloroacetyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4f). White solid. Yield 56%. mp 136–137°C. IR (KBr, cm^{-1}) *v*: 2985–2854 (C–H), 1695 (C═O), 1617–1449 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.80–8.22 (m, 4H, Ar-H), 4.81–4.89 (m, 1H, N-CH), 3.86–3.94 (m, 1H, N-CH), 0.89–1.32 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 164.79, 157.92, 134.44, 127.15, 126.96, 122.44, 120.00, 116.44, 93.81, 90.41, 52.78, 50.25, 17.63, 10.83.

N-acetoxyacetyl-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4g). White solid. Yield 64%. mp 117–118°C. IR (KBr, cm^{-1}) *v*: 3400 (N–H), 2988–2868 (C–H), 1737 (C═O), 1657 (C═O), 1607–1430 (C═C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.58–7.04 (m, 4H, Ar-H), 4.65–5.10 (m, 3H, O═C-CH_2, N-CH), 4.03 (s, 1H, N-H), 3.43–3.62 (m, 1H, N-CH), 2.14–2.15 (d, J = 3.0 Hz, 3H, O═C-CH_3), 0.91–1.20 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 160.32, 155.78, 127.49, 116.57, 114.48, 109.55, 106.22, 104.00, 51.93, 42.06, 39.57, 12.19, 10.36, 7.89; HRMS *m/z*. Calcd. for $C_{14}H_{18}N_2O_3$: 262.1317. Found: 263.1394 $[M + H]^+$.

N,N′-bis(acetoxyacetyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4h). White solid. Yield 68%. mp 137–138°C. IR (KBr, cm^{-1}) *v*: 3064–2941 (C–H), 1742 (C═O), 1681 (C═O), 1605–1431 (C═C). ^1H NMR (600 MHz, $CDCl_3$, ppm): δ:

7.33 (s, 4H, Ar-H), 5.13–5.14 (m, 2H, 2 × CO-CH), 4.92–4.97 (d, J = 14.4 Hz, 2H, 2 × COCHO), 4.47–4.51 (d, J = 14.4 Hz, 2H, 2 × N-CH), 2.12 (s, 6H, 2 × O═C-CH_3), 1.01–1.03 (d, J = 6.3 Hz, 6H, 2 × CH_3). ^{13}C NMR (150 MHz, $CDCl_3$, ppm): δ: 170.54, 170.39, 165.74, 165.43, 133.44, 133.44, 127.53, 127.53, 124.57, 123.41, 61.66, 61.66, 49.31, 49.31, 20.44, 20.44, 15.19, 9.81; HRMS m/z. Calcd. for $C_{18}H_{22}N_2O_6$: 362.1477. Found: 363.1555 $[M + H]^+$.

N,N′-bis(phenoxyacetyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (4i). White solid. Yield 75%. mp 161–162°C. IR (KBr, cm^{-1}) v: 3060–2857 (C–H), 1688 (C═O), 1598–1445 (C═C). ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ: 6.75–7.61 (m, 14H, Ar-H), 5.02–5.04 (d, J = 14.4 Hz, 4H, 2 × Ar-O-CH_2), 4.67–4.70 (d, J = 15.0 Hz, 2H, 2 × N-CH), 0.96–0.97 (d, J = 6.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ: 165.81, 165.81, 157.68, 157.68, 132.74, 132.74, 129.35, 129.35, 129.35, 129.35, 127.04, 127.04, 125.87, 125.87, 120.94, 120.94, 114.33, 114.33, 114.33, 114.33, 65.77, 65.77, 52.96, 52.96, 15.09, 15.09; HRMS m/z. Calcd. for $C_{26}H_{26}N_2O_4$: 430.1892. Found: 431.1966 $[M + H]^+$.

N-chloroacetyl-2,3,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (4j). White oil. Yield 70%. IR (KBr, cm^{-1}) v: 3311 (N–H), 2973–2873 (C–H), 1663 (C═O), 1613–1447 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.01–7.50 (m, 3H, Ar-H), 5.14 (s, 1H, N–H), 4.28–4.29 (m, 2H, 2 × N-CH), 4.12–4.14 (d, J = 6.3 Hz, 2H, 2 × CH-Cl_2), 2.47 (s, 3H, Ar-CH_3), 1.01–1.20 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 165.03, 138.29, 133.70, 131.22, 128.57, 126.34, 124.00, 54.11, 42.09, 41.29, 21.13, 17.61, 15.23. HRMS m/z. Calcd. for $C_{13}H_{17}ClN_2O$: 252.1029. Found: 252.0310 $[M + H]^+$.

N,N′-bis(dichloroacetyl)-2,3,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (4k). White solid. Yield 69%. mp 127–128°C. IR (KBr, cm^{-1}) v: 3036–2871 (C–H), 1683 (C═O), 1586–1462 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.23–7.33 (m, 3H, Ar-H), 6.33–6.35 (d, J = 7.2 Hz, 2H, 2 × CH-Cl_2), 5.19–5.20 (d, J = 2.4 Hz, 2H, 2 × N-CH), 2.47 (s, 3H, Ar-CH_3), 1.04–1.06 (d, J = 5.7 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 162.51, 162.48, 139.68, 133.15, 130.61, 129.63, 126.44, 125.67, 63.99, 63.96, 54.95, 54.95, 21.41, 15.04, 15.00; HRMS m/z. Calcd. for $C_{15}H_{16}Cl_4N_2O_2$: 395.9965. Found: 397.0042 $[M + H]^+$.

N-trichloroacetyl-2,3,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (4l). Yellow solid. Yield 72%. mp 138–139°C. IR (KBr, cm^{-1}) v: 3324 (N–H), 2980–2852 (C–H), 1664 (C═O), 1620–1446 (C═C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ: 6.39–7.11 (m, 3H, Ar-H), 6.30–6.33 (d, J = 8.4 Hz, 1H, N–H), 4.48–4.50 (d, J = 6.0 Hz, 1H, N-CH), 3.43–3.46 (t, J = 4.8 Hz, 1H, N-CH), 2.13–2.15 (d, J = 6.3 Hz, 3H, Ar-CH_3), 1.06–1.13 (dd, J_1 = 6.3 Hz, J_2 = 14.1 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ: 160.47, 137.47, 136.14, 127.88, 125.70, 116.36, 114.82, 94.22, 52.49, 50.44, 22.22, 21.29, 17.39; HRMS m/z. Calcd. for $C_{13}H_{15}Cl_3N_2O$: 320.0250. Found: 343.0143 $[M + Na]^+$.

N-trichloroacetyl-2,3,7-trimethyl-1,2,3,4-tetrahydroquinoxaline (4m). White solid. Yield 80%. mp 160–161°C. IR (KBr, cm^{-1}) v: 3344 (N–H), 2996–2864 (C–H), 1655 (C═O), 1617–1447 (C═C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ: 8.31 (s, 1H, Ar-H), 6.17 (s, 2H, Ar-H), 5.08 (s, 1H, N–H), 2.72 (s, 2H, 2 × N-CH), 2.03 (s, 3H, Ar-CH_3), 1.01–1.03 (d, J = 5.7 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ: 160.47, 137.47, 136.14, 127.88, 125.70, 116.36, 114.82, 94.22, 52.49, 50.44, 22.22, 21.29, 17.39; HRMS m/z. Calcd. for $C_{13}H_{15}Cl_3N_2O$: 320.0250. Found: 343.0143 $[M + Na]^+$.

N,N′-bis(acetoxyacetyl)-2,3,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (4n). Yellow liquid. Yield 59%. IR (KBr, cm^{-1}) v: 2960–2854 (C–H), 1748 (C═O), 1680 (C═O), 1614–1434 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.09–7.71 (m, 3H, Ar-H), 4.76–5.10 (m, 4H, 2 × $COCH_2O$), 4.09–4.51 (m, 2H, 2 × N-CH), 2.31–2.38 (d, J = 19.2 Hz, 3H, Ar-CH_3), 2.02–2.14 (m, 6H, 2 × $COCH_3$), 1.16–1.26 (m, 3H, CH_3), 0.98–1.00 (d, J = 5.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 170.62, 170.62, 165.47, 165.47, 138.01, 133.17, 130.64, 128.23, 126.65, 125.87, 62.27, 61.54, 53.58, 53.58, 29.73, 21.25, 20.55, 15.24, 15.20; HRMS m/z. Calcd. for $C_{19}H_{24}N_2O_6$: 376.1634. Found: 377.1711 $[M + H]^+$.

N,N′-bis(phenoxyacetyl)-2,3,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (4o). White solid. Yield 63%. mp 136–137°C. IR (KBr, cm^{-1}) v: 3064–2862 (C–H), 1667 (C═O), 1589–1449 (C═C). ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ: 6.90–7.81 (m, 13H, Ar-H), 5.01–5.11 (m, 4H, 2 × Ar-O-CH_2), 4.35–4.36 (d, J = 4.8 Hz, 2H, 2 × N-CH) 2.22 (s, 3H, Ar-CH_3), 1.11–1.12 (d, J = 6.6 Hz, 6H, 2 × CH_3). ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ: 167.64, 167.45, 157.72, 157.71, 132.99, 129.48, 129.48, 129.48, 129.48, 125.38, 124.56, 123.68, 123.36, 123.12, 121.10, 121.10, 114.51, 114.51, 114.50, 114.50, 66.82, 66.82, 50.77, 50.77, 20.57, 16.63, 16.59; HRMS m/z. Calcd. for $C_{27}H_{28}N_2O_4$: 310.1681. Found: 333.1571 $[M + Na]^+$.

N,N′-bis(dichloroacetyl)-2,3-dimethyl-6-methoxyl-1,2,3,4-tetrahydroquinoxaline (4p). White solid. Yield 70%. mp 131–132°C. IR (KBr, cm^{-1}) v: 3017–2853 (C–H), 1697 (C═O), 1597–1462 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 6.95–7.34 (m, 3H, Ar-H), 6.31, 6.37 (s, 2H, 2 × $CHCl_2$), 5.18–5.21 (t, J = 5.4 Hz, 2H, 2 × N-CH), 3.89 (s, 3H, Ar-CH_3), 1.04–1.09 (dd, J_1 = 6.3 Hz, J_2 = 9.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 162.52, 162.52, 159.74, 134.42, 126.80, 126.65, 113.78, 111.89, 63.92, 63.92, 55.99, 55.99, 54.74, 15.05, 15.05; HRMS m/z. Calcd. for $C_{15}H_{16}Cl_4N_2O_3$: 411.9915. Found: 412.9990 $[M + H]^+$.

N-dichloroacetyl-3-phenyl-1,2-dihydro-2H-quinoxaline (6). Yellow solid. Yield 49%. mp 151–152°C. IR (KBr, cm^{-1}) v: 3065–3027 (C–H), 1676 (C═O), 1606–1445 (C═C),

1562 (C═N). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.51–8.22 (m, 10H, Ar-H, CH-Cl_2), 5.03 (s, 2H, N-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 143.44, 130.35, 130.25, 129.69, 129.60, 129.22, 128.70, 127.97, 127.62, 127.04, 119.24, 118.84, 114.99, 114.53, 54.73, 49.13.

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