Synthesis, Crystal Structure and Biological Activity of Novel *N*-substituted Diazabicyclo Derivatives

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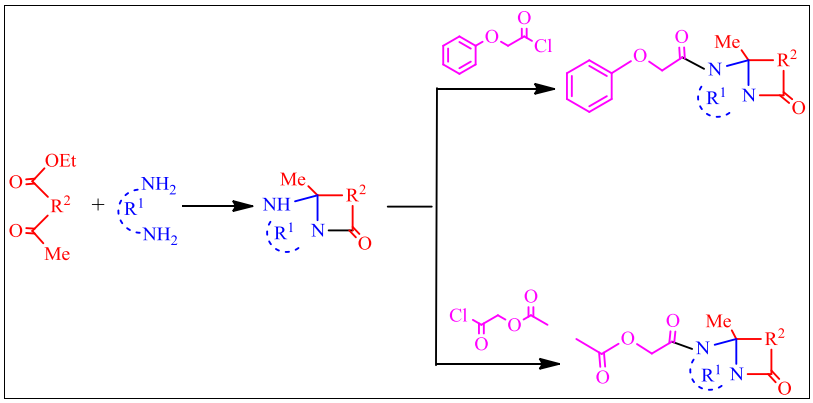


A series of *N*-substituted diazabicyclo derivatives were designed and synthesized based on the active subunit combination and structure–activity relationship theory. The compounds were prepared by levulinic acid or ester with diamine, then acylation with phenoxy acetyl chloride or acetoxy acetyl chloride. All the structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The single crystal of compound **4a** was determined by X-ray crystallography. The preliminary bioassay showed that all products could protect soybean against injury caused by 2,4-D butylate to some extent.

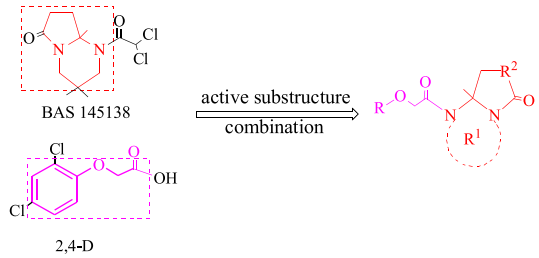
INTRODUCTION

Diazabicyclo derivatives were critically important used as synthons and biological activities materials. They were also used as medical or pharmaceutical intermediates, for example, anticancer agents, antibiotics and antibacterial agent [1–3]. Diazabicyclo derivatives have been investigated as potential herbicide safeners which protected the crop from the injury by herbicides [4]. Dichloroacetyl diazabicyclo derivatives were reported as a novel kind of herbicide safener [5]. They can protect crops from injury by chlorine acetamide herbicides, sulfonylurea herbicides, and imidazolinone herbicides [6,7].

Structure–activity relationship theory (SAR) is very important in the search for bioactive materials, and it provides useful molecular structure information for the target bioactivity [8]. Recently, many successful cases have been reported [9,10]. In the same way, the safeners supposed to be the herbicide antidotes if the herbicides and the safeners are similar at the molecular level [11]. As part of our ongoing work on nitrogen-containing heterocyclic safeners [12,13], herein we designed a series of novel substituted diazabicyclo drivatives utilizing active substructure combination and similarity theory (Scheme 1).

A variety of synthetic methods had been reported about diazabicyclo derivatives. 5-Substituted-furan-2(3H)-one and ethylenediamine were refluxed in anhydrous benzene to synthesize diazabicyclo derivatives [14]. Phenylenediamine and amyl-4-acetylenic acid were used as the starting materials, and Au (I)-catalyzed was added as catalyst to obtain di(tetra)hydrobenzimidazoles [15]. Aeberli proposed that 2-benzoyl benzoic acid and ethylenediamine were refluxed in toluene to obtain diazabicyclo derivatives [16]. Microwave-assisted synthesis was also applied to prepare 1,4-diketo-pyrrolo[3,4-c]-pyrroles derivatives by mixing and grinding of ethyl bromoacetate, benzonitrile, and zinc–copper couple under solvent-free conditions [17]. Diazabicyclo derivatives were also synthesized by diamine and ester with microwave irradiation [18]. In continuation of our previous investigations on the synthesis of nitrogen-containing heterocycles [19], herein we reported the synthesis of novel *N*-substituted diazabicyclo derivatives via cyclization and acylation without any expensive reagent or catalyst (Scheme 2). All the compounds' bioactivities were tested as herbicide safener.

Scheme 1. Design of the target compound. [Color figure can be viewed at wileyonlinelibrary.com]



RESULTS AND DISCUSSION

The synthesis of the compounds **3** was performed by the cycloaddition of diamine with ester in ethanol for stirring 8 h with 16%–72% yields (Table 1). The substitute group structure affected the yields significantly. The steric hindrance was weak with R^1 and R^2 being short-chain alkyl, so the yields of **3b** and **3c** were better than others, which were 60% and 72%, respectively. The steric hindrance effects caused by six-membered ring or benzene ring more obvious. It can be seen that the yields of **3 h** and **3i** were 16% and 19%, respectively. For compounds **3d** and **3h**, the starting material is the mixture of trans-cyclohexanediamine and cis-cyclohexanediamine, only cis-cyclohexanediamine reacted with ester which made the yields were lower. The yield of **3i** was only 19% that was caused by the conjugative effect between the amino and benzene.

Compound **4** was obtained by the acylation of compounds **3** with phenoxy acetyl chloride or acetoxy acetyl chloride in THF stirring for 2.5 h. The yields of *N*-phenoxyacetyl substitutes are significantly better than that of *N*-acetoxy acetyl substitutes (Table 2). The yields were influenced greatly with the steric hindrance of R^1. The yields were lower as the structure of R^1 being cyclohexyl, phenyl, or long-chain alkyl. It was hard for acyl chloride to react with *N* atom. The yields of **4j** and **4m** were low because the seven-membered ring was unstable with R^1 being $(CH_2)_4$. The cis-1,2-disubstituted cyclohexyl was unstable, which made the yields of **4f** and **4k** were not good as other compounds. The electron effect also affected the yield greatly. It can be seen that the yield of **4g** was 35%, far lower than others. This might be the phenyl electron-withdrawing conjugation effect decreased the electron density of *N* atom which made the acyl hard to react with the intermediate. The structure of R^2 has no significant effect on the yield of compounds **4**.

Table 1

The structures and the properties of compounds **3**

compound	R^1	R^2	mp (°C)	Yield (%)
3a	$-(CH_2)_2-$	$(CH_2)_2$	oil	60
3b	$-(CH_2)_3-$	$(CH_2)_2$	oil	72
3c	$-(CH_2)_4-$	$(CH_2)_2$	121–122	44
3d		$(CH_2)_2$	oil	31
3e	$-(CH_2)_2-$	$(CH_2)_3$	115–117	42
3f	$-(CH_2)_3-$	$(CH_2)_3$	118–119	37
3g	$-(CH_2)_4-$	$(CH_2)_3$	125–126	19
3h		$(CH_2)_3$	oil	16
3i		$(CH_2)_2$	107–109	19

The IR spectra of compounds **4** showed the bands at 2855–3071 cm^{-1} due to C–H. In the IR spectra, a characteristic carbonyl band at around 1645–1756 cm^{-1} split into two sharp or three peaks due to C═O. The ^1H NMR spectra of **4a–m** exhibited a signal in the range δ

Scheme 2. Route for the synthesis diazabicyclo derivatives.

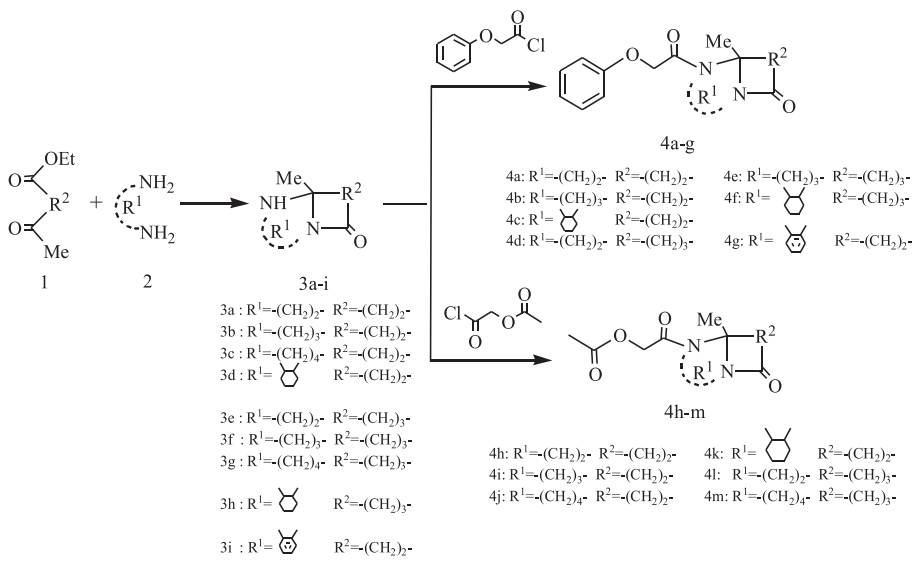


Table 2

The structures and the properties of compounds **4**

Compound	acyl	R^1	R^2	mp(°C)	Yield (%)
a	$C_6H_5OCH_2CO$–	–$(CH_2)_2$–	–$(CH_2)_2$–	136–138	62
b	$C_6H_5OCH_2CO$–	–$(CH_2)_3$–	–$(CH_2)_2$–	104–106	71
c	$C_6H_5OCH_2CO$–		–$(CH_2)_2$–	158–160	68
d	$C_6H_5OCH_2CO$–	–$(CH_2)_2$–	–$(CH_2)_3$–	166–167	63
e	$C_6H_5OCH_2CO$–	–$(CH_2)_3$–	–$(CH_2)_3$–	93–95	50
f	$C_6H_5OCH_2CO$–		–$(CH_2)_3$–	161–162	55
g	$C_6H_5OCH_2CO$–		–$(CH_2)_2$–	160–163	35
h	CH_3COOCH_2CO–	–$(CH_2)_2$–	–$(CH_2)_2$–	98–100	50
i	CH_3COOCH_2CO–	–$(CH_2)_3$–	–$(CH_2)_2$–	106–108	68
j	CH_3COOCH_2CO–	–$(CH_2)_4$–	–$(CH_2)_2$–	97–98	46
k	CH_3COOCH_2CO–		–$(CH_2)_2$–	116–119	48
l	CH_3COOCH_2CO–	–$(CH_2)_2$–	–$(CH_2)_3$–	156–158	63
m	CH_3COOCH_2CO–	–$(CH_2)_4$–	–$(CH_2)_3$–	107–110	41

1.92–1.59 ppm for the proton of CH_3–. In the ^{13}C NMR spectra, the signals observed in the region of δ 175.71–164.57 ppm accounted for the carbon of –C═O. The elemental analysis of **4** was agreed with the molecular formulas of these compounds.

The configuration of the target compound **4a** was confirmed via X-ray crystallography. The single crystal of **4a** was obtained by dissolving it in EtOAc, followed by slow evaporation at room temperature. The diffraction data of **4a** was collected with a Rigaku RAXIS-RAPID area detector using a graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 293(2) K. The structure was solved by direct methods using SHELXS-97 [20], and refined by full matrix least squares on F^2, SHELXL-97 [20]. The molecular structure of the compound **4a** was shown in Figure 1.

The bond distances of C(8)–N(1) and C(11)–N(2) [1.331(4) Å and 1.368(4) Å, respectively] are shorter than the normal C–N distance [C-*N* = 1.472 Å], which indicates the existence of p-π conjunction effect between *N* atom and carbonyl. The O(1)–C(1) distance (1.375 Å) is shorter than classical distance of O–C, due to the p-π conjugative effect between O(1) and benzene ring. The dihedral angle between the pyrrole ring (C11/C12/C13/C14/N2) and the imidazole ring (N1/C14/N2/C10/C9) is 47.48(101)°, forming a lounge chair with the pyrrole ring as the chair-back. The benzene ring is almost vertical to the imidazole ring with the dihedral angle being 85.51(110)°. The molecules are linked by intermolecular weak C–H…O bonds and van der Waals forces, which stabilized the crystal structure (Fig. 2). No significant π-π interactions were found in the crystal structure.

Compounds **4** were evaluated for their protection of soybean *in vivo* against the injury of 2,4-D butylate at the concentration of 50 mg/kg (Table 3). Compounds **4a–m** showed some recovery rate for plant height, plant fresh

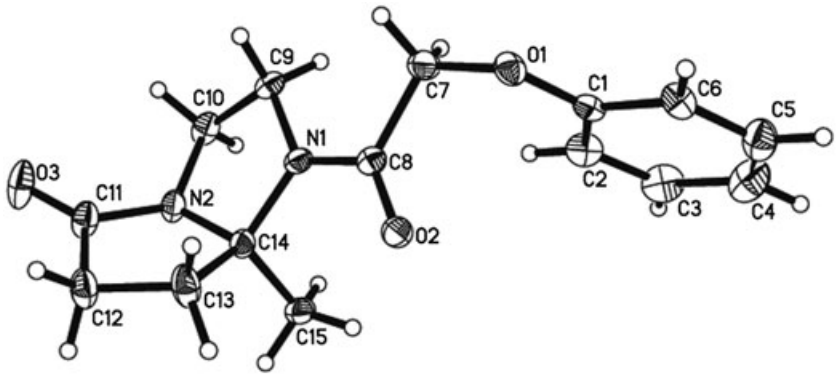


Figure 1. Molecular structure for compound **4a** at 30% probability level.

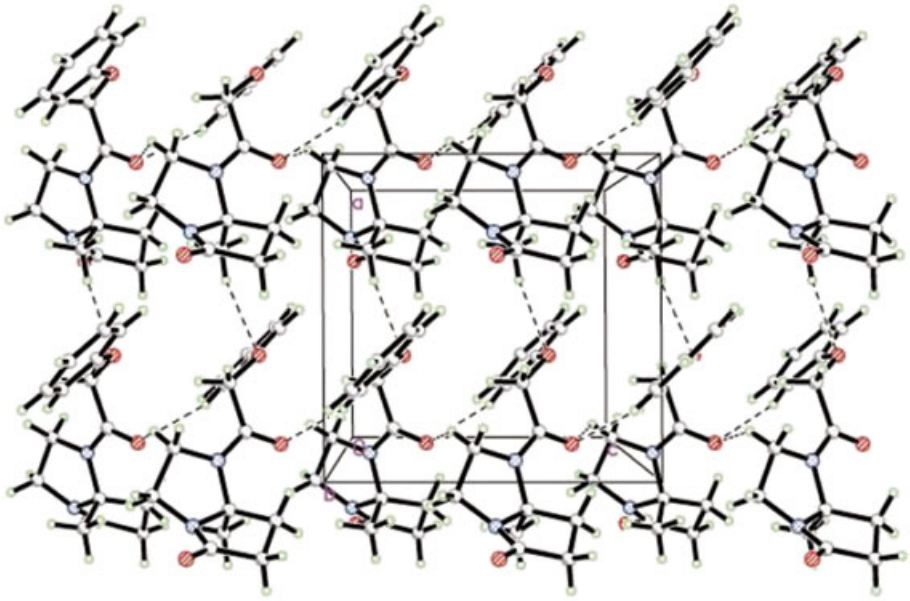


Figure 2. Packing view of the compound **4a**. [Color figure can be viewed at wileyonlinelibrary.com]

weight, root length, and root fresh weight. Among the compounds tested, the compounds with *N*-phenoxyacetyl led to good activity. Compound **4b** showed the best activity against the injury of 2,4-D butylate, even better than the commercialized safener, BAS-145138. The structure of **4b** is more similar as the combination of BAS-145138 and 2,4-D butylate, which indicated that the structure–activity correlations are useful tools for searching biological activity because they provide valuable information about chemical substituents that are necessary for the required bioactivity. However, compounds **4k** and **4m** did not show protection, they inhibited the root growth. The further bioassay was still investigated.

Table 3

Effect of compounds **4** to soybean growth indexes[a,b,c,d]

Products	Recovery of root length (%)	Recovery of Plant height (%)	Recovery of root weight (%)	Recovery of plant weight (%)
BAS-145138	98.10^{abcd}	96.97^{a}	97.96^{a}	70.58^{ab}
4a	94.95^{abcd}	91.65^{a}	80.99^{bc}	94.37^{a}
4b	144.63^{a}	100.73^{a}	102.91^{ab}	94.93^{a}
4c	79.01^{abcd}	61.07^{ab}	107.00^{ab}	50.99^{bc}
4d	47.85^{bcd}	65.82^{ab}	50.38^{cde}	34.98^{cdef}
4e	77.07^{abcd}	77.14^{a}	96.27^{ab}	35.99^{cde}
4f	84.46^{abcd}	57.85^{ab}	31.62^{de}	25.62^{cdef}
4g	34.14^{cd}	50.68^{ab}	80.24^{bc}	30.29^{cdef}
4h	106.68^{abc}	75.29^{a}	72.04^{bcd}	5.76^{fg}
4i	111.17^{ab}	90.61^{a}	68.57^{bcd}	5.90^{fg}
4j	96.59^{abcd}	80.60^{a}	16.37^{e}	38.48^{cd}
4k	44.91^{bcd}	50.33^{ab}	34.57^{de}	7.79^{efg}
4l	66.02^{bcd}	89.60^{a}	48.73^{cde}	43.31^{bcd}
4m	46.73^{bcd}	58.29^{ab}	17.92^{e}	14.81^{defg}

[a]data are means of three replicates
[b]Recovery Rate $(\%) = \frac{\text{Treated with compounds-Treat with 2,4-D butylate}}{\text{Contrast- Treat with 2,4-D butylate}}$
[c]water treated was used as contrast
[d]small letter is significant at the 0.05 level

CONCLUSIONS

A series of novel *N*-substituted diazabicyclo derivatives with phenoxyacetyl or acetoxyacetyl were synthesized via direct acylation. All of the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MS. To further confirm the structure of the synthesized products, the single-crystal structure of **4a** was determined. The recovery rate for plant height, plant fresh weight, root length, and root fresh weight of the compounds were investigated. Among the compounds tested, the compounds with *N*-phenoxyacetyl led to good activity. Compound **4b** exhibited the best activity against the injury of 2,4-D butylate, even better than the commercialized safener, BAS-145138, because the structure of **4b** is more similar as the combination of BAS-145138 and 2,4-D butylate.

EXPERIMENTAL

Reagents were obtained from commercial sources and used without further purification. The melting points were determined on a Beijing Taike melting point apparatus(X-4) and are uncorrected. The IR spectra were taken on a KJ-IN-27G infrared spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANVE 300 MHz, with $CDCl_3$ as

the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer. The mass spectrum was recorded on a Waters Xevo TQ spectrometer. X-ray diffraction data were collected on a Bruker AXSII CCD area-detector diffractometer, Mo Kα.

General procedure for the preparation of diazabicyclo derivatives 3. Ethyl levulinate (or ethyl 4-acetylbutyrate, 0.047 mol, 6.8 g) and diamine(0.25 mol) were mixed with 20 mL EtOH. The mixture was heated to reflux for 8 h, then vacuum distillation. The crude products were purified by column chromatography on silica gel eluting with dichloromethane and EtOH (6:1) or recrystallized with EtOAc and light petroleum. Analytically pure product was obtained by crystallization from a mixture of ethanol and hexanes.

5-methyl-8-oxa-1,4–diazabicyclo[3.3.0]octane (3a). Yellow oil. Yield 60%. IR (KBr, cm^{-1}) *v*: 3250 (N–H), 2972–2874 (C–H), 1685(C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 3.72–2.98 (m, 4H, N–$(CH_2)_2$–N), 1.92–2.84 (m, 4H, C–$(CH_2)_2$–C═O), 1.78(s, 1H, −HN–), 1.39(s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 175.97, 84.03, 47.09, 41.62, 35.24, 34.04, 24.75.

6-methyl-9-oxo-1,5-diazabicyclo[4.3.0]nonane (3b). Yellow oil. Yield 72%. IR (KBr, cm^{-1}) *v*: 3393 (N–H), 2968–2879 (C–H), 1654 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.12–4.06 (m, 1H, HN–), 3.09–2.14 (m, 6H, N–CH_2–C–CH_2–N, C–C–CH_2–C═O), 1.76–1.47 (m, 4H, N–C–CH_2–C–N, C–CH_2–C–C = O), 1.44 (s, 3H, CH3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 171.44, 73.76, 40.17, 35.92, 35.50, 29.21, 26.24, 21.16.

7-methyl-10-oxa-1,6-diazabicyclo[5.3.0]decane (3c). White solid. Yield 44%. m.p.121–122 °C. IR (KBr, cm^{-1}) *v*: 3305 (N–H), 2904–2854 (C–H), 1658 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 3.95–3.99 (d, J = 12 Hz, 1H, N–H), 2.49–2.96 (m, 4H, CH_2–N–C–N–CH_2), 1.84–2.41 (m, 4H, C–$(CH_2)_2$–C═O), 1.43–1.75, 1.23–1.28 (m, 4H, C–(CH_2)–C), 1.29 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 172.54, 77.84, 41.63, 38.29, 33.29, 32.34, 30.11, 27.76, 25.42.

3a-methyl-decahydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-1-one (3d). Yellow oil. Yield 31%. IR (KBr, cm^{-1}) *v*: 3303 (N-H), 2964–2864 (C-H), 1677 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 3.94–3.86 (m, 1H, N–H), 3.12–3.09 (m, 1H, N–CH), 2.68–2.58 (m, 1H, N–CH), 2.33–1.95 (m, 4H, C–CH_2–CH_2–C), 1.89–1.57, 1.26–1.17 (m, 8H, $(CH_2)_4$), 1.55 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 178.58, 83.04, 56.76, 55.79, 38.79, 33.13, 27.79, 27.33, 25.76, 23.58, 19.96.

5-methyl-9-oxa-1,4-Diazabicyclo[3.4.0]nonane (3e). White solid. Yield 42%. m.p.115–117 °C. IR (KBr, cm^{-1}) *v*: 3251 (N-H), 2960–2945 (C–H), 1615 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 3.80–3.71 (m, 1H, HN–), 3.37–2.43 (m, 4H, N–$(CH_2)_2$–N), 2.35–1.39 (m, 6H, C–$(CH_2)_3$–C), 1.29 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 167.87, 77.51, 43.40, 42.16, 35.37, 30.37, 23.46, 17.67.

6-Methy-10-oxa-1,5-diazabicyclo[4.4.0]decane (3f). White solid. Yield 37%. m.p.118–119 °C. IR (KBr, cm^{-1}) *v*: 3284 (N-H), 2946–2850 (C–H), 1614 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.71–4.67 (m,1H, N–H), 3.13–1.56 (m, 12H, 6 × CH_2), 1.49 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 168.58, 70.66, 39.46, 39.08, 35.88, 32.64, 27.56, 21.89, 16.90.

7-methy-11-oxa-1,6-Diazabicyclo[5.4.0]undecane (3g). White solid. Yield 19%. m.p.125–126 °C. IR (KBr, cm^{-1}) *v*: 3324 (N-H), 2914–2849 (C–H), 1606 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.13–4.09 (d, J = 13.8 Hz, 1H, HN–), 2.87–2.27 (m, 4H, CH2–N–C–N–CH2), 1.72–1.60 (m, 6H, N–C–$(CH_2)_3$–C═O), 1.60–1.47 (m, 4H, C–$(CH_2)_2$–C), 1.27 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 170.19, 73.67, 41.40, 40.21, 35.35, 31.95, 31.95, 26.52, 26.32, 17.58.

4a-methyl-decahydro-benzo[4,5]imidazo[1,2-a]pyridin-1-one (3h). Yellow oil. Yield 16%. IR (KBr, cm^{-1}) *v*: 3309 (N–H), 2933–2860 (C-H), 1696 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.15–4.05 (m, 3H, NH–, N–$(CH)_2$–N), 2.45–2.43 (m, 2H, C–CH_2–C = O), 2.35–1.79 (m, 8H, C–$(CH_2)_2$–C–C═O, N–CH_2–C–CH_2–N,), 1.65–1.19 (m, 7H, N–C–C–CH_2–CH_2–C–C–N, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 173.13, 60.33, 55.91, 53.08, 42.45, 33.23, 29.93, 25.82, 23.43, 19.99, 18.86, 14.22.

3a-methyl-2,3,3a,4-tetrahydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-1-one (3i). White solid. Yield 19%. m.p.107–109 °C. IR (KBr, cm^{-1}) *v*: 3326 (N–H), 2964–2906(C–H), 1616(C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 7.45–6.68 (m, 4H, Ph–), 4.19 (s, 1H, HN–), 2.82–2.37 (m, 4H, C–$(CH_2)_2$–C═O), 1.53 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 173.74, 142.75, 128.62, 125.25, 120.16, 115.44, 110.60, 85.60, 37.70, 33.64, 26.25.

General procedure for the preparation of N-substituted diazabicyclo derivatives 4. Et_3N (0.0168 mol) were added to compounds **3** (0.007 mol) in THF (30 mL) at 0–7 °C. Acyl chloride (0.01 mol) was added to the mixture and reaction monitored by TLC. The reaction was quenched with water and product extracted into ethyl acetate. The solution subsequently washed with sat. NH_4Cl aq, sat. Na_2CO_3 aq, and water. The organic phase was dried over anhydrous $MgSO_4$. After remove the solvent under reduced pressure, the products **4** were crystallized from EtOH and light petroleum. The physical and spectra data of the compounds **4a–m** were as follows:

N-Phenoxyacetyl-5-methyl-2-oxo-1,6-diazabicyclo[3.3.0]octane (4a). Transparent crystal. Yield 62%. m.p.136–138 °C. IR (KBr, cm^{-1}) *v*: 3043–2898 (C–H), 1656, 1706 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 7.29–7.27 (m, 2H, Ar–H), 7.00–6.91 (m, 3H, Ar–H), 4.57 (s, 2H, Ph–O–CH_2–),

4.22–3.23 (m, 4H, N–$(CH_2)_2$–N), 2.66–2.33 (m, 4H, C–$(CH_2)_2$–C═O), 1.64 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 175.52, 165.38, 157.67, 129.74, 129.74, 121.94, 121.94, 114.53, 84.13, 68.34, 45.72, 39.33, 33.88, 32.17, 23.25; MS (ESI) *m/z*: 275 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (%): C 65.68; H 6.61; N 10.21. Found: C 65.63; H 6.59; N 10.18.

Crystal data for compound 4a. $C_{15}H_{18}N_2O_3$, monoclinic, space group *Pc*, a = 8.3504(17) Å, b = 19.872(4) Å, c = 8.5986(17) Å, V = 1426.8(5) Å^3, β = 90.39(3) °, Z = 4, D_c = 1.277 g/cm^3, μ = 0.090 mm^{-1}, $F(000)$ = 584. Independent reflections were obtained in the range of $3.08° < \theta < 27.48°$, 4534. The final least-square cycle gave R_1 = 0.0573, ωR_2 = 0.1345 for 3412 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.290 and -0.224 e/Å^3, respectively. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC1532313. These data can be obtained free of charge from The Cambridge Crystallographic Data *via* http://www.ccdc.cam.ac.uk/data_request/cif

N-Phenoxyacetyl-6-methyl-9-oxo-1,5-diazabicyclo[4.3.0] nonane (4b). White solid. Yield 71%. m.p.104–106 °C. IR (KBr, cm^{-1}) *v*: 3054–2858 (C–H), 1689 1677, (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.29–6.89 (m, 5H, Ar-H), 4.68–4.47 (m, 2H, Ph–O–CH_2–), 4.08–2.92 (m, 4H, N– CH_2–C–CH_2–N), 2.65–2.20 (m, 4H, C–$(CH_2)_2$–C═O), 1.83–1.79 (m, 2H, N–C–CH_2–C–N), 1.58 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 173.16, 168.02, 157.63, 129.69, 129.69, 121.87, 114.52, 114.52, 84.14, 68.53, 41.70, 34.77, 33.88, 29.19, 22.93, 21.17; MS (ESI) *m/z*: 289 $[M + H]^+$. Anal. Calcd. for C16H20N2O3 (%): C 66.65; H 6.99; N 9.72. Found: C 66.61; H 7.03; N 9.76.

N-Phenoxyacetyl-3a-methyl-decahydro-1H-benzo[d]pyrrolo [1,2-a]imidazol-1-one (4c). White solid. Yield 68%. m. p.158–160 °C. IR (KBr, cm^{-1}) *v*: 3071–2890 (C–H), 1720 1664, (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.32–7.27 (m, 2H, Ar–H), 7.00–6.89 (m, 3H, Ar–H), 4.67–4.61 (m, 2H, Ph–O–CH_2–), 4.44–4.12 (m, 2H, N–CH–CH–N), 2.69–2.06 (m, 4H, C–$(CH_2)_2$–C═O), 2.06–1.43 (m, 8H, N–$(CH_2)_4$–N), 1.71 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 175.71, 165.76, 157.76, 129.75, 129.75, 121.95, 114.49, 114.49, 84.75, 67.89, 58.29, 52.60, 37.21, 32.65, 25.63, 25.63, 24.89, 17.74, 17.74; MS (ESI) *m/z*: 329 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{24}N_2O_3$ (%): C 69.49; H 7.37; N 8.53. Found: C 69.52; H 7.33; N 8.49.

N-Phenoxyacetyl-6-methyl-2-oxo-1,7-diazabicyclo[4.3.0] nonane (4d). White solid. Yield 63%. m.p. 166–167 °C. IR(KBr, cm^{-1}) *v*: 2955–2888 (C–H), 1645, 1645 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.29–6.91 (m, 5H, Ar–H), 4.59 (s, 2H, Ph–O–CH_2–), 3.73–3.04 (m, 4H, N–CH_2–CH_2–N), 2.46–1.87, 1.55–1.49 (m, 6H, C–$(CH_2)_3$–C═O), 1.61 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 167.78, 165.66. 157.69, 129.70, 129.70, 121.86, 114.56, 114.56, 78.81, 68.51, 43.46, 40.27, 32.97, 30.64, 22.24, 17.62; MS (ESI) *m/z*: 289 $[M + H]^+$. Anal. Calcd. for $C_{16}H_{20}N_2O_3$ (%): C 66.65; H 6.99; N 9.72. Found: C 66.69; H 6.94; N 9.70.

N-Phenoxyacetyl-6-methy-2-oxo-1,7-diazabicyclo[4.4.0] decane (4e). White solid. Yield 50%. m.p. 93–95 °C. IR (KBr, cm^{-1}) *v*: 3027–2878 (C–H), 1651, 1640 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.32–6.98 (m, 5H, Ar–H), 4.50 (s, 2H, Ph–O–CH_2–), 3.64–3.31 (m, 4H, N–CH_2–C–CH_2–N), 2.51–2.14, 1.70–1.66 (m, 8H, C–CH_2–C–CH_2–C═O, N–C–CH_2–C–N, C–CH_2–C–C═O), 1.92 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 171.67, 168.38, 157.48, 129.70, 129.70, 121.88, 114.82, 114.82, 67.36, 67.26, 38.06, 35.26, 35.26, 31.83, 29.25, 19.36, 19.16; MS (ESI) *m/z*: 303 $[M + H]^+$. Anal. Calcd. for $C_{17}H_{22}N_2O_3$ (%): C 67.53; H 7.33; N 9.26. Found: C 67.50; H 7.31; N 9.30.

4a–Methyl-5-(N-phenoxyacetyl)-decahydro-benzo[4,5]imidazo [1,2-a]pyridin-1-one (4f). White solid. Yield 55%. m.p. 161–162 °C. IR (KBr, cm^{-1}) *v*: 3064–2865 (C–H), 1723, 1641 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.30–7.29 (m, 2H, Ar–H), 7.02–6.91 (m, 3H, Ar–H), 4.72–4.65 (m, 2H, Ph–O–CH_2–), 4.42–4.20 (m, 2H, N–CH–CH–N), 2.46–2.09 (m, 4H, −CH_2–C–CH_2–C═O), 1.77–1.41 (m, 13H, N–$(CH_2)_4$–N, O═C–C–CH_2–C, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 168.63, 166.82, 157.71, 129.68, 129.68, 121.84, 114.48, 114.48, 79.71, 68.47, 54.58, 54.58, 33.71, 30.15, 27.02, 27.02, 25.90, 25.90, 24.77, 18.00; MS (ESI) *m/z*: 343 $[M + H]^+$. Anal. Calcd. for $C_{20}H_{26}N_2O_3$ (%): C 70.15; H 7.65; N 8.18. Found: C 70.20; H 7.61; N 8.21.

N-Phenoxyacetyl-3a-methyl-2,3,3a,4-tetrahydro-1H-benzo [d]pyrrolo[1,2-a]imidazol-1-one (4g). Yellow solid. Yield 35%. m.p. 160–163 °C. IR (KBr, cm^{-1}) *v*: 2987–2914 (C–H), 1720, 1680 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 7.63–7.41 (m, 4H, Ph–H), 7.13–6.94 (m, 5H, Ar–H), 4.93 (s, 2H, Ph–O–CH_2–), 3.12–2.57 (m, 4H, C–$(CH_2)_2$–C═O), 1.72 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 173.22, 164.57, 157.64, 129.74, 129.74, 125.24, 125.24, 124.78, 124.78, 122.11, 122.11, 116.90, 114.81, 114.81, 88.43, 67.91, 36.13, 33.40, 22.91; MS (ESI) *m/z*: 323 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (%): C 70.79; H 5.63; N 8.69. Found: C 70.77; H 5.59; N 8.68.

N-Acetoxychloroacetyl-5-methyl-2-oxo-1,6-diazabicyclo[3.3.0] octane (4h). White solid. Yield 50%. m.p. 98–100 °C. IR (KBr, cm^{-1}) *v*: 2981–2889 (C–H), 1750, 1698, 1653 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ: 4.54–4.49 (m, 2H, −CO–CH_2–O), 3.62–3.61 (m, 4H, N–CH_2–CH_2–N), 2.73–2.35 (m, 4H, C–$(CH_2)_2$–C═O), 2.16 (s, 3H, O═C–CH_3), 1.61(s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ: 175.56, 170.47, 163.81, 84.07, 61.67, 45.06, 39.17, 33.77, 32.14, 23.39, 20.53; MS (ESI) *m/z*: 241 $[M + H]^+$. Anal. Calcd. for $C_{11}H_{16}N_2O_4$ (%): C 54.99; H 6.71; N 11.66. Found: C 54.95; H 6.73; N 11.61.

***N*-Acetoxychloroacetyl-6-methyl-9-oxo-1,5-diazabicyclo[4.3.0] nonane (4i).** White solid. Yield 68%. m.p. 106–108 °C. IR (KBr, cm^{-1}) *v*: 2998–2875 (C–H), 1746, 1691, 1665 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.65–4.55 (m, 2H, −CO–CH_2–O), 3.53–2.93 (m, 4H, N–CH_2–C–CH_2–N), 2.69–2.33 (m, 4H, C–$(CH_2)_2$–C═O), 2.15 (s, 3H, O═C–CH_3), 1.82–1.78 (m, 2H, N–C–CH_2–C–N), 1.61 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 172.93, 170.07, 167.31, 85.00, 62.85, 36.55, 34.63, 28.94, 25.57, 23.82, 22.81, 20.76; MS (ESI) *m/z*: 255 $[M + H]^+$. Anal. Calcd. for $C_{12}H_{18}N_2O_4$ (%): C 56.68; H 7.13; N 11.02. Found: C 56.73; H 7.08; N 11.08.

***N*-Acetoxychloroacetyl-7-methyl-10-oxo-1,6-diazabicyclo[5.3.0] decane (4j).** White solid. Yield 46%. m.p. 97–98 °C. IR (KBr, cm^{-1}) *v*: 2962–2881 (C-H), 1748, 1695, 1663 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.78–4.51 (m, 2H, −CO–CH_2–O), 4.06–2.88 (m, 4H, N–CH_2–C–C–CH_2–N), 2.45–2.14 (m, 4H, C–$(CH_2)_2$–C═O), 2.16 (s, 3H, O═C–CH_3), 1.79–1.48 (m, 2H, N–C–CH_2–CH_2–C–N), 1.61 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 175.08, 169.57, 167.08, 81.38, 62.72, 39.91, 38.78, 32.14, 25.99, 25.55, 23.99, 23.81, 20.71; MS (ESI) *m/z*: 269 $[M + H]^+$. Anal. Calcd. for $C_{13}H_{20}N_2O_4$ (%): C 58.19; H 7.51; N 10.44. Found: C 58.12; H 7.50; N 10.39.

***N*-Acetoxychloroacetyl-3a-methyl-decahydro-1H-benzo[d] pyrrolo[1,2-a]imidazol-1-one (4k).** White solid. Yield 48%. m.p. 116–119 °C. IR (KBr, cm^{-1}) *v*: 2997–2864 (C–H), 1747, 1689, 1666 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.54 (s, 2H, −CO-CH_2-O), 4.12 (s, 2H, N–CH–CH–N), 2.63–2.35 (m, 4H, C–$(CH_2)_2$–C═O), 2.10 (s, 3H, O═C–CH_3), 1.88–1.31 (m, 8H, N–C–$(CH_2)_4$–C–N), 1.61 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 175.71, 170.56, 164.24, 84.50, 61.58, 58.28, 52.55, 37.21, 32.65, 26.83, 26.14, 25.60, 20.54, 20.54, 17.57; MS (ESI) *m/z*: 295 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{22}N_2O_4$ (%): C 61.21; H 7.53; N 9.52. Found: C 61.26; H 7.58; N 9.57.

***N*-Acetoxychloroacetyl-6-methyl-2-oxo-1,7-diazabicyclo[4.3.0] nonane (4l).** White solid. Yield 63%. m.p. 156–158 °C. IR (KBr, cm^{-1}) *v*: 2981–2889 (C–H), 1745, 1698, 1662 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.61–4.55 (m, 2H, −CO–CH_2–O), 3.59–3.02 (m, 4H, N–CH_2–CH_2–N), 2.48–2.34 (m, 2H, O═C–CH_2–), 2.19 (s, 3H, O═C–CH_3), 1.92–1.90, 1.41 (m, 4H, O = C–C–CH_2–CH_2), 1.59 (s, 3H, CH_3–). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 170.50, 167.82, 164.06, 78.85, 61.91, 42.72, 40.11, 33.23, 30.66, 22.27, 20.56, 17.66; MS (ESI) *m/z*: 255 $[M + H]^+$. Anal. Calcd. for $C_{12}H_{18}N_2O_4$ (%): C 56.68; H 7.13; N 11.02. Found: C 56.73; H 7.19; N 11.10.

***N*-Acetoxychloroacetyl-7-methy-11-oxo-1,6-diazabicyclo[5.4.0] undecane (4m).** White solid. Yield 41%. m.p. 107–110 °C. IR (KBr, cm^{-1}) *v*: 2960–2855 (C–H), 1756, 1653, 1653 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): *δ*: 4.83–4.53 (m, 2H, −CO–CH_2–O), 3.43–2.95 (m, 4H, N–CH_2–C–C–CH_2–N), 2.44–2.42 (m, 2H, O═C–CH_2–), 2.18 (s, 3H, O═C–CH_3), 2.31–2.24, 2.07 (m, 2H, O = C–C–C–CH_2), 1.94 (s, 3H, CH_3–), 1.87–1.55 (m, 6H, O═C–C–CH_2, N–C–CH_2–CH_2–C–N). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): *δ*: 171.00, 169.63, 167.11, 63.07, 63.07, 44.11, 42.75, 40.67, 38.61, 31.87, 26.74, 24.78, 20.82, 19.37; MS (ESI) *m/z*: 283 $[M + H]^+$. Anal. Calcd. for $C_{14}H_{22}N_2O_4$ (%): C 59.56; H 7.85; N 9.92. Found: C 59.50; H 7.78; N 9.90.

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