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Syntheses and characterizations of 2-nitrobenzaldehyde amino acid Schiff base reductive amination compounds

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Condensation of 2-nitrobenzaldehyde with five amino acid compounds (valine, glycine, leucine, aspartic acid, and glutamic acid) gives the corresponding Schiff bases, which upon treatment with sodium borohydride afford the reductive amination products **1**−**5**. Compounds **1**−**5** have been well characterized by FT-IR and ^{1}H NMR spectroscopic techniques, in addition to X-ray crystallography, from which the structure of compound **2** has been established. Compound **2** crystallizes in monoclinic space group $P2_1/c$, with a = 12.215(8), b = 8.096(5), c = 10.608(7) Å, β = 115.324(7), and Z = 4.

Keywords: 2-Nitrobenzaldehyde, Amino acid, Schiff base, Reductive amination, X-ray structure

2-Nitrobenzaldehyde, as an important intermediate for synthesizing drugs for treating cardiovascular and cerebrovascular diseases, has a good market prospect and is one of the most valuable organic intermediates to be developed at present[1,2]. For examples, interactions of 2-nitrobenzaldehyde with pyrrolidine and iron pentacarbonyl formed the quinazoline mixture, 3-arylquinolines could be synthesized from 2-nitrobenzaldehyde and β-nitroethenes, such heterocyclic compounds have a wide range of biological activities, such as anti-tumor, anti-endotoxin, anti-fungal and analgesic properties[3,4]. On the other hand, studies have shown that Schiff base compounds containing CH=N groups have certain bactericidal, anticancer and antitumor effects[5,6]. Therefore, the study of Schiff base compounds derived from 2-nitrobenzaldehyde and amino acids will be another hot spot in biochemistry and medicine research.

In the field of catalysis, amino acids are natural and cheap chiral sources, and some amino acid derivatives are widely used in asymmetric catalysis of various organic reactions[7,8]. For instance, the amino acid-derived Schiff base Co(II) complex has been used as a catalyst to selectively oxidize primary and secondary alcohols, benzoin derivatives and furans into corresponding aldehydes and ketones with excellent yield and short reaction time[9]. Moreover, the amino acid Schiff base complexes usually have a large conjugated system, which makes it have a certain fluorescence and thus be used as a fluorescent probe or a fluorescent sensor[10,11]. Herein we present syntheses of a series of 2-nitrobenzaldehyde amino acid Schiff base reductive amination compounds, of which one structure was characterized by single crystal X-ray diffraction analysis.

Experimental Section

General procedure

Ethyl acetate, petroleum ether and anhydrous ethanol were obtained from Nanjing Chemical Reagent Co., Ltd. L-valine, L-glycine, L-leucine, L-aspartic acid, L-glutamic acid, sodium ethoxide (98%) and sodium borohydride (98%) were purchased from Alfa Aesar Ltd. 2-Nitrobenzaldehyde was prepared according to the literature report[12]. Dichloromethane (AR) was purified by standard procedure. Infrared spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer with use of pressed KBr pellets. NMR spectra were recorded on a Bruker ALX 400 Plus spectrometer operating at 400 MHz for ^{1}H relative to TMS. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN analyzer.

General synthetic route for 2-nitrobenzaldehyde amino acid Schiff base reductive amination products

Amino acid (3.3 mmol), sodium hydroxide (2 M, 2.5 mL, 5 mmol) solution, 2-nitrobenzaldehyde

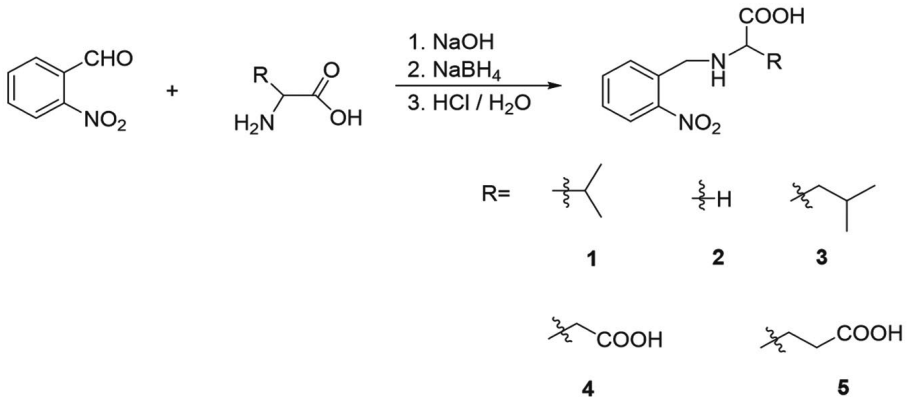
(0.41 g, 2.7 mmol) and ethanol (7.5 mL) was added to the two-neck flask and the mixture was stirred at RT for 30 min. After that, the mixture was cooled to 0℃ in an ice bath, and sodium borohydride (0.06 g, 1.6 mmol) was added to the reaction solution in batches, and the temperature was controlled to be lower than 5℃ during this process. Then the mixture was stirred at RT for 90 min. Subsequently, another part of 2-nitrobenzaldehyde (0.08 g, 0.55 mmol) in ethanol solution (2.5 mL) was added and stirred for 20 min. Eventually, sodium borohydride (0.010 g, 0.40 mmol) was added in batches, the reaction temperature was still controlled below 5°C, and the mixture was stirred at RT for additional 45 min. The reaction mixture was extracted with diethyl ether, and the water layer was filtered and adjusted *p*H value by concentrated hydrochloric acid (Scheme 1, Table 1).

2-Nitrobenzyl)valine, 1: ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.90 (d, 1H, *J* = 8.0 Hz, Ar−*H*), 7.67 (d, 2H, *J* = 8.0 Hz, Ar−*H*), 7.53−7.50 (m, 1H, Ar−*H*), 4.06−4.02 (d, *J* = 16 Hz, 1H, −N*H*), 3.80−3.76 (d, *J* = 16 Hz, 2H, −CH_2), 2.77−2.75 (d, *J* = 8.0 Hz, 1H, −C*H*NH), 1.84−1.79 (m, 1H, −C*H*$(CH_3)_2$), 0.86−0.83 (m, 6H, −CH_3); IR (KBr): 3440, *v*(N−H), 2967, *v*(C−H), 1607, *v*(COO−), 1515, *v*(−NO_2), 1456, *v*(C−N), 1399, *v*(COO−), 1358, *v*(−NO_2), 1325–983, *δ*(C−H), 840, *v*(C−N), 792–670 cm^{-1} (C−H).

2-Nitrobenzyl)glycine, 2: ^{1}H NMR (400 MHz, DMSO−d_6): δ 7.90 (d, 1H, *J* = 8.0 Hz, Ar−*H*), 7.72−7.65 (m, 2H, Ar−*H*), 7.50−7.46 (m, 1H, Ar−*H*), 3.91 (s, 2H, CH_2Ar), 2.77 (s, 2H, CH_2COOH); IR (KBr disc, cm^{-1}): 3318, *v*(N−H), 2920, 2845, *v*(C−H), 1613, *v*(COO−), 1527, *v*(NO_2), 1432, *v*(C−N), 1337, *v*(NO_2), 1185, *δ*(C−H), 858, *v*(C−N), 792−724 cm^{-1} (C−H).

2-Nitrobenzyl)leucine, 3: ^{1}H NMR (400 MHz, DMSO−d_6): δ 7.90 (d, 1H, *J* = 8.0 Hz, Ar−*H*), 7.67−7.65 (m, 2H, Ar−*H*), 7.53−7.50 (m, 1H, Ar−*H*), 4.08−4.04 (d, 1H, *J* = 16 Hz, N*H*), 3.82−3.78 (m, 2H, CH_2NH), 3.03−3.00 (m, 1H, C*H*COOH), 1.73−1.70 (m, 1H, C*H*$(CH_3)_2$), 1.35−1.32 (m, 2H, CH_2CH), 0.84−0.75 (dd, *J* = 28.4, 6.4 Hz, 6H, CH_3); IR (KBr): 3437, *v*(N−H), 2958, 2866, *v*(C−H), 1610, *v*(COO–), 1527, *v*(NO_2), 1456, *v*(C−N), 1405, *v*(COO–), 1349, *v*(NO_2), 1307−1027, *δ*(C−H), 843, *v*(C−N), 795−676 cm^{-1} (C−H).

2-Nitrobenzyl)aspartic acid, 4: ^{1}H NMR (400 MHz, DMSO−d_6): δ 7.96 (d, 1H, *J* = 8.0 Hz, Ar−*H*),



Scheme 1 — Synthesis of 2-nitrobenzaldehyde amino acid Schiff base reductive amination products 1−5

Table 1 — Physical characterization and elemental analysis of 2-nitrobenzaldehyde amino acid Schiff base reductive amination products

Compd	Mol. formula	Yield (%)	Elemental analysis					
			C (%)		H (%)		N (%)	
			Calcd	Found	Calcd	Found	Calcd	Found
1	$C_{12}H_{16}O_4N_2$	92	57.14	57.12	6.35	6.20	11.11	11.23
2	$C_9H_{10}O_4N_2$	87	51.43	51.40	4.76	4.69	13.33	13.35
3	$C_{13}H_{18}O_4N_2$	96	58.65	58.32	6.77	6.55	10.53	10.67
4	$C_{11}H_{12}O_6N_2$	88	49.25	49.12	4.48	4.51	10.45	10.47
5	$C_{12}H_{14}O_6N_2$	90	51.06	51.13	4.96	4.92	9.93	9.89

7.74−7.70 (m, 2H, Ar−*H*), 7.55−7.51 (m, 1H, Ar−*H*), 4.16−4.12 (m, 1H, N*H*), 4.01 (m, 1H, C*H*NH), 3.97 (m, 2H, CH_2NH), 2.63−2.57 (m, 2H, CH_2COOH); IR (KBr): 3443, ν(N−H), 2994, ν(C−H), 1715, ν(C=O), 1590, ν(COO−), 1524, ν(NO_2), 1465, ν(C−N), 1405, ν(COO−), 1340, ν(NO_2), 1262−947, δ(C−H), 887, ν(C−N), 864−649 cm^{-1} C−H).

2-Nitrobenzyl)glutamic acid, 5: ^{1}H NMR (400 MHz, DMSO−d_6): δ 8.04−7.41 (m, 4H, Ar−*H*), 4.08−4.04 (m, 1H, N*H*), 3.87−3.84 (m, 2H, CH_2NH), 3.08−3.06 (m, 1H, C*H*), 2.30−2.27 (m, 2H, CH_2CH), 1.82−1.70 (m, 2H, CH_2COOH); IR (KBr): 3440, ν(N−H), 3041, ν(C−H), 1703, ν(C=O), 1596, ν(COO−), 1533, ν(NO_2), 1441, ν(C−N), 1423, ν(COO−), 1349, ν(NO_2), 1259–941, δ(C−H), 858, ν(C−N), 813–667 cm^{-1} (C−H).

X-ray crystallography

A summary of crystallographic data and experimental details for (2-nitrobenzyl)glycine (**2**) are summarized in Table 2. Partial bond lengths (Å) and angles (°) of (2-nitrobenzyl)glycine (**2**) are summarized in Table 3. Intensity data were collected on a Bruker SMART APEX 2000 CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) at 296(2) K. The collected frames were processed with the software SAINT[13]. The data were corrected for absorption using the program SADABS[14]. Structures were solved by the direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL software packages[15,16]. All non-hydrogen atoms were refined anisotropically. The positions of all hydrogen atoms were generated geometrically (C$_{sp3}$–H = 0.96 and C$_{sp2}$–H = 0.93 Å), assigned isotropic thermal parameters, and allowed to ride on their respective parent carbon or nitrogen atoms before the final cycle of least-squares refinement.

Results and Discussion

A number of compounds of reduced Schiff base-amino acids have been reported before. The copper(II) complexes of reduced Schiff base N-(2-hydroxybenzyl)-amino acids show significant catalytic activity on the oxidation of 3,5-di-tert-butylcatechol[17]. The reduced Schiff base ligands N-(2-pyridylmethyl)-amino acids derived from substituted 2-pyridinealdehyde, form a class of

Table 2 — Crystallographic data and details for compound (2-nitrobenzyl)glycine (**2**)

Compound	**2**
Empirical formula	$C_9H_{10}N_2O_4$
Formula weight	210.19
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	12.215(8)
b (Å)	8.096(5)
c (Å)	10.608(7)
α (°)	90
β (°)	115.324(7)
γ (°)	90
V (Å^3)	948.3(11)
Z	4
D_{calc} (g cm^{-3})	1.472
Temperature (K)	296(2)
F(000)	440
μ(Mo-Kα) (mm^{-1})	0.118
Total refln	5719
Independent refln	2148
R_{int}	0.0283
Parameter	144
$R1$[a], $wR2$[b] ($I > 2\sigma(I)$)	0.0579/0.1641
$R1$[a], $wR2$[b] (all data)	0.0834/0.1878
GoF[c]	1.061
Final max/min difference peaks, e·Å^{-3}	0.561/ –0.237

[a] $R1 = ||F_o| - |F_c||/|F_o|$

[b] $wR2 = [w(|F_o^2| - |F_c^2|)^2/w|F_o^2|^2]^{1/2}$

[c] GoF = $[w(|F_o| - |F_c|)^2/(N_{obs} - N_{param})]^{1/2}$

Table 3 — Partial bond lengths (Å) and angles (°) of (2-nitrobenzyl)glycine (**2**)

Bond	Bond length (Å)	Bond	Bond length (Å)
O(1)–N(2)	1.210(2)	N(1)–C(8)	1.479(2)
O(2)–N(2)	1.203(3)	N(1)–C(7)	1.495(3)
O(3)–C(9)	1.247(2)	N(2)–C(1)	1.473(3)
O(4)–C(9)	1.236(2)	C(2)–C(7)	1.509(3)
Bond	Angles (°)	Bond	Angles (°)
C(8)–N(1)–C(7)	112.74(16)	N(1)–C(7)–C(2)	112.51(16)
O(2)–N(2)–O(1)	122.5(2)	N(1)–C(8)–C(9)	112.61(16)
O(2)–N(2)–C(1)	118.3(2)	O(4)–C(9)–O(3)	125.99(18)
O(1)–N(2)–C(1)	119.1(2)	O(4)–C(9)–C(8)	118.23(17)
C(6)–C(1)–N(2)	115.73(19)	O(3)–C(9)–C(8)	115.77(17)

multidentate ligands with flexible backbone useful in constructing interesting supramolecular structures[18]. In this paper, the research on the synthesis of the reduced Schiff base compounds derived from substituted 2-nitrobenzaldehyde also have a lot of potential applications. Based on the literature method[20], the preparation of compounds **1**−**5** is shown in Scheme 1. Condensation of 2-nitrobenzaldehyde with valine, glycine, leucine, aspartic acid, and glutamic acid gave corresponding Schiff bases, which upon treatment with sodium borohydride afforded the reductive amination products **1**−**5** in good to high yields (87%~96%). In the ^{1}H NMR spectra of the compounds **1**−**5**, it was found that the benzene ring proton signals were found in the region δ 8.04−7.41. The chemical shift of ArCH_2NH protons appeared at around δ 3.80. A typical ^{1}H NMR spectrum of compound **2** is given in Fig. 1. In the IR spectra of the compounds **1**−**5**, the peaks in the range of 3443−3318 cm^{-1} and 3041−2845 cm^{-1} were assigned to be ν(COO−H/N−H) and ν(C−H) groups, respectively. The peaks in the range of 1703−1715 cm^{-1} and 1613−1590 cm^{-1} could be ascribed for ν(C=O) and ν(C=C) moieties[21]. The peaks of 1533−1515 cm^{-1}, 1465−1432 cm^{-1} and 1423−1399 cm^{-1}, are assignable to $\nu(NO_2)$, ν(C−N) and ν(C=O) groups, respectively. Moreover, the bands in the range of 864−649 cm^{-1} are assignable to δ(C−H)[22]. A typical IR spectrum of compound **2** is given in Fig. 2.

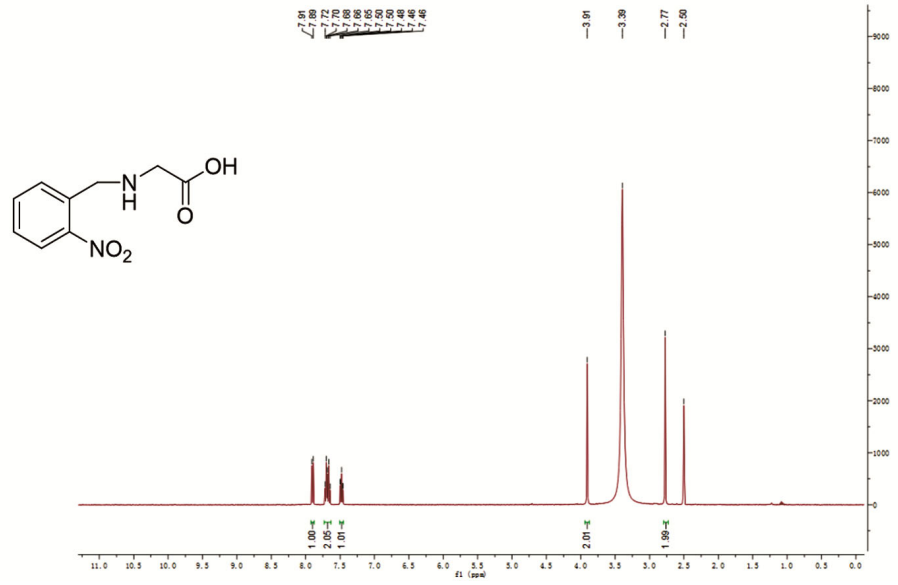


Fig. 1 — ^{1}H NMR of spectrum of compound **2**

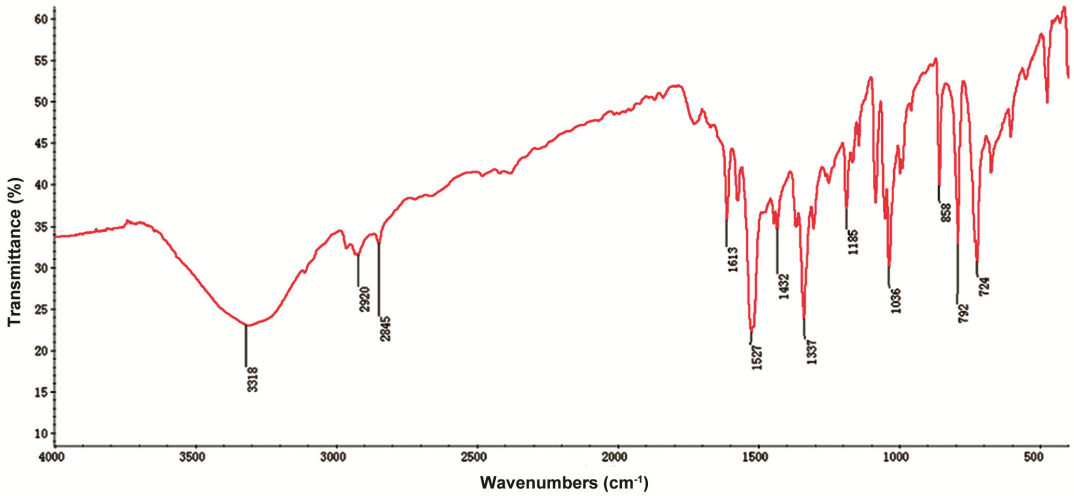


Fig. 2 — IR spectrum of compound **2**

Molecular structure of (2-nitrobenzyl)glycine (**2**) was further confirmed by X-ray crystallography, as shown in Fig. 3a. Selected bond lengths and angles are given in Table 2. Compound **2** crystallizes in the monoclinic space group $P2_1/c$. The bond length of N(1)–C(7) is 1.490(3) Å, indicative of its single bond character as a result of reductive amination. The bond lengths of C(9)–O(3) and C(9)–O(4) in carboxylic group are 1.242(3) and 1.239(3) Å, respectively, suggesting its good π-electron delocalized system. Similarly, the two N=O bonds of nitro group are 1.210(3) and 1.204(3) Å, respectively. The bond angles of O2−N2−O1, O4−C9−O3, and C8−N1−C7 are 122.9(2)°, 126.1(2)°, and 113.27(17)°, respectively, suggesting their according sp^2 and sp^3 hybrid orbitals. The bond angle of N1−C8−C9 is 112.20(18)°, similar to that in the similar compounds *N*-(*p*-nitrobenzyl) iminodiacetic acid (*ca.* 109.0°)[23] and *N*-(4-carboxybenzyl)iminodiacetic acid (*ca.* 112.4°)[24]. The dihedral angle of N−C−C skeleton plane of amino acids and benzene ring plane is 34.59°. In the stacking diagram of (2-nitrobenzyl)glycine (**2**), intermolecular hydrogen bonds are observed (Fig. 3b). One is connected by N−H…O intermolecular hydrogen bonds with N…O distance of 2.735(3) Å and ∠N−H…O of 171(3)°. The other is O−H…N intermolecular hydrogen bond with the O…N distance of 2.712(3) Å and ∠O−H…N bond angle of 174.7°.

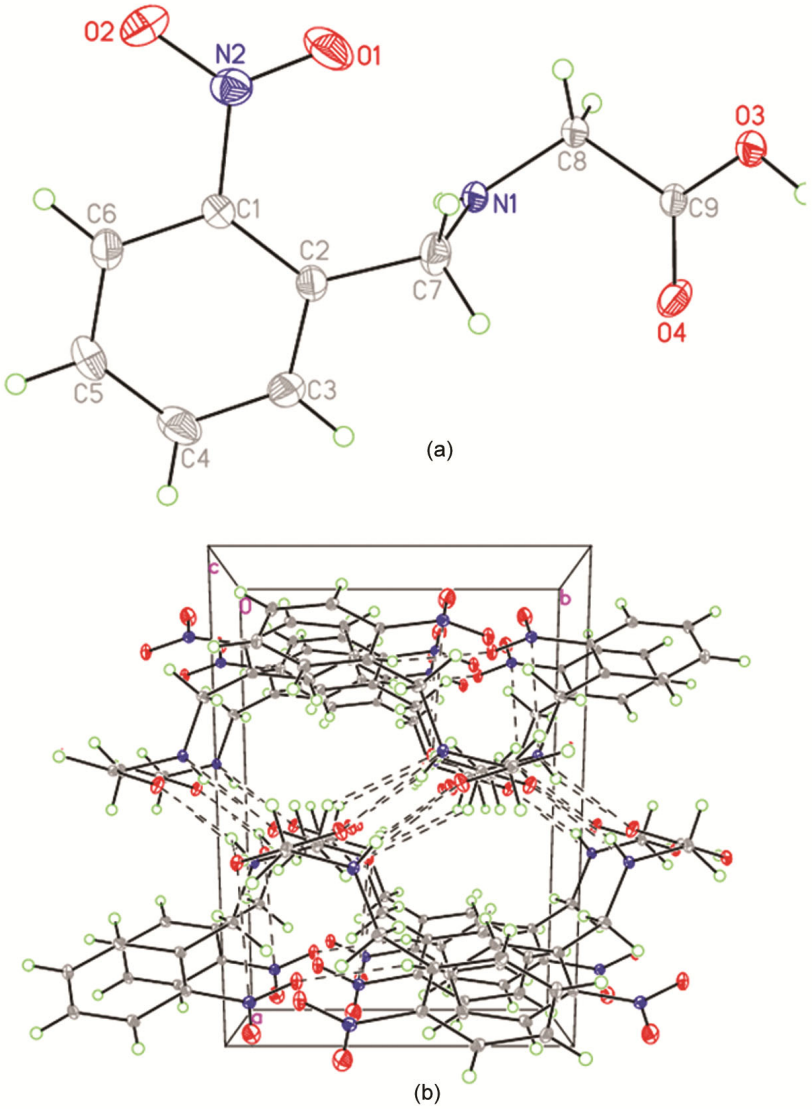


Fig. 3 — (a) Structure of (2-nitrobenzyl)glycine (**2**) showing the atom-labelling scheme of one molecule in the asymmetric unit. Hydrogen atoms are shown as small spheres of arbitrary radii and (b) packing structure of compound **2**, viewed along the *c* axis. Dashed lines indicate N−H···O and O−H···N hydrogen bonds

Conclusion

In summary, five new 2-nitrobenzaldehyde amino acid Schiff base reductive amination compounds were synthesized in a one-pot reaction with good to high yields (87%~96%), starting from 2-nitrobenzaldehyde, amino acid and sodium borohydride. Strong intermolecular hydrogen bonds of N−H…O and O−H…N were observed in such molecules with O…N distances being of about 2.72 Å. The dihedral angle of N−C−C skeleton plane of amino acid moiety and benzene ring is 34.59°. The coordination behaviour of such multi-dentate ligands to form stable transition metal complexes with special properties is underway in our lab.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Crystallographic data for (2-nitrobenzyl)glycine **2** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2131505. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1233-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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