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ORIGINAL PAPER

Highly regio- and diastereoselective synthesis of oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles, based on a post-Ugi condensation: joint experimental and computational study

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Abstract
A novel series of oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles were synthesized via a two-step pathway. In the first step, Ugi-four-component condensation of 2-formylindole, amines, (*E*)-4-alkoxy-4-oxobut-2-enoic acids, and isocyanides gave the corresponding Ugi-adducts. This adduct underwent intramolecular hydroamination in the presence of K_2CO_3 in CH_3CN at room temperature to afford diastereoselective synthesis of a range of oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles. A comparison of experimentally observed CD and UV–visible spectra with the theoretical DFT calculated ECD spectra was used to predict the major diastereomer.

Keywords Ugi reaction · 2-Formylindole · Multicomponent reaction · *α,β*-Unsaturated acids · Cyclization · Intramolecular hydroamination · DFT · ECD spectra

Introduction

Rapid access to molecular complexity, diversity, and, in particular, regioselectivity and stereoselectivity from simple starting materials is significantly useful in organic synthesis and drug discovery [1–6]. Multicomponent reactions (MCRs) offer a powerful tool to complexity-generating approach to readily conversion of three or more starting materials into a single product in an atom- and step-economical way in a one-pot manner. In recent decade, MCRs have offered an opportunity for the synthesis of various highly functionalized compounds. MCRs are an important synthetic strategy, since they allow easy access to numerous libraries of organic products including those that comprise various functional groups [7–9]. In this regard, combining an MCR with an already established post-MCR transformation, typically a cyclization process, has been proven to be a powerful strategy to generate highly functionalized heterocyclic compounds [10]. Nevertheless, the efficiency of these sequential MCRs/post-MCRs processes, generally leading to single framework of various heterocyclic systems. This limitation can be accredited to the discouraging challenge fronting current synthesis for accomplishing the high levels of region and stereoselectivity [11].

Thus, the power of the MCR/post-transformation sequence should be reinforced using the linear MCR-adduct, which upon cyclization giving various and divergent heterocyclic framework. The Ugi-4CR is by far one of the most fruitful multicomponent reactions resulted in high structural diversity and molecular complexity. Remarkably, the Ugi-4CR gives majorly a linear peptide scaffold, which can be used in several sequential reactions, the so-called post-Ugi transformations comprising cyclization of Ugi-4CR products leading into the construction of various heterocyclic systems, especially for the purpose of drug discovery [12]. In Ugi-four-component reaction, a wide range of commercially available or easily

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accessible starting materials, namely aldehydes, amines, isocyanides, and carboxylic acids, are used to provide a large library of acyclic Ugi-adducts [13, 14]. Post-condensation reactions of these Ugi-adducts offer a particularly effective sequential reaction for the formation of diverse complex products, including an extensive range of heterocyclic systems [8, 15–21]. Natural and synthetic heterocyclic compounds bearing indole motifs have attracted considerable interest from both structural and biological points of view [22, 23]. Post-condensation reactions of Ugi-4CR adducts give several biologically important heterocycles which was screened being proven to act as antidepressant [24–26], anti-bacterial [27–31], anti-inflammatory [32] and being analgesics, etc [33].

Indole is one of the most projecting and important moiety heterocyclic systems in natural products and pharmaceutical compounds [34]. In addition, it is a privileged synthon from the point of view of diversity, since there are at least three reactive sites in its structure. A plethora of indole derivatives exhibiting diverse biologically activities have been synthesized via MCRs [35].

In 2015, the importance and diversity of post-Ugi-4CRs for the construction of a divergently oriented heterocyclic systems has been extensively reviewed [12]. We are interested in heterocyclic chemistry [36–45] and reported the synthesis of several heterocyclic systems via MCRs [46–53]. We have also recently reported the synthesis of various heterocyclic systems via the appropriate post-Ugi-adducts reaction [54–58]. Herein, we wish to report a transition metal-free catalyzed and highly region- and diastereoselective approach towards the synthesis of oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles.

Experimental

Chemicals

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Melting points are uncorrected. IR spectra were recorded on an FT-IR Tensor 27 Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz Spectrometer in DMSO-d_6 as solvent. A Leco CHNS, model 932 was used for elemental analysis. All products were characterized using IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy and elemental analysis (see Electronic Supplementary Information (ESI).

General procedure

General procedure for the synthesis of Ugi-adduct 3a–j

To a stirred solution of 2-formylindole (1 mmol) and amine (1 mmol) in MeOH (5 mL), carboxylic acid (1 mmol) and then isocyanide (1 mmol) at reflux were added. The reaction process was monitored by TLC. After 24 h, the residue was filtered and washed with methanol and Et_2O. The solid was dried collected as pure product and used for further reactions.

General procedure for synthesis of oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles 4a–j

A mixture of Ugi product **5** (1 mmol) and K_2CO_3 (0.5 mmol) in dry CH_3CN (5 mL) was stirred at room temperature for 7–12 h. After completion of reaction (checked by TLC), water (20 mL) was added to the reaction mixture and it was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography using ethyl acetate/petroleum ether = 1/3 as eluent and silica gel as stationary phase.

Spectral data

(*E*)-Methyl 4-(2(cyclohexylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl) (*p*-tolyl)amino)-4-oxobut-2-enoate (tolyl) amino)-4-oxobut-2-enoate (3a)

White powder, m.p.: 228–231 °C; FT-IR (KBr): ν_{max} = 3391, 3270, 3090, 2926, 2850, 1729, 1653, 1612, 1564, 1451, 1251, 1175, 1091, 792, 733 cm$^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.45 (m, 10H), 2.12 (s, 3H), 3.66 (m, 1H,), 3.68 (s, 3H), 5.88 (d, J = 12.0 Hz, 1H), 6.09 (s, 1H), 6.26 (d, J = 12.0, 1H), 7.09 (m, 8H), 8.10 (d, J = 7.7 Hz, 1H), 10.99 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 20.6, 24.6, 25.3, 32.2, 48.2, 51.7, 57.9, 102.9, 111.2, 118.7, 119.9, 121.1, 124.5, 127.1, 128.8, 129.5, 132.5, 135.8, 136.4, 137.2, 165.3, 165.9, 166.9 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_4$: C, 71.01; H, 6.60; N, 8.87; found: C, 71.18; H, 6.41; N, 8.79.

(*E*)-methyl 4-(2-(cyclohexylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl)(3-methoxyphenyl)amino)-4-oxo-but−2-enoate (3b)

White powder, m.p.: 187–190 °C; FT-IR (KBr): ν_{max} = 3292, 3082, 2928, 2850, 1731, 1652, 1598, 1489, 1417, 1222, 1169, 1038, 789, 736 cm$^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.85 (m, 10H), 3.50 (s, 3H), 3.66 (m, 1H), 3.68 (s, 3H), 5.90 (d, J = 12.0 Hz, 1H), 6.10 (s, 1H), 6.26 (s, 1H), 6.32 (d, J = 12.0 Hz, 1H), 6.99 (m, 8H), 8.11 (d, J = 7.8 Hz, 1H), 10.99 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.7, 25.2, 32.2, 48.2, 51.7, 54.9, 57.9, 103.1, 111.2, 113.9, 115.5, 118.7, 119.9, 121.2, 122.1, 124.7, 127.1, 128.7, 132.3, 135.6, 136.2, 139.9, 158.7, 165.1, 165.9, 166.9 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58; found C, 68.45; H, 6.19; N, 8.47.

(*E*)-Methyl 4-(2-(cyclohexylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl)(4-methoxyphenyl)amino)-4-oxo-but-2-enoate (3c)

White powder, m.p.: 224–227 °C; FT-IR (KBr): ν_{max} = 3288, 3082, 2927, 2850, 1731, 1648, 1617, 1509, 1414, 1240, 1170, 796, 740 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.46 (m, 10H), 3.60 (s, 3H), 3.66 (m, 1H), 3.69 (s, 3H), 5.88 (d, J = 12.0 Hz, 1H), 6.09 (s, 1H), 6.24 (s, 1H), 6.29 (d, J = 12.0 Hz, 1H), 6.99 (m, 8H), 8.08 (d, J = 7. 8 Hz, 1H), 10.97 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.6, 25.2, 32.2, 48.2, 51.7, 55.0, 57.8, 102.9, 111.2, 113.2, 118.7, 119.9, 121.1, 124.2, 127.2, 130.9, 131.5, 132.5, 136.1, 136.2, 158.4, 165.5, 165.9, 166.9 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58; found: C, 68.54; H, 6.45; N, 8.48.

(*E*)-Methyl 4-(4-chlorophenyl)(2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)amino)-4-oxo-but-2-enoate (3d)

White powder, m.p.: 240–244 °C; FT-IR (KBr): ν_{max} = 3294, 3086, 2927, 2851, 1731, 1649, 1559, 1490, 1410, 1241, 1094, 782, 741 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.43 (m, 10 H), 3.69 (s, 3H), 5.92 (d, J = 12.0 Hz, 1H), 6.10 (s, 1H), 6.28 (s, 1H), 6.32 (d, J = 12.0 Hz, 1H), 6.10 (m, 8H), 8.16 (d, J = 7.8 Hz, 2H), 11.02 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.5, 25.2, 32.2, 48.2, 51.7, 57.7, 103.1, 111.2, 118.8, 120.0, 121.3, 124.8, 127.1, 128.1, 131.6, 132.1, 135.7, 136.2, 137.9, 165.1, 165.7, 166.9 ppm; elemental analysis: calcd for $C_{27}H_{28}ClN_3O_4$: C, 65.65; H, 5.71; N, 8.51; found: C, 65.53; H, 5.65; N, 8.59.

(*E*)-Ethyl-4-(4-chlorophenyl)(2-(cyclohexyl-amino(-1-(1*H*-indol-2-yl)-2-oxoethyl)-amino)-4-oxo-but-2-enoate (3e)

White powder, m.p.: 240–243 °C; FT-IR (KBr): ν_{max} = 3296, 3088, 2979, 2851, 1725, 1650, 1561, 1490, 1416, 1231, 1179, 1094, 1018, 963, 783 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.44 (m, 13H), 3.65 (m, 1H), 4.15 (m, 2H), 5.90 (d, J = 12.Hz, 1H), 6.11 (s, 1H), 6.30 (d, J = 12.0 Hz, 2H), 7.11 (m, 8H), 8.18 (d, J = 7.6 Hz, 1H), 11.02 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 13.9, 24.6, 25.2, 32.2, 48.2, 57.7, 60.5, 103.1, 111.3, 118.8, 120.0, 121.3, 125.1, 127.1, 128.1, 131.7, 132.1, 132.5, 135.7, 136.3, 137.9, 165.2, 165.3, 166.9 ppm; elemental analysis: calcd for $C_{28}H_{30}ClN_3O_4$: C, 66.20; H, 5.95; N, 8.27; found: C, 66.32; H, 5.75; N, 8.36.

(*E*)-Ethyl 4-(2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)(*p*-tolyl)amino)-4-oxobut-2-enoate (3f)

White powder, m.p.: 218–221 °C; FT-IR (KBr): ν_{max} = 3294, 3092, 2926, 2853, 1728, 1651, 1617, 1567, 1418, 1223, 1022, 737, 675 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.46 (m, 13H), 2.13 (s, 3H), 3.67 (m, 1H), 4.15 (m, 2H), 5.86 (d, J = 12.0 Hz, 1H), 6.09 (s, 1H), 6.26 (d, J = 12.0 Hz, 1H), 7.08 (m, 8H), 6.72 (s, 1H), 8.10 (d, J = 7.84 Hz, 1H), 10.96 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 13.9, 20.6, 24.6, 25.2, 32.2, 48.2, 57.9, 60.4, 102.9, 111.2, 118.7, 119.9, 121.1, 124.6, 127.1, 128.7, 129.5, 132.5, 135.9, 136.4, 137.3, 165.4, 165.4, 166.9 ppm; elemental analysis: calcd for $C_{29}H_{33}N_3O_4$: C, 71.44; H, 6.82; N, 8.62; found: C, 71.53; H, 6.71; N, 8.53.

(*E*)-ethyl 4-(benzyl (2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)amino)-4-oxobut-2-enoate (3g)

White powder, m.p.: 139–142 °C; FT-IR (KBr): ν_{max} = 3291, 3073, 2928, 2851, 1725, 1652, 1599, 1419, 1217, 1034, 738, 686 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.42 (m, 13H), 3.18 (m,1H), 3.45 (m, 1H), 3.82 (d, J = 15.2 Hz, 1H,), 4.14 (m, 2H), 5.27 (d, J = 12.0 Hz, 1H), 5.35 (s, 1H), 5.55 (d, J = 12.0 Hz, 1H), 6.47 (s, 1H), 7.27 (m, 9H), 8.52 (d, J = 7.6 Hz, 1H), 10.98 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 13.9, 24.2, 25.1, 31.7, 32.2, 40.4, 48.3, 53.9, 57.8, 60.5, 97.7, 109.6, 119.2, 120.6, 121.6, 127.6, 128.0, 128.6, 129.5, 134.1, 1360, 136.9, 166.7, 167.3, 170.4 ppm; elemental analysis: calcd for $C_{29}H_{33}N_3O_4$: C, 71.44; H, 6.82; N, 8.62; found: C, 71.48; H, 6.74; N, 8.53.

(*E*)-Isopropyl4-(4-chlorophenyl)(2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)-amino)-4-oxo-but-2-enoate (3h)

White powder, m.p.: 210–213 °C; FT-IR (KBr): ν_{max} = 3357, 3296, 3086, 2927, 2851, 1721, 1653, 1558, 1416, 1232, 1099, 830, 741 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.12 (m, 3H), 1.22 (d, J = 6.3 Hz, 3H,), 1.24 (d, J = 6.3 Hz, 3H,), 1.28 (m, 2H), 1.68 (m, 5H), 3.66 (m, 1H), 4.95 (m, 1H), 5.87 (s, J = 12.0 Hz, 1H), 6.93 (s, 1H), 6.26 (d, J = 12.0 Hz, 2H), 7.11 (m, 8H), 8.17 (d, J = 7.8 Hz, 1H,) 11.00 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.4, 24.7, 25.2, 32.2, 48.1, 57.6, 68.1, 103.1, 111.3, 118.8, 119.9, 121.3, 125.4, 127.1, 128.1, 131.7, 132.1, 132.5, 135.6, 136.3, 137.9, 164.8, 165.2, 166.8 ppm; elemental analysis: calcd for $C_{29}H_{32}ClN_3O_4$: C, 66.72; H, 6.18; N, 8.05; found: C, 66.65; H, 6.24; N, 8.16.

(*E*)-Isopropyl 4-(2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)(*p*-tolyl)amino)-4-oxobut-2-enoate (3i)

White powder, m.p.: 205–208 °C; FT-IR (KBr): ν_{max} = 3285, 3053, 2929, 2853, 1723, 1652, 1614, 1555, 1417, 1223, 1147, 1223, 1147, 798, 737 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.47 (m, 16H), 2.13 (s, 3H,), 3.66 (m, 1H), 4.95 (m, 1H), 6.09 (d, J = 12 Hz, 1H), 6.24 (s, 1H), 6.26 (d, J = 12.0 Hz, 2H,), 7.10 (m, 8H), 8.10 (d, J = 7. 9 Hz, 1H), 10.94 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6):

20.7, 21.3, 24.6, 24.7, 25.3, 48.3, 68.1, 102.9, 111.3, 118.7, 119.9, 121.1, 124.8, 126.5, 127.2, 129.7, 132.5, 135.9, 136.4, 137.3, 164.9, 165.5, 166.9 ppm; elemental analysis: calcd for $C_{30}H_{35}N_3O_4$: C, 71.83; H, 7.03; N, 8.38; found: C, 71.74; H, 7.12; N, 8.47.

(*E*)-isopropyl4-(2-(cyclohexyl-amino)-1-(1*H*-indol-2-yl)-2-oxoethyl)(4-methoxyphenyl)amino)-4-oxobut-2-enoate (3j)

White powder, m.p.: 200–203 °C; FT-IR (KBr): ν_{max} = 3289, 3252, 2929, 2851, 1719, 1650, 1510, 1419, 1225, 1022 798, 740 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.13 (m, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 6.3 Hz, 3H), 1.28 (m, 2H), 1.69 (m, 5H), 3.60 (s, 3H), 4.95 (m, 1H), 6.08 (s, 1H), 5.82 (d, J = 12.0 Hz, 1H), 6.08 (s, 1H), 6.26 (d, J = 12.0 Hz, 2H), 6.99 (m, 8H), 8.09 (d, J = 7.9 Hz, 1H), 10.94 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.4, 24.7, 25.3, 32.2, 48.1, 55.1, 57.7, 68.0, 102.9, 111.2, 113.2, 118.7, 121.1, 124.5, 127.15, 130.8, 131.5, 136.16, 158.5, 165.7, 166.9 ppm; elemental analysis: calcd for $C_{30}H_{35}N_3O_5$: C, 69.61; H, 6.82; N, 8.12; found: C, 69.72; H, 6.71; N, 8.23.

Methyl 2-(1-(cyclohexylcarbamoyl)-3-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-4-yl)-acetate (4a)

White powder, m.p.: 212–215 °C; FT-IR (KBr): ν_{max} = 3337, 3061, 2924, 2854, 1724, 1686, 1651, 1512, 1423, 1267, 1023, 802, 745 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.36 (m, 10H), 2.35 (s, 3H), 3.15 (m, 1H), 3.45 (m, 2H), 3.67 (s, 3H), 5.58 (m, 1H), 5.66 (s, 1H), 6.55 (s, 1H), 7.37 (m, 8H), 8.50 (d, J = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.1, 24.6, 25.5, 32.6, 48.7, 52.4, 54.9, 62.2, 98.1, 110.0, 120.9, 122.2, 127.0, 128.5, 130.2, 134.7, 137.6, 138.9, 167.6, 167.8, 171.4 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_4$: C, 71.01; H, 6.60; N, 8.87; found: C, 71.12; H, 6.51; N, 8.76.

Methyl 2-(1-(cyclohexylcarbamoyl)-2-(3-methoxy phenyl)-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*] -indol-4-yl)acetate (4b)

White powder, m.p.: 206–209 °C; FT-IR (KBr): ν_{max} = 3350, 3058, 2927, 2852, 1765, 1719, 1683, 1599, 1490, 1431, 1281, 1170, 1091, 1045, 777, 743, 695, 617 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.45 (m, 10 H), 3.15 (m, 1H), 3.45 (m, 1H), 3.60 (m, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 5.60 (m, 1H), 5.70 (s, 1H), 6.55 (s, 1H), 7.24 (m, 8H), 8.53 (d, J = 8.0 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.6, 25.5, 32.0, 32.6, 48.7, 52.4, 55.0, 55.8, 62.0, 62.1, 98.1, 110.0, 112.8, 113.8, 119.2, 120.9, 121.2, 122.3, 128.5, 130.2, 134.7, 142.6, 160.2, 167.8, 171.4 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58; found: C, 68.51; H, 6.47; N, 8.49.

Methyl 2-(1-(cyclohexylcarbamoyl)-2-(4-methoxy phenyl)-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*] indol-4-yl)acetate (4c)

White powder, m.p.: 185–189 °C; FT-IR (KBr): ν_{max} = 3350, 3056, 2923, 2852, 1727, 1689, 1650, 1540, 1512, 1451, 1183, 1028, 982, 793, 745 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.42 (m, 10H), 3.152 (m, 1H), 3.67 (s, 2H), 3.67 (s, 3H), 3.79 (s, 3H), 5.57 (m, 1H), 5.72 (s, 1H), 6.61 (s, 1H), 7.32 (m, 8H), 8.71 (d, J = 8.0 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.7, 25.5, 32.1, 32.6, 48.7, 52.4, 54.9, 62.3, 98.3, 109.9, 114.8, 120.9, 121.2, 122.1, 128.5, 128.5, 130.4, 134.1, 134.6, 158.9, 167.8, 171.4 ppm; elemental analysis: calcd for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58; found: C, 68.61; H, 6.43; N, 8.44.

Methyl-2-(2-(4-chlorophenyl)-1-(cyclohexyl-carbamoyl)-3-oxo-1,2,3,4-tetrahydropyrazino-[1,2-*a*] indol-4-yl)acetate (4d)

White powder, m.p.: 157–160 °C; FT-IR (KBr): ν_{max} = 3388, 3352, 3064, 2926, 2852, 1714, 1683, 1576, 1453, 1371, 1282, 1095, 778, 740 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.43 (m, 10H), 3.15 (m, 1H), 3.45 (m, 2H), 3.68 (s, 3H), 5.61 (m, 1H), 5.71 (s, 1H), 6.57 (s, 1H), 7.38 (m, 8H), 8.54 (d, J = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.6, 25.5, 31.2, 32.1, 32.6, 48.7, 52.4, 54.9, 62.0, 98.3, 110.0, 120.9, 121.2, 122.3, 128.5, 129.1, 129.9, 132.5, 134.7, 140.2, 167.6, 167.8, 171.3 ppm; elemental analysis: calcd for $C_{27}H_{28}ClN_3O_4$: C, 65.65; H, 5.71; N, 8.51; found: C, 65.74; H, 5.63; N, 8.40.

Ethyl-2-(2-(4-chlorophenyl)-1-(cyclohexyl-carbamoyl)-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]- indol-4-yl)acetate (4e)

White powder, m.p.: 117–120 °C; FT-IR (KBr): ν_{max} = 3342, 3293, 3061, 2927, 2852, 1749, 1689, 1550, 1454, 1368, 1238, 1214, 1041, 702, 613 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.22 (m, 13H), 1.74 (m, 2H), 3.00 (m, 1H), 4.14 (m, 2H), 5.62 (m, 1H), 5.80 (s, 1H), 6.63 (s, 1H), 7.39 (m, 8H), 8.73 (d, J = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.6, 25.5, 25.6, 32.5, 32.8, 48.8, 54.9, 61.1, 61.9, 98.4, 110.0, 120.7, 121.2, 122.2, 128.5, 129.1, 129.7, 130.1, 132.5, 134.7, 140.2, 167.1, 167.9, 170.9 ppm; elemental analysis: calcd for $C_{28}H_{30}ClN_3O_4$: C, 66.20; H, 5.95; Cl, 6.98; N, 8.27; found: C, 66.33; H, 5.82; N, 8.35.

Ethyl-2-(1-(cyclohexylcarbamoyl)-3-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-4-yl) -acetate (4f)

White powder, m.p.: 163–166 °C; FT-IR (KBr): ν_{max} = 3340, 3057, 2925, 2855, 1720, 1687, 1651, 1513, 1419, 1257, 1108, 807, 746 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.44 (m, 13H), 2.30 (s, 3H), 3.11 (m, 1H), 3.40 (m, 1H), 3.51 (m, 1H), 4.14 (m, 2H), 5.59 (m, 1H), 5.70 (s, 1H), 6.59 (s, 1H), 7.37 (m, 8H), 8.57 (d, *J* = 8.0 Hz, 1H,) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.1, 24.6, 25.5, 32.6, 40.9, 48.7, 54.9, 61.0, 62.2, 98.2, 110.1, 121.2, 122.2, 126.9, 128.5, 130.3, 134.7, 137.6, 138.9, 167.7, 167.9, 171.0 ppm; elemental analysis: calcd for $C_{29}H_{33}N_3O_4$: C, 71.44; H, 6.82; N, 8.62; found: C, 71.56; H, 6.70; N, 8.50.

Ethyl 2-(2-benzyl-1-(cyclohexylcarbamoyl)-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]-indol-4-yl) -acetate (4g)

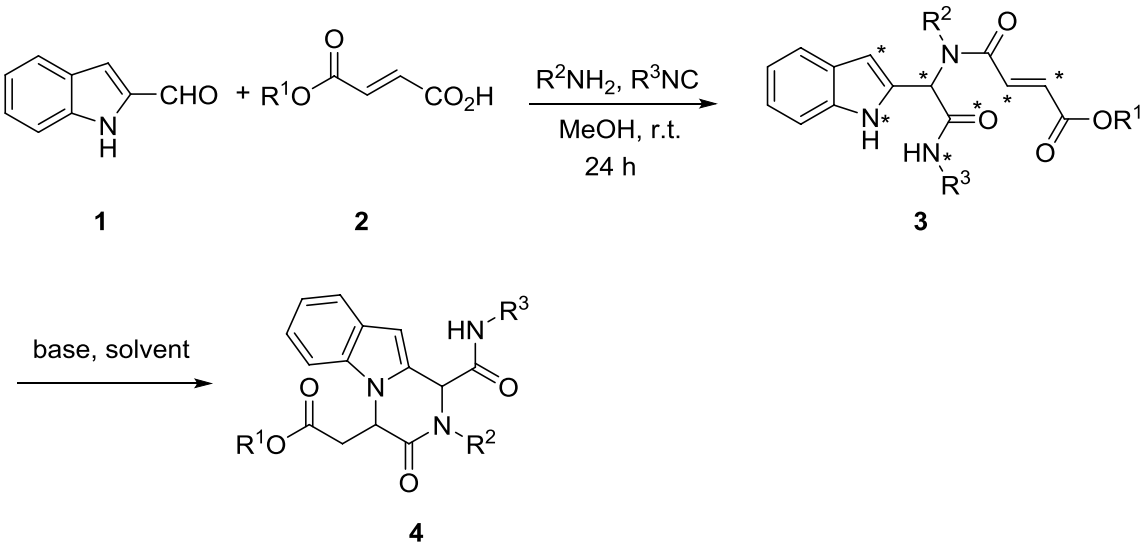
White powder, m.p.: 143–146 °C; FT-IR (KBr): ν_{max} = 3353, 3053, 2932, 2855, 1719, 1690, 1660, 1536, 1455, 1293, 1217, 1166, 1080, 960, 738, 704 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.50 (m, 10H), 3.03 (m, 3H), 3.48 (m, 1H), 3.84 (m, 3H), 4.15 (m, 2H), 5.29 (m, 1H), 5.37 (s, 1H), 5.57 (m, 1H), 6.49 (s, 1H), 7.33 (m, 9H), 8.54 (d, *J* = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 14.5, 24.6, 25.6, 32.1, 32.7, 48.8, 54.4, 58.2, 61.0, 98.1, 110.05, 120.8, 122.1, 128.1, 128.4, 129.1, 129.9, 134.6, 136.4, 167.1, 167.7, 170.9 ppm; elemental analysis: calcd for $C_{29}H_{33}N_3O_4$: C, 71.44; H, 6.82; N, 8.62; found: C, 71.37; H, 6.94; N, 8.50.

Isopropyl-2-(2-(4-chlorophenyl)-1-(cyclohexyl-carbamoyl)-3-oxo-1,2,3,4-tetrahydropyrazino-[1,2-*a*]-indol-4-yl)acetate (4h)

White powder, m.p.: 129–132 °C; FT-IR (KBr): ν_{max} = 3334, 3060, 2928, 2854, 1726, 1687, 1546, 1491, 1421, 1255, 1101, 1018, 824, 667 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.81 (m, 16H), 3.05 (m, 1H), 3.42 (m, 2H), 4.97 (m, 1H), 5.62 (m, 1H), 5.73 (s, 1H), 6.59 (s, 1H), 7.37 (m, 8H), 8.59 (d, *J* = 7.6 Hz, 1H,) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.8, 24.6, 25.5, 31.2, 32.1, 32.6, 41.2, 48.8, 54.9, 61.9, 68.5, 98.3, 110.1, 121.2, 122.2, 128.5, 129.1, 129.9, 132.5, 134.7, 140.2, 167.6, 167.9, 170.5 ppm; elemental analysis: calcd for $C_{29}H_{32}ClN_3O_4$: C, 66.72; H, 6.18; N, 8.05; found: C, 66.63; H, 6.27; N, 8.14.

Isopropyl2-(1-(cyclohexylcarbamoyl)-3-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-4-yl)-acetate (4i)

White powder, m.p.: 199–202 °C; FT-IR (KBr): ν_{max} = 3325, 3055, 2930, 2854, 1731, 1690, 1648, 1537, 1424, 1370, 1255, 1104, 783, 740 $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO): δ = 1.45 (m, 16H), 2.34 (s, 3H), 3.05 (m, 1H), 3.36 (m, 1H), 3.51 (m, 1H), 4.98 (m, 1H), 5.55 (m, 1H), 5.69 (s, 1H), 6.57 (s, 1H), 7.37 (m, 8H), 8.58 (d, *J* = 8.0 Hz, 1H,) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 21.1, 22.1, 24.62, 25.5, 32.1, 32.6, 41.3, 48.7, 54.9, 68.5, 98.1, 110.1, 121.2, 122.1, 126.9, 128.5, 130.3, 134.7, 137.5, 138.9, 167.9, 170.6 ppm; elemental analysis: calcd for $C_{30}H_{35}N_3O_4$: C, 71.83; H, 7.03; N, 8.38; found: C, 71.75; H, 7.15; N, 8.25.



Scheme 1 Synthesis of Ugi-adducts **3** and their post-regioselective cyclization to **4**

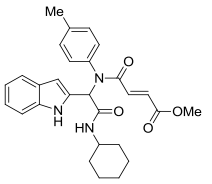
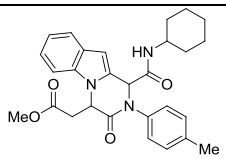
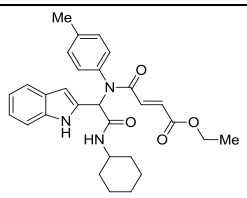
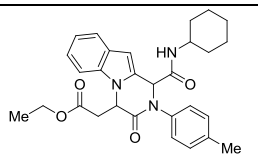
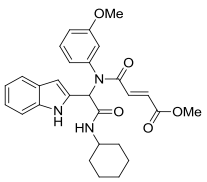
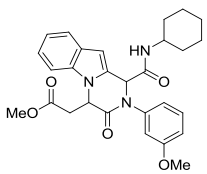
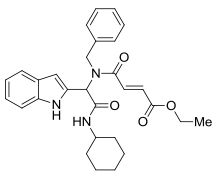
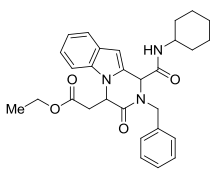
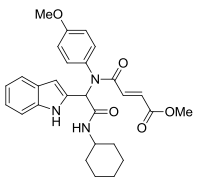
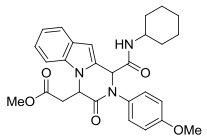
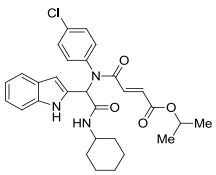
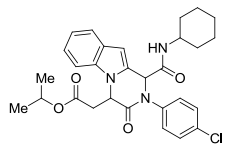
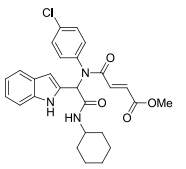
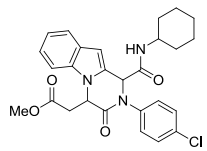
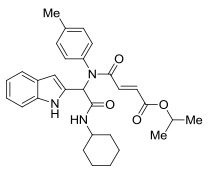
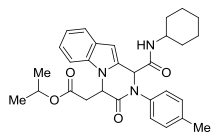
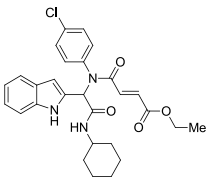
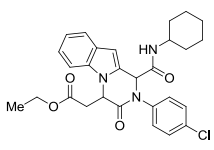
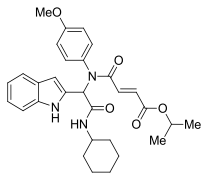
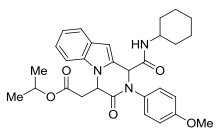
Isopropyl 2-(1-(cyclohexylcarbamoyl)-2-(4-methoxyphenyl)-3-oxo-1,2,3,4-tetrahydropyrazino-[1,2-*a*]indol-4-yl)acetate (4j)

White powder, m.p.: 187–190 °C; FT-IR (KBr): ν_{max} = 3369, 3318, 3065, 2980, 2931, 2854, 1725, 1689, 1656, 1512, 1454, 1369, 1246, 1104, 1032, 956, 787, 738, $cm^{-1;}$ ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.12 (m, 6H), 1.43 (m, 10H), 3.05 (m, 1H), 3.39 (m, 1H), 3.58 (m, 1H), 3.80 (s, 3H), 4.97 (m, 1H), 5.59 (m, 1H), 5.64 (s, 1H), 6.54 (s, 1H), 7.32 (m, 8H), 8.48 (d, *J* = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 22.1, 24.6, 25.5, 32.1, 32.6, 39.4, 39.6, 41.3, 48.7, 54.9, 55.9, 62.5, 68.5, 98.1, 110.1, 114.9, 120.9, 122.1, 128.5, 130.3, 134.2, 134.7, 158.9, 167.8, 167.9, 170.6 ppm; elemental analysis: calcd for $C_{30}H_{35}N_3O_5$: C, 69.61; H, 6.82; N, 8.12; found: C, 69.73; H, 6.70; N, 8.24.

Results and discussion

Initially, we synthesized Ugi-4CR product **3a** via the condensation of easily accessible 2-formylindole **1** with commercially available butenoic acid **2a**, *p*-toluidine toluidine, and cyclohexyl isocyanide as a model reaction. Expectedly, this reaction proceeded smoothly, at room temperature when MeOH was used as solvent to give the corresponding Ugi-adduct **3a** in high yield (Scheme 1, Table 1). It is worthwhile to mention, before finding the above-optimized

Table 1 Synthesis of Ugi-adducts **3a–j** and their post-regioselective cyclization to **4a–j**

Entry	Ugi-adducts 3	Products 4	Entry	Ugi-adducts 3	Products 4
1	 **3a**, 96%	 **4a**, 90%	6	 **3f**, 90%	 **4f**, 83%
2	 **3b**, 93%	 **4b**, 83%	7	 **3g**, 83%	 **4g**, 79%
3	 **3c**, 95%	 **4c**, 90%	8	 **3h**, 85%	 **4h**, 80%
4	 **3d**, 90%	 **4d**, 85%	9	 **3i**, 88%	 **4i**, 78%
5	 **3e**, 89%	 **4e**, 84%	10	 **3j**, 88%	 **4j**, 79%

reaction conditions, a series of experiments were conducted using different solvents in different temperature. The best results regarding the yields of products were obtained using MeOH as solvent at room temperature within 24 h. As shown in Table 1, the other derivatives of linear diamide **3** were prepared under the above-mentioned optimal reaction conditions.

We decided to attempt the cyclization process of **3**. In our delight, compound **4a** was formed in a basic media. For selection of base and solvent, we examined different bases such as K_2CO_3, Cs_2CO_3, DABCO, Na_2CO_3, NaOH, KO*t*-Bu, Et_3N, and pyridine in CH_3CN, DMF, and CH_2Cl_2 as solvent. Finally, we realized that K_2CO_3 in CH_3CN gives the best result in term of yields and rate of conversion at room temperature (Tables 1, 2, entry 1). As shown in with star Scheme 1, for Ugi-adduct **3**, it has five potential nucleophile positions and two potential electrophile positions which could form a mixture of different heterocycles. Surprisingly, the spectral analysis of isolated compound confirmed one diastereoisomer of methyl 2-(1-(cyclohexylcarbamoyl)-3-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-4-yl)acetate **4a**. This regioselective cyclization is probably achieved via the control of some elements such as the distinctive nucleophilicity and affinity of the reactive sites as well as size of ring in **4a** for different promoters provided by the deliberate choice of reaction conditions which allows the regioselective cyclizations to afford a definite, instead of diverse sets of heterocyclic compounds.

To find and optimize the selectivity and yield of the product **4a**, various reaction conditions were examined. Inorganic bases such as Na_2CO_3, Cs_2CO_3, NaOH, and KO*t*-Bu and organic bases as Et_3N, DABCO, and pyridine in different solvents did not give better results (Table 2, entries 1–10). Using $AlCl_3$ gave also **4a** but in low yield (Table 2, entry 11). Thus, various linear Ugi-4CR adducts were cyclized in the presence of K_2CO_3 in CH_3CN (Scheme 1).

To evaluate the scope and limitations of the reaction, all substrates **3** possessing electron-rich as well as electron-poor substituents underwent intramolecular hydroamination reaction leading to the formation of the related products **4** in 7–12 h and good yields (78–90%). As it is clear, compound **4a** has two chiral centers, and, thus, can be existed in four diastereomeric forms, as illustrated in Fig. 1.

All products were characterized using IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy and elemental analysis [see Electronic Supplementary Information (ESI)]. Next, we decided to go further and examine the diastereoselectivity of the above-mentioned reaction and determine the structure of the major diastereomer, using experimental and computational ECD spectra. The definition of electronic circular dichroism (ECD) is relatively specific for chiral molecules. There are no known reports for the characterization of non-chiral molecules using ECD. Although there were no chiral reagents used in this investigation, the computational ECD was used to predict the major diastereomer that will form, by comparison with the experimental CD study. Although the simulation of an ECD spectrum is not clearly documented [59], this technique to determine the relative configuration of asymmetric adducts is gaining popularity [60]. To determine the relative configuration of the reaction products, the ECD was calculated for the four possible diastereomers of **4a, 4g, 4i**, and **4j** using time-dependent density functional theory (TDDFT) to simulate the experimentally observed ECD spectrum [61, 62]. For this discussion, the details of the resolution of structure **4a** are presented. The possible diastereomers (Fig. 1) were constructed with the (*S,R*), (*R,S*), (*S,S*), and (*R,R*) absolute configurations and then optimized.

The experimental ECD measurements were carried out in acetonitrile. Hence, the self-consistent reaction field (SCRF) with polarizable continuum model (PCM) was used for the simulation of the solution state ECD spectra in acetonitrile [63]. A comparison of the experimentally measured CD for **4a** and the computed ECD spectra of the four possible diastereomers of **4a** are presented in Fig. 2. From the experimental CD, it can be seen that it is best matched with the solution state ECD spectrum of **4a″** (Fig. 2c). UV–visible spectrum of the experimental CD measurement as well as the ECD calculation were also compared (Fig. 3). Here, only the UV–visible spectrum of **4a″** is presented. As can be realized, there is a perfect match with the experimental UV–visible spectrum. The configuration of **4a** was also confirmed by X-ray crystallography (Fig. 4b, ESI). The crystallographic data of **4a**, calculated and experimental ECD and UV–visible spectra of **4g**, **4i** and **4j**, and the XYZ coordinates and all the optimized gas-phase structures are presented in the ESI.

Table 2 The effect of various conditions on the intramolecular hydroamination reaction of **3a**[a]

Entry	Base/acid	Solvent	Time (h)	Isolated yield (%) **4a**
1	K_2CO_3	CH_3CN	7	90
2	K_2CO_3	CH_2Cl_2	12	50
3	K_2CO_3	DMF	12	80
4	Cs_2CO_3	CH_3CN	5	–[b]
5	DABCO	DMF	12	20
6	Et_3N	DMF	12	–[b]
7	Na_2CO_3	DMF	12	20
8	Pyridine	DMF	12	20
9	NaOH	DMF	5	–[b]
10	K*t*OBu	DMF	5	–[b]
11	$AlCl_3$	CH_2Cl_2	12	20

[a]**3a** (0.5 mmol), promotor (0.5 mmol), solvent (5 mL) at room temperature

[b]Complex mixture of products

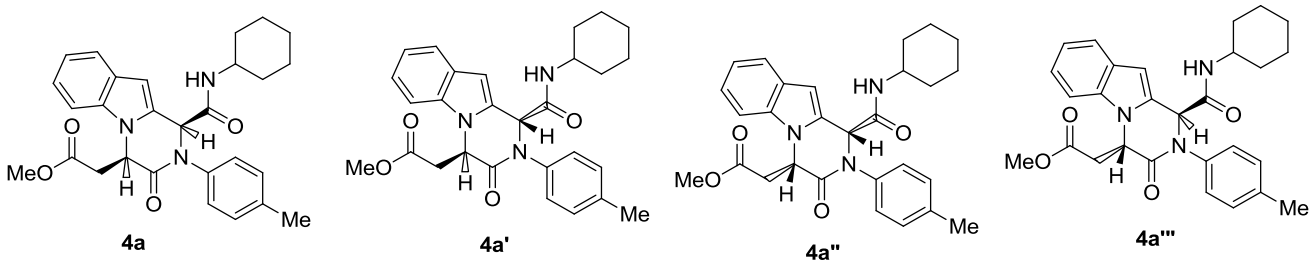


Fig. 1 The four possible diastereomers of **4a**

Furthermore, for comparison of the experimental and theoretical chemical shifts, the optimized geometry of compound **4a** in gas phase was re-optimized in DMSO at the same level of calculations. Calculated chemical shifts of methyl 2-(1-(cyclohexylcarbamoyl)-3-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-4-yl)-acetate **4a** are reported in spectral data section in the bracket. The good agreement between experimental and theoretical chemical shifts shows the reliability of DFT calculations for these series of molecules.

All calculations were performed using the Gaussian 98 [64] software. The geometry optimization of all studied compounds was performed employing a hybrid Hartree–Fock-density functional scheme, the adiabatic connection method-Becke three-parameter with Lee–Yang–Parr (B3LYP) functional of density functional theory (DFT)

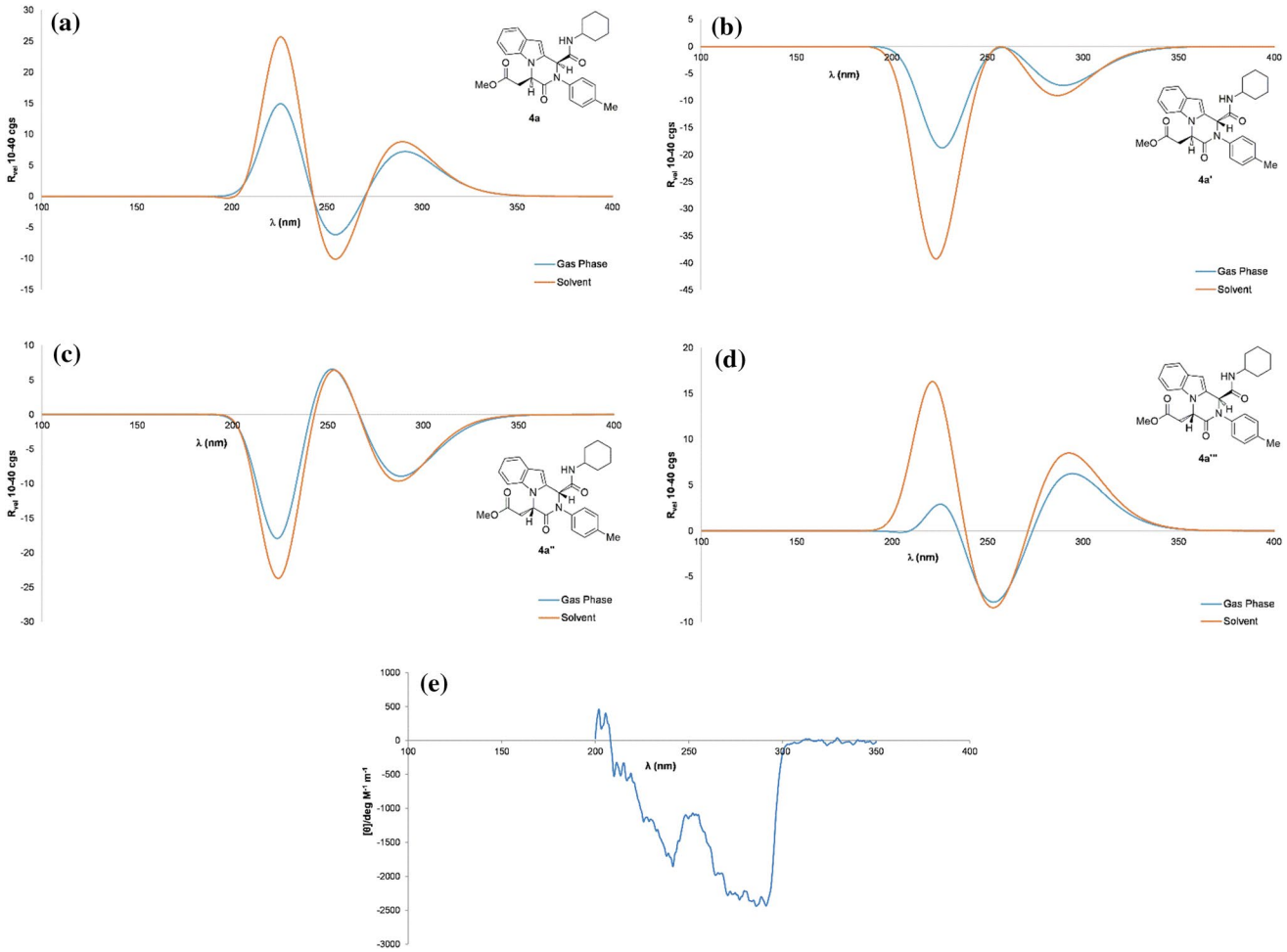


Fig. 2 **a**–**d** Calculated ECD spectra of the four possible diastereomers of **4a; e** Experimental CD of **4a**

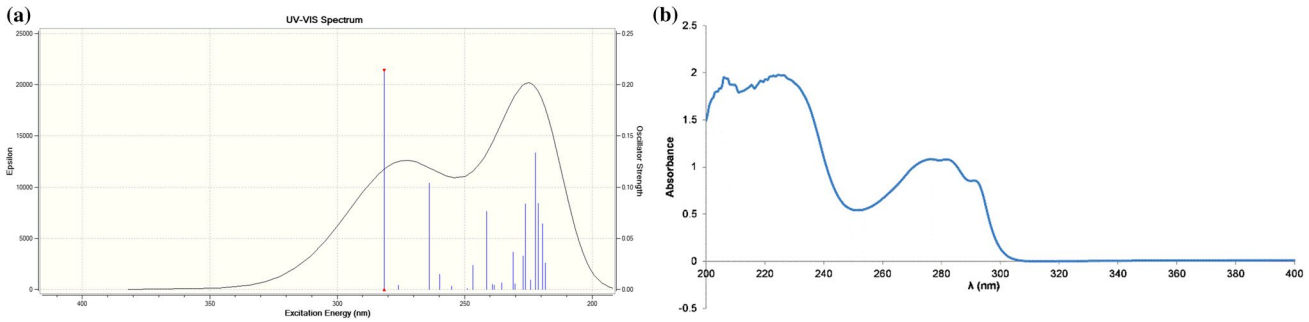


Fig. 3 **a** Calculated UV–visible spectrum of **4a″** in acetonitrile; **b** Experimental UV–visible spectrum of **4a**

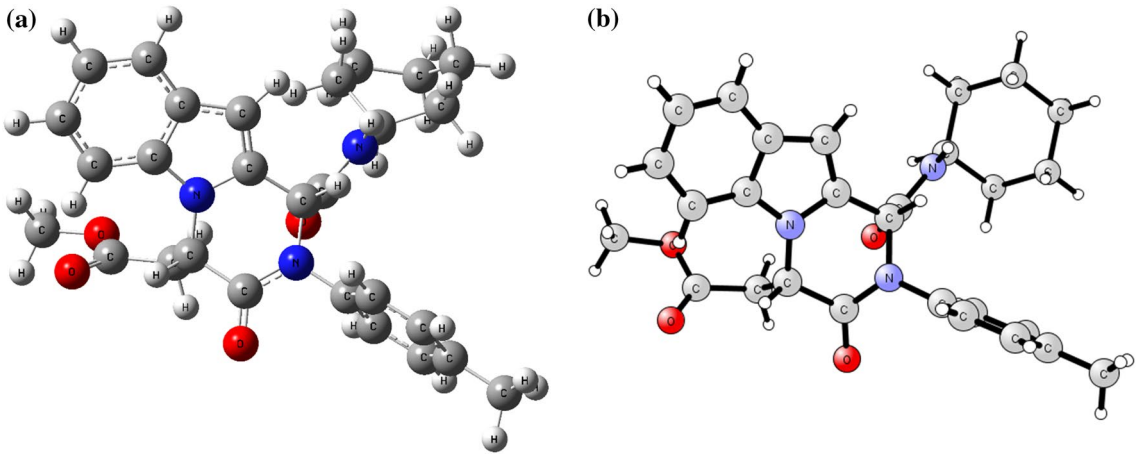


Fig. 4 **a** Optimized **4a″** in the gas phase; **b** X-ray structure of **4a**

using the Hartree–Fock-density functional scheme [65, 66] with the 6–311 + + G^{**} basis set. Full optimizations were performed without any symmetry constrains. Harmonic vibrational frequencies were computed to confirm that an optimized geometry correctly corresponds to a local minimum that has only real frequencies. The solvent effects on the conformational equilibrium were investigated with using polarized continuum (overlapping spheres) model (PCM) of Tomasi and co-workers [63] at the same level of calculations. Solvation calculations were carried out for acetonitrile and DMSO with the geometries optimization for these solvents.

NMR computations of absolute shielding were performed using the GIAO method [67] at the DFT optimized structure in present of solvent. The ^{1}H and ^{13}C chemical shifts were calculated using the corresponding absolute shielding calculated for Me_4Si at the same level of theory.

Conclusion

In conclusion, a two-step synthetic method for the synthesis of novel oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole derivatives is described via a convenient Ugi 4-CR of butenoic acids, 2-formylindole, amines, and isocyanides, followed by the selective intramolecular hydroamination cyclization in the presence of K_2CO_3 in CH_3CN at room temperature. Computational and experimental ECD and UV–visible spectroscopy were successfully used to predict the major diastereomer.

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References

1. B.M. Trost, Science **254**, 1471 (1991)
2. L.F. Tietze, Chem. Rev. **96**, 115 (1996)
3. P.A. Wender, S.T. Handy, D.L. Wright, Chem. Ind. **765**, 767 (1997)
4. S.L. Schreiber, Science **287**, 1964 (2000)
5. A. Dömling, I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
6. A. Domling, Chem. Rev. **106**, 17 (2006)
7. J.D. Sunderhaus, S.F. Martin, Chem. Eur. J. **15**, 1300 (2009)
8. B.B. Touré, D.G. Hall, Chem. Rev. **109**, 4439 (2009)
9. B. Ganem, Acc. Chem. Res. **42**, 463 (2009)
10. A. Váradi, T.C. Palmer, R.N. Dardashti, S. Majumdar, Molecules **21**, 19 (2016)
11. N.A. Afagh, A.K. Yudin, Angew. Chem. Int. Ed. **49**, 262 (2010)
12. U.K. Sharma, N. Sharma, D.D. Vachhania, E.V. Van der Eycken, Chem. Soc. Rev. **44**, 1836 (2015)
13. I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, Angew. Chem. **71**, 386 (1959)
14. I. Ugi, C. Steinbrückner, Angew. Chem. 72, 2671960 (1959)
15. J. Isaacson, Y. Kobayashi, Angew. Chem. Int. Ed. **48**, 1845 (2009)
16. A. Dömling, B. Beck, U. Eichelberger, S. Sakamuri, S. Menon, Q.-Z. Chen, Y. Lu, L.A. Wessjohann, Angew. Chem. Int. Ed. **45**, 7235 (2006)
17. M.J. Thompson, B. Chen, J. Org. Chem. **74**, 7084 (2009)
18. W. Erb, J.-P. Neuville, L. Zhu, J. Org. Chem. **74**, 3109 (2009)
19. D.G. Riveraa, L.A. Wessjohann, J. Am. Chem. Soc. **131**, 3721 (2009)
20. D. Coffinier, L. El Kaim, L. Grimaud, Org. Lett. **11**, 995 (2009)
21. L.A. Wessjohann, D.G. Rivera, O.E. Vercillo, Chem. Rev. **109**, 796 (2009)
22. G. Cuny, M. Bois-Choussy, J. Zhu, J. Am. Chem. Soc. **126**, 14475 (2004)
23. U.K. Sharma, N. Sharma, D.D. Vachhani, E.V. Van der Eycken, Chem. Soc. Rev. **44**, 1836 (2015)
24. A. Aygun, U. Pindur, Curr. Med. Chem. **10**, 1113 (2003)
25. F.R. deSa´Alves, E.J. Barreiro, C.A. Fraga, Med. Chem. **9**, 782 (2009)
26. M. Ishikura, K. Yamada, T. Abe, Nat. Prod. Rep. **27**, 1630 (2010)
27. R.J. Sundberg, *The Chemistry of Indoles* (Academic Press, New York, 1970)
28. R.J. Sundberg, in *Comprehensive Heterocyclic Chemistry*, ed. by A.R. Katritzky, C.W. Rees (Pergamon Press, Oxford, 1984), Vol. 4
29. J.A. Joule, E.J. Thomas, ed., *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*, vol. 10 (George Thieme Verlag, Stuttgart, 2000), Chap. 10
30. G.W. Gribble, in *Comprehensive Heterocyclic Chemistry II*, vol. 2, ed. by A.R. Katritzky, C.W. Ress, E.F.V. Scriven, C.W. Bird (Pergamon Press, Oxford, 1996), p. 207
31. R.J. Sundberg, *Indoles*, (Academic Press, London, 1996)
32. D. Zhou, P. Zhou, D.A. Evrard, K. Meagher, M. Webb, B.L. Harrison, D.M. Huryn, J. Golembieski, G.A. Hornby, L.E. Schechter, D.L. Smith, T.H. Andree, R.E. Mewshaw, Bioorg. Med. Chem. **16**, 6707 (2008)
33. J.D. Williams, S.T. Nguyen, S. Gu, X. Ding, M.M. Butler, T.F. Tashjian, T.J. Opperman, T.L. Bowlin, R.G. Panchal, S. Bavari, N.P. Peet, D.T. Moir, Bioorg. Med. Chem. Lett. **21**, 7790 (2013)
34. M.Z. Zhang, Q. Chen, G.F. Yang, Eur. J. Med. Chem. **89**, 421 (2015)
35. M. Shiri, Chem. Rev. **112**, 3508 (2012)
36. M.M. Heravi, T. Alishiri, Adv. Heterocycl. Chem. **113**, 1 (2014)
37. M.M. Heravi, B. Talaei, Adv. Heterocycl. Chem. **113**, 143 (2014)
38. M.M. Heravi, S. Khaghaninejad, M. Mostofi, Adv. Heterocycl. Chem. **112**, 1 (2014)
39. M.M. Heravi, S. Khaghaninejad, N. Nazari, Adv. Heterocycl. Chem. **112**, 183 (2014)
40. M.M. Heravi, B. Talaei, Adv. Heterocycl. Chem. **114**, 147 (2015)
41. M.M. Heravi, V.F. Vavsari, Adv. Heterocycl. Chem. **114**, 77 (2015)
42. M.M. Heravi, V. Zadsirjan, Adv. Heterocycl. Chem. **117**, 261 (2015)
43. M.M. Heravi, B. Talaei, Adv. Heterocycl. Chem. **118**, 195 (2016)
44. M. Shiri, M. Ranjbar, Z. Yasaei, F. Zamanian, B. Notash, Org. Biomol. Chem. **15**, 10073 (2017)
45. M. Shiri, Z. Faghihi, H.A. Oskouei, M.M. Heravi, B. Notash, Sh. Fazelzadeh, RSC Adv. **6**, 92235 (2016)
46. S. Sadjadi, M.M. Heravi, N. Nazari, RSC Adv. **6**, 53203 (2016)
47. F. Nemati, M.M. Heravi, A. Elhampour, RSC Adv. **5**, 45775 (2015)
48. M.M. Heravi, E. Hashemi, Y.S. Beheshtiha, K. Kamjou, M. Toolabi, N. Hosseintash, J. Mol. Catal. A Chem. **392**, 173 (2014)
49. M.M. Heravi, F. Mousavizadeh, N. Ghobadi, M. Tajbakhsh, Tetrahedron Lett. **55**, 1226 (2014)
50. M.M. Heravi, S. Moghimi, Tetrahedron Lett. **53**, 392 (2012)
51. M.M. Heravi, S. Sadjadi, N. Mokhtari Haj, H.A. Oskooie, F.F. Bamoharram, Catal. Commun. **10**, 1643 (2009)
52. M.M. Heravi, M. Daraie, Molecules **21**, 441 (2016)
53. A. Rezvanian, M.M. Heravi, Z. Shaabani, M. Tajbakhsh, Tetrahedron **73**, 2017 (2009)
54. M. Shiri, Z. Bozorgpour-Savadjani, J. Iran. Chem. Soc. **12**, 389 (2015)
55. M. Shiri, S.Z. Mirpour-Marzoni, Z. Bozorgpour-Savadjani, B. Soleymanifard, H.G. Kruger, Monatsh. Chem. **145**, 1947 (2014)
56. S.M. hiri, B. Farajpour, Z. Bozorgpour-Savadjani, S.A. Shintre, N.A. Koorbanally, H.G. Kruger, B. Notash, Tetrahedron **71**, 5531 (2015)
57. B. Soleymanifard, M.M. Heravi, M. Shiri, M.A. Zolfigol, M. Rafiee, H.G. Kruger, T. Naicker, F. Rasekhmanesh, Tetrahedron Lett. **53**, 3546 (2012)
58. V. Zadsirjan, M. Shiri, M.M. Heravi, T. Hosseinnejad, S.A. Shintre, N.A. Koorbanally, Res. Chem. Intermed. **43**, 2119 (2017)
59. K. Maruoka, M. Akakura, S. Saito, T. Ooi, H. Yamamoto, J. Am. Chem. Soc. **116**, 6153 (1994)
60. H.J. Zhu, *Organic Stereochemistry: Experimental and Computational Methods* (2015), p. 163
61. P.J. Stephens, N. Harada, Chirality **22**, 229 (2010)
62. S.S. Makhathini, S.K. Das, T. Singh, P.I. Arvidsson, H.G. Kruger, H. Gunosewoyo, T. Govender, T. Naicker, Arkivoc **3**, 134 (2016)
63. G. Scalmani, M.J. Frisch, B. Mennucci, J. Tomasi, R. Cammi, V. Barone, J. Chem. Phys. **124**, 94107 (2006)
64. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B.G. Johnson, W. Chen, M.W. Wong, J.L. Andres, M. Head-Gordon, E.S. Replogle, J.A. Pople, *Gaussian 98 (Revision A.1)*. (Gaussian, Inc., Pittsburgh PA, 1998)
65. R.G. Parr, W. Yang, *Density-Functional Theory of Atoms and Molecules* (Oxford University Press, Oxford, 1989)
66. R.M. Dickson, A.D. Becke, J. Phys. Chem. 100, 16105 (1196)
67. K. Wolinski, J.F. Hilton, P.J. Pulay, J. Am. Chem. Soc. **112**, 825 (1990)