Tetrahedron 69 (2013) 3480–3485

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient and diastereoselective synthesis of hydrazino amides via a novel one-pot three-component reaction

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ARTICLE INFO

Article history:
Received 16 November 2012
Received in revised form 31 January 2013
Accepted 18 February 2013
Available online 24 February 2013

Dedicated to Dr. M. Vahid Dastjerdi for her brilliant contribution in Iranian health system

Keywords:
α-Hydrazino amides
α-Hydrazino pseudopeptides
One-pot three-component reaction
Isocyanide-based multicomponent reaction
Diastereoselectivity

ABSTRACT

An efficient one-pot three-component synthesis of a series of α-hydrazino amides, obtained in high diastereoselectivity and yield, was realized starting from cyclic ketones, hydrazides, and isocyanides in the presence of 10 mol % *p*-TsOH in ethanol at room temperature. The synthetic protocol was optimized and the observed diastereoselectivity was measured using ^{1}H NMR spectroscopy.

1. Introduction

Hydrazides constitute an important class of biologically active organic compounds.[1] Hydrazides and their condensation products have displayed diverse range of biological activities including anticonvulsant, antidepressant, anti-inflammatory, antimalarial, anticancer, antimicrobial, anti-HIV and tuberculostatic activities.[2] Prescribed agents featuring the hydrazide scaffold include the antidepressant isocarboxazid (Marplan®) and the antitubercular isoniazid. Hydrazides have also been used as important intermediates in synthesis of various heterocyclic compounds[3] and peptidomimetic and peptide backbones (e.g., azapeptides, azatides, hydrazino peptides and many more other compounds).[4]

Although to the best of our knowledge, hydrazino amides[5] are useful in preparing more proteolytically stable analogues of natural bioactive pseudopeptides with preserved biological activity, the reports are very scarce on synthesis of hydrazino peptides. Some time ago Krasavin et al. reported the synthesis of hydrazino pseudopeptide motifs via Ugi reaction of *N*-acyl hydrazones with an isocyanide and trifluoroacetic acid.[6] The Ugi reaction is the best known isocyanide-based multicomponent reaction (IMCR), offering facile access to diverse compound libraries.[7]

IMCRs can be considered one of the breakthrough reaction classes of the last century.[8] IMCRs are advantageous due to features such as atom economy, simple experimental procedures, mild reaction conditions, execution of reactions in green reaction media like water or ethanol, high yields, and their one-pot character.[9] Therefore, IMCRs have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[10] Although the great utility of isocyanide-based multicomponent reactions in the synthesis of heterocyclic compounds, stereochemical control still represents a challenge.[11] Usually in Passerini and Ugi reactions a new stereogenic center is generated, but most reactions reported so far suffer from low or absence of stereoselectivity.[12] Consequently, developing methods to make these reactions more diastereoselective is an important goal.

This investigation is a continuation of our previous studies on isocyanide-based multicomponent reactions[13] and deals with the diastereoselective synthesis of hydrazino pseudopeptide motifs through the novel one-pot three-component reaction of cyclic ketones, hydrazides, and isocyanides (Scheme 1).

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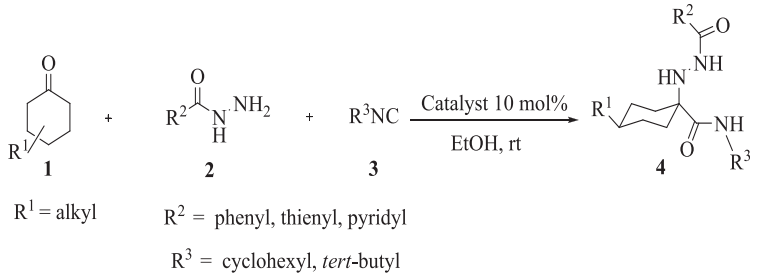
0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.02.056



Scheme 1. Diastereoselective synthesis of hydrazine amide motifs through the novel three-component reaction of cyclic ketones, hydrazides, and isocyanides.

2. Results and discussion

In our initial study, 4-*tert*-butylcyclohexanone **1i** was treated with benzhydrazide **2i** and *tert*-butylisocyanide **3i** in ethanol at room temperature as a model reaction, but the desired product was not obtained even after heating the reaction mixture to 80 °C. However, when the reaction was performed in the presence of catalytic amount (10%) of *p*-toluene sulfonic acid, the desired product **4i** was obtained in 79% yield (Scheme 2).

Scheme 2. The model reaction for the synthesis of **4i**.

In an effort to optimize the reaction, reaction conditions were investigated by adding catalytic amounts (10 mol %) of different type of catalysts including metal catalysts; zinc chloride/zirconium oxychloride, and Brønsted acid catalysts: phosphorous acid, *p*-toluene sulfonic acid, camphor sulfonic acid, ascorbic acid, *S*-1,1-binaphthyl-2,2-diylhydrogen phosphate (Table 1).

Table 1
Effect of metal catalysts and Brønsted acid catalysts on the formation of hydrazino amide **4i**

Entry	Catalysts	Catalyst [%]	Yield[a] [%]
1	*p*-TsOH	10	79
2	$ZrOCl_2$	10	20
3	$ZnCl_2$	10	Trace
4	H_3PO_3	10	80
5	Camphor sulfonic acid	10	80
6	Ascorbic acid	10	Trace
7	*S*-1,1-Binaphthyl-2,2-diylhydrogenphosphate	10	30

[a] In all cases time of reactions was 24 h, except using *p*-TsOH time of reaction was 16 h.

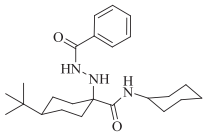
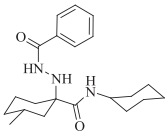
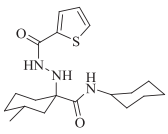
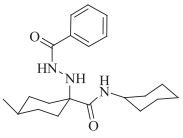
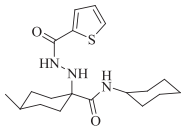
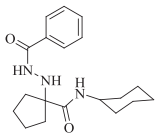
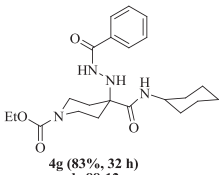
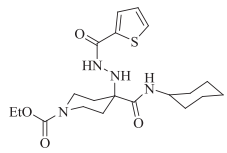
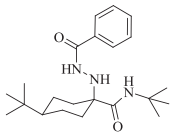
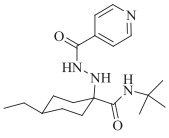
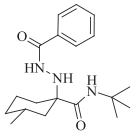
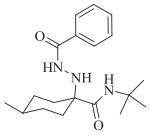
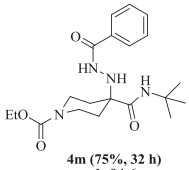
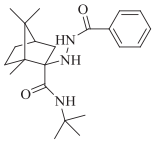
The best result among these catalysts was achieved with *p*-toluene sulfonic acid. Another essential factor, which affects the performance of a catalytic reaction is the amount of catalyst used. In order to optimize the catalyst amount, different amounts of *p*-toluene sulfonic acid were used. In the presence of 5, 10, 20, 30% of *p*-TsOH, the yield of hydrazino pseudopeptide **4i** obtained was 40, 79, 80, and 80%, respectively. The best result was obtained with 10 mol % of *p*-toluene sulfonic acid catalyst. The model reaction was carried out in three different solvents (EtOH, toluene, and THF) the obtained yields for the model reaction were 79, 30, and 20%, respectively. According to these results, ethanol was the most optimal solvent. Consequently, the optimal reaction conditions were as follows: catalyst, *p*-TsOH; catalyst amount, 10 mol %; reaction media, ethanol. The scope of the reaction was studied using different starting materials after determining the best reaction conditions. The results are summarized in Table 2.

Meanwhile, the reaction of a variety of different aromatic aldehydes with benzhydrazide and *tert*-butylisocyanide was examined. However, these reactions only led to formation of imine and the nucleophilic attack of isocyanide didn't occur.

We believe that the reaction is diastereoselective. This claim was checked with investigation of the model reaction (**4i**). After the completion of the reaction, the mixture was evaporated and the ^{1}H NMR data of the crude product showed the existence of two diastereomers. The ratios of diastereomers were also assigned based on the peak area for the –NH–N*H*–CO, which resonated at δ 9.42 and 9.60 ppm for axial and equatorial positions in two diastereomers. The ratio of distinguished peaks was 86:14. The ratios of the diastereomers were also characterized for other products in the same way and were included in Table 2. Two diastereomers have different solubility in ethanol. They could be separated by crystallization. The mixture was crystallized in minimum of ethanol as the solvent. The major diastereomer was crystallized and the other one was soluble in ethanol. The crystalline form was filtered and its ^{1}H NMR showed the existence of single diastereomer. The diastereoselectivity of the model reaction was analyzed using ^{1}H NMR spectroscopy of the crude product mixture.

The yields of the reactions were reported according to the amount of purified single major diastereomer **4a**–**n** as the single purified diastereomer. The structures of the products **4a**–**n** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4i** consisted of multiplet signals for the methylene groups of cyclohexyl ring at δ 0.83–1.80 ppm, a doublet for NH at δ 5.30 ppm and a multiplet was observed at δ 7.45–7.94 ppm for aromatic protons and –NH (*tert*-butyl) of amide and a doublet for amide proton of NH–N*H*–COPh at δ 9.40 ppm. Data arising from a combined analysis of 2D H–H COSY allowed us to assign signals of the ^{1}H NMR spectrum of compound

Table 2
One-pot three-component reaction of cyclic ketones, hydrazides, and isocyanides for the synthesis of hydrazino amides **4a**–**n**

 4a (68%, 16 h)[a] dr 70:30	 4b (60%, 16 h) dr 62:38	 4c (70%, 32h) dr 74:26
 4d (75%, 16 h) dr 78:22	 4e (70%, 32 h) dr 75:25	 4f (77%, 16 h) dr 79:21
 4g (83%, 32 h) dr 88:12	 4h (76%, 32 h) dr 92:8	 4i (80%, 16 h) dr 86:14
 4j (70%, 16 h) dr 71:29	 4k (79%, 16 h) dr 93:7	 4l (80%, 16 h) dr 91:9
 4m (75%, 32 h) dr 94:6	 4n (90% , 16 h) dr 95:5	

[a]In all cases, the yields of isolated single diastereomer are reported.

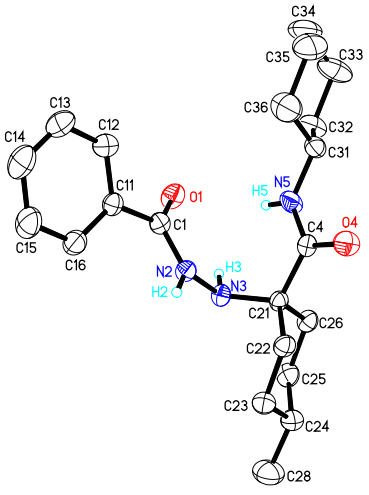
4i. 2D H–H-COSY spectrum was used to determine the relationship between –NH–N*H*–CO and the other –NH amide proton. According to this result, it is clear that two –NH protons have correlation at δ 5.30 and 9.40 ppm, which could confirm the relation between –NH of amide and amine (–NH–NH–CO). Another amide proton resonates at δ 7.94 ppm, which shows that there is no correlation with other protons. The proton decoupled ^{13}C NMR spectrum of **4i** showed 14 distinct resonances in agreement with the proposed structure.

Meanwhile, for two samples **4d** and **4k** the single crystals were obtained and the ORTEP structure could confirm their structure (Fig. 1). The X-ray data for two single crystals **4d**, **4k** showed clearly the orientation of the substituent and this was evidence to confirm getting the single diastereomer.

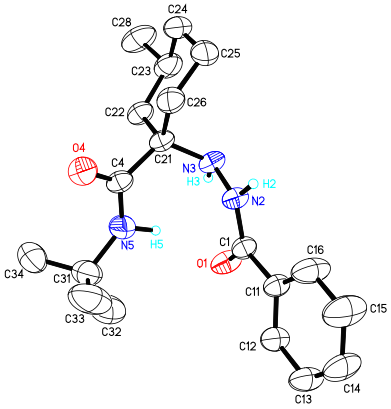
The possible mechanism for the formation of product is shown in Scheme 3. It is conceivable that the initial event is the formation of imine. In the presence of acid catalyst it could convert to its iminium salt, which is more active compared to its imine form. Therefore, the presence of *p*-toluene sulfonic acid could facilitate the addition of isocyanide, and without adding the acid catalyst the reaction doesn't proceed and the imine is the final product. There are two possibilities for the addition of isocyanides to iminium ion. The transition state for axial attack suffers from steric strain between 1,3 axial hydrogens and the incoming isocyanide reagent. But addition of isocyanide through equatorial attack is more suitable with low steric effect **6i**. The final step is water nucleophilic addition on the activated nitrile moiety and formation of compound **4i**.

3. Conclusion

In summary, we have reported a novel multicomponent reaction led to diastereoselective synthesis of hydrazine pseudopeptide derivatives. The desired products **4a**–**n** were formed in good yields upon mixing readily available substrates in the presence of 10 mol % *p*-toluene sulfonic acid catalyst. The broad scope, operational simplicity, practicability, high yields and mild reaction conditions render it an attractive approach for the generation of different hydrazino amides and hydrazine pseudopeptides. Moreover, these products can be used for the synthesis of hydrazino acids, amino amides, and also azapeptides.

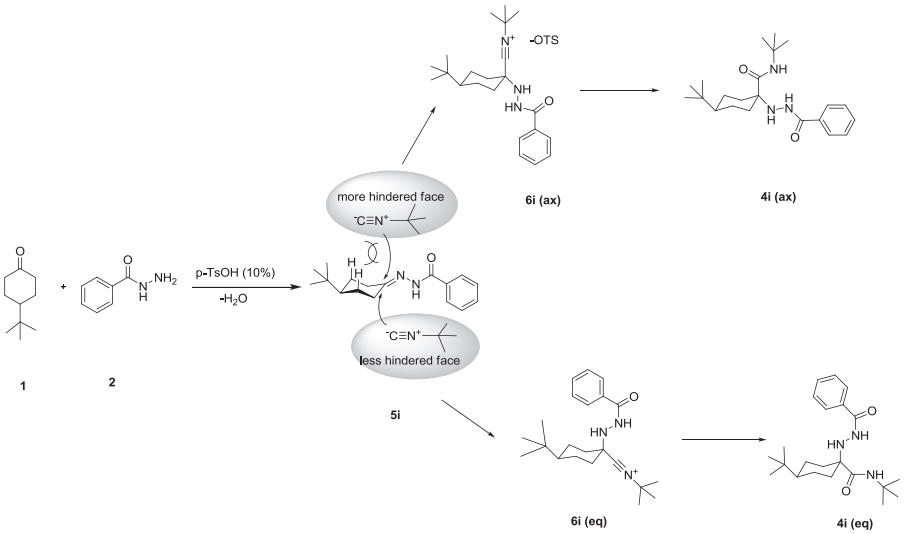


4d



4k

Fig. 1. ORTEP structure of compounds **4d** and **4k**.



Scheme 3. Proposed mechanism for the synthesis of hydrazino amides **4a**–**n** through isocyanide three-component reaction.

4. Experimental section

4.1. General

Commercially available materials were used without further purification. Melting points were determined on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-500 AVANCE, DRX-300 AVANCE spectrometers at 500 and 300 MHz for ^{1}H NMR, 125 and 75 MHz for ^{13}C NMR. DMSO-d_6 was used as solvent. High-resolution mass spectra were recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

4.2. General procedure for the synthesis of α-hydrazino amides

To a solution of ketone **1** (1 mmol), hydrazide **2** (1 mmol) and isocyanide **3** (1.2 mmol) in 5 mL EtOH was added *p*-TSOH·H_2O (0.02g, 10 mol %). The mixture was stirred for 16–32 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1:3), the product was precipitated by addition of 10 mL of diisopropylether. The precipitate was filtered off and then crystallized from ethanol.

4.2.1. Compound ***4a****: (1SR,4SR)-1-(2-benzoylhydrazinyl)-4-tert-butyl-N-cyclohexylcyclohexane carboxamide.* Yield 271 mg, 68% as a white solid; mp 240–243 °C; R_f (33% EtOAc/hexane) 0.33; ν_{max} (KBr) 3296, 3224, 3091, 1650, 1627 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.83 (s, 9H, *t*-Bu), 0.93–1.79 (m, 19H, $H_{Cyclohexyl}$), 3.29–3.40 (m, 1H, CHN), 5.30 (d, 1H, *J* 4.0 Hz, NH), 7.45 (t, 2H, *J* 7.5 Hz, H_{Ar}), 7.52 (t, 1H, *J* 7.5 Hz, H_{Ar}), 7.71 (d, 2H, *J* 7.5 Hz, H_{Ar}), 8.15 (d, 1H, *J* 7.5 Hz, NH), 9.39 (d, 1H, *J* 4.0 Hz, NH); δ_C (125 MHz, DMSO-d_6) 21.6, 24.5, 25.2, 27.5, 30.9, 32.1, 32.2, 47.0, 47.5, 63.2, 127.4, 128.2, 131.2, 133.6, 167.3, 174.1; HRMS (ESI): $[M+H]^+$ found 400.2964. $C_{24}H_{38}N_3O_2$ requires 400.2964.

4.2.2. Compound ***4b****: (1SR,3SR)-1-(2-benzoylhydrazinyl)-N-cyclohexyl-3-methylcyclohexane carboxamide.* Yield 214 mg, 60% as a white solid; mp 217–220 °C; R_f (33% EtOAc/hexane) 0.32; ν_{max} (KBr) 3292, 3228, 3088, 1653, 1623 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.82 (d, 3H, *J* 5.0 Hz, Me), 1.04–1.74 (m, 19H, H–Cyclohexyl), 3.42–3.44 (m, 1H, CHN), 5.32 (s, 1H, NH), 7.44 (*t*, 2H, *J* 7.0 Hz, H_{Ar}), 7.51 (*t*, 1H, *J* 7.0 Hz, H_{Ar}), 7.71 (d, 2H, *J* 7.0 Hz, H_{Ar}), 8.16 (d, 1H, J 7.5 Hz, NH), 9.42 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 20.7, 22.7, 24.6, 25.3, 26.4, 29.8, 32.2, 34.0, 39.3,47.5, 64.3, 127.5, 128.3, 131.3, 133.7, 167. 6, 174.0; HRMS (ESI): $[M+H]^+$ found 358.2495. $C_{21}H_{32}N_3O_2$ requires 358.2496. $[M+Na]^+$ found 380.2315. $C_{21}H_{31}N_3NaO_2$ requires 380.2317.

4.2.3. Compound ***4c****: (1SR,3SR)-N-cyclohexyl-3-methyl-1-(2-(thiophene-2-carbonyl)hydrazinyl) cyclohexane carboxamide.* Yield 254 mg, 70% as a white solid; mp 208–211 °C; R_f (33% EtOAc/hexane) 0.31; ν_{max} (KBr) 3293, 3239, 3090, 1618 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.83 (br s, 3H, $-CH_3$), 1.09–1.73 (m, 19H, H–Cyclohexyl), 3.31–3.40 (m, 1H, –CHN), 5.28 (s, 1H, NH), 7.13 (s, 1H, H–thiophene), 7.76 (m, 2H, H–thiophene), 8.11 (s, 1H, NH), 9.31 (br s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 24.5, 24.9, 25.0, 25.3, 26.3, 29.6, 32.1, 33.1, 34.0, 47.4, 64.3, 127.8, 128.6, 131.0, 137.8, 162.0, 173.9; HRMS (ESI): $[M+H]^+$ found 364.2056. $C_{19}H_{30}N_3O_2S$ requires 364.2057. $[M+Na]^+$ found 386.1876. $C_{19}H_{29}N_3NaO_2S$ requires 386.1877.

4.2.4. Compound ***4d****: (1SR,4SR)-1-(2-benzoylhydrazinyl)-N-cyclohexyl-4-methylcyclohexane carboxamide.* Yield 268 mg, 75% as a white solid; mp 242–244 °C R_f (33% EtOAc/hexane) 0.32; ν_{max} (KBr) 3296, 3230, 3089, 1626 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.87 (d, 3H, *J* 4.0 Hz, $-CH_3$), 1.05–1.72 (m, 19H, H–Cyclohexyl), 3.31–3.34 (m, 1H, –CHN), 5.32 (d, 1H, *J* 3.5 Hz, NH), 7.44 (*t*, 2H, *J* 7.5 Hz, H–Ar), 7.52 (*t*, 1H, *J* 7.5 Hz, H–Ar), 7.71 (d, 2H, *J* 7.5 Hz, H–Ar), 8.15 (d, 1H, *J* 8.0 Hz, NH), 9.37 (d, 1H, *J* 3.5 Hz, NH); δ_C (125 MHz, DMSO-d_6) 22.4, 24.5, 25.3, 29.2, 30.4, 31.3, 32.1, 47.4, 63.1, 127.4, 128.2, 131.3, 133.6, 167.4, 174.0; HRMS (ESI): $[M+H]^+$ found 358.2489. $C_{21}H_{32}N_3O_2$ requires 358.2489. $[M+Na]^+$ found 380.2308. $C_{21}H_{31}N_3NaO_2$ requires 380.2308.

Colourless crystal (plate), dimensions 1.04×0.32×0.07 mm^3, crystal system monoclinic, space group $P2_1/c$, Z=8, a=9.7842(6) Å, b=17.6143(11) Å, c=23.5526(16) Å, α=90°, β=97.886(2)°, γ=90°, V=4020.7(4) Å^3, ρ=1.188 g/cm^3, T=200(2) K, θ_{max}=25.12°, radiation Mo Kα, λ=0.71073 Å, 0.3° ω-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.71and a completeness of 99.4% to a resolution of 0.84Å, 34,173 reflections measured, 7116 unique (R(int)=0.0443), 4935 observed ($I>2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[14] based on the Laue symmetry of the reciprocal space, μ=0.08 mm^{-1}, T_{min}=0.92, T_{max}=0.99, structures of **4d** and **4k** solved

by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package,[15] 493 parameters refined, hydrogen atoms were treated using appropriate riding models, except of those at the nitrogen atoms, which were refined isotropically, goodness of fit 1.07 for observed reflections, final residual values $R1(F)$=0.047, $wR(F^2)$= 0.104 for observed reflections, residual electron density −0.19 to 0.17 e Å^{-3}. CCDC 910985 contains the supplementary crystallographic data for this paper.

4.2.5. Compound ***4e****: (1SR,4SR)-N-cyclohexyl-4-methyl-1-(2-(thiophene-2-carbonyl)hydrazinyl)cyclohexane carboxamide.* Yield 253 mg, 70% as a white solid; mp 215–216 °C; R_f (33% EtOAc/hexane) 0.4; ν_{max} (KBr) 3352, 3299, 3240, 1630, 1616 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.87 (d, 3H, *J* 4.0 Hz, −CH_3), 1.07–1.69 (m, 19H, H−Cyclohexyl), 3.39–3.41 (m, 1H, −CHN), 5.29 (s, 1H, NH), 7.12 (t, 1H, *J* 4.0 Hz, H−thiophene), 7.75 (d, 1H, *J* 5.0 Hz, H−thiophene), 7.81 (d, 1H, *J* 3.3 Hz, H−thiophene), 8.14 (d, 1H, *J* 8.0 Hz, NH), 9.29 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 22.3, 24.7, 25.3, 29.2, 30.4, 31.3, 32.1, 47.4, 63.1, 127.9, 128.6, 131.0, 137.8, 161.9, 174.0; HRMS (ESI): $[M+H]^+$ found 364.20555. $C_{19}H_{30}N_3O_2S$ requires 364.20561.

4.2.6. Compound ***4f****: (1SR)-1-(2-benzoylhydrazinyl)-N-cyclohexylcyclopentane.* Yield 253 mg, 77% as a white solid; mp 200–202 °C; R_f (33% EtOAc/hexane) 0.4; ν_{max} (KBr) 3295, 3224, 3087, 1625 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.04–1.91 (m, 18H, H−Cyclopentyl, Cyclohexyl), 3.45–3.47 (m, 1H, −CHN), 5.19 (d, 1H, *J* 3.5 Hz, NH), 7.45 (*t*, 2H, *J* 7.5 Hz, H−Ar), 7.52 (*t*, 1H, *J* 7.5 Hz, H−Ar), 7.75 (d, 2H, *J* 7.5 Hz, H−Ar), 8.27 (d, 1H, *J* 7.5 Hz, NH), 9.55 (d, 1H, *J* 3.5 Hz, NH); δ_C (125 MHz, DMSO-d_6) 24.6, 24.7, 25.3, 32.2, 34.7, 47.6, 72.4, 127.4, 128.4, 131.4, 133.4, 167.4, 173.7; HRMS (ESI): $[M+H]^+$ found 330.2178. $C_{19}H_{28}N_3O_2$ requires 330.2179. $[M+Na]^+$ found 352.1998. $C_{19}H_{27}N_3NaO_2$ requires 352.1999.

4.2.7. Compound ***4g****: (1SR,4SR)-ethyl 4-(2-benzoylhydrazinyl)-4-(cyclohexylcarbamoyl)piperidine-1-carboxylate.* Yield 345 mg, 83% as a white solid; mp 176–177 °C; R_f (33% EtOAc/hexane) 0.45; ν_{max} (KBr) 3283, 3229, 3086, 1699, 1624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.16 (*t*, 3H, *J* 6.5 Hz, −CH_3), 1.03–1.87 (m, 14H, H−Cyclohexyl), 3.32–3.45 (m, 3H, −CHN, −CH_{ax}N), 3.55–3.62 (m, 2H, −CH_{eq}N), 4.02 (q, 2H, *J* 7.0 Hz, −OCH_2), 5.62 (d, 1H, *J* 4.0 Hz, NH), 7.46 (t, 2H, *J* 7.5 Hz, H−Ar), 7.52 (t, 1H, *J* 7.5 Hz, H−Ar), 7.73 (d, 2H, *J* 7.5 Hz, H−Ar), 8.12 (d, 1H, *J* 7.5 Hz, NH), 9.57 (d, 1H, *J* 4.0 Hz, NH); δ_C (125 MHz, DMSO-d_6) 14.6, 24.6, 25.2, 30.4, 30.7, 32.0, 47.6, 60.5, 62.0, 127.4, 128.3, 131.4, 133.4, 154.6, 167.4, 172.6; HRMS (ESI): $[M+H]^+$ found 417.2500. $C_{22}H_{33}N_4O$ requires 417.2501. $[M+Na]^+$ found 439.2319. $C_{22}H_{32}N_4NaO_4$ requires 439.2320.

4.2.8. Compound ***4h****: (1SR,4SR)-ethyl 4-(cyclohexylcarbamoyl)-4-(2-(thiophene-2-carbonyl)hydrazinyl)piperidine-1-carboxylate.* Yield 320 mg, 76% as a white solid; mp 205–206 °C; R_f (33% EtOAc/hexane) 0.40; ν_{max} (KBr) 3289, 3081, 2926, 1704, 1650 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.16 (t, 3H, *J* 6.5 Hz, −CH_3), 1.07–1.85 (m, 14H, H −cyclohexyl), 3.34–3.49 (m, 3H, −CHN, −CH_{ax}N), 3.52–3.59 (m, 2H, −CH_{eq}N), 4.02 (q, 2H, *J* 6.5 Hz, −OCH_2), 5.58 (s, 1H, NH), 7.71 (t, 1H, *J* 4.0 Hz, H−thiophene), 7. 77 (d, 2H, *J* 4.0 Hz, H−thiophene), 8.08 (d, 1H, *J* 7.5 Hz, NH), 9.50 (s, 1H, NH), 9.56 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 14.6, 24.5, 25.2, 30.4, 30.8, 32.0, 47.5, 60.6, 62.0, 127.9, 128.6, 131.2, 137.6, 154.6, 161.9, 172.6; HRMS (ESI): $[M+H]^+$ found 423.2063. $C_{20}H_{31}N_4O_4S$ requires 423.2064. $[M+Na]^+$ found 445.1882. $C_{20}H_{30}N_4NaO_4S$ requires 445.1883.

4.2.9. Compound ***4i****: (1SR,4SR)-1-(2-benzoylhydrazinyl)-N-4-di-tert-butylcyclohexane carboxamide.* Yield 298 mg, 80% as a white solid; mp 197–200 °C; R_f (33% EtOAc/hexane) 0.34; ν_{max} (KBr) 3290, 3066, 2958, 1631 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.83 (s, 9H, *t*-Bu), 0.91–0.96 (m, 1H, H−cyclohexyl), 1.18 (s, 9H, *t*-Bu), 1.31–1.80 (m, 8H, H−cyclohexyl), 5.30 (d, 1H, *J* 3.0 Hz, NH), 7.45 (t, 2H, *J* 7.5 Hz, H−Ar), 7.52 (t, 1H, *J* 7.5 Hz, H−Ar), 7.72 (d, 2H, *J* 7.5 Hz, H−Ar), 7.94 (s, 1H, NH), 9.40 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 21.7, 27.5, 28.2, 30.9, 32.2, 47.1, 49.5, 63.6, 127.5, 128.2, 131.2, 133.7, 167.4, 174.6; HRMS (ESI): $[M+H]^+$ found 374.2803. $C_{22}H_{36}N_3O_2$ requires 374.2803. $[M+Na]^+$ found 396.2623. $C_{22}H_{35}N_3NaO_2$ requires 396.2624.

4.2.10. Compound ***4j****: (1SR,4SR)-N-tert-butyl-4-ethyl-1-(2-isonicotinoylhydrazinyl)cyclohexane carboxamide.* Yield 242 mg, 70% as a white solid; mp 235–238 °C; R_f (33% EtOAc/hexane) 0.3; ν_{max} (KBr) 3295, 3252, 3077, 1634 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.84 (t, 3H, *J* 7.0 Hz, −CH_3), 1.07–1.76 (m, 20H, H−cyclohexyl,CH_2−CH_3, *t*-Bu), 5.43 (s, 1H, NH), 7.61 (d, 2H, *J* 5.0 Hz, H−pyridyl), 7.85 (s, 1H, NH), 8.70 (d, 2H, *J* 5.0 Hz, H−pyridyl), 9.62 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 11.4, 26.9, 28.2, 29.2, 30.3, 38.1, 49.5, 63.9, 121.6, 140. 8, 150.1, 165.8, 174.3; HRMS (ESI): $[M+H]^+$ found 347.2441. $C_{19}H_{31}N_4O_2$ requires 347.2441.

4.2.11. Compound ***4k****: (1SR,3SR)-1-(2-benzoylhydrazinyl)-N-tert-butyl-3-methylcyclohexane carboxamide.* Yield 261 mg, 79% as a white solid; mp 202–204 °C; R_f (33% EtOAc/hexane) 0.43; ν_{max} (KBr) 3310, 3284, 3100, 3050, 3010, 1638 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.82 (d, 3H, *J* 7.0 Hz, −CH_3), 1.17 (s, 9H, *t*-Bu), 1.18–1.80 (m, 8H, H−cyclohexyl), 2.40–2.48 (m, 1H, H−cyclohexyl), 5.31 (s, 1H, NH), 7.11–7.20 (m, 1H, H−Ar), 7.50–7.60 (m, 2H, H−Ar), 7.69 (d, 2H, *J* 8.0 Hz, H−Ar), 7.93 (s, 1H, NH), 9.40 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 20.7, 22.6, 26.4, 27.1, 28.2, 29.6, 34.0, 49.5, 51.1, 64.7, 125.5, 127.5, 128.1, 128.2, 131.2, 133.8, 167.6, 174.0; HRMS (ESI): $[M+H]^+$ found 332.2335. $C_{19}H_{30}N_3O_2$ requires 332.2336. $[M+Na]^+$ found 354.2155. $C_{19}H_{29}N_3NaO_2$ requires 354.2156. Colourless crystal (needle), dimensions 0.89×0.09×0.07 mm^3, crystal system monoclinic, space group $P2_1/c$, Z=4, a=10.961(2) Å, b=18.093(3) Å, c=9.6927(19) Å, α=90°, β=99.845(5)°, γ=90°, V=1893.9(6) Å^3, ρ=1.162 g/cm^3, T=200(2) K, θ_{max}=25.03°, radiation Mo Kα, λ=0.71073 Å, 0.3° ω-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.14 and a completeness of 99.7% to a resolution of 0.84 Å, 14,447 reflections measured, 3334 unique (R(int)=0.1909), 2680 observed ($I>2\sigma(I)$), 235 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H_2, H_3, and H_5 at the nitrogen atoms, which were refined isotropically, goodness of fit 1.11 for observed reflections, final residual values $R1(F)$=0.088, $wR(F^2)$=0.199 for observed reflections, residual electron density −0.31 to 0.52 e Å^{-3}. CCDC 910986 contains the supplementary crystallographic data for this paper.

4.2.12. Compound ***4l****: (1SR,4SR)-1-(2-benzoylhydrazinyl)-N-tert-butyl-4-methylcyclohexane carboxamide.* Yield 264 mg, 80% as a white solid; mp 241–243 °C; R_f (33% EtOAc/hexane) 0.42; ν_{max} (KBr) 3332, 3290, 3256, 1640, 1629 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.86 (d, 3H, *J* 2.5 Hz, −CH_3), 1.18 (s, 9H, *t*-Bu), 1.29–1.71 (m, 9H, H−Cyclohexyl), 5.31 (d, 1H, *J* 3.0 Hz, NH), 7.45 (t, 2H, *J* 7.5 Hz, H−Ar), 7.52 (t, 1H, *J* 7.5 Hz, H−Ar), 7.71 (d, 2H, *J* 7.5 Hz, H−Ar), 7.92 (s, 1H, NH), 9.35 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 22.3, 28.2, 29.3, 30.4, 31.4, 49.5, 63.5, 127.4, 128.2, 131.2, 133.7, 167.4, 174.5; HRMS (ESI):$[M+H]^+$ found 332.2334. $C_{19}H_{30}N_3O_2$ requires 332.2334. $[M+Na]^+$ found 354.2154. $C_{19}H_{29}N_3NaO_2$ requires 354.2154.

4.2.13. Compound ***4m****: (1SR,4SR)-ethyl 4-(2-benzoylhydrazinyl)-4-(tert-butylcarbamoyl) piperidine-1-carboxylate.* Yield 292 mg, 75% as a white solid; mp 184–187 °C; R_f (33% EtOAc/hexane) 0.4; ν_{max} (KBr) 3420, 3363, 3143, 1620, 1570 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.17–1.30 (m, 3H, CH_3), 1.20 (s, 9H, *t*-Bu), 1.65–1.72 (m, 2H, −CH_{ax}), 1.75–1.85 (m, 2H, −CH_{eq}), 3.25–3.45 (m, 2H, −CH_{ax}N), 3.58–3.60 (m, 2H,

$-CH_{eq}N$), 4.02 (*q*, 2H, *J* 7.5 Hz, $-OCH_2$), 5.62 (br s, 1H, NH), 7.46 (t, 2H, *J* 7.5 Hz, H–Ar), 7. 53 (t, 1H, *J* 7.5 Hz, H–Ar), 7.72 (d, 2H, *J* 7.5 Hz, H–Ar), 7.88 (s, 1H, NH), 9.56 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 14.6, 27.1, 28.1, 30.5, 49.7, 55.8, 60.6, 62.4, 125.5, 127.4, 128.3, 131.4, 133.5, 154.7, 167.4, 173.3; HRMS (ESI): $[M+H]^+$ found 391.2345. $C_{20}H_{31}N_4O_4$ requires 391.2345. $[M+Na]^+$ found 413.2167. $C_{20}H_{30}N_4NaO_4$ requires 413.2169.

4.2.14. Compound ***4n****: (1R,2SR,4S)-2-(2-benzoylhydrazinyl)-N-tert-butyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide.* Yield 243 mg, 90% as a white solid; mp 198–200 °C; R_f (33% EtOAc/hexane) 0.45; ν_{max} (KBr) 3167, 3013, 2941, 1660, 1645 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 0.75 (s, 6H, 2-CH_3), 0.90 (s, 9H, *t*-Bu),0.98 (s, 3H, $-CH_3$), 1.15–1.80 (m, 4H, 2-CH_2), 1.87–2.00 (m, 1H, –CH), 2.10 (d, 1H, *J* 17.0 Hz, –CH), 2.60 (d, 1H, *J* 17.0 Hz, –CH), 3.30 (br s, 1H, NH), 7.45 (br s, 3H, H–Ar), 7.78 (br s, 3H, H–Ar, –NH), 10.19 (s, 1H, NH); δ_C (75 MHz, DMSO-d_6) 11.5, 18.5, 19.3, 26.9, 32.4, 34.7,43.4, 47.6, 52.6, 127.6, 128.3, 131.2, 134.3, 163.1, 173.3; HRMS (ESI): $[M-C_5H_{10}NO]^+$ found 271.1805. $C_{17}H_{23}N_2O$ requires 271.1805. $[M-C_5H_{10}NO+Na]^+$ found 293.16246. $C_{17}H_{22}N_2NaO$ requires 293.16243. $[2M-C_5H_{10}NO+Na]^+$ found 563.3356. $C_{34}H_{44}N_4NaO_2$ requires 563.3356.

Acknowledgements

S.B. gratefully acknowledges Iran National Science Foundation (INSF). We are also thanking Iranian Ministry of Health and Medicinal Education and also Presidential Office Deputy of Science and Technology for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2013.02.056.

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