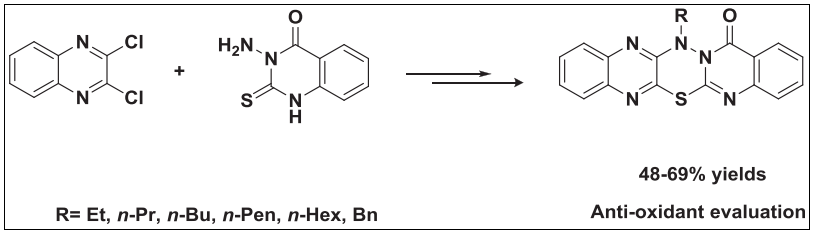
# Synthesis and Antioxidant Evaluation of Quinoxalino[2′,3′:5,6][1,3,4] thiadiazino[2,3-*b*]quinazolin-15-ones: Derivatives of a Novel Ring System

Mahsa Mousavi, Mehdi Bakavoli,* Ali Shiri, and Hossein Eshghi

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran
*E-mail: mbakavoli@um.ac.ir; mbakavoli@yahoo.com

Received July 31, 2017
DOI 10.1002/jhet.3078
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).




Quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-*b*]quinazolin-15-one, a novel fused heterocyclic system, was synthesized from a one-pot condensation reaction of 2,3-dichloroquinoxaline and 3-amino-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one under mild condition. Derivatization was performed on treatment of the titled compound with several alkyl bromides. *In vitro* antioxidant activity of the synthesized compounds was evaluated.

*J. Heterocyclic Chem.*, **00,** 00 (2017).

## INTRODUCTION

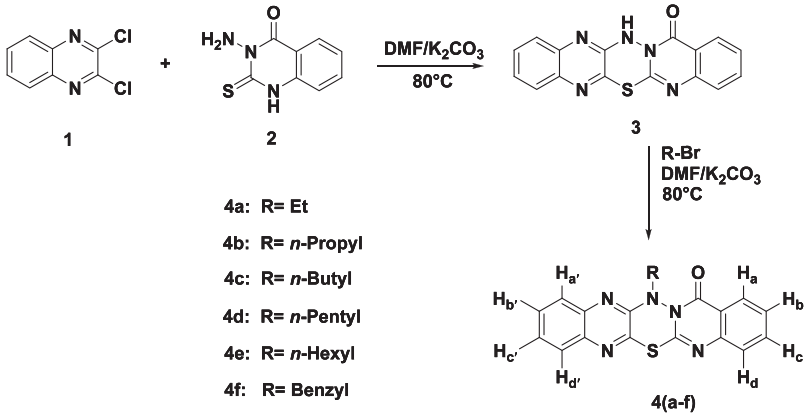
Quinazolines and quinoxalines are pharmacologically important motifs possessing a wide range of biological and pharmaceutical activities. Quinoxalines are core units in a number of medicines with diverse properties like anticancer [1], antibacterial [2], antiviral [3], anti-HIV [4], and anti-inflammatory [5]. Moreover, scientists have already determined many therapeutic activities of quinazolines including antibacterial [6], antivirus [7], anti-cytotoxin [8], anticancer [9], antimalarial [10], anti-spasm [11], anti-inflammation [12], and others. From the synthetic point of view, treatment of 4-amino-1, 2,4-triazole-3-thiols with 2,3-dichloroquinoxalines in refluxing ethanol [13,14] or in the presence of sodium acetate under microwave irradiation [15] can afford the bioactive [1,2,4]triazolo-thiadiazino[5,6-*b*]quinoxalines. Thiadiazino[2,3-*b*]quinazolin-6-ones can also be obtained from hetrocyclization of substituted quinazolines [16] through a simple nucleophilic substitution reaction. A literature survey disclosed that there are few examples available on antioxidant evaluation of these bioactive skeletons [17,18]. Obviously, combination of two or more moieties into one can result in discovery of new bioactive molecules with improved biological activities. In this regard and in continuation of our previous research in this field [19,20], we wish to report the combination of quinazoline and quinoxaline moieties via formation of a thiadiazine core to afford a novel pentacyclic ring system. Antioxidant activity of the new system and its derivatives was evaluated.

## RESULTS AND DISCUSSION

**Chemistry.** As illustrated in Scheme 1, a synthetic pathway was designed for preparation of the desired pentacyclic compound **(3)** and its derivatives **4(a–f)**. 2,3-Dichloroquinoxaline **(1)** was conveniently synthesized according to the previously published procedure [21]. 3-Amino-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **(2)** was prepared from the reaction of methyl 2-isothiocyanatobenzoate with hydrazine hydrate in diethyl ether [22]. Reaction of compound **1** with **2**, in a mixture of dimethylformamide (DMF)/$K_2CO_3$ at 80°C, afforded the 13*H*,15*H*-quinoxalino [2′,3′,5,6] [1,3,4] thiadiazino[2,3-*b*]quinazolin-15-one **(3)**, as the novel pentacyclic system. In $^1$H NMR spectral analysis, emerging a $D_2O$-exchangeable signal at δ = 7.96 ppm for NH group and a set of multiplet signals at δ = 6.74–8.02 ppm belonging to the aromatic C-H bonds properly implies to the formation of **3**. Moreover, detecting a molecular ion peak at *m/z* = 319 ($M^+$), along with the complimentary results of micro analytical data, confirms the synthesis of the titled ring system. Further treatment of compound **3** with various alkylbromides in a mixture of DMF/ $K_2CO_3$ at 80°C, furnished the substituted derivatives **4(a–f)**.

Structural characterization of the newly synthesized derivatives **4(a–f)** was fully accomplished through the experimental spectroscopic and elemental analysis data. As an example, $^1$H NMR spectrum of compound **4a** shows a triplet signal at δ = 1.36 ppm, a quartet signal at δ = 4.23 ppm, and multiplet signals at δ = 7.03–8.1 ppm

**Scheme 1.** The synthetic pathway for the preparation of compounds **4(a–f).**




belonging to methyl, methylene, and aromatic hydrogens of phenyl groups, respectively. Furthermore, disappearance of the stretching vibrational band for N─H bond at 3236 $cm^{-1}$ in infrared (IR) spectrum of **4a** indicates the successful alkylation of N─H group in the final product. Emerging a molecular ion peak at $m/z$ = 347 ($M^+$) in Mass spectrum, in addition to the micro analytical data assessments, fully supports the molecular formula of $C_{18}H_{13}N_5OS$ for compound **4a**. Similar results were obtained for other derivatives **4(b–f)**.

**Evaluation of antioxidant activity.** Antioxidant activity of all the synthesized compounds **3** and **4(a–f)** was determined using DPPH free radical scavenging assay at different concentrations and compared with that of ascorbic acid as the standard antioxidant. The evaluation was performed at λ = 517 nm using ultraviolet–visible spectrophotometer (UV-2100 RAY Leigh, Beijing, China), according to the previously published method [23]. The results are reported as the mean values ± standard deviation of three independent experiments and are presented as $IC_{50}$ values in Table 1.

**Table 1**

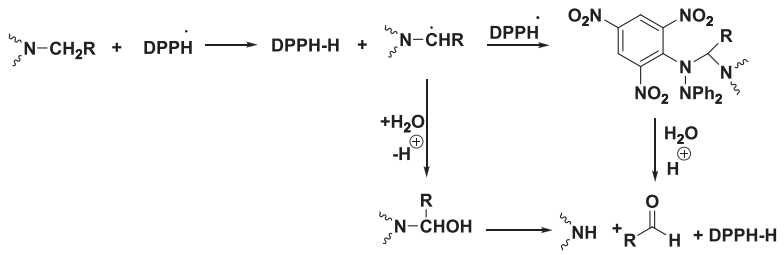
Antioxidant evaluation of the synthesized compounds **3** and **4(a–f)**.

| Products | $IC_{50}$[a] | Products | $IC_{50}$ |
|---|---|---|---|
| **3** | 0.1020 ± 0.0003 | **4d** | 0.0536 ± 0.0005 |
| **4a** | 0.1187 ± 0.0001 | **4e** | 0.0594 ± 0.0007 |
| **4b** | 0.1016 ± 0.0001 | **4f** | 0.0525 ± 0.0002 |
| **4c** | 0.0708 ± 0.0002 | AA[b] | 0.0224 ± 0.0004 |

[a]The required concentrations of the compounds (μmol/mL) to inhibit 50% of the radicals.
[b]Ascorbic acid.

Scavenging property of ascorbic acid against DPPH radical was completely significant. Heterocyclic derivatives were ranked based on the inhibitory activities in the following order **4f** > **4d** > **4e** > **4c** > **4b** > **3** > **4a**. According to the proposed mechanism by Baciocchi *et al.* [24], it seems that *H*-abstraction from the N─$CH_2$ groups and the stability of the resulting free radicals are the main factors responsible for the observed differences (Scheme 2). Antioxidant activity was improved with the increase of the length of the alkyl side chain on compounds **4(a–e)**. Indeed, the *n*-pentyl and *n*-hexyl side chains presented better activities as were predicted [25]. Compound **4f** containing benzyl substituent shown the best scavenging activity, it could be because of the more effectively distribution of unpaired electron in the produced radicals (phenyl *vs*. alkyl). Compound **3** unexpectedly exhibited low DPPH radical inhibitory activity, nevertheless, it possesses good *H*-donating N─H bond.

**Scheme 2.** The proposed mechanism of product oxidation by DPPH.



## CONCLUSION

13*H*,15*H*-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-*b*]quinazolin-15-one (**3**), a novel fused pentacyclic system, was synthesized in quantitative yield from a condensation reaction between 2,3-dichloroquinoxaline (**1**) and 3-amino-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**2**) in DMF. The cyclization reaction is so facile and takes place in one step, under mild conditions. More derivatives were obtained on further treatment of the newly synthesized compound (**3**) with several alkylbromides under the similar conditions. Antioxidant activity of all synthesized compounds was determined using the DPPH free radical scavenging assay, and the results are reported.

## EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9200 melting point apparatus. The infrared spectra were obtained on Avatar 370 Fourier transform infrared (FTIR) Thermo Nicolet, and only noteworthy absorptions were listed. The $^{1}$H NMR (300 MHz) and the $^{13}$C NMR (75 MHz) spectra were recorded on a Bruker Advance DRX-300 Fourier transformer spectrometer. Chemical shifts were reported in ppm downfield from tetramethylsilane as internal standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyzer.

**Synthesis of 13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one (3)**. To a mixture of 2,3-dichloroquinoxaline **(1)** (1 mmol, 197 mg) and 3-amino-2-thioxo-2,3-dihydroquinazolin −4(1H)-one **(2)** (1 mmol, 193 mg) in DMF at 80°C, was added $K_2CO_3$ (2 mmol, 276 mg). The reaction mixture was left stirring at 80°C for 5 h and then cooled to room temperature. The orange precipitate was filtered off and recrystallized from DMF to yield the bright yellow powder 13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one **(3)**. Yield = 73%; mp > 300°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$, 25°C): δ 6.76 (t, 1H, *J* = 9 Hz, quinazoline-$H_b$), 6.99 (dd, 1H, *J* = 6 Hz, *J* = 3 Hz, quinazoline-$H_d$), 7.12 (t, 1H, *J* = 9 Hz, quinoxaline-$H_{c'}$), 7.19 (dd, 1H, *J* = 3 Hz, *J* = 6 Hz, quinoxaline-$H_{d'}$), 7.34 (t, 1H, *J* = 6 Hz, quinoxaline-$H_{b'}$), 7.40 (d, 1H, *J* = 9 Hz, quinoxaline-$H_{a'}$), 7.62 (t, 1H, *J* = 6 Hz, quinazoline-$H_c$), 7.96 (s, 1H, $D_2O$-exchangeable NH), 7.99 (dd, 1H, *J* = 3 Hz, *J* = 6 Hz, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, DMSO-$d_6$, 25°C); δ 119.6 (quinazoline-C-$H_b$), 120.9 (quinazoline-C-$H_d$), 124.4 (quinoxaline-C-$H_{b'}$), 125.8 (quinoxaline-C-$H_{c'}$), 126.6 (quinazoline-C-$H_c$), 126.9 (quinoxaline-C-$H_{a'}$), 129.0 (quinoxaline-C-$H_{d'}$), 133.3 (quinazoline-C-$H_a$), 136.4 (C─CO), 142.5 (N─C═C─$H_{a'}$), 145.6 (N─C═C─$H_{d'}$), 145.8 (S─$C_{(quinoxaline)}$═N), 147.5 (N─C═C─$H_d$), 152.0 (NH─C═N), 156.9 (S─$C_{(quinazoline)}$═N), 162.7 (CO). FTIR (KBr disk, $\nu_{max}$): 3236 [─NH], 2918 [─$CH_2$], 1685 [─C═O], 1607[─C═N], 1548 [─C═N] cm$^{-1}$. MS (*m/z*) 319 ($M^+$), 161 ($M^+$- NH-quinazoline). *Anal*. Calcd for $C_{16}H_9N_5OS$: C, 60.18; H, 2.84; N, 21.93; S, 10.04. Found: C, 60.09; H, 2.80; N, 21.85; S, 9.90.

**General procedure for synthesis of 13-alkyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one 4(a–f)**. To a mixture of compound (**3**) (1 mmol, 319 mg) and $K_2CO_3$ (1 mmol, 138 mg) in DMF at room temperature, was added appropriate alkylbromide (1.2 mmol). The reaction was heated to 80°C for 4 h. After the completion of reaction which was monitored by thin-layer chromatography using *n*-hexane/ ETOAc (2:1) as eluent, the mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was washed with water and further purified by column chromatography to yield the desired products **4(a–f)**.

***13-Ethyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one (4a)***. Yellow powder, yield = 68%; mp 215–218°C (decomposed); $^{1}$H NMR (300 MHz, $CDCl_3$, 25°C): δ 1.36 (t, 3H, *J* = 9 Hz, $CH_3$), 4.23 (q, 2H, *J* = 12 Hz, *J* = 21 Hz, $CH_2$─N), 7.03–7.08 (m, 2H, quinazoline-$H_b$,$H_d$), 7.29–7.36 (m, 2H, quinoxaline-$H_{c'}$,$H_{d'}$), 7.43 (t, 2H, *J* = 9 Hz, quinoxaline-$H_{a'}$,$H_{b'}$), 7.61 (t, 1H, *J* = 6 Hz, quinazoline-$H_c$), 8.17 (d, 1H, *J* = 9 Hz, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 10.7 ($CH_3$), 39.5 ($CH_2$─N), 113.1 (quinazoline-C-$H_b$), 121.4 (quinazoline-C-$H_d$), 123.1 (quinoxaline-C-$H_{b'}$), 126.1 (quinoxaline-C-$H_{c'}$), 126.7 (quinazoline-C-$H_c$), 127.7 (quinoxaline-C-$H_{a'}$), 128.7 (quinoxaline-C-$H_{d'}$), 130.7 (quinazoline-C-$H_a$), 132.3 (C─CO), 133.9 (N─C═C─$H_{a'}$), 134.5 (N-C═C─$H_{d'}$), 137.5 (S─$C_{(quinoxaline)}$═N), 145.7 (N─C═C─$H_d$), 146.3 (NH─C═N), 146.5 (S─$C_{(quinazoline)}$═N), 157.2 (CO). FTIR (KBr disk, $\nu_{max}$): 2923 [─$CH_2$], 1704 [─C═O], 1547[─C═N], 1527[─C═N] cm$^{-1}$. MS (*m/z*) 347 ($M^+$), 318 ($M^+$ – Et). *Anal*. Calcd for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16; S, 9.23. Found: C, 62.39; H, 3.86; N, 20.08; S, 9.03.

***13-Propyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino[2,3-b]quinazolin-15-one (4b)***. Yellow powder, yield = 63%; mp 180–183°C (decomposed); $^{1}$H NMR (300 MHz, $CDCl_3$, 25°C): δ 1.17 (t, 3H, *J* = 9 Hz, $CH_3$), 1.84–1.97 (m, 2H, $CH_2$), 4.23 (t, 2H, *J* = 6 Hz, $CH_2$─N), 7.12–7.19 (m, 2H, quinazoline-$H_b$,$H_d$), 7.42 (m, 2H, quinoxaline-$H_{c'}$,$H_{d'}$), 7.54 (t, 2H, *J* = 6 Hz, quinoxaline-$H_{a'}$,$H_{b'}$), 7.72 (t, 1H, *J* = 9 Hz, quinazoline-$H_c$), 8.29 (dd, 1H, *J* = 6, J = 3, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 11.5 ($CH_3$), 19.0 ($CH_2$), 45.8 ($CH_2$─N), 113.1 (quinazoline-C-$H_b$), 121.4 (quinazoline-C-$H_d$), 123.1 (quinoxaline-C-$H_{b'}$), 126.1 (quinoxaline-C-$H_{c'}$), 126.7 (quinazoline-C-$H_c$), 127.7

(quinoxaline-C-$H_{a'}$), 128.7 (quinoxaline-C-$H_{d'}$), 130.7 (quinazoline-C-$H_a$), 132.3 (C—CO), 133.9 (N—C=C—$H_{a'}$), 134.5 (N—C=C—$H_{d'}$), 137.5 (S—$C_{(quinoxaline)}$=N), 145.7 (N—C=C—$H_d$), 146.1 (NH—C=N), 146.5 (S—$C_{(quinazoline)}$=N), 157.2 (CO). FTIR (KBr disk, $\nu_{max}$): 2920 [—$CH_2$], 1698 [—C=O], 1545 [—C=N], 1526 [—C=N] $cm^{-1}$. MS (*m/z*) 361 ($M^+$), 318 ($M^+$ – Pr). *Anal*. Calcd for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38; S, 8.87. Found: C, 63.29; H, 4.11; N, 19.41; S, 8.79.

***13-Butyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino [2,3-b]quinazolin-15-one (4c).*** Yellow powder, yield = 61%; mp 148–152°C (decomposed); $^1$H NMR (300 MHz, $CDCl_3$, 25°C): δ 1.06 (t, 3H, *J* = 6 Hz, $CH_3$), 1.54–1.64 (m, 2H, $CH_2$), 1.78 (m, 2H, $CH_2$), 4.25 (t, 2H, *J* = 6 Hz, $CH_2$—N), 7.14 (t, 2H, *J* = 9 Hz, quinazoline-$H_b$,$H_d$), 7.41 (m, 2H, quinoxaline-$H_{c'}$,$H_{d'}$), 7.52 (t, 2H, *J* = 9 Hz, quinoxaline-$H_{a'}$,$H_{b'}$), 7.70 (t, 1H, *J* = 6 Hz, quinazoline-$H_c$), 8.27 (d, 1H, *J* = 9 Hz, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 13.8 ($CH_3$), 20.3 ($CH_2$—Me), 27.6 ($CH_2$—Et), 44.15 ($CH_2$—N), 113.3 (quinazoline-C-$H_b$), 121.4 (quinazoline-C-$H_d$), 123.0 (quinoxaline-C-$H_{b'}$), 126.1 (quinoxaline-C-$H_{c'}$), 126.7 (quinazoline-C-$H_c$), 127.6 (quinoxaline-C-$H_{a'}$), 128.7 (quinoxaline-C-$H_{d'}$), 130.6 (quinazoline-C-$H_a$), 132.6 (C—CO), 133.8 (N—C=C—$H_{a'}$), 134.4 (N—C=C—$H_{d'}$), 137.8 (S—$C_{(quinoxaline)}$ = N), 145.7 (N—C=C—$H_d$), 146.2 (NH—C=N), 146.6 (S—$C_{(quinazoline)}$=N), 157.2 (CO). FTIR (KBr disk, $\nu_{max}$): 2922 [—$CH_2$], 1708 [—C=O], 1547 [—C=N], 1527 [—C=N] $cm^{-1}$. MS (*m/z*) 375 ($M^+$), 318 ($M^+$ – Bu). *Anal*. Calcd for $C_{20}H_{17}N_5OS$: C, 63.98; H, 4.56; N, 18.65; S, 8.54. Found C, 63.90; H, 4.67; N, 18.71; S, 8.40.

***13-Pentyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino [2,3-b]quinazolin-15-one (4d).*** Yellow powder, yield = 54%; mp 133–136°C (decomposed); $^1$H NMR (300 MHz, $CDCl_3$, 25°C): δ 0.88 (t, 3H, *J* = 6 Hz, $CH_3$), 1.37–1.48 (m, 4H, $2CH_2$), 1.64–1.81 (m, 2H, $CH_2$), 4.12 (t, 2H, *J* = 6 Hz, $CH_2$—N), 7.01 (t, 2H, *J* = 9, quinazoline-$H_b$, $H_d$), 7.19–7.33 (m, 2H, quinoxaline-$H_{c'}$,$H_{d'}$), 7.36–7.43 (m, 2H, quinoxaline-$H_{a'}$,$H_{b'}$), 7.58 (t, 1H, *J* = 4 Hz, quinazoline-$H_c$), 8.15 (d, 1H, *J* = 9, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 14.0 ($CH_3$), 22.4 ($CH_2$—Me), 25.2 ($CH_2$—Et), 29.1 ($CH_2$—Pr), 44.3 ($CH_2$—N), 113.3 (quinazoline-C-$H_b$), 121.4 (quinazoline-C-$H_d$), 123.0 (quinoxaline-C-$H_{b'}$), 126.0 (quinoxaline-C-$H_{c'}$), 126.6 (quinazoline-C-$H_c$), 127.6 (quinoxaline-C-$H_{a'}$), 128.6 (quinoxaline-C-$H_{d'}$), 130.6 (quinazoline-C-$H_a$), 132.5 (C—CO), 133.8 (N—C=C—$H_{a'}$), 134.4 (N—C=C—$H_{d'}$), 137.7 (S—$C_{(quinoxaline)}$=N), 145.7 (N—C=C—$H_d$), 146.2 (NH—C=N), 146.5 (S—$C_{(quinazoline)}$=N), 157.1 (CO). FTIR (KBr disk, $\nu_{max}$): 2920 [—$CH_2$], 1708 [—C=O], 1548 [—C=N], 1529 [—C=N] $cm^{-1}$. MS (*m/z*) 389 ($M^+$), 318 ($M^+$ – Pentyl). *Anal*. Calcd for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98; S, 8.23. Found C, 64.81; H, 4.93; N, 17.91; S, 8.12.

***13-Hexyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino [2,3-b]quinazolin-15-one (4e).*** Yellow powder, yield = 48%; mp 119–123°C (decomposed); $^1$H NMR (300 MHz, $CDCl_3$, 25°C): δ 0.84 (t, 3H, *J* = 6 Hz, $CH_3$), 1.18–1.27 (m, 4H, $2CH_2$), 1.44–1.49 (m, 2H, $CH_2$), 1.68–1.80 (m, 2H, $CH_2$), 4.12 (t, 2H, *J* = 4 Hz, $CH_2$—N), 7.02 (t, 2H, *J* = 6 Hz, quinazoline-$H_b$,$H_d$), 7.26–7.48 (m, 4H, quinoxaline-$H_{c'}$,$H_{d'}$, $H_{a'}$,$H_{b'}$), 7.69 (t, 1H, *J* = 3 Hz, quinazoline-$H_c$), 8.17 (d, 1H, *J* = 6 Hz, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 14.0 ($CH_3$), 22.6 ($CH_2$—Me), 25.5 ($CH_2$—Et), 26.7 ($CH_2$—Pr), 31.5 ($CH_2$—Bu), 44.4 ($CH_2$—N), 113.3 (quinazoline-C-$H_b$), 121.4 (quinazoline-C-$H_d$), 123.0 (quinoxaline-C-$H_{b'}$), 126.1 (quinoxaline-C-$H_{c'}$), 126.6 (quinazoline-C-$H_c$), 127.6 (quinoxaline-C-$H_{a'}$), 128.7 (quinoxaline-C-$H_{d'}$), 130.6 (quinazoline-C-$H_a$), 132.6 (C—CO), 133.8 (N—C=C—$H_{a'}$), 134.4 (N—C=C—$H_{d'}$), 137.7 (S—$C_{(quinoxaline)}$=N), 145.7 (N—C=C—$H_d$), 146.3 (NH—C=N), 146.5 (S—$C_{(quinazoline)}$=N), 157.1 (CO). FTIR (KBr disk, $\nu_{max}$): 2926 [—$CH_2$], 1707 [—C=O], 1549 [—C=N], 1529 [—C=N] $cm^{-1}$. MS (*m/z*) 403 ($M^+$), 318 ($M^+$ – Hexyl). *Anal*. Calcd for $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36; S, 7.95. Found C, 65.51; H, 5.30; N, 17.33; S, 7.90.

***13-Benzyl-13H,15H-quinoxalino[2′,3′:5,6][1,3,4]thiadiazino [2,3-b]quinazolin-15-one (4f).*** Yellow powder, yield = 69%; mp 153–156°C (decomposed); $^1$H NMR (300 MHz, $CDCl_3$, 25°C): δ 5.46 (s, 2H, $CH_2$—N), 7.2 (s, 5H, Bz), 7.47 (t, 1H, *J* = 9 Hz, quinazoline-$H_b$), 7.57 (d, 1H, *J* = 9 Hz, quinazoline-$H_d$), 7.67–7.78 (m, 3H, quinoxaline-$H_{c'}$, $H_{d'}$, $H_{b'}$), 8.02 (t, 2H, *J* = 12 Hz, $H_{a'}$, $H_c$), 8.28 (d, 1H, *J* = 9 Hz, quinazoline-$H_a$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C); δ 55.75 ($CH_2$-Ph), 121.6 (quinazoline-C-$H_b$), 126.4 (quinazoline-C-$H_d$), 126.9 (quinoxaline-C-$H_{b'}$), 127.2 (quinoxaline-C-$H_{c'}$), 128.1 (Bz), 128.3 (Bz), 128.5 (quinazoline-C-$H_c$), 128.8 (quinoxaline-C-$H_{a'}$), 128.9 (quinoxaline-C-$H_{d'}$), 130.5 (quinazoline-C-$H_a$), 134.5 (C—CO), 134.9 (N—C=C—$H_{a'}$), 139.5 (N—C=C—$H_{d'}$), 140.2 (Bz), 145.7 (S—$C_{(quinoxaline)}$=N), 146.1 (N—C=C—$H_d$), 148.7 (NH—C=N), 153.2 (S—$C_{(quinazoline)}$=N), 157.9 (CO). FTIR (KBr disk, $\nu_{max}$): 2925 [—$CH_2$], 1695 [—C=O], 1578 [—C=N], 1556 [—C=N] $cm^{-1}$. MS (*m/z*) 409 ($M^+$), 302 ($M^+$ – NBz). *Anal*. Calcd for $C_{23}H_{15}N_5OS$: C, 67.47; H, 3.69; N, 17.10; S, 7.83. Found C, 67.43; H, 3.58; N, 17.19; S, 7.69.

**Acknowledgments.** The authors gratefully acknowledge the Research Council of Ferdowsi University of Mashhad as the funder of this project for its partial financial support (3/33579).

## REFERENCES AND NOTES

[1] Burguete, A.; Pontiki, E.; Litina, D. H.; Villar, R.; Vicente, E. Bioorg Med Chem Lett 2007, 17, 6439.

[2] Lindsley, C. W.; Zhao, Z.; Leister, W.H.; Robinson, R. G.; Barnett S. G.; R.E.Defeo-Jones R.E. Bioorg Med Chem Lett 15, 2005, 761.

[3] El-Tombary, A. A. S A Med Chem 2014, 10, 521.

[4] More, S. V.; Sastry, M. N. V.; Wang, C. C. F Tetrahedron Lett 2005, 46, 6345.

[5] Burguete, A.; Pontiki, E.; Hadjipavlou-Litina, D.; Ancizu, S.; Villar, R.; Solano, B.; Moreno, E.; Torres, E.; Pérez, S.; Aldana, I. Chem Biol Drug Des 2011, 77, 255.

[6] Rohini, R.; Muralidhar Reddy, P.; Shanker, K.; Hu, A. V Eur J Med Chem 2010, 45, 1200.

[7] Amin, M. A. M M Pharma Chemica 2012, 4, 1323.

[8] Chandrika, P. M.; Yakaiah, T.; Narsaiah, B.; Sridhar, V.; Venugopal, G.; Rao, J. V.; Kumar, K. P.; Murthy, U. S. N. R R Indian J Chem 2009, 48B, 840.

[9] Chandregowda, V.; Kush, A. K. G Eur J Med Chem 2009, 44, 3046.

[10] Guillon, J.; Moreau, S.; Ronga, L.; Basmacyian, L.; Cohen, A.; Rubio, S.; Bentzinger, G.; Savrimoutou, S.; Azas, N.; Mullié, C. P Lett Drug Des Discov 2016, 13, 932.

[11] Jatav, V.; Kashaw, S. P Med Chem Res 2008, 17, 205.

[12] Alagarsamy, V.; Solomon, V. R. K Bioorg Med Chem 2007, 15, 235.

[13] Hassan, A. Y. Sulfur Silicon Relat Elem 2009, 184, 2759.

[14] Mohan, J. A Indian J Heterocycl Chem 2011, 21, 117.

[15] Shiradkar, M. R.; Padhalingappa, M. B.; Bhetalabhotala, S.; Akula, K. C.; Tupe, D. A.; Pinninti, R. R. S Bioorg Med Chem 2007, 15, 6397.

[16] Sunder, S.; Peet, N.P. J Heterocycl Chem 16, 1979, 1339.

[17] Vijayakumar, B.; Kumar, C. P.; Sivaprasad, G.; Nirosha, K.; Rokkam, S. E Intl J Novel Tr Pharm Sci 2011, 1, 1.

[18] Hossain, M. M.; Hossain, M. M.; Muhib, M. H.; Mia, M. R.; Kumar, S. A Bangladesh Med Res Counc Bull 2012, 38, 47.

[19] Rahimizadeh, M.; Shiri, A.; Ranaei, M.; Bakavoli, M. Heterocycl Commun 2012, 18, 39.

[20] Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Eshghi, H.; Vaziri-Mehr, S.; Pordeli, P. M Heterocycl Commun 2011, 17, 49.

[21] Krishnan, V. S. H.; Chowdary, K. S. K Indian J Chem 1999, 38B, 1371.

[22] Cherbuliez, E.; Wilhalm, B.; Jaccard, S. J Helv Chim Acta 1967, 50, 2563.

[23] Vijaya Bhaskara, M.; Reddy, D.; Srinivasulu, K.; Peddanna, Ch.; Apparao, P. R. Synth Commun 45, 2015, 2592.

[24] Baciocchi, E.; Calcagni, A. O J Org Chem 2008, 73, 4110.

[25] Rodríguez, J.; Arán, V. J.; Boiani, L.; Olea-Azar, C.; Laura Lavaggi, M.; González, M.; Cerecetto, H.; Diego Maya, J.; Carrasco-Pozo, C. H Bioorg Med Chem 2009, 17, 818.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.