A new pathway for the preparation of biologically active 2-substituted 1,5-dihydrobenzo[e][1,2,4]oxadiazepines and related compounds by palladium-catalyzed cyclization of amidoximes with o-iodobenzyl bromide or 2-bromo-3-chloromethylpyridine

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Abstract
A simple palladium-catalyzed one-pot synthesis of 2-substituted 1,5-dihydrobenzo[e][1,2,4]-oxadiazepines from corresponding (E)-amidoximes and o-iodobenzyl bromide or 2-bromo-3-chloromethylpyridine is described. Of the derivatives prepared 2-[6-(quinolin-2-ylsulfanyl)-hexyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine exhibits high activity on HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) cancer cell lines.

Keywords: 2-Substituted 1,5-dihydrobenzo[e][1,2,4]oxadiazepines, palladium catalyst, coupling, (E)-amidoximes, o-iodobenzyl bromide, 2-bromo-3-chloromethylpyridine

Introduction

Seven-membered heterocycles are often present in the wide range of biologically active molecules. Several recent chemical review articles were dedicated to the synthesis and transformation of seven membered rings. Furthermore, two chapters on the chemistry of seven-membered rings with three heteroatoms at the positions 1, 2 and 4 have appeared. 3,5,7-Trisubstituted 4,7-dihydro-1,2,4-oxadiazepines have been prepared via a two step method starting from enones using NH₂CONHOH/MeONa then Me₂SO₄/KOH, and the intramolecular condensation of methyl 2-chloro-2-(phenylcarbamoylimidoylaminoxyxycyclopropyl)acetate in the presence of NaH in acetonitrile leading to 9-chloro-6-phenyl-5,7-diaza-4-oxaspiro[2,6]non-5-en-8-one has also been reported. Recently we published articles on palladium catalyzed synthesis of 3-substituted 1,2,4-oxadiazepines from (E)-O-(2-iodophenylmethyl)amidoximes. However, there are no general methods for the synthesis of benzo or pyridine fused substituted 1,2,4-oxadiazepines directly from (E)-amidoximes.
**Results and Discussion**

Herein we report a novel and simple palladium-catalyzed one-pot method for the preparation of 2-substituted 1,5-dihydrobenzo[e][1,2,4]oxadiazepines directly from the corresponding \( E \)-amidoximes and \( o \)-iodobenzyl bromide (11a) or 2-bromo-3-chloromethylpyridine (11b) by \( O \)-alkylation/\( N \)-arylation tandem reaction. The first reaction step includes selective \( O \)-alkylation of amidoximes 1-10\(^{11}\) in the system halide 11a or 11b/solid Cs\(_2\)CO\(_3\)/dry dioxane leading to (\( E \))-\( O \)-[2-halophenyl(or pyridyl)methyl]amidoxime intermediates.\(^{11}\) Our previous experiments showed that the optimal reaction temperature for the successful amidoxime \( O \)-alkylation was ca. 60 °C.\(^{12}\) The second reaction step is Pd(0)-catalyzed cyclization of \( (E)\)-\( O \)-[2-halophenyl (or pyridyl)-methyl]amidoxime intermediates. This step was successfully carried out at ca. 120 °C. The high activity of palladium catalysts in \( N \)-arylation of amidoxime \( O \)-alkyl derivatives was previously demonstrated.\(^{12}\) However, to the best of our knowledge, the palladium catalyzed intramolecular cyclization of oxime \( O \)-ethers has not yet been studied. Beside this some articles were dedicated to palladium-catalyzed \( N \)-arylation of amidoximes with aryl halides.\(^{13}\)

Thus, interaction of \( E \)-isomers of aromatic 1-2 and quinoline amidoximes 3 with \( o \)-iodobenzyl bromide (11a) or 2-bromo-3-chloromethylpyridine (11b) in the system solid dry Cs\(_2\)CO\(_3\)/Pd\(_2\)(dba)\(_3\)/Xantphos leads to corresponding oxadiazepines 12-16 isolated in 23-60% yields by column chromatography (Scheme 1, Table 1, entries 1-5).\(^{12}\) Corresponding aromatic or quinoline nitriles were isolated as minor side-products as a result of palladium mediated deoximation under basic conditions. Benzylic amidoximes 4 and 5 react similarly to aromatic amidoximes leading to corresponding 1,2,4-oxadiazepines 17 and 18 in 42 or 49 % yields, respectively (Scheme 1, Table 1, entries 6 and 7). Interestingly, in the case of the amidoxime 5 the double cyclization product was not observed by GC-MS and \( ^1\)H NMR methods presumably because the proposed pyrrolooxadiazepine ring system suffered from increased steric hindrance.

Aliphatic amidoximes 6-10 also readily react with \( o \)-iodobenzyl bromide (11a) or 2-bromo-3-chloromethylpyridine (11b) in the same system leading to corresponding oxadiazepines in 17-52% yields (Table 1, entries 8-13).

![Scheme 1](image-url)
The structure of compound 17 was supported by single crystal X-ray structural data (Figure 1). The atoms N(4), C(5), C(6) and C(7) in the seven-membered cycle lie in one plane, which correspond to the benzene ring plane of C(6), C(5), C(15), C(16), C(17), C(18). The atoms O(1), N(2) and C(3) deviate from this plane by 1.032(5), 0.641(6) and 0.326(7) Å, respectively. The dihedral angle between this plane and the benzyl group plane is equal 74.4(8)º. The C(3)–N(2) bond length [1.294(6) Å] indicates that the double bond weakly takes part in the molecular structure conjugation. In the crystal structure all contacts between the molecules correspond to sums of van der Waals radii.

**Figure 1.** A perspective view of compound 17 showing the thermal ellipsoids and the atomic labels followed in the text.

The experimental data suggests that the double cyclization forming two large membered rings can be achieved in the case of 2-bromophenyl amidoxime (for example, compound 10). Our first experiments showed that cyclization of oxime 10 in the system 2-iodobenzyl bromide (11a)/solid Cs₂CO₃/Pd₂(dba)₃/Xantphos/dry dioxane afforded oxadiazepine 24 as a main product in 32% yield. Bicyclic product 25 was identified by LC-MS and ¹H NMR only in trace amounts because of the side reactions in the synthesis of nine-membered ring (for example oligomerization of intermediate 24 in the presence of palladium catalyst) (Table 1, entry 13).

![Scheme 2](image-url)
It was found that the system benzyl bromide/solid Cs$_2$CO$_3$/Pd$_2$(dba)$_3$/Xantphos/dioxane was the best for the one pot $O$-alkylation/$N$-arylation tandem reaction of oxime 26 leading to 2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one $O$-benzyloxime (27) in 62% yield (Scheme 2).

**Table 1.** Synthesis of 3-substituted 1,2,4-oxadiazepines 12-24 from $E$-oximes 1-10 and o-iodobenzyl bromide or 2-bromo-3-chloromethylpyridine in the system solid Cs$_2$CO$_3$/Pd$_2$(dba)$_3$-/Xantphos/dry dioxane at 60 °C for 12 h then 120 °C for 24-48 h

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<th>Oxime</th>
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<th>Reaction time, (h)</th>
<th>Products</th>
<th>Yield, (%)</th>
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<th>Products</th>
<th>Yield, (%)</th>
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\( \text{Compound 25 was registered by LC-MS and }^1 \text{H NMR spectra.} \)

Scheme 3
The proposed mechanism of formation of desired 1,2,4-oxadiazepines 12-24 included selective oxime O-alkylation leading to an intermediate A, which undergo oxidative addition of (Xantphos)Pd(0) complex leading to an intermediate B. Cyclization of tautomeric form C afforded products 12-24 as result of reductive elimination (Scheme 3).

![Scheme 4]

The above data suggests that similar cyclization reaction was carried out using (E)-acetophenone O-(2-iodobenzyl)oxime (28), prepared from acetophenone oxime and 2-iodobenzyl bromide (11a), in the presence of base/Pd$_2$(dba)$_3$/Xantphos/dioxane system (Scheme 4). The influence of base on the cyclization of ether 28 to oxazepine 29 was studied. Thus, cyclization of the oxime ether 28 in the system Cs$_2$CO$_3$ (3 equiv)/Pd$_2$(dba)$_3$ (4 mol %)/Xantphos (4 mol %) gave the desired product 29 in 55% yield (GC-MS data). While the replacement of solid dry Cs$_2$CO$_3$ by t-BuOK diminished the yield of product 29 to 45%. The use of solid KOH as base in the palladium-catalyzed cyclization of 29 was essentially ineffective. Unfortunately, product 29 was unstable and therefore was characterized by $^1$H NMR and GC-MS only.

**Table 2.** Cytotoxicity of 2-[4-(thiazol-2-ylthio)butyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (19) and 2-[6-(quinolin-2-ylthio)hexyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (23) IC$_{50}$ (µg/mL)

<table>
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<th>Compound</th>
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<th>MG-22A, IC$_{50}$</th>
<th>3T3, LD$_{50}$, mg/kg</th>
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Cytotoxic activity of compounds 19 and 23 was tested *in vitro* on two monolayer tumor cell lines: MG-22A and HT-1080 (Table 2). These compounds were selected from a wide range of 3-substituted 1,2,4-oxadiazepines because of high activity of corresponding quinoline and thiazole containing N-hydroxy-ω-(hetarylmethoxy or hetarylthio)alkanamidines, the synthesis and cytotoxicity of which were presented in our earlier work.$^{11c}$ Beside this, compounds 19 and 23 formally are masked amidoxime O-benzyl ethers. Thus, compound 23 exhibit high activity on both cancer cell lines. N-Hydroxy-7-(quinolin-2-ylsulfanyl)heptanamidine$^{11c}$ exhibits similar cytotoxicity to compound 23. However, compound 19 was inactive on the MG-22A and HT-1080 cancer cell lines.
Toxicity of compounds 19 and 23 (LD$_{50}$ 313 and 639 mg/kg) was detected on mouse normal fibroblasts.

Conclusions

In conclusion, a simple palladium-catalyzed one pot synthesis of fused 3-substituted 1,2,4-oxadiazepines from corresponding (E)-amidoximes and o-iodobenzyl bromide or 2-bromo-3-chloromethylpyridine was developed. It was also demonstrated that the system benzyl bromide/solid Cs$_2$CO$_3$/Pd$_2$(dba)$_3$/Xantphos/dioxane was an excellent for O-alkylation/N-arylation tandem reaction of oxime 26 leading to 2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one O-benzyl oxime (27) in 62% yield by one pot method. Some of prepared compounds, which formally are masked amidoxime O-benzyloximes, were tested as cytotoxic agents. 2-[6-(Quinolin-2-ylsulfanyl)hexyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (23) exhibits high activity on HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) cancer cell lines.

Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury BB 400 MHz in CDCl$_3$ using HMDSO as internal standard. LC-MS spectra were recorded on Alliance Waters 2695 instrument and Waters 3100 mass detector. Column chromatography was performed with silica gel 0,035-0,070 mm (Acros). Oximes 1-10 and 26 we prepared as described in article. $^{11}$c 2-Iodobenzyl bromide (11a) (AlfaAesar), Pd$_2$(dba)$_3$ (Acros), Xantphos (Acros), Cs$_2$CO$_3$ (Acros), and dioxane (extra dry over molecular sieves, Acros) were used without purification. Diffraction data were collected at −50 °C on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å). The crystal structure of compound 17 was solved by direct methods and refined by full-matrix least squares using the programs. $^{14}$ All nonhydrogen atoms were refined in anisotropical approximation, all H-atoms were refined by riding model. Crystal data for 17: monoclinic; $a = 5.9170(5)$, $b = 24.0941(7)$, $c = 8.488(2)$ Å, $\beta = 92.089(4)^\circ$; $V = 1209.3(4)$ Å$^3$, $Z = 4$, $\mu = 0.084$ mm$^{-1}$; space group is $P 2_1/n$. A total of 6715 reflection intensities were collected up to $2\theta_{\text{max}} = 55^\circ$; for structure refinement 1132 independent reflections with $I > 2\sigma(I)$ were used. The final $R$-factor is 0.0971. For further details, see crystallographic data for 17 deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 828013. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. All prepared compounds are new and were characterized by melting point, $^1$H NMR, $^{13}$C NMR spectra, LC-MS and high resolution mass spectroscopy (by exception of compounds 20, 24 and 29 due to instability).
Typical procedure for the preparation of fused 3-substituted 1,2,4-oxadiazepines (12-24) directly from oximes (1-10)

Mixture of oxime 1-10 (1 mmol), o-halobenzyl halide 11a or 11b (0.30 g, 1 mmol), Pd2(dba)3 (36.6 mg, 0.04 mmol), Xantphos (23.2 mg, 0.04 mmol) and anhydrous Cs2CO3 (1.30 g, 4 mmol) in dry dioxane (3 mL) was heated at 60 °C for 12 h then at 120 °C for 24-48 h in glass reactor under argon. Reaction mixture was diluted (EtOAc, 30 mL), filtered, solvent was removed under reduced pressure and crude residue was chromatographed on silica (EtOAc/hexane, 1:2 or 1:1), see Table 1.

2-Phenyl-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (12). Colorless solid. mp 156-158 °C. LC-MS, 225 (M$^+$+1). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm): 5.04 (s, 2H, CH$_2$), 6.66 (bs, 1H, NH), 6.84 (d, 1H, J = 8.0 Hz, 9-H), 6.93 (t, 1H, J = 7.6 Hz, 7-H), 7.07 (d, 1H, J = 7.6 Hz, 6-H), 7.20 (t, 1H, J = 8.0 Hz, 8-H), 7.41-7.53 (m, 4H, 3'-, 4'-, 5'-H and 6-H in Py), 7.77 (d, 2H, J = 8.0 Hz, 4'-H), 8.13 and 8.19 (both d, 2H, J = 8.8 Hz, 5'-H), 9.39 (bs, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm): 77.24 (CH$_2$), 117.68, 121.39, 127.45, 127.69, 128.33, 128.81, 129.86, 130.89, 133.52, 139.46, 157.35. HRMS: m/z [M+1]$^+$ calcd for C$_{14}$H$_{12}$N$_2$O: 225.0980; found 225.0986.

2-(o-Tolyl)-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (14). Colorless solid. mp 188-190 °C. LC-MS, 239 (M$^+$+1). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm): 2.46 (s, 3H, Me), 5.02 (s, 2H, CH$_2$), 6.44 (bs, 1H, NH), 6.75 (d, 1H, J = 8.0 Hz, 9-H), 6.92 (t, 1H, J = 7.6 Hz, 7-H), 7.07 (d, 1H, J = 6.8 Hz, 6-H), 7.17 (t, 1H, J = 8.0 Hz, 4'-H), 7.24 (m, 3H, 3'-H, 4'-H and 5'-H), 7.36 (t, 1H, J = 6.8 Hz, 5'-H), 7.44 (d, 1H, J = 8.0 Hz, 6'-H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm): 19.53 (CH$_3$), 77.26 (CH$_2$), 117.56, 121.47, 126.00, 127.71, 128.36, 129.18, 130.04, 130.07, 130.74, 133.19, 136.91, 139.65, 156.63. HRMS: m/z [M+1]$^+$ calcd for C$_{15}$H$_{14}$N$_2$O: 239.1184; found 239.1173.

2-(o-Tolyl)-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (15). Colorless solid. mp 193-194 °C. LC-MS, 240 (M$^+$+1). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm): 2.50 (s, 3H, Me), 5.03 (s, 2H, CH$_2$), 6.69 (m, 1H, 7-H in Py), 7.25-7.44 (m, 5H, 3'-H, 4'-H, 5'-H, 6'-H and 6-H in Py), 7.54 (d, 1H, J = 7.6 Hz, 8-H in Py), 8.82 (bs, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm): 19.22 (Me), 74.74 (CH$_2$), 116.15, 124.22, 125.71, 129.17, 129.85, 130.46, 132.22, 135.34, 136.77, 146.42, 152.23, 157.01. HRMS: m/z [M+1]$^+$ calcd for C$_{14}$H$_{13}$N$_3$O: 240.1137; found 240.1138.

2-(Quinolin-2-yl)-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (16). Colorless solid. mp: 156-158 °C. LC-MS, 276 (M$^+$+1). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm): 5.07 (s, 2H, CH$_2$), 6.93 (t, 1H, J = 7.2 Hz, 7-H), 7.10 (m, 2H, 6- and 9-H), 7.24 (m, 1H, 8-H), 7.58 (t, 1H, J = 7.6 Hz, 6'-H), 7.75 (t, 1H, J = 8.0 Hz, 7'-H), 7.84 (d, 1H, J = 8.0 Hz, 4'-H), 8.13 and 8.19 (both d, 2H, J = 8.8 Hz, 3'- and 8'-H), 8.28 (d, 1H, J = 8.8 Hz, 5'-H), 9.39 (bs, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm): 77.57 (CH$_2$), 118.29, 118.41, 121.30, 127.42, 127.61, 127.73, 128.57, 128.69, 129.13,
129.93, 130.02, 137.02, 139.60, 145.96, 148.85, 151.06. HRMS: m/z [M+1]^+ calcd for C_{17}H_{13}N_{3}O: 276.1137; found 276.1129.

2-Benzyl-1,5-dihydrobenzo[e][1,2,4]oxadiazone (17). Colorless solid. mp: 110 °C. LC-MS, 239 [M^+]. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 3.59 (s, 2H, CH_2), 4.86 (s, 2H, OCH_2), 5.98 (bs, 1H, NH), 6.48-6.50, 6.75-7.02 and 7.18-7.29 (all m, 9H, Ph and C_6H_4). ^13C NMR (100 MHz, CDCl_3) δ (ppm): 39.84 (CH_2), 77.31 (OCH_2), 117.38, 121.37, 127.59, 127.60, 128.20, 128.85, 128.86, 129.16, 129.17, 130.00, 133.30, 139.55, 155.70. HRMS: m/z [M+1]^+ calcd for C_{15}H_{14}N_{2}O: 239.1184; found 239.1177.

2-(2-Bromo-phenylmethyl)-1,5-dihydrobenzo[e][1,2,4]oxadiazone (18). Colorless solid. mp: 140-142 °C. LC-MS, 318 (M^+). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 3.82 (s, 2H, CH_2), 4.90 (s, 2H, OCH_2), 6.55 (bs, 1H, NH), 6.66 (d, 1H, J = 8.4 Hz, aryl), 6.86 (t, 1H, J = 7.2 Hz, aryl), 6.99 (d, 1H, J = 7.6 Hz, aryl), 7.10-7.19 (m, 2H, aryl), 7.32 (t, 1H, J = 7.2 Hz, aryl), 7.50 (d, 1H, J = 7.6 Hz, aryl), 7.60 (s, 1H, J = 8.0 Hz, aryl). ^13C NMR (100 MHz, CDCl_3) δ (ppm): 39.41 (CH_2), 76.93 (OCH_2), 117.59, 121.40, 124.32, 127.57, 128.26, 128.30, 129.31, 130.07, 131.10, 133.03, 135.58, 139.52, 155.58. HRMS: m/z [M]^+ calcd for C_{15}H_{13}BrN_{2}O: 317.0291; found 317.0289.

2-[4-(Thiazol-2-ylsulfanyl)butyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazone (19). Colorless solid. mp: 82 °C. LC-MS, 320 (M^+). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.87 (m, 4H, CH_2(CH_2)_2), 2.36 (t, 2H, J = 7.2 Hz, CCH_2), 3.23 (m, 2H, SCH_2), 4.88 (s, 2H, OCH_2), 6.57 (s, 1H, NH), 6.75 and 6.99 (both d, 2H, J = 8.0 Hz, 6-H and 9-H), 6.86 and 7.13 (both t, 2H, J = 8.0 Hz, 7-H and 8-H), 7.20 and 7.63 (both d, 2H, J = 3.2 Hz, thiazole). ^13C NMR (100 MHz, CDCl_3) δ (ppm): 26.20 (CH_2), 28.38 (CH_2), 33.02 (CH_2), 33.06 (SCH_2), 77.20 (OCH_2), 117.42, 119.11, 121.22, 127.55, 128.22, 130.05, 139.83, 142.66, 156.84, 164.84. HRMS: m/z [M]^+ calcd for C_{15}H_{13}N_{2}OS: 320.0891; found 320.0886.

3-[4-(1,5-Dihydrobenzo[e][1,2,4]oxadiazipin-2-yl)-butyl]-3H-benzothiazol-2-one (20). Oil. LC-MS, 353 (M^+). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.71-1.87 (m, 4H, CH_2(CH_2)_2), 2.41 (t, 2H, J = 8.0 Hz, CCH_2), 4.06 (t, 2H, J = 6.0 Hz, NCH_2), 4.95 (s, 2H, OCH_2), 6.85 (t, 1H, J = 7.6 Hz, 7-H), 6.92-6.98 (m, 2H, 9-H and 3'-H), 7.09 (d, 1H, J = 8.0 Hz, 6-H), 7.14-7.20 (m, 2H, 1'-H and 8-H), 7.33 (t, 1H, J = 8.0 Hz, 2'-H), 7.43 (d, 1H, J = 8.8 Hz, 4'-H). ^13C NMR (100 MHz, CDCl_3) δ (ppm): 24.21 (CH_2), 26.59 (CH_2), 32.03 (CCH_2), 40.89 (NCH_2), 76.99 (OCH_2), 110.85, 117.75, 122.65, 123.45, 126.17, 127.30, 128.00, 128.25, 129.91, 134.27, 136.62, 140.24, 150.35, 160.44.

3-[4-(1,5-Dihydropyrido[2,3-e][1,2,4]oxadiazipin-2-yl)-butyl]-3H-benzothiazol-2-one (21). Colorless solid. mp: 158-160 °C. LC-MS, 355 (M^+). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.76-1.88 (m, 4H, CH_2(CH_2)_2), 2.44 (t, 2H, J = 7.2 Hz, CCH_2), 4.01 (t, 2H, J = 6.8 Hz, NCH_2), 4.79 (s, 2H, OCH_2), 6.81 (m, 1H, 7-H in Py), 7.06 (d, 1H, J = 8.0 Hz, 1'-H in C_6H_4), 7.15 (t, 1H, J = 7.6 Hz, 3'-H in C_6H_4), 7.28-7.32 (m, 2H, 6-H in Py and 2'-H in C_6H_4), 7.38 (bs, 1H, NH), 7.40 (d, 1H, J = 7.6 Hz, 4'-H in C_6H_4), 8.12 (d, 1H, J = 5.2 Hz, 8-H in Py). ^13C NMR (100 MHz, CDCl_3) δ (ppm): 24.13 (CH_2), 26.51 (CH_2), 32.55 (CH_2), 41.70 (NCH_2), 74.69 (OCH_2), 110.56, 116.70, 122.67, 122.81, 123.11, 124.32, 126.36, 135.47, 136.78, 147.17,
152.40, 156.97, 170.34. HRMS: m/z [M+1]^+ calcld for C_{18}H_{18}N_{4}O_{2}S: 355.1189; found 355.1202.

2-[5-(4-Phenylthiazol-2-ylsulfanyl)pentyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (22). Oil. LC-MS, 410 (M^+ + 1). ^1^H NMR (400 MHz, CDCl_3) δ (ppm): 1.56-1.88 (m, 6H, CH_2(CH_2)_3), 2.32 (t, 2H, J = 8.0 Hz, CCH_2), 3.26 (t, 2H, J = 7.2 Hz, SCH_2), 4.89 (s, 2H, OCH_2), 6.33 (bs, 1H, NH), 6.73 (d, 1H, J = 8.0 Hz, 9-H), 6.86 (t, 1H, J = 7.6 Hz, 8-H), 6.99 (d, 1H, J = 6.8 Hz, 6-H), 7.13 (t, 1H, J = 8.0 Hz, 7-H), 7.23 (t, 1H, J = 6.8 Hz, 4'-H), 7.53 (s, 1H, thiazole), 7.39 (t, 2H, J = 8.0 Hz, 3'- and 5'-H), 7.86 (d, 2H, J = 8.0 Hz, 2'- and 6'-H). ^13^C NMR (100 MHz, CDCl_3) δ (ppm): 26.96, 27.86, 28.81, 33.67, 34.31, 77.57 (OCH), 112.36, 117.38, 121.23, 126.23, 127.56, 128.14, 128.21, 128.68, 130.05, 134.05, 139.77, 155.33, 156.93, 164.75. HRMS: m/z [M+1]^+ calcld for C_{22}H_{23}N_{3}O_{2}S: 410.1321; found 410.1335.

2-[6-(Quinolin-2-ylsulfanyl)hexyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (23). Oil. LC-MS, 392 (M^+ + 1). ^1^H NMR (400 MHz, CDCl_3) δ (ppm): 1.49 and 1.69-1.80 (both m, 8H, CH_2(CH_2)_4), 2.34 (t, 2H, J = 8.4 Hz, CCH_2), 3.34 (t, 2H, J = 7.6 Hz, SCH_2), 4.89 (s, 2H, OCH_2), 6.12 (bs, 1H, NH), 6.69 (d, 1H, J = 8.0 Hz, 9-H), 6.87 (t, 1H, J = 7.6 Hz, 7-H), 6.99 (d, 1H, J = 7.4 Hz, 6-H), 7.11 (t, 1H, J = 8.0 Hz, 8-H), 7.19 (d, 1H, J = 8.4 Hz, 3'-H), 7.40 (t, 1H, J = 8.0 Hz, 6'-H), 7.62 (t, 1H, J = 8.0 Hz, 7'-H), 7.70 (d, 1H, J = 8.0 Hz, 5'-H), 7.86 (d, 1H, J = 8.4 Hz, 4'-H), 7.91 (m, 1H, 8'-H). ^13^C NMR (100 MHz, CDCl_3) δ (ppm): 27.37 (CH_2), 28.46 (CH_2), 28.47 (CH_2), 29.15 (CH_2), 29.53 (CH_2), 33.86 (CH_2), 77.31 (OCH_2), 117.29, 121.04, 121.21, 125.12, 125.90, 127.59, 128.20, 128.20, 128.77, 129.56, 130.85, 135.19, 139.74, 148.32, 157.08, 159.45. HRMS: m/z [M+1]^+ calcld for C_{22}H_{23}N_{3}O_{2}S: 392.1797; found 392.1803.

2-[4-(2-Bromophenoxy)butyl]-1,5-dihydrobenzo[e][1,2,4]oxadiazepine (24). Oil. LC-MS, 375 (M^+ + 1). ^1^H NMR (400 MHz, CDCl_3) δ (ppm): 1.86-1.90 (m, 4H, CH_2(CH_2)_2), 2.38 (t, 2H, J = 7.2 Hz, CCH_2), 4.01 (t, 2H, J = 7.6 Hz, OCH_2), 4.82 (s, 2H, OCH_2), 6.53 (bs, 1H, NH), 6.70-7.05 (m, 6H, 6-7, 9-4', 5', 6'-H), 7.16 (t, 1H, J = 8.8 Hz, 8-H), 7.43 (d, 1H, J = 6.4 Hz, 3'-H). ^13^C NMR (100 MHz, CDCl_3) δ (ppm): 21.01 (CH_2), 24.46 (CH_2), 27.72 (CH_2), 60.36 (OCH_2), 68.59 (OCH_2), 112.02, 113.23, 117.50, 121.19, 121.90, 127.49, 128.52, 130.03, 133.24, 139.78, 155.07, 157.11, 171.12.

2,3-Dihydrobenzo[b][1,4]thiazepin-4(5H)-one O-benzyl oxime (27). Oil. LC-MS, 285 (M^+ + 1). ^1^H NMR (400 MHz, CDCl_3) δ (ppm): 2.45 (t, 2H, J = 6.8 Hz, CCH_2), 3.11 (t, 2H, J = 6.4 Hz, SCH_2), 4.97 (s, 2H, OCH_2), 6.80 (d, 1H, J = 8.0 Hz, 6-H), 6.92 (t, 1H, J = 8.0 Hz, 8-H), 7.00 (bs, 1H, NH), 7.14 (t, 1H, J = 8.0 Hz, 7-H), 7.20 (m, 1H, 4'-H), 7.26 (m, 2H, 3'- and 5'-H), 7.33 (d, 2H, J = 6.4 Hz, 2'-H and 6'-H), 7.41 (d, 1H, J = 8.0 Hz, 9-H). ^13^C NMR (100 MHz, CDCl_3) δ (ppm): 27.82 (CCH_2), 33.27 (SCH_2), 75.53 (OCH_2), 122.19, 124.88. 125.03, 127.89, 128.30, 128.40, 129.79, 135.39, 137.78, 142.19, 151.18. HRMS: m/z [M+1]^+ calcld for C_{16}H_{16}N_{2}O_{2}S: 285.1062; found 385.1072.

4-Phenyl-1,5-dihydrobenzo[e][1,2]oxazepine (29). Oil. GC-MS, 224 (M^+ + 1). ^1^H NMR (400 MHz, CDCl_3) δ (ppm): 4.22 (d, 2H, J = 6.0 Hz, CCH_2), 5.24 (s, 2H, OCH_2), 7.25-7.72 (m, 9H, Ph and C_6H_4).
**In Vitro Cytotoxicity Assay.** Monolayer tumor cell lines –HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), 3T3 (mouse Swiss Albino embryo fibroblasts) - were cultured in standard medium (Dulbecco’s modified Eagle’s medium; DMEM) and supplemented with 10% fetal bovine serum (“Sigma”). Tumor cell lines were obtained from the ATCC. After the ampoule had thawed, cells from one to four passages were used in three concentrations test compound: 1, 10 and 100 $\mu$g mL$^{-1}$. About $10 \times 10^4$ cells mL$^{-1}$ were placed in 96-well plates immediately after compounds were added to the wells; the volume of each plate was 200 µL. The control cells without test compounds were cultured on separate plate. The plates were incubated for 72 h, 37 °C, 5% CO$_2$. The number of surviving cells was determined using tri(4-dimethylaminophenyl)methyl chloride (crystal violet: CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolinium bromide (MTT). The quantity on the control plate was taken in calculations for 100%. LD$_{50}$ was tested according “Alternative Toxicological Methods”. The program Graph Pad Prism® 3.0 was used for calculations ($r < 0.05$).

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**References**


