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A combinatorial access to 1,5-benzodiazepine derivatives and their evaluation for aldose reductase inhibition

Minodora Pozarentzi [a], Julia Stephanidou-Stephanatou [a,*], Constantinos A. Tsoleridis [a,*], Chariklia Zika [b], Vassilis Demopoulos [b]

[a] Department of Chemistry, Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Macedonia, Greece
[b] Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki 54124, Macedonia, Greece

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ABSTRACT

Aryldiazepinothiophenones **4** were prepared from the reaction of *o*-phenylenediamines with acetone in the presence of 2-mercaptocarboxylic acids along with thiazolobenzodiazepines **6**, thiazolobenzimidazoles **7** and 1,5-benzodiazepines **5**, which were obtained as by-products. The benzodiazepinothiophenones **4a**–**d** and the benzodiazepines **5a**–**d** were also isolated from the reaction of *o*-phenylenediamines **1a**–**c** with phorone. Structural assignments of the new compounds as well as complete assignment of ^{1}H and ^{13}C NMR signals were based on the analysis of their ^{1}H and ^{13}C NMR (1D and 2D), IR, MS and elemental analysis data. Compounds **4** were evaluated for aldose reductase inhibition and also as antioxidants.

1. Introduction

Heterocyclic compounds are highly ranked among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs.

Heterocyclic derivatives such as morphine alkaloids, β-lactam antibiotics and benzodiazepines are just a few examples from various pharmaceuticals featuring a heterocyclic component.[1] The benzodiazepine nucleus is a pharmacophoric scaffold and many benzodiazepines have recently received great attention, because of their wide range of therapeutic and pharmacological properties. Many members of the diazepine family are nowadays widely used as antianxiety, antidepressant, sedative, hypnotic, tranquilizing, anticonvulsant, antihistaminic, analgesic and anti-inflammatory agents.[2,3] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers.[4] In addition, 1,5-benzodiazepines are important intermediates for the synthesis of various fused ring heterocyclic compounds such as oxazino-,[5] triazolo-,[5–7] oxadiazolo-,[6] furano-,[5,8] pyrimido-, and pyrazolo-,[9] and pyrido-benzodiazepines.[10] Due to their wide range of biological, industrial and synthetic applications the development of mild, efficient and environmentally friendly protocols continues to be a challenging endeavour in synthetic organic chemistry. As a result, considerable attention has been drawn recently to new improved methods for the preparation of 1,5-benzodiazepines,[11] since diversely substituted benzodiazepine nuclei can serve as synthons for developing new drugs.

Some time ago, in an attempt to synthesize the fused thiazolobenzodiazepine scaffold, Chimirri et al.[12] studied the reaction of 1,5-benzodiazepine with 2-mercaptoacetic acid and isolated a thiazolobenzimidazole as the main reaction product (40% yield) along with a thienylbenzodiazepine (28% yield) (Scheme 1). Moreover, the same authors reported[13] the synthesis of thiazolobenzimidazoles by reacting *o*-phenylenediamine with carbonyl compounds in the presence of 2-mercaptocarboxylic acids.

2. Results and discussion

The above mentioned results of Chimirri in combination with our interest in the construction of heterocyclic scaffolds, and especially benzodiazepine derivatives,[14] led us to the development of a novel three component reaction involving *o*-phenylenediamines for the synthesis of benzodiazepines. Since one of the classical methods for the synthesis of benzodiazepines is the reaction of

* Corresponding authors. Tel.: +30 2310 997831; fax: +30 2310 997679.
E-mail addresses: ioulia@chem.auth.gr (J. Stephanidou-Stephanatou), tsolerid@chem.auth.gr (C.A. Tsoleridis).

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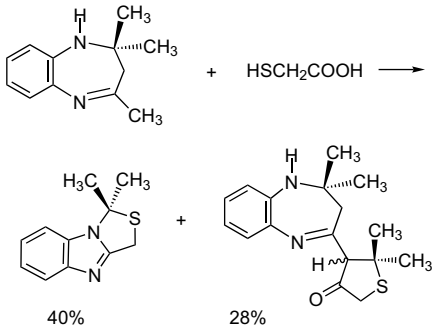
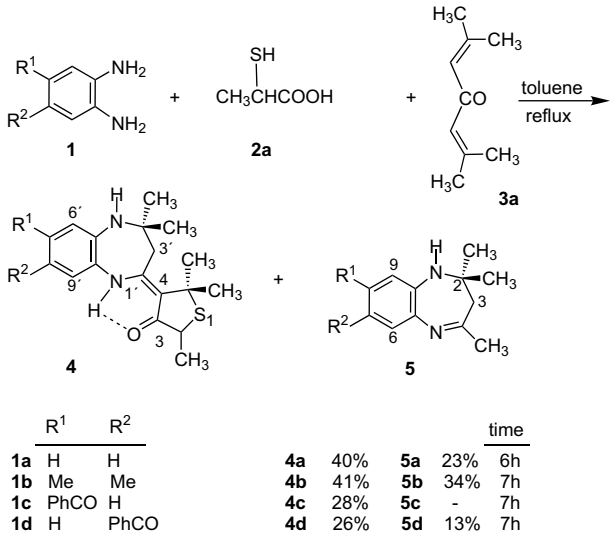


Scheme 1.

o-phenylenediamines with unsaturated carbonyl compounds, we embarked our investigation by reacting *o*-phenylenediamines **1** with phorone (**3a**, 1:2 molar ratio) in the presence of 2-mercaptopropionic acid (**2a**, 1.2 equiv) in expectation of isolating new benzodiazepine derivatives. Indeed, the reaction proceeded smoothly (toluene, reflux, 6–7 h) to give aryldiazepinothiophenones **4** (40–54% yield) along with benzodiazepines **5** (13–34% yield, Scheme 2).



	R^1	R^2					time
1a	H	H	**4a**	40%	**5a**	23%	6h
1b	Me	Me	**4b**	41%	**5b**	34%	7h
1c	PhCO	H	**4c**	28%	**5c**	-	7h
1d	H	PhCO	**4d**	26%	**5d**	13%	7h

Scheme 2. Reaction of *o*-phenylenediamines with phorone and 2-mercaptopropionic acid.

From the asymmetrically substituted 4-benzoyl-1,2-phenylenediamine (**1c**) both regio-isomeric aryldiazepino-thiophenones **4c** and **4d** were isolated in 28% and 26% yield (54% total yield), respectively, whereas only one benzodiazepine regio-isomer **5d** was selectively formed in 13% yield.

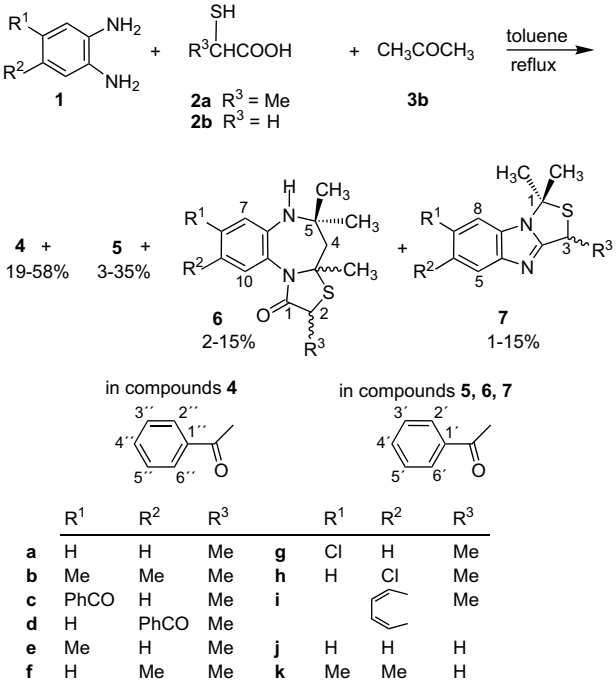
In order to investigate the possibility of a more general application of the method, *o*-phenylenediamine **1a** reacted with acetone in the presence of 2-mercaptopropionic acid (**2a**, 1.2 equiv) instead of phorone, since it was implied that under the reaction conditions used, phorone could be formed in situ from acetone. The reaction proceeded smoothly in refluxing toluene with excess acetone (4 equiv), whereupon the aryldiazepinothiophenone **4a** was isolated again (37%) as the main reaction product along with benzodiazepine **5a** (5%) and two more products, the thiazolobenzodiazepine **6a** (7%) and the thiazolobenzimidazole **7a** (1%). In order to optimize the yields of the benzodiazepine products **4** and **6** the reaction was thoroughly investigated with phenylenediamine **1a** and 2-mercaptopropionic acid (**2a**) by using various non-polar aromatic solvents, reaction temperatures and molar ratios of acetone (see Table 1). The optimized reaction conditions (Table 1, entry 3) concerning at least the yield of the main reaction product **4a**, were then employed by using a variety

Table 1
Investigation of reaction conditions

Entry	**1a**:**3b**:**2a**	Solvent[a]	Time (h)	**4a** (%)	**5a** (%)	**6a** (%)	**7a** (%)
1	1:1:1.2	Toluene	10	23		5	9
2	1:4:1.2	Toluene	10	37	5	7	1
3	1:6:1.2	Toluene	8	56[b]	23	3	2
4	1:8:1.2	Toluene	6	45	24		10
5	1:6:1.2	Benzene	10	51	18	4	4
6	1:6:1.2	Xylene[c]	7	12	15		4

[a] In refluxing solvent.
[b] The same reaction conditions were also applied by using a Dean–Stark apparatus and also under argon with no substantial differentiation in the yield and product ratio.
[c] A substantial amount of polymeric material was also formed.

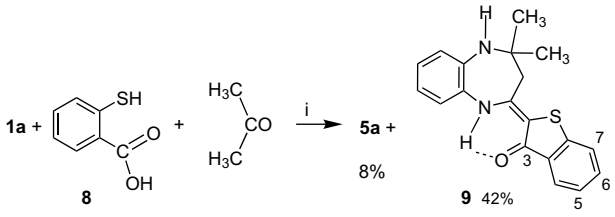
of diamines, 2-mercaptopropionic (**2a**) and 2-mercaptoacetic acid (**2b**), whereupon the aryldiazepinothiophenones **4** were always isolated as the main reaction products (19–58% yield), along with benzodiazepines **5** in 3–35% yield, thiazolobenzodiazepines **6** in 2–15% yield and thiazolobenzimidazoles **7** in 1–15% yield (Scheme 3).



	R^1	R^2	R^3		R^1	R^2	R^3
a	H	H	Me	**g**	Cl	H	Me
b	Me	Me	Me	**h**	H	Cl	Me
c	PhCO	H	Me	**i**			Me
d	H	PhCO	Me				
e	Me	H	Me	**j**	H	H	H
f	H	Me	Me	**k**	Me	Me	H

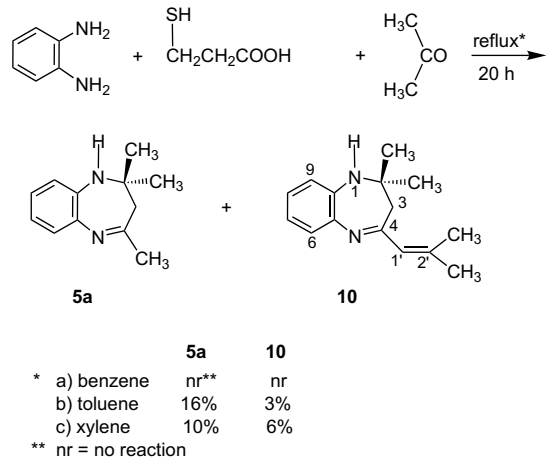
Scheme 3. Reaction of *o*-phenylenediamines with acetone and 2-mercapto-acetic or propionic acid.

Next, the use of an aromatic acid, thiosalicylic acid (**8**), was also investigated, whereupon the analogous to **4** benzodiazepinothiophenone **9** was furnished again as the main reaction product in 42% yield along with a small amount (8%) of the benzodiazepine **5a** (Scheme 4).

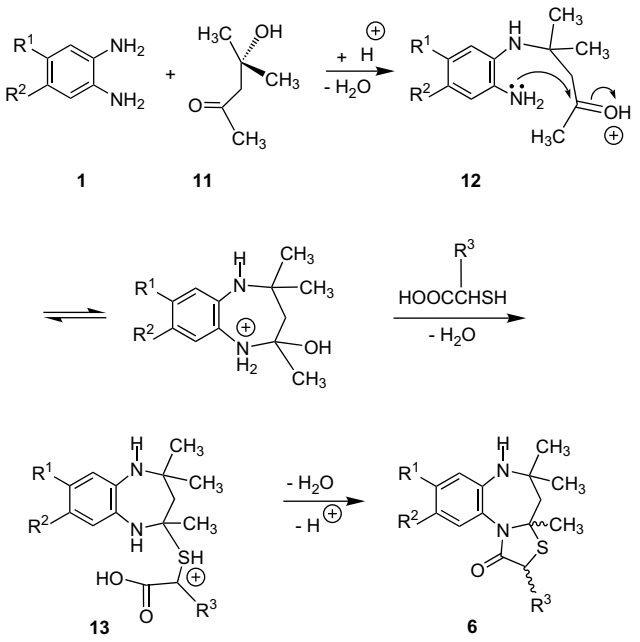


[i] reaction conditions: amine:acetone:acid = 1:4:1.2, reflux in toluene for 6 h

Scheme 4.



Scheme 5.



Scheme 6. Plausible reaction mechanism proposed for the formation of compounds **6**.

The possibility of formation of thiopyranobenzodiazepines by changing the 2-mercaptopropionic acid to 3-mercaptopropionic acid was also investigated, but unfortunately the expected products were not isolated. In fact, no reaction was observed after 20 h in boiling benzene, whereas in boiling toluene or xylene only small amounts of the benzodiazepines **5a** (10–16% yield) and **10** (3–6% yield) were formed, indicating that the acid was not incorporated in the reaction products, even though it was involved in the aldol condensation as acid catalyst (Scheme 5).

For the formation of the thiazolobenzodiazepines **6** a plausible mechanistic scheme involving aldol condensation of two acetone molecules (**11**) could be implicated, whereupon the initially formed intermediate **12** by addition of the 2-mercaptopropionic acid gives **13**, which by dehydration finally affords **6** (Scheme 6). In favour of the proposed mechanism is the fact that all previous[12] and also our attempts for the formation of **6** by reacting **5** with 2-mercaptopropionic acid were unsuccessful.

For the formation of compounds **4**, aldol condensation of an additional acetone molecule with **12** leads to the formation of intermediate **14** (Scheme 7). From the reaction of **14** with 2-mercaptopropionic acid **15** is formed, which by successive transformations and ring closure gives **16**. Subsequent new ring closure to **17** followed by tautomerization results to the isolated thiophenone **4**, which is formed on account of the additional stabilization energy of ~9.6 kcal/mol (calculated by PM6 for **4a**)[15] due to NH···O=C hydrogen bond and to the conjugation with the carbonyl group (Scheme 8). Additional proof for the proposed mechanism is offered by the isolation of **10** from the reaction with 3-mercaptopropionic acid (Scheme 5) excluding thus the possibility of **10** being an intermediate in the formation of **4**.

In order to gain a deeper insight into the reaction it was repeated with *N*-methyl phenylenediamine (**18**), whereupon two products were isolated in small yield, the benzodiazepine **19** (6% yield) and the benzimidazole **20** (30% yield), as shown in Scheme 9. The isolation of **19** with a structure analogous to that of **10** is also in favour to the proposed mechanism concerning the formation of **4**.

Concerning the reaction mechanism it appears that the substitution of one hydrogen by methyl diverts the course of the reaction, so an amount of thioglycolic acid reacts directly with *N*-methylphenylenediamine forming initially benzimidazole **21** from which, by reaction with the protonated aldol condensation product and through intermediate **22**, benzimidazole **20** is formed (Scheme 10).

Finally, the nature of the ketone used was also investigated. Therefore, acetone was replaced by butanone and acetophenone, and the reaction was repeated under the same reaction conditions. Acetophenone was chosen in the hope of increasing the yield of derivatives analogous to **6**, since there is no possibility of aldol condensation between three molecules.

Unfortunately, in all cases the expected target products analogous to **4** and **6** were not isolated. Instead, the benzodiazepines **23** and **24** were formed, respectively (Scheme 11). The lack of formation of the analogous to **6** thiazolobenzodiazepines can be attributed mainly to steric reasons. The formation of an intermediate analogous to **13** is most probably prohibited, due to the presence of an ethyl or phenyl instead of a methyl group in the N–C carbon that hinders the approach and reaction with 2-mercaptoacetic acid. For the formation of **23** with an acetyl substituent, instead as expected of an ethyl, no reasonable explanation can be proposed at the moment.

2.1. Structure assignment of the new compounds

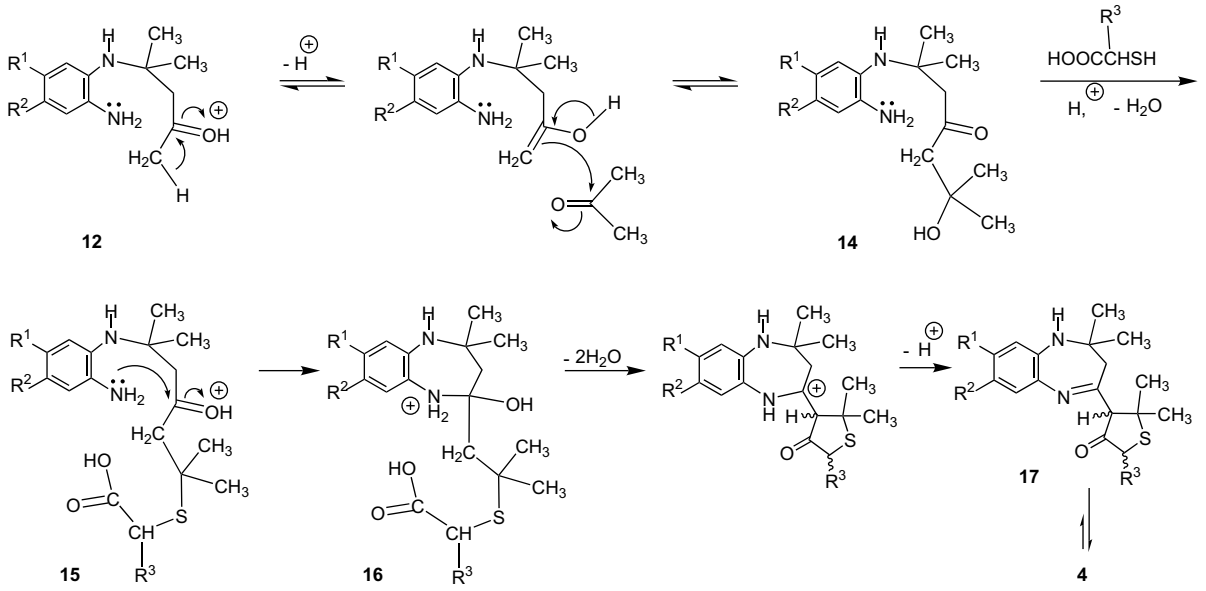
The assigned molecular structures of the new compounds **4**, **6**, **9**, **20** and **23** were based on rigorous spectroscopic analysis including IR, MS, NMR (^{1}H, ^{13}C, H–H COSY, C–H COSY and C–H COLOC) and elemental analysis data.

A detailed description of the structural assignment for the above compounds is included in Supplementary data. In Figure 1 the COLOC correlations observed via $^{2}J_{CH}$ and $^{3}J_{CH}$ in compound **4b** are depicted.[†]

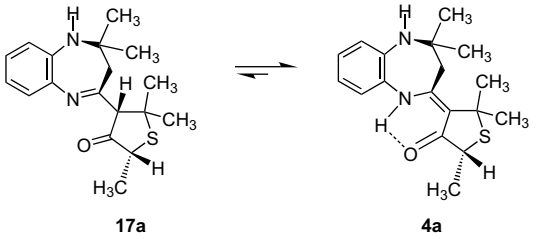
3. Biological evaluation

It has been previously reported[16] that a number of benzodiazepine derivatives, especially tetrazepam, are in vitro aldose reductase inhibitors. It is well established that the aldose reductase enzyme (AR, ALR2, EC 1.1.1.21) of the polyol metabolic pathway is implicated in the etiology of the secondary complications of diabetes. AR inhibitors (ARIs) have therefore been noted as possible pharmacotherapeutic agents.[17] Thus, in the search for ARIs of new chemotypes, the synthesized novel aryldiazepinothiophenone derivatives **4** were tested in vitro for their ability to inhibit rat lens AR. The performed assay was based on the spectrophotometric

[†] According to the above data the proposed by Chimirri et al.[12] imine structure **17a** should be revised to **4a**.



Scheme 7. Plausible reaction mechanism proposed for the formation of compounds **4**.



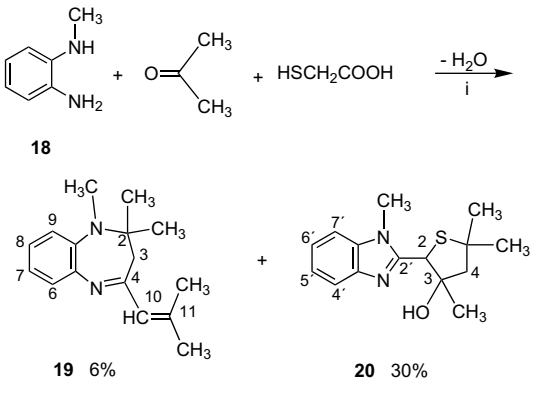
PM6 ΔH_f = -34.82[a] $\Delta\Delta H_f$ = 9.59 ΔH_f = -44.41

[a] in kcal/mol

Scheme 8.

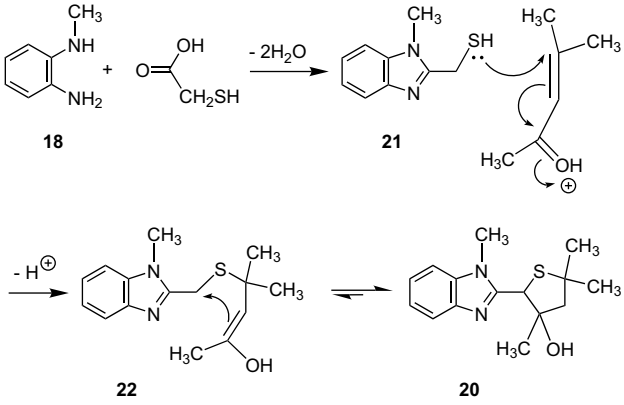
monitoring of NADPH oxidation, which is proven to be a quite reliable method.[18] It was found that the most active synthesized benzodiazepine derivative was compound **4k** (Table 2). Specifically, a concentration of 100 μM exhibited 88% inhibition, while at a concentration of 10 μM, 21%. It should be noted that this compound is significantly more active than tetrazepam, which shows inhibitory activity of only 37% at a concentration of 100 μM.[16]

Furthermore, the antioxidant potential of the synthesized benzodiazepine derivatives was evaluated in a homogeneous 2,2-

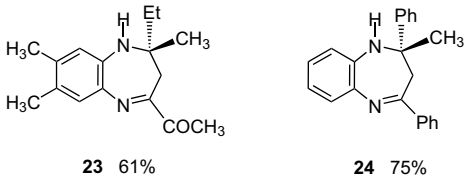


[i] Reaction conditions: toluene, reflux, 6 h

Scheme 9.



Scheme 10.



Scheme 11.

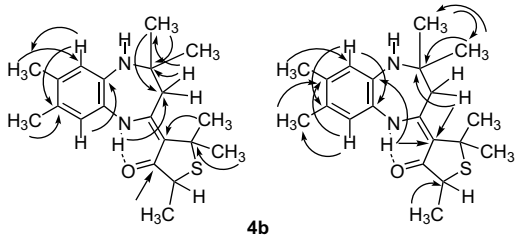


Figure 1. COLOC correlations via $^2J_{CH}$ and $^3J_{CH}$ observed in compound **4b**.

Table 2
Inhibition activities of aryldiazepinothiophenones **4** on rat lens ALR2

Compound	Inhibition (%)	
	0.1 mM[a]	0.01 mM
4a	54	
4b	0	
4d	29	
4e	7	
4g	36	
4h	0	
4i	31	
4j	0	
4k	88	21

[a] Concentration of the tested compounds.

Table 3
Antiradical activities of aryldiazepinothiophenones **4** in a DPPH test

Compound	Inhibition (%)		
	0.2 mM[a]	0.1 mM	0.05 mM
4a	16		
4b	67	41	28
4c	16	16	11
4d	14	14	8
4e	36	28	9
4g	32	29	29
4h	37	31	31
4i	14		
4j	21	20	9
4k	68	45	41

[a] Concentration of the tested compounds.

diphenyl-1-picrylhydrazyl stable free radical (DPPH) system. Oxidative stress is an important biochemical factor implicated in the long-term complications of diabetes mellitus.[19] Again, the most active derivative was compound **4k** (Table 3). Specifically, concentrations of 200 μM, 100 μM and 50 μM showed antioxidant potential of 68%, 45% and 41%, respectively. We believe that the above-presented experimental data could comprise the basis for the design of novel chemotypes, as pharmacotherapeutic agents for the treatment of the long-term diabetic complications.

4. Conclusions

In conclusion, we have shown that from cheap, easily accessible starting materials, namely *o*-phenylenediamines, phorone or acetone and mercaptocarboxylic acids, very interesting new benzodiazepine derivatives, the aryldiazepinothiophenones **4** and **9** can be isolated in good yields through a novel three component reaction. Moreover, compounds **4** were evaluated for aldose reductase inhibition and as antioxidants. Compound **4k** was found to be significantly more active than tetrazepam.

5. Experimental

5.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel (70–230 mesh). TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether/ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, using $CDCl_3$ as solvent. The chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in Hz. Second order ^{1}H spectra, where it was possible, were analyzed by simulation.[20] IR spectra were recorded on a Perkin–Elmer 297 spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra (EIMS) were obtained on a VG TS-250 instrument, *m*/*z* (relative intensity in %); ionization energy 70 eV. Elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR and COLOC). The MO calculations for minimum energy conformation of compounds were computed with the PM6 methods as implemented in the MOPAC2007 package.[15] All stationary points were refined by minimization of the gradient norm of the energy to at least 0.01 kcal/mol.

5.2. General procedure for the reaction of *o*-phenylenediamines with acetone and 2-mercaptopropionic acid

To a stirred solution of *o*-phenylenediamine derivative **1** (10 mmol) and acetone (3.48 g, 60 mmol) in dry toluene (50 mL) was added 2-mercaptopropionic acid (1.27 g, 12.0 mmol) and the mixture was heated under reflux for 6 h. The solvent was then evaporated in vacuo and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (7:1) of slowly increased polarity to afford in elution order products **4**–**7**.

5.2.1. From compound ***1a***

*5.2.1.1. 4-(4′,4′-Dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4a**).* Yellow crystals (1.17 g, 37%), mp 117–118 °C; IR (Nujol) ν_{max}: 3320, 1600, 1580, 1570 cm^{-1}. ^{1}H NMR: 1.37 (s, 3H, 4′-CH_3), 1.39 (s, 3H, 4′-CH_3), 1.51 (d, *J*=6.9 Hz, 3H, 2-CH_3), 1.71 (s, 3H, 5-CH_3), 1.74 (s, 3H, 5-CH_3), 2.64 (d, *J*=14.7 Hz, 1H, 3′-H), 2.68 (d, *J*=14.7 Hz, 1H, 3′-H), 3.01 (br s, 1H, 5′-H), 3.87 (q, *J*=6.9 Hz, 1H, 2-H), 6.69 (dd, *J*=8.3, 1.2 Hz, 1H, 6′-H), 6.84 (ddd, *J*=7.8, 7.0, 1.2 Hz, 1H, 8′-H), 6.94–7.00 (m, 2H, 7′,9′-H), 13.85 (br s, 1H, 1′-H). ^{13}C NMR: 19.2 (2-CH_3), 30.96 (4′-CH_3), 31.04 (4′-CH_3), 34.2 (5-CH_3), 34.5 (5-CH_3), 41.0 (C-3′), 45.5 (C-2), 49.1 (C-5), 58.8 (C-4′), 110.4 (C-4), 120.2 (C-8′), 120.7 (C-6′), 123.7 (C-9′), 125.6 (C-7′), 128.1 (C-9a′), 137.8 (C-5a′), 158.3 (C-2′), 198.3 (CO). EIMS *m*/*z* (%) 316 (100), 301 (78), 245 (8), 228 (11), 213 (16), 174 (18), 169 (25), 149 (15), 133 (75). Anal. Calcd for $C_{18}H_{24}N_2OS$ (316.46): C, 68.32; H, 7.64; N, 8.85. Found: C, 68.50; H, 7.55; N, 8.82.

*5.2.1.2. 1,1,3-Trimethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7a**).* Colourless oil (0.028 g, 1%); IR (Nujol) ν_{max}: 1605, 1575, 1520 cm^{-1}. ^{1}H NMR: 1.81 (d, *J*=7.0 Hz, 3H, 3-CH_3), 2.00 (s, 3H, 1-CH_3), 2.06 (s, 3H, 1-CH_3), 4.77 (q, *J*=7.0 Hz, 1H, 3-H), 7.22–7.28 (m, 2H, 6,7-H), 7.41 (dd, *J*=7.0, 1.5 Hz, 1H, 8-H), 7.74 (dd, *J*=8.0, 1.2 Hz, 1H, 5-H). ^{13}C NMR: 22.0 (3-CH_3), 31.3 (1-CH_3), 31.5 (1-CH_3), 38.4 (C-3), 67.3 (C-1), 109.8 (C-8), 120.4 (C-5), 122.1 (C-6)*, 122.3 (C-7)*, 130.9 (C-8a), 149.0 (C-4a), 160.6 (C-3a). EIMS *m*/*z* (%) 219 (M+1, 80), 204 (90), 186 (45), 171 (10), 147 (100), 120 (20), 104 (40). (The assignments indicated by an asterisk (*) may be interchanged.)

*5.2.1.3. 2,3a,5,5-Tetramethyl-3a,4,5,6-tetrahydro-thiazolo[3,2-a][1,5]-benzodiazepin-1(2H)-one (**6a**).* White crystals (0.193 g, 7%), mp 86–87 °C; IR (Nujol) ν_{max}: 3360, 1780, 1720, 1590 cm^{-1}. ^{1}H NMR: 1.18 (s, 3H, 5-CH_3), 1.43 (s, 3H, 5-CH_3), 1.61 (s, 3H, 3a-CH_3), 1.66 (d, *J*=7.2 Hz, 3H, 2-CH_3), 2.12 (d, *J*=14.9 Hz, 1H, 4-H), 2.24 (d, *J*=14.9 Hz, 1H, 4-H), 3.01 (br s, 1H, 6-H), 4.07 (q, *J*=7.2 Hz, 1H, 2-H), 6.68 (dd, *J*=8.0, 1.1 Hz, 1H, 7-H), 6.88 (ddd, *J*=7.5, 7.2, 1.1 Hz, 1H, 9-H), 7.08–7.12 (m, 2H, 8,10-H). ^{13}C NMR: 19.6 (2-CH_3), 31.0 (3a-CH_3), 31.7 (5-CH_3), 32.0

(5-CH_3), 42.2 (C-2), 53.1 (C-5), 54.7 (C-4), 66.2 (C-3a), 119.9 (C-7), 120.3 (C-9), 124.6 (C-10a), 128.4 (C-8), 130.1 (C-10), 142.8 (C-6a), 172.5 (C-1). EIMS *m/z* (%) 276 (100), 261 (98), 243 (22), 219 (12), 205 (8), 189 (35), 175 (99), 176 (80), 159 (28), 145 (15), 131 (96), 117 (40), 105 (22), 101 (23), 92 (56). Anal. Calcd for $C_{15}H_{20}N_2OS$ (276.40): C, 65.18; H, 7.29; N, 10.14. Found: C, 65.77; H, 7.25; N, 10.05.

*5.2.1.4. 2,3-Dihydro-2,2,4-trimethyl-(1H)-1,5-benzodiazepine (**5a**).* White crystals (0.206 g, 11%), mp 143–145 °C (Et_2O/petr. ether), (lit.[11d] 145–146 °C); IR (Nujol) ν_{max}: 3270, 1620, 1575 cm^{-1}. ^1H NMR: 1.35 (s, 6H, 2×2-CH_3), 2.23 (s, 2H, 3-H), 2.38 (s, 3H, 4-CH_3), 3.05 (br s, 1H, 1-H), 6.74 (dd, *J*=8.1, 1.3 Hz, 1H, 9-H), 6.98–7.03 (m, 2H, 7,8-H), 7.16 (dd, *J*=8.1, 1.5 Hz, 1H, 6-H). ^{13}C NMR: 29.8 (4-CH_3), 30.4 (2×2-CH_3), 45.1 (C-3), 68.2 (C-2), 121.6 (C-9), 122.0 (C-7), 125.4 (C-8), 126.8 (C-6), 137.9 (C-5a), 140.7 (C-9a), 172.2 (C-4).

*5.2.2. From compound **1b***

*5.2.2.1. 4-(1′,3′,4′,5′-Tetrahydro-4′,4′,7′,8′-tetramethyl-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4b**).* Yellow crystals (1.205 g, 35%), mp 150–151 °C; IR (Nujol) ν_{max}: 3380, 1605, 1560 cm^{-1}. ^1H NMR: 1.34 (s, 3H, CH_3-4′), 1.36 (s, 3H, CH_3-4′), 1.51 (d, *J*=6.9 Hz, 3H, CH_3-2), 1.70 (s, 3H, CH_3-5), 1.73 (s, 3H, CH_3-5), 2.14 (s, 3H, CH_3-8′), 2.16 (s, 3H, CH_3-9′), 2.61 (d, *J*=14.8 Hz, 1H, 3′-H), 2.64 (d, *J*=14.8 Hz, 1H, 3′-H), 3.24 (br s, 1H, 5′-H), 3.87 (q, *J*=6.9 Hz, 1H, 2-H), 6.49 (s, 1H, 6′-H), 6.77 (s, 1H, 9′-H), 13.9 (br s, 1H, 1′-H). ^{13}C NMR: 18.6 (8′-CH_3), 19.1 (7′-CH_3), 19.3 (2-CH_3), 30.8 (4′-CH_3), 30.9 (4′-CH_3), 34.2 (5-CH_3), 34.5 (5-CH_3), 41.2 (C-3′), 45.4 (C-2), 49.2 (C-5), 58.5 (C-4′), 109.9 (C-4), 121.4 (C-6′), 124.5 (C-9′), 125.8 (C-9a′), 129.0 (C-8′), 134.1 (C-7′), 135.4 (C-5a′), 158.6 (C-2′), 197.6 (C-3). EIMS *m/z* (%) 344 (82), 329 (100), 256 (15), 241 (41), 201 (45), 161 (59). Anal. Calcd for $C_{20}H_{28}N_2OS$ (344.51): C, 69.73; H, 8.19; N, 8.13. Found: C, 69.51; H, 8.13; N, 8.38.

*5.2.2.2. 1,1,3,6,7-Pentamethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7b**).* White crystals (0.025 g, 1%), mp 77–79 °C (lit.[14c] mp 78–79 °C); IR (Nujol) ν_{max}: 1610 cm^{-1}. ^1H NMR: 1.19 (s, 3H, 1-CH_3), 1.99 (d, *J*=6.3 Hz, 3H, 3-CH_3), 2.05 (s, 3H, 1-CH_3), 2.35 (s, 3H, 7-CH_3), 2.37 (s, 3H, 6-CH_3), 4.70 (q, *J*=6.3 Hz, 1H, 3-H), 7.18 (s, 1H, 8-H), 7.48 (s, 1H, 5-H). ^{13}C NMR: 20.2 (6-CH_3), 20.5 (7-CH_3), 22.0 (3-CH_3), 31.2 (1-CH_3), 31.5 (1-CH_3), 38.4 (C-3), 67.1 (C-1), 110.0 (C-8), 120.4 (C-5), 129.4 (C-6), 130.9 (C-7), 131.2 (C-8a), 147.6 (C-4a), 159.7 (C-3a). EIMS *m/z* (%) 247 (M, 64), 232 (41), 214 (36), 188 (10), 174 (100), 158 (32), 146 (9), 117 (9), 104 (22).

*5.2.2.3. 2,3a,5,5,8,9-Hexamethyl-3a,4,5,6-tetrahydro-thiazolo[3,2-a]-[1,5]benzodiazepin-1(2H)-one (**6b**).* White crystals (0.092 g, 3%), mp 158–160 °C; IR (Nujol) ν_{max}: 3310, 1650, 1605 cm^{-1}. ^1H NMR: 1.14 (s, 3H, 5-CH_3), 1.39 (s, 3H, 5-CH_3), 1.60 (s, 3H, 3a-CH_3), 1.66 (d, *J*=7.1 Hz, 3H, 2-CH_3), 2.08 (d, *J*=14.8 Hz, 1H, 4-H), 2.17 (s, 6H, 8-CH_3, 9-CH_3), 2.25 (d, *J*=14.8 Hz, 1H, 4-H), 2.95 (br s, 1H, 6-H), 4.06 (q, *J*=7.1 Hz, 1H, 2-H), 6.52 (s, 1H, 7-H), 6.89 (s, 1H, 10-H). ^{13}C NMR: 18.9 (9-CH_3), 19.2 (8-CH_3), 20.2 (2-CH_3), 30.8 (3a-CH_3), 31.3 (5-CH_3), 32.3 (5-CH_3), 42.5 (C-2), 53.3 (C-5), 55.9 (CH_2), 66.5 (C-3a), 122.2 (C-7), 122.8 (C-10a), 129.0 (C-9), 130.7 (C-10), 137.3 (C-8), 140.5 (C-6a), 172.7 (C-1). EIMS *m/z* (%) 304 (98), 289 (86), 271 (14), 201 (95), 161 (100). Anal. Calcd for $C_{17}H_{24}N_2OS$ (304.45): C, 67.07; H, 7.95; N, 9.20. Found: C, 67.22; H, 7.80; N, 9.37.

*5.2.2.4. 2,3-Dihydro-2,2,4,7,8-pentamethyl-(1H)-1,5-benzodiazepine (**5b**).* White crystals (0.62 g, 3%), mp 91–93 °C (Et_2O/petr. ether), (lit.[21] 93 °C); IR (Nujol) ν_{max}: 3320, 1630 cm^{-1}. ^1H NMR: 1.26 (s, 6H, 2×2-CH_3), 2.14 (s, 3H, 7-CH_3), 2.16 (s, 3H, 8-CH_3), 2.30 (s, 2H, 3-H), 3.10 (br s, 1H, NH), 6.50 (s, 1H, 9-H), 6.91 (s, 1H, 6-H). ^{13}C NMR: 18.8 (7-CH_3), 19.2 (8-CH_3), 29.8 (4-CH_3), 30.4 (2×2-CH_3), 45.3 (C-3), 67.8 (C-2), 122.8 (C-6,9), 127.9 (C-5a,7), 130.1 (C-8), 136.0 (C-9a), 171.5 (C-4). EIMS *m/z* (%) 216 (96), 202 (98), 185 (47), 173 (25), 161 (100), 159 (98), 144 (97), 130 (40), 118 (64), 91 (90). Anal. Calcd for $C_{14}H_{20}N_2$ (216.32): C, 77.73; H, 9.32; N, 12.95. Found: C, 77.91; H, 9.25; N, 12.82.

*5.2.3. From compound **1c***

*5.2.3.1. (4E)-4-(7′-Benzoyl-4′,4′-dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4c**).* Yellow crystals (1.176 g, 28%), mp 136–137 °C (Ethanol); IR (Nujol) ν_{max}: 3310, 1640, 1580, 1560 cm^{-1}. ^1H NMR: 1.38 (s, 3H, 4′-CH_3), 1.40 (s, 3H, 4′-CH_3), 1.51 (d, *J*=6.5 Hz, 3H, 2-CH_3), 1.72 (s, 3H, 5-CH_3), 1.74 (s, 3H, 5-CH_3), 2.70 (d, *J*=15.0 Hz, 1H, 3′-H), 2.76 (d, *J*=15.0 Hz, 1H, 3′-H), 3.8 (br s, 1H, 5′-H), 3.88 (q, *J*=6.5 Hz, 1H, 2-H), 7.00 (dd, *J*=8.8, 3.6 Hz, 1H, 8′-H), 7.21 (d, *J*=8.8 Hz, 1H, 9′-H), 7.28 (d, *J*=3.6 Hz, 1H, 6′-H), 7.45–7.51 (m, 2H, 3″,5″-H), 7.53–7.61 (m, 1H, 4″-H), 7.72–7.78 (m, 2H, 2″,6″-H), 13.88 (s, 1H, 1′-H). ^{13}C NMR: 18.8 (2-CH_3), 30.7 (4′-CH_3), 30.8 (4′-CH_3), 33.9 (5′-CH_3), 34.1 (5′-CH_3), 41.6 (C-3′), 45.5 (C-2), 48.9 (C-5), 57.6 (C-4′), 112.0 (C-4), 121.6 (C-6′), 123.0 (C-8′), 123.1 (C-9′), 128.2 (C-3″,5″), 129.8 (C-2″,6″), 131.6 (C-9a′), 132.2 (C-4″), 134.0 (C-7′), 137.0 (C-5a′), 137.8 (C-1″), 157.0 (C-2′), 195.5 (7′-CO), 199.6 (C-3). EIMS *m/z* (%) 420 (82), 419 (84), 405 (78), 404 (85), 388 (25), 348 (35), 332 (49), 317 (69), 301 (24), 277 (65), 261 (55), 237 (87), 209 (50), 193 (60), 169 (90), 159 (82), 132 (55), 105 (91), 77 (100). Anal. Calcd for $C_{25}H_{28}N_2O_2S$ (420.57): C, 71.40; H, 6.71; N, 6.66. Found: C, 71.27; H, 6.59; N, 6.68.

*5.2.3.2. (4E)-4-(8′-Benzoyl-4′,4′-dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4d**).* Yellow crystals (1.26 g, 30%), mp 169–170 °C (Ethanol); IR (Nujol) ν_{max}: 3325, 1620, 1595, 1565 cm^{-1}. ^1H NMR: 1.41 (s, 3H, 4′-CH_3), 1.43 (s, 3H, 4′-CH_3), 1.48 (d, *J*=7.0 Hz, 3H, 2-CH_3), 1.70 (s, 3H, 5-CH_3), 1.72 (s, 3H, 5-CH_3), 2.79 (d, *J*=15.0 Hz, 1H, 3′-H), 2.82 (d, *J*=15.0 Hz, 1H, 3′-H), 3.85 (q, *J*=7.0 Hz, 1H, 2-H), 4.44 (br s, 1H, 5′-H), 6.63 (d, *J*=8.4 Hz, 6′-H), 7.43–7.50 (m, 4H, 7′,9′,3″, 5″-H), 7.52–7.57 (m, 1H, 4″-H), 7.72 (d, *J*=7.5 Hz, 2H, 2″,6″-H), 13.88 (s, 1H, 1′-H). ^{13}C NMR: 19.0 (2-CH_3), 31.1 (4′-CH_3), 31.2 (4′-CH_3), 33.9 (5-CH_3), 34.2 (5-CH_3), 41.9 (C-3′), 45.5 (C-2), 48.9 (C-5), 56.0 (C-4′), 110.8 (C-4), 118.1 (C-6′), 124.4 (C-9a′), 127.0 (C-7′), 128.0 (C-9′), 128.3 (C-3″,5″), 129.4 (C-8′), 129.6 (C-2″,6″), 131.8 (C-4″), 138.4 (C-1″), 141.9 (C-5a′), 157.7 (C-2′), 194.6 (8′-CO), 198.7 (C-3). EIMS *m/z* (%) 420 (65), 419 (90), 405 (55), 404 (86), 358 (15), 348 (20), 331 (32), 316 (41), 300 (11), 277 (45), 238 (61), 209 (35), 193 (46), 169 (75), 153 (40), 105 (96), 77 (100). Anal. Calcd for $C_{25}H_{28}N_2O_2S$ (420.57): C, 71.40; H, 6.71; N, 6.66. Found: C, 71.61; H, 6.72; N, 6.54.

*5.2.3.3. 8-Benzoyl-2,3a,5,5-tetramethyl-3a,4,5,6-tetrahydro[1,3]-thiazolo[3,2-a][1,5]benzodiazepin-1(2H)-one (**6c**) and 9-benzoyl-2,3a,5,5-tetramethyl-3a,4,5,6-tetrahydro[1,3]thiazolo[3,2-a][1,5]benzodiazepin-1(2H)-one (**6d**).* An inseparable mixture (0.266 g, 7%) in a 2:1 ratio.

*5.2.3.4. 7-Benzoyl-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (**5d**).* Colourless oil (0.263 g, 9%); IR (Nujol) ν_{max}: 3320, 1635, 1580 cm^{-1}. ^1H NMR: 1.35 (s, 6H, 2×2-CH_3), 2.23 (s, 2H, 3-H), 2.36 (s, 3H, 4-CH_3), 2.95 (br s, 1H, 1-H), 6.71 (d, *J*=8.5 Hz, 1H, 9-H), 7.40–7.59 (m, 4H, 8,3″,4″,5″-H), 7.65 (d, *J*=1.8 Hz, 1H, 6-H), 7.71–7.77 (m, 2H, 2″,6″-H). ^{13}C NMR: 29.8 (4-CH_3), 30.6 (2×2-CH_3), 46.1 (C-3), 68.1 (C-2), 119.6 (C-9), 125.4 (C-8), 126.8 (C-6), 127.8 (C-3″,5″), 129.1 (C-2″,6″), 132.6 (C-4″), 134.4 (C-7), 137.9 (C-5a), 138.3 (C-1″), 143.1 (C-9a), 171.0 (C-4), 194.9 (7-CO). Anal. Calcd for $C_{19}H_{20}N_2O$ (292.37): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.18; H, 6.94; N, 9.66.

5.2.4. From compound ***1e***

*5.2.4.1. (4E)-4-(4′,4′,7′-Trimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4e**).* Yellow crystals (ethanol) (1.189 g, 36%), mp 50–52 °C; IR (Nujol) ν_{max}: 3330, 1600, 1580, 1570 cm^{-1}. ^1H NMR: 1.35 (s, 3H, 4′-CH_3), 1.38 (s, 3H, 4′-CH_3), 1.51 (d, J=6.9 Hz, 3H, 2-CH_3), 1.70 (s, 3H, 5-CH_3), 1.73 (s, 3H, 5-CH_3), 2.24 (s, 3H, 8′-CH_3), 2.64 (d, J=14.8 Hz, 1H, 3′-H), 2.67 (d, J=14.8 Hz, 1H, 3′-H), 3.65 (br s, 1H, 4′-H), 3.87 (q, J=6.9 Hz, 1H, 2-H), 6.50 (d, J=1.5 Hz, 1H, 6′-H), 6.61 (dd, J=7.9, 1.5 Hz, 1H, 8′-H), 6.86 (d, J=7.9 Hz, 1H, 9′-H), 13.90 (br s, 1H, NH). ^{13}C NMR: 19.3 (2-CH_3), 20.7 (7′-CH_3), 30.9 (4′-CH_3), 31.0 (4′-CH_3), 34.2 (5-CH_3), 34.5 (5-CH_3), 41.2 (C-3′), 45.4 (C-2), 49.2 (C-5), 58.2 (C-4′), 109.9 (C-4), 120.5 (C-8′), 121.2 (C-6′), 123.5 (C-9′), 126.3 (C-9a′), 135.4 (C-7′), 137.6 (C-5a′), 158.5 (C-2′), 197.5 (C-3). EIMS m/z (%) 330 (100), 315 (97), 299 (20), 283 (22), 269 (25), 259 (28), 242 (58), 227 (84), 209 (40), 193 (65), 187 (76), 169 (70), 163 (35), 147 (98). Anal. Calcd for $C_{19}H_{26}N_2OS$ (330.49): C, 69.05; H, 7.93; N, 8.48. Found: C, 69.19; H, 7.84; N, 8.45.

*5.2.4.2. (4E)-4-(4′,4′,8′-Trimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4f**).* Yellow oil (0.17 g, 5%); IR (Nujol) ν_{max}: 3360 cm^{-1}. ^1H NMR: 1.35 (s, 3H, 4′-CH_3), 1.38 (s, 3H, 4′-CH_3), 1.53 (d, J=7.0 Hz, 3H, 2-CH_3), 1.71 (s, 3H, 5-CH_3), 1.73 (s, 3H, 5-CH_3), 2.24 (s, 3H, 4′-CH_3), 2.58 and 2.67 (AB, J=14.8 Hz, 2H, CH_2), 3.88 (q, J=7.0 Hz, 1H, 2-H), 6.62 (d, J=7.7 Hz, 1H, 6′-H), 6.81 (s, 1H, 9′-H), 6.85 (d, 1H, J=7.7 Hz, 7′-H), 13.83 (br s, 1H, NH). ^{13}C NMR: 19.2 (2-CH_3), 20.3 (8′-CH_3), 30.7 (4′-CH_3), 30.8 (4′-CH_3), 34.2 (5-CH_3), 34.5 (5-CH_3), 41.0 (C-3′), 45.4 (C-2), 49.1 (C-5), 59.1 (C-4′), 110.3 (C-4), 120.5 (C-6′), 123.9 (C-9′), 126.3 (C-7′), 128.4 (C-9a′), 130.7 (C-8′), 135.3 (C-5a′), 158.5 (C-2′), 198.2 (C-3). EIMS m/z (%) 330 (22), 315 (35), 242 (6), 227 (8), 147 (94), 105 (100). Anal. Calcd for $C_{19}H_{26}N_2OS$ (330.49): C, 69.05; H, 7.93; N, 8.48. Found: C, 69.09; H, 7.80; N, 8.55.

*5.2.4.3. 1,1,3,7-Tetramethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7e**) and 1,1,3,6-tetramethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7f**).* As an inseparable mixture (colourless oil, 0.232 g, 10%) in a 6:4 ratio.

7e: ^1H NMR: 1.80 (d, J=6.9 Hz, 3H, 3-CH_3), 1.99 (s, 3H, 1-CH_3), 2.06 (s, 3H, 1-CH_3), 2.49 (s, 3H, 7-CH_3), 4.77 (q, J=6.9 Hz, 1H, 3-H), 7.09 (dd, J=8.2, 1.5 Hz, 1H, 6-H), 7.21 (d, J=1.5 Hz, 1H, 8-H), 7.62 (d, J=8.2 Hz, 1H, 5-H). ^{13}C NMR: 22.0 (3-CH_3), 22.1 (7-CH_3), 31.3 (1-CH_3), 31.5 (1-CH_3), 38.4 (C-3), 67.4 (C-1), 109.9 (C-8), 119.8 (C-5), 123.7 (C-6), 132.4 (C-7), 136.7 (C-8a), 146.9 (C-4a), 159.5 (C-3a). EIMS (mixture) m/z (%) 232 (M, 48), 231 (92), 216 (85), 199 (80), 173 (25), 159 (100), 158 (75), 157 (90), 131 (30).

7f: ^1H NMR: 1.79 (d, J=6.9 Hz, 3H, 3-CH_3), 1.98 (s, 3H, 1-CH_3), 2.05 (s, 3H, 1-CH_3), 2.47 (s, 3H, 6-CH_3), 4.76 (q, J=6.9 Hz, 1H, 3-H), 7.07 (dd, J=8.3, 1.5 Hz, 1H, 7-H), 7.30 (d, J=8.3 Hz, 1H, 8-H), 7.53 (d, J=1.5 Hz, 1H, 5-H).^{13}C NMR: 21.5 (3-CH_3), 21.8 (6-CH_3), 31.3 (1-CH_3), 31.6 (1-CH_3), 38.6 (C-3), 67.5 (C-1), 109.3 (C-8), 120.2 (C-5), 123.8 (C-7), 132.1 (C-6), 132.4 (C-8a), 149.2 (C-4a), 159.9 (C-3a).

*5.2.4.4. 2,3a,5,5,8-Pentamethyl-3a,4,5,6-tetrahydro[1,3]thiazolo[3,2-a][1,5]benzodiazepin-1(2H)-one (**6e**) and 2,3a,5,5,9-pentamethyl-3a,4,5,6-tetrahydro[1,3]thiazolo[3,2-a][1,5]benzodiazepin-1(2H)-ones (**6f**).* As a mixture in a ratio 2:1, (0.436 g, 15%).

From this mixture compound **6e**, which is the major isomer, could be obtained as a pure product on preparative TLC plate. White crystals, mp 155–157 °C; IR (Nujol) ν_{max}: 3390, 1690, 1600, 1580 cm^{-1}. ^1H NMR: 1.17 (s, 3H, 5-CH_3), 1.42 (s, 3H, 5-CH_3), 1.61 (s, 3H, 3a-CH_3), 1.65 (d, J=7.0 Hz, 3H, 2-CH_3), 2.11 (d, J=15.0 Hz, 1H, 4-H), 2.22 (d, J=15.0 Hz, 1H, 4-H), 2.25 (s, 3H, 8-CH_3), 3.17 (br s, 1H, 6-H), 4.06 (q, J=7.0 Hz, 1H, 2-H), 6.49 (s, 1H, 7-H), 6.69 (d, J=8.0 Hz, 1H, 9-H), 7.10 (d, J=8.0 Hz, 1H, 10-H). ^{13}C NMR: 19.8 (8-CH_3), 21.1 (2-CH_3), 31.1 (3a-CH_3), 31.9 (5-CH_3), 32.0 (5-CH_3), 42.4 (C-2), 53.3 (C-5), 55.0 (C-4), 66.3 (C-3a), 120.9 (C-9), 121.2 (C-7), 121.9 (C-10a), 130.0 (C-10), 138.6 (C-8), 142.6 (C-6a), 172.7 (C-1). EIMS m/z (%) 290 (96), 275 (98), 257 (45), 189 (90), 187 (98), 173 (35), 146 (100), 145 (95), 130 (50). Anal. Calcd for $C_{16}H_{22}N_2OS$ (290.42): C, 66.17; H, 7.64; N, 9.65. Found: C, 66.13; H, 7.60; N, 9.72.

*5.2.4.5. 2,2,4,8-Tetramethyl-2,3-dihydro-1H-1,5-benzodiazepine (**5e**).* White crystals (0.061 g, 3% yield) mp 40–41 °C; IR (Nujol) ν_{max}: 3300, 1630, 1590 cm^{-1}. ^1H NMR: 1.32 (s, 6H, 2×2-CH_3), 2.21 (s, 2H, 3-H), 2.27 (s, 3H, 8-CH_3), 2.34 (s, 3H, 4-CH_3), 2.96 (br s, 1H, 1-H), 6.53 (d, J=1.9 Hz, 1H, 9-H), 6.76 (dd, J=7.5, 1.9 Hz, 1H, 7-H), 7.04 (d, J=7.6 Hz, 1H, 6-H). ^{13}C NMR: 20.8 (8-CH_3), 29.8 (4-CH_3), 30.5 (2×2-CH_3), 45.2 (C-3), 67.6 (C-2), 122.0 (C-7), 122.6 (C-9), 126.1 (C-5a), 126.9 (C-6), 135.2 (C-8), 137.8 (C-9a), 171.3 (C-4). EIMS m/z (%) 203 (M+1, 63), 202 (M, 93), 188 (45), 187 (100), 147 (100). Anal. Calcd for $C_{13}H_{18}N_2$ (202.30): C, 77.18; H, 8.97; N, 13.85. Found: C, 77.33; H, 8.90; N, 13.97.

5.2.5. From compound ***1g***

*5.2.5.1. (4E)-4-(7′-Chloro-4′,4′-dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4g**).* Yellow oil (0.455 g, 13%); IR (Nujol) ν_{max}: 3300, 1590, 1570 cm^{-1}. ^1H NMR: 1.36 (s, 3H, 4′-CH_3), 1.38 (s, 3H, 4′-CH_3), 1.50 (d, J=6.9 Hz, 3H, 2-CH_3), 1.70 (s, 3H, 5-CH_3), 1.72 (s, 3H, 5-CH_3), 2.65 (d, J=14.8 Hz, 1H, 3′-H), 2.95 (d, J=14.8 Hz, 1H, 3′-H), 3.52 (br s, 1H, 5′-H), 3.86 (q, J=6.9 Hz, 1H, 2-H), 6.66 (d, J=2.1 Hz, 1H, 6′-H), 6.74 (dd, J=8.5, 2.1 Hz, 1H, 8′-H), 6.86 (d, J=8.5 Hz, 1H, 9′-H), 13.9 (br s, 1H, 1′-H). ^{13}C NMR: 19.1 (2-CH_3), 30.96 (4′-CH_3), 31.04 (4′-CH_3), 34.1 (5-CH_3), 34.4 (5-CH_3), 41.2 (C-3′), 45.5 (C-2), 49.0 (C-5), 57.9 (C-4), 110.7 (C-4), 199.2 (C-6′), 120.0 (C-8′), 124.7 (C-9′), 126.1 (C-9a′), 130.3 (C-7′), 138.8 (C-5a′), 157.9 (C-2′), 198.6 (C-3). EIMS m/z (%) 350/352 (50), 349/351 (100), 334/336 (81), 262/264 (23), 247/249 (34), 207/209 (35), 165/167 (90). Anal. Calcd for $C_{18}H_{23}ClN_2OS$ (350.91): C, 61.61; H, 6.61; N, 7.98. Found C, 61.95; H, 6.47; N, 7.85.

*5.2.5.2. (4E)-4-(8′-Chloro-4′,4′-dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4h**).* Yellow oil (0.210 g, 6%); IR (Nujol) ν_{max}: 3325, 1600, 1580 cm^{-1}. ^1H NMR: 1.35 (s, 3H, 4′-CH_3), 1.38 (s, 3H, 4′-CH_3), 1.50 (d, J=7.0 Hz, 2-CH_3), 1.70 (s, 3H, 5-CH_3), 1.72 (s, 3H, 5-CH_3), 2.63 (d, J=15.0 Hz, 1H, 3′-H), 2.65 (d, J=15.0 Hz, 1H, 3′-H), 3.30 (br s, 1H, 5′-H), 3.86 (q, J=7.0 Hz, 1H, 2-H), 6.60 (d, J=8.4 Hz, 1H, 6′-H), 6.90 (dd, J=8.4, 2.3 Hz, 7′-H), 6.97 (d, J=2.3 Hz, 9′-H), 13.8 (br s, 1H, 1′-H). ^{13}C NMR: 19.0 (2-CH_3), 30.9 (4′-CH_3), 31.0 (4′-CH_3), 34.1 (5-CH_3), 34.3 (5-CH_3), 40.9 (C-3′), 45.4 (C-2), 48.9 (C-5), 58.6 (C-4′), 111.1 (C-4), 121.0 (C-6′), 123.1 (C-9′), 125.1 (C-8′), 125.2 (C-7′), 129.0 (C-9a′), 136.5 (C-5a′), 157.8 (C-2′), 198.6 (C-3). EIMS m/z (%) 350/352 (25), 349/351 (42), 334/336 (27), 262/264 (10), 247/249 (16), 165/167 (100). Anal. Calcd for $C_{18}H_{23}ClN_2OS$ (350.91): C, 61.61; H, 6.61; N, 7.98. Found: C, 61.90; H, 6.50; N, 7.72.

*5.2.5.3. 7-Chloro-1,1,3-trimethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7g**).* Colourless oil (0.13 g, 5%); IR (neat) ν_{max}: 1650 cm^{-1}. ^1H NMR: 1.81 (d, J=6.8 Hz, 3H, 3-CH_3), 2.00 (s, 3H, 1-CH_3), 2.06 (s, 3H, 1-CH_3), 4.76 (q, J=6.8 Hz, 1H, 3-H), 7.23 (dd, J=8.5, 1.8 Hz, 1H, 6-H), 7.40 (d, J=1.8 Hz, 1H, 8-H), 7.63 (d, J=8.5 Hz, 1H, 5-H). ^{13}C NMR: 21.8 (3-CH_3), 31.2 (1-CH_3), 31.4 (1-CH_3), 38.3 (C-3), 67.0 (C-1), 109.9 (C-8), 122.8 (C-5), 122.8 (C-6), 128.0 (C-7), 131.3 (C-8a), 147.5 (C-4a), 160.1 (C-3a). EIMS m/z (%) 252/254 (M^+, 99), 237/239 (50), 219/221 (62), 207/209 (37), 179/181 (90). Anal. Calcd for $C_{12}H_{13}ClN_2S$ (252.76): C, 57.02; H, 5.18; N, 11.08. Found: C, 57.13; H, 5.21; N, 11.20.

*5.2.5.4. 8-Chloro-2,3a,5,5-tetramethyl-3a,4,5,6-tetrahydro[1,3]thiazolo-[3,2-a][1,5]benzodiazepin-1(2H)-one (**6g**).* White crystals (0.062 g, 2%), mp 163–164 °C; IR (Nujol) ν_{max}: 3340, 1660, 1580 cm^{-1}.^1H NMR: 1.20 (s, 3H, 5-CH_3), 1.44 (s, 3H, 5-CH_3), 1.61 (s, 3H, 3a-CH_3), 1.64 (d, J=7.1 Hz,

3H, 2-CH_3), 2.14 (d, J=15.2 Hz, 1H, 4-H), 2.21 (d, J=15.2 Hz, 1H, 4-H), 3.20 (br s, 1H, 6-H), 4.06 (q, J=7.1 Hz, 1H, 2-H), 6.66 (d, J=2.3 Hz, 1H, 7-H), 6.81 (dd, J=8.5, 2.3 Hz, 9-H), 7.03 (d, J=8.5 Hz, 1H, 10-H). ^{13}C NMR: 19.4 (2-CH_3), 31.3 (3a-CH_3), 31.5 (5-CH_3), 32.8 (5-CH_3), 42.4 (C-2), 53.6 (C-5), 54.1 (C-4), 66.2 (C-3a), 119.4 (C-7), 119.7 (C-9), 122.0 (C-10a), 131.4 (C-10), 133.9 (C-8), 144.0 (C-6a), 172.8 (C-1). EIMS m/z (%) 310/312 (95), 295/297 (93), 277/279 (35), 239/241 (10), 223/225 (37), 209/211 (95), 207/209 (95), 166/168 (100). Anal. Calcd for $C_{15}H_{19}ClN_2OS$ (310.84): C, 57.96; H, 6.16; N, 9.01. Found: C, 58.17; H, 6.07; N, 8.89.

*5.2.5.5. 6-Chloro-1,1,3-trimethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7h**).* Colourless oil (0.126 g, 5%). ^{1}H NMR: 1.80 (d, J=6.8 Hz, 3H, 3-CH_3), 2.00 (s, 3H, 1-CH_3), 2.05 (s, 3H, 1-CH_3), 4.76 (q, J=6.8 Hz, 1H, 3-H), 7.21 (dd, J=8.6, 1.9 Hz, 1H, 7-H), 7.32 (d, J=8.6 Hz, 1H, 8-H), 7.71 (d, J=1.9 Hz, 1H, 5-H). ^{13}C NMR: 21.9 (3-CH_3), 31.4 (1-CH_3), 31.6 (1-CH_3), 38.5 (C-3), 67.6 (C-1), 110.5 (C-8), 120.2 (C-5), 122.8 (C-7), 128.0 (C-6), 129.5 (C-8a), 149.8 (C-4a), 161.8 (C-3a). EIMS m/z (%) 253/255 (M+H, 95), 252/254 (M^+, 85), 237/239 (100), 219/221 (95), 207/209 (25), 178/180 (90), 167/169 (55). Anal. Calcd for $C_{12}H_{13}ClN_2S$ (252.76): C, 57.02; H, 5.18; N, 11.08. Found: C, 57.10; H, 5.25; N, 11.25.

*5.2.5.6. 9-Chloro-2,3a,5,5-tetramethyl-3a,4,5,6-tetrahydro[1,3]thiazolo-[3,2-a][1,5]benzodiazepin-1(2H)-one (**6h**).* White crystals (0.095 g, 3%), mp 180–181 °C; IR (Nujol) ν_{max}: 3340, 1640, 1580 cm^{-1}. ^{1}H NMR: 1.19 (s, 3H, 5-CH_3), 1.43 (s, 3H, 5-CH_3), 1.63 (s, 3H, 3a-CH_3), 1.65 (d, J=7.2 Hz, 3H, 2-CH_3), 2.12 (d, J=15.1 Hz, 1H, 4-H), 2.24 (d, J=15.1 Hz, 1H, 4-H), 3.20 (br s, 1H, 6-H), 4.07 (q, J=7.2 Hz, 1H, 2-H), 6.60 (d, J=8.5 Hz, 1H, 7-H), 7.06 (dd, J=8.5, 2.2 Hz, 8-H), 7.13 (d, J=2.2 Hz, 1H, 10-H). ^{13}C NMR: 19.7 (2-CH_3), 31.3 (3a-CH_3), 31.7 (5-CH_3), 32.3 (5-CH_3), 42.4 (C-2), 53.5 (C-5), 54.7 (C-4), 66.4 (C-3a), 121.2 (C-7), 124.3 (C-10a), 125.0 (C-9), 128.7 (C-8), 130.0 (C-10), 141.7 (C-6a), 172.8 (C-1). EIMS m/z (%) 310/312 (5), 295/297 (81), 281/283 (100), 208/210 (40), 197/199 (90), 158/160 (90). Anal. Calcd for $C_{15}H_{19}ClN_2OS$ (310.84): C, 57.96; H, 6.16; N, 9.01. Found: C, 58.15; H, 6.24; N, 9.11.

*5.2.5.7. 8-Chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (**5g**).* Colourless crystals (0.066 g, 3%), mp 94–96 °C (Et_2O/petr. ether), (lit.[22] 90–92 °C); IR (Nujol) ν_{max}: 3340, 1620, 1575 cm^{-1}. ^{1}H NMR: 1.33 (s, 6H, 2×2-CH_3), 2.21 (s, 2H, 3-H), 2.35 (s, 3H, 4-CH_3), 3.0 (br s, 1H, 1-H), 6.72 (d, J=2.2 Hz, 1H, 9-H), 6.92 (dd, J=8.5, 2.2 Hz, 1H, 7-H), 7.05 (d, J=8.5 Hz, 1H, 6-H). ^{13}C NMR: 29.8 (4-CH_3), 30.5 (2×2-CH_3), 45.2 (C-3), 67.7 (C-2), 120.8 (C-9), 121.6 (C-7), 125.5 (C-8), 128.2 (C-6), 138.5 (C-5a), 139.1 (C-9a), 172.6 (C-4). EIMS m/z (%) 222/224 (45), 207/209 (100), 166/168 (95), 131 (15). Anal. Calcd for $C_{12}H_{15}ClN_2$ (222.71): C, 64.71; H, 6.79; N, 12.58. Found: C, 64.69; H, 6.45; N, 12.66.

*5.2.5.8. 7-Chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (**5h**).* Colourless crystals (0.72 g, 32%), mp 244–246 °C (Et_2O/petr. ether); IR (Nujol) ν_{max}: 3340, 1620, 1570 cm^{-1}. ^{1}H NMR: 1.33 (s, 6H, 2×2-CH_3), 2.22 (s, 2H, 3-H), 2.35 (s, 3H, 4-CH_3), 2.8 (br s, 1H, 1-H), 6.66 (d, J=8.5 Hz, 1H, 9-H), 6.94 (dd, J=8.5, 2.0 Hz, 1H, 8-H), 7.12 (d, J=2.0 Hz, 1H, 6-H). ^{13}C NMR: 29.8 (4-CH_3), 30.4 (2-CH_3), 45.2 (C-3), 68.4 (C-2), 122.6 (C-9), 125.3 (C-8), 126.5 (C-6), 126.9 (C-7), 136.6 (C-5a), 141.7 (C-9a), 173.9 (C-4). EIMS m/z (%) 222/224 (95), 209/211 (93), 165/167 (100), 131/133 (95). Anal. Calcd for $C_{12}H_{15}ClN_2$ (222.71): C, 64.71; H, 6.79; N, 12.58. Found: C, 64.62; H, 6.54; N, 12.70.

*5.2.6. From compound **1i** [amine (10 mmol), acetone (60 mmol) and acid (12 mmol)]*

*5.2.6.1. (4E)-4-(4′,4′-Dimethyl-1′,3′,4′,5′-tetrahydro-2H-naphtho[2,3-b][1,4]diazepin-2′-ylidene)-2,5,5-trimethyldihydrothiophen-3(2H)-one (**4i**).* Yellow crystals (1.25 g, 34%), mp 156–158 °C; IR (Nujol) ν_{max}: 3320, 1580 cm^{-1}. ^{1}H NMR: 1.40 (s, 3H, 4′-CH_3), 1.43 (s, 3H, 4′-CH_3), 1.53 (d, J=6.5, 3H, 2-CH_3), 1.73 (s, 3H, 5-CH_3), 1.76 (s, 3H, 5-CH_3), 2.57 (d, J=14.9, 1H, 3′-H), 2.63 (d, J=14.9, 1H, 3′-H), 3.4 (br s, 1H, 5′-H), 3.90 (q, J=6.5, 1H, 2-H), 7.14 (s, 1H, 6′-H), 7.27–7.38 (m, 2H, 8′,9′-H), 7.42 (s, 1H, 11′-H), 7.60–7.69 (m, 2H, 7′,10′-H), 13.80 (s, 1H, 1′-H). ^{13}C NMR: 19.0 (2-CH_3), 30.97 (4′-CH_3), 31.00 (4′-CH_3), 34.4 (5-CH_3), 34.5 (5-CH_3), 39.6 (C-3′), 45.4 (C-2), 48.9 (C-5), 60.2 (C-4′), 111.1 (C-4), 116.4 (C-6′), 120.3 (C-11′), 124.3 (C-10′), 125.6, 125.7 (C-8′,9′), 127.0 (C-7′), 129.8 (C-11a′), 131.6 (C-10a′), 132.1 (C-6a′), 137.6 (C-5a′), 157.9 (C-2′), 199.4 (C-3). EIMS m/z (%) 366 (62), 351 (52), 278 (10), 263 (8), 223 (15), 209 (10), 196 (10), 183 (100), 169 (43), 105 (37). Anal. Calcd for $C_{22}H_{26}N_2OS$ (366.52): C, 72.09; H, 7.15; N, 7.64. Found: C, 71.84; H, 7.21; N, 7.57.

*5.2.6.2. 1,1,3-Trimethyl-3H-naphtho[2′,3′:4,5]imidazo[1,2-c][1,3]thiazole (**7i**).* Colourless oil (0.108 g, 4%). IR (Neat) ν_{max}: 1610 cm^{-1}. ^{1}H NMR: 1.86 (d, J=6.7 Hz, 3H, 3-CH_3), 2.09 (s, 3H, 1-CH_3), 2.15 (s, 3H, 1-CH_3), 4.80 (q, J=6.7 Hz, 1H, 3-H), 7.38–7.46 (m, 2H, 7-H, 8-H), 7.79 (s, 1H, 10-H), 7.92 (d, J=8.5 Hz, 1H, 9-H), 7.97 (d, J=6.9 Hz, 1H, 6-H), 8.19 (s, 1H, 5-H). ^{13}C NMR: 21.7 (3-CH_3), 31.0 (1-CH_3), 31.2 (1-CH_3), 38.5 (C-3), 67.4 (C-1), 105.7 (C-10), 117.1 (C-5), 123.8 (C-6), 124.6 (C-7)*, 126.3 (C-8)*, 128.3 (C-9), 129.9 (C-5a)*, 130.0 (C-9a)*, 131.6 (C-10a), 148.9 (C-4a), 164.8 (C-3a). Anal. Calcd for $C_{16}H_{16}N_2S$ (268.38): C, 71.61; H, 6.01; N, 10.44. Found: C, 71.80; H, 6.12; N, 10.57.

*5.2.6.3. 3a,4,5,6-Tetrahydro-2,3a,5,5-tetramethyl-naphtho[2,3-b]thiazolo[3,2-d][1,4]diazepin-1(2H)-one (**6i**).* White crystals (0.360 g, 11%), mp 189–190 °C; IR (Nujol) ν_{max}: 3280, 1660, 1610 cm^{-1}. ^{1}H NMR: 1.19 (s, 3H, 5-CH_3), 1.35 (s, 3H, 5-CH_3), 1.64 (s, 3H, 3a-CH_3), 1.68 (d, J=6.1 Hz, 3H, 2-CH_3), 2.10 (d, J=14.5 Hz, 1H, 4-H), 2.42 (d, J=14.5 Hz, 1H, 4-H), 3.5 (br s, 1H, 6-H), 4.12 (q, J=6.1 Hz, 1H, 2-H), 7.12 (s, 1H, 7-H), 7.29 (dd, J=8.1, 7.7 Hz, 1H, 10-H), 7.39 (dd, J=8.1, 7.7 Hz, 1H, 9-H), 7.61 (d, J=8.1 Hz, 1H, 8-H), 7.68 (s, 1H, 12-H), 7.73 (d, J=8.1 Hz, 1H, 11-H). ^{13}C NMR: 19.8 (2-CH_3), 31.2 (3a-CH_3), 31.6 (5-CH_3), 32.2 (5-CH_3), 42.4 (C-2), 53.95 (C-5), 54.00 (C-4), 66.2 (C-3a), 116.7 (C-7), 123.65 (C-12a), 123.70 (C-10), 125.7 (C-8), 126.7 (C-9), 127.7 (C-11), 129.2 (C-11a), 129.4 (C-12), 134.0 (C-7a), 141.4 (C-6a), 173.0 (C-1). EIMS m/z (%) 326 (86), 311 (78), 293 (21), 269 (15), 255 (14), 238 (44), 223 (92), 210 (72), 195 (57), 182 (100), 167 (54), 140 (62), 115 (75). Anal. Calcd for $C_{19}H_{22}N_2OS$ (326.46): C, 69.90; H, 6.79; N, 8.58. Found: C, 69.67; H, 6.60; N, 8.35.

5.3. Reaction of *o*-phenylenediamines with phorone and 2-mercaptopropionic acid

To a stirred solution of *o*-phenylenediamine (10 mmol) and phorone (2.765 g, 20 mmol), in dry toluene (50 mL) was added 2-mercaptopropionic acid (1.275 g, 12.0 mmol) and the mixture was heated under reflux for 6 h. The solvent was evaporated in vacuo and the crude product was purified on a silica gel column using petroleum ether/ethylacetate 15:1 as eluent to afford in elution order.

*5.3.1. From compound **1a***

*5.3.1.1. Compound **4a**.* 1.265 g, 40%.

*5.3.1.2. Compound **5a**.* 0.43 g, 23%.

*5.3.2. From compound **1b***

*5.3.2.1. Compound **4b**.* 1.07 g, 31%.

*5.3.2.2. Compound **5b**.* 1.015 g, 47%.

*5.3.3. From compound **1c***

*5.3.3.1. Compound **4c**.* 1.18 g, 28%.

*5.3.3.2. Compound **4d**.* 1.09 g, 26%.

*5.3.3.3. Compound **5d**.* 0.37 g, 13%.

5.4. Reaction of *o*-phenylenediamines with acetone and 2-mercaptoacetic acid

Acetone (3.48 g, 60 mmol) and 2-mercaptoacetic acid (1.104 g, 12.0 mmol) were added in dry toluene (50 mL) and the resulted solution was flushed with a stream of argon under stirring for 30 min. *o*-Phenylenediamine **1a** (or **1b**) (10 mmol) was added and the mixture was heated under reflux for 6 h under argon atmosphere. The solvent was evaporated in vacuo and the crude product was purified on a silica gel column using petroleum ether/ethyl-acetate 5:1 as eluent to obtain in elution order.

*5.4.1. From compound **1a***

*5.4.1.1. (4E)-4-(4′,4′-Dimethyl-1′,3′,4′,5′-tetrahydro-2H-1′,5′-benzodiazepin-2′-ylidene)-5,5-dimethyldihydrothiophen-3(2H)-one (**4j**).* Yellow crystals (1.36 g, 45%), mp 166–169 °C; IR (Nujol) ν_{max}: 3300, 1595, 1565 cm^{-1}. ^1H NMR: 1.37 (s, 6H, 2×4′-CH_3), 1.72 (s, 6H, 2×5-CH_3), 2.64 (s, 2H, 3′-H), 3.4 (br s, 1H, 5′-H), 3.64 (s, 2H, 2-H), 6.69 (d, *J*=8.0 Hz, 1H, 6′-H), 6.84 (dd, *J*=7.9, 6.9 Hz, 1H, 8′-H), 6.94–7.00 (m, 2H, 7′,9′-H), 13.77 (s, 1H, 1′-H). ^{13}C NMR: 31.0 (2×4′-CH_3), 34.0 (2×5-CH_3), 37.7 (C-2), 40.9 (C-3′), 51.5 (C-5), 59.0 (C-4′), 110.6 (C-4), 120.2 (C-8′), 120.6 (C-6′), 123.6 (C-9′), 125.6 (C-7′), 128.0 (C-9a′), 137.9 (C-5a′), 158.3 (C-2′), 196.1 (C-3). EIMS *m*/*z* (%) 302 (99), 287 (99), 213 (50), 195 (35), 179 (66), 173 (72), 155 (88), 149 (52), 133 (100), 99 (34), 92 (77). Anal. Calcd for $C_{17}H_{22}N_2OS$ (302.43): C, 67.51; H, 7.33; N, 9.26. Found: C, 67.43; H, 7.29; N, 9.45.

*5.4.1.2. 1,1-Dimethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7j**).* White crystals (0.20 g, 10%), mp 108–110 °C (lit[12] 108–110 °C). ^1H NMR: 2.04 (s, 6H, 2×1-CH_3), 4.34 (s, 2H, 3-H), 7.21–7.30 (m, 2H, 6-H, 7-H), 7.40–7.46 (m, 1H, 8-H), 7.72–7.74 (m, 1H, 5-H). ^{13}C NMR: 27.9 (1-CH_3), 29.5 (1-CH_3), 30.7 (C-3), 67.9 (C-1), 109.4 (C-8), 120.2 (C-5), 122.1 (C-6), 122.1 (C-7), 130.9 (C-8a), 149.0 (C-4a), 156.7 (C-3a). EIMS *m*/*z* (%) 204 (M^+, 65), 203 (70), 188 (70), 170 (100), 164 (65), 156 (70), 143 (60), 130 (70).

*5.4.1.3. Compound **5a**.* Crystals (0.498 g, 26%).

*5.4.2. From compound **1b***

*5.4.2.1. (4E)-4-(1′,3′,4′,5′-Tetrahydro-4′,4′-7′,8′-tetramethyl-2H-1′,5′-benzodiazepin-2′-ylidene)-5,5-dimethyldihydrothiophen-3(2H)-one (**4k**).* Yellow crystals (0.33 g, 10%), mp 180–183 °C (Et_2O/petr. ether); IR (Nujol) ν_{max}: 3310, 1610, 1570 cm^{-1}. ^1H NMR: 1.35 (s, 6H, 2×4′-CH_3), 1.71 (s, 6H, 2×5-CH_3), 2.15 (s, 3H, 8′-CH_3), 2.19 (s, 3H, 7′-CH_3), 2.60 (s, 2H, 3′-H), 2.80 (br s, 1H, 5′-H), 3.64 (s, 2H, 2-H), 6.50 (s, 1H, 6′-H), 6.75 (s, 1H, 9′-H), 13.79 (s, 1H, 1′-H). ^{13}C NMR: 18.4 (8′-CH_3), 18.9 (7′-CH_3), 29.5 (4′-CH_3), 30.7 (4′-CH_3), 33.8 (2×5-CH_3), 37.5 (C-2), 40.9 (C-3′), 51.5 (C-5), 58.7 (C-4′), 110.0 (C-4), 121.3 (C-6′), 124.2 (C-9′), 125.5 (C-9a′), 128.7 (C-8′), 134.0 (C-7′), 135.4 (C-5a′), 158.4 (C-2′), 195.2 (C-3). EIMS *m*/*z* (%) 330 (90), 315 (94), 241 (45), 201 (82), 175 (75), 160 (84), 145 (84), 137 (100), 119 (65), 77 (98). Anal. Calcd for $C_{19}H_{26}N_2OS$ (330.49): C, 69.05; H, 7.93; N, 8.48. Found: C, 69.11; H, 8.02; N, 8.54.

*5.4.2.2. 1,1,6,7-Tetramethyl-3H-thiazolo[3,4-a][1,3]benzimidazole (**7k**).* White crystals (0.35 g, 15%), mp 176–178 °C; IR (Nujol) ν_{max}: 1610 cm^{-1}. ^1H NMR: 2.00 (s, 6H, 2×1-CH_3), 2.34 (s, 3H, 7-CH_3), 2.36 (s, 3H, 6-CH_3), 4.28 (s, 2H, 3-H), 7.18 (s, 1H, 8-H), 7.46 (s, 1H, 5-H). ^{13}C NMR: 20.1 (6-CH_3), 20.5 (7-CH_3), 27.9 (2×1-CH_3), 30.1 (C-3), 67.8 (C-1), 110.0 (C-8), 120.3 (C-5), 128.2 (C-6), 130.1 (C-7), 131.2 (C-8a), 147.8 (C-4a), 155.9 (C-3a). EIMS *m*/*z* (%) 232 (M, 95), 217 (45), 199 (88), 159 (100). Anal. Calcd for $C_{13}H_{16}N_2S$ (232.34): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.74; N, 11.87.

*5.4.2.3. Compound **5b**.* Crystals (0.41 g, 20%).

5.5. From *o*-phenylenediamine (10 mmol), acetone (40 mmol) and 2-mercaptobenzoic acid (8, 12 mmol) are obtained in elution order

*5.5.1. (2E)-2-(4′,4′-Dimethyl-1′,3′,4′,5′-tetrahydro-2′H-1′,5′-benzodiazepin-2′-ylidene)-1-benzothiophen-3(2H)-one (**9**).* Yellow crystals (1.35 g, 42%), mp 162–164 °C; IR (Nujol) ν_{max}: 3380, 1605, 1560 cm^{-1}. ^1H NMR: 1.43 (s, 6H, 2×4′-CH_3), 2.64 (s, 2H, 3′-H), 3.2 (br s, 1H, 5′-H), 6.81 (dd, *J*=7.6, 1.5 Hz, 1H, 6′-H), 6.99 (ddd, *J*=7.5, 7.4, 1.5 Hz, 1H, 8′-H), 7.06 (ddd, *J*=7.6, 7.5, 1.8 Hz, 1H, 7′-H), 7.11 (dd, *J*=7.5, 1.8 Hz, 1H, 9′-H), 7.31 (ddd, *J*=7.9, 7.1, 1.0 Hz, 1H, 5-H), 7.48 (ddd, *J*=8.0, 7.1, 1.3 Hz, 1H, 6-H), 7.59 (ddd, *J*=8.0, 1.0, 0.7 Hz, 1H, 7-H), 8.00 (ddd, *J*=7.9, 1.3, 0.7 Hz, 1H, 4-H), 13.37 (br s, 1H, 1′-H). ^{13}C NMR: 30.5 (2×4′-CH_3), 44.3 (C-3′), 63.6 (C-4′), 104.7 (C-2), 122.1 (C-6′), 122.6 (C-8′), 123.2 (C-9′), 123.4 (C-7), 124.1 (C-5), 125.2 (C-4), 126.3 (C-7′), 129.9 (C-9a′), 131.2 (C-6), 134.5 (C-3a), 138.6 (C-5a′), 142.4 (C-7a), 157.8 (C-2′), 182.4 (C-3). EIMS *m*/*z* (%) 322 (M^+, 30), 308 (26), 307 (33), 293 (20), 254 (13), 237 (13), 215 (47), 172 (35), 159 (20), 133 (100). Anal. Calcd for $C_{19}H_{18}N_2OS$ (322.42): C, 70.78; H, 5.63; N, 8.69. Found: C, 70.61; H, 5.74; N, 8.63.

*5.5.2. Compound **5a**.* Crystals (0.15 g, 8%).

5.6. Reaction of *o*-phenylenediamine with acetone and 3-mercaptopropionic acid

Acetone (3.48 g, 60 mmol) and 3-mercaptopropionic acid (1.272 g, 12.0 mmol) were added in dry toluene (50 mL) and the resulting solution was flushed with a stream of argon under stirring for 30 min. *o*-Phenylenediamine (**1a**, 10 mmol) was added and the mixture was heated under reflux for 20 h under an argon atmosphere. The solvent was evaporated in vacuo and the crude product was purified on a silica gel column using petroleum ether/ethyl acetate (5:1) as eluent to obtain in elution order.

*5.6.1. 2,2-Dimethyl-4-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-1,5-benzodiazepine (**10**).* Colorless oil (0.046 g, 3%); IR (neat) ν_{max}: 3320, 1640, 1590 cm^{-1}. ^1H NMR: 1.30 (s, 6H, 2×2-CH_3), 1.92 (d, *J*=1.4 Hz, 3H, 2′-CH_3), 2.16 (d, *J*=1.4 Hz, 3H, 2′-CH_3), 2.25 (s, 2H, 3-H), 3.00 (br s, 1H, 1-H), 6.02 (sept, *J*=1.4 Hz, 1H, 1′-H), 6.71–6.75 (m, 1H, 9-H), 6.93–6.98 (m, 1H, 7-H), 6.98–7.02 (m, 1H, 8-H), 7.19–7.23 (m, 1H, 6-H). ^{13}C NMR: 20.6 (2′-CH_3), 27.5 (2′-CH_3), 30.4 (2×2-CH_3), 45.6 (C-3), 69.2 (C-2), 121.6 (C-9), 121.9 (C-7), 125.3 (C-8), 126.7 (C-1′), 127.5 (C-6), 137.8 (C-9a), 141.1 (C-5a), 145.0 (C-11), 169.4 (C-4). EIMS *m*/*z* (%) 228 (95), 213 (100), 197 (35), 188 (84), 173 (98), 157 (47), 133 (98), 132 (100), 121 (60), 108 (80). Anal. Calcd for $C_{15}H_{20}N_2$ (228.33): C, 78.90; H, 8.83; N, 12.27. Found: C, 78.97; H, 8.98; N, 12.42.

*5.6.2. Compound **5a**.* Crystals (0.30 g, 16%).

5.7. Reaction of *N*-methyl-*o*-phenylenediamine with acetone and 2-mercaptoacetic acid

Acetone (3.48 g, 60 mmol) and 2-mercaptoacetic acid (1.104 g, 12.0 mmol) and *N*-methyl-*o*-phenylenediamine (**18**, 10 mmol) were

processed as above and finally from the silica gel column were obtained in elution order.

*5.7.1. 1,2,2-Trimethyl-4-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-1,5-benzodiazepine (**19**).* Colourless oil (0.158 g, 6% yield.) ^{1}H NMR: 1.27 (s, 6H, 2×2-CH$_3$), 1.92 (s, 3H, 11-CH$_3$), 2.17 (s, 3H, 11-CH$_3$), 2.19 (s, 2H, 3-H), 2.69 (s, 3H, 1-CH$_3$), 6.01 (br s, 1H, 10-H), 6.8–6.9 (m, 1H, 9-H), 6.95–7.15 (m, 3H, 6,7,8-H).

*5.7.2. 3,5,5-Trimethyl-2-(1-methyl-1H-benzimidazol-2-yl)tetrahydrothiophene-3-ol (**20**).* Colourless oil (0.830 g, 30%); IR (Nujol) ν_{max}: 3320, 1610 cm^{-1}. ^{1}H NMR: 1.48 (s, 3H, 3-CH$_3$), 1.56 (s, 3H, 5-CH$_3$), 1.71 (s, 3H, 5-CH$_3$), 2.03 (d, *J*=14.3 Hz, 1H, 4-H), 2.38 (d, *J*=14.3 Hz, 1H, 4-H), 3.74 (s, 3H, 1′-CH$_3$), 4.66 (s, 1H, 2-H), 7.23–7.27 (m, 1H, 5′-H), 7.28–7.33 (m, 2H, 6′,7′-H), 7.69–7.73 (m, 1H, 4′-H). ^{13}C NMR: 27.0 (3-CH$_3$), 29.9 (1′-CH$_3$), 33.1 (5-CH$_3$), 34.5 (5-CH$_3$), 51.2 (C-2), 53.8 (C-5), 58.0 (C-4), 84.1 (C-3), 109.2 (C-7′), 119.7 (C-4′), 122.5 (C-5′)*, 122.9 (C-6′)*, 134.8 (C-7a′), 141.4 (C-3a′), 152.6 (C-2′). EIMS *m*/*z* (%) 277 (M^++1, 89), 259 (62), 177 (100), 145 (16), 132 (14). Anal. Calcd for $C_{15}H_{20}N_2OS$ (276.39): C, 65.18; H, 7.29; N, 10.14. Found: C, 65.01; H, 7.31; N, 10.13.

5.8. Reaction of 4,5-dimethyl-*o*-phenylenediamine with butanone and 2-mercaptopropionic acid

In a solution of 4,5-dimethyl-*o*-phenylenediamine (**1b**) (1.36 g, 10 mmol) in dry toluene (50 mL), butanone (2.88 g, 40 mmol) and 2-mercaptopropionic acid (1.27 g, 12.0 mmol) were added and the resulting solution was flushed with a stream of argon under stirring for 30 min and the mixture was heated under reflux for 6 h under an argon atmosphere. The solvent was evaporated in vacuo and the crude product was purified on a silica gel column using petroleum ether/ethyl acetate (15:1) as eluent to give.

*5.8.1. 4-Acetyl-2,3-dihydro-2-ethyl-2,7,8-trimethyl-(1H)-1,5-benzodiazepine (**23**).* Orange crystals (1.56 g, 61%), mp 86–88 °C (Et_2O/petr. ether); IR (Nujol) ν_{max}: 3370, 1660, 1590 cm^{-1}. ^{1}H NMR: 0.92 (t, *J*=7.6 Hz, 3H, 2-CH$_2$*CH*$_3$), 1.16 (s, 3H, 2-CH$_3$), 1.50 (q, *J*=7.6 Hz, 3H, 2-*CH*$_2$CH$_3$), 2.20 (s, 6H, 7-CH$_3$, 8-CH$_3$), 2.56 (s, 3H, 4-COCH$_3$), 2.63 (s, 2H, 3-H), 3.40 (br s, 1H, 1-H), 6.50 (s, 1H, 9-H), 7.26 (s, 1H, 6-H). ^{13}C NMR: 8.3 (2-CH$_2$*CH*$_3$), 18.5 (7-CH$_3$), 19.5 (8-CH$_3$), 24.3 (4-CO*CH*$_3$), 27.5 (2-CH$_3$), 35.7 (2-*CH*$_2$CH$_3$), 37.2 (C-3), 65.3 (C-2), 121.2 (C-9), 128.1 (C-7), 132.5 (C-6), 133.1 (C-5a), 137.8 (C-9a), 138.4 (C-8), 162.6 (C-4), 200.4 (4-CO). EIMS *m*/*z* (%) 258 (97), 225 (95), 215 (55), 188 (75), 161 (80), 145 (70), 118 (65), 91 (90), 55 (100). Anal. Calcd for $C_{16}H_{22}N_2O$ (258.36): C, 74.38; H, 8.58; N, 10.84. Found: C, 74.51; H, 8.69; N, 10.94.

5.9. Reaction of *o*-phenylenediamine with benzophenone and 2-mercaptopropionic acid

From an analogous procedure product **24** was isolated.

*5.9.1. 2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (**24**).* White crystals (2.34 g, 75%), mp 151–152 °C; IR (Nujol) ν_{max}: 3270, 1600, 1580 cm^{-1}. ^{1}H NMR: 1.68 (s, 3H, 2-CH$_3$), 2.89 (d, *J*=14.3 Hz, 1H, 3-H), 3.07 (d, *J*=14.3 Hz, 1H, 3-H), 3.44 (br s, 1H, 1-H), 6.73–6.78 (m, 1H, 9-H), 6.97–7.04 (m, 2H, 7,8-H), 7.10–7.22 (m, 6H, 3,4,5-H for both Ph), 7.29–7.32 (m, 1H, 6-H), 7.51–7.58 (m, 4H, 2,6-H for both Ph). ^{13}C NMR: 30.0 (2-CH$_3$), 43.1 (C-3), 73.7 (C-2), 121.6 (C-9), 121.7 (C-7), 125.6 (C-8), 126.4 (C-2′,6′), 127.2 (C-2″,6″), 127.5 (C-4′), 128.2 (C-6), 128.4 (C-3″,5″), 128.8 (C-3′,5′), 129.8 (C-4″), 138.3 (C-9a), 139.7 (C-1″), 140.2 (C-1′), 147.7 (C-5a), 167.6 (C-4). EIMS *m*/*z* (%) 312 (90), 297 (75), 235 (63), 195 (90), 165 (15), 152 (18), 133 (30), 103 (100).

6. Experimental in vitro assays

6.1. In vitro aldose reductase enzyme assay

The synthesized benzodiazepine derivatives were dissolved in 10% aqueous solution of DMSO. Lenses were quickly removed from Fischer-344 rats of both sexes following euthanasia. The experiments conform to the law for the protection of experimental animals (Republic of Greece) and are registered at the Veterinary Administration of the Republic of Greece. The enzyme preparation and assay were performed as previously described.[17,19] The compounds were tested at two final concentrations (100 μM and 10 μM). The experiments were performed in triplicate and the standard deviation was less than 10%.

6.2. DPPH assay

To investigate the antiradical activity of the synthesized benzodiazepine derivatives in a homogeneous system, a method based on the scavenging of the stable free radical DPPH was used.[19] The compounds were dissolved in 1 mL of absolute ethanol (400–100 μM) and added to 1 mL solution of DPPH in absolute ethanol (400 μM) to give final concentrations of 200–50 μM and 200 μM for the tested compounds and DPPH, respectively. The incubation period was 30 min at room temperature. The absorbance decrease of the ethanol solution of the stable free radical at 517 nm, in the presence of the tested compounds, was measured. The experiments were performed in triplicate and the standard deviation was less than 10%.

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Supplementary data

Structural assignment for representative compounds is included in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.080.

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