Synthesis and Biological Activities of Camphor Hydrazones and Imine Derivatives

Emerson T. da Silva  1, Adriele da Silva Araújo  1, Adriana M. Moraes  1, Leidiane A. de Souza  1, Maria Cristina Silva Lourenço  2, Marcus V. N. de Souza  1,*, James L. Wardell  1,3 and Solange M. S. V. Wardell  4

1 Fundação Oswaldo Cruz (Fiocruz), Instituto de Tecnologia em Fármacos Farmanguinhos, Rua Sizenando Nabuco, 100, Manguinhos 21041-250, Rio de Janeiro, Brazil; esilva@far.fiocruz.br (E.T.d.S.); adriele.cp2@gmail.com (A.d.S.A.); m_drik@yahoo.com.br (A.M.M.); araujo.leidiane91@gmail.com (L.A.d.S.); j.wardell@abdn.ac.uk (J.L.W.)

2 Instituto de Pesquisa Clínica Evandro Chagas (IPEC)Av. Brasil, 4365, Fiocruz, 21040-900 Rio de Janeiro, Brazil; cristina.lourenco@ipef.fiocruz.br

3 Department of Chemistry, University of Aberdeen, Aberdeen AB2 3UE, Scotland, UK

4 CHEMSOL, 1 Harcourt Road, Aberdeen AB15 5NY, Scotland, UK; solangewardell@gmail.com

* Correspondence: marcos_souza@far.fiocruz.br; Tel.: +55-2139772535

Academic Editor: Thomas Erker
Received: 25 August 2015; Accepted: 18 October 2015; Published: 18 October 2015

Abstract: Both sonochemical and classical methodologies have been employed to convert camphor, 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, C9H16C=O, into a number of derivatives including hydrazones, C9H16C=N-NHAr 3, imines, C9H16C=N-R 7, and the key intermediate nitroimine, C9H16C=N-NO2 6. Reactions of nitroamine 6 with nucleophiles by classical methods provided the desired compounds in a range of yields. In evaluations of activity against Mycobacterium tuberculosis, compound 7j exhibited the best activity (minimal inhibitory concentration (MIC) = 3.12 µg/mL), comparable to that of the antitubercular drug ethambutol. The other derivatives displayed modest antimycobacterial activities at 25–50 µg/mL. In in vitro tests against cancer cell lines, none of the synthesized camphor compounds exhibited cytotoxic activities.

Keywords: camphor; sonochemistry; hydrazones; imines; tuberculosis

1. Introduction

Camphor, 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, is a natural product used since antiquity in a wide range of applications, such as in food flavourings, fumigants, perfumes, cosmetics, household cleaners, and topically applied analgesics [1]. Natural camphor occurs in dextrorotatory form, i.e., R,R-(+)-camphor, and is obtained through distillation of the wood from the camphor laurel tree (Cinnamomum camphora) or by chemical transformation of other natural products, such as turpentine [1]. The laevorotatory form (S,S-Camphor) exists only in a synthetic form or in very little quantities in specific species of plants [2]. In chemistry, camphor has been used as a selector in chiral separations [3], as a shift reagent in nuclear magnetic resonance (NMR) [4], as a chiral auxiliary [5], and as part of a catalyst system [6] as well as a versatile chemical precursor [7]. In the medical chemistry field, studies have revealed that camphor possesses a range of useful biological activities, being an antiviral, antimicrobial, antitussive, and analgesic agent [8].

Despite the general importance of camphor and its derivatives in several fields, few antitubercular and anticancer studies have been described. There are very few reports on the use of sonochemistry in synthesizing camphor derivatives. To address the lack of information in these areas, we have conducted a comparative study of the uses of sonochemistry and classical methodologies in synthesizing camphor derivatives and an evaluation of these derivatives as potential antitubercular and anticancer agents.
2. Results and Discussion

2.1. Chemistry

The camphor derivatives were synthesized as shown in Scheme 1. Hydrazine 1, prepared from camphor and hydrazine hydrate (80%) in 90% yield, was coupled with different arenecarbaldehydes to produce 3 in 30%–90% yields. For the preparation of the series 3, sonochemistry was found to be far superior to classical methodologies; in particular by drastically reducing the reaction time from ca. 20 h to a few minutes: only in the sonochemical synthesis of compound 3e was a reaction time greater than one hour required, see Table 1. The oxime 4, synthesized from hydroxylamine hydrochloride in 90% yield, was reduced to the amine hydrochloride 5 in a 50% yield. Comparison of the reaction conditions for the synthesis of compound 6 from oxime 4 and sodium nitrite again showed the advantages of using a sonochemical approach. Compound 6 was a key intermediate due to its ready reaction by classical means with various nucleophiles, such as hydrazine and amines, to give compounds, 1, 7, and 9 (see Scheme 1). Yields of compounds 7 varied from 10% to 90%. It is of interest to note that ultrasonic irradiation was clearly inferior to classical methodologies in syntheses involving the nitroamine 6, although, as indicated above, compound 6 could be produced from 4 by both sonochemical and classical methodologies. Reduction of 7a to 8 occurred upon reaction with sodium borohydride.

### Table 1. Syntheses and antimycobacterial activity against Mycobacterium tuberculosis H37Rv (ATCC 27294) of hydrazones 3.

| Final Compound (3) | R¹ | R² | R³ | R⁴ | X | MIC (µg/mL) | Time Classic Method (h) | Yield (%) | Time Ultrasound Method a (min) |
|-------------------|----|----|----|----|---|-------------|--------------------------|-----------|-----------------------------|
| a | H | H | H | H | CH | Res | 20 | 64 | 5 |
| b | H | H | F | H | CH | Res | 20 | 80 | 5 |
| c | H | H | Cl | H | CH | Res | 20 | 71 | 5 |
| d | H | H | Br | H | CH | 50 | 20 | 57 | 5 |
| e | H | H | OH | H | CH | Res | 20 | 70 | 60 |
| f | H | H | OCH₃ | H | CH | 100 | 20 | 75 | 5 |
| g | H | H | NO₂ | H | CH | ins | 20 | 36 | 5 |
| h | H | Cl | H | H | CH | 100 | 20 | 70 | 5 |
| i | H | CN | H | H | CH | Res | 20 | 85 | 5 |
| j | H | OCH₃ | H | H | CH | Res | 20 | 61 | 5 |
| k | H | NO₂ | H | H | CH | ins | 20 | 50 | 5 |
| l | F | H | H | H | CH | Res | 20 | 68 | 5 |
| m | Cl | H | H | H | CH | 100 | 20 | 51 | 5 |
| n | Br | H | H | H | CH | 50 | 20 | 55 | 5 |
| o | OH | H | H | H | CH | 50 | 20 | 64 | 5 |
| p | NO₂ | H | H | H | CH | 25 | 20 | 77 | 5 |
| q | Cl | Cl | H | H | CH | Res | 20 | 78 | 5 |
| r | OH | OH | H | H | CH | 100 | 20 | 73 | 7 |
| s | OH | H | OH | H | CH | 100 | 20 | 30 | 10 |
| t | H | OH | OH | H | CH | 100 | 20 | 38 | 5 |
| u | OH | H | OH | H | CH | Res | 20 | 64 | 5 |
| v | OH | H | OCH₃ | H | CH | 50 | 20 | 78 | 18 |
| w | OH | H | NO₂ | H | CH | Res | 20 | 54 | 5 |
| x | H | H | H | H | N | 100 | 20 | 38 | 5 |

Res: resistant; ins: insoluble; MIC: minimal inhibitory concentration. * The yields were very similar for both classical and sonochemistry methodologies.

All compounds were characterized by ¹H-NMR, ¹³C-NMR, and infrared (IR) spectra as well as by mass spectrometry (MS) data, and additionally in the case of compound 3k by X-ray crystallography. The chemical shifts, multiplicities, and coupling constants in the ¹H-NMR spectra confirmed the proposed structures. In general, for compounds 3, the ¹H-NMR spectra showed the characteristic signal for the N=CH proton at 8.19–8.80 ppm. Furthermore, the IR spectra showed N=C stretching vibrations at 1624–1661 cm⁻¹. The chemical shifts of all aliphatic and aryl protons occurred in the
regions normally found. Compound 9, as is typical of acylhydrazones and as shown by the $^1$H-NMR spectrum, exists as an $E_N=C/E_C(O)NH$ and $E_N=C/Z_C(O)NH$ mixture (in a 5:1 ratio) of conformers in solution [9]. The IR spectrum of 9 showed a C=O stretching vibration at 1638 cm$^{-1}$.

![Diagram of synthetic scheme for the camphor derivatives.]

**Scheme 1.** General synthetic scheme for the camphor derivatives.

2.2. Crystallography

A number of derivatives, 3, were considered as candidates for structure determinations by X-ray crystallography. However, poor crystals or powders were generally obtained upon recrystallization from common organic solvents: the best crystals were obtained for 3k from solution in 2-MeOCH$_2$CH$_2$OH. Moreover, even here, the crystals were not great and the best refinement was only about 12%. However, the atom connections, bond lengths, and angles within the hydrazonyl side chain were securely determined.

The crystal structure was solved from data collected at 120(2)K [10–12]. The asymmetric unit consisted of a single molecule. The aliphatic carbon atoms within the camphor moiety were highly disordered: Figure 1a shows the atom arrangements and numbering scheme for the predominant form. The atoms in the side chain of the camphor fragment, C=N-NH-C$_6$H$_4$-NO$_2$-m, experienced no disorder,
with precise bond angles and lengths. This side chain is not completely planar, as indicated by the angles between the N1-N2-C11 chain and the nitro group with the attached benzene ring of 5.1(1) and 12.1(2)°, respectively. Due to the disorder of the camphor moiety, the C=N-NH-C₆H₄NO₂⁻m side chain appears to emerge from a hydrocarbon ball: an attempt to give an impression of this is shown in Figure 1b, in which space-filling forms have been used for the atoms in the camphor fragment. The molecule clearly has two extreme poles—a polar end and a non-polar end. Among our recent studies have been investigations of the structures of various biologically active hydrazones of the type heteroaryl-NH-N=CH-Ar, such as heteroaryl = -7-chloroquinolin-4-yl [13], quinoxalin-2-yl [14], 1,3-benzothiazol-2-yl [15], and 5-phenyl-1,3,4-thiadiazol-2-yl [16]. In all these cases, the heteroaryl groups are planar or nearly so and are thus much different sterically from the bulky, non-planar camphor unit. Such differences should affect the biological activities, solubilities, etc.

![Figure 1. (a) The atom arrangements and numbering scheme for molecule 3k: only the major form of the highly disordered camphor group has been illustrated. Probability ellipsoids have been drawn at the 50% level; Hydrogen atoms have been drawn as spheres of arbitrary radius, (b) a version of the molecule in which the camphor group atoms were drawn in space filling forms and the N-N=CHC₆H₄NO₂⁻m was drawn in ball-and-stick forms.](image-url)
Not drawn in Figure 1a is the intramolecular C6-H6A—N1 hydrogen bond. Bond angles and lengths in the C1-N1-N2-C11-C12 fragment and other selected parameters are listed in Table 2. As found in other hydrazones, the bond lengths in the hydrazonyl fragment indicate considerable electron delocalization [13–16]. The geometry of the (camphor)-C1-N1-N2-C11-C12 fragment is \((E,E)\). PLATON analysis indicated that molecules of 3k are linked into a 3-dimensional array via combinations of \(\pi\)(phenyl)-\(\pi\)(phenyl) stacking interactions and C3-H3A—O1 \(i\), C3-H3B—O1 \(ii\) and C15-H15—N1 \(iii\) intermolecular hydrogen bonds (symmetry operations: \(i = x, 1/2 + y, 1/2-z; ii = -x, -1-y, 1-z; iii = -x, -1/2+y, 1/2-z\) [17]. In this arrangement, the polar N-NH-C\(_6\)H\(_4\)-NO\(_2\)–chains are engulfed by the non-polar camphor balls, see Figure 1b.

### 2.3. Antimycobacterial Activity against Mycobacterium tuberculosis H\(_{37}Rv\) (ATCC 27294)

The antimycobacterial activities of the synthesized compounds were assessed against *M. tuberculosis* ATCC 27294 [18] using the microplate Alamar Blue assay (MABA) [19] (Tables 2 and 3). This methodology is nontoxic, uses a thermally-stable reagent and shows good correlation with proportional and BACTEC radiometric methods [20,21].

The antimycobacterial activities of hydrazones 3 and imines 7 are shown in Tables 2 and 3. It is noticeable that the majority of moderately active compounds 3, i.e., those having minimal inhibitory concentration (MIC) values equal to or less than 50 \(\mu\)g/mL, have *ortho*-sited substituents in the aryl ring: the most active is 3p (MIC value = 25 \(\mu\)g/mL) with an *ortho* nitro group. Among the other moderately active compounds are 3n (*o*-Br), 3o (*o*-OH), and 3v (*o*-OH-*p*-OMe). These substituents, OH, OMe, Br, and O\(_2\)N, exhibit a range of electronic effects and spatial needs. There is no apparent link between the activities and properties these substituents possess, so different mechanisms of activity are suggested. From our earlier studies and others reported in the literature on the biological activities of hydrazones and heteroaryl-NH-N=CH-Ar (e.g., heteroaryl = 2-quinoxalinyl, etc.) [14], compounds having an *ortho*-hydroxyl aryl group, such as Ar = *o*-HOC\(_6\)H\(_4\), were found to be particularly active. This activity was assigned to their ability to act as \(N,N,O\)-tridentate ligands in chelating essential metals such as iron, copper, and zinc. A similar role has been suggested for heteroaryl-NH-N=CH-pyridin-2-yl compounds. The derivatives, 3o and 3v, as well as 3x, however, at best can only operate as bidentate chelators which greatly reduce their ability to sequester any essential metal.

In a more limited study of the imines 7, the most active compound by far, with an MIC value of 3.12 \(\mu\)g/mL, was 7j with an *o*-hydroxyl group. This is comparable activity to that of the antitubercular drug ethambutol. No other compound 7 had an activity anywhere near that of 7j.

The isoniazid derivative 9 exhibited a moderate activity (50 \(\mu\)g/mL) while compounds 1, 2, and 4–6 did not exhibit antimycobacterial activity.

### Table 2. Selected bond lengths and angles, Å (°) in 3k.

|        | C2-N1  | N1-N2  | N2-C11 | N2-N1-C12 | N2-C11-C12 | C2-N1-N2-C11 |
|--------|--------|--------|--------|-----------|------------|-------------|
| C2-N1  | 1.272(5)| 1.420(4)| 1.268(5)| 1.122(3)  | 1.219(4)   | 1.173(3)    |
| N1-N2  |        | 1.218(5)| 1.467(5)| 1.235(4)  |            |             |
| N2-C11 |        |        | 1.467(5)| 1.235(4)  |            |             |
| N2-N1-C12|      |       |        | 1.235(4)  |            |             |
| N2-C11-C12|     |       |       |           |            |             |
| C2-N1-N2-C11| |       |       |           |            |             |
chelators which greatly reduce their ability to sequester any essential metal. At best can only operate as bidentate chelating essential metals such as iron, copper, and zinc. A similar role has been suggested for compounds having an activity anywhere near that of hydrazones and heteroaryl quinoxalinyl, etc. 

Table 3. Derivatives camphor 7 from nitroimine 6 and different amines and anilines.

| Final Compound (7) | R      | MIC (µg/mL) | Condition, Time | Yield (%) |
|-------------------|--------|-------------|-----------------|-----------|
| a                 | -CH₂Ph | Res         | CHCl₃, reflux, 4 h | 55        |
| b                 | -CH₂(CH₂)₂CH₃ | Res | CHCl₃, reflux, 4 h | 70        |
| c                 |        | Res         | CHCl₃, reflux, 3 h | 65        |
| d                 |        | Res         | CHCl₃, reflux, 3 h | 73        |
| e                 |        | Res         | CH₃CN, reflux, 48 h | 79        |
| f                 |        | 100         | CH₃CN, reflux, 30 h | 52        |
| g                 |        | 100         | CH₃CN, reflux, 43 h | 73        |
| h                 |        | Res         | CH₃CN, reflux, 17 h | 81        |
| i                 |        | Res         | CH₃CN, reflux, 48 h | 90        |
| j                 |        | 3.12        | CH₃CN, reflux, 20 h | 53        |
| k                 |        | Res         | CH₃CN, reflux, 48 h | 46        |
| l                 |        | Res         | CH₃CN, reflux, 64 h | 39        |
| m                 |        | Res         | CH₃CN, reflux, 24 h | 10        |
| n                 |        | Res         | CH₃CN, reflux, 72 h | 15        |

2.4. Cytotoxicity against Cancer Cell Lines

All compounds were tested in vitro against three human cancer cell lines: SF-295 (glioblastoma), OVCAR-8 (ovary), and HCT-116 (colon) (National Cancer Institute, Bethesda, MD, USA) at 5 µg/mL using the MTT assay. Unfortunately, none of the compounds prepared in this study displayed cytotoxicity activities.

2.5. Toxicity Risks

Only compounds 3r, 3v, 3x, 6, 7i, and 9 were indicated by the OSIRIS Property Explorer program [22] to possess potential toxicity risks.
3. Materials and Methods

Melting points were determined with a Fisatom 130 apparatus (Fisatom, São Paulo, Brazil) and are uncorrected. NMR spectra were determined using 400 or 500 MHz Bruker AC spectrometers (Karlsruhe, Germany). Infrared spectra were obtained using a Perkin-Elmer 467 FTIR spectrometer (Cleveland, OH, USA) with samples in potassium bromide disks. Mass spectra were recorded on the Agilent 122 5532 GC/MS column by electron impact (Santa Clara, CA, USA). The progress of the reactions was monitored by thin-layer chromatography (TLC) on 2.0 cm × 6.0 cm aluminum sheets (silica gel 60, HF-254, Merck, Kenilworth, NJ, USA) with a thickness of 0.25 mm, using ultraviolet light irradiation. For column chromatography, Merck silica gel (230–400 mesh) was used. Solvents and reagents were used without further purification. An ultrasonic homogenizer model Desruptor Eco Sonics (25 KHz, Eco Sonics, Indaiatuba, Brazil) was used to carry out the reactions at 90 W. Arenealdehydes and D-camphor (R,R-(+)-camphor) were obtained from commercial sources. Oxime 4 and nitroimine 6 were prepared from D-camphor following published procedures [23].

3.1. Synthesis of Nitroimine (6) Using Ultrasonic Irradiation

To a solution of the oxime 4 (4.32 g, 26.23 mmol) in acetic acid (130 mL), an aqueous solution of sodium nitrite was added (65 mL, 10%). The reaction mixture was irradiated with ultrasonic energy until TLC indicated the complete consumption of 4 (15 min). After cooling at 0 °C, a solution of NaOH (150 mL, 50%) was added and the mixture was extracted with ethyl acetate (4 × 50 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to furnish 6 as an oil (90% yield, 4.11 g).

3.2. Synthesis of (E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (1).

To a solution of camphor (3.0 g; 19.74 mmol) in n-propanol (50 mL) was added hydrazine hydrate (10 equivalents, 12.5 mL, 80%). The mixture was refluxed until TLC indicated completed consumption of the camphor (48 h). The reaction mixture was concentrated under vacuum and successively added (30 mL) to the residue water with stirring, along with ethyl acetate (30 mL). The organic layer was collected. The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic phases were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to leave a solid, melting point (mp): 50–53 °C (lit. [24] mp: 54–55 °C).

3.3. Synthesis of (1E,2E)-1,2-Bis(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (2).

To a solution of the hydrazine 1 (0.202 g; 1.22 mmol) in CHCl₃ (10 mL) nitroimine 6 was added (0.239 g; 1.22 mmol). The mixture was refluxed until TLC indicated the consumption of compound 6. An aqueous solution of Na₂CO₃ (10%, 20 mL) was added with stirring and the phases were separated. The aqueous phase was extracted with CHCl₃ (2 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (SiO₂, 70–230 mesh, AcOEt/n-Hex 10%) to afford the desired product in 57%, mp: 180–183 °C (lit. [25] mp: 186–187 °C). 1H-NMR (CDCl₃, 400 MHz) δ: 2.15–2.35 (2H, m, N=C-CH₂a), 1.15–1.95 (12H, m, 2CH, 2-N=C-CH₂b, 2-CH₂-CH₂), 1.03 (6H, s, 2-CH₃), 0.92 (6H, s, 2-CH₃), 0.79 (6H, s, 2-CH₃). 13C-NMR (CDCl₃, 100 MHz) δ: 175.96, 175.90, 52.45, 52.44, 43.82, 48.24, 47.64, 46.96, 43.82, 34.96, 18.58, 18.52, 17.71, 17.67, 10.14, 10.12. IR (KBr) v, cm⁻¹: 1669 (C=N). GC: 100% MS: (m/z, %): 300 (M⁺, 90), 231 (63), 150 (61), 109 (41).

3.4. General Procedures for the Synthesis of Camphor Hydrazone Derivatives (3)

(a) Without Sonication

To a solution of hydrazine 1 (0.25 g; 1.5 mmol) in ethanol (10 mL) was added the appropriate arenealdehyde (1 or 0.8 eq.). The reaction mixture was stirred for 20 h when TLC indicated the
consumption of the aldehyde. The hydrazone product was normally obtained pure after filtering and washing with cold ethanol or diethyl ether (5 to 10 mL). However, in some cases trituration or column chromatography was necessary, as indicated below.

(b) With Sonication

Similar amounts of reagents and solvents were used as in (a). The reaction mixture was irradiated with an ultrasonic probe until TLC indicated the reaction was complete. With the exception of the reaction producing 7e, all other reactions were complete in 5–18 min.

(1E,2E)-1-Benzylidene-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3a). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 80%, mp: 123–125 °C. 1H-NMR (CDCl3, 400 MHz) δ: 8.31 (1H, s, CH=N), 7.00–7.76 (4H, m, phenyl), 2.15–2.67 (2H, m, N=C-CH2), 1.90 (1H, t, CH, J = 4.28 Hz), 1.25–1.95 (4H, m, CH2-CH2), 1.10 (3H, s, CH3), 0.97 (3H, s, CH3), 0.84 (3H, s, CH3). 13C-NMR (CDCl3, 100 MHz) δ: 182.77, 157.70, 134.96, 130.68, 128.81, 128.29, 52.88, 48.13, 44.12, 36.21, 32.87, 27.52, 19.85, 19.02, 11.50. IR (KBr) v, cm−1: 1650 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22N2 + H]: 255.1861; Found: 255.1856.

(1E,2E)-1-(4-Fluorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3b). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 71%, mp: 125–127 °C. 1H-NMR (CDCl3, 400 MHz) δ: 8.30 (1H, s, CH=N), 7.35–7.75 (4H, m, phenyl), 2.15–2.71 (2H, m, N=C-CH2), 1.94 (1H, t, CH, J = 4.24 Hz), 1.20–1.95 (4H, m, CH2-CH2), 1.10 (3H, s, CH3), 0.97 (3H, s, CH3), 0.84 (3H, s, CH3). 13C-NMR (CDCl3, 100 MHz) δ: 181.03, 155.89, 135.10, 133.27, 129.44, 128.80, 52.27, 47.35, 43.18, 40.14, 35.35, 32.24, 26.71, 19.25, 18.50, 11.22. IR (KBr) v, cm−1: 1624 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22FN2 + H]: 273.1767; Found: 273.1765.

(1E,2E)-1-(4-Chlorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3c). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 57%, mp: 60–62 °C. 1H-NMR (CDCl3, 400 MHz) δ: 8.28 (1H, s, CH=N), 7.50–7.65 (4H, m, phenyl), 2.15–2.70 (2H, m, N=C-CH2), 1.94 (1H, t, CH, J = 4.28 Hz), 1.20–1.90 (4H, m, CH2-CH2), 1.09 (3H, s, CH3), 0.97 (3H, s, CH3), 0.84 (3H, s, CH3). 13C-NMR (CDCl3, 100 MHz) δ: 183.38, 156.61, 153.91, 132.09, 129.67, 125.01, 52.97, 47.35, 43.18, 40.14, 35.35, 32.24, 26.71, 19.25, 18.50, 11.22. IR (KBr) v, cm−1: 1650 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22ClN2 + H]: 289.1472; Found: 289.1456.

(1E,2E)-1-(4-Bromobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3d). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 70%, mp: 157–160 °C. 1H-NMR (CDCl3, 400 MHz) δ: 8.95 (1H, s, CH=N), 6.75–7.65 (4H, m, phenyl), 2.05–2.60 (2H, m, N=C-CH2), 1.90 (1H, t, CH, J = 4.20 Hz), 1.20–1.80 (4H, m, CH2-CH2), 0.99 (3H, s, CH3), 0.92 (3H, s, CH3), 0.76 (3H, s, CH3). 13C-NMR (DMSO, 100 MHz) δ: 179.88, 159.74, 157.18, 129.61, 125.39, 115.45, 52.01, 47.21, 43.13, 35.33, 32.26, 26.72, 19.22, 18.47, 11.28. IR (KBr) v, cm−1: 1625 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22BrN2 + H]: 333.0966; Found: 333.0957.

4-((E)-((E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)phenol (3e). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 20%). Yield: 70%, mp: 157–160 °C. 1H-NMR (DMSO, 400 MHz) δ: 9.95 (1H, s, OH), 8.24 (1H, s, CH=N), 6.75–7.65 (4H, m, phenyl), 2.05–2.60 (2H, m, N=C-CH2), 1.90 (1H, t, CH, J = 4.20 Hz), 1.20–1.80 (4H, m, CH2-CH2), 0.99 (3H, s, CH3), 0.92 (3H, s, CH3), 0.76 (3H, s, CH3). 13C-NMR (DMSO, 100 MHz) δ: 179.88, 159.74, 157.18, 129.61, 125.39, 115.45, 52.01, 47.21, 43.13, 35.33, 32.26, 26.72, 19.22, 18.47, 11.28. IR (KBr) v, cm−1: 1625 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22N2O + H]: 271.1810; Found: 271.1797.

(1E,2E)-1-(4-Methoxybenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3f). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 20%). Yield: 75%, mp: 67–69 °C.
Theoretical mass calculated for [C₁₈H₂₁N₂O + H]: 285.1967; Found: 285.1952.

(1E,2E)-1-(4-Nitrobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yldiene)hydrazine (3g). Purified by filtration and washing with cold ethyl ether. Yield: 36%; mp: 100–102 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.29 (1H, s, CH=N), 6.95–7.75 (4H, m, phenyl), 2.00–2.55 (2H, m, N=C-CH₂), 1.91 (1H, t, CH, J = 4.20 Hz), 1.20–1.80 (4H, m, CH₂-CH₂), 1.00 (3H, s, CH₃), 0.93 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 179.88, 159.74, 157.18, 129.61, 125.39, 115.45, 52.01, 47.21, 43.13, 35.33, 32.26, 26.72, 19.22, 18.47, 11.28. IR (KBr) ν, cm⁻¹: 1575 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₈H₂₁N₂O + H]: 285.1967; Found: 285.1952.

(1E,2E)-1-(3-Chlorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yldiene)hydrazine (3h). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 70%; mp: 58–60 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.33 (1H, s, CH=N), 7.48–7.82 (4H, m, phenyl), 2.09–2.61 (2H, m, N=C-CH₂), 1.92 (1H, t, CH, J = 4.04 Hz), 1.22–1.84 (4H, m, CH₂-CH₂), 1.00 (3H, s, CH₃), 0.93 (3H, s, CH₃), 0.80 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 181.34, 155.66, 136.57, 133.51, 130.65, 130.27, 127.18, 126.47, 52.35, 47.43, 35.39, 32.25, 26.72, 19.29, 18.53, 11.27. IR (KBr) ν, cm⁻¹: 1709, 1655 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁CIN₂ + H]: 289.1472; Found: 289.1477.

3-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydr azono)methyl]benzonitrile (3i). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 85%; mp: 93–94 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.39 (1H, s, CH=N), 7.65–8.18 (4H, m, phenyl), 2.49–2.52 (2H, m, N=C-CH₂), 2.10 (1H, t, CH, J = 3.92 Hz), 1.03–2.00 (4H, m, CH₂-CH₂), 1.01 (3H, s, CH₃), 0.94 (3H, s, CH₃), 0.77 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 181.59, 155.05, 135.52, 133.74, 131.33, 129.95, 118.27, 111.83, 52.31, 47.37, 43.09, 35.33, 32.15, 26.63, 19.20, 18.44, 11.16. IR (KBr) ν, cm⁻¹: 1647 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁CIN₂ + H]: 280.1814; Found: 280.1822.

(1E,2E)-1-(3-Methoxybenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yldiene)hydrazine (3j). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 61%, oil. ¹H-NMR (DMSO, 400 MHz) δ: 8.29 (1H, s, CH=N), 7.00–7.37 (4H, m, phenyl), 3.78 (3H, s, O-CH₃), 2.09–2.51 (2H, m, N=C-CH₂), 1.91 (1H, t, CH, J = 4.04 Hz), 1.25–1.38 (4H, m, CH₂-CH₂), 1.00 (3H, s, CH₃), 0.93 (3H, s, CH₃), 0.77 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 182.46, 159.77, 157.26, 136.12, 129.60, 121.31, 116.87, 111.87, 55.31, 52.66, 47.92, 43.89, 35.97, 32.63, 27.29, 19.63, 18.81, 11.28. IR (KBr) ν, cm⁻¹: 1653 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₈H₂₃N₃O₂ + H]: 285.1967; Found: 285.1964.

(1E,2E)-1-(3-Nitrobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yldiene)hydrazine (3k). Purified by filtration and washing with cold ethyl ether. Yield: 50%; mp: 110–113 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.59 (1H, s, phenyl), 8.49 (1H, s, CH=N), 7.70–8.55 (3H, s, phenyl), 2.10–2.65 (2H, m, N=C-CH₂), 1.94 (1H, t, CH, J = 4.08 Hz), 1.20–1.85 (4H, m, CH₂-CH₂), 1.02 (3H, s, CH₃), 0.94 (3H, s, CH₃), 0.78 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 184.41, 155.04, 148.66, 136.58, 133.66, 129.64, 124.80, 122.55, 52.97, 48.07, 43.88, 36.19, 32.63, 27.28, 19.64, 18.80, 11.22; IR (KBr) ν, cm⁻¹: 1648 (C=N); HRMS (ESI, +H): Theoretical mass calculated for [C₁₈H₂₃N₃O₂ + H]: 300.1712; Found: 300.1710.
127.39, 124.72, 124.69, 121.68, 121.58, 116.09, 115.88, 52.25, 47.35, 43.07, 35.32, 32.13, 26.62, 19.20, 18.44, 11.15. IR (KBr) v, cm⁻¹: 1640 (C=N). MS (ESI, +H): 278.

(1E,2E)-1-(2-Chlorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3m). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 5%). Yield: 51%, mp: 66–69 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.58 (1H, s, CH=N), 7.40–8.05 (3H, m, phenyl), 2.05–2.65 (2H, m, N=C-CH₂), 1.93 (1H, t, CH, J = 4.04 Hz), 1.20–1.85 (4H, m, CH₂-CH₂), 1.01 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 181.93, 152.98, 133.80, 132.10, 130.20, 129.86, 129.79, 129.44, 52.31, 47.38, 43.08, 35.38, 32.12, 26.62, 19.20, 18.44, 11.15. IR (KBr) v, cm⁻¹: 1651 (C=N); HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁ClN₂ + H⁺]: 289.1472; Found: 289.1471.

(1E,2E)-1-(2-Chlorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3n). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 5%). Yield: 55%, mp: 88–90 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.52 (1H, s, CH=N), 7.39–8.00 (4H, m, phenyl), 1.94–2.51 (2H, m, N=C-CH₂), 1.93 (1H, t, CH, J = 4.02 Hz), 1.23–1.80 (4H, m, CH₂-CH₂), 1.02 (3H, s, CH₃). ¹³C-NMR (DMSO, 100 MHz) δ: 181.99, 155.28, 133.08, 132.64, 132.34, 128.15, 127.95, 124.12, 52.32, 47.38, 43.07, 35.40, 32.11, 26.61, 19.20, 18.43, 11.15. IR (KBr) v, cm⁻¹: 1657 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁BrN₂ + H⁺]: 333.0966; Found: 333.0978.

2-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)methyleno)methylphenol (3o). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 64%, mp: 54–57 °C. ¹H-NMR (CDCl₃, 400 MHz) δ: 12.00 (1H, s, OH), 8.61 (1H, s, CH=N), 6.85–7.40 (4H, m, phenyl), 2.10–2.75 (2H, m, N=C-CH₂), 2.00 (1H, t, CH, J = 4.28 Hz), 1.20–1.95 (4H, m, CH₂-CH₂), 1.12 (3H, s, CH₃). ¹³C-NMR (CDCl₃, 100 MHz) δ: 185.26, 162.27, 160.05, 132.48, 132.12, 119.46, 118.18, 117.00, 53.23, 48.44, 44.02, 36.49, 32.78, 27.43, 19.82, 18.96, 11.40. IR (KBr) v, cm⁻¹: 1650, 1624 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁O₂ + H⁺]: 271.1810; Found: 271.1797.

(1E,2E)-1-(2-Nitrobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3p). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 77%, mp: 72–75 °C. ¹H-NMR (CDCl₃, 400 MHz) δ: 8.53 (1H, s, CH=N), 7.65–8.05 (4H, m, phenyl), 2.05–2.55 (2H, m, N=C-CH₂), 1.93 (1H, t, CH, J = 4.28 Hz), 1.20–1.95 (4H, m, CH₂-CH₂), 1.01 (3H, s, CH₃). ¹³C-NMR (CDCl₃, 100 MHz) δ: 181.48, 152.76, 148.73, 133.36, 131.13, 129.38, 128.34, 124.32, 52.30, 47.43, 43.04, 35.31, 32.08, 26.64, 19.18, 18.42, 11.14. IR (KBr) v, cm⁻¹: 1647 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁NO₂ + H⁺]: 300.1712; Found: 300.1707.

(1E,2E)-1-(2,3-Dichlorobenzylidene)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine (3q). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 78%, mp: 69–72 °C. ¹H-NMR (DMSO, 400 MHz) δ: 8.60 (1H, s, CH=N), 7.42–8.00 (3H, m, phenyl), 2.10–2.60 (2H, m, N=C-CH₂), 1.92 (1H, t, CH, J = 4.24 Hz), 1.03–1.70 (4H, m, CH₂-CH₂), 1.02 (3H, s, CH₃). ¹³C-NMR (CDCl₃, 100 MHz) δ: 182.43, 153.04, 133.74, 132.39, 132.28, 131.75, 128.43, 126.55, 52.49, 47.52, 43.17, 35.49, 32.20, 25.70, 19.30, 18.53, 11.23. IR (KBr) v, cm⁻¹: 1650 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₁Cl₂N₂ + H⁺]: 323.1082; Found: 323.1082.

3-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazonomethyl)benzene-1,2-diol (3r). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 73%, mp: 104–106 °C. ¹H-NMR (CDCl₃, 400 MHz) δ: 12.36 (1H, s, OH), 8.59 (1H, s, CH=N), 6.75–7.01 (3H, m, phenyl), 2.17–2.75 (2H, m, N=C-CH₂), 2.01 (1H, t, CH, J = 4.28 Hz), 1.25–1.95 (4H, m, CH₂-CH₂), 1.12 (3H, s, CH₃). ¹³C-NMR (CDCl₃, 100 MHz) δ: 185.29, 162.20, 147.08, 144.95, 122.99, 119.77, 117.84, 117.39, 53.30, 48.47, 44.04, 36.43, 32.76, 27.42, 19.83, 18.95, 11.38. IR (KBr) v, cm⁻¹: 1643 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₇H₂₂N₂O₂ + H⁺]: 287.1760; Found: 287.1785.
4-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)benzene-1,3-diol (3s). Purified by filtration and washing with cold ethyl ether. Yield: 25%, mp: 183–185 °C. 1H-NMR (DMSO, 500 MHz) δ: 12.01 (1H, s, OH), 10.15 (1H, s, OH), 8.59 (1H, s, CH=N), 6.25–7.35 (3H, m, phenyl), 2.08–2.65 (2H, m, N=C=CH2), 1.94 (1H, t, CH, J = 4.00 Hz), 1.30–1.90 (4H, m, CH2-CH2), 1.00 (3H, s, CH3). 13C-NMR (DMSO, 120 MHz) δ: 181.71, 161.66, 161.63, 161.12, 110.22, 107.84, 102.33, 52.39, 47.62, 43.18, 35.41, 32.25, 26.68, 19.28, 18.51, 11.26. IR (KBr) v cm⁻¹: 1661 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22N2O2 + H]: 287.1760; Found: 287.1775.

4-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)benzene-1,2-diol (3t). Purified by filtration and washing with cold ethyl ether. Yield: 38%, mp: 186–190 °C. 1H-NMR (DMSO, 400 MHz) δ: 8.16 (1H, s, OH), 7.24 (1H, s, OH), 8.16 (1H, s, CH=N), 6.76–7.24 (3H, m, phenyl), 2.08–2.15 (2H, m, N=C=CH2), 1.91 (1H, t, CH, J = 4.04 Hz), 1.21–1.85 (4H, m, CH2-CH2), 0.99 (3H, s, CH3), 0.92 (3H, s, CH3). 13C-NMR (DMSO, 100 MHz) δ: 157.57, 146.84, 143.69, 127.53, 122.90, 115.17, 113.92, 52.90, 48.11, 43.84, 36.14, 32.64, 27.24, 19.64, 18.78, 11.29. IR (KBr) v cm⁻¹: 1663 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22N2O2 + H]: 287.1760; Found: 287.1778.

2-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)benzene-1,4-diol (3u). Purified by filtration and washing with cold ethyl ether. Yield: 64%, mp: 218–220 °C. 1H-NMR (DMSO, 400 MHz) δ: 10.94 (1H, s, OH), 9.00 (1H, s, OH), 8.60 (1H, s, CH=N), 6.74–6.94 (3H, m, phenyl), 2.09–2.60 (2H, m, N=C=CH2), 1.96 (1H, t, CH, J = 3.92 Hz), 1.24–1.87 (4H, m, CH2-CH2), 1.02 (3H, s, CH3), 0.94 (3H, s, CH3), 0.76 (3H, s, -CH3). 13C-NMR (DMSO, 100 MHz) δ: 185.44, 161.54, 153.99, 148.00, 120.10, 117.89, 117.55, 117.16, 53.06, 48.24, 43.78, 36.30, 32.55, 27.20, 19.61, 18.74, 11.18. IR (KBr) v cm⁻¹: 1651 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C17H22N2O2 + H]: 287.1760; Found: 287.1773.

4-Methoxy-2-((E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)phenol (3v). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Yield: 78%, mp: 77–80 °C. 1H-NMR (DMSO, 400 MHz) δ: 12.07 (1H, 1s, OH), 8.64 (1H, s, CH=N), 6.47–7.47 (3H, m, phenyl), 3.78 (3H, s, OCH3), 2.00–2.70 (2H, m, N=C=CH2), 1.96 (1H, t, CH, J = 4.04 Hz), 1.23–1.87 (4H, m, CH2-CH2), 1.01 (3H, s, CH3). 13C-NMR (DMSO, 400 MHz) δ: 182.32, 163.37, 162.91, 162.06, 161.46, 161.04, 160.66, 133.31, 132.70, 111.40, 111.37, 107.10, 106.68, 100.95, 100.83. IR (KBr) v cm⁻¹: 1651, 1633 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C18H24N2O2 + H]: 301.1916; Found: 301.1915.

5-Nitro-2-((E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)phenol (3w). Purified by filtration and washing with cold ethanol. Yield: 54%, mp: 138–141 °C. 1H-NMR (DMSO, 400 MHz) δ: 12.77 (1H, s, OH), 8.80 (1H, s, CH=N), 7.12–8.61 (3H, m, phenyl), 2.14–2.65 (2H, m, N=C=CH2), 1.98 (1H, t, CH, J = 3.76 Hz), 1.41–1.97 (4H, m, CH2-CH2), 1.38 (3H, s, CH3), 1.36 (3H, s, CH3), 1.35 (3H, s, CH3). 13C-NMR (DMSO, 100 MHz) δ: 184.41, 164.08, 158.45, 139.80, 127.51, 126.75, 118.49, 117.34, 52.73, 47.70, 43.15, 35.44, 32.14, 26.54, 19.25, 18.46, 11.10. IR (KBr) v cm⁻¹: 1628 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C18H24N2O3 + H]: 316.1661; Found: 316.1651.

2-((E)-(E)-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)methyl)pyridine (3x). Purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 30%). Yield: 38%, oil. 1H-NMR (DMSO, 400 MHz) δ: 8.64 (1H, m, phenyl), 8.19 (1H, s, CH=N), 7.80–8.00 (3H, m, phenyl), 2.05–2.55 (2H, m, N=C=CH2), 1.92 (1H, t, CH, J = 4.12 Hz), 1.05–1.97 (4H, m, CH2-CH2), 1.01 (3H, s, CH3), 0.93 (3H, s, CH3). 13C-NMR (DMSO, 100 MHz) δ: 181.05, 156.64, 152.95, 149.58, 136.79, 124.91, 120.86, 52.37, 47.45, 43.18, 35.33, 32.20, 26.70, 19.25, 18.51, 11.20. IR (KBr) v cm⁻¹: 1641 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C16H21N3 + H]: 256.1814; Found: 256.1800.
1,7,7-Trimethylbicyclo[2.2.1]heptan-2-amine hydrochloride 5 [26]. A stirred solution of the oxime 4 (2.0 g, 12.40 mmol) in MeOH (120 mL) was hydrogenated using 5 bar pressure of H₂ and 10% Pd/C (0.12 g) for 48 h at 80 °C. The reaction mixture was filtered, rotary evaporated, and the oily residue dissolved in acetone (20 mL). The solution was acidified (pH = 2) with gaseous HCl. The precipitate of the hydrochloride 5 was collected, washed with cold acetone, and dried under vacuum. Yield: 0.75 g, 50%.

1H-NMR (DMSO, 400 MHz) δ: 7.96 (3H, sbr, NH₃), 3.00 (1H, m, CH-NH₃), 1.70–1.89 (3H, m, N=C-CH₂, CH), 1.10–1.69 (4H, m, CH₂-CH₂), 0.94 (3H, s, CH₃), 0.90 (3H, s, CH₃), 0.81 (3H, s, CH₃). 13C-NMR (DMSO, 100 MHz) δ: 57.17, 47.48, 46.66, 44.15, 35.75, 35.71, 26.17, 20.02, 19.93, 11.42. IR (KBr) ν, cm⁻¹: 3039 (NH). MS (m/z, %): 153 (M⁺, 43), 108 (25), 95 (99), 82 (100), 70 (24).

3.5. General Synthetic Procedure for the Imine Derivatives 7

The appropriate amine (1.5–2 equivalents) was added with stirring to a solution of nitroimine 1 (1.0–3.0 mmol) in CHCl₃ or CH₂CN (15–20 mL). The reaction mixture was refluxed until TLC indicated the consumption of 1 or lack of further reaction (3–72 h). The products 7a–7d were obtained pure after adequate procedure: the reaction solution (in this case chloroform) was extracted with a saturated aqueous solution of NaHCO₃ (3 × 5 mL). The organic layer was washed with a saturated aqueous solution of brine (5 mL) and dried over MgSO₄. The solvents were removed by rotary evaporation to furnish the product pure in accordance with spectra analyses (in these reactions the use of recrystallized oxime was necessary).

The products 7e–7n, after evaporation of the solvent, were purified by column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%–50%).

(E)-1-Phenyl-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine (7a) [27]. Yield: 55%, oil. 1H-NMR (MeOD, 400 MHz) δ: 7.21–7.35 (5H, m, phenyl), 4.47 (2H, dd, J = 14.3 Hz), 1.95–2.50 (3H, m, N=C-CH₂, CH), 1.10–1.70 (4H, m, CH₂-CH₂), 1.00 (3H, s, CH₃), 0.96 (3H, s, CH₃), 0.79 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz) δ: 57.17, 47.48, 46.66, 44.15, 35.75, 35.71, 26.17, 20.02, 19.93, 11.42. IR (KBr) ν, cm⁻¹: 3039. MS (ESI, +H): 242.

(E)-N-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)butan-1-amine (7b) [28]. Yield: 70%, oil. 1H-NMR (MeOD, 400 MHz) δ: 3.15–3.27 (m, 2H, N-CH₂), 1.15–2.40 (11H, m, CH, CH₂-cyclohexyl), 0.96 (s, 3H, CH₃), 0.93 (3H, s, CH₃ side chain), 0.92 (3H, s, CH₃), 0.75 (s, 3H, CH₃). 13C-NMR (MeOD, 100 MHz) δ: 53.67, 52.34, 47.09, 44.08, 35.62, 32.94, 32.45, 27.75, 20.93, 19.79, 19.22, 14.28, 11.71. IR (KBr) ν, cm⁻¹: 1677 (C=N). MS (ESI, +H): 208.

(E)-N-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)cyclopropanamine (7c). Yield: 65%, oil. 1H-NMR (MeOD, 400 MHz) δ: 2.65–2.75 (m, 1H, N-CH), 1.95–2.50 (2H, m, N=C-CH₂) 1.93 (t, 1H, CH, J = 7.2 Hz), 1.15–1.90 (4H, m, CH₂-CH₂), 0.93 (3H, s, CH₃), 0.91 (3H, s, CH₃), 0.76 (3H, s, CH₃), 0.71–0.74 (m, 4H, cyclopropyl). 13C-NMR (MeOD, 100 MHz) δ: 52.82, 46.45, 43.31, 35.34, 33.52, 31.90, 26.99, 19.25, 18.75, 11.44, 7.61, 7.38. IR (KBr) ν, cm⁻¹: 1677 (C=N). HRMS (ESI, +H): Theoretical mass calculated for C₁₃H₁₅N⁺ H: 192.1752; Found: 192.1744.

(E)-N-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)cyclohexanamine (7d) [29]. Yield: 73%, oil. 1H-NMR (MeOD, 400 MHz) δ: 3.07 (m, 1H, N-CH), 1.15–2.55 (17H, m, N=C-CH₂, CH, CH₂-CH₂-camphor, CH₂(CH₂)₃CH₂-cyclohexyl), 0.96 (3H, s, -CH₃), 0.91 (3H, s, -CH₃), 0.75 (3H, s, -CH₃). 13C-NMR (MeOD, 100 MHz) δ: 52.82, 46.45, 43.31, 35.34, 33.52, 31.90, 26.99, 19.25, 18.75, 11.44, 7.61, 7.38. IR (KBr) ν, cm⁻¹: 1683 (C=N). GC: 100%, MS (m/z, %): 233 (M⁺, 25), 205 (100), 136 (17), 109 (16), 95 (16).

(E)-4-Fluoro-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7e). Yield: 79%, oil. 1H-NMR (MeOD, 400 MHz) δ: 7.07 (4H, m, phenyl), 2.15–2.25 (1H, m, =C-CH₂), 1.75–1.97 (4H, m, -N=C-CH₂, CH, CH₂), 1.25–1.55 (2H, m, CH₂), 1.07 (3H, s, CH₃), 1.00 (3H, s, CH₃), 0.87 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz) δ: 189.73, 162.38, 159.99, 148.78, 148.76, 122.57, 122.49, 116.97, 116.75, 55.56, 45.30, 37.60, 33.21,
(E)-4-Chloro-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7f). Yield: 52%, mp: 34–36 °C. 1H-NMR (MeOD, 400 MHz): δ: 6.60–7.27 (4H, m, phenyl); 2.14–2.22 (1H, m, N=N=C-CH₃); 1.68–1.95 (4H, m, N=C-CH₃, CH, CH₂), 1.15–1.55 (2H, m, CH₂), 1.07 (3H, s, CH₃); 0.97 (3H, s, CH₃); 0.85 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz): δ: 185.74, 150.77, 128.76, 128.28, 120.85, 54.09, 47.20, 43.74, 36.23, 31.99, 27.38, 19.54, 18.99, 11.16. IR (KBr) v, cm⁻¹: 1680 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₆H₂₀FN⁺ + H⁺]: 246.1658; Found: 246.1658.

(E)-B-Bromo-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7g). Yield: 73%, oil. 1H-NMR (MeOD, 400 MHz): δ: 6.61–7.39 (4H, m, phenyl), 2.10–2.20 (1H, m, N=N=C-CH₃), 1.65–1.95 (4H, m, N=C-CH₃, CH, CH₂), 1.20–1.55 (2H, m, CH₂), 1.07 (3H, s, CH₃), 0.97 (3H, s, CH₃), 0.85 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz): δ: 184.22, 151.10, 131.73, 121.51, 131.54, 53.79, 46.73, 43.16, 35.48, 31.56, 26.77, 19.25, 18.77, 11.23. IR (KBr) v, cm⁻¹: 1604 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₆H₂₀Cl⁺ + Br⁺ + H⁺]: 306.0857; Found: 306.0856.

(E)-4-Hydroxy-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7h) [30]. Yield: 81%, mp: 142–144 °C. 1H-NMR (DMSO, 400 MHz): δ: 9.02 (1H, s, OH); 6.50–6.76 (4H, m, phenyl); 2.11–2.20 (1H, m, N=N=C-CH₃), 1.70–1.90 (4H, m, N=C-CH₃, CH, CH₂), 1.20–1.45 (2H, m, CH₂), 0.96 (3H, s, CH₃), 0.92 (3H, s, CH₃), 0.77 (3H, s, CH₃). 13C-NMR (DMSO, 100 MHz): δ: 182.32, 153.14, 143.17, 120.47, 115.39, 53.56, 46.48, 43.24, 40.13, 35.64, 31.70, 26.90, 19.28, 18.82, 11.46. IR (KBr) v, cm⁻¹: 1665 (C=N). GC: 100%, MS (m/z, %): 243 (M⁺, 100), 160 (40), 135 (46), 134 (20), 95 (32).

(E)-4-Methoxy-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7i) [31]. Yield: 90%, mp: 41–43 °C. 1H-NMR (MeOD, 400 MHz): δ: 6.60–6.90 (4H, m, phenyl); 3.75 (3H, s, OCH₃), 2.15–2.26 (1H, m, N=N=C-CH₃), 1.75–1.95 (4H, m, N=C-CH₃, CH, CH₂), 1.25–1.55 (2H, m, CH₂), 0.96 (3H, s, CH₃), 0.92 (3H, s, CH₃), 0.77 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz): δ: 189.25, 158.06, 145.45, 122.13, 115.63, 56.01, 55.47, 45.32, 37.71, 33.26, 28.30, 19.45, 11.78. IR (KBr) v, cm⁻¹: 1675 (C=N). GC: 99%, MS (m/z, %): 257 (M⁺, 100%), 174 (30), 149 (33), 95 (23).

(E)-2-Hydroxy-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7j) [32]. Yield: 53%, mp: 94–96 °C. 1H-NMR (DMSO, 400 MHz): δ: 8.83 (1H, s, OH); 6.50–6.85 (4H, m, phenyl), 2.10–2.25 (1H, m, N=N=C-CH₃), 1.65–1.90 (4H, m, N=C-CH₃, CH, CH₂), 1.10–1.25 (2H, m, CH₂), 0.99 (3H, s, CH₃), 0.92 (3H, s, CH₃), 0.83 (3H, s, CH₃). 13C-NMR (DMSO, 100 MHz): δ: 183.86, 146.58, 139.20, 123.47, 120.37, 119.18, 115.75, 53.75, 46.98, 43.24, 36.58, 31.76, 26.96, 19.39, 18.89, 11.34. IR (KBr) v, cm⁻¹: 1668 (C=N). GC: 96%, MS (m/z, %): 243 (88), 228 (60), 172 (62), 134 (68), 95 (100).

(E)-2,5-Dimethoxy-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)aniline (7k). Yield: 46%, oil. 1H-NMR (MeOD, 400 MHz): δ: 6.25–6.92 (3H, m, phenyl), 3.72 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 2.13–2.28 (1H, m, N=N=C-CH₃), 1.60–1.90 (4H, m, N=C-CH₃, CH, CH₂), 1.20–1.55 (2H, m, CH₂), 1.08 (3H, s, CH₃), 0.99 (3H, s, CH₃), 0.92 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz): δ: 190.60, 155.88, 145.16, 142.30 114.59, 109.98, 108.57, 56.89, 56.18, 55.71, 45.34, 38.31, 33.34, 28.28, 20.08, 19.52, 11.65. IR (KBr) v, cm⁻¹: 1682 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C₁₅H₂₀N₂H⁺ + H⁺]: 288.1964; Found: 288.1962.

(E)-N-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)pyridin-2-amine (7l) [33]. Yield: 39%, oil. 1H-NMR (MeOD, 400 MHz): δ: 6.75–8.35 (4H, m, phenyl), 2.20–2.55 (1H, m, N=N=C-CH₃), 1.70–1.90 (4H, m, N=C-CH₃, CH, CH₂), 1.20–1.50 (2H, m, CH₂), 0.99 (3H, s, CH₃), 0.94 (3H, s, CH₃), 0.82 (3H, s, CH₃). 13C-NMR (MeOD, 100 MHz): δ: 185.33, 163.31, 148.45, 137.87 118.99, 115.07, 53.84, 46.83, 43.16, 35.88, 31.49, 26.78, 19.28, 18.78, 11.21. IR (KBr) v, cm⁻¹: 1681 (C=N). GC: 100, MS (m/z, %): 228 (45), 213 (72), 200 (100), 185 (65), 78 (48).
(E)-N-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)pyridin-4-amine (7m).

Yield: 10%, oil. 1H-NMR (MeOD, 400 MHz) δ: 6.70–8.45 (4H, m, phenyl), 2.10–2.20 (1H, m, N=C-CH3), 1.65–1.92 (4H, m, N=C-CH3, CH, CH2), 1.20–1.50 (2H, m, CH2), 0.98 (3H, s, CH3), 0.94 (3H, s, CH3), 0.82 (3H, s, CH3).

13C-NMR (MeOD, 100 MHz) δ: 173.30, 140.90, 118.48, 57.07, 45.58, 39.64, 33.11, 28.00, 20.09, 19.45, 11.65. IR (KBr) ν, cm⁻¹: 1682 (C=N). HRMS (ESI, +H): Theoretical mass calculated for [C15H30N2 + H]: 229.1705; Found: 229.1695.

3.6. Synthesis of N-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (8) [34].

To a solution of the compound 7a (0.37 g; 1.53 mmol) in methanol (10 mL), NaBH₄ (0.116 g; 3.06 mmol) was added slowly at room temperature. The reaction was refluxed until TLC analysis indicated total consumption of 7a. After cooling to room temperature, water (10 mL) was added and the mixture was stirred for 30 min. The solvents were removed by rotary evaporation and the residue was suspended in aqueous K₂CO₃ (10 mL, 10% solution) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and evaporated to furnish the crude product which was purified using column chromatography on silica gel (70–230 mesh, AcOEt/n-Hex 10%). Compound 8 was obtained in a 25% yield as an oil. 1H-NMR (CDCl₃, 400 MHz) δ: 7.20–7.35 (5H, m, phenyl), 3.70 (1H, dd, CH₃Ph, J = 13.0 Hz), 2.59 (1H, dd, CH₂Ph, J = 13.0Hz), 1.00–1.70 (10H, m, CH-CH₂, CH, CH₂-CH₂, CH₃), 0.89 (3H, s, CH₃), 0.81 (3H, s, CH₃). 13C-NMR (CDCl₃, 100 MHz) δ: 128.45, 128.32, 127.62, 126.88, 66.44, 52.81, 48.67, 46.99, 45.55, 38.98, 37.07, 27.60, 20.83, 20.80, 12.42. IR (KBr) ν, cm⁻¹: 3067 (NH). GC: 97%, MS (m/z, %): 243 (M⁺, 47), 172 (83), 120 (25), 95 (53), 91 (100).

3.7. Synthesis of N′-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)isonicotinohydrazide (9).

Isonicotinohydrazide (0.28 g; 2.13 mmol) was added to a solution of 1 (0.40 g; 2.13 mmol) in acetonitrile (20 mL). The reaction mixture was refluxed until TLC analysis indicated the consumption of 1. The precipitate was collected, washed with cold ethanol, and dried under vacuum. The residue was triturated in refluxing ethanol for 2 hours. After cooling at 5 °C, the solid was collected and dried under vacuum to furnish 9. Yield: 60%, mp: 216–218 °C (lit. [35]: 205–207 °C). 1H-NMR (DMSO, 400 MHz) δ: (mixture of isomers E/Z: 5:1) 10.64 (s, NH, Z isomer), 10.48 (1H, s, NH), 8.72 (2H, d, phenyl, J = 5.9 Hz), 8.66 (2H, d, phenyl, Z isomer), 7.71 (2H, d, phenyl, J = 5.9 Hz), 7.59 (2H, m, phenyl, Z isomer), 2.55–2.65 (1H, m, N=C-CH₃), 2.10 (1H, d, N=C-CH₃, J = 17.7 Hz), 1.95 (1H, t, CH, J = 4.2 Hz), 1.15–1.90 (4H, m, CH₂-CH₂), 0.99 (3H, s, CH₃), 0.91 (3H, s, CH₃), 0.87 (3H, s, CH₃), 0.76 (3H, s, CH₃), 0.70 (s, CH₃, Z isomer). 13C-NMR (DMSO, 100 MHz) δ: 178.01, 163.34, 149.48, 148.49 (Z), 141.86, 123.78 (Z), 121.93, 53.26, 44.08, 43.96, 34.59, 33.66 (Z), 32.21, 18.54 (Z), 18.43, 17.63, 10.12. IR (KBr) ν, cm⁻¹: 1638 (C=N). GC: 100%, MS (m/z, %): 256 (76), 139 (66), 123 (48), 106 (100).

3.8. Biological Evaluation against Mycobacterium tuberculosis

The antmycobacterial activities of all tested compounds were assessed against M. tuberculosis ATCC 27294, using the microplate Alamar Blue assay (MABA, Tables 2 and 3). Briefly, 200 microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates (Falcon, 3072: Becton Dickinson, Lincoln Park, NJ, USA) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 µL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI, USA) and a serial dilution of the tested compounds was made directly on the plate. The final drug concentrations tested were 3 to 100.0 µg/mL. Plates were covered and sealed with
parafilm and incubated at 37 °C for five days. After this time, 25 microliters of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake, OH, USA) reagent and 10% Tween 80 were added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC was defined as the lowest drug concentration which prevented a color change from blue to pink.

3.9. Cytotoxicity against Cancer Cell Lines

Compounds (5.0 µg/mL) were tested for their cytotoxic activity against three human cancer cell lines: OVCAR-8 (ovary), SF-295 (glioblastoma), and HCT-116 (colon) (National Cancer Institute, Bethesda, MD, USA). All cell lines were maintained in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 °C with 5% CO₂. Each compound was dissolved with DMSO until reaching the final concentration. The final concentration of DMSO in the culture medium was kept constant, below 0.1% (v/v). All compounds were incubated with the cells for 72 h. The negative control received the same amount of DMSO (0.001% in the highest concentration). The cell viability was determined by the reduction of the yellow dye 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a blue formazan product as described by Mosmann [36]. Unfortunately, none of the compounds prepared in this study displayed cytotoxicity activities.

Acknowledgments: The authors would like to acknowledge CNPq and Fiocruz for financial and infrastructure assistance.

Author Contributions: E.T.d.S., M.V.N.d.S. conceived and designed the experiments and wrote the paper; A.M.M., A.d.S.A., L.A.d.S. performed the experiments; J.L.W. and S.M.S.V.W. analyzed the data; M.C.S.L. performed the biological evaluation.

Conflicts of Interest: The authors declare no conflict of interest.

References and Notes

1. Chen, W.; Vermaak, I.; Viljoen, A. Camphor—A Fumigant during the Black Death and a Coveted Fragrant Wood in Ancient Egypt and Babylon—A Review. Molecules 2013, 18, 5434–5454. [CrossRef] [PubMed]

2. You, C.; Guo, S.; Zhang, W.; Yang, K.; Geng, Z.; Du, S.; Wang, C.; Deng, Z. Identification of repellent and insecticidal constituents from Artemisia mongolica essential oil against Lasioderma serricorne. J. Chem. 2015, 2015, 549057. [CrossRef]

3. Li, Z.-J.; Yao, J.; Tao, Q.; Jiang, L.; Lu, T.-B. Enantioselective Recognition and Separation of Racemic 1-Phenylethanol by a Pair of 2D Chiral Coordination Polymers. Inorg. Chem. 2013, 52, 11694–11696. [CrossRef] [PubMed]

4. Wenzel, T.J.; Wenzel, B.T. Diamagnetic lanthanide tris β-diketonates as organic-soluble chiral NMR shift reagents. Chirality 2008, 21, 6–10. [CrossRef] [PubMed]

5. Cody, J.A.; Boeckman, R.K. Terpene derived auxiliaries. Camphor and pinene derived auxiliaries. Compr. Chirality 2012, 3, 42–105.

6. Chelucci, G. Synthesis and application in asymmetric catalysis of camphor-based pyridine ligands. Chem. Soc. Rev. 2006, 35, 1230–1243. [CrossRef] [PubMed]

7. Money, T.A. Chiral starting material in natural product synthesis. Nat. Prod. Rep. 1985, 2, 253–289. [CrossRef] [PubMed]

8. Sokolova, A.S.; YarOVaya, O.I.; Shernyukov, A.V.; Pokrovsky, M.A.; Pokrovsky, A.G.; Lavrinenko, V.A.; Zarubaev, V.V.; Tretiak, T.S.; Anfimov, P.M.; Kiselev, O.I.; et al. New quaternary ammonium camphor derivatives and their antiviral activity, genotoxic effects and cytotoxicity. Bioorg. Med. Chem. 2013, 21, 6690–6698. [CrossRef] [PubMed]

9. Cardoso, L.F.; Bispo, M.I.; Kaiser, C.R.; Wardell, J.L.; Wardell, S.M.; Lourenço, M.C.; Bezerra, F.A.; Soares, R.P.; Rocha, M.N.; de Souza, M.V. Anti-tuberculosis evaluation and conformational study of N-acylhydrazones containing the thiophene nucleus. Arch. Pharm. Chem. Life Sci. 2014, 347, 432–448. [CrossRef] [PubMed]
10. Data for compound 3k were obtained at 100(2) K with Mo-Kα radiation by means of the Rigaku Saturn724+ (2×2 bin mode) diffractometer. Data collection, data reduction and unit cell refinement were carried out under the control of the program CrystalClear-SM Expert 2.0. Data were collected at the NCS Crystallographic Service, based at the University of Southampton, England. Correction for absorption was achieved by a semi-empirical method based upon the variation of equivalent reflections with Rigaku program equivalent to SADABS 2007/2. The program MERCURY was used in the preparation of the Figures. SHELXL.97 and PLATON were used in the calculation of molecular geometry. The structures were solved by direct methods using SHELXS-97 and fully refined by means of the program SHELXL-97 [8]. All hydrogen atoms were placed in calculated positions.

11. Sheldrick, G.M. A short history of SHELX. Acta Crystallogr. 2008, A64, 112–122. [CrossRef] [PubMed]

12. Crystal data collected at 100(2) K, colourless crystal: 0.42 \times 0.19 \times 0.03 \text{ mm}; Formula:C_{17}H_{21}N_{3}O_{2}; M = 299.37; monoclinic, \( P2_1/c \); \( a = 14.3207(10) \text{ Å}, \( b = 10.4920(8) \text{ Å}, \( c = 11.0426(8) \text{ Å}, \( \beta = 108.670(2)^\circ \), \( z = 4 \), \( V = 1571.87(19)\text{Å}^3 \); independent reflections 2817 [R(int) = 0.04], observed reflections 2754 [I > 2σ(I)]; parameters refined 204; number of restraints 18; R(F) 0.122 [I > 2σ(I)]; Largest diff. peak 1.54 e Å^{-3}. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, deposition number 1405803. Full details of the crystal structure determination in cif format are available in the online version, at doi: (to be inserted Copies of these can be obtained free of charge on written application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033); on request by e-mail to deposit@ccdc.cam.ac.uk or by access to http://www.ccdc.cam.ac.uk).

13. Howie, R.A.; de Souza, M.V.; Ferreira, M.L.; Kaiser, C.R.; Wardell, J.L.; Wardell, S.M. Structures of ary aldehyde 7-chloroquinoline-4-hydrazone s: Supramolecular arrangements derived from N-H-\cdots-N, C-H-\cdots-X \((X = \text{N, O, or π})\) and π-\cdots-π interactions. Z. Kristallogr. 2010, 225, 440–447. [CrossRef]

14. De Souza, M.V.; Nogueira, T.C.; Wardell, S.M.; Wardell, J.L. Crystal structures of (E)-2-(2-benzylidenehydrazinyl)quinoxalines: Persistent N-H-\cdots-N intermolecular hydrogen bonds but variable π-\cdots-π interactions. Z. Kristallogr. 2014, 229, 587–594. [CrossRef]

15. Lindgren, E.B.; Yoneda, J.D.; Leal, K.Z.; Nogueira, A.F.; Vasconcelos, T.R.; Wardell, J.L.; Wardell, S.M. Structures of hydrazones, (E)-2-(1,3-benzothiazolyl)-NH-N=CHAr, [Ar =4-(pyridin-2-yl)phenyl, pyrrol-2-yl, thien-2-yl and furan-2-yl]: Difference in conformations and intermolecular hydrogen bonding. J. Mol. Struct. 2013, 1036, 19–27. [CrossRef]

16. Carvalho, S.A.; Harrison, W.T.; Fraga, C.A.; da Silva, E.F.; Wardell, J.L.; Wardell, S.M. 5-Phenyl-2-(benzaldehydrazonyl)-1,3,4-thiadiazoles, potential trypanocidal agents: Consistent dimer formation via N-H-\cdots-X of intermolecular hydrogen bonds. Z. Kristallogr. 2009, 224, 598–606. [CrossRef]

17. Steed, J.W.; Gale, J.P. Crystal engineering. In Supramolecular Chemistry: From Molecules to Nanomaterials; Tiekink, E.R.T., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2012; Volume 6, pp. 2791–2828.

18. Canetti, J.; Rist, E.; Grosset, R. Measurement of sensitivity of the tuberculosis bacillus to antibacillary drugs by the method of proportions. Methodology, resistance criteria, results and interpretation. Rev. Tuberc. Pneumol. 1963, 27, 212–215.

19. Franzblau, S.G.; Witzig, R.S.; McLaughlin, J.C.; Torres, P.; Madico, G.; Hernandez, A.; Degnan, M.T.; Cook, M.B.; Quenzer, V.K.; Ferguson, R.M.; et al. Rapid, low-technology MIC determination with clinical Mycobacterium tuberculosis isolates by using the microplate Alamar Blue assay. J. Clin. Microbiol. 1998, 36, 362–366. [PubMed]

20. Reis, R.S.; Neves, L., Jr.; Lourenço, S.L.; Fonseca, L.S.; Lourenço, M.C. Comparison of flow cytometric and Alamar Blue tests with the proportional method for testing susceptibility of Mycobacterium tuberculosis to rifampin and isoniazid. J. Clin. Microbiol. 2004, 42, 2247–2248. [CrossRef] [PubMed]

21. Vanitha, J.D.; Paramasivan, C.N. Evaluation of microplate Alamar blue assay for drug susceptibility testing of Mycobacterium avium complex isolates. Diagn. Microbiol. Infect. Dis. 2004, 49, 179–182. [CrossRef] [PubMed]

22. Organic Chemistry Portal. Available online: http://www.organic-chemistry.org/prog/peo/ (accessed on 30 March 2015).
Page, P.C.; Murrell, V.L.; Limousin, C.; Laffan, D.D.; Bethell, D.; Slawin, A.M.; Smith, T.A. The First Stable Enantiomerically Pure Chiral N-H Oxaziridines: Synthesis and Reactivity. J. Org. Chem. 2000, 65, 4204–4207. [CrossRef] [PubMed]

Barton, D.H.; McGhie, J.F.; Batten, P.L. On the oxidation of hydrazones by lead tetra-acetate. J. Chem. Soc. C 1970, 1033–1042. [CrossRef]

Nanjundaswamy, H.M.; Fasha, M.A. Rapid, Chemoselective and Facile Synthesis of Azines by Hydrazine/12. Synth. Commun. 2007, 37, 3417–3420. [CrossRef]

Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. Synthesis of C1-Symmetric Chiral Secondary Diamines and Their Applications in the Asymmetric Copper(II)-Catalyzed Henry (Nitroaldol) Reactions. J. Org. Chem. 2011, 76, 588–600. [CrossRef] [PubMed]

Mostowicz, D.; Bejecka, C. Absolute configuration at chiral nitrogen in oxaziridines. J. Org. Chem. 1977, 42, 3917–3921. [CrossRef]

Francesca, C.; Leriverend, C.; Metzner, P. Carbon versus sulfur addition of nucleophiles to sulfines: The case of amines. Tetrahedron Lett. 1993, 34, 6741–6742.

Markovic, S.; Markovic, V.; Jokovic, M.D.; Todorovic, N.; Joksovic, L.; Divjakovic, V.; Trifunovic, S. Debromination of endo-(+)-3-bromocamphor with primary amines. J. Braz. Chem. Soc. 2013, 24, 1099–1108.

Saccardi, P.; Romagnoli, E. Some new compounds of camphor with amines. Arch. Farmacol. Sper. Sci. Affin 1927, 43, 197–204.

Love, B.E.; Ren, J. Synthesis of Sterically Hindered Imines. J. Org. Chem. 1993, 58, 5556–5557. [CrossRef]

Suquet, M.; Callet, G.; Raveux, R. Antifibrillant compounds derived from phenyl (2-hydroxy-phenyl)amine and from exo-2-[2-hydroxyphenyl] amino-bornane. Bull. Soc. Chim. France 1962, 444–455.

Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kuerzinger, A.; Obermann, U. Asymmetric catalysis. XLVI. Enantioselective hydrosilylation of ketones with [Rh(COD)Cl]2 and optically active nitrogen ligands. J. Organomet. Chem. 1989, 370, 17–31. [CrossRef]

Li, S.J.; Mi, A.; Yang, G.; Jiang, Y. Facile preparation of some highly hindered chiral 1,2-diphenyl-2-(N-monoalkyl)amino alcohols and N-benzylbornamine. Synth. Commun. 1992, 22, 1497–1503. [CrossRef]

Bhat, M.A.; Al-Omar, M.A. Synthesis, characterization, and in vitro anti-Mycobacterium tuberculosis activity of terpene Schiff bases. Med. Chem. Res. 2013, 22, 4522–4528. [CrossRef]

Mosmann, T.J. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. J. Immunol. Meth. 1983, 65, 55–63. [CrossRef]

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).