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ORIGINAL ARTICLE

Synthesis and antimicrobial studies of novel 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones

Seeman Umamatheswari, and Senthamaraikannan Kabilan

Department of Chemistry, Annamalai University, Annamalai Nagar - 608 002, Tamilnadu India

Abstract

New series of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones (compounds **9–16**) was obtained from the corresponding 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones. The synthesized compounds have been characterized by their elemental, analytical, and spectral studies. Besides, these reported compounds were screened for their antibacterial and antifungal activities against a spectrum of microbial organisms. These studies proved that against bacteria, compounds **10** and **11** against *Bacillus subtilis*, compound **13** against *Salmonella typhi*, show maximum inhibition potency at low concentration (6.25 μg/mL), whereas against fungal, compounds **11**, **13**, and **16** against *Candida albicans* and compounds **12** and **13** against *Cryptococcus neoformans*, showed beneficial antifungal activity at minimum concentration (6.25 μg/mL).

Keywords: Azabicyclo[3.3.1]nonan-9-ones, thiosemicarbazones, antibacterial activity, antifungal activity

Introduction

Microbial infections are associated with rates of attributable morbidity and mortality [1]. The resistance of common pathogens to standard antibiotic therapies is rapidly becoming a major public health problem throughout the world. The incidence of multidrug-resistant Gram-positive and Gram-negative bacteria is increasing and the infections caused by them are becoming problematic now-a-days [2]. There is an urgent need for the discovery of new compounds endowed with antimicrobial activity.

Many compounds with a thiosemicarbazone moiety exhibit significant biological properties [3] because thiourea unit (NHCSNH) can easily form chelation with metal ions like iron, zinc, magnesium, and so on. Thiosemicarbazones are a class of small molecules that have been evaluated against *Plasmodium falciparum*, *Trypanosoma brucei*, and *Trypanosoma cruzi* for various diseases. The effectiveness of thiosemicarbazone analogues in treating these diseases is reported due to their activity against cysteine proteinases including rhodesain [4–10]. Moreover compounds with a thiosemicarbazones structure are known to possess tranquilizing, muscle relaxing, psychoanaleptic, hypnotic, ulcerogenic, antidepressant, antibacterial, antifungal, analgesic, and anti-inflammatory properties [11–15].

Jeyaraman and Avila [16] have reviewed the importance of bicyclic compounds as intermediates in the synthesis of a several physiologically active compounds. Similarly, Lijinsky and Taylor [17] have found that the presence of substituents at both the α-positions to that of "N" in piperidin-4-one is important to exert marked biological properties. In addition, several interesting investigations have been made through piperidine-based heterocyclic compounds and exhibited numerous biological properties such as antibacterial, antifungal, antitumor, antiarrhythmic, antithrombic, calcium antagonist, hypotensive, and neuroleptic activities [18,19]. An essential component of the search for new leads in drug-designing program is the synthesis of molecules that are novel and resemble known biologically active molecule by virtue of the presence of some pharmacophoric groups. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and useful molecules. Apart from the biological importance, these bridged bicyclic compounds exhibit twin-chair, chair-boat, or twin-boat conformations possessing interesting stereochemistry. In connection with our earlier work and as part of our ongoing research programme [20–25], we have planned to design a system that combines both bioactive azabicyclo[3.3.1]nonane

Address for Correspondence: Kabilan Senthamaraikannan, Annamalai University, Chidambaram, India. E-mail: drskabilan08@gmail.com

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and thiosemicarbazone components together to give a compact structure like title compounds.

Experimental

Microbiology

Materials. The bacterial strains, viz., *Staphylococcus aureus* (ATCC-25825), *Bacillus subtilis* (ATCC-451), *Salmonella typhi* (ATCC-24915), *Escherichia coli* (ATCC-25835), and *Klebsiella pneumonia* (ATCC-15490) and antifungal strains, viz., *Cryptococcus neoformans* (ATCC-3312), *Candida albicans* (ATCC-3122), *Rhizopus oryzae* (ATCC-9363), *Aspergillus niger* (ATCC-598), and *Aspergillus flavus* (ATCC-485) are procured from National Chemical Laboratory, Pune, India.

In vitro antibacterial and antifungal activity

The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB; Hi-media, Mumbai, India) for fungi and in Nutrient broth (NB, Hi-media) for bacteria by the 2-fold serial dilution method [26]. The test compounds were dissolved in dimethyl sulphoxide (DMSO) to obtain 1 mg/mL stock solutions. Seeded broth (broth containing microbial spores) was prepared in NB from 24-h-old bacterial cultures on nutrient agar (Hi-media) at 37°C ± 1°C, whereas fungal spores from 24-h to 7-day-old Sabourauds agar slant cultures were suspended in SDB. The colony-forming units (cfu) of the seeded broth were determined by plate count technique and adjusted with the help of McFarland standards in the range of 104–105 cfu per mL. The final inoculum size was 105 cfu/mL for antibacterial assay and 1.1–1.5 × 102 cfu/mL for antifungal assay. Testing was performed at pH 6.5 ± 0.2 for bacteria and pH 5.6 ± 0.2 for fungi. Exactly 0.2 mL of the solution of test compound was added to 1.8 mL of seeded broth to form the first dilution. One millilitre of the first dilution solution was diluted with a further 1 mL of the seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control and likewise solvent controls were also run simultaneously. The tubes were incubated in biological oxygen demand (BOD) incubators at 37°C ± 1°C for bacteria and 28°C ± 1°C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi except *C. albicans*) of incubation. Ciprofloxacin and amphotericin B were used as standards for bacterial and fungal studies, respectively.

Chemistry

Thin-layer chromatography (TLC) was carried out to monitor the course of the reaction and purity of the product. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in KBr (pellet forms) on AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimetres) are listed. ^{1}H NMR spectra were recorded at 500 MHz on BRUKER AMX 500 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 125.76 MHz on BRUKER AMX 500 MHz spectrometer in $CDCl_3$. For compounds **1–7** (except compound **5**), GCMS were recorded on GC model: Varian GC-MS-Saturn 2200 Thermo, capillary column VF5MS (5% phenyl–95% methyl polysiloxane), 30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, temperature of column range from 50°C to 280°C (10°C/min), and injector temperature 250°C. For compounds **9–16**, ES-HRMS was recorded on QTof-Mico YA 263 instrument except compounds **11** and **13**.

By employing the literature precedent of Baliah and Jeyaraman [27], all the parent 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones (compounds **1–8**) were prepared by the condensation of appropriate ketones, aldehydes, and ammonium acetate in 1:2:1 ratio using ethanol as solvent.

2,4-Diphenyl-3-azabicyclo[3.3.1]nonan-9-one (compound 1)

IR (cm^{-1}): 3317 (N–H stretching), 3057, 3026, 2926, 2857, 2794 (C–H stretching), 1708 (C=O stretching), 1598 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.54–7.30, (m, 10H, aryl protons); 4.39 (d, 2H, J = 2.40 Hz, H-2a and H-4a); 2.89 (m, 1H, H-7a); 2.47 (br s, 1H, H-1, H-5); 1.93 (dd, 1H, J = 5.86, 1.46 Hz, H-8e); 1.90 (dd, 1H, J = 5.88, 1.48 Hz, H-6e); 1.87 (br s, 1H NH); 1.74–1.64 (m, 2H, H-6a and H-8a); 1.38 (quin, 1H, H-7e). ^{13}C NMR (δ ppm): 217.58 (C-9), 141.37 (C-2′ and C-4′), 128.61(C-2″ and C-4″), 127.62 (C-2‴ and C-4‴), 126.96 (C-2‴ and C-4‴); 64.81 (C-2 and C-4); 54.05 (C-1 and C-5); 29.14 (C-6 and C-8); 21.21 (C-7). GCMS: m/z = 292.22 (M+1).

2,4-Bis(4-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 2)

IR (cm^{-1}): 3318 (N–H stretching); 3071, 2970, 2921, 2852 (C–H stretching); 1707 (C=O stretching); 1603 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.10–7.51 (m, 8H, aromatic protons); 4.40 (d, 2H, J = 2.20 Hz, H-2a and H-4a); 2.83 (m, 1H, H-7a), 2.44 (br s, 2H, H-1 and H-5), 1.92 (d, 1H, J = 5.48 Hz, H-8e), 1.88 (d, 2H, J = 5.48 Hz, H-6e and NH); 1.76–1.67 (m, 2H, H-6a and H-8a); 1.41 (quin, 1H, H-7e). ^{13}C NMR (δ ppm): 216.90 (C-9); 163.46, 161.01 (C-2‴ and C-4‴), 136.94, 136.92 (C-2′ and C-4′), 128.49, 128.41 (C-2″ and C-4″), 115.61, 115.40 (C-2‴ and C-4‴); 64.17 (C-2, C-4); 53.95 (C-1, C-5); 28.97 (C-6, C-8); 21.15 (C-7). GCMS m/z = 328.17 (M+1).

2,4-Bis(3-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 3)

IR (cm^{-1}): 3315 (N–H stretching); 3073, 2978, 2930, 2910, 2852, 2815 (C–H stretching); 1712 (C=O stretching); 1614, 1589 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.40–7.02 (m, 8H, aryl protons); 4.42 (d, 2H, J = 1.60 Hz, H-2a and H-4a); 2.80 (m, 1H, H-7a); 2.49 (br s, 2H, H-1, H-5); 1.94 (d, 2H, J = 4.80 Hz, H-8e, NH); 1.90 (d, 1H, J = 5.20 Hz, H-6e); 1.78–1.68 (m, 2H, H-6a and H-8a), 1.42 (quin, 1H, H-7e). ^{13}C NMR (δ ppm): 216.48 (C-9); 164.40, 161.95 (fluoro bearing C-2‴, C-4‴); 143.88, 143.82 (C-2′, C-4′), 130.31, 130.23 (C-2‴, C-4‴); 122.58, 122.56 (C-2″, C-4″), 114.75, 114.54, 114.04, 113.82 (C-4‴); 64.19 (C-2 and C-4); 53.78 (C-1 and C-5); 29.14 (C-6 and C-8); 21.17 (C-7). GCMS m/z = 327.42 (M$^+$).

2,4-Bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 4)

IR (cm^{-1}): 3314 (N–H stretching); 3063, 2921, 2852, 2800 (C–H stretching); 1709 (C=O stretching); 1590 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.48–7.38 (m, 8H, aromatic protons); 4.39 (d, 2H, J=2.20 Hz, H-2a and H-4a); 2.80 (m, 1H, H-7a); 2.44 (br s, 2H, H-1 and H-5); 1.90 (d, 1H, J=4.76 Hz, H-8e); 1.87 (d, 2H, J=4.76 Hz, H-6e and NH); 1.76–1.66 (m, 2H, H-6a and H-8a); 1.40 (quin, 1H, H-7e). ^{13}C NMR (δ ppm): 216.64 (C-9); 139.63 (C-2′, C-4′); 133.43 (C-2‴ and C-4‴); 128.88 (C-2″ and C-4″); 128.28 (C-2‴ C-4‴); 64.17 (C-2, C-4); 53.77 (C-1, C-5); 29.00 (C-6, C-8); 21.14 (C-7). GCMS m/z=359.13 (M^+); m/z=361 (M+2 isotopic peak).

2,4-Bis(2-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 5)

IR (cm^{-1}): 3305 (N–H stretching); 3063, 2973, 2931, 2905, 2852, 2821 (C–H stretching); 1706 (C=O stretching); 1589, 1567 (C=C stretching-Ph. ^{1}H NMR (δ ppm): 4.85 (d, 2H, J=2.40 Hz, H-2a, H-4a); 2.88 (m, 1H, H-7a); 2.77 (br s, 2H, H-1, H-5); 1.90 (d, 1H, J=4.80 Hz, H-8e); 1.87 (dd, 1H, J=4.80, 1.60 Hz, H-6e); 1.81–1.71 (m, 2H, H-6a, H-8a); 1.66 (br s, 1H, NH); 1.41 (quin, 1H, H-7e); 8.05–7.27 (m, 8H, aromatic protons). ^{13}C NMR (δ ppm): 216.34 (C-9); 138.17 (C-2′ and C-4′), 132.69 (chloro bearing C-2″ and C-4″); 130.17 (C-2″ and C-4″); 128.78 (C-2‴ and C-4‴); 128.90, 126.92 (other aromatic carbons); 61.01 (C-2 and C-4); 49.67 (C-1 and C-5); 29.65 (C-6 and C-8); 20.93 (C-7).

2,4-Bis(4-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 6)

IR (cm^{-1}): 3315 (N–H stretching); 3024, 2939, 2859 (C–H stretching); 1714 (C=O stretching); 1599, 1564 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.43–7.21 (m, 8H, aromatic protons); 4.37 (d, J=2.20 Hz, H-2a, H-4a); 2.89 (m, H-7a), 2.44 (br s, H-1, H-5); 2.36 (s, CH_3 at C-2‴ and C-4‴); 1.95 (dd, J=5.86, 1.46 Hz, H-8e); 1.92 (dd, J=5.32, 1.64 Hz, H-6e, NH); 1.75–1.65 (m, H-6a, H-8a); 1.37 (quin, H-7e). ^{13}C NMR (δ ppm): 217.99 (C-9); 138.46 (C-2′ and C-4′); 137.22 (C-2‴ and C-4‴); 129.29, 126.90 (other aromatic carbons); 64.71 (C-2, C-4); 54.21 (C-1, C-5); 29.18 (C-6, C-8); 21.27 (C-7); 21.22 (CH_3 at C-2‴ and C-4‴). GCMS m/z=320.21(M+1).

2,4-Bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 7)

IR (cm^{-1}): 3307 (N–H stretching); 3005, 2968, 2933, 2831 (C–H stretching); 1705 (C=O stretching); 1610, 1584 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.46–6.93 (m, 8H, aromatic protons); 4.34 (d, 2H, J=2.56 Hz, H-2a and H-4a); 3.28 (s, 6H, OCH_3 at C-2‴ and C-4‴); 2.88 (m, 1H, H-7a); 2.41 (br s, 2H, H-1 and H-5); 1.96 (d, 1H, J=4.40 Hz, H-8e); 1.92 (d, 1H, J=4.76 Hz, H-6e); 1.87 (br s, 1H, NH); 1.74–1.64 (m, 2H, H-6a, H-8a); 1.38 (quin, 2H, H-7e). ^{13}C NMR (δ ppm): 217.88 (C-9); 158.98 (C-2‴ and C-4‴), 136.51(C-2′ and C-4′), 132.27(C-2″ and C-4″), 113.89 (C-2‴ and C-4‴); 64.36 (C-2 and C-4); 55.29 (OCH_3 at C-2‴ and C-4‴); 54.24 (C-1 and C-5); 29.05 (C-6 and C-8); 21.22 (C-7). GCMS m/z=351.38 (M^+).

2,4-Bis(3-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (compound 8)

IR (cm^{-1}): 3310 (N–H stretching); 3073, 2933, 2930, 2826 (C–H stretching); 1708 (C=O stretching); 1609, 1583 (C=C stretching-Ph). ^{1}H NMR (δ ppm): 7.31–6.84 (m, 8H, aromatic protons); 4.37 (d, J=2.20 Hz, H-2a, H-4a), 3.84 (s, 6H, OCH_3 at C-2‴ and C-4‴); 2.86 (m, H-7a); 2.48 (br s, H-1, H-5); 1.97 (dd, J=5.68, 1.48 Hz, H-8e); 1.93 (dd, J=4.76, 1.48 Hz, H-6e); 1.90 (s, NH), 1.75–1.65 (m, H-6a, H-8a); 1.38 (quin, H-7e). ^{13}C NMR (δ ppm): 217.55 (C-9); 159.83 (methoxy bearing C-2‴ and C-4‴); 143.03 (C-2′ and C-4′); 129.61(C-2‴ and C-4‴), 119.27, 112.97(C-2″ and C-4″), 114.6 (C-2‴ and C-4‴); 64.65 (C-2 and C-4); 55.29 (OCH_3 at C-2‴ and C-4‴); 54.03 (C-1 and C-5); 29.23 (C-6 and C-8); 21.18 (C-7).

General method for synthesis of N′-(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compounds 9–16)

A mixture of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one (0.01 mol) and 4′-phenylthiosemicarbazide (0.01 mol) in ethanolic chloroform (1:1 mixture, 50 mL) was refluxed for 4 h in acidic medium. After cooling, the solid product was filtered and washed with excess of water and recrystallized from methanol. The recrystallized product further purified by column chromatography *n*-hexane:ethyl acetate (4:1) as eluent to get pure thiosemicarbazones.

N′-(2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ylidine) bezenecarbothiohydrazides (compound 9)

IR (cm^{-1}): 3352, 3282, 3258 (N–H stretching); 3058, 3039, 2964, 2912 (C–H stretching); 1616 (C=N stretching). ^{1}H NMR (δ ppm): 9.21 (s, 1H, NHCS); 8.43 (s, 1H, CSNHPh); 7.61–7.23 (m, 15H, aryl protons); 4.41 (d, J=2.0 Hz, 1H, H-2a); 4.29 (d, J= 2.0 Hz, 1H, H-4a); 3.11 (s, 1H, H-5); 2.83 (m, 1H, H-7a); 2.48 (s, 1H, H-1); 1.79 (dd, 3H, J=5.88, 1.48 Hz, H-6e, H-8e and NH); 1.46 (m, 3H, H-6a, H-8a and H-7e). ^{13}C NMR (δ ppm): 172.19 (C=S); 169.68 (C=N); 142.67 (C-2′); 142.39 (C-4′); 138.46 (C-4a); 128.42 (C-4b), 128.39 (C-4c), 127.61, 127.51 (C-2″ and C-4″); 127.31, 127.14 (C-2‴ and C-6‴); 126.89 (C-2‴ and C-6‴); 123.67 (C-4d); 65.01 (C-2); 63.98 (C-4); 45.01 (C-1); 36.34 (C-5); 29.08 (C-8); 25.98 (C-6); 20.51 (C-7). HRMS (ES): m/z=441.1119 (M+H).

N′-(2,4-Bis(4-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compound 10)

IR (cm^{-1}): 3352, 3261, 3158 (N–H stretching); 3059, 2960, 2936, 2892, 2856, 2798 (C–H stretching); 1638 (C=N stretching). ^{1}H NMR (δ ppm): 9.21 (s, 1H, NHCS); 8.43 (s, 1H, NHPh); 7.27–7.56 (m, 13 H, aryl protons); 7.11 (q, 4H, protons *meta* to fluorine atom); 4.36 (d, J=2.5 Hz, 1H, H-2a); 4.22 (d, J=1.88 Hz 1H, H-4a); 2.96 (s, 1H, H-5); 2.51 (s, 1H, H-1); 2.80 (m, 1H, H-7a); 1.81 (m, 3H, H-6e, H-8e and NH); 1.36–1.55 (m, 3H, H-6a and H-8a and H-7e). ^{13}C NMR (δ ppm): 176.12 (C=S); 167.05 (C=N); 163.89, 161.65 (C-2‴

and C-4‴); 138.07, 136.28 (C-2′ and C-4′); 139.06 (C-4a); 128.62 (C-4b), 128.38 (C-4c), 128.24, 127.88 (C-2″ and C-6″), 127.67 (C-4d), 115.61, 115.11 (C-2‴ and C-6‴); 64.88 (C-2); 63.44 (C-4); 46.56 (C-1); 35.12 (C-5); 29.91 (C-8); 26.87 (C-6); 25.42 (C-7). HRMS (ES): m/z = 477.2324 (M+H).

N′-(2,4-Bis(3-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compound 11)

IR (cm^{-1}): 3397, 3251, 3142 (N–H stretching); 3068, 2989, 2946, 2866 (C–H stretching); 1639 (C=N stretching). ^{1}H NMR (δ ppm): 9.21 (s, 1H, NHCS); 8.62 (s, 1H, CSNHPh); 6.96–7.44 (m, 13H, protons *ortho* and *meta* to the fluorine atom); 4.43 (d, J = 2.5 Hz, 1H, H-2a); 4.24 (d, J = 2.5 Hz, 1H, H-4a); 2.94 (s, 1H, H-5); 2.72 (m, 1H, H-7a); 2.54 (s, 1H, H-1); 1.80 (b s, 3H, H-6e, H-8e and NH); 1.39–1.57 (m, 2H, H-6a and H-8a); 1.44 (quintet, 1H, H-7e). ^{13}C NMR (δ ppm): 169.98 (C=S); 161.79 (C=N); 164.35, 161.56 (C-2‴ and C-4‴); 144.13 (C-2′); 143.76 (C-4′); 138.27 (C-4a); 130.96, 122.76, 122.41, 121.76, 114.74, 114.63, 114.20, 113.93, 113.69 (other aryl carbons); 64.16 (C-2); 63.22 (C-4); 46.24 (C-1); 39.15 (C-5); 28.67 (C-8); 27.57 (C-6); 21.41 (C-7).

N′-(2,4-Bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compound 12)

IR (cm^{-1}): 3379, 3245 (N–H stretching); 3056, 2997, 2948, 2892, 2735 (C–H stretching); 1641 (C=N stretching). ^{1}H NMR (δ ppm): 9.91(s, 1H, NHCS); 8.91 (s, 1H, CSNHPh); 7.01–7.50 (13H, aromatic protons); 4.39 (d, J =2.5 Hz, 1H, H-2a); 4.21 (d, J = 2.0 Hz, 1H, H-4a); 2.85 (s, 1H, H-5); 2.49 (s, 1H, H-1); 2.78 (m, 1H, H-7a); 1.84 (dd, 3H, H-6e, H-8e and NH); 1.40–155 (m, 2H, H-6a and H-8a); 1.45 (quintet, 1H, H-7e). ^{13}CNMR (δ ppm): 169.46 (C=S); 159.99 (C=N); 140.28 (C-2′); 138.27 (C-4′); 138.96 (C-4a); 133.68, 133.35 (C-2‴ and C-4‴) 128.93 (C-4b); 128.75 (C-4c); 128.43, 128.19 (C-2″ and C-6″) 127.96 (C-4d); 126.23 (C-2‴ and C-6‴); 64.87 (C-2); 63.42 (C-4); 46.41 (C-1); 39.13 (C-5); 28.53 (C-8); 27.32 (C-6); 21.34 (C-7). HRMS (ES): m/z = 509.1408 (M+H); m/z = 510.1392 (M+2).

N′-(2,4-Bis(2-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compound 13)

IR (cm^{-1}): 3386, 3247, 3143 (N–H stretching); 3042, 2976, 2967, 2946, 2883 (C–H stretching); 1629 (C=N stretching). ^{1}H NMR (δ ppm): 9.87 (s, 1H, NHCS); 8.29 (s, 1H, CSNHPh); 8.01 (t, 2H, protons *ortho* to chlorine atom); 7.11–7.42 (m, 11H, other aryl protons); 4.72 (d, J = 2.5 Hz, 1H, H-2a); 4.62(d, J = 2.0 Hz 1H, H-4a); 3.18 (d, J = 2.0 Hz, 1H, H-5); 2.79 (m, 2H, H-1 and H-7a); 1.79 (dd, 3H, H-6e, H-8e and NH); 1.61 (m, 2H, H-6a and H-8a); 1.39 (quintet, 1H, H-7e). ^{13}C NMR (δ ppm): 169.34 (C=S); 159.15 (C=N); 138.65 (C-2′); 138.03 (C-4′); 139.01 (C-4a); 133.01, 130.10 (chloro bearing C-2″ and C-6″); 128.95, 128.56, 127.43, 126.19, 126.59, 125.01, 121.43 (other aryl carbons); 62.43 (C-2); 60.58 (C-4); 42.19 (C-1); 35.03 (C-5); 29.18 (C-8); 27.20 (C-6); 21.32 (C-7).

2,4-Bis(4-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones (compound 14)

IR (cm^{-1}): 3392, 3256, 3141 (N–H stretching); 3068, 2992, 2972, 2932, 2888, 2797 (C–H stretching); 1642 (C=N stretching). ^{1}H NMR (δ ppm): 9.90 (s, 1H, NHCS); 8.47 (s, 1H, CSNHPh); 7.01–7.44 (m, 13H, aryl protons); 4.38 (d, J = 2.5 Hz, 1H, H-2a); 4.23 (d, J = 2.0 Hz, 1H, H-4a); 2.91 (s, 1H, H-5); 2.47 (s, 1H, H-1); 2.79 (m, 1H, H-7a); 2.31, (s, 6H, CH_3 at C-2‴ and C-4‴); 1.86 (dd, 3H, H-6e, H-8e and NH); 1.38–1.52 (m, 2H, H-6a and H-8a), 1.41 (quintet, 1H, H-7e). ^{13}C NMR (δ ppm): 168.42 (C=S); 157.73 (C=N); 138.10, 137.23 (C-2′ and C-4′); 139.06 (C-4a); 136.90 (C-2‴ and C-4‴), 129.38 (C-4b), 129.05 (C-4c), 127.19 (C-2″ and C-6″), 126.76(C-2‴ and C-6‴), 125.12 (C-4d) (other aryl carbons); 65.43 (C-2); 63.91 (C-4); 46.57 (C-1); 39.32 (C-5); 29.47 (C-8); 28.14 (C-6); 21.29 (C-7); 21.09 (CH_3 at C-2‴ and C-4‴); HRMS (ES): m/z = 469.1983 (M+H).

N′-(2,4-Bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-ylidine)bezenecarbothiohydrazides (compound 15)

IR (cm^{-1}): 3335, 3238, 3186 (N–H stretching); 3012, 2998, 2947, 3286, 2849 (C–H stretching); 1629 (C=N stretching). ^{1}H NMR (δ ppm): 9.86 (s, 1H, NHCS); 8.88 (s, 1H, CSNHPh); 6.93–7.47 (m, 13H, aryl protons); 4.31 (d, J = 2.5 Hz, 1H, H-2a); 4.21 (s, 1H, H-4a); 3.82 (d, 6H, OCH_3 at C-2‴ and C-4‴); 2.81 (s, 1H, H-5); 2.78 (m, 1H, H-7a); 2.45 (s, 1H, H-1); 1.90 (dd, 3H, H-6e, H-8e and NH); 1.45 (m, 3H, H-6a and H-8a and H-7e). ^{13}C NMR (δ ppm): 167.19 (C=S); 158.56, 159.01 (C-2‴ and C-4‴); 156.32 (C=N); 138.06 (C-4a); 134.12, 133.31 (C-4′ and C-2′); 129.91(C-4b); 127.81(C-4c); 127.56 (C-2″ and C-6″); 126.11 (C-4d); 113.92, 113.80 (C-2‴ and C-6‴); 65.01(C-2); 63.36 (C-4); 55.01 (OCH_3 at C-2″ and C-4‴); 46.43 (C-1); 39.12 (C-5); 29.06 (C-8); 27.31 (C-6); 22.13 (C-7). HRMS (ES): m/z = 501.2298 (M+H).

2,4-Bis(3-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones (compound 16)

IR (cm^{-1}): 3359, 3278, 3143 (N–H stretching); 3043, 3021, 2968, 2943, 2879, 2874, 2768 (C–H stretching); 1612 (C=N stretching). ^{1}H NMR (δ ppm): 9.81 (s, 1H, NHCS); 8.83 (s, 1H, CSNHPh); 6.81–7.43; (m, 13H, aryl protons). 4.36 (d, 1H, H-2a); 4.23 (d, 1H, H-4a); 3.78 (s, 6H, OCH_3 at C-2‴ and C-4‴); 2.83 (m, 1H, H-7a); 2.94 (s, 1H, H-5); 2.49 (s, 1H, H-1); 1.82 (dd, 3H, H-6e, H-8e and NH); 1.43–1.54 (m, 2H, H-6a, H-8a and H-7e). ^{13}C NMR (δ ppm): 168.14 (C=S); 159.13, 159.07 (C-2‴ and C-4‴); 156.09 (C=N); 143.32, 142.98 (C-2′ and C-4′); 138.90 (C-4a); 129.48 (C-4b), 129.05 (C-4c), 126.25 (C-4d), 125.97, 119.23, 119.06, 113.34, 112.98 (other aryl carbons); 65.09 (C-2); 63.41 (C-4); 55.21 (OCH_3 at C-2‴ and C-4‴); 46.39 (C-1); 39.35 (C-5); 28.76 (C-8); 27.47 (C-6); 21.25 (C-7); HRMS (ES): m/z = 500.9981 (M+H).

Results and discussion

Chemistry

The parent bicyclic ketones (2,4-diaryl-3-azabicyclo [3.3.1] nonan-9-ones) were prepared according to the literature precedent by Baliah and Jeyaraman [27]. The ketones upon treatment with 4′-phenylthiosemicarbazide in the presence of few drops of mineral acid afforded two different products, viz., 2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones (**9**–**16**) and arylthiosemicarbazones

(**9a–16a**) (Scheme 1). The formation of by-product (arylthiosemicarbazones) is due to poor mass balance while using mineral acids (HCl or H_2SO_4) as catalyst in the condensation of high molecular parent ketones with thiosemicarbazide. The cleavages of the products were studied by retro mannich mechanism followed by condensation reaction. Further, no more by-products were found to be formed after workup. The analytical data of the compounds **1**–**16** are given in Table 1.

In order to investigate the spectral assignments of reported compounds **9**–**16**, compound **9** is taken as the representative compound. The IR spectra of compound **9** show a collective absorption bands appeared in the region 3352–3258 cm^{-1}, which is assigned to NH stretching frequency, and C=N stretching frequency appeared as strong and intense bands at 1616 cm^{-1}, respectively.

For the representative compound **9**, H,H-COSY, NOESY, and HSQC were recorded to assign all the signals unambiguously, and to establish the stereochemistry. The H,HCOSY/NOESY and HSQC correlations are reproduced in Tables 2 and 3.

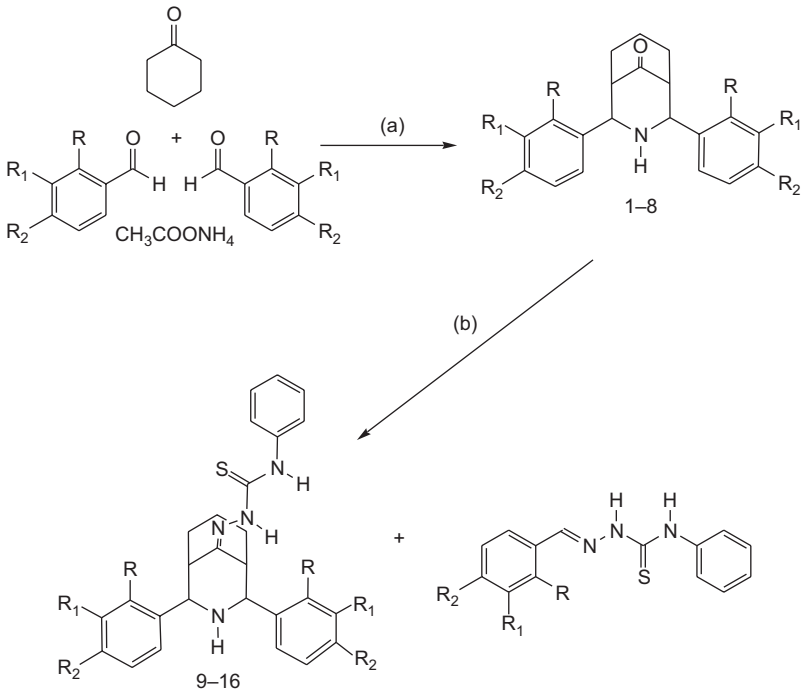
Assignment of proton chemical shifts and stereochemistry

In compound **9**, two broad singlets at 8.43 ppm (1H) and 9.21 ppm (1H) are due to NH protons of thiosemicarbazone moiety, which are disappeared in the D_2O exchange NMR spectrum. Of the two singlets, the upfield signal at 8.43 has NOE with the proton signal at 3.11 ppm (H-5); hence, the broad singlet at 8.43 assigned to NH proton at 2′ of thiosemicarbazone moiety. Consequently, the broad singlet at 9.21 ppm unequivocally assigned to the NH proton at 4′ of thiosemicarbazone moiety. According to the D_2O exchange NMR, the multiplet centred at 1.79 ppm corresponding to three protons is reduced to two protons, because of D_2O exchange, which indicates that the NH proton resonance also overlapped the multiplet.

There are two broad singlets at 3.11 (1H) and 2.48 (1H) ppm with the half-width $W_{1/2}$ of 11.40 and 11.38 Hz, respectively. The broad singlet nature and half-width values suggest that they are due to the bridgehead protons H-1 and H-5. Further, the observed weak correlation between 3.11 and 2.48 ppm strongly implies that the correlation is due to long-range coupling between the bridgehead protons because of the "W" arrangement of those protons (Figure 1).

The difference between H-1 and H-5, that is, $\Delta\delta$, is 0.63 ppm whereas in the corresponding bicyclic ketone, the bridgehead protons H-1 and H-5 appear together at 2.47 ppm (2H) as a broad singlet with a $W_{1/2}$ of 11.46 Hz. Because of nonbonding interaction between the N–N(2′) and C(5)-H bonds (Figure 2), the H-5 proton is deshielded, the deshielding magnitude is quite large (0.64 ppm). But there is no change in another bridgehead proton H-1, except for slight deshielding of 0.01 ppm. The positions, appearance, spectral width, and correlations strongly suggest that the signals at 3.11 and 2.48 ppm are due to the bridgehead protons H-5 (*syn* α) and H-1 (*anti* α). Though the bridgehead protons appear as two separate signals, both are broad singlets and their half-widths are also similar to that of its parent ketone **1**. Hence, this suggests that the thiosemicarbazone derivative also adopts the twin-chair conformation.

The signals at 4.41 (d, J = 2.0 Hz) and 4.33 ppm (d, J = 2.0 Hz) are due to benzylic protons and they only have correlations with the bridgehead protons H-1 and H-5; hence,



Scheme 1. Reagent and conditions: (a) EtOH/warm, room temperature, 2–10 days and (b) MeOH-$CHCl_3$, $H_2NNHCSNHPh/H^+$, reflux, 90–100°C 4 h.

we can unambiguously assign the signals to H-2 and H-4. Further, they have close proximity (NOE) with each other, hence indicating their orientation as axial. Except for axial orientation of the protons at C-2 and C-4, there is otherwise no possibility of NOE between them in the chair conformation. As a consequence of the observed NOE, we can conclude that the orientation of the phenyl groups on the same carbons should be equatorial. Moreover, 1,3-diequatorial orientation of the bulkier substituents is more favourable in the chair conformation. Further, the observed strong NOE of the *ortho* protons with H-7a/H-8e/H-6e also supports the equatorial orientation of the phenyl groups and the twin-chair conformation.

In addition to the "W" correlation, both H-1 and H-5 have correlations with the doublet at 1.79 ppm (3H, due to overlapped NH) and multiplet at 1.46 (3H) ppm. It is usually observed that the chemical shift difference of protons in the cyclohexane chair conformation is positive ($\Delta\delta_{eq,ax} = \delta_{eq} - \delta_{ax}$, is ′0.3 ppm), owing to the leading hyperconjugation of the C–C single bond [28]. The multiplets with average difference of 0.33 ppm suggest that they are due to C-6 and C-8 protons. Further, the assignments and chair conformation of the cyclohexane part are confirmed by their NOE (Figure 3). Moreover, the observed NOE between the multiplet at 2.83 ppm and the aryl protons supports attribution of the multiplet to H-7a (endocyclic proton, which is spatially very close to the *ortho* protons).

Of the five set of aromatic signals, the double doublet centred at 7.46 ppm (2H) coupled with the doublet at 7.59 (2H) and triplet at 7.21 ppm (1H). This observation suggests that the signals at 7.59, 7.46, and 7.21 ppm are due to the phenyl protons of thiosemicarbazone moiety 4b, 4c, and 4d, respectively. The remaining two sets of aryl signals, a multiplet centred at 7.36 (4H) and at 7.27(6H) ppm, and the multiplet at 7.36 ppm, have NOE with H-1/H-2a/H-7a/H-8e of the protons. Hence, the multiplet at 7.36 ppm is assigned to *ortho* protons (H-2″/H-4″). Consequently, the multiplet at 7.27 ppm is due to H-2‴/H-4‴, H-2⁗/H-4⁗ protons.

Table 1. Analytical data for compounds **1**–**16**.

Entry	R	R^1	R^2	Yield (%)	Melting point (°C)	Mass $(M+1)^+$
1	H	H	H	49	185–186	292.22
2	H	H	F	47	198–199	328.17
3	H	F	H	43	192–193	327.42 (M^+)
4	H	H	Cl	48	174–175	359.13 (M^+); 361 (M+2)
5	Cl	H	H	52	218	—
6	H	H	CH_3	59	160–162	320.21
7	H	H	OCH_3	49	174–175	351.38 (M^+)
8	H	OCH_3	H	53	160–161	—
9	H	H	H	78	168–170	441.1119
10	H	H	F	81	202–203	477.2324
11	H	F	H	79	180–182	—
12	H	H	Cl	76	224–226	509.1408; 510.1392 (M+2)
13	Cl	H	H	72	198–200	—
14	H	H	CH_3	89	169–170	469.1983
15	H	H	OCH_3	81	148–150	501.2298
16	H	OCH_3	H	79	159–161	500.9981

The observed m/z value is within ±0.4% from their theoretical value.

Table 3. Correlations in the HSQC spectrum of compound **9**.

Signal (d (ppm))	Correlations in HSQC
7.59 (d, 2H, H-4b)	128.42
7.46 (dd, 2H, H-4c)	128.39
7.35–7.39 (m, 4H, H-2″/H-4″)	127.61–126.89
7.33 (m, 6H, H-2‴/ H-4‴, H-2⁗/H-4⁗)	127.61–126.89
7.21 (t, 1H, H-4d)	123.67
4.41 (d, 1H, H-2a)	65.01
4.29 (s, 1H, H-4a)	63.98
3.11 (s, 1H, H-5e)	36.34
2.83 (m, 1H, H-7a)	20.51
2.48 (b s, 1H, H-1e)	45.01
1.79 (dd, 3H, H-6e, H-8e and NH)	25.98, 29.08
1.46 (m, 3H, H-6a, H-8a and H-7e)	25.98, 29.08, 20.51
9.21 (s, 1H, NHCS)	—
8.43 (s, 1H, CSNHPh)	—

Table 2. Correlations in the H,H-COSY and NOESY spectra of compound **9**.

Signal (d (ppm))	Correlations in H,H-COSY	Correlations in NOESY
7.59 (d, 2H, H-4b)	7.46	7.46 (s), 7.21 (s)
7.46 (dd, 2H, H-4c)	7.59, 7.21	7.59 (s), 7.21 (s)
7.35–7.39 (m, 4H, H-2″/H-4″)	7.29–7.32	7.29–7.32 (s), 4.41 (s), 4.29 (s)
7.25–7.30 (m, 6H, H-2‴/ H-4‴, H-2⁗/H-4⁗)	7.35–7.39	7.35–7.39
7.21 (t, 1H, H-4d)	7.46	7.59, 7.46
4.41 (d, 1H, H-2a)	2.48	7.35–7.39 (s), 4.29, 2.48 (s), 1.79 (w)
4.29 (s, 1H, H-4a)	3.11, 1.46 (w)	7.35–7.39 (s), 4.41, 3.11 (s), 1.79 (w)
3.11 (s, 1H, H-5)	4.29 (s), 2.48 (w) 1.79 (w), 1.46	7.35–7.39 (s), 4.29 (s), 1.79, 1.46
2.83 (m, 1H, H-7a)	1.46, 1.79, 1.46	7.35–7.39 (w), 1.46
2.48 (b s, 1H, H-1)	4.41 (s), 1.79, 1.46, 3.11 (w)	7.35–7.39 (w), 4.41 (s), 1.46 (w)
1.79 (dd, 3H, H-6e, H-8e and NH)	3.11, 2.83, 1.46	7.35–7.39, 1.46
1.46 (m, 3H, H-6a, H-8a and H-7e)	4.29 (w), 3.11, 2.83, 1.46	1.79, 2.83
9.21 (s, 1H, NHCS)	—	8.43, 3.11
8.43 (s, 1H, CSNHPh)	—	9.21

s, strong correlation; w, weak correlation.

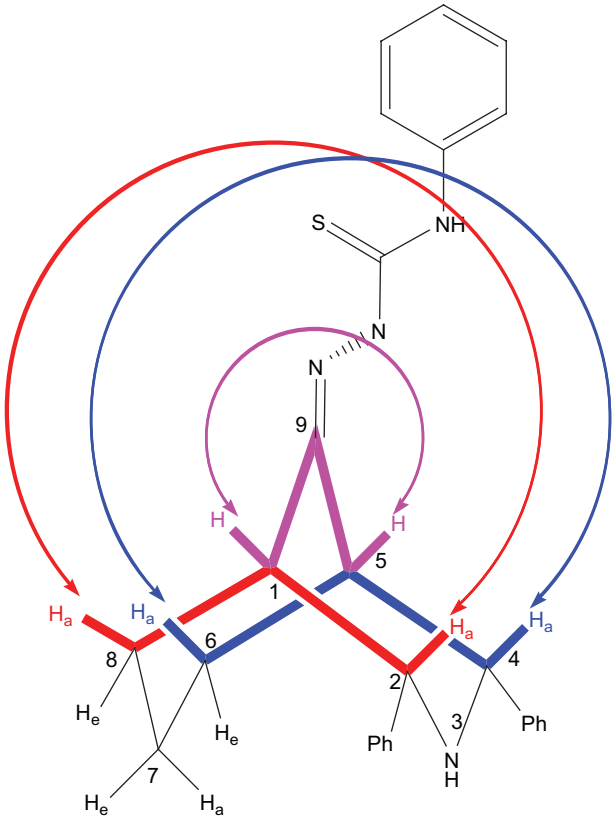


Figure 1. Correlations between the protons that are in "W" arrangements, from the H,H-COSY spectrum of compound **9**.

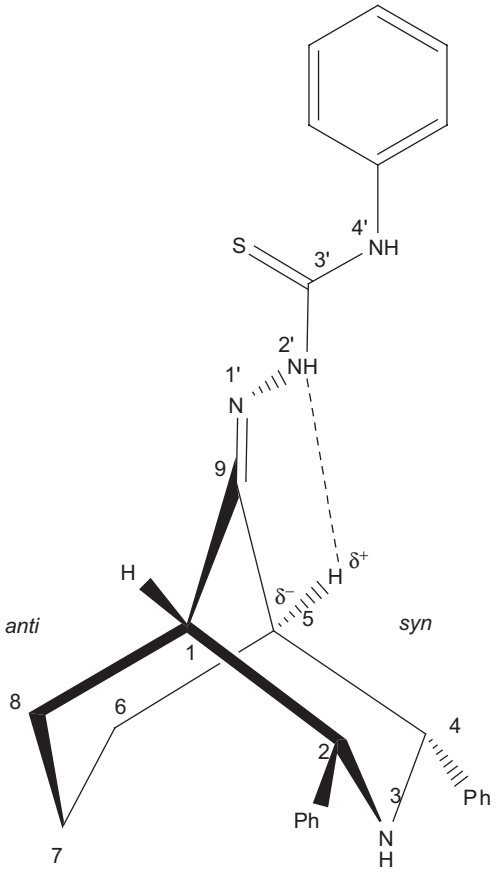


Figure 2. Non-bonded interaction between C–H(5) and N–NH group.

Overall, the chemical shifts, splitting pattern, H,H correlation, and NOE suggest that the compound is in twin-chair conformation with equatorial orientation of the phenyl groups, as depicted in Figure 3. Further, the twin-chair conformation is evidenced by the $W_{1/2}$ of H-1 and H-5; these values are in good agreement with the corresponding ketone and with literature values for the flattened twin-chair conformation of similar bicycles. If one of the cycles adopts a boat conformation, the resonances for the bridgehead protons H-1 and H-5 should be apparent doublets with coupling constants of about 18 Hz [29]. In addition, the observed long-range couplings between H-2a and H-8a and between H-4a and H-6a are due to the "W" arrangement of those protons and this is only possible when the bicycle is in the twin-chair conformation (Figure 1). Similarly, ^{1}H NMR signals of other bicyclic thiosemicarbazones **10**–**16** are assigned and summarized in the "Experimental" section.

Assignment of carbon chemical shifts

All the proton-bonded carbon signals of the representative compound **9** were unambiguously assigned using HSQC spectrum. In the downfield region, five less intense signals that appear at 169.68, 172.19, 142.67, 142.39, and 138.46 ppm have no correlation with any proton signals of the molecule, which indicates that these signals are due to quaternary carbons. Of the five signals, 138.46, 142.67, and 142.39 ppm are due to the 4′-phenyl, C-2′, and C-4′ ipso carbons, respectively, and the signals at 169.68 and 172.19 ppm are due to the resonance of C=N and C=S carbons, respectively. The HSQC correlations are reproduced in Table 3.

Antimicrobial evaluation

In order to find the effect of potency of inhibitions in compounds **9**–**16** by *in vitro* method, we modified different substituents at phenyl groups in 2,4-diaryl-3-azabicyclo[3.3.1] nonan-9-one 4′-phenylthiosemicarbazones. The reported compounds were tested against bacterial strains, viz., *S. aureus* (ATCC-25825), *B. subtilis* (ATCC-451), *S. typhi* (ATCC-24915), *E. coli* (ATCC-25835), and *K. pneumonia* (ATCC-15490) using the literature precedent by Dhar et al., [26], and their MIC values are depicted in Table 4.

A glance at the MIC values in Table 4 indicates that compound **9** against *S. aureus* exhibit minimum inhibition activity. However, *para* or *meta* fluorophenyl-substituted compound **10** against *B. subtilis* and *S. typhi* and compound **11** against *B. subtilis* exerted significant inhibition. The compound **10**, which was inactive against *K. pneumonia* even at maximum concentration (200 μg/mL).

Surprisingly, replacement of fluorine function by chlorine in compounds **10** and **11** (compounds **12** and **13**, respectively), compound **12** against *K. pneumonia*, was

found to show superior activity than others. However, compound **12** against *S. aureus/E. coli* and *B. subtilis* shows a reversal in activity, by 8- and 4-fold, respectively, due to replacement of fluorine by chlorine. Instead of halogens, methyl or methoxy function substituted compound **14** against *E. coli* and compound **15** against *K. pneumonia* markedly elevated the maximum inhibition potency at minimum concentration (12.5 μg/mL).

The *in vitro* antifungal activity of the reported compounds **9**–**16** were examined with five fungal strains, viz., *C. albicans* (ATCC-3122), *R. oryzae* (ATCC-9363), *C. neoformans* (ATCC-3312), *A. niger* (ATCC-598), and *A. flavus* (ATCC-485) and amphotericin B was used as standard drug. The obtained MIC values of the tested compounds and standard are depicted in Table 5 that indicates all the tested compounds exhibit a varied range 6.25–200 μg/mL. Unsubstituted phenyl groups in compound **9** recorded minimum to moderate activity (100–200 μg/mL) against all the tested organisms except *A. flavus*, which did not show any inhibition potency even at maximum concentration at 200 μg/mL. However, due to introduction of fluorine atom at the *meta* or *para* position of phenyl groups in compound **9** (compounds **10** and **11**) noticed minimum to moderate inhibition potency against all the tested fungal organisms with MIC ranging from 6.25 to 100 μg/mL, in which, compound **11** against *A. albicans* shows superior inhibition potency at minimum concentration (6.25 μg/mL). Modification of fluorine substituent by chlorine in compound **10** (compound **12**) registered minimum antifungal activity against all the used strains. By changing the position of chloro substitution in compound **12** *para* to *ortho* (compound **12**) 16- and 2-fold increased activity were noticed against *C. albicans* and *R. oryzae*. Replacement of one proton by methyl analogue in compound **9** (compound **14**), the activity was increased against all the strains except against *A. flavus*, which is inactive even at maximum concentration (200 μg/mL). Due to modification of methyl analogue by methoxy group in compound **14**, compounds **15** and **16** show moderate activity against the entire tested fungal strains. Among the compounds under the antifungal study, compounds **9** and **14** against *A. flavus* seldom show inhibition even at maximum concentration (200 μg/mL).

From the close survey of the *in vitro* antibacterial and antifungal results against a panel of microbial organisms, it was revealed that the electron-withdrawing substituents

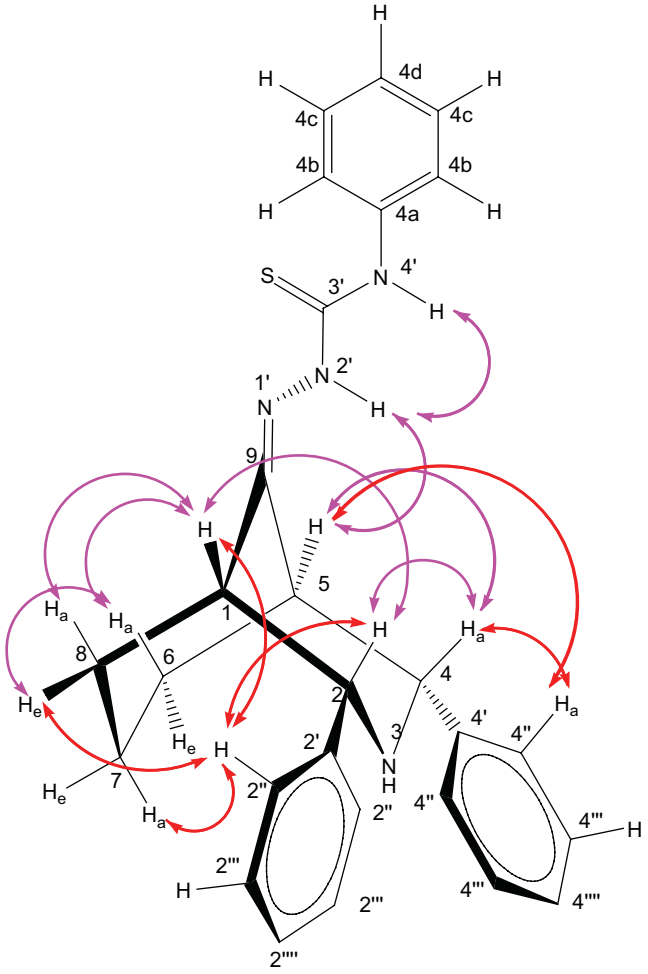


Figure 3. Twin-chair conformation with equatorial orientation of the phenyl groups at C-2 and C-4; supported by the NOE observed in the NOESY spectrum of compound **9**. For clarity, the NOE between the *ortho* and ring protons is shown by red colour lines.

Table 4. Antibacterial activity of compounds **9**–**16** against selected bacterial strains (MIC in μg/mL).

	Minimum inhibitory concentration (MIC) in μg/mL				
Compound	*S. aureus*	*B. subtils*	*S. tyhpi*	*E. coli*	*K. pneumonia*
9	200	100	200	100	200
10	50	6.25	12.5	50	—
11	25	6.25	100	25	100
12	100	50	50	100	12.5
13	25	25	6.25	25	100
14	100	50	50	12.5	50
15	100	100	50	100	12.5
16	50	100	200	200	—
Ciprofloxacin	25	12.5	50	25	25

—, no inhibition even at maximum concentration 200 μg/mL.

Table 5. Antifungal activity of compounds **9**–**16** against selected fungal strains (MIC in μg/mL).

	Minimum inhibitory concentration (MIC) in μg/mL				
Compound	*C. albicans*	*R. oryzae*	*C. neoformans*	*A. niger*	*A. flavus*
9	200	200	100	200	—
10	50	50	50	12.5	50
11	6.25	25	12.5	50	100
12	100	50	6.25	100	50
13	6.25	25	6.25	100	50
14	100	100	50	25	—
15	25	25	100	50	25
16	6.25	50	100	100	25
Amphotericin -B	25	25	25	50	50

—, no inhibition even at maximum concentration 200 μg/mL.

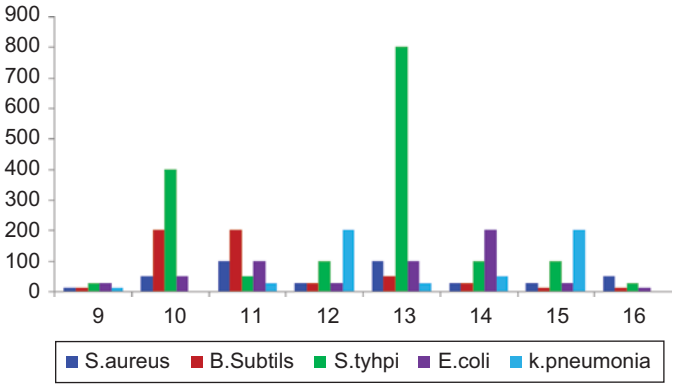


Figure 4. Comparison of potency of compounds **9**–**16** with ciprofloxacin (as standard) against bacterial strains from serial dilution method.
Scheme 1: Schematic diagram showing the synthesis of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones.

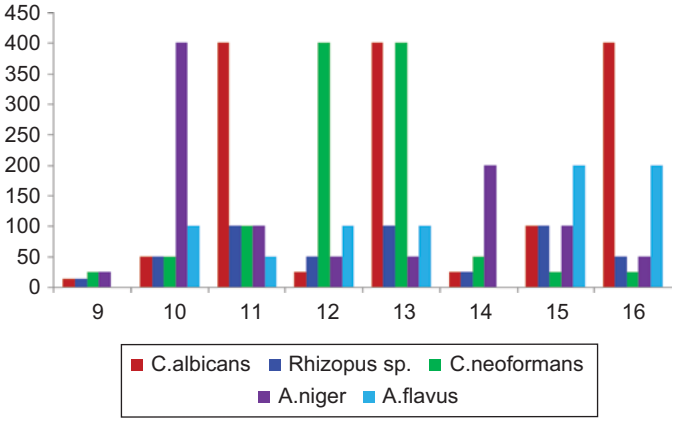


Figure 5. Comparison of potency of compounds **9**–**16** with amphotericin B (as standard) against fungal strains from serial dilution method.

at the *ortho*/*meta*/*para* position of the phenyl groups at C-2 and C-4 of the 3-azabicyclononane pharmacophore had remarkable activity against all the tested organisms.

A comparison of potency of the compounds **9**–**16** is given in the form of Figures 4 and 5 by employing the following the equation.

$$\text{Potency} = \frac{\text{MIC(mg/mL) of reference}}{\text{MIC(mg/mL) of tested compound}} \times 100$$

A close survey of the *in vitro* antibacterial and antifungal activity profile of the new 2,4-diaryl-3-azabicyclo[3.3.1] nonan-9-one 4′-phenylthiosemicarbazones (**9**–**16**) against the tested bacterial and fungal organisms gives a clear picture about the structure–activity correlations among compounds **9**–**16** under study. Compounds with electron-withdrawing groups (fluoro and chloro) and electron-donating groups (methyl or methoxy) function at the aryl groups present at the C-2 and C-4 positions of the azabicyclo[3.3.1]nonan-9-one moiety exerted a varied range of biological activities, while the activity was not significant for compound **9** without any substituent at the phenyl groups.

Among compounds **10**–**16**, compounds **10** and **11** against *B. subtilis*, compound **13** against *S. typhi*, compound **14** against *E. coli*, compounds **12** and **15** against *K. pneumonia* were shown to be significant in their antibacterial potency at 6.25 and 12.5 μg/mL. Furthermore, their activity was also on a par with the standard drugs used and for some compounds was even higher than the activity of the standard drugs. Though most of the compounds studied exhibited moderate to significant antibacterial activity, compound **10** (with *o*-chlorophenyl group at the C-2 and C-4 positions) was found to exert a pronounced effect against all the tested organisms.

Similarly, against the tested fungal strains, compounds **11**, **13**, and **16** against *C. albicans*, compounds **11**–**13** against *C. neoformans*, compound **10** against *A. niger* recorded enhanced activity at 6.25 and 12.5 μg/mL. However, the activity of compound **11** against all the tested organisms was found to be superior to the other compounds and with an even higher activity than the standard.

Conclusions

A close examination of the *in vitro* antibacterial and antifungal activity profile of the differently substituted novel 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one

4′-phenylthiosemicarbazones (**9**–**16**) against the tested bacterial and the fungal strains provides a structure–activity relationship, which reveals that the compounds with fluorine or chlorine substituents were found to be more active against all the tested organisms. The method of action of these compounds is unknown. These observations may promote a further development of this group of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one 4′-phenylthiosemicarbazones (**9**–**16**), which may lead to compounds with better a pharmacological profile than standard drugs and serve as templates for the construction of better drugs to fight bacterial and fungal infections.

Declaration of interest

Authors have no declaration of interest.

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