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Design, synthesis and biological evaluation of novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones as a new class of antimicrobial agents

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ABSTRACT

New series of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones (**9**–**16**) obtained from the corresponding 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones (**1**–**8**) upon cyclization with ethylbromoacetate in the presence of sodium acetate–acetic acid buffer afforded novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones (**17**–**24**). The synthesized compounds have been characterized by their elemental, analytical and spectral studies. Besides, the reported compounds were screened for their antibacterial and antifungal activities against a spectrum of microbial organisms. These studies proved that compounds **11**/**18**/**20**/**23** against *Staphylococcus aureus*, **19**/**20**/**24** against *Salmonella typhi* show maximum inhibition potency at low concentration (6.25 μg/ml) whereas **18**/**19** against *Candida albicans* and **19**/**20**/**21** against *Rhizopus* sp. showed beneficial antifungal activity at minimum concentration.

Thiazolidinones are an interesting backbone unit in medicinal chemistry and responsible for numerous pharmacological properties and biological activity[1] which gives the considerable research interest in this area has been done towards the synthesis of thiazolidinone unit. Jeyaraman and Avila[2] have reviewed the importance of bicyclic compounds as intermediates in the synthesis of a several physiologically active compounds. Similarly, Lijinsky and Taylor[3] 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.[4] An essential component of the search for new leads in drug designing program is the synthesis of molecules, which are novel still 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[5] we planned to design a system, which combines both bioactive piperidine and thiazolidinone components together to give a compact structure like title compounds.

Many compounds with a thiosemicarbazone moiety exhibit significant biological properties,[6] because thiourea unit (NHCSNH) can easily form chelation with metal ions like iron, zinc, magnesium etc. The parent bicyclic ketones (2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones) were prepared according to the literature precedent by Baliah et al.[7] The ketones upon treatment with thiosemicarbazide 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.

Thiazolidin-4-ones are well known for their pharmacological activities. Literature survey reveals that several substituted thiazolidinones have prepared from different synthetic routes.[8] In the present work, an attempt has been made to undertake the synthesis of title compounds through the cyclization of key intermediate 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones

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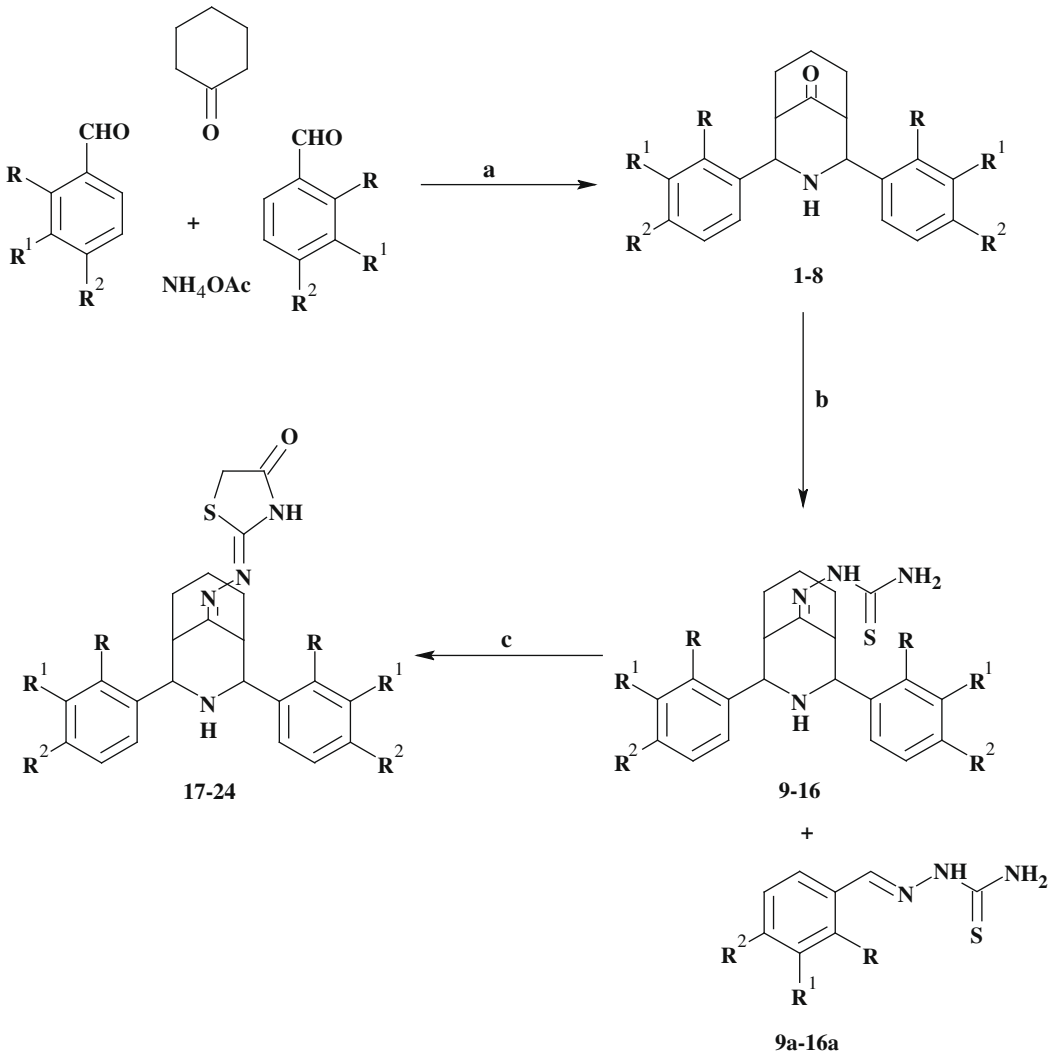

Scheme 1. Schematic diagram showing the synthesis of 1,3-thiazolidinones. Reagent and conditions: (a) EtOH/warm, rt→24 h; (b) MeOH–$CHCl_3$, $H_2NNHCSNH_2/H^+$, reflux, 80 °C→3 h; (c) EtOH, $BrCH_2COOC_2H_5$, CH_3COONa/CH_3COOH, reflux, 80 °C→4 h.

with ethylbromoacetate under reflux condition (80 °C at 4 h) afforded 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones **(17–24)**. Moreover in order to study the reactivity, varied conditions such as (i) sodium acetate or acetic acid (ii) mixture of sodium acetate and acetic acid (iii) without sodium acetate or acetic acid were attempted for cyclization. Of the three different reaction conditions, one with mixture of sodium acetate and acetic acid condition afforded the target molecules (**17–24)** with good yield, wherein the mixture of sodium acetate and acetic acid act as buffer system to maintain the pH (4.5–5.0) value of the reaction solution and avoid the C=N cleavage. During the course of reaction, excess of sodium acetate was used to scavenge the hydrogen bromide whereas acetic acid act as the cyclizing agent. However, reactions without acetic acid and sodium acetate afforded **(17–24)** poor yield. Therefore, under optimal conditions, compounds (**17–24**) were synthesized and characterized by spectral and analytical methods. The analytical data of the compounds 9–**24** are given in Table 1. To comprehend the structure–activity relationship well, numberings of the target compound are done (Fig. 1).

In order to investigate the spectral assignments of reported compounds (**9–24**), **9** and **17** are taken as the representative compounds. The IR spectra of compounds **9** and **17** shows a collective absorption bands appeared in the region 3152–3397 cm^{-1} which is assigned to NH stretching frequency whereas C=N stretching frequency appeared as strong and intense bands at 1648 and 1644 cm^{-1}, respectively. Generally, the amide carbonyl stretching frequency was noted in the region 1630–1690 cm^{-1}. But in **17**, the amide carbonyl group shows a strong absorption band at 1713 cm^{-1}. This is due to extended conjugation over the thiazolidinone unit.

All the synthesized compounds were characterized by ^1H and ^{13}C NMR spectral studies and the results were compared and assigned the signals with the help of earlier reports.[9] In compounds **9** and **17**, the benzylic protons appeared, two different signals viz. 4.36, 4.26 ppm and 4.39, 4.26 ppm, respectively. Of the two compound signals, deshielded signal is assigned to *anti*-H_{2a} proton while shielded one is attributed to *syn*-H_{4a} proton. Similarly, the bridgehead protons also resonated as two different signals at 2.97, 2.50 ppm and 3.56, 2.57 ppm for compounds **9** and **17**, respectively. Unlike, the *syn* α-bridgehead proton (H_{5e}) shows highly deshielded region than *anti* α-bridgehead proton (H_{1e}). This is due to the non-bonded (spatial) interaction between H_{5e} proton and 'N' in thiosemicarbazone or thiazolidinone unit (Fig. 2). Owing to this interaction, *syn* α-carbon get partially negative charge and the attached proton acquires a slight positive charge (Fig. 2). Based

Table 1
Analytical data for compounds **9–24**

Entry	R	R^1	R^2	Yield (%)	Mp (°C)	Elemental analysis					
						C (%)		H (%)		N (%)	
						Found	Calcd	Found	Calcd	Found	Calcd
9	H	H	H	65	160	–	69.20	–	6.64	–	15.37
10	H	H	F	60	196	62.95	62.98	5.55	5.48	13.98	13.99
11	H	F	H	65	172	–	62.98	–	5.48	–	13.99
12	H	H	Cl	67	202	58.21	58.20	5.12	5.12	12.95	12.93
13	Cl	H	H	69	210	–	58.20	–	5.12	–	12.93
14	H	H	CH_3	71	150	70.37	70.38	7.19	7.18	14.27	14.25
15	H	H	OCH_3	85	133	–	65.07	–	6.65	–	13.20
16	H	OCH_3	H	75	141	–	65.07	–	6.65	–	13.20
17	H	H	H	72	220	68.25	68.29	5.99	5.98	13.88	13.85
18	H	H	F	75	212	–	62.71	–	5.03	–	12.70
19	H	F	H	72	164	62.71	62.71	5.00	5.03	12.72	12.70
20	H	H	Cl	77	153	–	58.35	–	4.68	–	11.83
21	Cl	H	H	79	150	58.34	58.35	4.71	4.68	11.81	11.83
22	H	H	CH_3	74	143	69.43	69.41	6.52	6.52	12.93	12.95
23	H	H	OCH_3	78	202	64.64	64.63	6.07	6.07	12.05	12.06
24	H	OCH_3	H	76	90	–	64.63	–	6.07	–	12.06

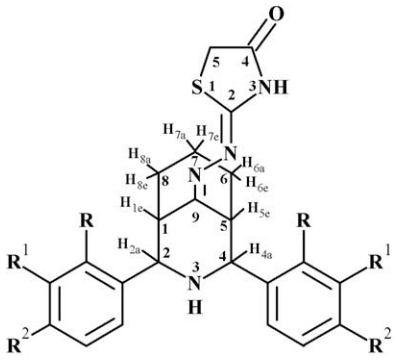

Figure 1. A well numbered target molecules (**17–24**).

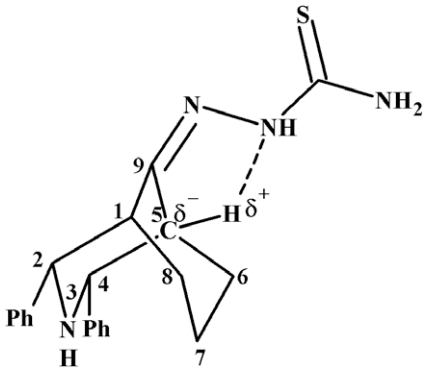

Figure 2. Non-bonded interaction between $C_{5(He)}$ and NH group.

on this statement, shielded signal is attributed to H_{1e} proton whereas deshielded signal is assigned to H_{5e} proton. However in both **9** and **17**, the signal to the methylene protons in cyclohexane ring, a well resolved multiplet appeared at 2.83 and 2.82 ppm, respectively, which corresponds to one proton integral. Hence, these signals are attributed to H_{7a} proton. In **9**, the H_{6e} and H_{8e} protons appeared as double doublet at 1.84 ppm whereas H_{6a}, H_{8a} and H_{7e} protons resonated as multiplet in the region 1.40–1.58 ppm. But in **17**, all the methylene proton signals in the cyclohexane ring (H_{6a}, H_{6e}, H_{7e}, H_{8a} and H_{8e}) are merged together (except H_{7a}) and appeared as multiplet with five protons integral value. Moreover in **17**, a broad singlet resonated at 2.09 ppm with one proton integral value is unambiguously assigned to NH proton while the same proton in **9** found to merge with H_{6e} and H_{8e} proton signals. However, there are two broad singlets for **9** at 8.92 and 6.50 ppm which corresponds to one and two protons integral values are assigned to NH and NH_2 protons, respectively, in thiosemicarbazone moiety. In **17**, the exchangeable NH proton (thiazolidinone ring) appeared as a singlet at 11.60 ppm and the methylene protons (thiazolidinone unit) appeared as a sharp singlet at 3.74 ppm with two proton integral value. In general, the aromatic proton signals appeared at down field region due to their ring current or anisotropic effect. Owing to this in compounds **9** and **17**, the aromatic proton signals resonated in the region 7.25–7.80 ppm as multiplet.

In ^{13}C NMR spectrum of compound **17**, a collection of signals resonated in the aliphatic region at 32.92, 28.81, 27.65 and 21.23 ppm. Of the four signals in the aliphatic region, signals at 28.81, 27.65 and 21.23 ppm are assigned to C_8, C_6 and C_7, respectively. One more signal at 32.92 ppm is attributed to C_5 methylene carbon in the thiazolidinone ring. In addition to this, the benzylic carbon signals C_2 and C_4 resonated at 64.94 and 63.57 ppm, respectively, whereas the bridgehead carbons C_1 and C_5 appeared at 45.91 and 39.88 ppm, respectively. Moreover, a collection of signals appeared in the region 142.54–126.77 ppm which are unambiguously assigned to aryl carbons. Apart from the assigned signals, two unassigned signals resonated in the most down field region at 173.98 and 163.00 ppm and these signals belong to C=O and C=N carbons respectively (refer Supplementary data).

In order to find the effect of potency of inhibitions in **9–24** by in vitro method, we modified different substituents at phenyl groups in 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones and 2-[(2,4-diaryl-3-azabicyclo[3.3.1] nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones. The reported compounds were tested against bacterial strains viz., *Staphylococcus aureus* (ATCC-25825), *Bacillus subtilis* (ATCC-451), *Salmonella typhi* (ATCC-24915), *Escherichia coli* (ATCC-25835) and *Klebsiella pneumonia* (ATCC-15490) using the literature precedent by Dhar et al.,[10] and their MIC values are depicted in Table 2. A glance at the MIC values in Table 2 indicates that compound **9** against *S. aureus* exhibit minimum inhibition activity. However, *para* or *meta* fluorophenyl substituted compounds **10** against *B. subtilis* and *S. typhi* and **11** against *S. aureus*, *B. subtilis* and *K. pneumonia* exerted significant inhibition. The compound **10**, which was inactive against *E. coli* even at maximum concentration (200 μg/ml).

In thiazolidinone compounds with fluorine substituent, **18** against *S. aureus* and **19** against *S. typhi* shows good antibacterial

Table 2
Antibacterial activity of compounds **9**–**24** against selected bacterial strains (MIC in μg/ml)

Compound	Minimum inhibitory concentration (MIC) in μg/ml				
	S. aureus	*B. Subtils*	*S. tyhpi*	*E. coli*	*K. pneumonia*
9	50	100	200	100	200
10	50	25	12.5	—	100
11	6.25	25	50	100	25
12	25	100	100	6.25	200
13	200	100	50	100	50
14	12.5	100	—	50	100
15	25	50	200	50	100
16	50	50	200	25	100
17	50	25	100	12.5	50
18	6.25	25	12.5	50	100
19	100	50	6.25	100	—
20	6.25	25	6.25	100	50
21	100	100	50	25	—
22	25	25	100	50	25
23	6.25	50	100	100	25
24	100	100	6.25	50	50
Streptomycin	50	12.5	50	12.5	25

—, No inhibition even at maximum concentration.

Table 3
Antifungal activity of compounds **9**–**24** against selected fungal strains (MIC in μg/ml)

Compound	Minimum inhibitory concentration (MIC) in μg/ml				
	C. neoformans	*C. albicans*	*Rhizopus* sp.	*A. niger*	*A. flavus*
9	100	200	—	200	200
10	25	50	100	100	6.25
11	25	25	100	25	50
12	25	25	50	100	6.25
13	100	200	25	100	100
14	200	200	100	200	—
15	50	—	200	200	100
16	100	50	100	50	—
17	50	50	200	—	200
18	25	6.25	100	200	100
19	12.5	6.25	6.25	100	50
20	12.5	25	6.25	25	100
21	100	50	6.25	25	50
22	100	100	50	—	25
23	50	100	200	100	—
24	100	50	100	50	200
Amphotericin B	25	25	25	50	50

—, No inhibition even at maximum concentration.

activity at very low concentration (6.25 μg/ml). Besides, **18** against *S. typhi* exhibit significant activity. Surprisingly replacement of fluorine function by chlorine in **10**, **11**, **18** and **19** (compounds **12**, **13**, **20** and **21**, respectively), compounds **12** against *E. coli* and **20** against *S. typhi*, were found to show superior activity than others. However, **12** against *B. subtilis* and *K. pneumonia* shows a reversal in activity, by two and three fold respectively, due to replacement of fluorine by chlorine. Instead of halogens, methyl or methoxy function substituted compounds **14** and **23** against *S. aureus* and **24** against *S. typhi* markedly elevated the maximum inhibition potency at minimum concentration (6.25 μg/ml).

The in vitro antifungal activity of the reported compounds **9-24** were examined with five fungal strains viz. *Cryptococcus neoformans* (ATCC-3312), *Candida albicans* (ATCC-3122), *Rhizopus* sp. (ATCC-2915), *Aspergillus niger* (ATCC-598) and *Aspergillus flavus* (ATCC-485). Here, Amphotericin B was used as standard drug. The obtained MIC values of the tested compounds and standard are depicted in Table 3 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 *Rhizopus* sp. which did not show any inhibition potency even at maximum concentration at 200 μg/ml whereas the same unsubstituted phenyl group in thiazolidinone compound (**17**) shows one and twofold enhancement in the antifungal activity against *C. neoformans* and *C. albicans*, respectively. However, due to introduction of fluorine functionality at the *meta* or *para* position of phenyl groups in **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, **10** against *A. flavus* shows superior inhibition potency at minimum concentration (6.25 μg/ml) whereas thiazolidinone compounds **18** against *C. albicans* and **19** against *C. neoformans*, *C. albicans* and *Rhizopus* sp. exhibited well pronounced activity. Unlike, **18** and **19** against *A. niger* exhibit one third decrease the inhibition potency upon cyclization. Modification of fluorine substituent by chlorine in **10**, **11**, **18** and **19** (compounds **12**, **13**, **20** and **21**, respectively) registered minimum antifungal activity against all the used strains, except **20** and **21** which shows superior activity against *Rhizopus* sp. In addition, **19** against *C. neoformans*, *C. albicans* and *A. niger* and **21** against *A. niger* produced considerable impact on antifungal activity. Replacement of one proton by methyl analogue in **9** (compound **14**) against *C. neoformans* and *Rhizopus* sp., the activity was decreased and enhanced, respectively, by onefold rate. The compound **14**, which was inactive against *A. flavus* become potent by the cyclization of thiosemicarbazone whereas **14** against *C. neoformans*, *C. albicans* and *Rhizopus* sp. have registered minimum to moderate antifungal activity. Due to modification of methyl analogue by methoxy group in **14** and **22** (compounds **15**, **16**, **23** and **24**) shows moderate activity against the entire tested fungal strains. Among the compounds under the antifungal study, **9** against *Rhizopus* sp., **14**, **16** and **23** against *A. flavus*, **15** against *C. albicans* and **17** and **22** against *A. niger* seldom show inhibition even at maximum concentration (200 μg/ml).

In conclusion, we have synthesized a novel biologically important thiosemicarbazones and their thiazolidinones. From the close survey of the in vitro antibacterial and antifungal results against a panel of microbial organisms revealed that the compound with fluorine or chlorine substituents were found to be more active against all the tested organisms.

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Supplementary data

Complete experimental details and spectral data (IR, ^{1}H NMR and ^{13}C NMR) for all the reported compounds data were given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.093.

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